https://doi.org/10.1070/RCR4988

Advances in the synthesis of heterocycles bearing an endocyclic urea moiety

Andrey V. Smolobochkin,* Almir S. Gazizov, Alexander R. Burilov, Mikhael A. Pudovik, Oleg G. Sinyashin

Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, ul. Arbuzova 8, 420088 Kazan, Russian Federation

The review systematizes and summarizes data on the synthesis of structurally diverse cyclic ureas published over the last 10 years. Saturated and unsaturated monocyclic ureas, as well as fused heterocycles containing one urea moiety, are considered. Data on the biological activity of selected compounds of this type are provided. The synthetic approaches to cyclic carbamides are classified in terms of the reaction type and the source of a carbonyl group.
The bibliography includes 235 references.

Contents

1. Introduction 395
2. Synthesis of cyclic ureas from compounds bearing a carbonyl group 396
   2.1. Reactions involving isocyanates 396
   2.2. Reactions of diamines with phosgene and its analogues 398
   2.3. Reactions involving carbon oxides 400
3. Cyclization of acyclic ureas 401
   3.1. Intramolecular reactions 402
   3.2. Intermolecular reactions 405
4. Synthesis of cyclic ureas *via* the Biginelli reaction 407
5. Amidation of carbamates 409
6. Synthesis of ureas from cyclic precursors 410
7. Other examples of the synthesis of cyclic ureas 411
8. Conclusion 413
9. List of acronyms 413

1. Introduction

Currently, cyclic ureas have found practical applications as drugs for the treatment of various medical conditions. For example, such derivatives can be used in the treatment of human immunodeficiency virus (HIV)[1–8] and hepatitis C;[9] they have antifungal,[10] antitumour,[11–14] antioxidative,[15] anticonvulsant,[16] anti-inflammatory,[17] antimicrobial,[18] nootropic,[19] and antidepressant[20,21] activities, also they are antagonists of neurokinin-1 (NK1)[22] and fibrinogen receptors[23] (Fig. 1). Data on the ability of these compounds to inhibit 5-alpha-reductase,[24] to block calcium channels,[25,26] and to show anticoagulant properties are available.[27] Icilin (see Fig. 1) and its analogues stimulate cold receptors in the skin and mucous membranes.[28] It is important to note that some of the derivatives of cyclic ureas are rather widely used as pharmaceuticals, among them are antibiotic Avibaktam,[29] psychotropic agent Mebikar,[30] and anti-nauseant Domperidon.[31–34] High biological activity of these systems is attributable to the fact that in a series of natural compounds there are sites containing a cyclic urea fragment. Examples may be found in biotin — a water-soluble B vitamin,[35–39] agelastatin alkaloids,[40,41] displaying various biological activities,[42–46] spiroleucettadine alkaloid,[47–49] *etc*.

It is noteworthy that in addition to biological activity, cyclic ureas also possess a variety of other practical useful properties: *N*,*N*′-dimethylpropylene ureas find application as polar aprotic organic solvents,[50–52] and selected bicyclic ureas are used to create polymeric electrolyte membranes.[53]

These data on the high practical significance of cyclic ureas determine the importance and relevance of the further

A.V.Smolobochkin. PhD in Chemistry, Researcher at the IOPC RAS.
E-mail: smolobochkin@iopc.ru
Current research interests: chemistry of heterocyclic and organophosphorus compounds and nitrogen-containing acetals.
A.S.Gazizov. Doctor of Chemical Sciences, Senior Researcher at the same Institute.
E-mail: agazizov@iopc.ru
Current research interests: chemistry of calixarenes, nitrogen-containing acetals, and heterocyclic compounds.
A.R.Burilov. Doctor of Chemical Sciences, Professor, Head of laboratory at the same Institute. E-mail: burilov@iopc.ru
Current research interests: chemistry of nitrogen- and phosphorus-containing calix[4]resorcinarenes, acyclic polyphenols, acetals, and aldehydes, supramolecular chemistry.
M.A.Pudovik. Doctor of Chemical Sciences, Professor, Leading Researcher at the same Institute.
E-mail: pudovik@iopc.ru
Current research interests: chemistry of organophosphorus- and organosilicon compounds and calixarenes.
O.G.Sinyashin. Academician, Doctor of Chemical Sciences, Professor, Director of the same Institute.
E-mail: oleg@iopc.ru
Current research interests: chemistry of organoelement compounds; synthesis, structure, and properties of organophosphorus and organometallic compounds; chemistry of fullerenes and their organic derivatives; electrochemical synthesis, and catalysis.

Received 2 August 2020

© 2021 Uspekhi Khimii, ZIOC RAS, Russian Academy of Sciences and IOP Publishing Limited

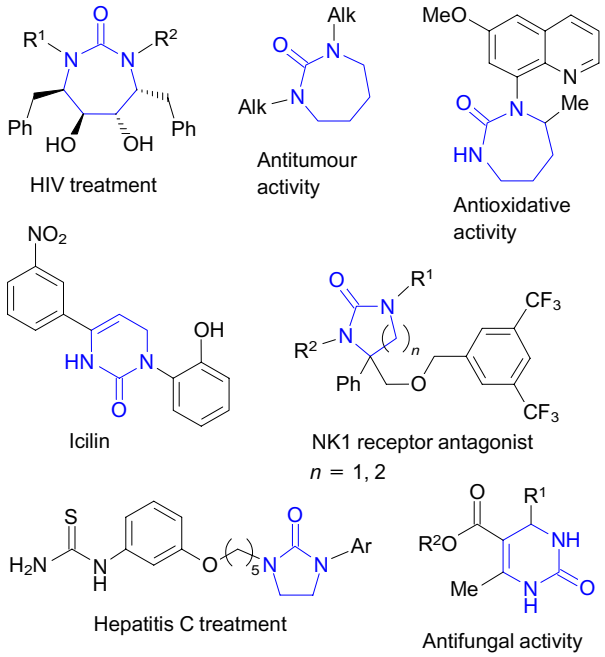


Figure 1. Biologically active cyclic ureas.

development of methods for their synthesis based on the targeted modification of endocyclic and exocyclic functional substituents, and the search for new synthetic routes to such derivatives possessing potential biological activity.

It should be noted that the synthesis of acyclic ureas was the topic of many reviews,[54–58] whereas no systematic analysis of synthetic approaches towards their cyclic analogues has been performed over the recent decades.

There are only two reviews [59, 60] in the literature in which the synthesis of cyclic ureas was mentioned. In the article by Petersen,[59] dated 1973, the methods for cyclization of a linear urea moiety were selectively provided. Importantly, at present there are virtually no review publications devoted to the methods for the synthesis of cyclic ureas utilizing carbon oxides and carbonates as sources of the carbonyl group, which attract special attention in terms of green chemistry. Sartori and Maggi [60] considered in detail the main approaches towards the synthesis of ureas published before 2001, however, the authors did not assign a separate section to cyclic ureas. In the present review, the data on the synthesis of cyclic ureas over the last 10 years are summarized, and the advantages and drawbacks of various approaches are discussed.

The methods for the synthesis of cyclic ureas can be divided into seven groups differing from each other in the source of a carbonyl group (Fig. 2). This division can be explained by the fact that the methodology of formation of cyclic ureas is based, *inter alia*, on the approach that uses organic or inorganic compounds containing a carbonyl group [isocyanates, phosgene and its analogues, carbon oxide (II or IV)] as building blocks. Within this approach, the methods for the synthesis of cyclic ureas, can be based on reactions with isocyanates (path *a*), reactions of diamines with phosgene and its safe analogues (path *b*), or carbon oxides (path *c*). The last-mentioned approach appears to be promising for the synthesis of heterocycles containing an urea moiety. Another method includes an intramolecular or intermolecular cyclization of the urea moiety (path *d*). One more approach (path *e*) is based on

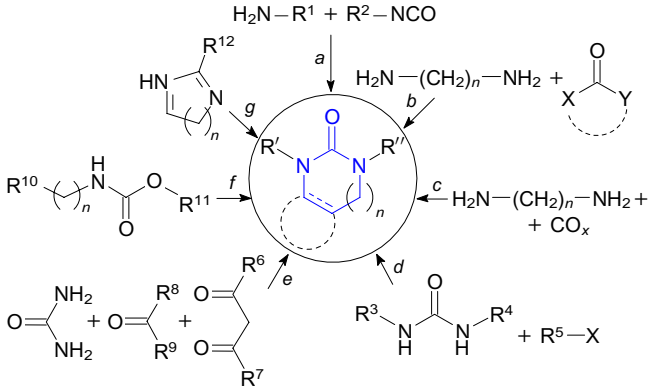


Figure 2. Methods for the synthesis of cyclic ureas.

the Biginelli reaction which proceeds in a three-component system of urea–carbonyl compounds–1,3-diketone and gives derivatives of 3,4-dihydropyrimidin-2(1*H*)-ones, which show showing a broad range of biological activities.[61–63] The Biginelli reaction was a subject of several reviews [64–66] covering the period before 2016. Taking this into account, the present review will consider only publications published after 2016. The synthesis of heterocycles *via* amidation of carbamates (path *f*), as well as examples of urea synthesis from the cyclic precursors (path *g*) are addressed in separate Sections. It should be noted that this review does not include the studies on cucurbit[*n*]urils [67–74] and glycolurils,[19, 75] since they were discussed in the corresponding generalizing publications. Moreover, we provide limited data on the production of uretdiones (1,2-azetidin-2,4-diones) [76–81] and imidazol-2-ones,[82, 83] the chemistry of which has been discussed in sufficient detail in other review publications.

Thus, the analysis of the state-of-the-art data on the synthesis of cyclic ureas provided in this review makes it possible to assess the prospects for their further development, to point out the most important approaches and environmentally friendly methods. Such an analysis opens up new scientific horizons and prospects for this area, shows 'points of growth' not only for organic chemists, but also for specialists in medicinal, supramolecular, ecological, and polymer chemistry, and also allows for applying the presented relevant information to form new modern approaches to the targeted design of various scaffolds with a cyclic urea moiety.

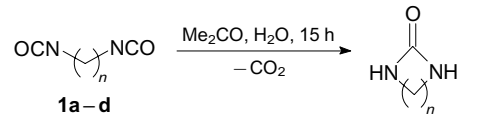
2. Synthesis of cyclic ureas from compounds bearing a carbonyl group

2.1. Reactions involving isocyanates

A key method for the synthesis of cyclic ureas relies on using isocyanates as base compounds. Thus, diisocyanates **1a–d** in aqueous acetone can undergo an intramolecular cyclization to give macrocyclic ureas **2a–d** in low yields (Scheme 1). The authors [84] found that in this process one of isocyanate groups is hydrolyzed to an amine moiety, which reacts with the second isocyanate group affording a cyclic urea **2**.

When *N*-alkylaziridine-2-carboxylates **3** are treated with isocyanates, a three-membered ring expansion is observed, thereby paving the way to the synthesis of imidazolidin-2-one derivatives **4a–h** (Scheme 2) with high regio- and stereoselectivity.[85]

Scheme 1

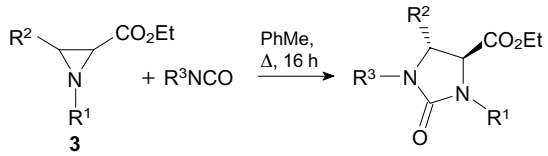


1a–d

n = 9 (**a**), 10 (**b**), 11 (**c**), 12 (**d**)

2a–d (15–16%)

Scheme 2



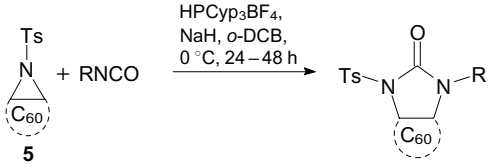
3

4a–h (70–95%)

R^1 = Pr^i: R^2 = Ph, R^3 = Pr^n (**a**); R^2 = 4-ClC_6H_4, R^3 = Pr^n (**b**); R^2 = Ph, R^3 = Bn (**c**); R^1 = Cyp: R^2 = Ph, R^3 = Pr^n (**d**); R^2 = 4-ClC_6H_4, R^3 = Pr^n (**e**); R^1 = Cy: R^2 = Ph, R^3 = Pr^n (**f**); R^2 = 4-ClC_6H_4, R^3 = Pr^n (**g**); R^1 = cyclo-C_8H_{15}, R^2 = Ph, R^3 = Pr^n (**h**); Cyp = cyclo-C_5H_9, Cy = cyclo-C_6H_{11}

An expansion of an aziridine ring to imidazolidine one in the reaction of fullerene C_{60} derivatives **5** with a broad series of isocyanates (Scheme 3) bearing both alkyl and aryl substituents, in the presence of phosphonium salts, has been reported.[86] At present, ureas annulated with fullerene C_{60} have not found any practical application. However, functionalized fullerenes, including compounds **6a–i**, are of interest due to their unique physicochemical properties, which possibly lead to the future use of such systems in various fields of science and technology.[87,88]

Scheme 3



5

6a–i (62–86%)

R = 4-$Bu^nC_6H_4$ (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-$MeOC_6H_4$ (**e**), 4-IC_6H_4 (**f**), 4-$EtO_2CC_6H_4$ (**g**), 2-IC_6H_4 (**h**), 2-$NO_2C_6H_4$ (**i**); C_{60} is fullerene C_{60}, Ts is *p*-toluenesulfonyl (tosyl)

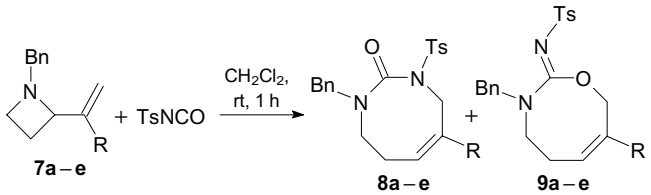
o-DCB is *o*-dichlorobenzene

The cycloaddition reaction between 2-vinylazetidines **7a–e** and tosyl isocyanate proceeds as a [6+2] process in dichloromethane at room temperature. Products **8a–e** and **9a–e** were isolated as mixtures of compounds, in which cyclic ureas predominated (Scheme 4).[89]

Available 1-mesyl-1,2,3-triazoles **10** readily undergo rhodium-catalyzed reactions with isocyanates, thereby providing imidazolones **11a–m** in high yields (Scheme 5). The authors[90] assume that under these conditions, the reactive carbenes are generated, reacting with isocyanate to give the target compounds **11**.

When phenyl isocyanate reacts with acyclic diamines **12a–f** in the presence of lanthanum bis(trimethylsilyl)-amide, cyclocarbonylation of diamines to the corresponding cyclic ureas **13a–f** is observed (Scheme 6).[91]

Scheme 4

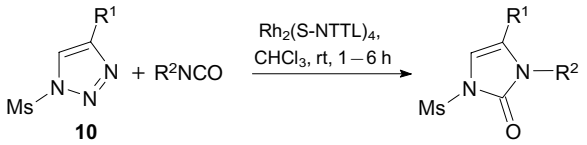


7a–e **8a–e** **9a–e**

rt is room temperature

Compound **7–9**	R	Yield **8** (%)	Yield **9** (%)
a	H	71	19
b	Me	65	18
c	Ph	77	0
d	4-$MeOC_6H_4$	67	6
e	4-$F_3CC_6H_4$	89	3

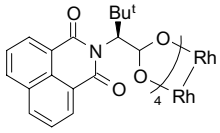
Scheme 5



10

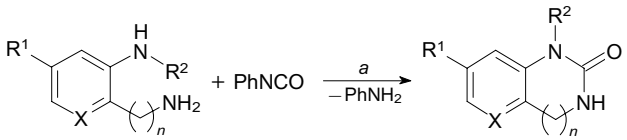
11a–m (80–95%)

R^1 = Ph: R^2 = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-$F_3CC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 3-FC_6H_4 (**f**), Bu^n (**g**); R^1 = 4-$F_3CC_6H_4$: R^2 = 4-ClC_6H_4 (**h**), Bn (**i**); R^1 = 4-MeC_6H_4: R^2 = 4-ClC_6H_4 (**j**), $ClCH_2CH_2$ (**k**), $BrCH_2CH_2CH_2$ (**l**); R^1 = 3-FC_6H_4, R^2 = 4-BrC_6H_4 (**m**)



Ms is methanesulfonyl (mesyl)

Scheme 6



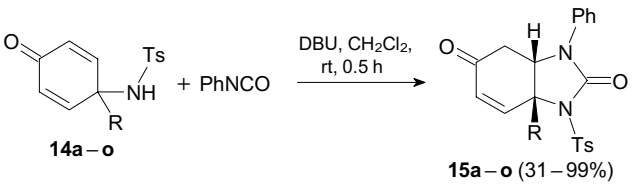
12a–f **13a–f** (88–96%)

(*a*) La[N(TMS)$_2$]$_3$, PhMe, 80 °C, 24 h;
n = 0, X = CH, R^2 = H: R^1 = H (**a**), Me (**b**), Cl (**c**); n = 0, X = N, R^1 = R^2 = H (**d**); n = 1, X = CH: R^1 = R^2 = H (**e**); R^1 = H, R^2 = Me (**f**); TMS is trimethylsilyl

The reaction of phenyl isocyanate with cyclohexadienones **14a–o**, bearing a secondary amino group, is catalyzed by 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU). Under mild conditions, it furnishes tetrahydro-1*H*-benzo[*d*]imidazole-2,6-diones **15a–o** in good yield and with high diastereoselectivity (Scheme 7).[92]

Pereshivko *et al.*[93,94] reported an effective method to obtain imidazolidon-2-ones having a multiple bond in the 5-position of the heterocycle (Scheme 8). The reaction of tosyl isocyanate with alkynes **16a–l**, bearing an amino group, implies the formation of intermediate acyclic ureas, which cyclize to give imidazolidine-2-ones **17a–l** in the

Scheme 7



R = Me (**a**), Et (**b**), Bu^n (**c**), CH_2=CH (**d**), Ph (**e**), 4-FC_6H_4 (**f**), 4-ClC_6H_4 (**g**), 4-BrC_6H_4 (**h**), 4-$F_3CC_6H_4$ (**i**), 3-ClC_6H_4 (**j**), 4-MeC_6H_4 (**k**), 3-MeC_6H_4 (**l**), 2-MeC_6H_4 (**m**), 4-$MeOC_6H_4$ (**n**), 3-$MeOC_6H_4$ (**o**)

Scheme 8

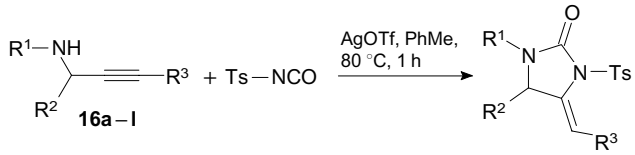


Table 1. Synthesis of imidazolidin-2-ones from (alkynylmethyl)amines (see Scheme 8).[93,94]

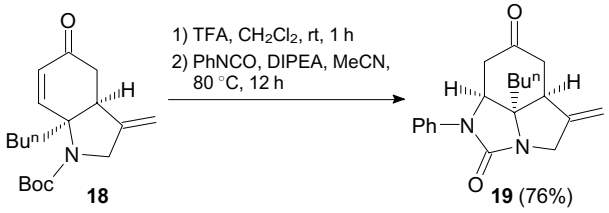
Compounds **16**, **17**	R^1	R^2	R^3	Yield (%)
a	4-$MeOC_6H_4$	Bu^i	Ph	80
b	Bn	Pr^n	Ph	91
c	Bn	*p*-Tol	Ph	67
d	cyclo-C_8H_{15}	n-C_5H_{11}	Ph	83
e	4-$MeOC_6H_4$	4-FC_6H_4	4-Bu^tC_6H_4	72
f	4-$MeOC_6H_4$	Pr^n	Bn	77
g	4-$MeOC_6H_4$	$PhCH_2CH_2$	Bn	57
h	4-$MeOC_6H_4$	Et	3-Th	47
i	$MeOCH_2CH_2$	Pr^n	4-Pr^nC_6H_4	46
j	Bn	Ph	Cyp	55
k	Ph	Ph	Ph	46
l	Bu^t	Bu^i	4-FC_6H_4	51

Note. The following designations are used: Tol is methylphenyl, Th is thienyl.

presence of silver(I) trifluoromethanesulfonate (triflate, OTf) (Table 1).

An original approach to obtain fused cyclic ureas has been proposed.[95,96] This procedure involves the removal of *tert*-butoxycarbonyl (Boc) protecting group in bicycle **18** with trifluoroacetic acid (TFA) followed by the treatment with phenyl isocyanate, which reacts with the generated amine moiety (Scheme 9). An intramolecular aza-Michael reaction in the intermediate acyclic urea affords octahydroimidazoindol-2-one **19** in a high yield.

Scheme 9

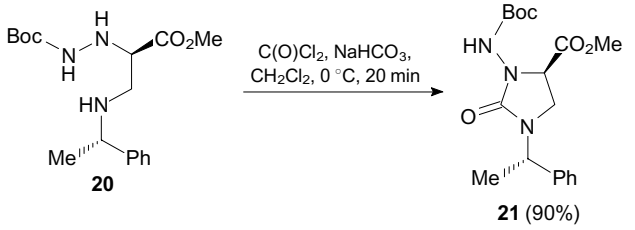


DIPEA is diisopropylethylamine

2.2. Reactions of diamines with phosgene and its analogues

Phosgene is widely used in organic chemistry as an agent providing a sufficiently easy introduction of a carbonyl group.[97,98] Cyclization of hydrazide **20** to imidazolidinone **21** in the presence of phosgene could be taken as an example.[99] This reaction proceeds at a high rate, and the product is formed in high yield (Scheme 10).

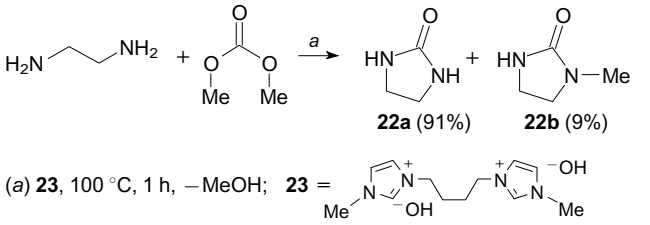
Scheme 10



However, the use of high-toxic gaseous phosgene has its drawbacks, at first the need to comply with safety measures. Moreover, the chemical processes involving phosgene produce hydrochloric acid as a by-product. In the last decades, there has been a tendency to replace phosgene with its safe analogues such as alkyl carbonates, 1,1′-carbonyldiimidazole, oxalyl chloride, diphosgene, and triphosgene, which are liquids or solids, thus greatly simplifying manipulations of these substances.

Thus, a mixture of cyclic ureas **22a**,**b** is formed on treating ethylenediamine with dimethyl carbonate in ionic liquid **23**, serving additionally as a catalyst (Scheme 11).[100] In this case, unsubstituted product **22a** is the major one. This method complies with the principles of green chemistry, since it provides a high rate of production of the product in a rather high yield under solvent-free conditions.

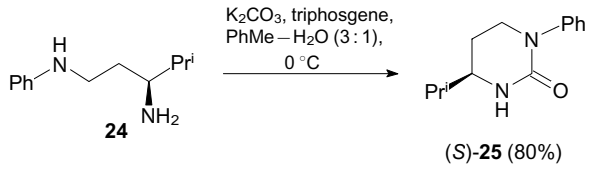
Scheme 11



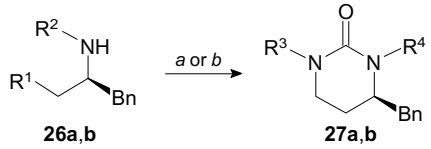
(*S*)-4-Methyl-*N*-phenylpentane-1,3-diamine (**24**) cyclizes under the action of phosgene in the presence of potassium carbonate to give (*S*)-4-isopropyl-1-phenyltetrahydropyrimidin-2(1*H*)-one (**25**) in a high yield (Scheme 12).[101]

Yamashita *et al.*[102] described two methods to obtain tetrahydropyrimidin-2-one derivatives (Scheme 13). The first method (conditions *a*) is based on Boc-deprotection of compound **26a** followed by treatment with triphosgene to afford cyclic urea **27a**. The second method (conditions *b*) involves the reduction of a nitrile group of compound **26b** to an amino group, which enters the cyclization with phosgene and furnishes tetrahydropyrimidin-2-one **27b**.

Scheme 12



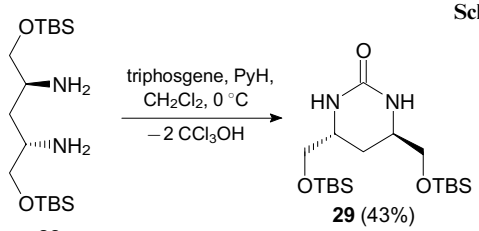
Scheme 13



(*a*) 1) TFA, CH_2Cl_2, rt, 0.5 h; 2) triphosgene, DIPEA, rt, 1 h (47%);
(*b*) 1) $NiCl_2$, $NaBH_4$, MeOH, rt, 10 min; 2) triphosgene, DIPEA, rt, 2 h (47%);
26: R^1 = $PhNHCH_2$, R^2 = Boc (**a**); R^1 = NC, R^2 = Ts (**b**);
27: R^3 = Ph, R^4 = H (**a**); R^3 = H, R^4 = Ts (**b**)

O'Leary and co-workers [103] synthesized 4,6-disubstituted tetrahydropyrimidinone **29** by the reaction of diamine **28** with triphosgene in dichloromethane (Scheme 14).

Scheme 14

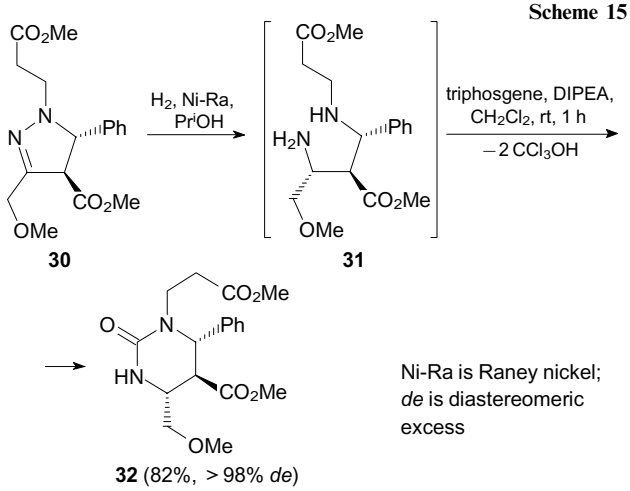


TBS is *tert*-butyldimethylsilyl, PyH is pyridine

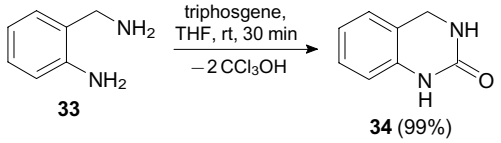
Reduction of pyrazole **30** gives an acyclic diamine **31**, which reacts with triphosgene to provide cyclic urea **32**. It should be noted that this reaction occurs with high diastereoselectivity (Scheme 15).[104]

Cyclization of 2-(aminomethyl)aniline (**33**) with triphosgene in THF at room temperature gave 3,4-dihydroquinazolin-2(1*H*)-one (**34**) in almost quantitative yield (Scheme 16).[105]

Scheme 15

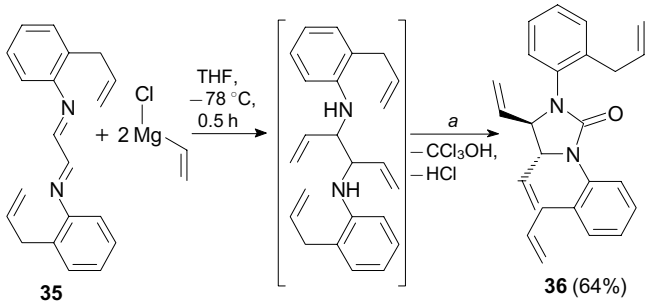


Scheme 16



Grubbs and co-workers [106] reported a two-step synthetic route towards cyclic urea, comprising the initial reaction of diimine **35** with Norman reagent in THF. The subsequent addition of diphosgene solution in dichloromethane to the reaction mixture in the presence of triethylamine gives product **36** in moderate yield (Scheme 17).

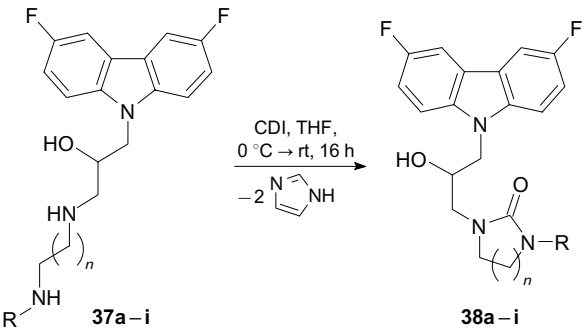
Scheme 17



(*a*) diphosgene, Et_3N, CH_2Cl_2, 0 °C, 2 h

The reaction between acyclic diamines **37a**–**i** and 1,1′-carbonyldiimidazole (CDI) in THF for 16 h produces cyclic ureas **38a**–**i** (Scheme 18), which show good antihyperglycemic activity.[107] It is difficult to estimate the effectiveness of the suggested method since the original work does not indicate the yields of the products.

Scheme 18

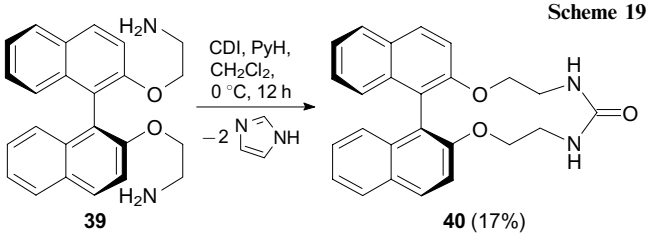


n = 1: R = H (**a**), Me (**b**), Et (**c**), Pr^i (**d**), Ph (**e**);
n = 2: R = H (**f**), Me (**g**), Et (**h**), Pr^i (**i**), Ph (**i**)

When studying the reaction of diamine **39** with carbonyldiimidazole in dichloromethane in the presence of pyridine, Taniguchi *et al.*[108] isolated a macrocyclic compound **40** containing 1,1′-binaphthalene moiety in modest yield (Scheme 19).

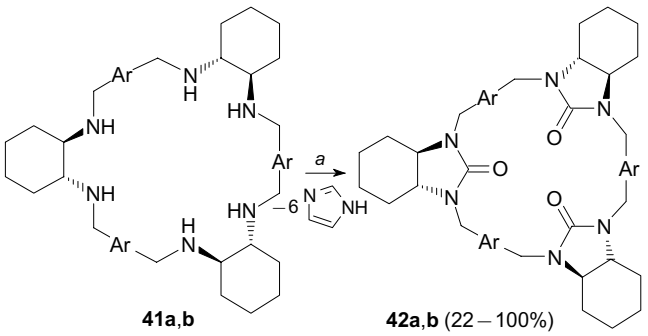
A study [109] should be mentioned concerning the reaction of trianglamines **41a**,**b** with 1,1′-carbonyldiimidazole to afford heteromacrocycles **42a**,**b** (Scheme 20). A distinctive feature of the obtained compounds is their ability to form

Scheme 19



39 **40** (17%)

Scheme 20



41a,**b** **42a**,**b** (22–100%)

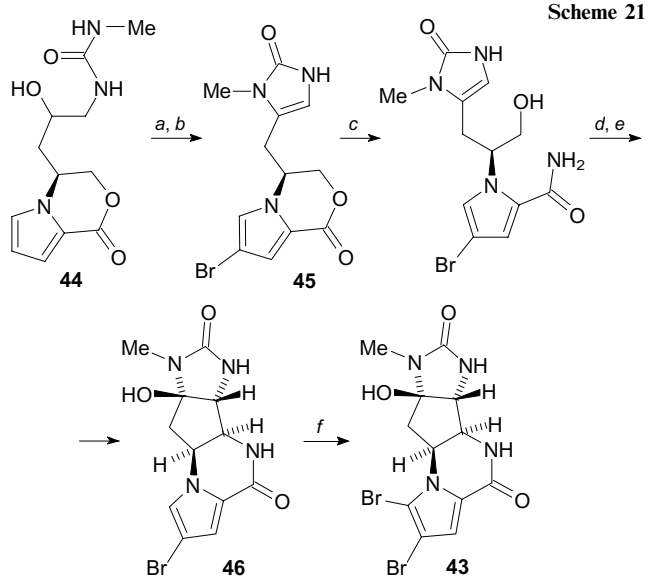
(*a*) CDI, CH_2Cl_2, rt, 24 h; Ar = (**a**), (**b**)

stable chiral metallogels with Ag^I, Cu^I, and Cu^{II} salts in *N*,*N*-dimethylformamide.

In a series of works [110–112], a multi-step enantioselective synthesis of agelastatine B (**43**) is described (Scheme 21). Bromination of the pyrrole ring in the starting compound **44** is initially carried out, and the subsequent treatment with oxalyl chloride is followed by cyclization of the urea moiety to give imidazol-2-one **45**. Then, several steps resulting in bromination of intermediate **46** provide the target alkaloid **43**.

The methods to obtain cyclic ureas as set down in this Section, based on the reactions of various amines with

Scheme 21



44 **45** **46** **43**

(*a*) NBS, MeOH, rt; (*b*) $(COCl)_2$, DMSO, Et_3N, 7 °C → rt (37%);
(*c*) NH_3, MeOH, 4 °C (90%); (*d*) 1) $(COCl)_2$, DMSO, 7 °C;
2) DIPEA, 7 °C → rt (85%); (*e*) 0.1 N HCl (aq.), rt, (29%);
(*f*) NBS, MeOH, rt (90%); NBS is *N*-bromosuccinimide

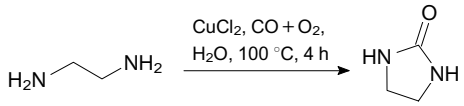
isocyanates, phosgene, and its analogues, are the most simple to perform. Such reactions usually proceed under mild conditions, at high rates, and give good product yields. Despite the toxicity of some reagents, this synthetic approach is often used to obtain complex biologically active compounds, particularly, alkaloids.

2.3. Reactions involving carbon oxides

In recent decades, reactions using carbon monoxide (carbonylation [113, 114]) and carbon dioxide (carboxylation [115–117]) have become important. This is due to the high availability of carbon oxides and the development of novel catalysts providing good yields of the target products in these processes.

Thus, oxidative carbonylation of ethylenediamine in the presence of copper(II) chloride was described, which afforded imidazolidin-2-one (**22a**) (Scheme 22).[118]

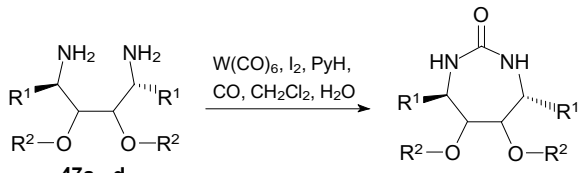
Scheme 22



22a (90%)

Oxidative carbonylation of chiral diamines **47a**–**d** to give derivatives of 1,3-diazepan-2-one **48a**–**d** has been described.[119, 120] The process is catalyzed by tungsten hexacarbonyl, and molecular iodine is used as an oxidant (Scheme 23).

Scheme 23

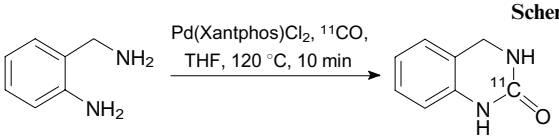


47a–**d** **48a**–**d** (38–83%)

R^1 = Me: R^2 = H (**a**), R^2–R^2 = CMe_2 (**b**);
R^1 = Bn: R^2 = H (**c**), R^2–R^2 = CMe_2 (**d**)

2-(Aminomethyl)aniline (**33**) reacts with ^{11}C-labelled CO in the presence of palladium catalyst to give 3,4-dihydroquinazolin-2(1*H*)-one (**34**) (Scheme 24). The proposed method allows obtaining isotopically labelled cyclic ureas.[121]

Scheme 24

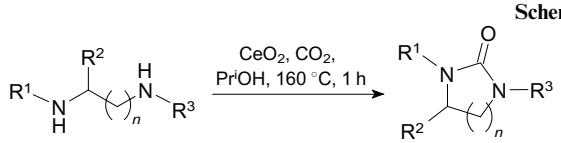


33 **34** (20%)

Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

To synthesize cyclic ureas **22a**,**b**, **49a**–**d**, **50a**,**b**, a catalytic reaction of diamines with gaseous CO_2 may be useful (Scheme 25, Table 2). As a catalyst, cerium dioxide acts in this case; the target products are formed in high yields.[122, 123]

Scheme 25



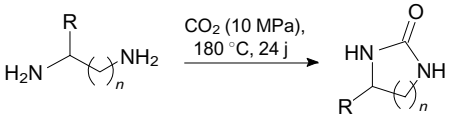
22a,**b**, **49a**–**d**, **50a**,**b**

Table 2. Synthesis of cyclic ureas from diamines and CO_2 catalysed by CeO_2 (see Scheme 25).[122, 123]

Compound	*n*	R^1	R^2	R^3	Yield (%)
22a	1	H	H	H	96
22b	1	Me	H	H	96
49a	1	Pr^i	H	H	96
49b	1	Et	H	H	96
49c	1	H	Me	H	96
49d	1	Me	H	Me	98
50a	2	H	H	H	90
50b	2	Me	H	H	88

At the same time, some known methods to obtain cyclic ureas do not require the use of metal complex catalysis. In 2010, the reaction of acyclic diamines with CO_2 was reported,[124] making it possible to obtain the cyclic urea derivatives **22a**, **49c**, and **50a** in high yields in the absence of catalysts and organic solvents (Scheme 26).

Scheme 26

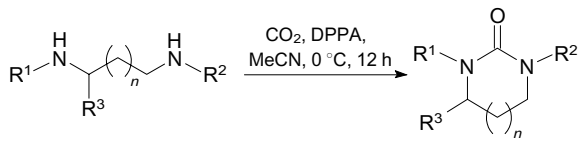


n = 1: R = H (**22a**), Me (**49c**);
n = 2, R = H (**50a**)

22a, **49c**, **50a**
(67–97%)

Muñoz and co-workers [125] synthesized such ureas **49**–**51** *via* the reaction of amines with CO_2 in the presence of diphenylphosphoryl azide (DPPA) in acetonitrile

Scheme 27



49c,**e**–**h**, **50c**, **51a**

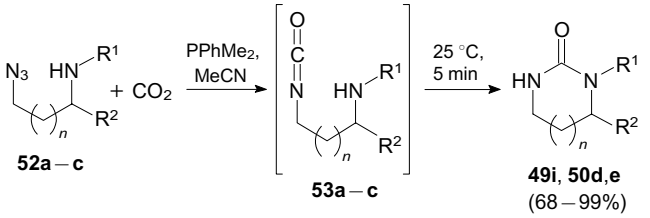
Table 3. Synthesis of cyclic ureas from diamines and CO_2 in the presence of diphenylphosphoryl azide (see Scheme 27).[125]

Compound	*n*	R^1	R^2	R^3	Yield (%)
49c	0	H	H	Me	86
49e	0	Bn	Bn	H	85
49f	0	Cy	Cy	H	93
49g	0	H	1,3-Diphenyl-prop-2-yl	H	86
49h	0	Pr^i	1,3-Diphenyl-prop-2-yl	H	91
50c	1	Bn	Bn	Me	94
51a	2	Bn	Bn	H	73

(Scheme 27, Table 3). It is noteworthy, that DPPA is a highly toxic and potentially explosive substance.

Azides **52a**–**c** were found [126] to react with CO_2 in the presence of dimethylphenylphosphine to provide isocyanates **53a**–**c**, which readily undergo an intramolecular cyclization to generate ureas **49i**, **50d**,**e** under mild conditions (Scheme 28).

Scheme 28

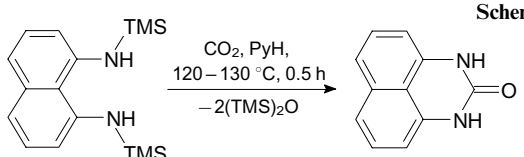


52a–**c** **53a**–**c** **49i**, **50d**,**e** (68–99%)

n = 1: R^1 = Bn, R^2 = H (**52a**, **53a**, **50d**); R^1 = 2-$ThCH_2$, R^2 = H (**52b**, **53b**, **50e**); *n* = 0, R^1 = H, R^2 = Ph (**52c**, **53c**, **49i**)

The reaction of bis-silylated naphthyldiamine **54** with CO_2 in the presence of pyridine affords 1*H*-perimidin-2(3*H*)-one (**55**) in the quantitative yield (Scheme 29).[127]

Scheme 29



54 **55** (99%)

The synthesis of carbamides with CO and CO_2 taken as carbonylation agents has recently attracted the attention of researchers primarily due to the availability of renewable reactants. The drawback of this method is the need for high temperatures and pressures. However, it should be noted that the proposed procedure has good prospects for obtaining novel cyclic ureas including those isotopically labelled.

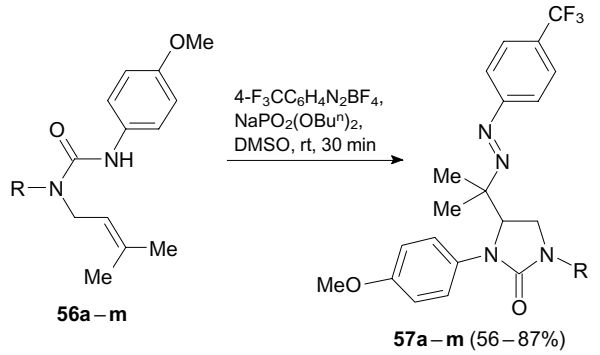
3. Cyclization of acyclic ureas

One of the most common methods for the synthesis of ureas is based on cyclization of compounds containing an acyclic urea moiety, and this method can be implemented both in intra- and intermolecular versions. The intramolecular cyclization is typical of ureas representing either unsaturated systems or compounds capable of forming multiple bonds in the course of the reaction. Since the nucleophilicity of the nitrogen atom in ureas is not high,[128, 129] harsh reaction conditions or the use of base catalysis are necessary for the intramolecular reaction to occur, which significantly improves the reactivity of the nitrogen atoms. As bases, both inorganic (sodium hydride, potassium and caesium carbonates), and organic {triethylamine, DBU, DIPEA, 1,4-diazabicyclo[2.2.2]octane (DABCO), sodium formate, caesium acetate, potassium *tert*-butoxide} compounds are utilized. In the case of intermolecular cyclization, the rearrangement of structural fragments occurs either directly in the precursor or during the formation of a cyclic system. The advantage of the second approach is the possibility to obtain a wider range of cyclic ureas.

3.1. Intramolecular reactions

Alkenes **56a–m** bearing a carbamide moiety undergo an intramolecular cyclization on treatment with aryldiazonium salts. Using this method, various imidazolidin-2-ones **57a–m** were obtained under mild conditions and in high yields (Scheme 30).[130]

Scheme 30

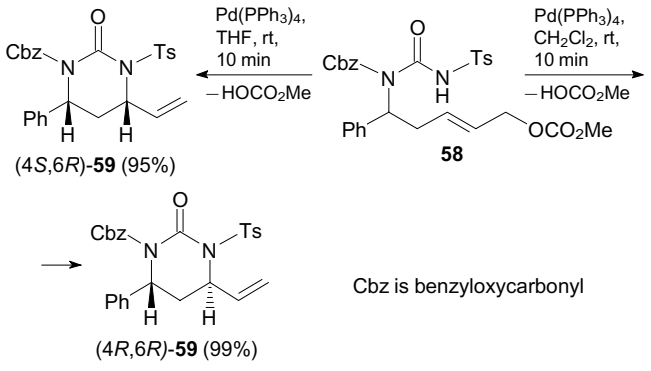


56a–m **57a–m** (56–87%)

R = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-ClC$_6$H$_4$ (**c**), 4-BrC$_6$H$_4$ (**d**), 4-FC$_6$H$_4$ (**e**), 4-F$_3$COC$_6$H$_4$ (**f**), 4-AcNHC$_6$H$_4$ (**g**), 4-MeSC$_6$H$_4$ (**h**), 4-NCC$_6$H$_4$ (**i**), 3-MeC$_6$H$_4$ (**j**), Bn (**k**), Bu^n (**l**), cyclo-C$_3$H$_5$ (**m**)

Diastereoselective synthesis of tetrahydropyrimidin-2-one derivatives *via* palladium-catalyzed intramolecular cyclization of alkene **58** containing an urea functionality, is reported.[131–133] A notable feature of this reaction is the predominant formation of a particular diastereomer depending on the solvent nature: in some cases, the diastereomer ratio (*dr*) exceeds 20 : 1. In THF, the authors managed to isolate *syn*-isomer (4*S*,6*R*)-**59** in almost quantitative yield, while in dichloromethane, *anti*-isomer (4*R*,6*R*) - **59** is predominantly formed (Scheme 31).

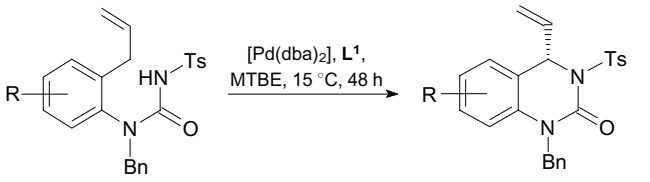
Scheme 31



Wang *et al.*[134] developed a stereoselective method for cyclization of ureas **60a–k** catalyzed by palladium complex with a chiral ligand, 1,3,2-dioxaphosphepane (**L^1**). As a result, compounds **61a–k** with high value of enantiometic excess (*ee*) were obtained (Scheme 32).

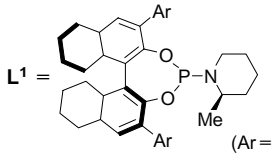
An intramolecular cyclization of alkenes **62a–f**, comprising an acyclic urea moiety, under catalysis with palladium(II) trifluoroacetate in toluene affords nitrogen-containing heterocycles **63a–f** in moderate to high yiels (Scheme 33).[135]

Scheme 32



60a–k **61a–k** (44–98%, *ee* > 91%)

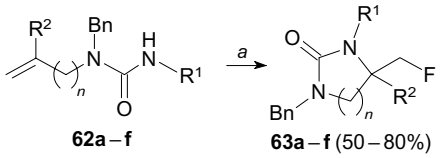
R = 4-Me (**a**), 4-OMe (**b**), 4-Pr^i (**c**), 4-CF$_3$ (**d**), 4-F (**e**), 4-Cl (**f**), 4-Br (**g**), 5-Me (**h**), 5-CF$_3$ (**i**), 5-OCF$_3$ (**j**), 6-F (**k**);



(Ar = 3,5-(F$_3$C)$_2$C$_6$H$_3$)

dba is dibenzylideneacetone, MTBE is methyl *tert*-butyl ether

Scheme 33



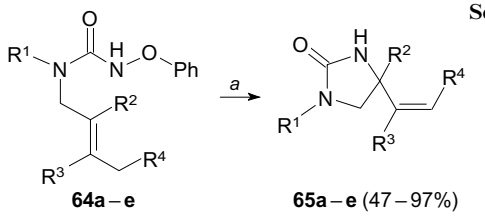
62a–f **63a–f** (50–80%)

(*a*) Pd(O$_2$CCF$_3$)$_2$, PhI(O$_2$CBu^t)$_2$, AgF, 2-MeO-BQ, (CF$_3$)$_2$CHOH, PhMe, rt, 24 h; *n* = 1: R^1 = Et, R^2 = H (**a**), R^1 = Et, R^2 = Me (**b**), R^1 = Me, R^2 = H (**c**), R^1 = Bn, R^2 = H (**d**), R^1 = Ph, R^2 = H (**e**); *n* = 2, R^1 = Et, R^2 = H (**f**); 2-MeO-BQ is 2-methoxy-1,4-benzoquinone

Xu *et al.*[136] reported an intramolecular cyclization of *N*-phenoxy ureas **64a–e** containing a multiple bond *via* the aza-Heck reaction which is also catalyzed by a palladium compound (Scheme 34, Table 4). The reaction furnishes diversely substituted imidazolidinones **65a–e**.

Refluxind alkynes **66a–k** in aqueous isopropanol for 4 hours in the presence of dichlorobis(triphenylphosphino)-palladium(II), afforded 1,3-benzodiazepin-2-one derivatives

Scheme 34



64a–e **65a–e** (47–97%)

(*a*) [(PhCH=CHCH$_2$O)PdCl]$_2$, P(OCH$_2$CF$_3$)$_3$, PhMgBr, Et$_3$N, MeCN, 50 °C

Table 4. Synthesis of cyclic ureas *via* the cyclization of *N*-phenoxy ureas (see Scheme 34).[136]

Compounds **64**, **65**	R^1	R^2	R^3	R^4	Yield (%)	Note
a	Bn	H	Me	H	92	
b	Bn	Me	H	H	62	
c	H	H	H	Me	74	
d	3,4-Cl$_2$C$_6$H$_3$CH$_2$	H	H	OBn	47	*trans* : *cis* = 1 : 1
e	MeOCH$_2$CH(Ph)	H	Me	H	97	*dr* = 50 : 50

Scheme 35

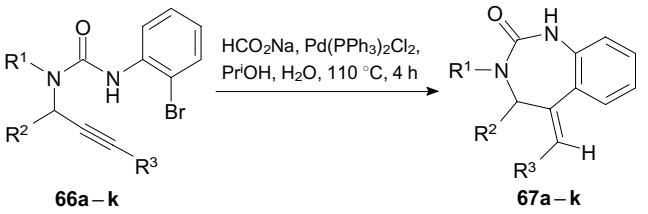


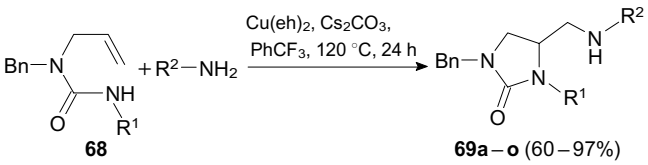
Table 5. Synthesis of cyclic ureas *via* the cyclization of alkynes bearing a carbamide moiety (see Scheme 35).[137]

Compounds **66**, **67**	R^1	R^2	R^3	Yield (%)
a	Bn	Pr^n	Ph	61
b	Bn	Bu^i	4-FC_6H_4	50
c	Bn	Bu^i	4-$F_3CC_6H_4$	64
d	Bu^n	Pr^n	Ph	62
e	Bu^n	Bu^i	4-NCC_6H_4	62
f	4-$MeOC_6H_4$	Pr^n	Ph	51
g	4-$MeOC_6H_4$	Bu^i	Ph	42
h	4-$MeOC_6H_4$	Ph	Ph	39
i	4-$MeOC_6H_4$	Bu^n	Ph	50
j	4-$MeOC_6H_4$	Pr^n	3-Th	45
k	4-$MeOC_6H_4$	Pr^n	Pr^n	46

67a–k (Scheme 35, Table 5)[137] displaying a broad range of biological activities.[138–141]

Copper(II)-catalyzed intramolecular cyclization of *N*-allylureas **68** in the presence of aniline derivatives allows for the synthesis of various imidazolidin-2-ones **69a–o** (Scheme 36).[142]

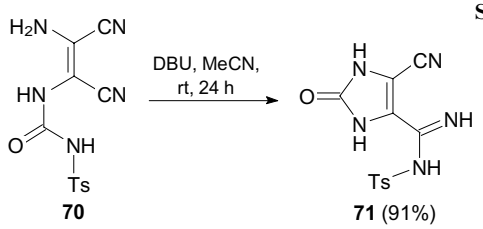
Scheme 36



R^1 = Ph: R^2 = Ph (**a**), 4-ClC_6H_4 (**b**), 4-FC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 4-$F_3CC_6H_4$ (**e**), 4-$Pr^iC_6H_4$ (**f**), 2-ClC_6H_4 (**g**), 3-$O_2NC_6H_4$ (**h**), 3-$MeOC_6H_4$ (**i**), Ts (**j**), Bz (**k**); R^1 = Ts: R^2 = Ph (**l**), 4-ClC_6H_4 (**m**); R^1 = 1-Naph, R^2 = Ph (**n**); R^1 = Bz, R^2 = Ph (**o**);
eh is 2-ethyl hexanoate, Naph is 1-naphthyl

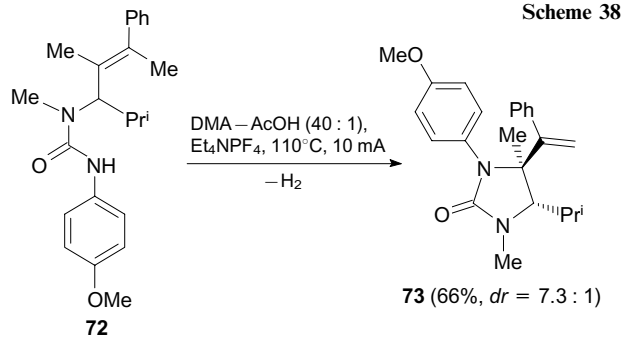
An intramolecular cyclization of *N*-carbamoyl tosylamide **70** in the presence of DBU in acetonitrile at room temperature affords imidazol-2-one **71** in high yield (Scheme 37).[143]

Scheme 37



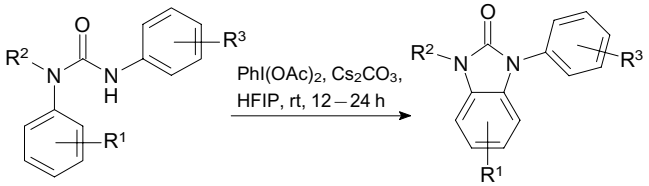
There are published data on the electrocatalytic cyclization of urea **72** in the tetraethylammonium hexafluorophosphate (Et_4NPF_6)–dimethylacetamide (DMA)–acetic acid buffer system, providing imidazolidin-2-one **73** as a mixture of diastereomers (Scheme 38).[144]

Scheme 38



The authors[145] suggested a convenient method for the synthesis of substituted imidazolidin-2-ones *via* oxidative amidation of *N*,*N*′-diarylureas **74a–x**. This method pro-

Scheme 39



HFIP is 1,1,1,3,3,3-hexafluoropropan-2-ol

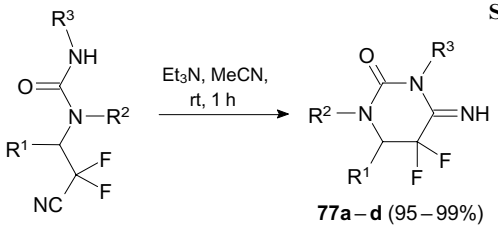
Table 6. Synthesis of cyclic ureas *via* the cyclization of diarylcarbamides (see Scheme 39).[145]

Compounds **74**, **75**	R^1	R^2	R^3	Yield (%)
a	H	Me	H	71
b	H	Et	H	68
c	H	Pr^i	H	64
d	H	Bu^n	H	59
e	H	Cy	H	61
f	H	All	H	33
g	H	Bn	H	46
h	H	Me	2-Me	42
i	H	Me	3-Me	56
j	H	Me	4-Me	67
k	H	Me	4-F	48
l	H	Me	4-Cl	87
m	H	Me	3-Cl	82
n	H	Me	2-Cl	55
o	H	Me	4-Br	66
p	H	Me	4-CF_3	52
q	H	Me	3-CO_2Me	35
r	3-Me	Me	H	63
s	4-Me	Me	H	79
t	4-F	Me	H	59
u	4-Cl	Me	H	63
v	4-Br	Me	H	74
w	4-CO_2Me	Me	H	40
x	H	Ph	H	88

vides an access to compounds **75a–x** under mild conditions from available reactants in moderate and high yields (Scheme 39, Table 6). Diarylureas **74a–x** with electron-donating groups R^1 and R^3 were found to provide higher product yields compared to compounds substituted with electron-withdrawing groups in benzene rings. The presence of long-chain aliphatic substituents R^2 decreases the yield of the target product. In the authors' opinion, this is due to the steric hindrance in the substrate.

Acyclic ureas **76a–d** bearing strong electron-withdrawing substituents in the presence of triethylamine readily cyclize to give iminopyrimidinones **77a–d**, which were isolated in almost quantitative yields (Scheme 40).[146]

Scheme 40

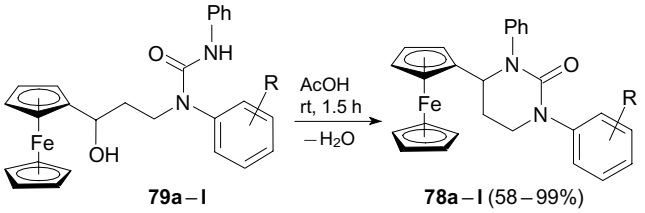


76a–d **77a–d** (95–99%)

R^1 = Ph, R^2 = Me: R^3 = Ph (**a**), 4-ClC$_6$H$_4$ (**b**);
R^1 = 2-Th, R^2 = Bn: R^3 = Ph (**c**), 4-ClC$_6$H$_4$ (**d**)

Cyclic ureas **78a–l** substituted with a ferrocenyl moiety can be obtained by an intramolecular cyclization of hydroxy ureas **79a–l** in acetic acid (Scheme 41).[147] The proposed method is characterized is simple and does not require the use of costly catalysts.

Scheme 41



79a–l **78a–l** (58–99%)

R = H (**a**), 2-OMe (**b**), 4-OMe (**c**), 4-Me (**d**), 2-F (**e**), 4-F (**f**), 3-F (**g**), 4-Cl (**h**), 2-Me (**i**), 4-Br (**j**), 3-Br (**k**), 2-Br (**l**)

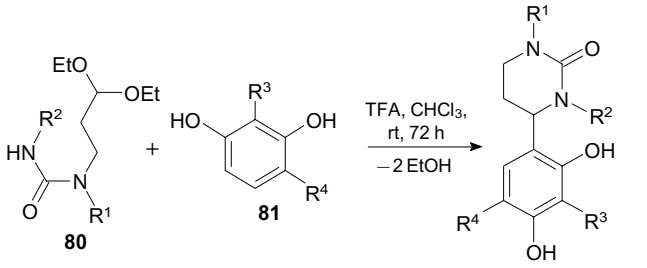
The cascade reaction of 3,3-diethoxypropyl urea derivatives **80** in trifluoroacetic acid in the presence of resorcinol derivatives **81** makes it possible to obtain various 4-aryl-substituted tetrahydropyrimidin-2(1*H*)-ones **82a–g** (Scheme 42).[148,149]

The acid-catalyzed reaction of phosphonate **83** with resorcinol derivatives gives an inseparable mixture of regioisomeric 5-arylimizadolin-2-ones **84a–c** and 4-arylimidazolin-2-ones **85a–c** (Scheme 43).[150–152] Nevertheless, the diastereomer ratio was shown to depend significantly on the nature of the resorcinol derivative in use.

An original cascade reaction of 1-(2,2-dimethoxyethyl)-1,3,3-trimethylurea (**86**), which occurs under catalysis with trifluoromethanesulfonic acid in the presence of 2-methylresorcinol (**81a**), became the first example of the synthesis of the hitherto unknown cyclic urea **87** containing an endocyclic quaternary nitrogen atom (Scheme 44).[153]

Mention should be made of studies[154–156] that describe the heterocycle expansion in indoline-1-carboxamides

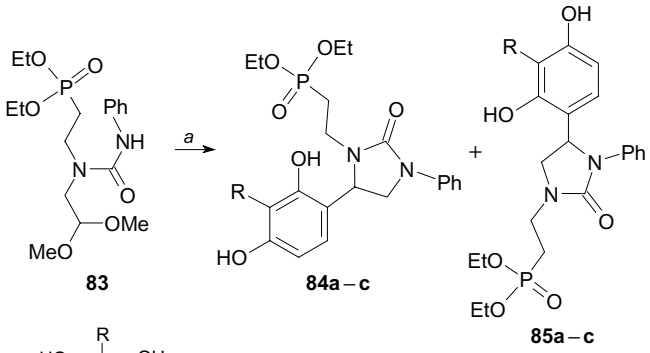
Scheme 42

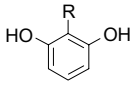


82a–g (24–89%)

82: R^1 = $CH_2P(O)(C_6H_{13}\text{-n})_2$, R^2 = Ph, R^4 = H: R^3 = H (**a**), Me (**b**), OH (**c**); R^1 = H, R^3 = H, R^4 = Cl: R^2 = H (**d**), Ph (**e**), 1-Naph (**f**), n-C_6H_{13} (**g**)

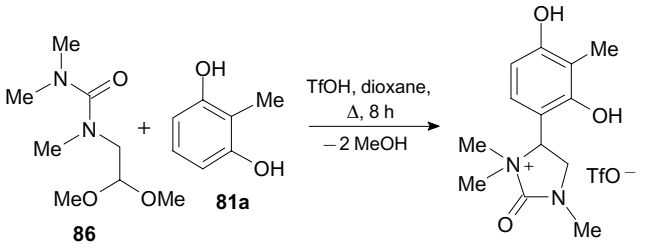
Scheme 43



(*a*)  (**81**), TFA, $CHCl_3$, 20 °C, 20 h, –2 MeOH;

R = H (**a**), Me (**b**), OH (**c**)

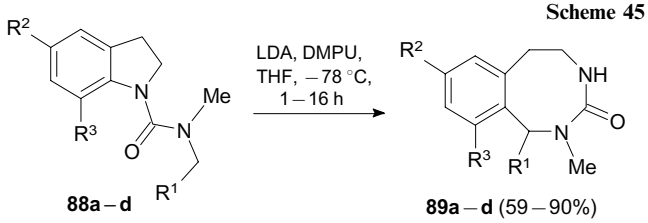
Scheme 44



87 (45%)

88a–d through their cyclization in the presence of lithium diisopropylamide (LDA) and *N*,*N*′-dimethylpropylidene urea (DMPU) to generate benzodiazocin-2-one derivatives **89a–d** (Scheme 45).

Scheme 45



89a–d (59–90%)

R^1 = Ph: R^2 = R^3 = H (**a**), R^2 = OMe, R^3 = H (**b**); R^2 = H, R^3 = Me (**c**); R^1 = 2-Th, R^2 = R^3 = H (**d**)

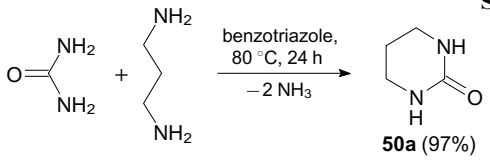
To summarize, intramolecular cyclization is typical for ureas which are either unsaturated systems or compounds capable of forming multiple bonds in the course of the reaction. An important feature of transformations described in this Section is the formation of ureas with different ring sizes containing exocyclic functional groups. These reactions are distinguished by the ease of implementation and available reactants. The yields of the obtained cyclic ureas are close to quantitative, and in some cases, such cyclizations proceed stereoselectively. Mention should also be made of a novel promising trend in the synthesis of cyclic ureas that is based on original cascade reactions of linear analogues bearing an acetyl moiety, involving resorcinol and its derivatives. This original procedure provides an access to various cyclic ureas containing phenol or polyphenol groups.

3.2. Intermolecular reactions

Another common approach to obtain cyclic ureas is an intermolecular cyclization involving open-chain ureas and their derivatives. For condensation with urea, in most cases, it is necessary that the second reactant is at least bifunctional. For this purpose, diamines, α- and β-diketones, ninhydrines, *etc*., can be used.

Carbamide nitrogen atoms are known to have low reactivity, therefore, both in intramolecular and in intermolecular cyclizations bases are usually used as catalysts. Thus, an example of transamidation of a carboxamide with propane-1,2-diamine (Scheme 46) has been reported [157] providing tetrahydropyrimidin-2(1*H*)-one (**50a**) in almost quantitative yield.

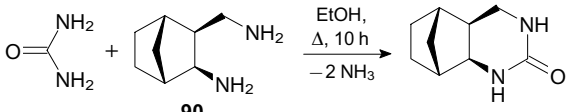
Scheme 46



50a (97%)

Shafikova *et al.*[158] carried out transamination of a carboxamide with diamine **90** in refluxing ethanol for 10 h to obtain product **91** (Scheme 47).

Scheme 47

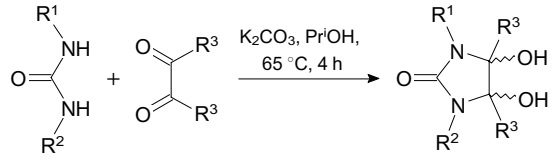


90 **91** (42%)

The synthesys of 4,5-dihydroxyimidazolidin-2-ones **92a**–**I** has been reported.[159–162] This method is based on the condensation of carbamides with 1,2-dicarbonyl compounds in refluxing isopropanol in the presence of potassium carbonate acting as a base catalyst (Scheme 48). Derivatives **92** were isolated as a mixture of diastereomers.

1,1,1,4,4,4-Hexafluorobutane-2,3-dione reacts with substituted carbamides similarly, to give diastereomeric mixtures of imidazolidin-2-ones **93a**–**c** (Scheme 49).[163] It is noteworthy that this reaction proceeds on cooling in the absence of any catalysts. This is probably due to the influence of strong electron-withdrawing substituents in perfluorodiacetyl, which increase the electrophilicity of

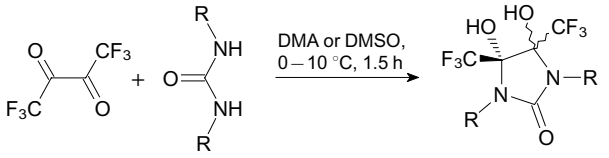
Scheme 48



92a–**i** (10–70%)

$R^1 = R^2 = Me$, $R^3 = Ph$ (**a**); $R^1 = R^3 = H$, $R^2 = Cy$ (**b**); $R^3 = H$: $R^1 = R^2 = H$ (**c**), Me (**d**), Et (**e**); $R^1 = Me$, $R^3 = H$: $R^2 = Bu^t$ (**f**), Ph (**g**), Cy (**h**); $R^1 = Et$, $R^2 = Ph$, $R^3 = H$ (**i**)

Scheme 49



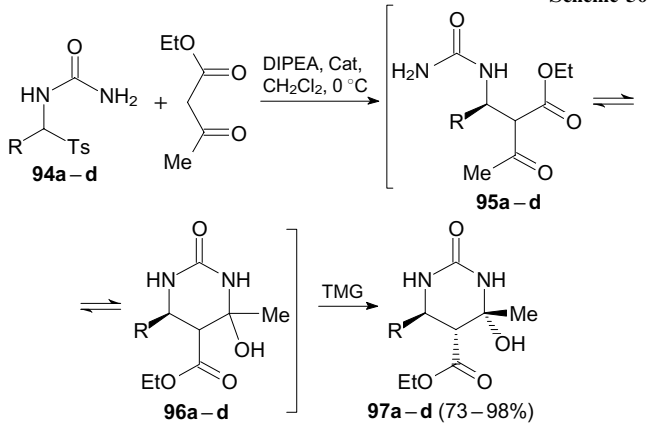
93a–**c** (60–90%)

Compound **93**	R	*cis* : *trans*
a	H	~ 90 : 10
b	Me	~ 13 : 87
c	Et	~ 57 : 43

carbonyl carbon atoms, thereby allowing the process to be carried out under mild conditions.

Lillo and Saá [164] reported the diastereo- and enantioselective synthesis of 4-hydroxytetrahydropyrimidin-2-ones based on the reaction between substituted ureas **94a**–**d** and acetoacetic ester (Scheme 50). The authors suggested that the nucleophilic substitution of the tosyl group with the CH-anion of acetoacetic ester results in the formation of intermediate acyclic adducts **95a**–**d**, which are in equilibrium with cyclic urea derivatives **96a**–**d**. The addition of 1,1,3,3-tetramethylguanidine (TMG) inhibits the retro-

Scheme 50



94a–**d** **95a**–**d** **96a**–**d** **97a**–**d** (73–98%)

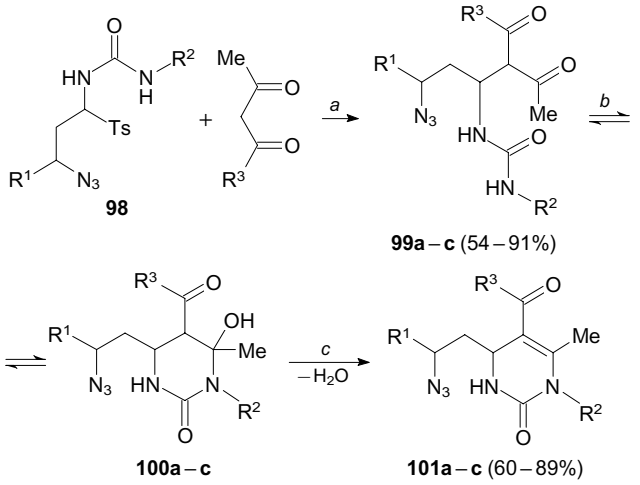
93–**97**	R	*dr*	*ee* (**97**), %
a	Ph	88 : 12	93
b	4-FC_6H_4	92 : 8	94
c	3-FC_6H_4	89 : 11	88
d	3-$MeOC_6H_4$	91 : 9	86

Cat =

Mannich reactions and shifts the equilibrium towards the formation of cyclic products **97a–d**.

1,3-Diketones enter the similar reaction with tosylureas **98** (Scheme 51). This leads to the corresponding dicarbonyl derivatives **99a–c** containing a substituted urea moiety in the 2-position, which were isolated in the individual state.[165–170] Acidification of compounds **99a–c** with *p*-toluenesulfonic acid at room temperature generates 4-hydroxytetrahydropyrimidin-2-ones **100a–c**, which undergo dehydration on heating to give 1,2,3,4-tetrahydropyrimidin-2-ones **101a–c** as a mixture of diastereomers.

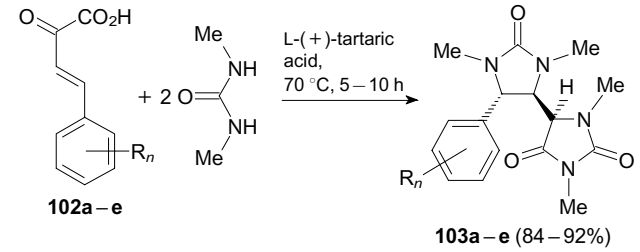
Scheme 51



(*a*) NaH; (*b*) TsOH, MeCN, rt, 8 h; (*c*) TsOH, EtOH, Δ, 8 h;
$R^1 = R^2 = H$, $R^3 = Me$ (**a**); $R^1 = H$, $R^2 = R^3 = Me$ (**b**);
$R^1 = Me$, $R^2 = H$, $R^3 = Ph$ (**c**)

β,γ-Unsaturated keto acids **102a–e** react with 1,3-dimethylurea in the presence of L-(+)-tartaric acid to afford functionalized imidazolidin-2-ones **103a–e** with good diastereoselectivity (*anti*:*syn* = ~2:1) (Scheme 52).[171] A feature of this reaction is that it is solvent-free.

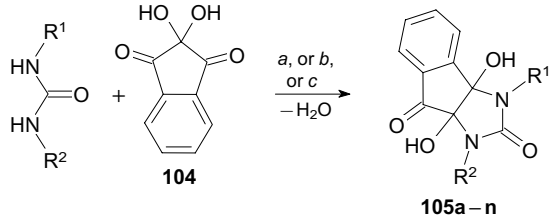
Scheme 52



R_n = 4-CN (**a**), 4-Me (**b**), 4-Br (**c**), 3-Cl (**d**), 2,4-Cl_2 (**e**)

The possibility to obtain the derivatives of tetrahydroindeno[1,2-*d*]imidazole *via* the reaction of substituted ureas with ninhydrin (**104**) has been reported (Scheme 53).[172–176] The yield of the target product depends on the reaction conditions. Thus, compound **105a** is formed quantitatively when carrying out this reaction in refluxing aqueous THF (conditions *a*),[172] while compound **105b** is obtained in refluxing acetic acid (conditions *b*).[173] Products **105c–n** were synthesized in refluxing benzene (conditions *c*).[174–176] Unfortunately, the authors provided no yields of individual compounds, which made it difficult to assess the effect of

Scheme 53

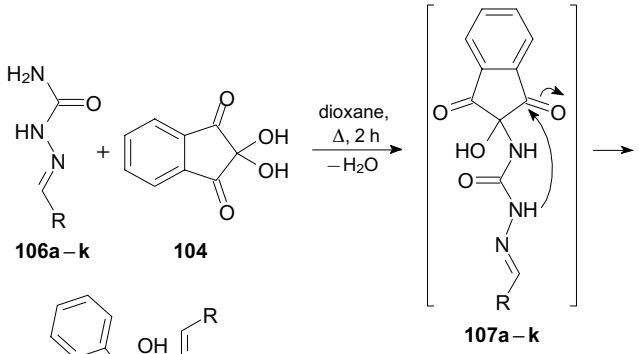


(*a*) H_2O, THF, Δ (100% yield); (*b*) AcOH, Δ, 15 min (100%);
(*c*) PhH, Δ, 1 ч (85–90%);
$R^1 = R^2 = H$ (**a**), Ph (**b**); $R^1 = Et$, $R^2 = 4\text{-}O_2NC_6H_4$ (**c**);
$R^1 = Pr^n$: $R^2 = 4\text{-}EtC_6H_4$ (**d**), $4\text{-}ClC_6H_4$ (**e**), Ph (**f**);
R^1 = cyclo-C_3H_5: $R^2 = 4\text{-}O_2NC_6H_4$ (**g**), $4\text{-}EtC_6H_4$ (**h**), $4\text{-}ClC_6H_4$ (**i**), Ph (**j**); $R^1 = Ph$: $R^2 = 4\text{-}O_2NC_6H_4$ (**k**), $4\text{-}EtC_6H_4$ (**l**), $4\text{-}ClC_6H_4$ (**m**);
$R^1 = PhCH(Me)$, $R^2 = Et$ (**n**)

substituents in the starting acyclic ureas on the yields of the products **105**.

Condensation of semicarbazones **106a–k** with ninhydrin **104** in boiling dioxane occurs within 2 h (Scheme 54).[177–179] The authors suggest that acyclic intermediates **107a–k** are formed initially and are then converted to heterocyclic ureas **108a–k**, some of which exhibit antimicrobial and antifungal activities.[179]

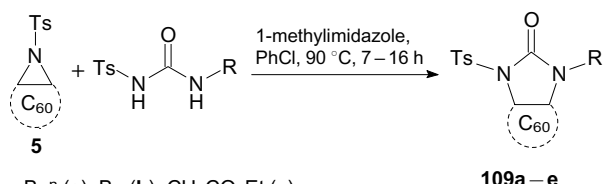
Scheme 54



R = Ph (**a**), 2-HOC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 2-$MeOC_6H_4$ (**e**), 4-ClC_6H_4 (**f**), 4-BrC_6H_4 (**g**), 4-$O_2NC_6H_4$ (**h**), 2-ClC_6H_4 (**i**), 2-$O_2NC_6H_4$ (**j**), PhCH=CH (**k**)

The reaction of tosylurea with *N*-tosylaziridinofullerene **5**, following the double nucleophilic substitution mechanism, results in the formation of fulleroimidazolidinones **109a–e** smoothly and in good yields (Scheme 55).[180] It was shown that the reactivity of alkyl-substituted ureas is higher than that of their aryl-substituted analogues.

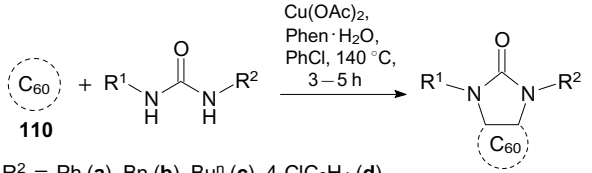
Scheme 55



R = Bu^n (**a**), Bn (**b**), CH_2CO_2Et (**c**), All (**d**), $CH_2CH(OMe)_2$ (**e**)

The diamidation of fullerene C_{60} (**110**) with substituted ureas, catalyzed with copper(II) acetate, affords fulleroimidazolidinones **111a–i** in one step (Scheme 56).[181] The major issue of the present method are the low yields of the target products.

Scheme 56



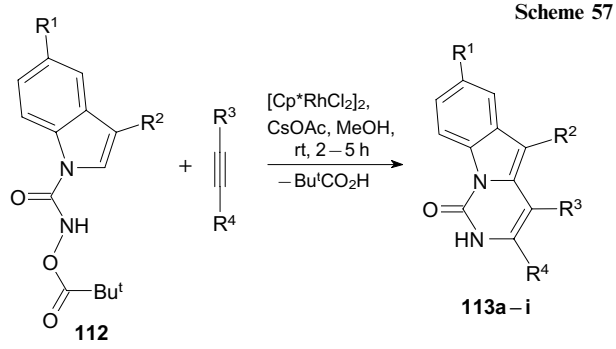
110

$R^1 = R^2$ = Ph (**a**), Bn (**b**), Bu^n (**c**), 4-ClC_6H_4 (**d**), 4-MeC_6H_4 (**e**), 4-$MeOC_6H_4$ (**f**); R^1 = Ph: $R^2 = Bu^n$ (**g**), 2-$MeOC_6H_4$ (**h**); $R^1 = Bu^n$, R^2 = 4-$MeO_2CC_6H_4$ (**i**); Phen is phenanthroline

111a–i (9–21%)

Using an intermolecular cyclization of indole derivatives **112** with alkynes, catalyzed with rhodium(III) complex $[Cp^*RhCl_2]_2$ ($Cp^*$is pentamethylcyclopentadienyl), fused cyclic ureas **113a–i** were obtained (Scheme 57, Table 7).[182]

Scheme 57



112

113a–i

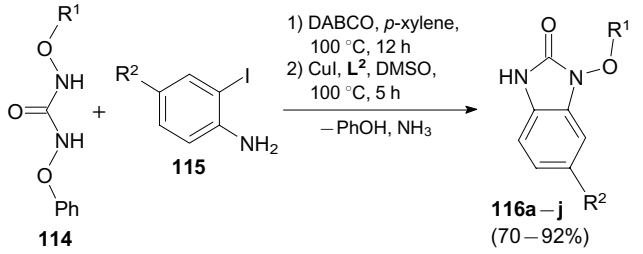
Table 7. Synthesis of annulated cyclic ureas *via* the cyclization of indole derivatives with alkynes (see Scheme 57).[182]

Compounds **113**	R^1	R^2	R^3	R^4	Yield (%)
a	H	H	Pr^n	Pr^n	93
b	H	H	Et	Et	70
c	H	H	CH_2OH	CH_2OH	92
d	H	H	Me	Ph	62
e	H	H	H	Bu^t	70
f	H	H	H	Bu^n	70
g	Et	H	Pr^n	Pr^n	97
h	OMe	H	Pr^n	Pr^n	90
i	H	Me	CH_2OH	CH_2OH	71

The cascade reaction between 1-phenoxy ureas **114** and 2-iodoanilines **115** furnishes substituted 1,3-dihydro-2*H*-benzo[*d*]imidazol-2-ones **116a–j** (Scheme 58).[183] This process is catalyzed with 1,4-diazabicyclo[2.2.2]octane or copper(I) iodide.

The synthesis using 1,3-diallyl-1-phenylurea (**117**) as a reactant to obtain fused (**118**) and cage (**119**) urea derivatives *via* the Diels–Alder reaction was described.[184] Both 2-bromofuran and 9-bromoanthracene react with compound **117** (Scheme 59). The authors optimized the reaction conditions, choosing a palladium-Xantphos complex as a catalyst, potassium *tert*-butoxide as a base, thus providing the high diastereoselectivity (dr = >20 : 1) of the process.

Scheme 58



114

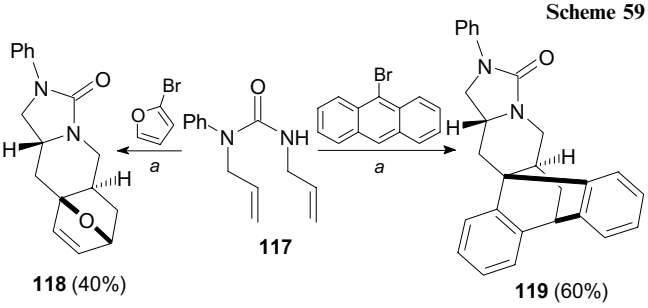
115

116a–j (70–92%)

R^1 = Me: R^2 = H (**a**), Me (**b**), F (**c**), Cl (**d**), Br (**e**), CF_3 (**f**), CO_2Me (**g**); R^2 = H: R^1 = Bn (**h**), All (**i**), Cy (**j**);

L² = Me–N(H)–N(H)–Me

Scheme 59



118 (40%)

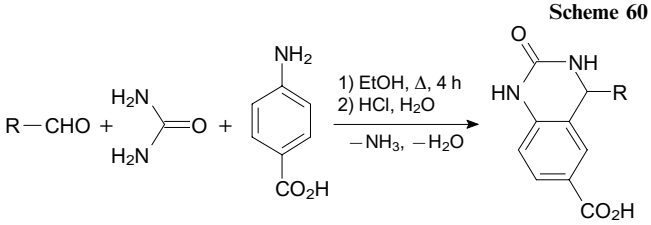
117

119 (60%)

(*a*) $Pd_2(dba)_3$, Xantphos, Bu^tONa, *p*-xylene, 130 °C, 24 h

An unusual condensation in a urea–aldehyde–*p*-aminobenzoic acid ternary system has been reported. The reaction proceeds in refluxing ethanol and provides sufficiently easy access to 2-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid derivatives **120a**,**b** (Scheme 60).[185, 186]

Scheme 60



R = H (**a**), Ph (**b**)

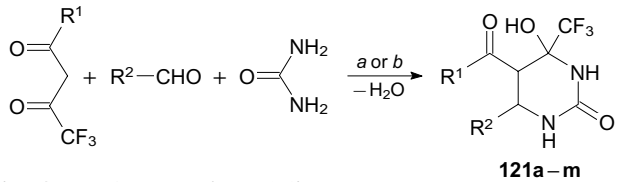
120a,**b** (60–67%)

The above-mentioned results on the intermolecular cyclization of acyclic ureas suggest the possibility of their use in designing complex molecular systems. As a part of this approach, the condensation of commercially available ninhydrin with ureas should be noted, as opening up extensive prospects for the one-step synthesis of various polycyclic compounds.

4. Synthesis of cyclic ureas *via* the Biginelli reaction

The Biginelli reaction,[187] a three-component reaction involving urea, acetoacetic ester, and aldehyde, was discovered more than a century ago. However, the interest in it is only increasing with time, since its target products — dihydropyrimidinones (cyclic ureas) — have found widespread application in the pharmaceutical industry. Several 4-hydrotetrahydropyrimidin-2-one derivatives **121a–m**

Scheme 61

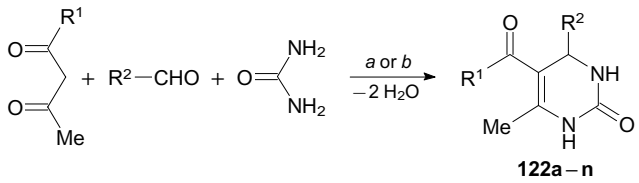


(*a*) TsOH, MeCN, Δ, 3 h (79–90%);
(*b*) $H_{14}NaP_5W_{29}MoO_{110}/SiO_2$, solvent-free, 80 °C, 1.5 h (91–97%); R^1 = 2-Th: R^2 = Ph (**a**), 4-FC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-BrC_6H_4 (**d**), 4-MeC_6H_4 (**e**), 3,4-$(MeO)_2C_6H_3$ (**f**), 3,4,5-$(MeO)_3C_6H_2$ (**g**); R^1 = OEt: R^2 = Ph (**h**), 4-$MeOC_6H_4$ (**i**), 4-BrC_6H_4 (**j**), 4-ClC_6H_4 (**k**), 4-$O_2NC_6H_4$ (**l**), 2-Fu (**m**); Fu is furyl

(Scheme 61) were proposed to be obtained by condensation of aromatic aldehydes, 1,3-dicarbonyl compounds, and urea in the presence of *p*-toluenesulfonic acid (conditions *a*)[188, 189] or Preyssler heteropolyacid ($H_{14}NaP_5W_{29}MoO_{110}$) as a catalyst (conditions *b*). In the latter case, the reaction proceeds smoothly under solvent-free conditions and provides compounds **121h–m** in high yields.[190, 191]

Using nanocomposite based on polyethylene glycol and sulfonated montmorillonite (PEG-SANM) as a catalyst makes it possible to obtain 3,4-dihydropyrimidin-2(1*H*)-one derivatives **122a–l** in almost quantitative yields without the use of organic solvents (conditions *a* in Scheme 62).[192] Replacing the nanocomposite with a Lewis acid — zinc chloride — increases the reaction time up to 24 h and decreases the yields of the target products **122m–o** (conditions *b*).[193]

Scheme 62

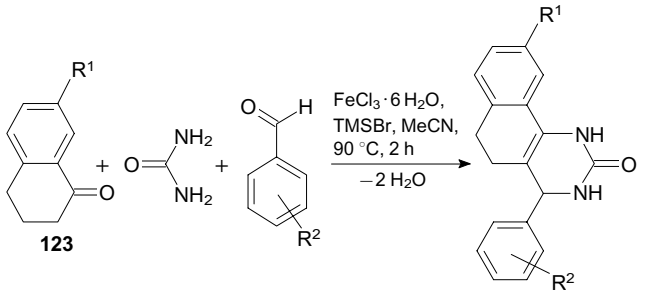


(*a*) PEG-SANM, solvent-free, 80 °C, 5 h (90–98%);
(*b*) $ZnCl_2$, solvent-free, 60 °C, 8–24 h (42–85%);
R^1 = OEt: R_2 = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 2-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 3-$O_2NC_6H_4$ (**f**), 2-$O_2NC_6H_4$ (**g**), 4-MeC_6H_4 (**h**), 2-Fu (**i**); R^1 = Me: R^2 = Ph (**j**), 4-$O_2NC_6H_4$ (**k**), 3-$MeOC_6H_4$ (**l**), R^1 = OMe, R^2 is 5-(hydroxymethyl)furan-2-yl (**m**); R^1 = OBu^t, R^2 is 5-(hydroxymethyl)furan-2-yl (**n**)

A three-component reaction between 3,4-dihydronaphthalen-1(2*H*)-one derivatives **123**, urea, and aromatic aldehydes catalyzed with $FeCl_3 \cdot 6H_2O$–TMSBr system (Scheme 63) has been described.[194] This reaction proceeds readily under mild conditions to afford cyclic ureas **124a–i** in high yields.

Varying even one component in the Biginelli reaction allows designing rather complex structures. Thus, condensation of ketone **125**, aldehydes, and urea in the presence of sodium alkoxide produces steroids **126a–f** containing a cyclic urea moiety (Scheme 64). The process is carried out under ultrasonic (method *a*)[195] or microwave (MW, method *b*)[196] irradiation. In the latter case, it is possible to shorten the reaction time down to 10 min, but at the same time the yields of the products **126g–l** decrease.

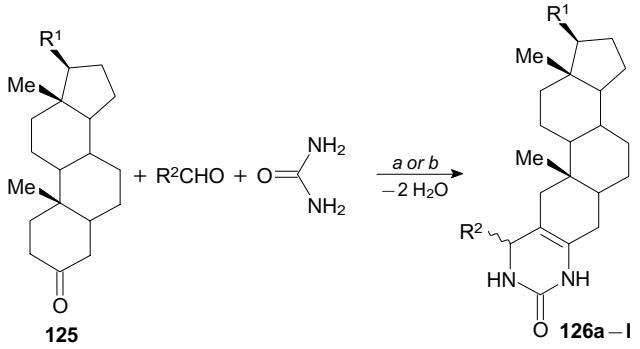
Scheme 63



R^1 = H: R^2 = H (**a**), 3-CN (**b**), 3-Me (**c**), 4-F (**d**), 2-Br (**e**), 4-NO_2 (**f**), 3-Cl (**g**); R^1 = Br, R^2 = H (**h**); R^1 = NO_2, R^2 = H (**i**)

124a–i (82–90%)

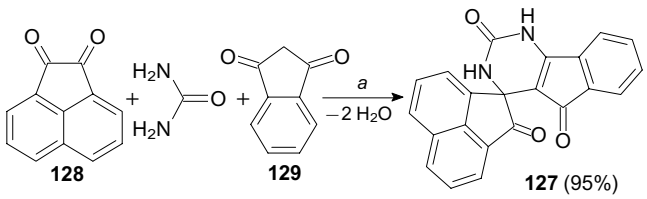
Scheme 64



(*a*) – NaOEt, Pr^iOH, ultrasound, rt, 15 min (88–94%);
(*b*) MW, 110 °C, 10 min (60–69%); R^1 = $CH(Me)(CH_2)_3CHMe_2$: R^2 = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 3-BrC_6H_4 (**d**), Pr^n (**e**), Bu^n (**f**); R^1 = OAc: R^2 = Ph (**g**), 4-FC_6H_4 (**h**), 4-MeC_6H_4 (**i**), 4-BrC_6H_4 (**j**), 4-$MeOC_6H_4$ (**k**), 4-$O_2NC_6H_4$ (**l**)

The synthesis of a spirocyclic compound **127** showing antimicrobial activity is described,[197] based on the reaction of a cyclic 1,2-diketone **128**, urea, and indane-1,3-dione **129** in the presence of $NiCo_2O_4$@Ni(BDC) nanocatalyst, where BDC is terephthalic acid (Scheme 65).

Scheme 65



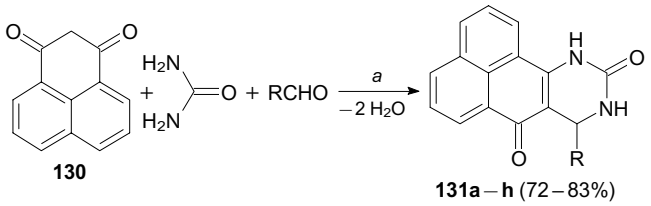
(*a*) $NiCo_2O_4$@Ni(BDC), Δ, 180 min

Phenalene-1,3-dione (**130**) reacts with urea and benzaldehyde derivative under catalysis with $CuCl_2$ to afford heterocycles **131a–h**, which contain an urea moiety (Scheme 66).[198]

The reaction of cyclopentanone with urea and aromatic aldehydes enables the synthesis of bicyclic compounds **132a–m** (Scheme 67).[199]

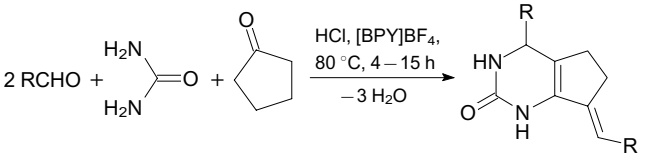
Analysis of the current studies on the Biginelli reaction demonstrates new possibilities of this unique three-component transformation in obtaining complex cyclic and poly-

Scheme 66



(*a*) $CuCl_2$, 80 °C, 40–78 min;
R = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 3-$O_2NC_6H_4$ (**c**), 2,4-$(O_2N)_2C_6H_3$ (**d**), 4-MeC_6H_4 (**e**), 3-$O_2NC_6H_4$ (**f**), 4-ClC_6H_4 (**g**), 4-BrC_6H_4 (**h**)

Scheme 67



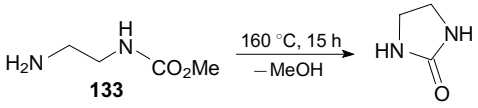
R = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 3-$O_2NC_6H_4$ (**c**), 2,3-$(O_2N)_2C_6H_3$ (**d**), 4-MeC_6H_4 (**e**), 3-$O_2NC_6H_4$ (**f**), 4-ClC_6H_4 (**g**), 4-BrC_6H_4 (**h**), 4-FC_6H_4 (**i**), 3-BrC_6H_4 (**j**), 4-NCC_6H_4 (**k**), 2-BrC_6H_4 (**l**), 2-ClC_6H_4 (**m**); $[BPY]BF_4$ is 1-n-butylpyridinium tetrafluoroborate

cyclic compounds. Due to the simplicity of this approach and high yields of the target cyclic ureas, various modifications of such reaction will remain synthetically attractive for a long time to come.

5. Amidation of carbamates

There are a number of publications in the literature devoted to a less common synthetic approach to cyclic ureas from acyclic precursors, namely, amidation of carbamates. For example, heating methyl(2-aminoethyl)carbamate (**133**) in an autoclave at 160 °C for 15 h gives imidazolidin-2-one **22a** (Scheme 68).[200] With a prolonged reaction time, the yield of the product **22a** decreases due to the formation of 1-methylimidazolidin-2-one as a by-product (**22b**).[200]

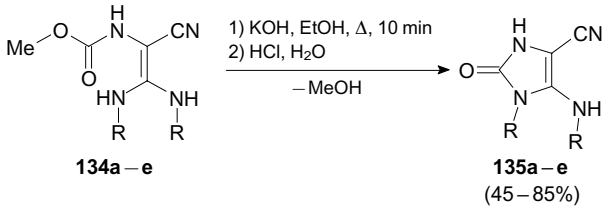
Scheme 68



Cyclization of compounds **134a–e** in refluxing ethanol in the presence of potassium hydroxide for 10 min with the follow-up treatment with hydrochloric acid furnished substituted 1*H*-imidazol-2(3*H*)-ones **135a–e** (Scheme 69).[201]

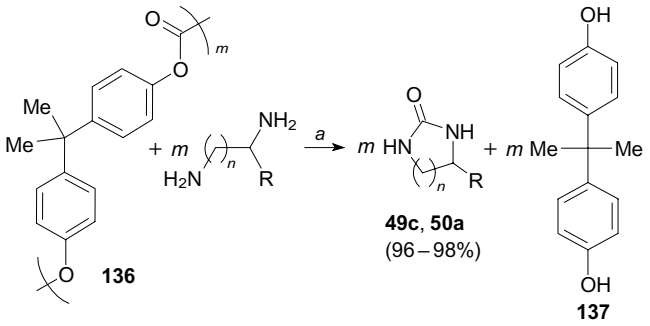
A convenient method of chemical processing of polycarbonates derived from bisphenol A using a catalyst composed of zinc oxide and tetra-n-butylammonium chloride nanoparticles (NPs) has been proposed. Therein, polycarbonate **136** undergoes amidation to give cyclic urea **49c** or **50a** and bisphenol A (**137**) (Scheme 70). An exhaustive depolymerization can be carried out at 100 °C within 7 h, the catalyst is regenerated and reused several times without loss of activity.[202]

Scheme 69



R = Me (**a**), Pr (**b**), Bn (**c**), Ph (**d**), *p*-Tol (**e**)

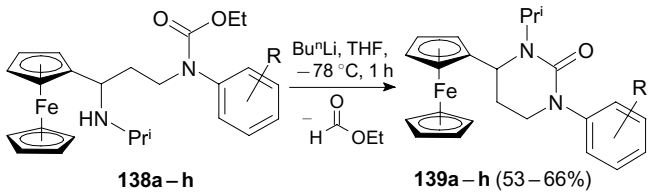
Scheme 70



(*a*) ZnO-NPs/Bu^n_4NCl, THF, 100 °C, 7 h;
n = 1, R = Me (**49c**); *n* = 2, R = H (**50a**)

Cyclization of carbamates **138a–h** in the presence of Bu^nLi in THF furnishes 4-ferrocenyltetrahydropyrimidin-2-ones **139a–h** in good yields (Scheme 71).[203]

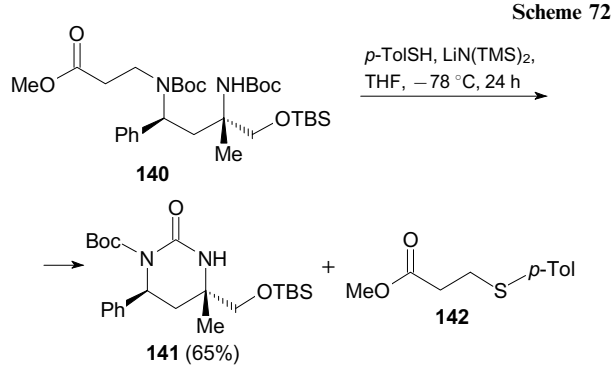
Scheme 71



R = H (**a**), 3-OMe (**b**), 4-Me (**c**), 4-Bu^n (**d**), 2-F (**e**), 4-F (**f**), 3-Cl (**g**), 4-Cl (**h**)

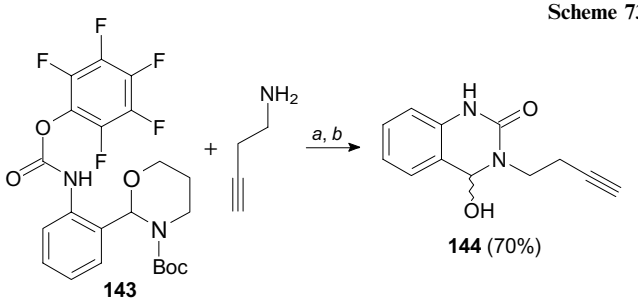
An intramolecular cyclization of a Boc-protected amine **140** to tetrahydropyrimidin-2-one **141**, where the source of the carbonyl group is the *tert*-butoxycarbonyl protecting group, is reported.[204] The retro-Michael reaction leads to the elimination of the methylpropanoate moiety as an ester **142** (Scheme 72).

Scheme 72



The reaction of 1,3-oxazinane **143** with 1-amino-3-butyne in the presence of *N*-ethylmorpholine in DMF at room temperature followed by treatment with trifluoroacetic acid affords an urea **144** (Scheme 73).[205–207]

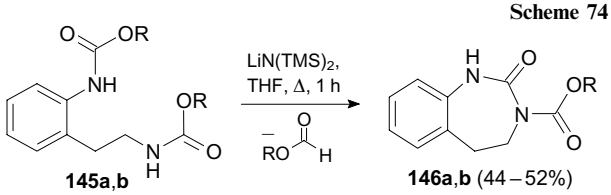
Scheme 73



(*a*) *N*-ethylmorpholine, DMF, rt, 1 h; (*b*) TFA, CH_2Cl_2, rt, 12 h

Amidation of bis-carbamates **145a**,**b** using lithium bis(trimethylsilyl)amide in THF for 1 h provided 1,3-benzodiazepinone derivaties **146a**,**b** (Scheme 74).[208]

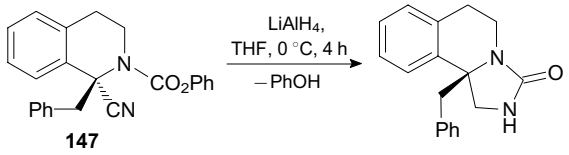
Scheme 74



R = Me (**a**), Bu^i (**b**)

Shirakawa *et al.*[209] utilized $LiAlH_4$ to reduce the cyano group in 1,2,3,4-tetrahydroisoquinoline **147** to the amine one, which amidated the carbamate moiety affording compound **148** (Scheme 75).

Scheme 75



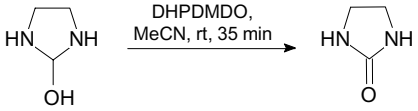
Despite the fact that amidation of carbamates is not widely used for the synthesis of cyclic ureas, within this approach, an original method for the chemical processing of polycarbonates has been proposed, which makes it possible to obtain cyclic ureas and regenerate bisphenol A virtually quantitatively. In the future, this method can be used in the recycling of polycarbonate products, which makes it possible to address some environmental challenges.

6. Synthesis of ureas from cyclic precursors

The examples of the synthesis of heterocycles containing urea moieties presented in this Section are based on the reduction or oxidation of cyclic precursors. Among the general drawbacks of such an approach, there is the need for the preliminary preparation of the starting heterocyclic compound, which often complicates the synthetic protocol and diminishes the product yields. It should be noted that most transformations require the use of metal-containing catalysts.

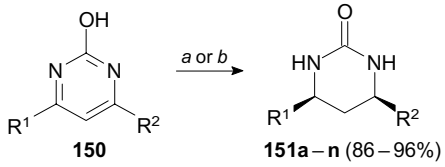
Azarifar *et al.*[210] developed an easy and effective method of oxidation of imidazolidin-2-ol (**149**), which is carried out at room temperature using *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO) as a catalyst. Under these conditions, the target imidazolidin-2-one (**22a**) is formed in high yield (Scheme 76).

Scheme 76



Iridium-catalyzed hydrogenation of 4,6-disubstituted 2-hydroxypyrimidines **150** produces chiral cyclic ureas **151a–g** with excellent diastereo- and enantioselectivities

Scheme 77



(*a*) $[Ir(COD)Cl]_2$, (*S*,*S*)-f-binaphane, TCCA, H_2 (800 psi), EtOH–Pr^{i}OH (1 : 2), 40 °C, 24 h; (*b*) $Pd(OCOCF_3)_2$, (*R*,*S*)-PPF-PBu$^t_2$, $PhCO_2H$, H_2, TFE, 80 °C, 24 h;
TCCA is 1,3,5-trichloroisocyanuric acid,
TFE is tetrafluoroethylene, COD is cycloocta-1,5-diene,

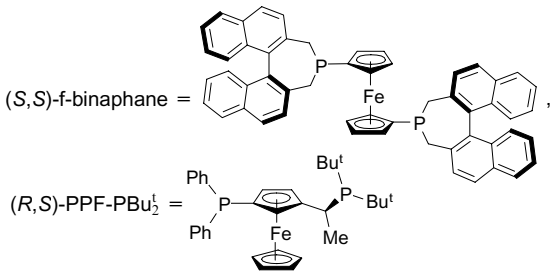


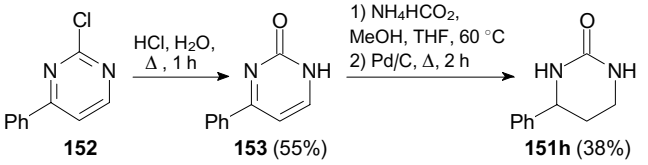
Table 8. Synthesis of cyclic ureas *via* hydrogenation of 2-hydroxypyrimidines (see Scheme 77).[211, 212]

Compounds **150**, **151**	R^1	R^2	Yield (%)	*ee* (%)
a	Me	3,4-$(MeO)_2C_6H_3$	89	90
b	Me	3,4-$Cl_2C_6H_3$	90	91
c	Me	4-ClC_6H_4	94	93
d	Me	4-FC_6H_4	91	96
e	Me	4-$F_3CC_6H_4$	86	83
f	Et	Ph	90	96
g	Pr^i	Ph	89	83
h	H	Ph	90	95
i	H	4-MeC_6H_4	93	90
j	H	3-MeC_6H_4	93	96
k	H	3,4-$Me_2C_6H_3$	82	90
l	H	4-$F_3CC_6H_4$	96	87
m	H	4-FC_6H_4	95	93
n	H	3-$MeOC_6H_4$	95	96

(conditions *a* in Scheme 77, Table 8).[211] In the follow-up study,[212] a palladium salt was used as a catalyst, providing (4*R*,6*S*)-4,6-disubstituted tetrahydropyrimidin-2(1*H*)-ones **151h–n** (conditions *b*) in good yields and high stereoselectivity.

Chloropyrimidine **152** is hydrolyzed in concentrated hydrochloric acid to give 4-phenyl-1,2-dihydropyrimidin-2-one (**153**), the catalytic hydrogenation of which affords 4-phenyltetrahydropyrimidin-2(1*H*)-one (**151h**) in a moderate yield (Scheme 78).[213]

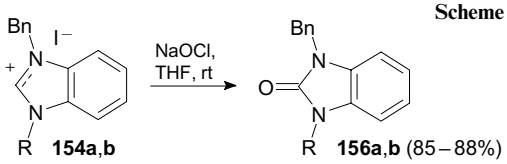
Scheme 78



152 **153** (55%) **151h** (38%)

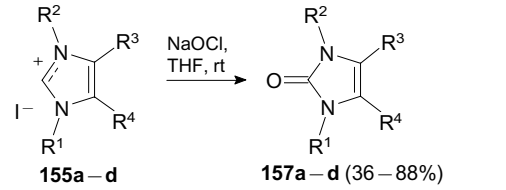
A rather unusual synthetic approach towards cyclic ureas is the oxidation of imidazolium salts (Scheme 79). Thus, the salts **154a**,**b** and **155a–d** react with sodium hypochlorite to give the derivatives of 1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **156a**,**b** and 1,3-dihydro-2*H*-imidazol-2-one **157a–d**.[214]

Scheme 79



154a,**b** **156a**,**b** (85–88%)

R = Me (**a**), Bn (**b**)



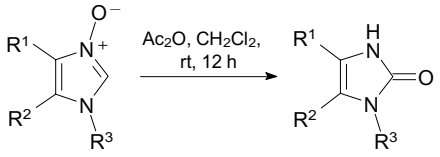
155a–d **157a–d** (36–88%)

R^1 = Me: R^2 = Me, R^3 = R^4 = Ph (**a**); R^2 = Bn, R^3 = R^4 = Ph (**b**); R^2 = Bn, R^3 = R^4 = H (**c**); R^1 = Bn, R^2 = Me, R^3 = Ph, R^4 = H (**d**)

The synthesis of imidazol-2-ones **158a–f** *via* the treatment of 1*H*-imidazole 3-oxides **159a–f** with an acetic anhydride solution in dichloromethane is described (Scheme 80).[215–219]

Addition of hexafluoroacetone hydrate (HFAH) to a solution of *N*-oxides **160a–d** in dichloromethane generates

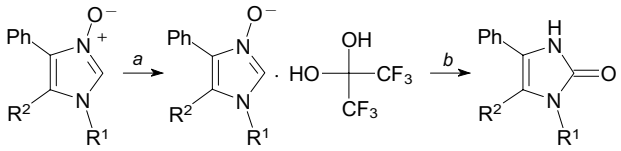
Scheme 80



159a–f **158a–f** (48–73%)

R^2 = R^3 = Me: R^1 = C(O)NHMe (**a**), C(O)NHPh (**b**); R^1 = R^2 = Ph: R^3 = $(CH_2)_2OAc$ (**c**), $(CH_2)_4OAc$ (**d**), $(CH_2)_2NHAc$ (**e**), $(CH_2)_3NHAc$ (**f**)

Scheme 81



160a–d **161a–d** **162a–d** (49–72%)

(*a*) HFAH, CH_2Cl_2, 0 °C, 30 min; (*b*) melting, 10 min;
R^1 = R^2 = Me (**a**); R^1 = Cy, R^2 = Ph (**b**); R^1 = All, R^2 = Me (**c**); R^1 = OAc, R^2 = Ph (**d**)

complexes **161a–d**, which are converted into substituted 1,3-dihydro-2*H*-imidazol-2-ones **162a–d** upon heating (Scheme 81).[220,221]

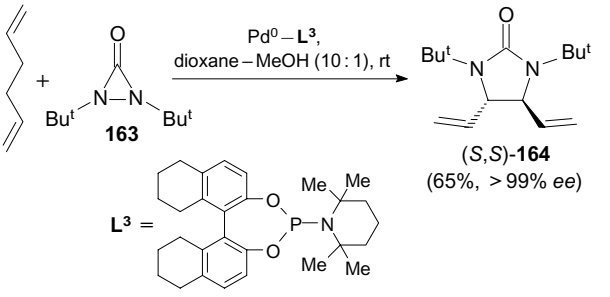
As noted above, the methods for the synthesis of cyclic ureas provided in this Section have not yet been widely used in the synthetic practice because of the experimental challenges in the synthesis of the starting compounds and expensive catalysts. However, such synthetic approaches demonstrate a diversity of methods for obtaining cyclic ureas, which can be used in the future.

7. Other examples of the synthesis of cyclic ureas

Below are selected examples of the preparation of heterocycles bearing a carbamide moiety that were not included in the previous Sections. At the same time, various molecules act as sources of the carbonyl group, *e.g.*, aldehydes, isocyanates, carbamates, methanol, *N*-methyl-1*H*-imidazole-1-carboxamide, 1,2-di-*tert*-butyldiaziridin-3-one. There are mono- and bimolecular reactions, ring-expansion reactions, and transformations catalyzed with metals and their salts, Brønsted and Lewis acids, among these processes.

Based on the Pd-catalyzed reaction of hexa-1,5-diene and 1,2-di-*tert*-butyldiaziridin-3-one (**163**), imidazolidin-2-one **164** was synthesized in one step (Scheme 82).[222–225] It is noteworthy that the process occurs under mild conditions and with good enantioselectivity.

Scheme 82

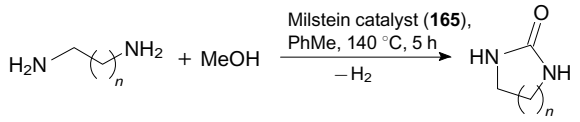


(*S*,*S*)-**164** (65%, > 99% *ee*)

The reaction of methanol with diamines to afford ureas **22a**, **50a**, and **51b**, with the use of a commercially available Milstein catalyst, [carbonylchlorohydrido[6-(di-*tert*-butylphosphinomethyl)-2-(*N*,*N*-diethylaminomethyl)pyridino]ruthenium(II) (**165**), is original (Scheme 83).[226–228] In this case, hydrogen is formed as a by-product.

Sawant *et al.*[229,230] suggested an approach towards 3,4-dihydroquinazolin-2(1*H*)-ones. As starting compounds, aldehydes **166** were used, which underwent cyclization in the presence of ammonium acetate in acetic acid to generate

Scheme 83



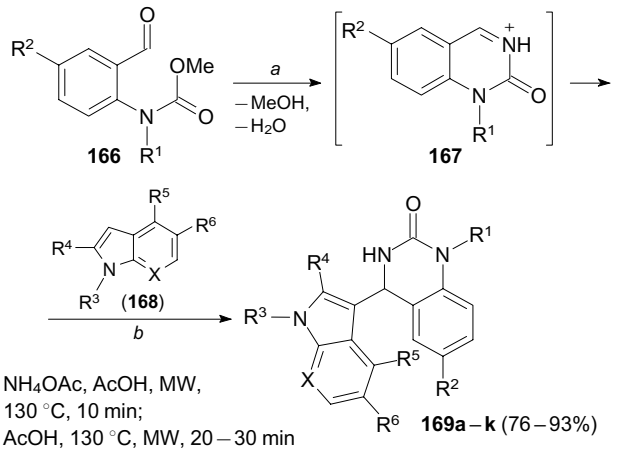
n = 1 (**22a**), 2 (**50a**), 3 (**51b**)

supposedly iminium cations **167**. The latter, in turn, reacted with (aza)indoles **168** yielding the target compounds **169a–k** (Scheme 84, Table 9).

Condensation of ketones with paraformaldehyde in a low-melting L-(+)-tartaric acid–*N*,*N*-dimethylurea (DMU) mixture gave rise to compounds **170a–f** (Scheme 85).[231] The distinctive feature of this reaction is the exceptional formation of the *syn*-stereomer, which is more stable according to quantum chemical calculations.

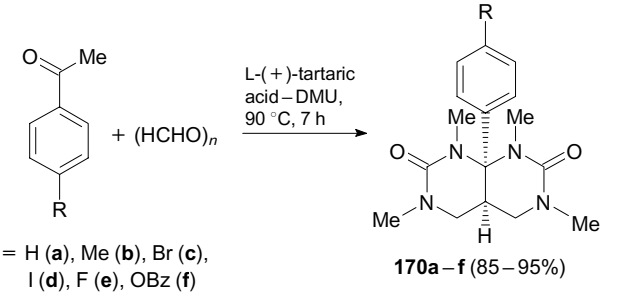
The method for the synthesis of agelastatin A (**171**), a potent antitumour alkaloid, was reported (Scheme 86).[232] Azide **172** was subjected to catalytic hydrogenation and then reacted with *N*-methyl-1*H*-imidazole-1-carboxamide to give urea **173**. Cyclization of the urea moiety followed by bromination gives the target polycyclic alkaloid **171**.

Scheme 84



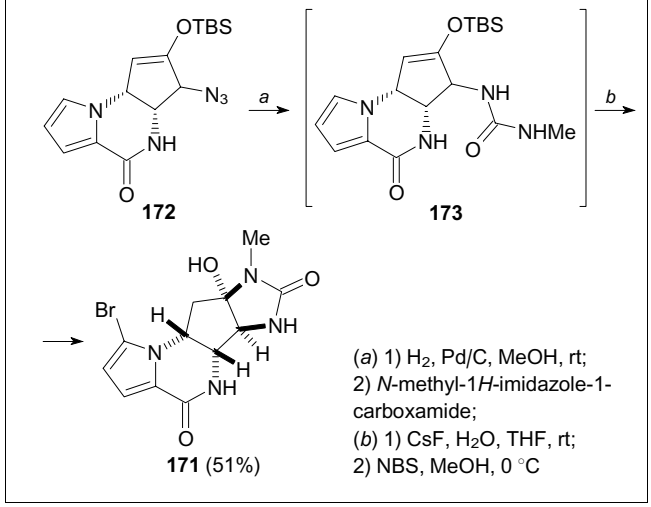
(*a*) NH_4OAc, AcOH, MW, 130 °C, 10 min;
(*b*) AcOH, 130 °C, MW, 20–30 min

Scheme 85



R = H (**a**), Me (**b**), Br (**c**), I (**d**), F (**e**), OBz (**f**)

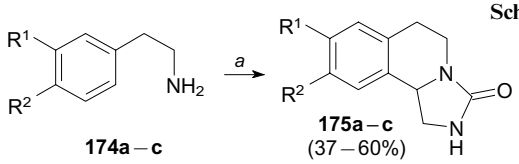
Scheme 86



(*a*) 1) H_2, Pd/C, MeOH, rt;
2) *N*-methyl-1*H*-imidazole-1-carboxamide;
(*b*) 1) CsF, H_2O, THF, rt;
2) NBS, MeOH, 0 °C

The reaction of amines **174a–c** and 2-(isocyanatomethyl)-1,3-dioxolane with subsequent treatment with hydrochloric acid provides imidazoisoquinoline derivatives **175a–c** (Scheme 87).[233]

Scheme 87



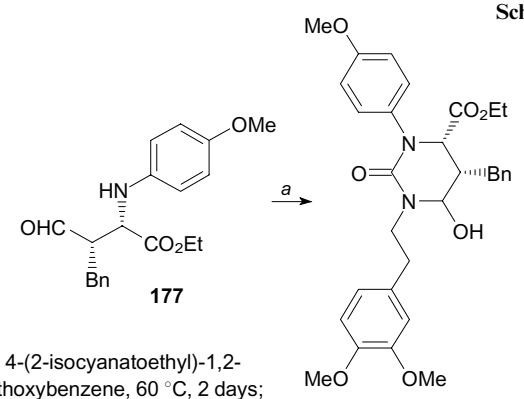
(*a*) 1) 2-(isocyanatomethyl)-1,3-dioxolane, THF, rt, 21 h;
2) HCl, MeOH, 55 °C, 5 days ; $R^1 = R^2$ = OMe (**a**), OH (**b**);
R^1 = OMe, R^2 = H (**c**)

The proposed method to obtain the substituted tetrahydropyrimidin-2-one **176**[234] comprises the initial reaction of aromatic amine **177** with an isocyanate followed by the

Table 9. Synthesis of cyclic ureas from aldehydes and (aza)indoles (see Scheme 84).[229, 230]

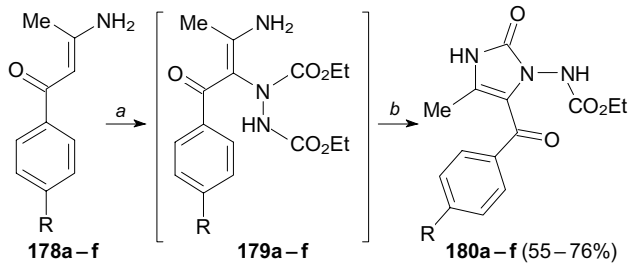
Compounds **169**	R^1	R^2	R^3	R^4	R^5	R^6	X	Yield (%)
a	H	OMe	H	H	H	H	CH	92
b	H	Br	H	H	H	H	CH	91
c	H	F	H	H	H	H	CH	88
d	Bn	H	H	H	H	H	CH	86
e	H	H	H	H	H	Me	CH	93
f	H	H	H	H	H	Br	CH	91
g	H	H	H	H	H	Ph	CH	91
h	H	H	H	H	CO_2Me	H	CH	83
i	H	H	H	Me	H	OMe	CH	76
j	H	H	Me	H	H	H	CH	84
k	H	H	H	Ph	H	H	N	90

Scheme 88



(*a*) 1) 4-(2-isocyanatoethyl)-1,2-dimethoxybenzene, 60 °C, 2 days; 2) TFA, 1,4-dioxane, rt, 4 h

Scheme 89



(*a*) DEAD, EtOH, rt, 2 h; (*b*) NaOH, EtOH, rt, 48 h; R = SMe (**a**), H (**b**), Cl (**c**), SO_2Me (**d**), F (**e**), Br (**f**)

cyclization of the generated urea in the presence of trifluoroacetic acid (Scheme 88).

Amines **178a–f** were found to react with diethyl azodicarboxylate (DEAD) to afford hydrazides **179a–f**, which cyclize into 1,3-dihydro-2*H*-imidazol-2-ones **180a–f** at room temperature in the presence of sodium hydroxide (Scheme 89).[235]

8. Conclusion

Analysis of the literature data given in this review, related to the methods of synthesis of cyclic ureas, allows us to assess the prospects for the further development of this area. A serious shortcoming of the isocyanate method is the laborious synthesis of the starting substituted isocyanates, associated with the use of toxic phosgene. Handling this chemical requires special precautions and special laboratory conditions, which greatly complicates the process. In terms of the green chemistry concept, most promising are procedures based on the use of safe, highly reactive synthetic analogues of phosgene, namely, carbonates and 1,1′-carbonyldiimidazole.

It is necessary to note the appearance in the last years of a large number of publications on the synthesis of cyclic ureas with the use of available carbon oxides. Nevertheless, a serious obstacle to the widespread application of such reactions in laboratory practice is the use of high pressure.

A promising method providing an approach to substituted cyclic ureas is an acid-catalyzed cyclization of carbonyl compounds and acetals containing urea moieties in the presence of an external nucleophile, generally, of an aromatic nature. An important advantage of such cascade reactions is the possibility to vary the nature of starting compounds over a wide range, thereby paving the way to the direct synthesis of functionalized cyclic ureas.

An interest in a three-component reaction between ureas, various dicarbonyl compounds, and aldehydes (the Biginelli reaction) does not fade for years. This approach provides the one-step synthesis of various tetrahydropyrimidinones showing a broad spectrum of biological activities. Distinctive features of this unique reaction are the high yields of the target product, ease of implementation, and the possibility to carry out the reaction without a solvent, which allows classifying such transformations as relating to green chemistry.

A high potential of the hydrogenation reaction of 4,6-disubstituted 2-hydroxypyrimidines should also be mentioned, as providing an access to cyclic ureas in good yields and high stereoselectivity. However, the use of cyclic precursors which are to be obtained in advance, as well as costly metal-containing catalysts, complicates the implementation of this synthetic approach.

A number of methods for the synthesis of various cyclic ureas that have been described recently and were covered in this review are targeted and aimed at developing novel pharmaceutical drugs. A prominent example is the synthesis of agelastatin A, which is a potent antitumour polycyclic alkaloid.

To summarize, the development of novel synthetic approaches towards cyclic and polycyclic ureas based on the cascade and multi-component reactions, involving electrochemical activation and effective metal-containing catalysts including nanocatalysts, and on replacing toxic reactants with low-toxic ones, seems to be a promising trend in modern organic chemistry.

9. List of acronyms

The following acronyms were used in the review:
Boc — *tert*-butoxycarbonyl,
Cbz — benzyloxycarbonyl,
CDI — 1,1′-carbonyldiimidazole,
Cp — cyclopentadienyl,
Cp* — pentamethylcyclopentadienyl,
Cy — cyclohexyl,
Cyp — cyclopentyl,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
dba — dibenzylidene acetone,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
de — diastereomeric excess,
DEAD — diethyl azodicarboxylate,
DIPEA — diisopropylethylamine,
DMA — dimethylacetamide,
DMPU — *N*,*N*′-dimethylpropylideneurea,
DMU — *N*,*N*-dimethylurea,
DPPA — diphenylphosphoryl azide,
dr — diastereomeric ratio,
ee — enantiomeric excess,
LDA — lithium diisopropylamide,
MTBE — methyl *tert*-butyl ether,
TBS — *tert*-butyldimethylsilyl,
TMS — trimethylsilyl,
TMG — 1,1,3,3-tetramethylguanidine,
TFA — trifluoroacetic acid.

References

1. G.V.De Lucca, U.T.Kim, J.Liang, B.Cordova, R.M.Klabe, S.Garber, L.T.Bacheler, G.N.Lam, M.R.Wright, K.A.Logue, S.Erickson-Viitanen, S.S.Ko, G.L.Trainor. *J. Med. Chem.*, **41**, 2411 (1998)
2. G.V.De Lucca. *J. Org. Chem.*, **63**, 4755 (1998)
3. G.V.De Lucca, J.Liang, I.De Lucca. *J. Med. Chem.*, **42**, 135 (1999)
4. R.F.Kaltenbach, M.Patel, R.E.Waltermire, G.D.Harris, B.R.Stone, R.M.Klabe, S.Garber, L.T.Bacheler, B.C.Cordova, K.Logue, M.R.Wright, S.Erickson-Viitanen, G.L.Trainor. *Bioorg. Med. Chem. Lett.*, **13**, 605 (2003)
5. P.Y.S.Lam, Y.Ru, P.K.Jadhav, P.E.Aldrich, G.V.De Lucca, C.J.Eyermann, C.-H.Chang, G.Emmett, E.R.Holler, W.F.Daneker, L.Li, P.N.Confalone, R.J.McHugh, Q.Han, R.Li, J.A.Markwalder, S.P.Seitz, T.R.Sharpe, L.T.Bacheler, M.M.Rayner, R.M.Klabe, L.Shum, D.L.Winslow, D.M.Kornhauser, D.A.Jackson, S.Erickson-Viitanen, C.N.Hodge. *J. Med. Chem.*, **39**, 3514 (1996)
6. M.Patel, J.D.Rodgers, R.J.McHugh, B.L.Johnson, B.C.Cordova, R.M.Klabe, L.T.Bacheler, S.Erickson-Viitanen, S.S.Ko. *Bioorg. Med. Chem. Lett.*, **9**, 3217 (1999)
7. M.Ferrara, F.Fiore, V.Summa, C.Gardelli. *Bioorg. Med. Chem. Lett.*, **20**, 5031 (2010)
8. C.Gardelli, E.Nizi, E.Muraglia, B.Crescenzi, M.Ferrara, F.Orvieto, P.Pace, G.Pescatore, M.Poma, M.del R.R.Ferreira, R.Scarpelli, C.F.Homnick, N.Ikemoto, A.Alfieri, M.Verdirame, F.Bonelli, O.Gonzalez Paz, M.Taliani, E.Monteagudo, S.Pesci, R.Laufer, P.Felock, K.A.Stillmock, D.Hazuda, M.Rowley, V.Summa. *J. Med. Chem.*, **50**, 4953 (2007)
9. I.-J.Kang, L.-W.Wang, S.-J.Hsu, C.-C.Lee, Y.-C.Lee, Y.-S.Wu, A.Yueh, J.-C.Wang, T.-A.Hsu, Y.-S.Chao, J.-H.Chern. *Bioorg. Med. Chem. Lett.*, **19**, 6063 (2009)
10. O.M.Singh, S.J.Singh, M.B.Devi, L.N.Devi, N.I.Singh, S.-G.Lee. *Bioorg. Med. Chem. Lett.*, **18**, 6462 (2008)
11. C.-D.Li, S.L.Mella, A.C.Sartorelli. *J. Med. Chem.*, **24**, 1089 (1981)
12. A.I.Markosyan, S.V.Dilanyan, S.A.Gabrielyan, F.G.Arsenyan, R.S.Sukasyan, B.T.Garibdzhanyan. *Pharm. Chem. J.*, **44**, 352 (2010)
13. N.M.Abdel Gawad, H.H.Georgey, R.M.Youssef, N.A.El-Sayed. *Eur. J. Med. Chem.*, **45**, 6058 (2010)
14. W.Liao, G.Hu, Z.Guo, D.Sun, L.Zhang, Y.Bu, Y.Li, Y.Liu, P.Gong. *Bioorg. Med. Chem.*, **23**, 4410 (2015)
15. M.Šimunoviå, I.Perkoviå, B.Zorc, K.Ester, M.Kralj, D.Hadjipavlou-Litina, E.Pontiki. *Bioorg. Med. Chem.*, **17**, 5605 (2009)
16. S.Cortes, Z.-K.Liao, D.Watson, H.Kohn. *J. Med. Chem.*, **28**, 601 (1985)
17. Patent WO 2007060689 A (2007)
18. A.Mobinikhaledi, N.Foroughifar, T.Mosleh, A.Hamta. *Phosphorus, Sulfur, Silicon Relat. Elem.*, **187**, 728 (2012)
19. A.N.Kravchenko, V.V.Baranov, G.A.Gazieva. *Russ. Chem. Rev.*, **87**, 89 (2018)
20. A.N.Kravchenko, V.V.Baranov, L.V.Anikina, Y.B.Vikharev, I.S.Bushmarinov, Y.V.Nelyubina. *Russ. J. Bioorg. Chem.*, **38**, 550 (2012)
21. A.S.Berlyand, O.V.Lebedev, A.A.Prokopov. *Pharm. Chem. J.*, **47**, 176 (2013)
22. H.-J.Shue, X.Chen, N.-Y.Shih, D.J.Blythin, S.Paliwal, L.Lin, D.Gu, J.H.Schwerdt, S.Shah, G.A.Reichard, J.J.Piwinski, R.A.Duffy, J.E.Lachowicz, V.L.Coffin, F.Liu, A.A.Nomeir, C.A.Morgan, G.B.Varty. *Bioorg. Med. Chem. Lett.*, **15**, 3896 (2005)
23. R.M.Keenan, J.F.Callahan, J.M.Samanen, W.E.Bondinell, R.R.Calvo, L.Chen, C.DeBrosse, D.S.Eggleston, R.C.Haltiwanger, S.M.Hwang, D.R.Jakas, T.W.Ku, W.H.Miller, K.A.Newlander, A.Nichols, M.F.Parker, L.S.Southhall, I.Uzinskas, J.A.Vasko-Moser, J.W.Venslavsky, A.S.Wong, W.F.Huffman. *J. Med. Chem.*, **42**, 545 (1999)
24. G.H.Rasmusson, G.F.Reynolds, N.G.Steinberg, E.Walton, G.F.Patel, T.Liang, M.A.Cascieri, A.H.Cheung, J.R.Brooks, C.Berman. *J. Med. Chem.*, **29**, 2298 (1986)
25. H.Zhang, X.Xu, H.Chen, S.Ali, D.Wang, J.Yu, T.Xu, F.Nan. *Acta Pharmacol. Sinica*, **36**, 1137 (2015)
26. J.C.Barrow, K.E.Rittle, T.S.Reger, Z.-Q.Yang, P.Bondiskey, G.B.McGaughey, M.G.Bock, G.D.Hartman, C.Tang, J.Ballard, Y.Kuo, T.Prueksaritanont, C.E.Nuss, S.M.Doran, S.V.Fox, S.L.Garson, R.L.Kraus, Y.Li, M.J.Marino, V.Kuzmick Graufelds, V.N.Uebele, J.J.Renger. *ACS Med. Chem. Lett.*, **1**, 75 (2010)
27. J.Cui. *Bioorg. Med. Chem.*, **11**, 3379 (2003)
28. L.De Petrocellis, G.Ortar, A.Schiano Moriello, E.M Serum, D.B.Rusterholz. *Bioorg. Med. Chem. Lett.*, **25**, 2285 (2015)
29. D.Y.Wang, M.I.Abboud, M.S.Markoulides, J.Brem, C.J.Schofield. *Future Med. Chem.*, **8**, 1063 (2016)
30. A.V.Val'dman, I.V.Zaikonnikova, M.M.Kozlovskaya, I.E.Zimakova. *Bull. Exp. Biol. Med.*, **89**, 621 (1980)
31. S.C.Reddymasu, I.Soykan, R.W.McCallum. *Am. J. Gastroenterol.*, **102**, 2036 (2007)
32. J.A.Barone. *Ann. Pharmacother.*, **33**, 429 (1999)
33. I.L.Swann, E.N.Thompson, K.Qureshi. *BMJ*, **2**, 1188 (1979)
34. P.Janssen, S.M.Harris, M.Jones, T.Masaoka, R.Farré, H.Törnblom, L.VanOudenhove, M.Simrén, J.Tack. *Am. J. Gastroenterol.*, **108**, 1382 (2013)
35. J.Zempleni, S.S.K.Wijeratne, Y.I.Hassan. *BioFactors*, **35**, 36 (2009)
36. A.Chapman-Smith, J.E.Cronan Jr. *J. Nutr.*, **129**, 477S (1999)
37. J.Hymes, K.Fleischhauer, B.Wolf. *Biochem. Mol. Med.*, **56**, 76 (1995)
38. A.Marquet, B.Tse Sum Bui, D.Florentin. *Vitam. Horm.*, **61**, 51 (2001)
39. R.Rodriguez-Melendez, J.Zempleni. *J. Nutr. Biochem.*, **14**, 680 (2003)
40. M.D Ambrosio, A.Guerriero, C.Debitus, O.Ribes, J.Pusset, S.Leroy, F.Pietra. *J. Chem. Soc., Chem. Commun.*, 1305 (1993)
41. A.Guerriero, M.D Ambrosio, G.Chiasera, F.Pietra. *Helv. Chim. Acta*, **77**, 1895 (1994)
42. L.Meijer, A.-M.Thunnissen, A.White, M.Garnier, M.Nikolic, L.-H.Tsai, J.Walter, K.Cleverley, P.Salinas, Y.-Z.Wu, J.Biernat, E.-M.Mandelkow, S.-H.Kim, G.Pettit. *Chem. Biol.*, **7**, 51 (2000)
43. A.H.Antropow, K.Xu, R.J.Buchsbaum, M.Movassaghi. *J. Org. Chem.*, **82**, 7720 (2017)
44. Z.Li, T.Kamon, D.A.Personett, T.Caulfield, J.A.Copland, T.Yoshimitsu, H.W.Tun. *MedChemComm.*, **3**, 233 (2012)
45. Z.Li, D.Shigeoka, T.R.Caulfield, T.Kawachi, Y.Qiu, T.Kamon, M.Arai, H.W.Tun, T.Yoshimitsu. *MedChemComm.*, **4**, 1093 (2013)
46. S.Tilvi, C.Moriou, M.-T.Martin, J.-F.Gallard, J.Sorres, K.Patel, S.Petek, C.Debitus, L.Ermolenko, A.Al-Mourabit. *J. Nat. Prod.*, **73**, 720 (2010)
47. R.A.Lamb, N.T.Lucas, G.Lessene, B.C.Hawkins. *J. Org. Chem.*, **83**, 10120 2018)
48. R.A.Lamb, N.S.Aberle, N.T.Lucas, G.Lessene, B.C.Hawkins. *Angew. Chem., Int. Ed.*, **56**, 14663 (2017)
49. R.Lamb, G.Lessene, B.Hawkins. *Synlett*, **29**, 1125 (2018)
50. T.Mukhopadhyay, D.Seebach. *Helv. Chim. Acta*, **65**, 385 (1982)

51. E.Juaristi, P.Murer, D.Seebach. *Synthesis*, 1243 (1993)
52. E.Juaristi, M.Hernández-Rodríguez, H.López-Ruiz, J.Aviña, O.Muñoz-Muñiz, M.Hayakawa, D.Seebach. *Helv. Chim. Acta*, **85**, 1999 (2002)
53. S.B.Tayade, V.M.Dhavale, A.S.Kumbhar, S.Kurungot, P.Lönnecke, E.Hey-Hawkins, B.Pujari. *Dalton Trans.*, **46**, 6968 (2017)
54. T.P.Vishnyakova, I.A.Golubeva, E.V.Glebova. *Russ. Chem. Rev.*, **54**, 249 (1985)]
55. D.F.Kutepov. *Russ. Chem. Rev.*, **31**, 633 (1962)
56. I.Gallou. *Org. Prep. Proced. Int.*, **39**, 355 (2007)
57. F.Bigi, R.Maggi, G.Sartori. *Green Chem.*, **2**, 140 (2000)
58. N.Volz, J.Clayden. *Angew. Chem., Int. Ed.*, **50**, 12148 (2011)
59. H.Petersen. *Synthesis*, 243 (1973)
60. G.Sartori, R.Maggi. In *Four Carbon-Heteroatom Bonds: X – CX, X = C = X, X$_2$C = X, CX$_4$ (Ser. Science of Synthesis. Category 3*. Vol. 18). (Ed. J.G.Knight). (Stuttgart: Thieme Verlag, 2005). P. 665
61. Â.de Fátima, T.C.Braga, L.da S.Neto, B.S.Terra, B.G.F.Oliveira, D.L.da Silva, L.V.Modolo. *J. Adv. Res.*, **6**, 363 (2015)
62. R.Kaur, S.Chaudhary, K.Kumar, M.K.Gupta, R.K.Rawal. *Eur. J. Med. Chem.*, **132**, 108 (2017)
63. C.O.Kappe. *Eur. J. Med. Chem.*, **35**, 1043 (2000)
64. C.O.Kappe, A.Stadler. In *Organic Reactions*. Vol. 63. (Hoboken, NJ: Wiley, 2004). P. 1
65. C.O.Kappe. *Tetrahedron*, **49**, 6937 (1993)
66. H.Nagarajaiah, A.Mukhopadhyay, J.N.Moorthy. *Tetrahedron Lett.*, **57**, 5135 (2016)
67. J.Lü, J.-X.Lin, M.-N.Cao, R.Cao. *Coord. Chem. Rev.*, **257**, 1334 (2013)
68. X.-L.Ni, S.-F.Xue, Z.Tao, Q.-J.Zhu, L.F.Lindoy, G.Wei. *Coord. Chem. Rev.*, **287**, 89 (2015)
69. J.W.Lee, S.Samal, N.Selvapalam, H.-J.Kim, K.Kim. *Acc. Chem. Res.*, **36**, 621 2003)
70. O.A.Gerasko, D.G.Samsonenko, V.P.Fedin. *Russ. Chem. Rev.*, **71**, 741 (2002)
71. P.Cintas. *J. Inclusion Phenom. Mol. Recognit. Chem.*, **17**, 205 (1994)
72. M.Kölbel, F.M.Menger. *Adv. Mater.*, **13**, 1115 (2001)
73. A.E.Rowan, J.A.A.W.Elemans, R.J.M.Nolte. *Acc. Chem. Res.*, **32**, 995 (1999)
74. J.A.A.W.Elemans, A.E.Rowan, R.J.M.Nolte. *Ind. Eng. Chem. Res.*, **39**, 3419 2000)
75. N.N.Makhova, L.I.Belen'kii, G.A.Gazieva, I.L.Dalinger, L.S.Konstantinova, V.V.Kuznetsov, A.N.Kravchenko, M.M.Krayushkin, O.A.Rakitin, A.M.Starosotnikov, L.L.Fershtat, S.A.Shevelev, V.Z.Shirinian, V.N.Yarovenko. *Russ. Chem. Rev.*, **89**, 55 (2020)
76. D.A.Wicks, Z.W.Wicks. *Prog. Org. Coat.*, **36**, 148 (1999)
77. Z.W.Wicks. *Prog. Org. Coat.*, **9**, 3 (1981)
78. D.A.Wicks, Z.W. Wicks. *Prog. Org. Coat.*, **41**, 1 (2001)
79. D.Simón, A.M.Borreguero, A.de Lucas, J.F.Rodríguez. *Waste Manag.*, **76**, 147 (2018)
80. D.K.Chattopadhyay, K.V.S.N.Raju. *Prog. Polym. Sci.*, **32**, 352 (2007)
81. A.A.Caraculacu, S.Coseri. *Prog. Polym. Sci.*, **26**, 799 (2001)
82. M.M.Antonova, V.V.Baranov, A.N.Kravchenko. *Chem. Heterocycl. Compd.*, **51**, 395 (2015)
83. G.Mloston, M.Jasinski, A.Wróblewska, H.Heimgartner. *Curr. Org. Chem.*, **20**, 1359 (2016)
84. N.-W.Wu, J.Rebek. *J. Am. Chem. Soc.*, **138**, 7512 (2016)
85. M.A.Tabarki, R.Besbes. *Tetrahedron Lett.*, **56**, 1837 (2015)
86. Y.Takeda, H.Kawai, S.Minakata. *Chem. – Eur. J.*, **19**, 13479 (2013)
87. P.A.Troshin, R.N.Lyubovskaya. *Russ. Chem. Rev.*, **77**, 305 (2008)
88. E.N.Karaulova, E.I.Bagrii. *Russ. Chem. Rev.*, **68**, 889 (1999)
89. S.Koya, K.Yamanoi, R.Yamasaki, I.Azumaya, H.Masu, S.Saito. *Org. Lett.*, **11**, 5438 (2009)
90. S.Chuprakov, S.W.Kwok, V.V.Fokin. *J. Am. Chem. Soc.*, **135**, 4652 (2013)
91. Y.Jing, R.Liu, Y.Lin, X.Zhou. *Sci. China Chem.*, **57**, 1117 (2014)
92. H.Jin, C.Dai, Y.Huang. *Org. Lett.*, **20**, 5006 (2018)
93. O.P.Pereshivko, V.A.Peshkov, J.Jacobs, L.Van Meervelt, E.V.Van der Eycken. *Adv. Synth. Catal.*, **355**, 781 (2013)
94. O.P.Pereshivko, V.A.Peshkov, A.A.Peshkov, J.Jacobs, L.Van Meervelt, E.V.Van der Eycken. *Org. Biomol. Chem.*, **12**, 1741 (2014)
95. K.K.Gollapelli, S.Donikela, N.Manjula, R.Chegondi. *ACS Catal.*, **8**, 1440 (2018)
96. R.R.Anugu, R.Chegondi. *J. Org. Chem.*, **82**, 6786 (2017)
97. W.Schneider, W.Diller. In *Ullmann's Encyclopedia of Industrial Chemistry*. (Weinheim: Wiley-VCH, 2000). P. 624
98. J.-P.Senet. *CR Acad. Sci. IIC*, **3**, 505 (2000)
99. P.Amabili, M.Calvaresi, G.Martelli, M.Orena, S.Rinaldi, F.Sgolastra. *Eur. J. Org. Chem.*, 907 (2019)
100. A.H.Tamboli, H.A.Bandal, H.Kim. *Chem. Eng. J.*, **306**, 826 (2016)
101. M.Chouhan, R.Sharma, V.A.Nair. *Org. Lett.*, **14**, 5672 (2012)
102. T. Yamashita, P.C.Knipe, N.Busschaert, S. Thompson, A.D.Hamilton. *Chem. – Eur. J.*, **21**, 14699 (2015)
103. D.Frain, F.Kirby, P.McArdle, P.O'Leary. *Org. Chem. Int.*, Art. ID 293945 (2012)
104. M.Hori, A.Sakakura, K.Ishihara. *J. Am. Chem. Soc.*, **136**, 13198 (2014)
105. C.M.Grombein, Q.Hu, S.Rau, C.Zimmer, R.W.Hartmann. *Eur. J. Med. Chem.*, **90**, 788 (2015)
106. J.Li, I.C.Stewart, R.H.Grubbs. *Organometallics*, **29**, 3765 (2010)
107. P.S.Humphries, R.Bersot, J.Kincaid, E.Mabery, K.McCluskie, T.Park, T.Renner, E.Riegler, T.Steinfeld, E.D.Turtle, Z.-L.Wei, E.Willis. *Bioorg. Med. Chem. Lett.*, **28**, 293 (2018)
108. T.Taniguchi, T.Suzuki, H.Satoh, Y.Shichibu, K.Konishi, K.Monde. *J. Am. Chem. Soc.*, **140**, 15577 (2018)
109. N.Prusinowska, J.Szymkowiak, M.Kwit. *J. Org. Chem.*, **83**, 1167 (2018)
110. Y.Yao, X.Wang, G.Liang. *Tetrahedron*, **73**, 4538 (2017)
111. M.Movassaghi, D.S.Siegel, S.Han. *Chem. Sci.*, **1**, 561 (2010)
112. S.Han, D.S.Siegel, K.C.Morrison, P.J.Hergenrother, M.Movassaghi. *J. Org. Chem.*, **78**, 11970 (2013)
113. W.Bertleff. *Carbonylation (Ser. Ullmann's Encyclopedia of Industrial Chemistry)*. (Weinheim: Wiley-VCH, 2000)
114. M.Beller, B.Cornils, C.D.Frohning, C.W.Kohlpaintner. *J. Mol. Catal. A: Chem.*, **104**, 17 (1995)
115. P.Braunstein, D.Matt, D.Nobel. *Chem. Rev.*, **88**, 747 (1988)
116. A.M.Appel, J.E.Bercaw, A.B.Bocarsly, H.Dobbek, Wiley-VCH, D.L.DuBois, M.Dupuis, J.G.Ferry, E.Fujita, R.Hille, P.J.A.Kenis, C.A.Kerfeld, R.H.Morris, C.H.F.Peden, Wiley-VCH, A.R.Portis, S.W.Ragsdale, T.B.Rauchfuss, J.N.H.Reek, L.C.Seefeldt, R.K.Thauer, G.L.Waldrop. *Chem. Rev.*, **113**, 6621 (2013)
117. K.Sekine, T.Yamada. *Chem. Soc. Rev.*, **45**, 4524 (2016)
118. M.Casiello, F.Iannone, P.Cotugno, A.Monopoli, N.Cioffi, F.Ciminale, A.M.Trzeciak, A.Nacci. *J. Mol. Catal. A: Chem.*, **407**, 8 (2015)
119. A.K.Darko, F.C.Curran, C.Copin, L.McElwee-White. *Tetrahedron*, **67**, 3976 2011)
120. L.Zhang, A.K.Darko, J.I.Johns, L.McElwee-White. *Eur. J. Org. Chem.*, 6261 2011)
121. S.Roslin, P.Brandt, P.Nordeman, M.Larhed, L.Odell, J.Eriksson. *Molecules*, **22**, 1688 (2017)
122. A.Primo, E.Aguado, H.Garcia. *ChemCatChem*, **5**, 1020 (2013)
123. M.Tamura, K.Noro, M.Honda, Y.Nakagawa, K.Tomishige. *Green Chem.*, **15**, 1567 (2013)
124. C.Wu, H.Cheng, R.Liu, Q.Wang, Y.Hao, Y.Yu, F.Zhao. *Green Chem.*, **12**, 1811 (2010)

125. J.Paz, C.Pérez-Balado, B.Iglesias, L.Muñoz. *J. Org. Chem.*, **75**, 3037 (2010)
126. A.Del Vecchio, F.Caillé, A.Chevalier, O.Loreau, K.Horkka, C.Halldin, M.Schou, N.Camus, P.Kessler, B.Kuhnast, F.Taran, D.Audisio. *Angew. Chem., Int. Ed.*, **57**, 9744 (2018)
127. M.Xu, A.R.Jupp, M.S.E.Ong, K.I.Burton, S.S.Chitnis, D.W.Stephan. *Angew. Chem., Int. Ed.*, **58**, 5707 (2019)
128. I.B.Blagoeva, I.G.Pojarlieff, D.T.Tashev, A.J.Kirby. *J. Chem. Soc., Perkin Trans. 2*, 347 (1989)
129. V.P.Kozyukov, V.D.Sheludyakov, V.F.Mironov. *Russ. Chem. Rev.*, **44**, 413 (1975)
130. R.Abrams, Q.Lefebvre, J.Clayden. *Angew. Chem., Int. Ed.*, **57**, 13587 (2018)
131. S.Bretzke, S.Scheeff, F.Vollmeyer, F.Eberhagen, F.Rominger, D.Menche. *Beilstein J. Org. Chem.*, **12**, 1111 (2016)
132. M.Morgen, S.Bretzke, P.Li, D.Menche. *Org. Lett.*, **12**, 4494 (2010)
133. J.Wu, K.-C.Zhu, P.-W.Yuan, J.S.Panek. *Org. Lett.*, **14**, 3624 (2012)
134. P.-S.Wang, M.-L.Shen, T.-C.Wang, H.-C.Lin, L.-Z.Gong. *Angew. Chem., Int. Ed.*, **56**, 16032 (2017)
135. T.Wu, J.Cheng, P.Chen, G.Liu. *Chem. Commun.*, **49**, 8707 (2013)
136. F.Xu, S.A.Shuler, D.A.Watson. *Angew. Chem., Int. Ed.*, **57**, 12081 (2018)
137. G.Wang, C.Liu, B.Li, Y.Wang, K.Van Hecke, E.V.Van der Eycken, O.P.Pereshivko, V.A.Peshkov. *Tetrahedron*, **73**, 6372 (2017)
138. L.Wei, X.Gao, R.Warne, X.Hao, D.Bussiere, X.Gu, T.Uno, Y.Liu. *Bioorg. Med. Chem. Lett.*, **20**, 3897 (2010)
139. A.W.Shaw, D.V.Paone, D.N.Nguyen, C.A.Stump, C.S.Burgey, S.D.Mosser, C.A.Salvatore, R.Z.Rutledge, S.A.Kane, K.S.Koblan, S.L.Graham, J.P.Vacca, T.M.Williams. *Bioorg. Med. Chem. Lett.*, **17**, 4795 (2007)
140. T.M.Williams, C.A.Stump, D.N.Nguyen, A.G.Quigley, I.M.Bell, S.N.Gallicchio, C.B.Zartman, B.-L.Wan, K.Della Penna, P.Kunapuli, S.A.Kane, K.S.Koblan, S.D.Mosser, R.Z.Rutledge, C.Salvatore, J.F.Fay, J.P.Vacca, S.L.Graham. *Bioorg. Med. Chem. Lett.*, **16**, 2595 (2006)
141. P.Joshi, C.Anderson, H.Binch, S.Hadida, S.Yoo, D.Bergeron, C.Decker, E.Ter Haar, J.Moore, M.Garcia-Guzman, A.Termin. *Bioorg. Med. Chem. Lett.*, **24**, 845 (2014)
142. F.C.Sequeira, B.W.Turnpenny, S.R.Chemler. *Angew. Chem., Int. Ed.*, **49**, 6365 (2010)
143. A.-S.S.Hamad Elgazwy, N.S.M.Ismail, H.S.A Elzahabi. *Bioorg. Med. Chem.*, **18**, 7639 (2010)
144. P.Xiong, H.-H.Xu, H.-C.Xu. *J. Am. Chem. Soc.*, **139**, 2956 (2017)
145. J.Yu, C.Gao, Z.Song, H.Yang, H.Fu. *Eur. J. Org. Chem.*, 5869 (2015)
146. M.D.Kosobokov, M.I.Struchkova, D.E.Arkhipov, A.A.Korlyukov, A.D.Dilman. *J. Fluorine Chem.*, **154**, 73 (2013)
147. A.Minić, D.Stevanović, I.Damljanović, A.Pejović, M.Vukićević, G.A.Bogdanović, N.S.Radulović, R.D.Vukićević. *RSC Adv.*, **5**, 24915 (2015)
148. L.I.Vagapova, K.V.Matylitskii, A.R.Burilov, A.R.Garifzyanov, M.A.Pudovik. *Russ. J. Gen. Chem.*, **88**, 2442 (2018)
149. A.V.Smolobochkin, T.S.Rizbayeva, A.S.Melyashova, A.R.Burilov, M.A. Pudovik, O.G.Sinyashin, A.S.Gazizov. *ChemistrySelect*, **4**, 9322 (2019)
150. A.V.Smolobochkin, A.S.Gazizov, K.V.Matylitskii, L.I.Vagapova, A.R.Burilov, M.A.Pudovik. *Russ. J. Gen. Chem.*, **89**, 1934 (2019)
151. M.S.Khakimov, A.S.Gazizov, A.R.Burilov, M.A.Pudovik, A.I.Konovalov. *Russ. J. Gen. Chem.*, **79**, 1163 (2009)
152. A.V.Smolobochkin, A.S.Gazizov, N.K.Otegen, J.K.Voronina, A.G.Strelnik, A.I.Samigullina, A.R.Burilov, M.A.Pudovik. *Synthesis*, **52**, 3263 (2020)
153. A.S.Gazizov, M.S.Khakimov, A.R.Burilov, M.A.Pudovik, D.B.Krivolapov, I.A.Litvinov, A.I.Konovalov. *Russ. Chem. Bull., Int. Ed.*, **58**, 238 (2009)
154. J.E.Gazizov, N.K.Otegen, J.K.Voronina, A.G.Strelnik, A.I.Samigullina, A.Hall, J.V.Matlock, J.W.Ward, K.V.Gray, J.Clayden. *Angew. Chem., Int. Ed.*, **55**, 11153 (2016)
155. J.E.Hill, J.V.Matlock, Q.Lefebvre, K.G.Cooper, J.Clayden. *Angew. Chem., Int. Ed.*, **57**, 5788 (2018)
156. J.E.Hill, Q.Lefebvre, L.A.Fraser, J.Clayden. *Org. Lett.*, **20**, 5770 (2018)
157. T.B.Nguyen, A.Al-Mourabit, L.Ermolenko, M.-E.Tran Huu Dau. *Heterocycles*, **88**, 403 (2014)
158. E.A.Shafikova, D.V.Petrov, T.A Sapozhnikova, N.J.Baschenko, V.A.Dokichev. *Chem. Heterocycl. Compd.*, **45**, 685 (2009)
159. A.N.Kravchenko, V.V.Baranov, Y.V.Nelyubina, G.A.Gazieva, I.V.Svitan ko. *Russ. Chem. Bull., Int. Ed.*, **61**, 64 (2012)
160. V.V.Baranov, Y.V.Nelyubina, A.N.Kravchenko, N.G.Kolotyrkina, K.A.Biriukova. *Tetrahedron Lett.*, **56**, 6085 (2015)
161. V.V.Baranov, A.A.Galochkin, Y.V.Nelyubina, A.N.Kravchenko, N.N.Makhova. *Synthesis*, **52**, 2563 (2020)
162. V.V.Baranov, M.M.Antonova, Y.V.Nelyubina, N.G.Kolotyrkina, I.E.Zanin, A.N.Kravchenko, N.N.Makhova. *Mendeleev Commun.*, **24**, 173 (2014)
163. L.V.Saloutina, A.Y.Zapevalov, P.A.Slepukhin, M.I.Kodess, V.I.Saloutin, O.N.Chupakhin. *Chem. Heterocycl. Compd.*, **50**, 958 (2014)
164. V.J.Lillo, J.M.Saá. *Chem. – Eur. J.*, **22**, 17182 (2016)
165. A.A.Fesenko, P.A.Solovyev, A.D.Shutalev. *Tetrahedron*, **66**, 940 (2010)
166. A.A.Fesenko, A.D.Shutalev. *Tetrahedron Lett.*, **53**, 6261 (2012)
167. A.A.Fesenko, A.D.Shutalev. *J. Org. Chem.*, **78**, 1190 (2013)
168. A.A.Fesenko, A.D.Shutalev. *Tetrahedron*, **70**, 5398 (2014)
169. A.A.Fesenko, M.S.Grigoriev, A.D.Shutalev. *J. Org. Chem.*, **82**, 8085 (2017)
170. P.A.Solovyev, A.A.Fesenko, A.D.Shutalev. *J. Fluorine Chem.*, **182**, 28 2016)
171. S.Gore, K.Chinthapally, S.Baskaran, B.König. *Chem. Commun.*, **49**, 5052 (2013)
172. M.R.Mohammadizadeh, N.Firoozi. *Tetrahedron Lett.*, **51**, 2467 (2010)
173. R.M.Ghalib, R.Hashim, S.F.Alshahateet, S.H.Mehdi, O.Sulaiman, K.-L.Chan, V.Murugaiyah, A.Jawad. *J. Chem. Crystallogr.*, **42**, 783 (2012)
174. I.R.Sadarangani, S.Bhatia, D.Amarante, I.Lengyel, R.A.Stephani. *Bioorg. Med. Chem. Lett.*, **22**, 2507 (2012)
175. C.Yang, F.A.X.Schanne, S.Yoganathan, R.A.Stephani. *Bioorg. Med. Chem. Lett.*, **26**, 2912 (2016)
176. H.J.Patel, J.Sarra, F.Caruso, M.Rossi, U.Doshi, R.A.Stephani. *Bioorg. Med. Chem. Lett.*, **16**, 4644 (2006)
177. R.M.Ghalib. *Russ. J. Org. Chem.*, **55**, 412 (2019)
178. J.A.W.Jong, M.-E.Moret, M.C.Verhaar, W.E.Hennink, K.G.F.Gerritsen, C.F.van Nostrum. *ChemistrySelect*, **3**, 1224 (2018)
179. Y.Saini, R.Khajuria, R.Kaur, S.Kaul, T.Sharma, S.Gupta, V.K.Gupta, R.Kant, K.K.Kapoor. *Synth. Commun.*, **47**, 1159 (2017)
180. M.-L.Xing, X.-W.Lu, C.-B.Miao, J.-X.Li, X.-Q.Sun, H.-T.Yang. *J. Org. Chem.*, **79**, 11774 (2014)
181. H.-T.Yang, Y.-C.Tan, Y.Yang, X.-Q.Sun, C.-B.Miao. *J. Org. Chem.*, **81**, 1157 (2016)
182. Y.Zhang, J.Zheng, S.Cui. *J. Org. Chem.*, **79**, 6490 (2014)

183. Q.Wang, J.An, H.Alper, W.-J.Xiao, A.M.Beauchemin. *Chem. Commun.*, **53**, 13055 (2017)
184. D.R.White, J.P.Wolfe. *Org. Lett.*, **17**, 2378 (2015)
185. V.K.Singh, H.Sharma, S.K.Singh, L.Gangwar. *Chem. Biol. Drug Des.*, **82**, 119 (2013)
186. S.Rani, L.Sridhar, R.Srivastava, V.K.Singh. *Cancer Biother. Radiopharm.*, **28**, 494 (2013)
187. P.Biginelli, P.Gazz. *Chim. Ital.*, **23**, 360 (1893)
188. R.Liang-Ce, Y.Zha, S.Xia, L.Ji, J.Zhang, P.Cai. *J. Heterocycl. Chem.*, **53**, 56 2016)
189. H.F.Zohdi, N.M.Rateb, S.M.Elnagdy. *Eur. J. Med. Chem.*, **46**, 5636 (2011)
190. V.Palermo, Á.Sathicq, T.Constantieux, J.Rodríguez, P.Vázquez, G.Romanelli. *Catal. Lett.*, **145**, 1022 (2015)
191. Á.Sathicq, D.Ruiz, T.Constantieux, J.Rodriguez, G.Romanelli. *Synlett*, **25**, 881 (2014)
192. S.Z.Dalil Heirati, F.Shirini, A.F.Shojaei. *RSC Adv.*, **6**, 67072 (2016)
193. W.Fan, Y.Queneau, F.Popowycz. *Green Chem.*, **20**, 485 (2018)
194. F.Zhao, X.Jia, P.Li, J.Zhao, J.Huang, H.Li, L.Li. *Molecules*, **22**, 1503 (2017)
195. M.Dutta, J.Gogoi, K.Shekarrao, J.Goswami, S.Gogoi, R.Boruah. *Synthesis*, **44**, 2614 (2012)
196. Á.Baji, T.Kiss, J.Wölfling, D.Kovács, N.Igaz, M.K.Gopisetty, M.Kiricsi, É.Frank. *J. Steroid Biochem. Mol. Biol.*, **172**, 79 (2017)
197. S.Farhadi, M.A.Ghasemzadeh, S.S.Aghaei. *ChemistrySelect*, **4**, 729 (2019)
198. M.K.Mohammadi. *Bull. Chem. Soc. Ethiop.*, **32**, 149 (2018)
199. Y.Wan, R.Yuan, H.Xu, C.Wang, J.Qi, H.Wu. *J. Heterocycl. Chem.*, **51**, E123 (2014)
200. J.Liu, Y.Xie, L.Ye, H.Yan, S.Tu. *Org. Prep. Proced. Int.*, **46**, 453 (2014)
201. S.A.Chumachenko, O.V.Shablykin, A.P.Kozachenko, T.V.Osadchuk, V.S.Brovarets. *Chem. Heterocycl. Compd.*, **47**, 336 (2011)
202. F.Iannone, M.Casiello, A.Monopoli, P.Cotugno, M.C.Sportelli, R.A.Picca, N.Cioffi, M.M.Dell'Anna, A.Nacci. *J. Mol. Catal. A: Chem.*, **426**, 107 (2017)
203. A.Pejović, B.Danneels, T.Desmet, B.Cham, T.Van Nguyen, N.Radulović, R.Vukićević, M.D'hooghe. *Synlett*, **26**, 1195 (2015)
204. T.M.T.Tong, T.Soeta, T.Suga, K.Kawamoto, Y.Hayashi, Y.Ukaji. *J. Org. Chem.*, **82**, 1969 (2017)
205. Y.Wang, A.Ø.Madsen, F.Diness, M.Meldal. *Chem. – Eur. J.*, **23**, 13869 (2017)
206. F.Diness, M.Meldal. *Chem. – Eur. J.*, **15**, 7044 (2009)
207. F.Diness, M.Meldal. *Biopolymers*, **94**, 236 (2010)
208. C.Dengiz, S.Özcan, E.Şahin, M.Balci. *Synthesis*, 1365 (2010)
209. S.Shirakawa, K.Liu, H.Ito, T.N.Le, K.Maruoka. *Adv. Synth. Catal.*, **353**, 2614 2011)
210. D.Azarifar, Z.Najminejad, K.Khosravi. *J. Iran. Chem. Soc.*, **10**, 979 (2013)
211. G.-S.Feng, L.Shi, F.-J.Meng, M.-W.Chen, Y.-G.Zhou. *Org. Lett.*, **20**, 6415 2018)
212. G.-S.Feng, M.-W.Chen, L.Shi, Y.-G.Zhou. *Angew. Chem., Int. Ed.*, **57**, 5853 (2018)
213. S.Subramanian, P.R.Boggu, J.Yun, S.-H.Jung. *Arch. Pharm. Res.*, **41**, 251 (2018)
214. H.M.Lima, C.J.Lovely. *Org. Lett.*, **13**, 5736 (2011)
215. G.Mloston, M.Jasiński. *Collect. Czech. Chem. Commun.*, **75**, 871 (2010)
216. A.Kravchenko, M.Antonova, V.Baranov, Y.Nelyubina. *Synlett*, **26**, 2521 (2015)
217. R.U.Gutiérrez, A.Rebollar, R.Bautista, V.Pelayo, J.L.Várgas, M.M.Montenegro, C.Espinoza-Hicks, F.Ayala, P.M.Bernal, C.Carrasco, L.G.Zepeda, F.Delgado, J.Tamariz. *Tetrahedron: Asymmetry*, **26**, 230 (2015)
218. M.M.Antonova, V.V.Baranov, Y.V.Nelyubina, A.N.Kravchenko. *Chem. Heterocycl. Compd.*, **50**, 503 (2014)
219. V.V.Baranov, M.M.Antonova, V.A.Karnoukhova, A.N.Kravchenko. *ARKIVOC*, (iii), 63 (2017)
220. G.Mlostoń, M.Jasiński. *ARKIVOC*, (vi), 162 (2011)
221. M.M.Antonova, V.V.Baranov, Y.V.Nelyubina, A.N.Kravchenko. *Chem. Heterocycl. Compd.*, **50**, 1203 (2014)
222. B.Zhao, X.Peng, Y.Zhu, T.A.Ramirez, R.G.Cornwall, Y.Shi. *J. Am. Chem. Soc.*, **133**, 20890 (2011)
223. X.Hu, Z.Cao, Z.Liu, Y.Wang, H.Du. *Adv. Synth. Catal.*, **352**, 651 (2010)
224. B.Zhao, H.Du, Y.Shi. *J. Org. Chem.*, **74**, 4411 (2009)
225. Y.Zhu, Y.Shi. *Chem. – Eur. J.*, **20**, 13901 (2014)
226. T.Chen, G.Zeng, Z.Lai, K.-W.Huang. *J. Memb. Sci.*, **515**, 212 (2016)
227. S.H.Kim, S.H.Hong. *Org. Lett.*, **18**, 212 (2016)
228. J.Kothandaraman, S.Kar, R.Sen, A.Goeppert, G.A.Olah, G.K.S.Prakash. *J. Am. Chem. Soc.*, **139**, 2549 (2017)
229. R.T.Sawant, M.Y.Stevens, L.R.Odell. *ACS Omega*, **3**, 14258 (2018)
230. R.T.Sawant, M.Y.Stevens, C.Sköld, L.R.Odell. *Org. Lett.*, **18**, 5392 (2016)
231. S.Gore, S.Baskaran, B.Koenig. *Adv. Synth. Catal.*, **354**, 2368 (2012)
232. I.Tsuchimochi, Y.Kitamura, H.Aoyama, S.Akai, K.Nakai, T.Yoshimitsu. *Chem. Commun.*, **54**, 9893 (2018)
233. A.Ionescu, D.Cornut, S.Soriano, C.Guissart, P.Van Antwerpen, I.Jabin. *Tetrahedron Lett.*, **54**, 6087 (2013)
234. T.Uchida, M.Rodriquez, S.L.Schreiber. *Org. Lett.*, **11**, 1559 (2009)
235. J.Bezenšek, U.Grošelj, K.Stare, J.Svete, S.Branko. *ARKIVOC*, (ii), 294 (2014)