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α-Acyl lactams in the synthesis of physiologically active compounds

V G Nenajdenko, E P Zakurdaev, E S Balenkova

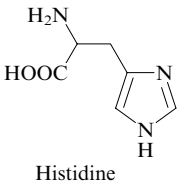
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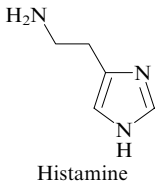
Abstract. Data on the methods of synthesis and the reactivity of α-acyl lactams are described systematically and generalized. The attention is focused on the recent achievements in the synthesis of heterocyclic compounds and biologically active substances from α-acyl lactams and cyclic imines derived from the latter compounds. The bibliography includes 168 references.

I. Introduction

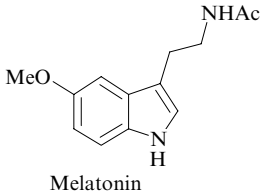
α-Acyl lactams are convenient building blocks for the synthesis of carbonyl compounds and cyclic imines, which are, in turn, used in the synthesis of heterocyclic compounds with an aminoalkyl group and compounds containing a cyclic amine moiety. Natural amino acids, alkaloids, physiologically active compounds and medications belong to these derivatives. Heteroaromatic compounds with an aminoalkyl group are of particular interest because of high biological activity associated with their efficient interactions with serotoninergic, melatoninergic, adrenergic and other receptors. The structures of some natural compounds containing heteroaromatic rings or cyclic amine moieties are presented below.



Histidine



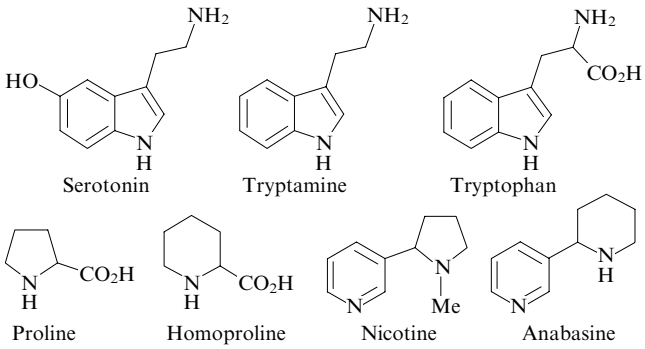
Histamine



Melatonin

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The design of new heterocyclic systems, investigation of their properties and the development of efficient and convenient procedures for the synthesis of the already known heterocyclic compounds are acute problems in modern organic chemistry. Nitrogen heterocycles, which are involved in most alkaloids, many biologically active substances and medications are most abundant heterocyclic compounds. Carbonyl compounds are widely used in the synthesis of heterocyclic compounds. Aminocarbonyl compounds open a direct route to hetarylalkylamines.

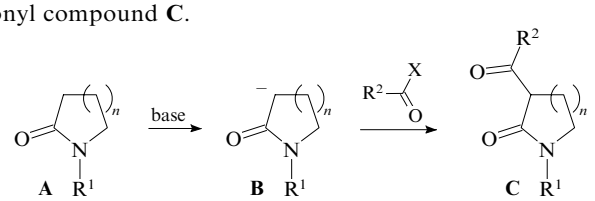
Lactams contain an aminoalkyl group and an amide moiety convenient for modifications. Many lactams are inexpensive, commercially available reagents. The acylation of lactam anions affords α-acyl lactams containing the 1,3-dicarbonyl system whose carbonyl groups show substantially different reactivity. This opens possibilities for chemo- and regioselective heterocyclization in reactions with asymmetric binucleophiles. At the same time, modifications of lactams give rise to aminocarbonyl compounds, which can be used to synthesize heterocyclic compounds with an aminoalkyl group.

II. Methods of synthesis of α-acyl lactams

1. Acylation of lactams

It is convenient to classify the methods of introduction of acyl groups into lactam molecules according to the nature of the electrophilic species that attacks the carbanionic carbon atom in the α position of lactams. The reaction can be represented by the following general scheme: the depro-

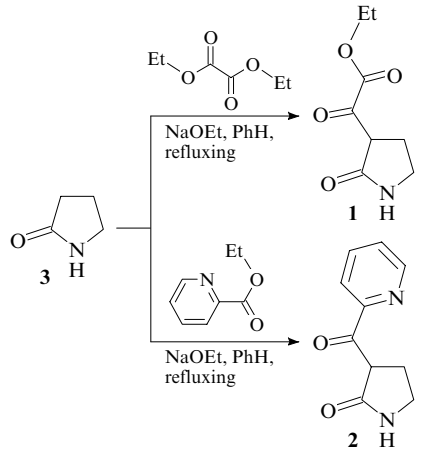
tonation of an *N*-protected cyclic amide **A** with a strong base giving rise to a C-carbanion **B** followed by the reaction of the latter with an acylating agent to form a 1,3-dicarbonyl compound **C**.



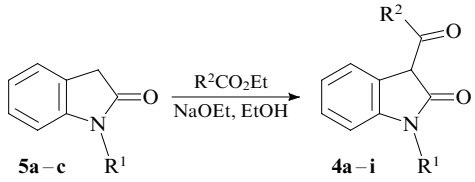
R^1, R^2 = Alk, Ar.

a. Acylation with esters and their derivatives

Acyl lactams **1** and **2** were synthesized for the first time using esters as acylating agents. *N*-Unprotected lactams were initially used due to ready availability. For example, pyrrolidone (**3**) was employed in the reactions with diethyl oxalate [1] or ethyl picolinate.[2]



The synthesis of 3-acylindolin-2-ones **4** has attracted considerable attention because of the presence of the indole moiety in the reaction products and the ready availability of the starting compounds. The condensation of various esters was most often performed with the use of *N*-unprotected indolin-2-one (**5a**), but some reactions were carried out with its *N*-Me or *N*-Et derivatives.

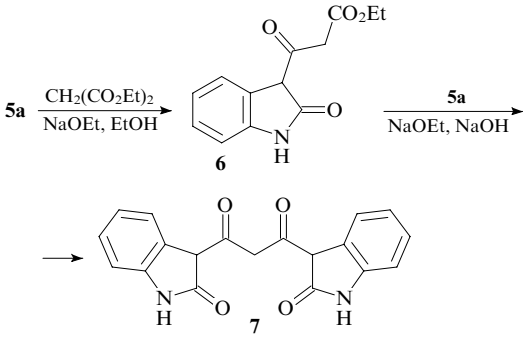


R^1 = H (**a**), Me (**b**), Et (**c**).

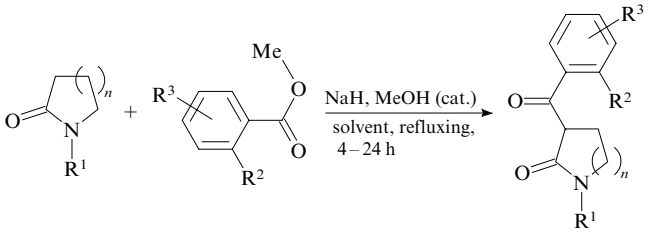
Compound **4**	R^1	R^2	Yield (%)	Ref.
a	H	$PhCH_2$	90	3
b	H	$EtCO_2CH_2$	90	4
c	H	$EtCO_2$	95	5
d	H	Me	25	5
e	H	$NCCH_2$	41	5
f	H	$HOCH_2$	–	5
g	H	$MeOCH_2$	–	5
h	Me	$EtCO_2$	100	6
i	Et	Me	56	7

Other strong bases, for example, NaOMe in MeOH [5] or KOEt in Et_2O,[8] have also found use. The reactions with *N*,*N*-dimethylglycine ethyl ester [9] and ethyl piperidineacetate [10] give oxindole derivatives containing an amino acid substituent.

In the presence of an excess of lactam and bifunctional acylating agents, the *in situ* synthesized acyl lactam **6** undergoes further transformations. This reaction was used to prepare [5] derivative **7**.

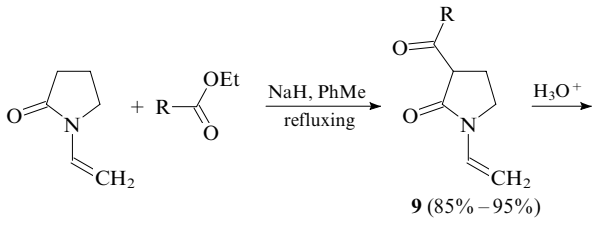


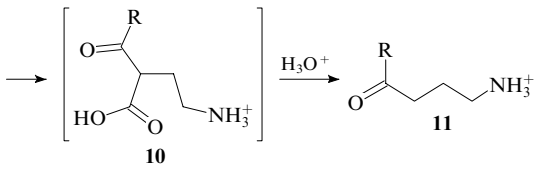
Sodium hydride in the presence of a catalytic amount of methanol proved to be the reagent of choice for the synthesis of salicylic [11] and anthranilic [12] acid derivatives **8** (with HO and NH groups). The introduction of the *o*-methoxy group, other conditions being the same, requires the use of solvents with higher boiling points (toluene instead of benzene) and a longer reaction time because of a decrease in the electron-withdrawing properties of the ester group. In the reactions with benzoic acids containing amino or amido groups, THF served as the solvent. The replacement of the methylamino group by the acetamide group results in an decrease in the reaction time and a slight increase in the yield of the product, whereas an increase in the ring size leads to a strong decrease in the yield, particularly, in the case of caprolactam (n = 3).



R^1 = Me, Ph, Bn; R^2 = HO, MeO, MeNH, AcHN;
R^3 = H, 4-Ph, 5-MeO; n = 1–3.

Due to the progress in the chemistry of lactams, such reagents as *N*-vinylpyrrolidone became commercially available. The vinyl substituent has an important advantage over other protecting groups. Thus, the vinyl substituent can easily be removed by heating α-acyl lactams **9** in mineral acid solutions, which is accompanied by hydrolysis of



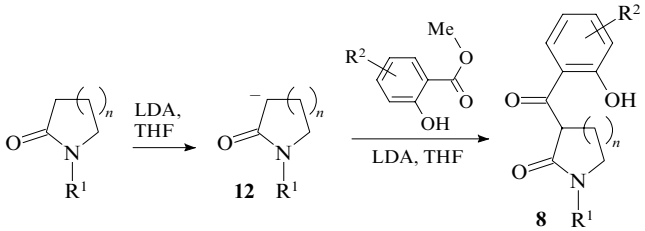


10 **11**

R = Alk, Ar.

lactams to form keto acids **10**, which undergo decarboxylation to give amino ketones **11**.[13]

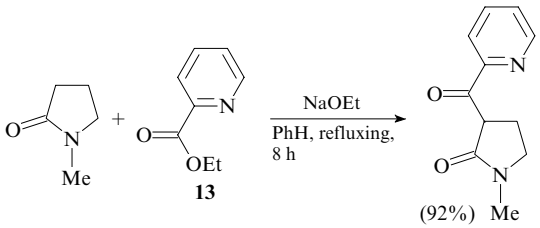
The use of lithium diisopropylamide (LDA) having strongly basic and weakly nucleophilic properties allows the synthesis of lithium enolates of *N*-protected lactams **12**, which react with different acylating agents even at low temperatures. The reactions with LDA afford target products **8** in higher yields even in the case of weaker electrophiles (dihydroxybenzoic acid esters). The deprotonation of lactams is the rate-determining step, as demonstrated by varying the reaction time and temperature.



12 **8**

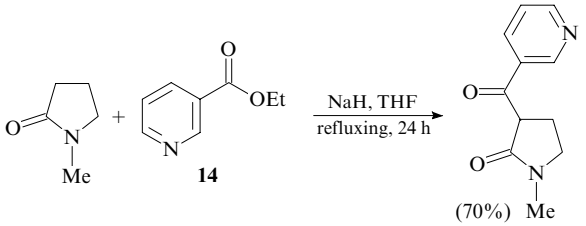
n = 1, R^1 = Me, R^2 = 3-Me-4-OH (30%);
n = 2: R^1 = Me, R^2 = H (87%); R^1 = 4-MeO$(CH_2)_4$, R^2 = H (82%).

In one of the pioneering studies on the synthesis of acyl lactams, pyridine derivatives were prepared as the starting compounds for the synthesis of nicotine and anabasine analogues.[14] More recently, the reactions of *N*-methylpyrrolidone in benzene have been performed with ethyl picolinate (**13**) and ethyl 2-quinolinecarboxylate in the presence of sodium ethoxide.[15]



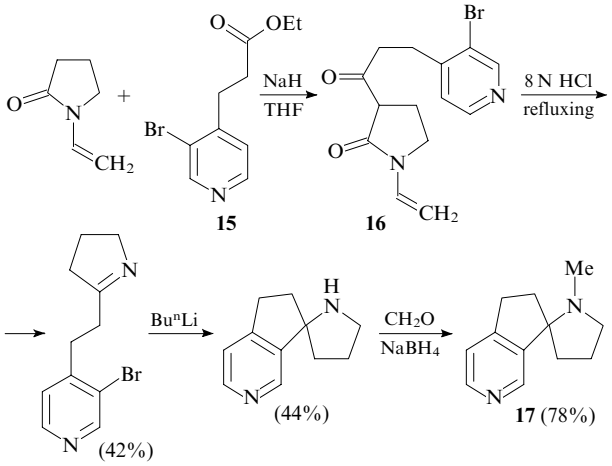
13 (92%)

Sodium hydride in tetrahydrofuran also proved to be a convenient condensing agent in the synthesis of derivatives of nicotinic (**14**)[16] and 3-(3-bromo-4-pyridyl)propionic (**15**)[17] acids. Acyl lactam **16** was used also for the synthesis of spiro-fused nicotine derivative **17**. For a number of compounds, the ability to replace [^{3}H]cytisine (in rat forebrain specimens) was investigated with the use of (−)-nicotine as the reference compound. It appeared that the *S* enantiomer of compound **17** has a high affinity for cytisine-binding sites (the corresponding constant



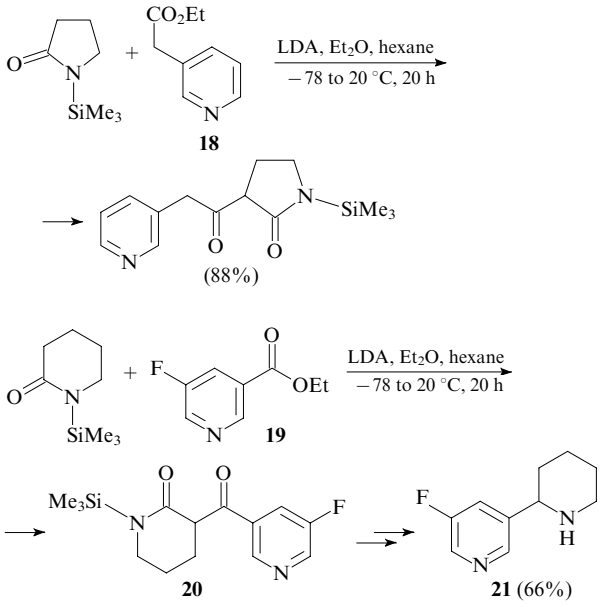
14 (70%)

K_i = 4.79 nmol), whereas its *R* enantiomer does not have this property.



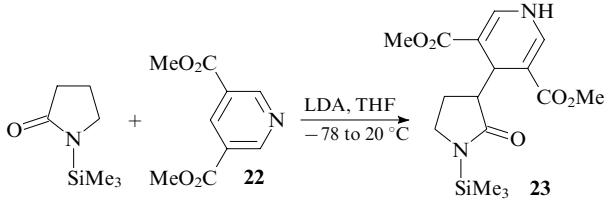
15 **16** **17** (78%)

At the same time, LDA is the reagent of choice for the synthesis of derivatives of 3-pyridylacetic (**18**)[18] and 5-fluoronicotinic (**19**)[19] acids. Compound **20** was used in the synthesis of 5-fluoroanabasine (**21**).



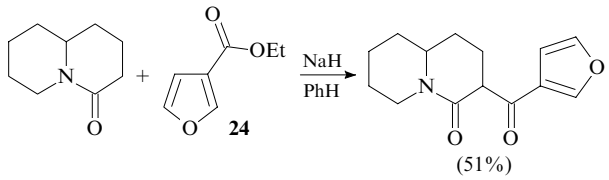
18 (88%) **19** **20** **21** (66%)

In some cases, the reaction follows an unusual pathway. Thus the condensation of the *N*-trimethylsilylpyrrolidone with pyridine derivative **22** does not afford the corresponding acyl lactam; instead, the reaction involves the attack of the carbanion on position 4 of the pyridine ring to form product **23**.[20]

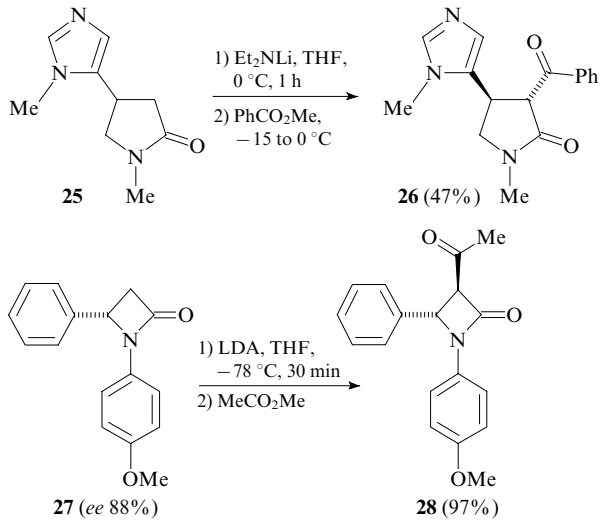


22 **23**

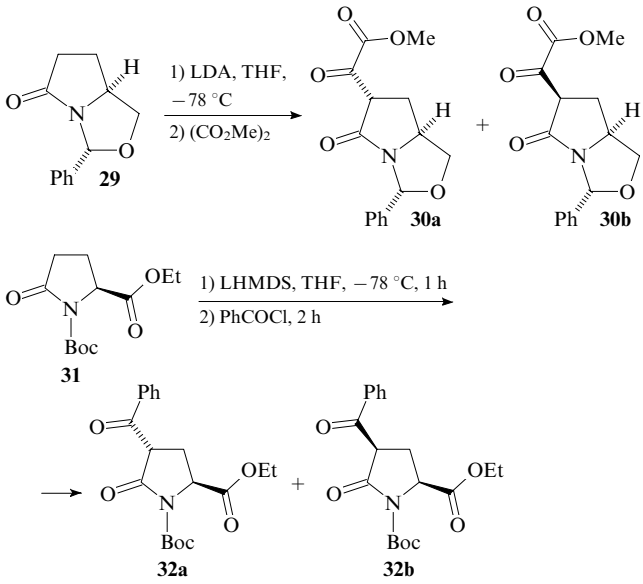
In addition to azaheterocyclic acid esters, the reactions were carried out with furancarboxylic acid esters (for example, with ester **24**).[21]



Substituents in the lactam ring create steric hindrance to the interaction of the lactam anion with electrophiles. As a rule, the attack of an acylating agent results in the *trans* arrangement of the substituents in lactams. For example, substituted pyrrolidone **25** reacts with methyl benzoate to give exclusively *trans* derivative **26**.[22] By the use of chiral lactams, individual diastereomers of acyl lactams can be synthesized. For example, *S*-lactam **27** gives α-acetyl derivative **28** in high yield.[23]

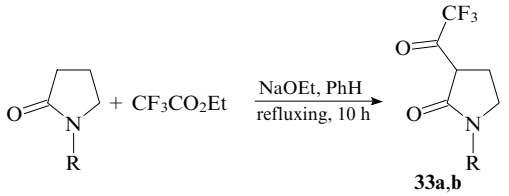


An increase in the distance between the acylated atom of a lactam and the asymmetric centre leads to a substantial decrease in the diastereoselectivity of the reaction. For example, the acylation of bicyclic lactam **29** with dimethyl oxalate affords isomers of products **30** in a ratio of 2.6 : 1 (25% total yield),[24] whereas no stereoselectivity was observed in the acylation of pyroglutamic acid derivative **31** with benzoyl chloride (the ratio of the products **32a** : **32b** = 1 : 1, 75% total yield) (the acylation with carboxylic acid halides is discussed in more detail in the next section).[25]



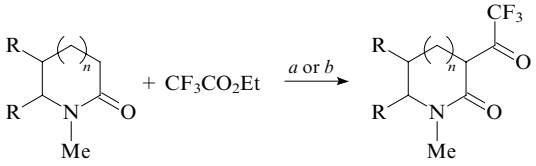
Boc is *tert*-butoxycarbonyl, LHMDS is lithium hexamethyldisilazide.

Due to an extensive progress in the chemistry of fluorine-containing compounds, the synthesis of trifluoroacetyl lactams **33** has attracted great attention. The publication [26] is one of the pioneering studies (it should be noted that attempts to perform this reaction with ethyl perfluorobutyrate failed).



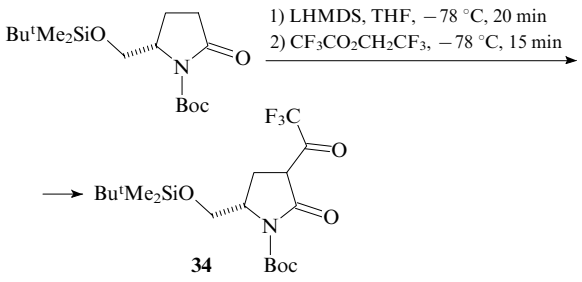
R = Me (**a**, 62%), Et (**b**, 59%).

This approach to the synthesis of trifluoroacetyl derivatives of lactams has found wide use.[27]

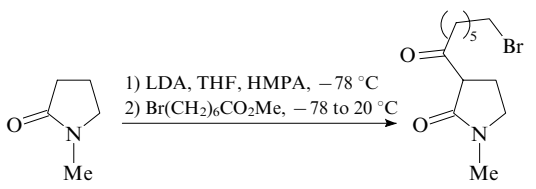


Conditions (*a*) R = H, *n* = 0, 1, or R – R is benzo, *n* = 1; (1) NaH, THF, refluxing; (2) CF_3CO_2Et (1.5 equiv.);
Conditions (*b*) R = H, *n* = 2 or R – R is benzo, *n* = 2; (1) LDA, −78 °C; (2) CF_3CO_2Et (1.2 equiv.), −20 °C.

The coupling of lithium hexamethyldisilazide (a strong and sterically hindered base) with trifluoroethyl trifluoroacetate (a more active electrophile) makes it possible to rapidly introduce the trifluoroacetyl group into chiral lactams at low temperatures and to prepare products in quantitative yields (for example, derivative **34**).[28] Under the same conditions, the reactions with methyl formate give 3-formyl lactams.[29]

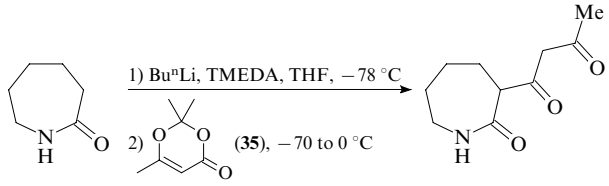


Surprisingly, the reaction with the use of methyl 7-bromoheptanoate did not afford the desired alkylation product; instead, only acylated lactam was obtained.[30]

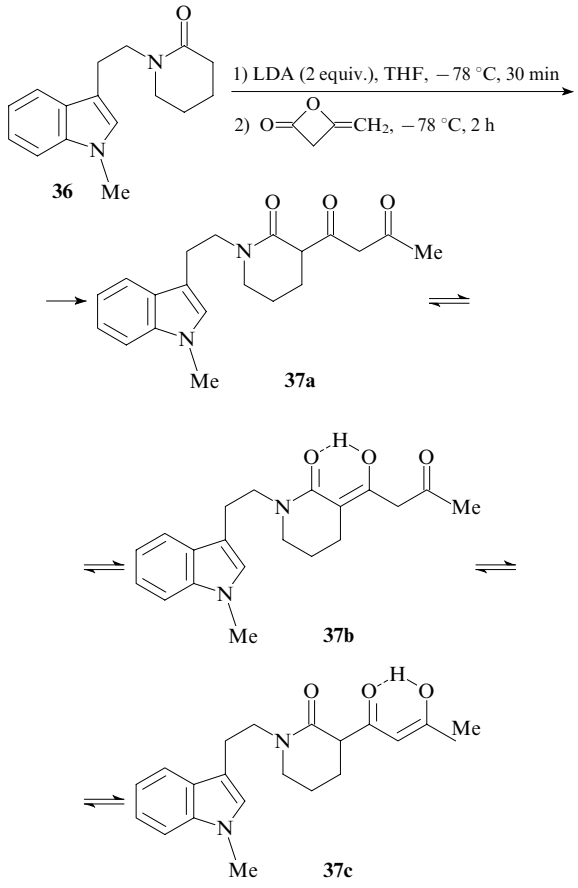


HMPA is hexamethylphosphoramide.

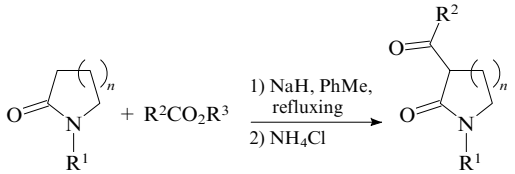
n-Butyllithium in the presence of tetramethylenediamine (TMEDA) can be used for the deprotonation of unprotected lactams. It should be noted that acetoacetic ester derivative **35** served as the electrophile.[31]



The reaction of indole derivative **36** was performed with diketene.[32, 33] Product **37** (35% yield) contains the 1,3,5-tricarbonyl system and exists as a mixture of one ketone form (**37a**) and two enol forms (**37b**,**c**). The chemical shifts (δ) of the enolic proton in the ^{1}H NMR spectrum are 15.20 and 15.36 ppm for enols **37b** and **37c**, respectively.

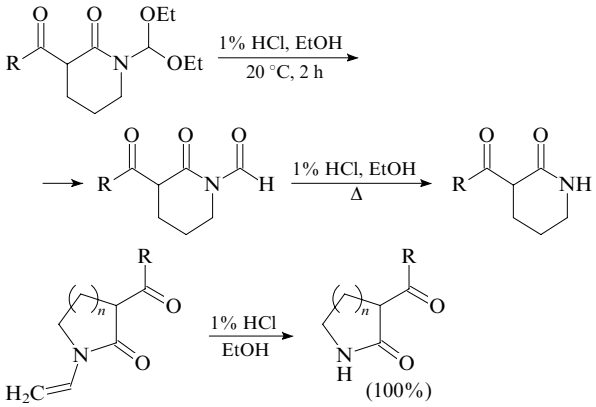


The influence of the nature of the protecting group, the ring size and the nature of the ester on the synthesis of α-acyl lactams under the action of NaH was comprehensively investigated.[34] A wide range of products containing five-, six- or seven-membered rings and various acyl groups were synthesized. Among these substituents were (hetero)-aromatic (with electron-donating and electron-withdrawing substituents), aliphatic, sterically hindered and cage groups. The reaction rate and the yield depend most strongly on the nature of esters; the ring size also has an effect on the yield. Thus, the yields of seven-membered acyl lactams are 5%–8% lower than those of five-membered lactams containing the same substituents.



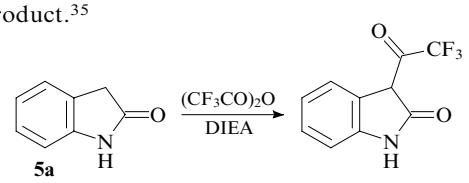
n = 1, 2, R^1 = CH_2=CH; n = 3, R^1 = $CH(OEt)_2$; R^2 = Het, Ar, Alk, cyclo-Alk; R^3 = Me, Et.

A preparative method was developed for the deprotection of the nitrogen atom in acyl lactams.[34] The diethoxymethyl group can be partially hydrolyzed to the formyl group; this group can be completely hydrolyzed as well (by refluxing with 1% HCl). The vinyl group can be removed from five- or seven-membered acyl lactams by refluxing with dilute hydrochloric acid. This gives rise to *N*-unsubstituted acyl lactams in high yields (it should be noted that the lactam ring opening does not occur under these conditions).



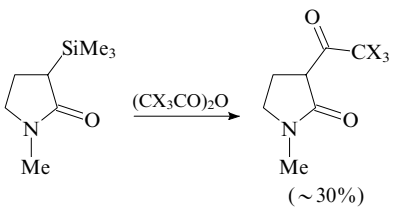
b. Acylation with carboxylic acid anhydrides and halides

More active carboxylic acid derivatives, *viz*., carboxylic acid anhydrides and halides, can also be used as acylating agents. For example, an attempt to introduce a protecting group at the nitrogen atom of indolin-2-one (**5a**) resulted in the formation of the 3-trifluoroacetyl derivative as the only product.[35]



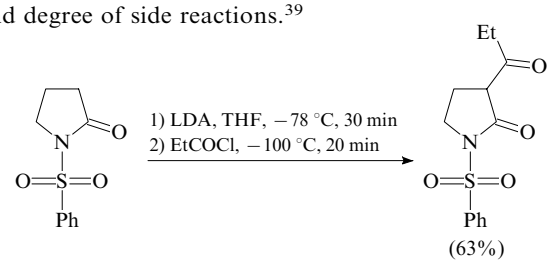
DIEA is *N*,*N*-diisopropylethylamine.

The acylation of 3-trimethylsilylpyrrolidones can be performed in the absence of bases and solvents; this reaction leads to the C–Si bond cleavage and gives acyl lactam.[36]

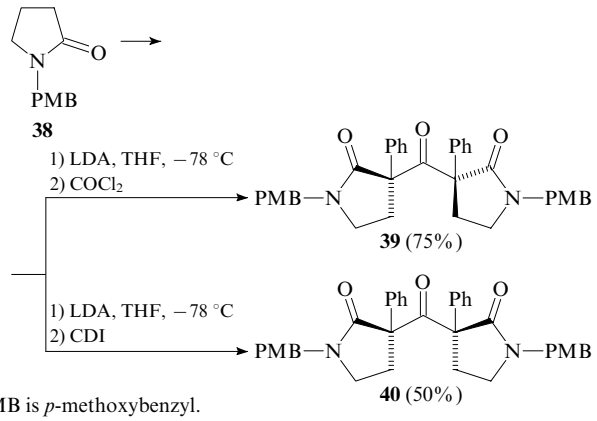


X = F, Cl.

The reactions with the use of acid chlorides as acylating agents can be performed at lower temperatures (in the presence of LHMDS [37] or LDA [38] at −78 °C) compared to esters and anhydrides, resulting in a decrease in the number and degree of side reactions.[39]

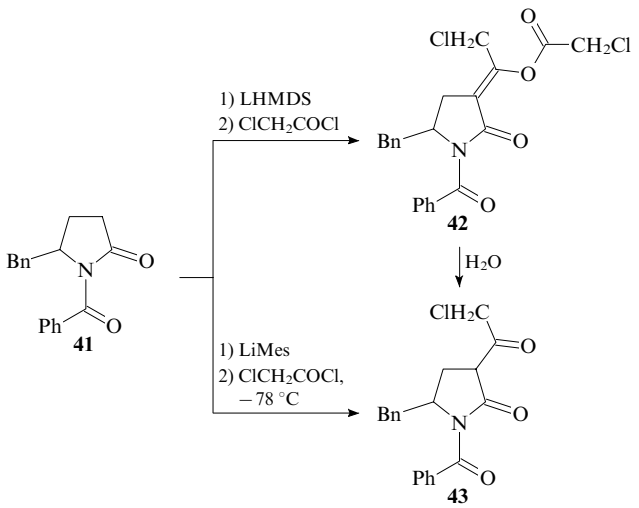


The reaction of phosgene with the anion generated from substituted lactam **38** in the reaction with LDA is diastereoselective and yields acyl lactam **39** (as a racemic mixture). It should be noted that the reaction with carbonyldiimidazole (CDI) is also diastereoselective and affords acyl lactam **40** with another configuration (*meso* form).[40]

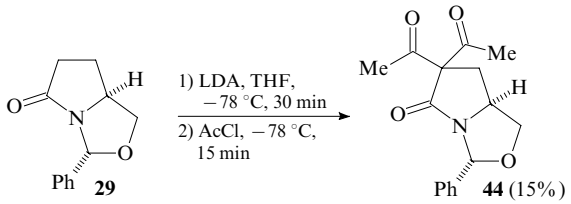


PMB is *p*-methoxybenzyl.

The reactions of protected lactams **41** with halogen-substituted acid halides in the presence of strong bases result exclusively in acylation; alkylation products were not detected. Two different products can be obtained depending on the nature of the base.[41] Thus, the reaction with LHMDS followed by the addition of chloroacetyl chloride affords enol chloroacetate **42**, which is readily hydrolyzed to give *C*-acylation product **43** in 77% yield; the latter compound can also be prepared (almost quantitatively) from the starting lactam with the use of the sterically more hindered base, *viz*., mesityllithium (LiMes).[42]



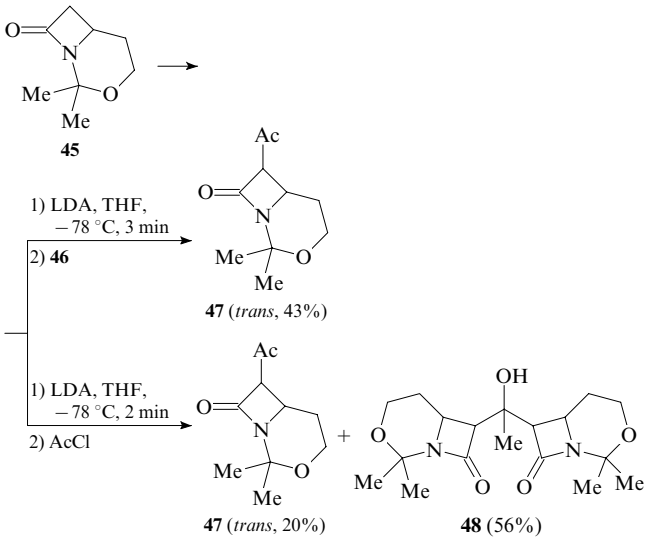
In some cases, the reactions with acyl halides give exclusively diacylation products. For example, bicyclic lactam **29** is transformed into product **44**.[43]



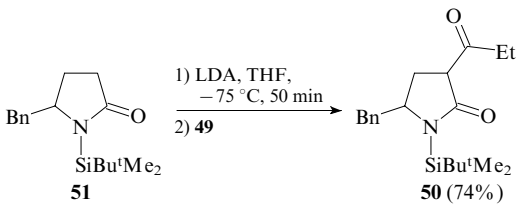
On the whole, the acylation of lactams with acyl halides and acid anhydrides is a convenient route to α-acyl lactams, but this reaction requires a thorough selection of the reaction conditions (the temperature, the solvent and the base).

c. Acylation with N-acylimidazoles and lactams

Due to the low electrophilicity of the carbonyl carbon atom in amides, these compounds have found wide use in the synthesis of acyl lactams, when substrates contain labile functional groups (in this case, the use of acid halides or esters leads to the formation of by-products). For example, the use of 1-acetylimidazole (**46**) as the acylating agent (instead of AcCl) in the reaction of lactam **45** made it possible to increase the yield of the target product **47** by a factor of two and avoid the formation of bis-derivative **48**.[44]

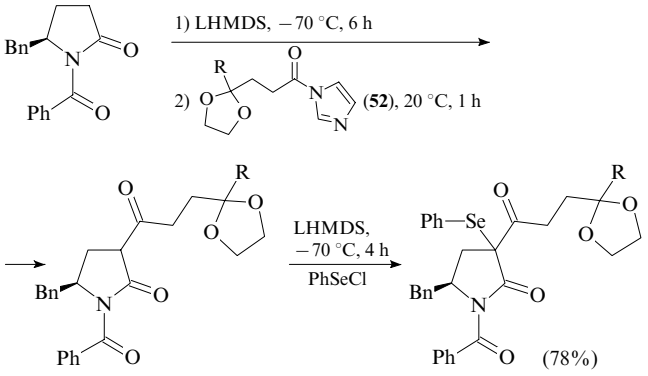


Acyl lactam **51** is readily generated from lactam **50** within 1 h in the reaction with 1-propylimidazole (**49**).[39]

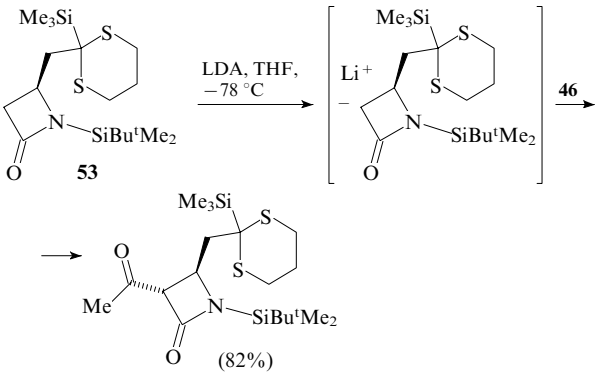


The carbonyl group in *N*-acylimidazole **52** and lactam **53** was protected with the dioxolane [45] and dithiane groups,

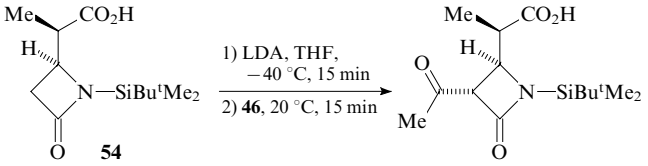
respectively, which are stable under mild acylation conditions of lactams (LHMDS in THF).[46]



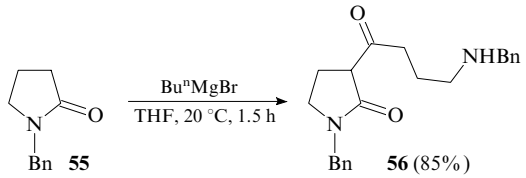
R is 2,8-dimethyldeca-4,6,8-trienyl.



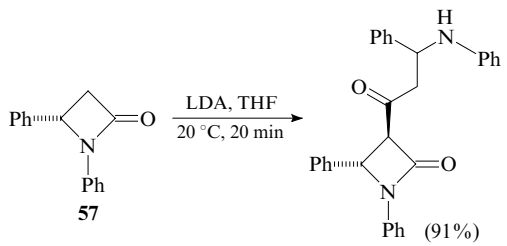
N-Acylimidazoles proved to be good acylating agents in the reactions with chiral lactams (for example, with four-membered lactam **54**).[47]



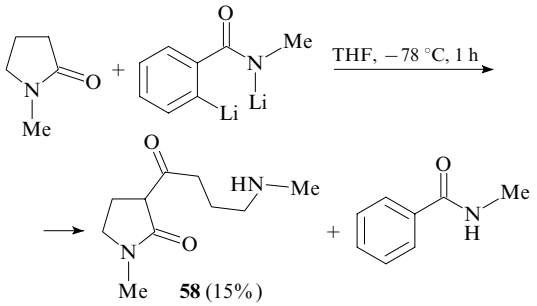
In the absence of acylating agents, the reaction of *N*-protected pyrrolidone **55** with Bu^nMgBr affords the self-condensation product, *viz*., α-acyl lactam **56**.[48]



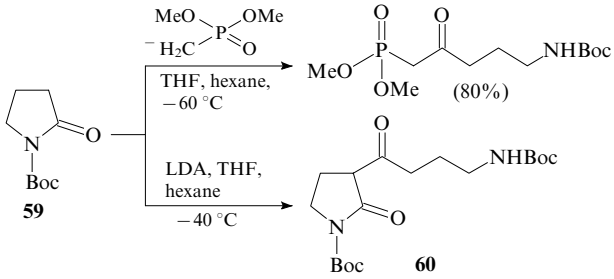
An analogous reaction was observed for four-membered lactam **57** under the action of LDA.[49]



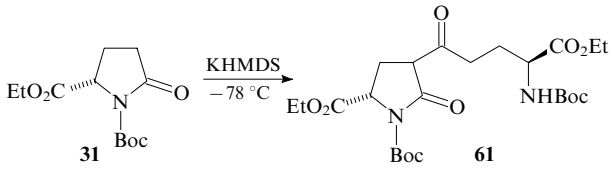
Upon the treatment of *N*-methylpyrrolidone with the lithium dianion of *N*-methylbenzamide, self-condensation product **58** was also isolated as the only product, whereas the target reaction (the addition of ArLi at the amide group) was not observed.[50]



In the study,[51] the reaction of the lithium salt of dimethyl methylphosphonate was compared with the competitive self-condensation of *N*-protected pyrrolidone **59**, and the latter (side) reaction giving rise to product **60** was demonstrated to proceed at −40 °C.



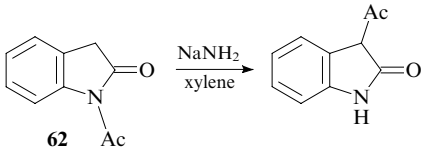
Pyroglutamic acid derivative **31** can also undergo self-condensation to form polyfunctional compound **61**, when the condensation is performed with KHMDS generating a more reactive enolate.[25]

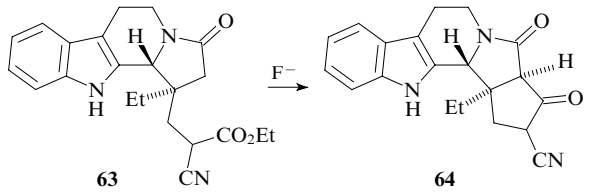


The use of amides, particularly those generated *in situ*, as acylating agents often makes it possible to avoid side reactions due to low reactivity of these compounds. As a result, these compounds are increasingly used in the synthesis. The self-condensation of lactams is a convenient preparative route to α-aminoalkylacyl lactams, which are difficult to synthesize by other methods.

d. Intramolecular acylation

Several examples of the intramolecular acylation of lactams, including the transfer of the acetyl group in indolin-2-one **62** (Ref. 52) and the Dieckmann condensation of β-carboline derivative **63** with fluoride ions giving rise to pentacyclic compound **64**,[53] were documented.

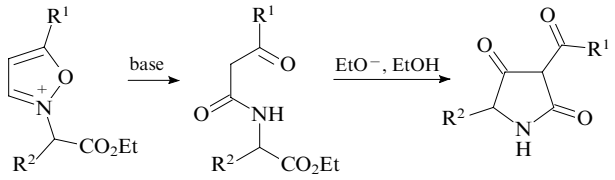




63 **64**

2. Synthesis of α-acyl lactams by cyclization

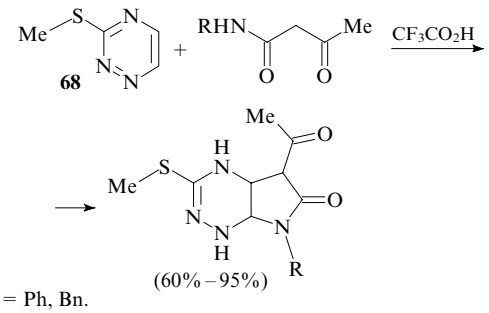
The transformation of isoxazolium salts **65** proceeds through the ring opening and ring formation; these salts can be cleaved under the action of difference bases (NaOH, Na_2CO_3) at room temperature, and the resulting unstable β-keto amides **66** undergo cyclization to form tetramic acid derivatives **67**.[54]



65 **66** (50% – 60%) **67** (55% – 65%)

R^1 = Me, Ph; R^2 = H, Me.

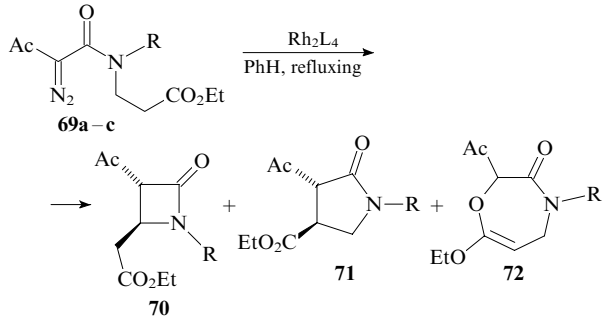
1,4-Diazine salts and 1,2,4-triazines add to *N*-substituted acetoacetamides to form fused α-acyl lactams.[55] An example is the reaction of triazine **68**.



(60% – 95%)

R = Ph, Bn.

Rhodium(II) salts are efficient catalysts for intramolecular cyclization of *N*,*N*-disubstituted diazoacetoacetamides **69a** – **c** giving rise to three possible cyclization products **70** – **72**.[56]

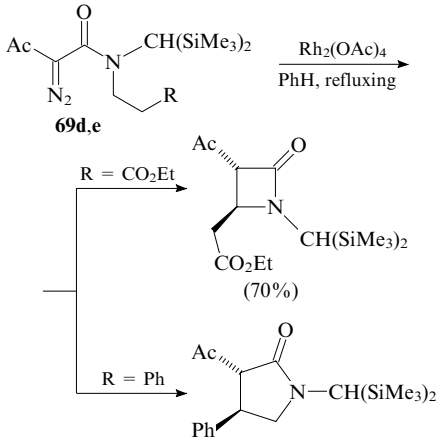


69a – **c** **70** **71** **72**

R = Bu^t (**a**), CH_2Bu^t (**b**), Bu^n (**c**).

Compound **69**	L	Yield (%)		
		70	**71**	**72**
a	AcO	96	0	0
b	$C_3F_7CO_2$	20	4	76
c	AcNH	14	71	15

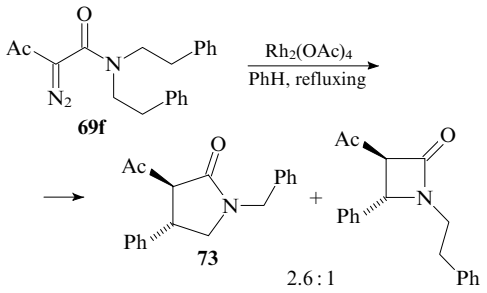
The *N*-bis(trimethylsilyl)methyl group controls the stereoselectivity of the insertion of carbene generated from diazoamides **69d**,**e** in the reactions with rhodium acetate. The reaction can afford both four- and five-membered acyl lactams depending on the structure of the starting amide.[57, 58]



69d,**e** (70%)

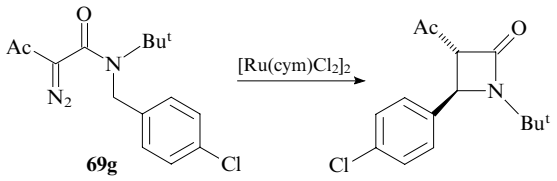
R = CO_2Et (**d**), Ph (**e**).

If the $CH(SiMe_3)_2$ group in compound **69e** is replaced with Bu^t, the reaction becomes nonselective and gives two lactams in a ratio of 1 : 1 (in a total yield of 94%).[59] The analogous formation of a mixture of lactams (in 73% yield) was observed for diphenethyl-substituted amide **69f**.[60] Five-membered lactam **73** was used for the synthesis of the antidepressant rolipram.



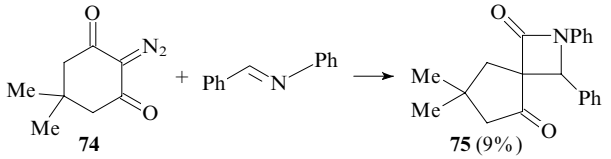
69f **73** 2.6 : 1

The stereoselective cyclization of diazoamide **69g** was performed in the presence of $[Ru(cym)Cl_2]_2$ (cym is *p*-cymol) as the catalyst. The reaction is stereospecific and proceeds with high yield (99%).[61] This transformation is catalyzed also by other ruthenium catalysts.[62]



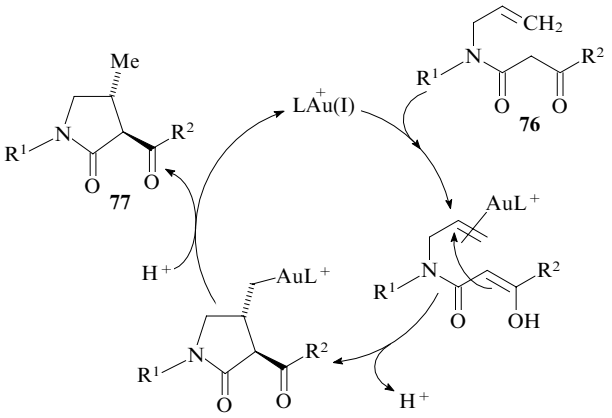
69g

The reaction of 2-diazodimedone (**74**) with benzylideneaniline affords four-membered acyl lactam **75**, though in low yield.[63]



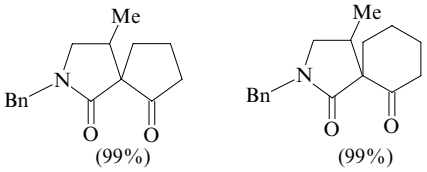
74 **75** (9%)

Recently, the cyclization of allylamides of keto acids **76** catalyzed by different transition metals has been documented. For example, the regioselective formation of five-membered acyl lactams **77** occurs under the action of gold(I) complexes (the [Au{PBu^t_2(*o*-biphenyl)}]Cl – AgOTf system) under mild conditions.[64] It should be noted that the cyclization is, as a rule, stereoselective and affords the target products in a nearly quantitative yield.

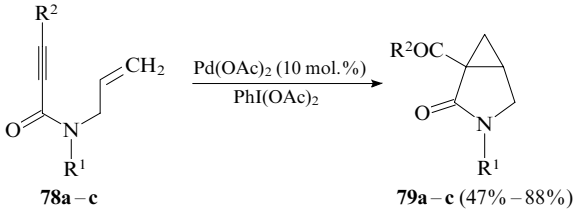


R^1	R^2	Yield **77** (%)
Bn	Me	99
Me	Me	94
Bn	Ph	99

Spirocyclic derivatives are generated also in high yields (as mixtures of diastereomers) from allylamides of cycloalkanonecarboxylic acids.

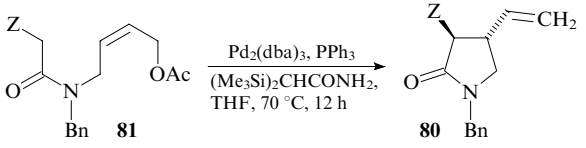


A somewhat different domino cyclization for 1,6-enynes **78** affords five-membered lactams **79** containing the cyclopropane fragment.[65,66]



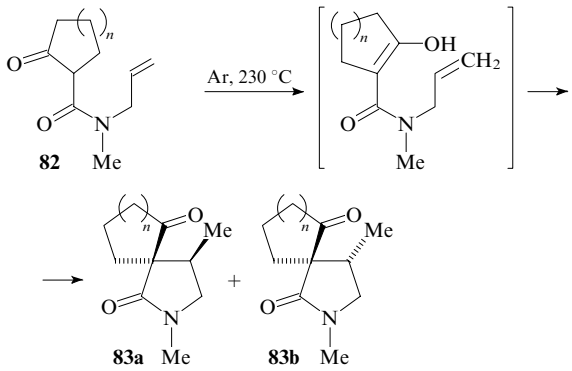
R^1 = Me, R^2 = Ph (**a**); R^1 = Ts: R^2 = Ph (**b**), Bu^n (**c**).

3,4-Disubstituted pyrrolidones **80** were synthesized by the intramolecular allylic alkylation of stable enolate anions of acetamides **81** containing the electron-withdrawing substituent Z. All reactions yield exclusively the *trans* stereoisomers.[67]



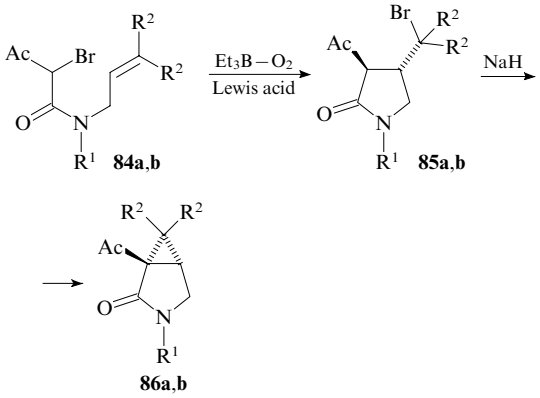
dba is dibenzylideneacetone; Z = Ac (77%), CN (70%), $PhSO_2$ (78%), $(EtO)_2PO$ (80%).

N-Allylamides of 2-oxocyclopentane- and cyclohexanecarboxylic acids **82** undergo the thermal rearrangement to form spirolactams **83a**,**b**; in both cases (*n* = 1, 2), a mixture of diastereomers (**83a** : **83b** = 9 : 1) was obtained.[68]



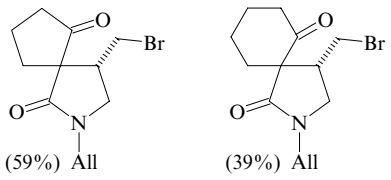
n = 1 (15%), 2 (57%).

A number of convenient methods were developed for the synthesis of various lactam derivatives based on the cyclization reactions due to a wide range of available starting acyclic compounds. For example, the radical cyclization of *N*-substituted allylamides of α-bromo keto acids **84** proceeds in the presence of the triethylborane – oxygen system and is catalyzed by different Lewis acids. In the case of $Yb(OTf)_3$ or $Mg(ClO_4)_2$, the reaction is *trans*-stereoselective and is accompanied by the closure of the five-membered ring of lactams **85**. The subsequent treatment of bromoalkyl derivatives **85** with bases affords bicyclic acyl lactams **86** containing the three-membered ring. The reaction of allylamide **84a** gives a mixture of products **85a** and **86a** in a total yield of 64% – 73% (depending on the nature of the Lewis acid) already in the first step.



R^1 = All, R^2 = H (**a**); R^1 = Bu^t, R^2 = Me (**b**).

If the starting keto acid amides contain the cyclic ketone moiety, the analogous cyclization affords spirolactams in rather high yields.

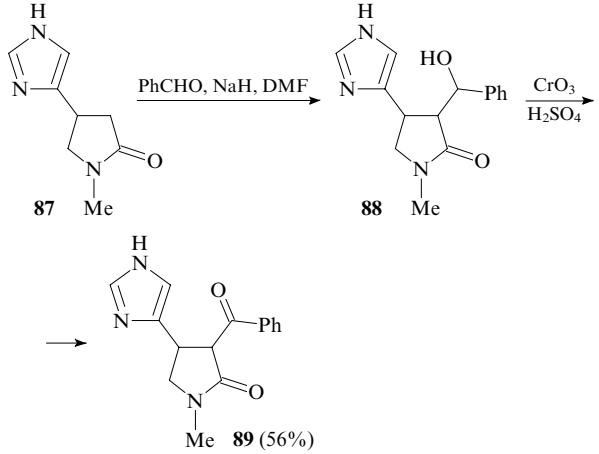


The above-described bicyclic lactams are very attractive as reactants for the design of physiologically active com-

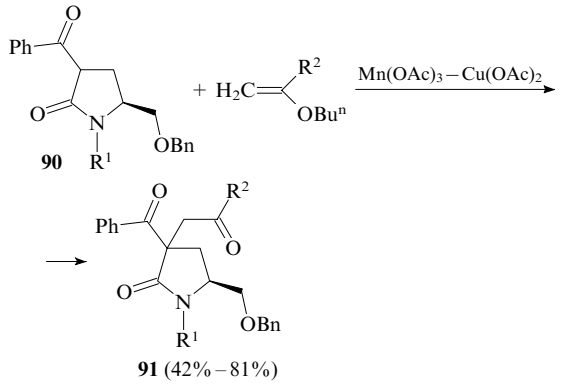
pounds because such structural fragments are involved in many natural compounds or drugs.[69]

3. Other methods for the synthesis of α-acyl lactams

The hydroxyalkylation of *N*-substituted lactam **87** with benzaldehyde followed by oxidation of product **88** with the Jones reagent afford the corresponding α-benzoyl lactam **89**.[70]

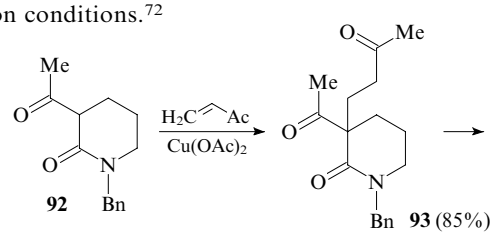


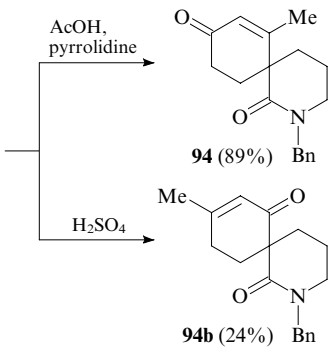
The alkylation of α-acyl lactams **90** with butyl vinyl ether in the presence of the manganese(III) acetate–copper acetate catalytic system gives substituted lactams **91** containing the quaternary carbon atom. The radical alkylation is diastereoselective, proceeds with high yield, and produces substituted pyrrolidones **91** containing two carbonyl groups.[71]



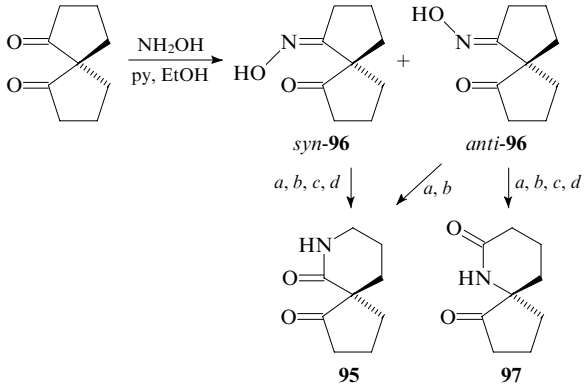
R^1 = Me, Bn; R^2 = H, Me, Ph.

The analogous alkylation of acyl lactam **92** was carried out with methyl vinyl ketone in the presence of copper acetate. The resulting diacyl lactam **93** undergoes condensation to spirocyclic lactams **94a**,**b** depending on the reaction conditions.[72]



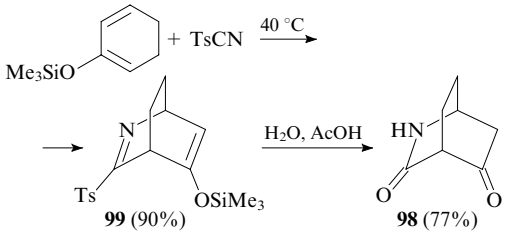


Chiral spirocyclic acyl lactam **95** was synthesized by the Beckman rearrangement from enantiomerically pure bicyclic oxime *syn*-**96**. Either lactam **97** isomeric to lactam **95** or a mixture of both isomeric compounds is formed from isomer *anti*-**96** depending on the reaction conditions. The optical purity of the products is retained.[73] The highest yields and selectivity were achieved in the reactions with PPA ethyl ester ($P_2O_5 + Et_2O$).

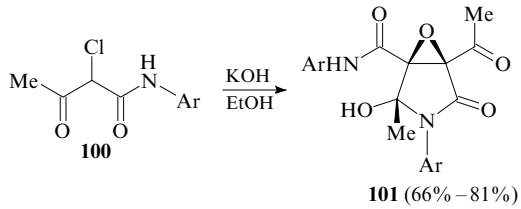


(*a*) polyphosphoric acid (PPA), 120 °C;
(*b*) P_2O_5 (8%) in $MeSO_3H$, 20 °C;
(*c*) $P_2O_5 + Et_2O$, PhH, 20 °C;
(*d*) PPA is trimethylsilyl ester PPA, PhH, 20 °C; py is pyridine.

Recently, bicyclic acyl lactam **98** has been synthesized by the hetero-Diels–Alder reaction of tosyl cyanide with cyclohexenone trimethylsilyl enol ether. The hydrolysis of adduct **99** that is formed *via* cycloaddition affords the target crystalline α-acyl lactam **98** in good yield.[74]



The unusual dimerization of α-chloroacetoacetanilides **100** in basic conditions gives polysubstituted acyl lactams **101** in high yields.[75]

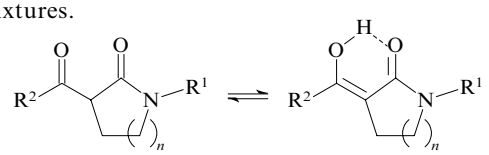


100 **101** (66% – 81%)

Ar = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-CNC_6H_4, 2,4-$Me_2C_6H_3$, 2,6-$Cl_2C_6H_3$.

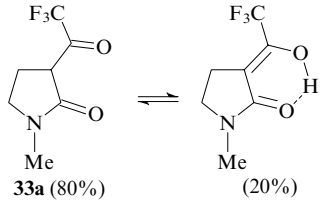
III. Keto – enol tautomerism of α-acyl lactams

The keto – enol tautomerism of 5 – 7-membered α-acyl lactams was studied by ^1H and ^{13}C NMR spectroscopy.[34] It was shown that six-membered α-acyl lactams exist predominantly in the enol form, in which the double bond is conjugated with the aromatic ring and the amide carbonyl group. The enol form can exist as *cis* and *trans* isomers. However, since the *cis* arrangement of the carbonyl group is stabilized by an intramolecular hydrogen bond, only one isomer exists, as confirmed by ^1H and ^{13}C NMR data. The dependence of the keto – enol tautomerism on the ring size and the nature of the acyl and protecting groups was investigated. No enol form was observed for seven-membered acyl lactams. For five-membered acyl lactams, enols are present as a minor tautomer. The enol formation depends primarily on the ring size of acyl lactams and the electron-withdrawing properties of the acyl substituent. Apparently, the formation of a new six-membered ring with the involvement of the enolic hydrogen causes the least distortion of the geometry of α-acyl lactams in the case of six-membered piperidin-2-ones. The tautomeric equilibrium is less effected by the substituent at the nitrogen atom of α-acyl lactam; the polar electron-withdrawing groups increase the fraction of the enol form in the reaction mixtures.



R^1 = H, Me, CH=CH_2, CHO, $CH(OEt)_2$; R^2 = Alk, Ar; n = 1, 2.

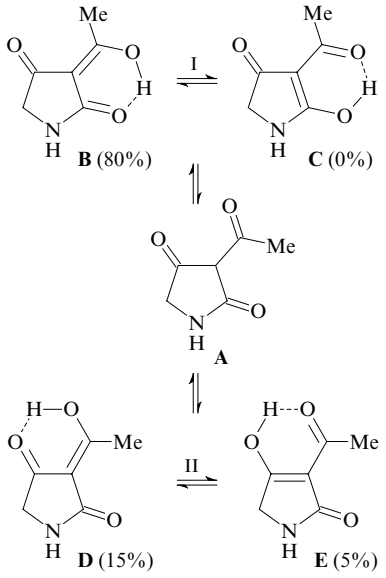
Earlier, the keto – enol tautomerism has been studied for *N*-methyl-3-trifluoroacetylpyrrolidin-2-one (**33a**)[26] and *N*-substituted α-acetoacetylvalerolactam (**37**) (see Section II.1.a).[33] In this case, the existence of enol form is attributed to the presence of the strong electron-withdrawing CF_3 group and the 1,3,5-tricarbonyl system, respectively.



33a (80%) (20%)

This equilibrium was studied in more detail for 3-acetylpyrrolidine-2,4-dione (Scheme 1).[76, 77] Semiempirical quantum chemical calculations (AM1 method) showed that, according to the heats of formation, the tautomer **B** is more stable than the tautomer **D**, the tautomers **C** and **E** being even less stable.[78] These results are in good agreement with the experimental data presented in Scheme 1. The tautomer **A** is postulated only as the transition state between two rapid equilibria (I and II).

Scheme 1



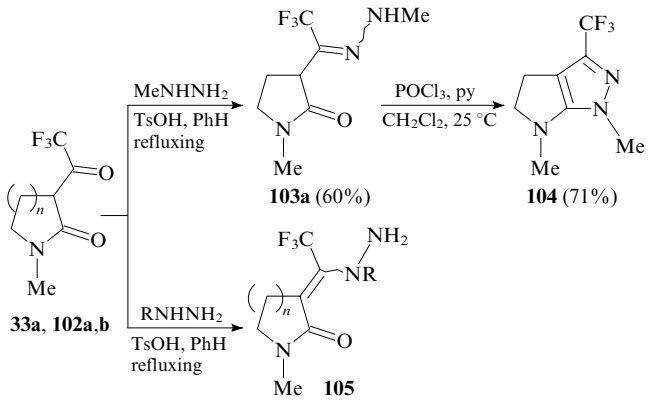
B (80%) **C** (0%) **A** **D** (15%) **E** (5%)

IV. Synthetic application of α-acyl lactams

1. Reactions of acyl lactams with binucleophiles. Synthesis of aminoalkyl-substituted heterocycles

The carbonyl groups in the 1,3-dicarbonyl system of α-acyl lactams strongly differ in the reactivity, which opens possibilities for chemo- and regioselective heterocyclizations of asymmetric binucleophiles. It should be noted that the reactions of α-acyl lactams with binucleophiles afford various heterocyclic derivatives containing an aminoalkyl substituent, due to which these compounds are very attractive for studying the physiological activity and designing new drugs.

The reactions of lactams **33a** and **102a**,**b** with hydrazine derivatives were documented. It should be noted that hydrazone **103a** was subjected to cyclization with $POCl_3$ resulting in the formation of pyrazole **104** in high yield.[27] In the case of R = H, Ph, n = 1 – 3 or R = Me, n = 2, 3, the products were obtained as ene hydrazines **105**, and attempts to perform cyclization of the latter compounds failed.

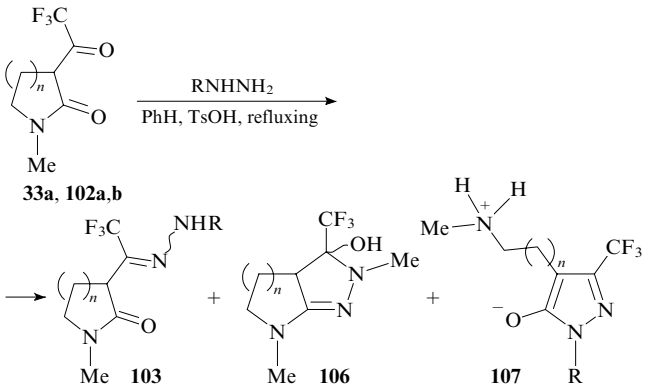


33a, **102a**,**b** **103a** (60%) **104** (71%) **105**

n = 1 (**33a**), 2 (**102a**), 3 (**102b**); R = H; n = 1 – 3; R = Me, n = 2, 3; R = Ph, n = 1 (46% – 74%).

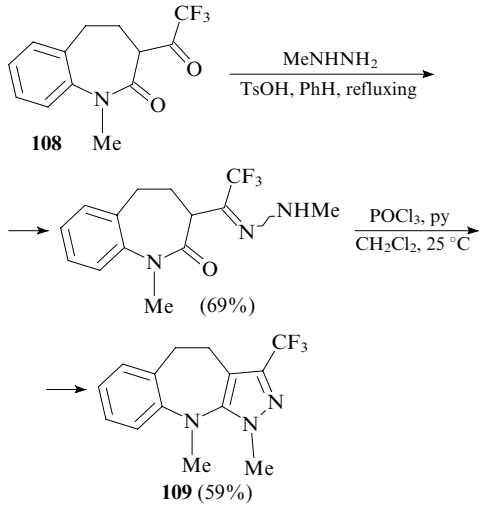
More recently, these authors have comprehensively studied the compositions of the heterocyclization products

of acyl lactams **33a** and **102a**,**b** depending on the nature of hydrazines.[79] It appeared that hydrazone **103** is easily formed only for R = H, $n = 1$ (in 74% yield). For R = Me, $n = 1$, hydrazone **103a** can be isolated (in 60% yield) by chromatographic separation instead of distillation; compound **106** (as a mixture of diastereomers) was simultaneously produced in ~4% yield. In other cases, the cleavage products of the starting ring **107** were obtained. All attempts to subject hydroxypyrazoles **107** to cyclization giving rise to pyrrolinopyrazoles ($POCl_3$, $SOCl_2$ and PPA in the presence of pyridine) failed.

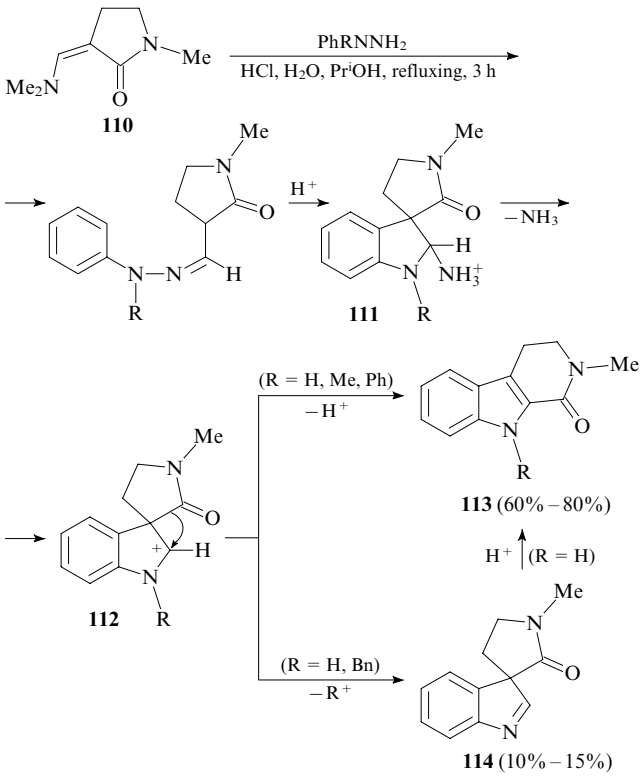


R	*n*	Yield of **107** (%)	R	*n*	Yield of **107** (%)
H	1	0	Me	2	73
Me	1	72	H	2	59
Ph	1	67	H	3	73

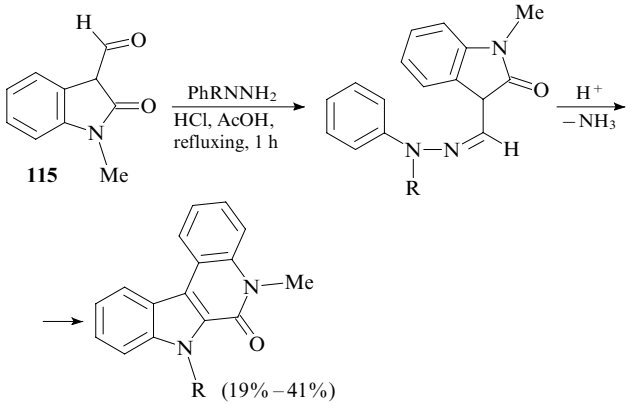
The reaction of seven-membered acyl lactam **108** with $MeNHNH_2$ also results in the heterocyclization giving pyrazole **109**.[27]



Unexpected results were obtained in the study of the reaction of *N*-methyl-3-formylpyrrolidone enamine **110** with various arylhydrazines. The Fischer reaction initially affords cation **111**, from which NH_3 is eliminated to give spiroindoline cation **112**. The latter is stabilized *via* the H^+ elimination followed by the migration of one of the bonds in the spirolactam. It was shown that the amide moiety of lactams migrates to form tetrahydro-β-carbolines **113**.[80] In the case of R = Bn, $PhCH_2^+$ is also partially eliminated from cation **112**. The resulting indolenine **114** is rearranged into *N*-unsubstituted tetrahydro-β-carboline **113**.

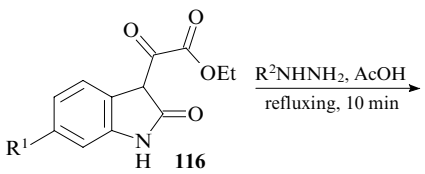


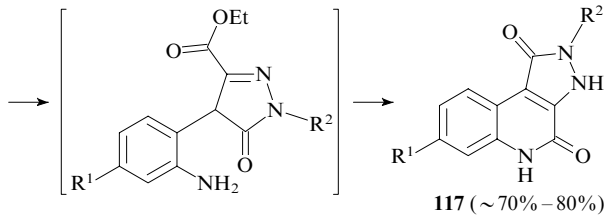
The reaction of indolin-2-one **115** with arylhydrazines proceeds analogously but under more drastic conditions and with lower yields. In the authors' opinion, this is associated with the fact the ring expansion of oxindole having a degree of aromaticity is more difficult to perform compared to the lactam ring.[81]



R = H, Me, Ph.

Acyl lactams based on indolin-2-one **116** were also used in the heterocyclization to synthesize pyrazoloquinoline derivatives **117**.[82]

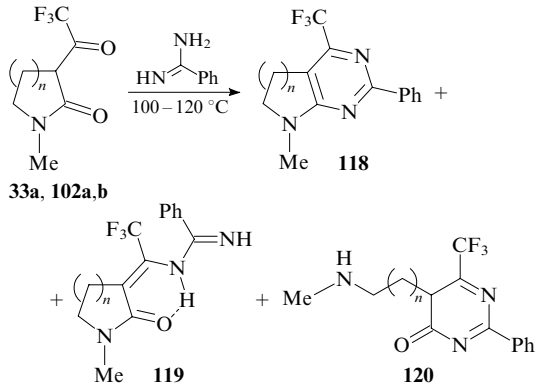




117 (~70%–80%)

R^1 = H, Cl; R^2 = Me, Ph, Bn.

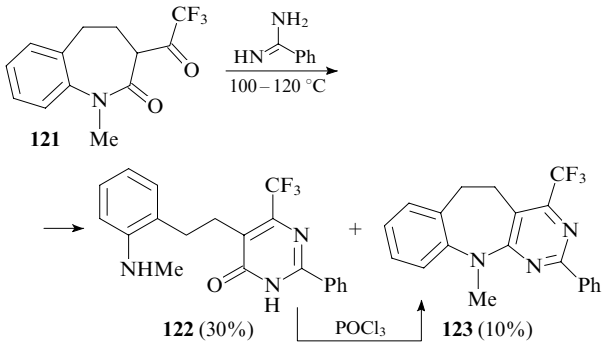
The heating of benzamidine with five-, six- and seven-membered α-trifluoroacetyl lactams leads to heterocyclization, the yields of product **118** in the reactions with five-membered acyl lactams being lower than those in the case of six-membered lactams.[83] The reaction is accompanied by the formation of by-products **119** and **120**. Attempts to perform the analogous reactions with thiourea or acetamidine failed. The replacement of the trifluoromethyl group with the phenyl or 4-(trifluoromethyl)phenyl group results in the formation of a mixture of products in low total yield (~5%).



33a, **102a**,**b**

n	Yield (%)		
	118	**119**	**120**
1	14	3	0
2	40	0	0
3	0	31	41

For seven-membered benzolactam **121**, the heterocyclization accompanied by the ring opening is a preferred reaction. The resulting pyrimidin-4-one **122** was transformed into product **123** in 70% yield by refluxing in excess $POCl_3$.

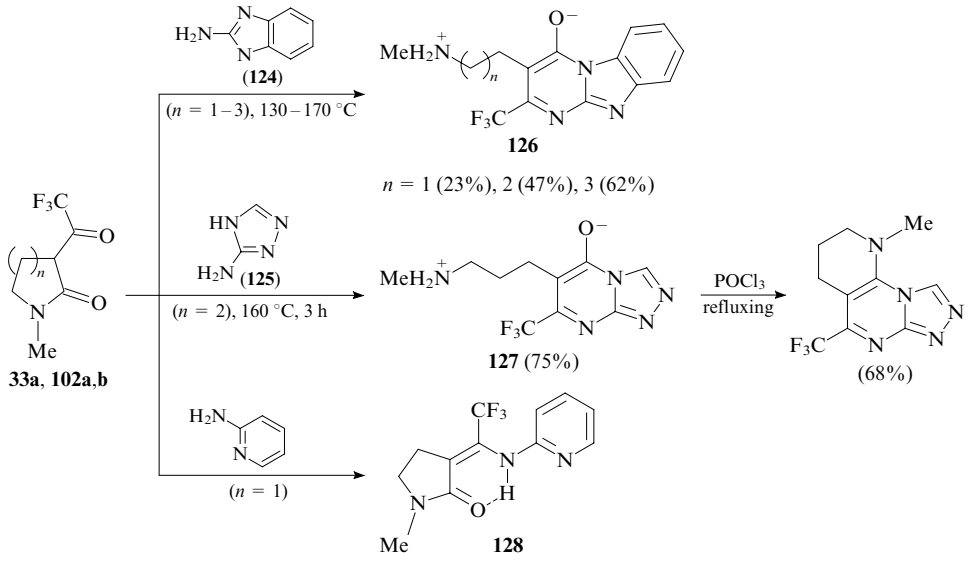


The use of 2-aminoazoles **124** and **125** as 1,3-binucleophiles allows the synthesis of fused heterocycles **126** and **127** containing an aminoalkyl group. The reaction of 2-aminopyridine affords the corresponding enamine **128** as the only product. It should be noted that compound **127** can be subjected to cyclization by refluxing in $POCl_3$, whereas products **126** did not undergo cyclization (Scheme 2).[84]

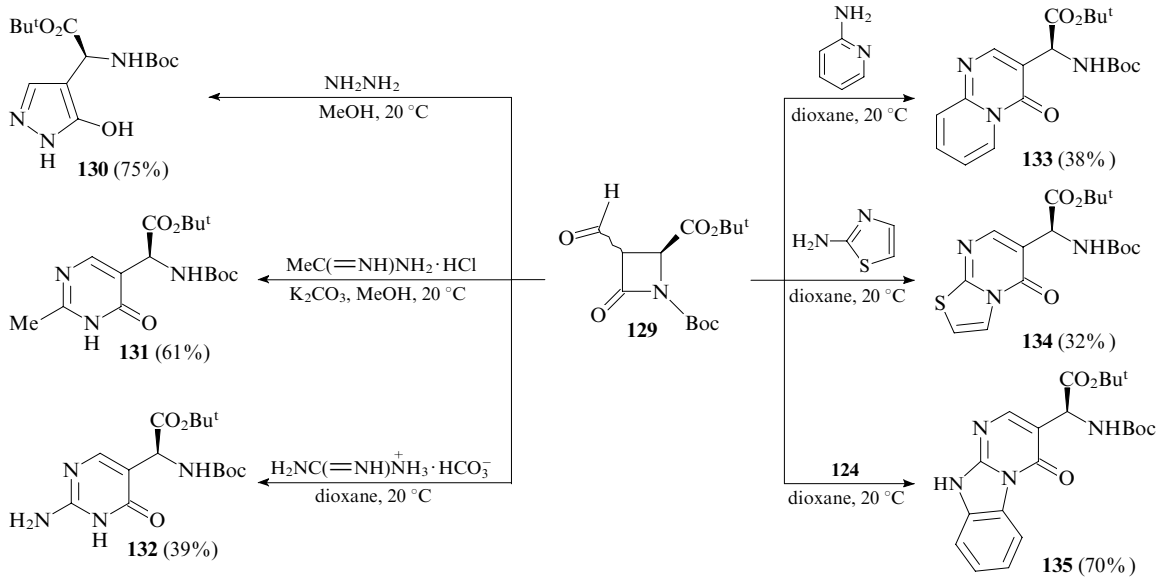
Four-membered lactam **129** regioselectively reacts with a wide range of 1,2- and 1,3-N,N-binucleophiles as a 1,3-dicarbonyl compound at the formyl and amide groups with retention of chirality. This reaction was used to synthesize hetaryl-substituted L-glycines **130**–**135** protected at the amino and carboxy groups. However, the reactions with hydroxylamine afford complex mixtures of compounds (Scheme 3).[85]

A universal approach to the synthesis of aminoalkyl derivatives of pyrazole and oxazole based on the reaction of α-acyl lactams with different binucleophiles was developed in the study.[86] To investigate the influence of the nature of the acyl and protecting groups on the course of the reaction, 5–7-membered α-acyl lactams **136** containing aromatic, heteroaromatic, aliphatic, sterically hindered and cage acyl groups were used. The reaction with hydrazine proceeds under mild conditions to give 5-substituted 4-aminoalkylpyrazol-3-ones **137** in virtually quantitative yield. The reaction has a general character. Thus, the nature of the

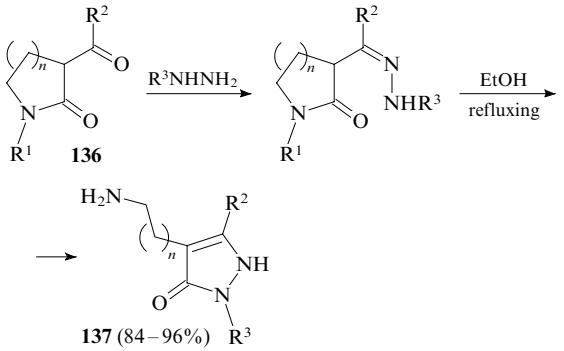
Scheme 2



Scheme 3

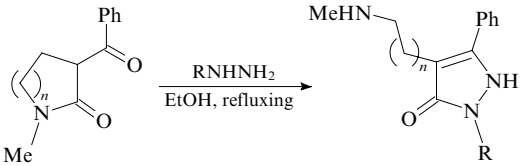


acyl group and the ring size of acyl lactam have no effect on the yield and the reaction pathway. In all cases, the protecting group R^1 at the nitrogen atom is completely removed in the course of the reaction. To examine the general character of heterocyclization of acyl lactams, other nucleophiles, such as semicarbazide, thiosemicarbazide and aminoguanidine (which are 1,2-, 1,3- and 1,4-binucleophiles) were used. In all cases, the reactions afforded compounds corresponding to the 1,2-binucleophilic character of the reagents.



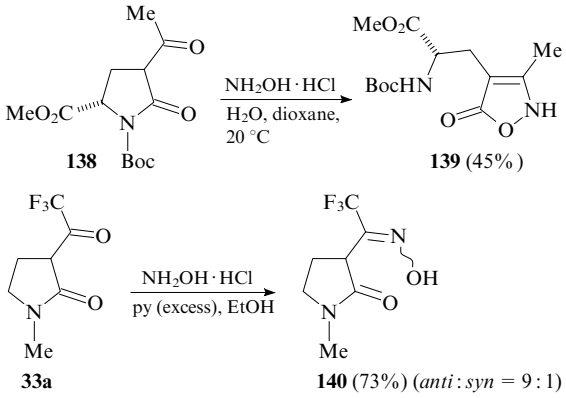
R^1 = CH=CH_2 (n = 1, 3), $CH(OEt)_2$ (n = 2); R^2 = Ar, Het, Alk, 1-Ad, Cy; R^3 = $NHNH_2$, $C(O)NH_2$, $C(=S)NH_2$, $C(=NH)NH_2$; Ad is adamantyl.

N-Methylated α-acyl lactams react analogously with hydrazine and phenylhydrazine to give *N*-methyl derivatives of substituted pyrazoles.

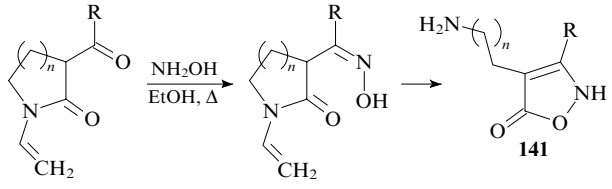


R = Ph (n = 1, 88%), H (n = 2, 92%).

The reaction of α-acyl lactam **138** with hydroxylamine was used for the synthesis of analogues of new antifungal antibiotic **139**.[87] The treatment of lactam **33a** with hydroxylamine affords exclusively oxime **140**.[30] Attempts to perform heterocyclization giving rise to isoxazole derivatives failed.



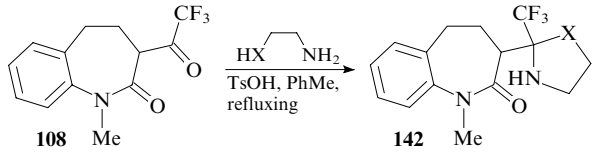
The reactions of α-acyl lactams with hydroxylamine were investigated in more detail in the studies.[86] It was found that the ring size and particularly the nature of the acyl group in lactams strongly influence the yield and the heterocyclization pathway. Thus, for compounds with R = 3-Py or 4-Py (Py is pyridyl), the reaction affords isoxazoles **141**, whereas the conditions of heterocyclization were not found for compounds with R = 2-Py or pyrazinyl. The reactions using *N*-methylated lactams do not give isoxazoles as well; instead, oximes are formed as the final products.



n = 1: R = Ph, 3-BrC_6H_4, 3-Py, 4-Py (61%–89%); n = 3, R = Ph (35%).

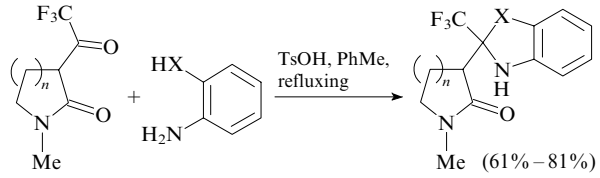
Investigations of the reactions of seven-membered α-trifluoroacetyl lactam **108** with 2-aminoethanol and ethylenediamine showed that these reactions are accompanied by the closure of the saturated five-membered heterocycles to form products **142**.[88,89] As part of continuing research on

the heterocyclization, the authors performed the reactions of various lactams with *o*-aminophenol and *o*-aminothiophenol.[90] In all cases, the cyclization occurred only at the acyl group.



108 **142**

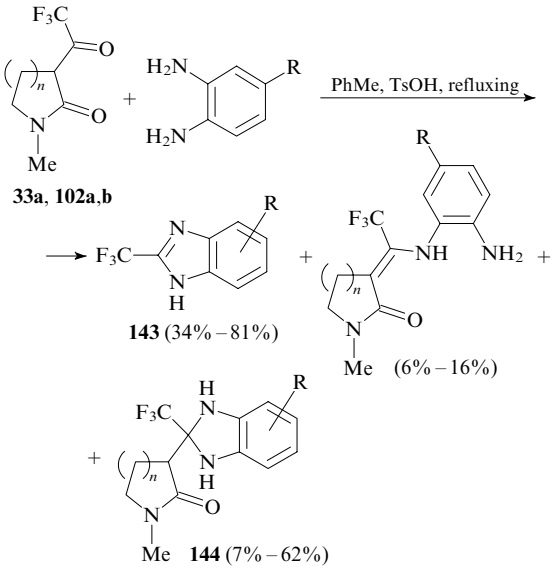
X = NH (76%), O (65%).



33a, **102a**,**b**

X = O, S.

The use of substituted *o*-phenylenediamines results in deacylation of acyl lactams and the formation of benzimidazoles **143**. However, the reactions of phenylenediamines containing electron-withdrawing substituents (Cl, COPh, NO_2) give the corresponding benzimidazolines **144** as the major product.



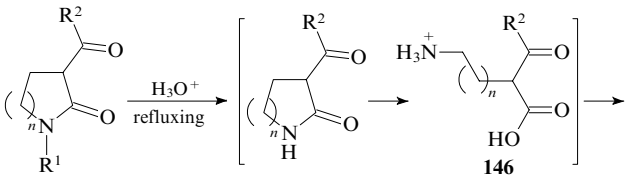
33a, **102a**,**b**

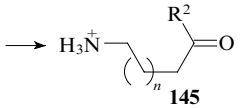
R = H, Me, PhCO, Cl, NO_2; n = 1–3.

2. Synthesis of amino ketones and cyclic imines and their reactions

a. Synthesis and cyclization of amino ketones

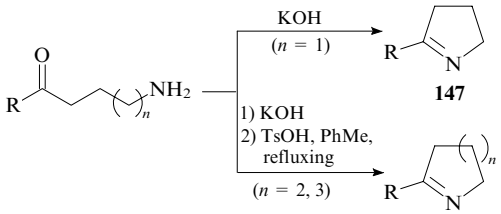
The hydrolysis accompanied by decarboxylation is one of most widely used reactions of α-acyl lactams. These reactions afford amino ketones **145**, which can be transformed into 2-substituted cyclic imines.[13, 17]





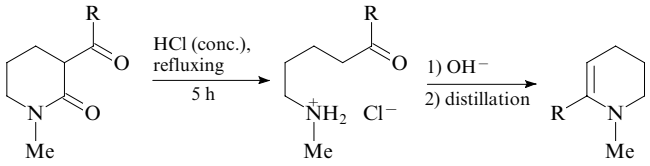
R^1 is the protecting group; R^2 = Alk, Ar, Het.

The reactions proceed successively through the deprotection under acid catalysis and the subsequent hydrolysis of lactams to α-acyl-ω-amino acids **146**. The further heating leads to decarboxylation of acids **146**, giving salts of amino ketones **145**.[91] The treatment of the latter compounds with strong bases either directly affords cyclic imines **147** (in the case of five-membered lactams) or gives mixtures of an amino ketone and a cyclic imine, which can be completely transformed into cyclic imines.



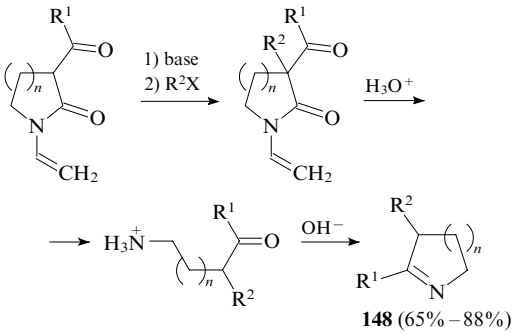
R = Alk, Ar, Het.

If the deprotection of the nitrogen group does not occur under the reaction conditions, the decarboxylation of lactams affords 2-substituted tetrahydropyridines.[92]



R = 3-Py (76%), 4-Py (90%).

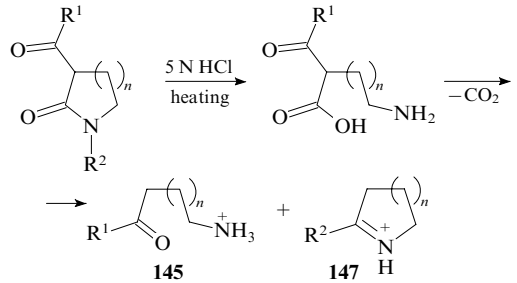
An important advantage of the synthesis of amino ketones from α-acyl lactams is that it can give 2,3-disubstituted cyclic imines **148** by the cleavage of alkylated acyl lactams. This method produces the target compounds in good yields, readily available lactams and esters are used as the starting compounds, and the products can easily be isolated from the reaction mixture. However, the substrates containing substituents unstable in an acidic medium (for example, phenoxy, benzyloxy, furyl and cyclopropyl groups) cannot be used for the synthesis of cyclic amines according to this method.[13, 93]



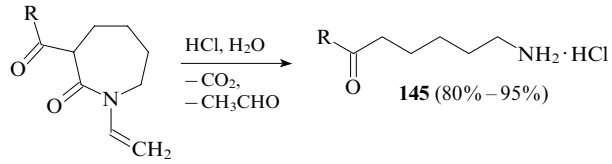
R^1 = Alk, Ar; R^2 = Me, Et, Bn; n = 1–3.

α-Acyl lactams are convenient precursors for aminocarbonyl compounds. As demonstrated by NMR spectroscopy,[94] the hydrolysis of five-membered α-acyl lactams

affords cyclic imine hydrochlorides containing amino ketones as an impurity; in the case of six-membered lactams, the linear and cyclic forms are obtained in approximately equal amounts. At the same time, the reactions of seven-membered acyl lactams give pure amino ketone hydrochlorides in high yields.

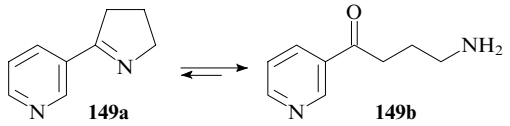


R^1 = Ph, 4-$MeOC_6H_4$, Bn, Et, 3-Py, 4-Py;
R^2 = CH═CH_2, CHO; n = 1, 2.

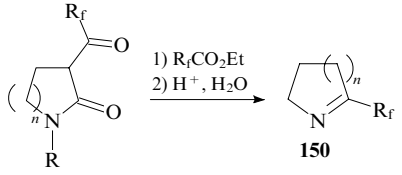


R = Ph, 4-$MeOC_6H_4$, Bn, Et, 3-Py, 4-Py.

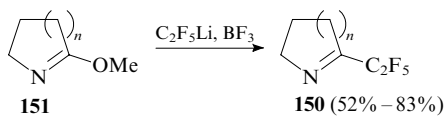
The character of the reactivity of aminocarbonyl compounds depends on the form (cyclic imine or amino ketone) in which they exist. Thus, myosmine (**149**) reacts with hydrazine and hydroxylamine in aqueous solutions as amino ketone **149b**.[95] The detailed ^1H and ^{13}C NMR investigation of the equilibrium depending on the pH value of the medium[96,97] showed that the amino ketone–cyclic imine equilibrium is shifted to the cyclic form under neutral conditions, and this equilibrium is shifted to the acyclic form only in a strongly acidic medium.



Cyclic imines **150** containing the perfluorinated substituent (R_f) in the α position have promise as reagents for the synthesis of compounds containing several pharmacophoric moieties. Some such derivatives were synthesized from perfluoroacyl-substituted lactams. The addition of pentafluoroethyllithium to cyclic imidates **151** was used as an alternative route to pentafluoroethyl derivatives.[98–100]



R = CH═CH_2, CH(CO_2Et), $SiMe_3$; R_f = CF_3, C_2F_5; n = 1–3.



n = 1–3.

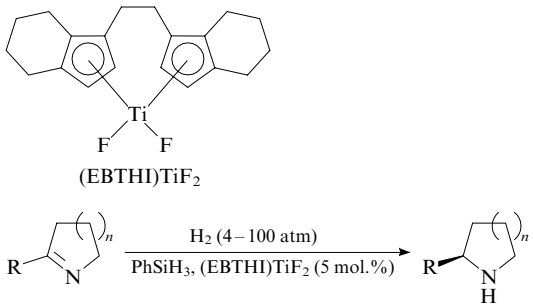
Imines are analogues of carbonyl compounds due to which they have similar chemical properties. The nucleophilic and electrophilic addition, cycloaddition and reduction are the most typical reactions of imines.

b. Synthesis of cyclic amine derivatives

Since the pyrrolidine and piperidine rings are involved in many physiologically active compounds and alkaloids (nicotine, anabasine, coniine), a large number of methods were developed for the reduction of cyclic imines. The reduction of cyclic imines to amines with complex hydrides is the most commonly used laboratory method. Cyclic amines can be synthesized in good yields by reducing imines with sodium cyanoborohydride in methanol or with sodium borohydride in a methanol–acetic acid mixture (4 : 1),[101] ethanol,[102] methanol,[103] acetic acid,[104] water or a dioxane–water mixture.[105] Diisobutylaluminium hydride[104] and lithium aluminium hydride in diethyl ester[106,107] also reduce cyclic imines to amines.

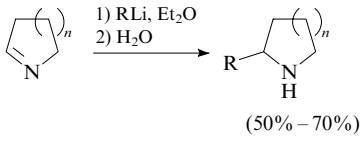
The catalytic hydrogenation of cyclic imines to amines is free of many drawbacks typical of the reduction with complex hydrides. Imines were transformed into amines under a hydrogen pressure from 1 to 20 atm with the use of platinum oxide in acetic acid,[108] palladium on carbon in 10% hydrochloric acid[104] or Raney nickel in ethanol.[107]

Since the modern medical chemistry and pharmacology constantly require enantiomerically pure organic compounds, several methods were developed for the asymmetric reduction of cyclic imines to chiral amines. The best results were obtained with the use of ethylene[bis(tetrahydroindenyl)]titanocene derivatives, for example, of (EBTHI)TiF_2, as the catalyst;[109–111] 2-substituted 5–7-membered cyclic amines were synthesized in good yields with an enantiomerical purity of 99%.



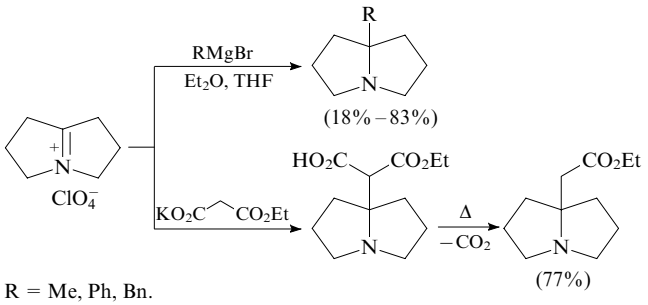
R = Alk, Ar, Het, Bn; n = 1–3.

Organolithium compounds readily add to pyrrolines and piperidines.[112] This reaction is an important method for the synthesis of cyclic amine derivatives.



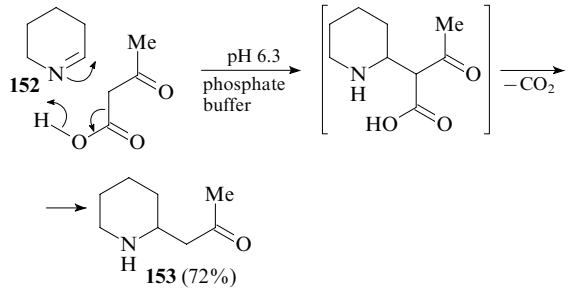
R = Ph, Py, Bu^n, Bu^t; n = 1, 2.

Grignard reagents and CH-acids add to cyclic imines and bicyclic iminium salts.[113]

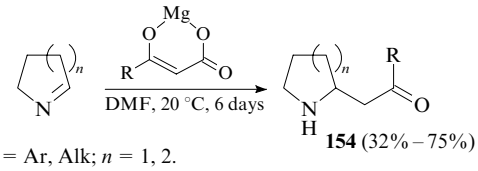


R = Me, Ph, Bn.

The treatment of piperidine (**152**) with acetoacetic acid affords isopelletierine (**153**).[114]

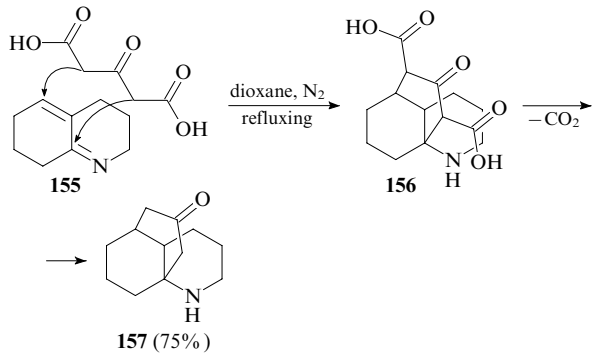


The reactions of magnesium enolates of acylacetic acids with 2-unsubstituted cyclic imines give amino ketones **154**.[115]

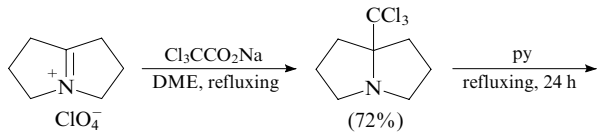


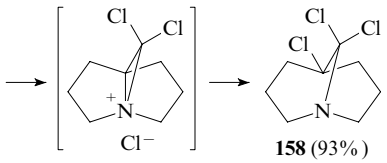
R = Ar, Alk; n = 1, 2.

Like α,β-unsaturated carbonyl systems, conjugated imines **155** are involved in the 1,3-addition reactions to form cage structures **156** and **157**.[116]

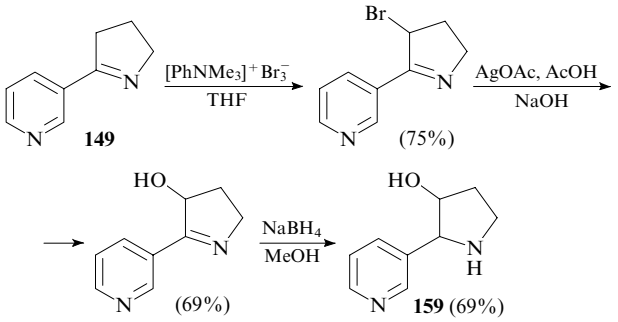


The addition of the trichloromethyl anion, which is generated *in situ* by refluxing sodium trichloroacetate in 1,2-dimethoxyethane (DME), to the bicyclic iminium salt was documented.[117] Successive transformations of the addition product afford bicyclic compound **158**.

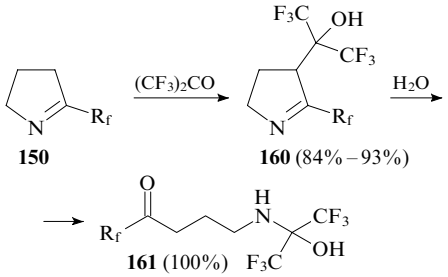




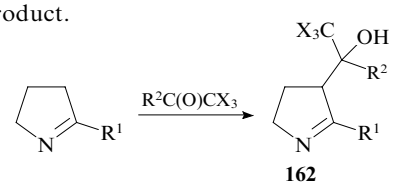
The reaction of myosmine (**149**) with trimethylanilinium tribromide produces 3′-bromomyosmine, which can be transformed into 3′-hydromyosmine; the reduction of the latter gives 3-hydroxynornicotine (**159**).[103]



Cyclic imines **150** containing the perfluoroalkyl substituent react with activated carbonyl compounds bearing the trifluoromethyl or trichloromethyl group (hexafluoroacetone, chloral or methyl trifluoropyruvate) under mild conditions (in the absence of catalysts and without heating). The reaction proceeds as the aldol condensation and affords imino alcohols **160**. After the treatment with water, the products of the reaction with hexafluoroacetone undergo the ring opening to form hemiaminals **161**.[118]

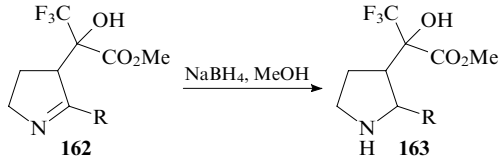


Analogous condensation products **162** are generated in the reactions of cyclic imines with chloral and methyl trifluoropyruvate. It should be noted that these reactions are highly diastereoselective (*de* up to 97%). The thermodynamically more stable diastereomer of alcohol **162** having the *syn*-(*erythro*) configuration is formed as the major product.

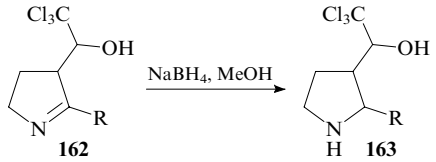


R^1	Yield (%)	*de* (%)	R^1	Yield (%)	*de* (%)
R^2 = CO_2Me, X = F			R^2 = H, X = Cl.		
Bu^t	71	94	Bu^t	69	96
Ph	81	89	Ph	87	92
4-MeC_6H_4	90	90	4-MeC_6H_4	85	94
4-$MeOC_6H_4$	89	93	4-$MeOC_6H_4$	85	95
4-FC_6H_4	92	74	4-FC_6H_4	84	80
2-Furyl	78	94	2-Furyl	75	97
4-Py	91	88	4-Py	90	90

Imino alcohols **162** are precursors of substituted pyrrolidines **163** containing an alcoholic moiety in the β position. The reduction with sodium borohydride in methanol affords compounds **163** with moderate diastereoselectivity.



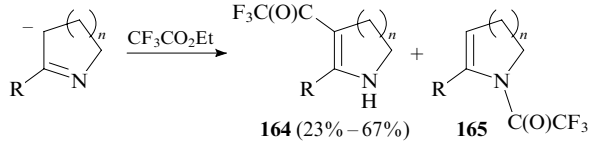
R	Yield (%)	*trans*-**163**, %
4-$MeOC_6H_4$	82	57
4-FC_6H_4	87	82
2-Furyl	80	78



R	Yield (%)	*trans*-**163**, %
4-$MeOC_6H_4$	89	71
4-FC_6H_4	91	70
2-Furyl	89	72
4-Py	67	88

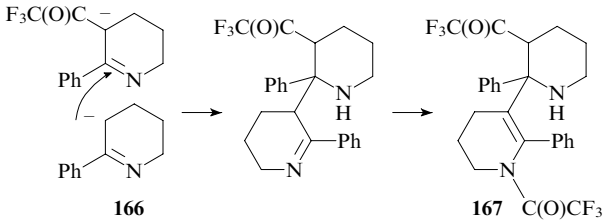
c. Synthesis of enamino ketones and heterocyclizations based on these compounds

Studies of the trifluoroacetylation of cyclic imines showed [119] that the treatment with two equivalents of trifluoroacetic anhydride in the presence of pyridine affords only *N*-trifluoroacetyl derivatives,[120] whereas the further *C*-trifluoroacetylation does not occur due apparently to the strong electron-withdrawing properties of the CF_3CO group, resulting in a substantial decrease in the nucleophilicity of the double bond. However, an alternative one-step approach based on the trifluoroacetylation of alkali metal enamides [121] gives *C*-trifluoroacetyl derivatives of cyclic imines.[119] The trifluoroacetylation of lithium enamide affords a mixture of the *C*- and *N*-trifluoroacetylation products (**164** and **165**) in a ratio of 9 : 1. An impurity of *N*-trifluoroacetyl derivative **165** can easily be separated. It is necessary to use two equivalents of the metallating agent; otherwise, the yield of the reaction product is at most 35% – 40%. The reason is that the aminoenone that is formed upon trifluoroacetylation is more acidic than the starting imine and, consequently, it protonates enamides thus removing them from the reaction zone.

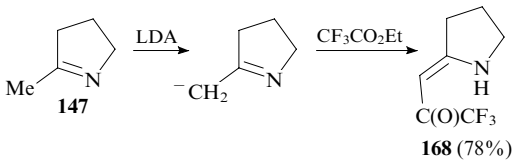


R = Ar, Bu^n; *n* = 1 – 3.

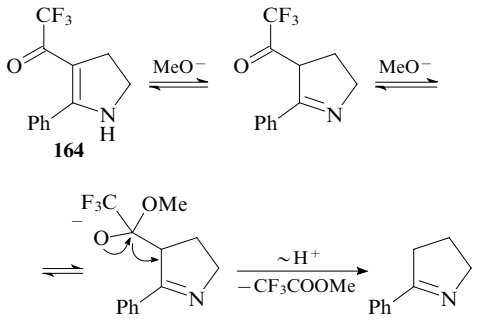
The trifluoroacetylation of six-membered imine **166** affords by-product **167** (up to 25%). The reaction performed in a more dilute solution results in an increase in the yield of the target product **164** to 67%.



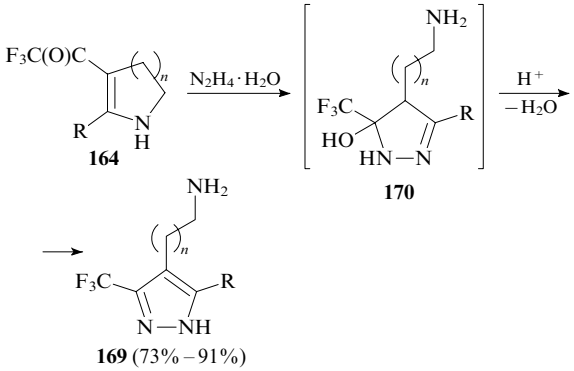
It should be noted that the trifluoroacetylation of imine **147** (R = Me) proceeds at the methyl group and gives enamino ketone **168** in 78% yield.



Under the action of sodium methoxide in methanol, the trifluoroacetyl derivative of enamine **164** easily undergoes *C*-deacylation to the corresponding imine.

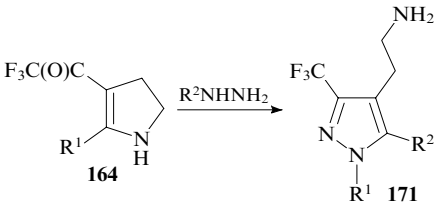


β-Trifluoroacetyl enamines **164** were used in the reactions with hydrazine and hydroxylamine to synthesize pyrazoles and isoxazoles containing the trifluoromethyl group and an aminoalkyl moiety. These compounds are of interest for organic and medical chemistry because of their high biological activity.[122, 123] The reactions of amino enones **164** with hydrazine give the corresponding pyrazoles **169** through the intermediate formation of pyrazolines **170**. The treatment of the reaction mixture with acids affords the target pyrazoles as the only product.



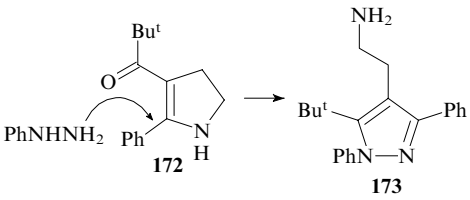
R = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$; *n* = 1 – 3.

In spite of the presence of two electrophilic centres in amino enone **164** (*n* = 1), the reaction with substituted hydrazines produces only one isomer of pyrazole **171** corresponding to the addition of arylhydrazine at the trifluoroacetyl moiety of the molecule.[119]

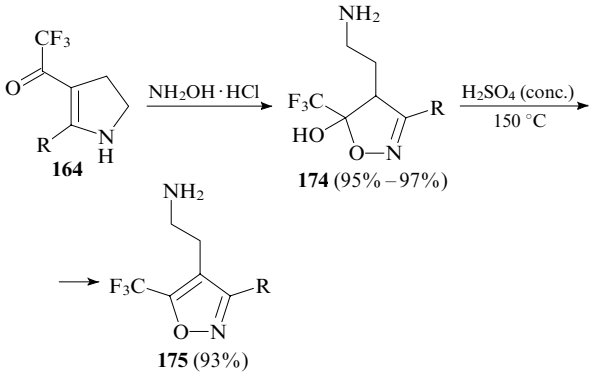


R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
Ph	Ph	85	Ph	benzodi-oxan-6-yl	92
Ph	4-BrC_6H_4	90			
Ph	3-ClC_6H_4	92	4-$Me_2NC_6H_4$	Ph	90
Ph	3-$CF_3C_6H_4$	60	4-$MeOC_6H_4$	Ph	88
Ph	2,4-$F_2C_6H_3$	82	Ph	Me	84
Ph	4-$MeOC_6H_4$	91	4-$Me_2NC_6H_4$	Me	82
			4-$MeOC_6H_4$	Me	77

Unlike the reaction of fluorinated derivative **164**, the reaction of nonfluorinated analogue **172** proceeds at the imine fragment rather than at the carbonyl group, *i.e.*, the reversed regiochemistry of heterocyclization is observed and the reaction affords product **173**.



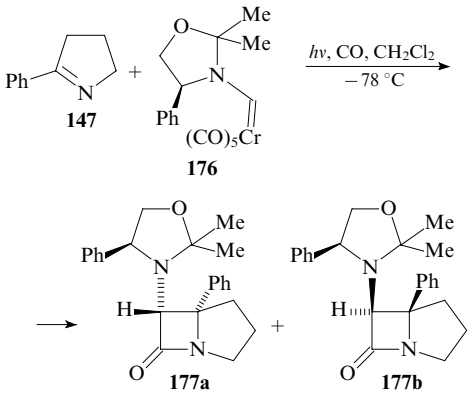
The reaction of enamino ketones **164** with hydroxylamine hydrochloride in ethanol gives isoxazolines **174**. Initially, the oxygen centre of hydroxylamine attacks the substrate, and the only diastereomer of isoxazoline is formed. The products are very stable to dehydrating agents and are not transformed into the corresponding isoxazoles upon refluxing in toluene with *p*-toluenesulfonic acid, by heating in concentrated sulfuric acid to 80 °C or under the action of polyphosphoric acid. However, isoxazoles **175** can be prepared in high yields by heating compounds **174** in concentrated sulfuric acid at 150 °C over a long period of time.[119]



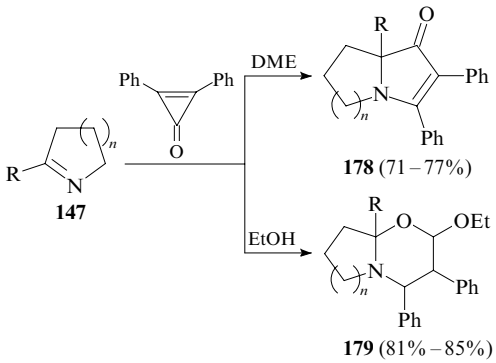
R = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$.

d. Cycloaddition reactions

Cyclic imines are involved in various cycloaddition reactions. Thus, the reaction of imine **147** (R = Ph) with optically active chromium carbene complex **176** gives a mixture of diastereomeric bicyclic lactams **177a**,**b** (in a total yield of 70%), with product **177b** predominating (ratio is 1 : 2), which is consistent with less steric hindrance in the formation of the latter product.[124]



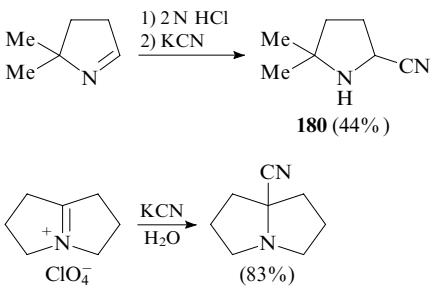
The result of the reaction of diphenylcyclopropenone with imines **147** depends on the reaction medium. Thus, the reaction in an aprotic solvent gives pyrrolinone **178**, whereas the reaction in ethanol affords oxazines **179**.[125]



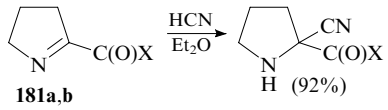
R = Me, Et, Ph, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 2,5-$(MeO)_2C_6H_3$; n = 1, 2.

e. Synthesis of carboxylic and phosphonic amino acid derivatives

The addition of the cyanide anion is one of the most important reactions of cyclic imines. This reaction affords α-aminonitriles (for example, compound **180**), which can be transformed into amino acids or amino acid esters and can be reduced to aldehydes or primary amines. Due to the presence of the strongly polarized double bond, 2-substituted iminium salts readily bind the cyanide anion.[126, 127]



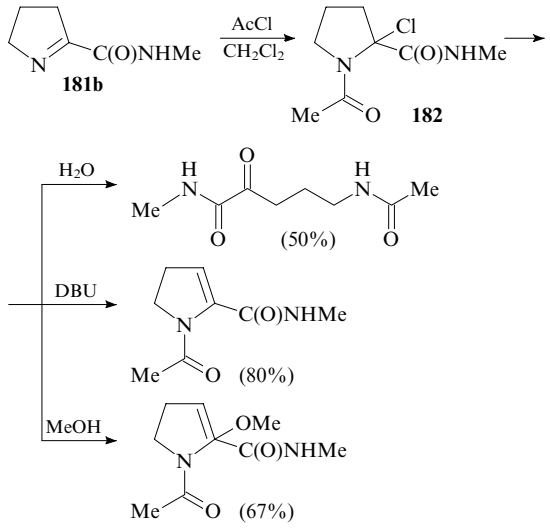
The addition of cyanides to 2-alkyl- or 2-aryl-substituted cyclic imines was not documented. However, data on the addition of gaseous hydrocyanic acid to dehydroproline derivatives **181** in diethyl ether were reported in the literature.[128]



181a,**b**

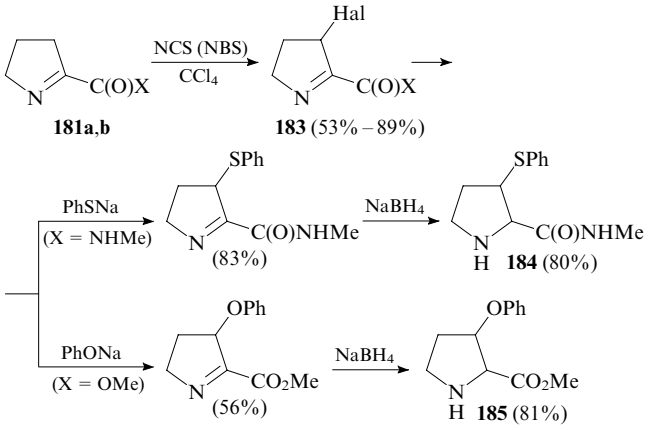
X = OMe (**a**), NHMe (**b**).

The electrophilic addition of different acyl chlorides to dehydroproline derivatives **181** was investigated.[128] The resulting 2-chloramides **182** can be transformed into various cyclic or linear products.



DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

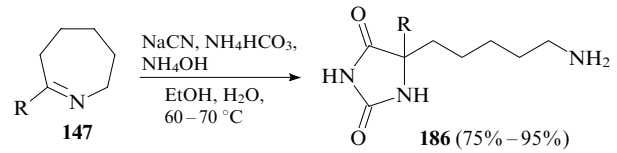
Dehydroproline derivatives **181** can be used as the starting compounds to synthesize the corresponding 3-halogen-substituted derivatives by the treatment with *N*-chloro- (NCS) or *N*-bromosuccinimide (NBS) in carbon tetrachloride. Halogen-substituted derivatives of cyclic imines **183** are readily involved in the reactions with different nucleophiles (hydroxide, alkoxide and thiolate anions) and are then reduced to the corresponding 2,3-disubstituted cyclic amines **184** and **185**.[105, 129]



181a,**b**

Cyclic imines and amino ketones, which were prepared from acyl lactams, were used for the synthesis of hydantoins, which were then tranformed into 2-substituted analogues of the amino acids ornitine, lysine and homolysine.[130] 5,5-Disubstituted hydantoins have attracted attention not only as convenient precursors for the synthesis of α-amino acids but also due to a broad spectrum of biological activities, in particular, as antiparasitic, anticonvulsant and antiarrhythmic drugs.[131] The latest studies showed that these compounds are highly active as aldose reductase inhibitors.[132] The acid or basic hydrolysis of 5,5-disubstituted hydantoins affords α-substituted analogues of natural amino acids, which are of interest for modern bioorganic and medical chemistry and pharmacology. These compounds are also important as a basis for many alkaloids, biologically active compounds and modern medications.[130] The Strecker reaction in the Bucherer – Bergs modification is the most convenient route to hydantoins.[133]

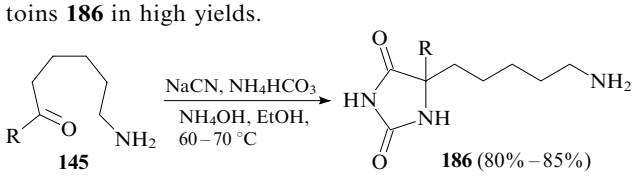
The Bucherer – Bergs reaction of five- and six-membered cyclic imines **147** (R = Ph, n = 1, 2) gives complex mixtures of products containing the starting imine as the major component. However, in the case of the seven-membered cyclic imine (R = Ph, n = 3), the corresponding hydantoin, *viz*., 5-(5-aminopentyl)-5-phenylimidazolidine-2,4-dione (**186**, R = Ph), was synthesized in 87% yield. The reaction has a general character and can be performed with imines containing aromatic, heteroaromatic or bulky alkyl substituents.[130]



147

R = Ar, Het, Bu^t.

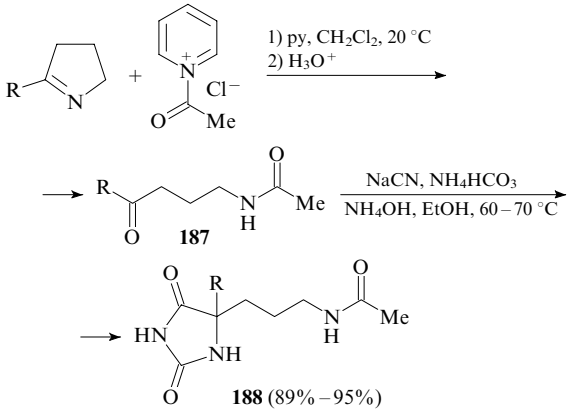
It was hypothesized[130] that under the reaction conditions, seven-membered imines are partially hydrolyzed to give aminohexanones, and it is amino ketone form **145** that is involved in the reaction to give hydantoin **186**. It was shown that 6-aminohexanones **145** actually form hydantoins **186** in high yields.



145

R = Ph, 3-Py.

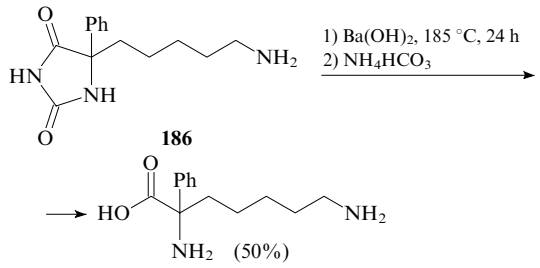
The use of amido ketones instead of five-membered cyclic imines facilitates the Bucherer – Bergs reaction. For example, 5-phthalimidopentan-2-one gives the corresponding hydantoin in 80% yield.[134] It appeared that *N*-(3-acylpropyl)acetamides **187**, which are prepared by acylation of cyclic imines, are also converted in hydantoins **188** in high yields.[130]



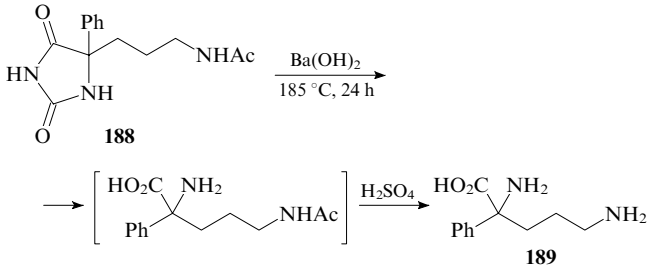
R = Ar, Het, Alk.

5,5-Disubstituted hydantoins are very stable to both acid and basic hydrolysis.[135] However, hydantoin **186**

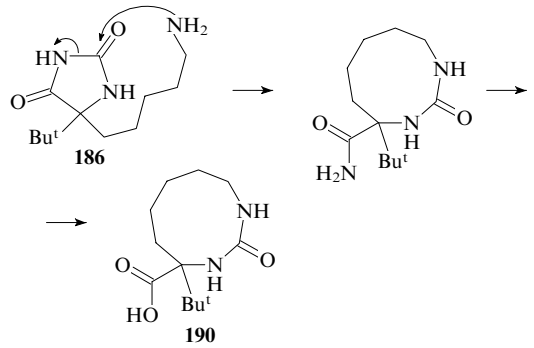
(R = Ph) can be hydrolyzed by heating in a saturated $Ba(OH)_2$ solution in an autoclave at 185 °C for 24 h.



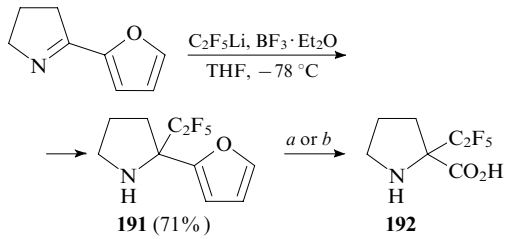
In the case of hydantoin **188** (R = Ph), the acetamide group is hydrolyzed by the treatment of the reaction mixture with a stoichiometric amount of H_2SO_4 to form amino acid **189**.



Under these conditions, the hydrolysis of imidazolidine-2,4-dione **186** (R = Bu^t) unexpectedly produced nine-membered cyclic urea derivative **190**, which can be attributed to the intramolecular attack of the aminopentyl moiety on the carbamide carbonyl group followed by hydrolysis of the exocyclic amide group.[130]

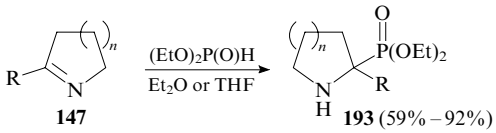


Pentafluoroethyl-substituted 2-(2-furyl)pyrrolidine **191** was used in the synthesis of α-pentafluoroethylproline (**192**). The selective oxidation of the furyl group was performed with the use of ozone or the sodium periodate–ruthenium chloride system. The target amino acid **192** can be prepared in higher yield by ozonolysis.[99]



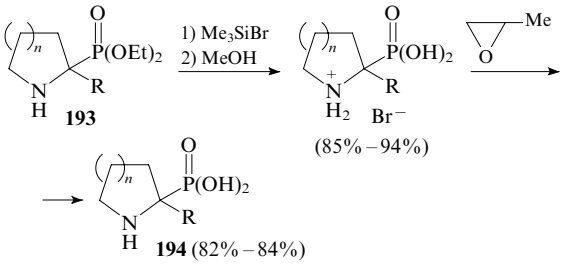
(*a*) O_3, MeOH, −78 °C (84%);
(*b*) $NaIO_4$, $RuCl_3$, MeCN–CCl_4–H_2O (41%).

α-Aminophosphonates and the corresponding aminophosphonic acids have received attention for many years due to high biological activity. Many such compounds have found practical application.[136] Five-, six- and seven-membered cyclic imines smoothly react with diethyl phosphite at room temperature to give the corresponding α-aminophosphonates **193** in high yields. The reactions are catalyzed by boron trifluoride etherate. It appeared that the reaction is very sensitive to the steric factor. For example, attempts to prepare phosphonates from *tert*-butyl-substituted imines failed.[137]



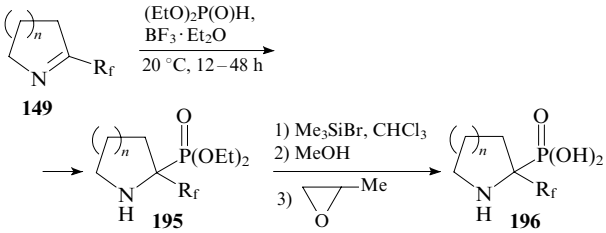
R = Alk, Ar; *n* = 1–3.

Aminophosphonates **193** were transformed into the corresponding acids **194** by the successive treatment with trimethylbromosilane in methanol and propylene oxide. The IR spectra of acids **194** show that these compounds exist as zwitterions.



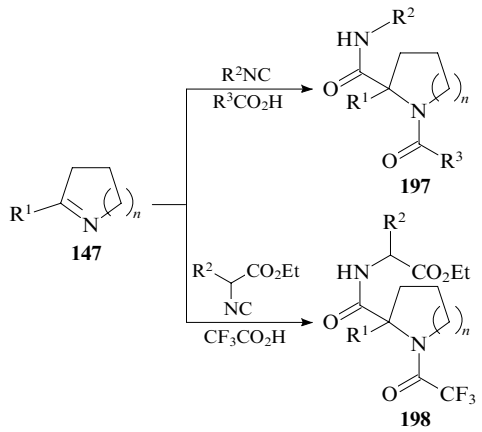
R = Alk, Ar, Het; *n* = 1–3.

The addition of diethyl phosphite to imines **149** containing the trifluoromethyl or pentafluoroethyl group proceeds analogously. However, in spite of the higher electrophilicity of these imines, the reaction proceeds only in the presence of boron trifluoride etherate. The hydrolysis of phosphonates **195** also affords the corresponding acids **196** in the free state.[138]



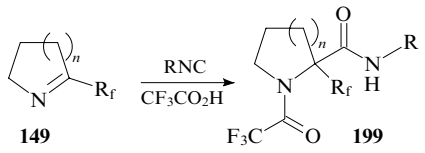
R_f = CF_3, C_2F_5; *n* = 1, 2.

One of the drug design strategies is based on modifications of natural amino acids, for example, by introducing a substituent at the α position. In recent years, the approach based on the introduction of the trifluoromethyl group has gained wide acceptance.[139–141] The Ugi reaction is one of the most efficient methods for the synthesis of amino acid derivatives.[142] In the case of 2-substituted cyclic imines **147**, this reaction provides a route to α-substituted prolines and their homologues **197**. The reaction with the use of isonitriles prepared from natural amino acids gives semisynthetic dipeptides **198** containing a residue of a natural amino acid and substituted proline and homoproline.[143]



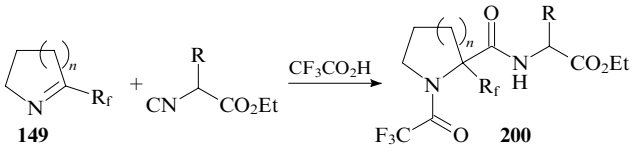
R^1 = Me, Pr^i, Bu^n, Bu^t, cyclo-C_5H_9, Ph, Bn; R^2 = Me, Ph, CH_2Cl, $CHCl_2$, CCl_3, CF_3; R^3 = Bn, 4-BrC_6H_4, $EtO_2C(CH_2)_3$, EtO_2CCMe_2; n = 1, 2.

This approach proved to be efficient also for imines **149** containing the trifluoromethyl or pentafluoroethyl group.[144,145] Amino acid derivatives **199** were synthesized according to this method.



n	R_f	R	Yield (%)	n	R_f	R	Yield (%)
1	CF_3	Bu^t	80	2	CF_3	4-$MeOC_6H_4CH_2$	89
1	CF_3	Bn	81	2	C_2F_5	Bn	70
1	C_2F_5	Bu^t	61	2	C_2F_5	4-$EtOC_6H_4CH_2$	71
2	CF_3	Bu^t	63	3	CF_3	Bu^t	59
2	CF_3	Et	75	3	CF_3	4-$MeOC_6H_4CH_2$	70

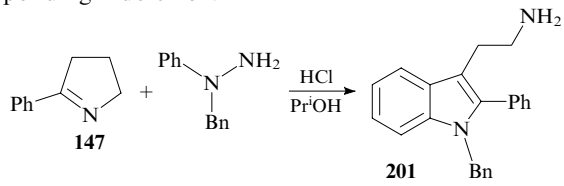
The reactions with isonitriles synthesized from amino acids provide high yields of the corresponding dipeptides **200** containing a residue of proline or its homologues with the perlfuoroalkyl group at the α position.



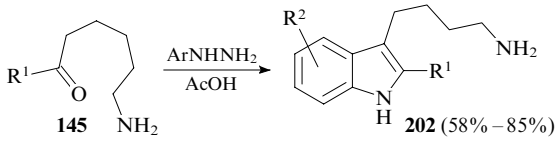
n	R_f	R	Yield (%)	n	R_f	R	Yield (%)
1	CF_3	Me	61	2	CF_3	H	79
1	CF_3	Bn	60	2	CF_3	Me	56
1	CF_3	$MeS(CH_2)_2$	67	2	CF_3	$MeS(CH_2)_2$	44
1	CF_3	$EtO_2C(CH_2)_2$	51	2	CF_3	$EtO_2C(CH_2)_2$	50
1	CF_3	(indol-3-yl)-methyl	59	2	C_2F_5	Me	50
				3	CF_3	H	54
1	C_2F_5	Me	53	3	CF_3	Me	59

f. Synthesis of aminoalkylindoles and their derivatives

A wide range of cyclic imines and their derivatives (amino ketones) were used as the starting compounds for the synthesis of indoles with an aminoalkyl group.[146–148] Aminoalkylindoles serve as the a basis for many indole alkaloids, biologically active compounds and drugs.[149,150] Derivatives of 2-substituted 3-aminoalkylindoles have attracted great attention due to high selectivity with respect to serotonin[151,152] and melatonin receptors,[153] as well as with respect to receptors controlling gonadotropin release.[154] The reaction of 2-phenylpyrroline with 1-benzyl-1-phenylhydrazine was reported[155] to produce the corresponding indole **201**.[155]

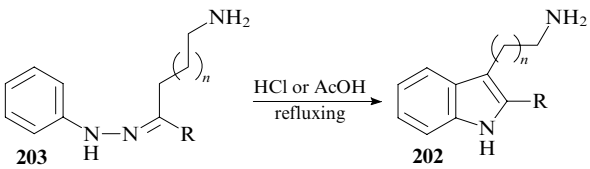


In the studies,[146,147] a new approach was developed for the synthesis of 2-substituted 3-aminoalkylindoles **202** based on the reaction of arylhydrazones with cyclic imines and amino ketones. This approach was used to synthesize substituted tryptamine homologues **202** in high yields by the one-step procedure with the use of readily available reagents.[146]



R^1 = Ph, 3-Py; Ar = $R^2_nC_6H_{4-n}$ (R^2_n = 4-Br, 4-MeO, 3,5-Me_2, 2,4-F_2, 2,4-Cl_2).

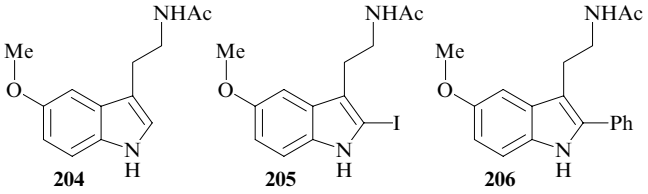
The synthesis of indoles by the Fischer reaction involves the formation of arylhydrazones **203** followed by their rearrangement into indoles **202**. It was found that the Fischer rearrangement is rigidly controlled by the length of the alkylamino group and the nature of the substituent in amino ketone arylhydrazones. In the case of hydrazones generated from seven-membered cyclic imines, the Fischer rearrangement occurs regardless of the nature of the substituent in the carbonyl compounds; however, arylhydrazones generated from five- and six-membered cyclic imines, which do not contain a pyridine moiety, are not involved in the Fischer reaction.[146]



n	R	Yield (%)	n	R	Yield (%)
1	Ph	0	3	3-$MeOC_6H_4$	57
1	2-Py	94	3	4-ClC_6H_4	72
1	3-Py	79	3	4-BrC_6H_4	62
1	4-Py	97	3	3,4-$Cl_2C_6H_3$	77
1	3-quinolyl	73	3	2-Py	87
2	Ph	0	3	3-Py	88
2	3-Py	80	3	4-Py	82
3	Ph	85	3	2-thienyl	82
3	3-MeC_6H_4	65			

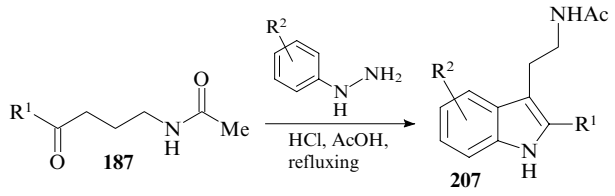
Melatonin (**204**), the hormone secreted by the pineal gland at the base of the brain, is the most well-known representative of *N*-acylaminoalkylindoles. Melatonin controls the circadian rhythm (internal 24-h biological clock)

and, in addition to the hormonal action, serves as a strong antioxidant.[156] Preliminary studies suggest its ability to strengthen the immune system.[157] The use of melatonin in the treatment of mental disorders and cardiovascular diseases was investigated.[158] The molecular mechanisms forming the basis of neuroprotective[159] and antitumour properties[160] of melatonin are extensively studied. The introduction of a substituent at position 2 of the indole ring of melatonin increases the affinity for receptors and the efficiency of derivatives[153] partially due to the fact that the steric effect hinders the mobility of the side chain at the position C(3) and facilitates the incorporation of the molecule into the receptor active site. For example, 2-iodomelatonin (**205**) and 2-phenylmelatonin (**206**) exhibit affinity for the melatonin receptors ML_1 and ML_2 approximately ten times higher than that of melatonin.[161]



204 **205** **206**

A method was developed[148] for the transformation of cyclic imines into amido ketones under the action of a mild acylating agent (*N*-acetylpyridinium chloride). This method was used to synthesize amido ketones containing aromatic and heteroaromatic substituents in good yields starting from five-membered imines (as well as from six-membered imines with benzyl substituents). It appeared that amido ketones **187** are readily involved into the Fischer reaction in the presence of HCl in AcOH as the catalyst to form the corresponding melatonin derivatives **207** in yields from good to virtually quantitative.

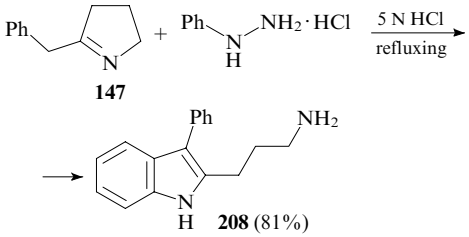


187 **207**

R^1	R^2	Yield (%)	R^1	R^2 (see [a])	Yield (%)
Ph	H	93	Ph	5-F	64
4-MeC_6H_4	H	95	Ph	5-Cl	87
2,4-$(MeO)_2C_6H_3$	H	65	Ph	5-Br	80
2-Furyl	H	43	Ph	5-MeO	85
2-Thienyl	H	66	Ph	7-Et	84

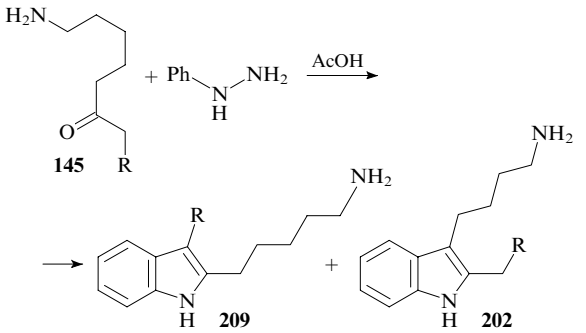
[a] The position of the substituent in the indole ring is indicated.

2-Aminoalkylindoles (isotryptamines) are much less known because of the lack of convenient methods of synthesis. According to the views on the rearrangement mechanisms for arylhydrazones, the introduction of cyclic imines containing the free CH_2 group at position 2 or amino ketones with two CH_2 groups at the α position with respect to the carbonyl group allows the Fischer reaction to follow two pathways.[162] The reaction of 2-benzylpyrroline (**147**, R = Bn) with phenylhydrazine affords 2-aminoalkylindole **208**, which is the first representative of the previously unknown 3-arylisohomotryptamines. The thorough analysis of the reaction products showed that the second isomer is not formed.



147 **208** (81%)

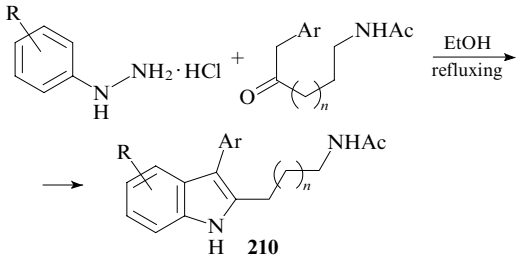
As in the case of cyclic imine **147** (R = Bn), the reactions of aminohexanones **145** (R = Ph, Me) with phenylhydrazine proceed predominantly toward the shorter aliphatic chain. As a result, isotrihomotryptamines **209** were synthesized for the first time. An analysis of the reaction mixture by ^1H NMR spectroscopy showed that this reaction gives also 2-alkyldihomotryptamines **202**. In the case of R = Ph and Me, the ratio of the reaction products is ~17 : 1 and ~5 : 1, respectively. An increase in the selectivity of the Fischer reaction with compounds containing aryl substituents can be associated with the conjugation of the double bond of the intermediate ene hydrazine with the aromatic moiety.



145 **209** **202**

R = Ph (83%), Me (70%) R = Ph (5%), Me (14%)

An analogous approach was used to synthesize isomelatonin derivatives **210**. Due to milder reaction conditions, exclusively indoles containing the amidoalkyl group at position 2 were obtained.[163]



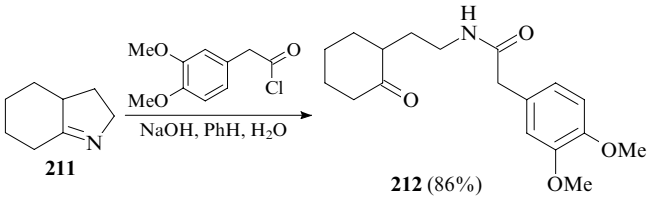
210

Ar	R (see [a])	*n*	Yield (%)	Ar	R (see [a])	*n*	Yield (%)
Ph	H	1	77	Ph	5-F	1	87
Ph	5-Me	1	84	Ph	5-Cl	1	83
3-MeC_6H_4	H	1	49	Ph	5-Br	1	90
2-MeC_6H_4	H	2	78	Ph	5-I	1	87
2-$MeOC_6H_4$	H	2	68	Ph	5-MeO	1	93
4-FC_6H_4	H	2	66	Ph	5-CN	1	32
4-ClC_6H_4	H	1	77	Ph	4- and 6-Br (1 : 1)	1	72
4-MeC_6H_4	H	2	81				
4-$MeOC_6H_4$	H	2	71	Ph	7-CF_3	1	55

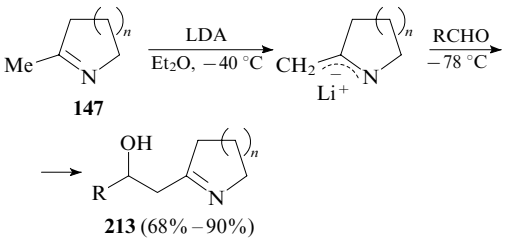
[a] The position of the substituent in the indole ring is indicated.

g. Other transformations

The treatment of cyclic imines **211** with arylacetic chloride in a two-phase system directly affords amido ketones **212**.[164]

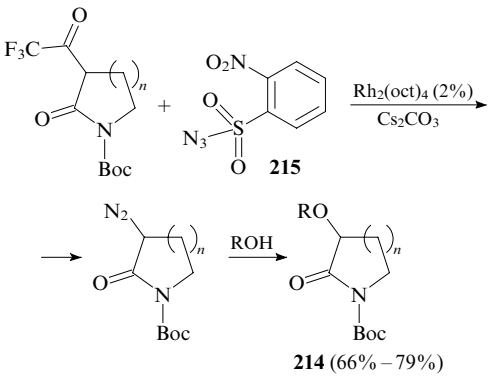


2-Alkyl- and 2-benzyl-substituted cyclic imines are deprotonated with strong bases (for example, with lithium diisopropylamide) to form azaenolates, which react with aldehydes. The resulting imino alcohols **213** can undergo further transformations, for example, can be reduced to the corresponding amino alcohols.[165–167]



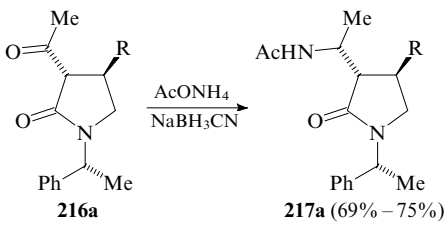
R = Alk, Bn; n = 1, 2.

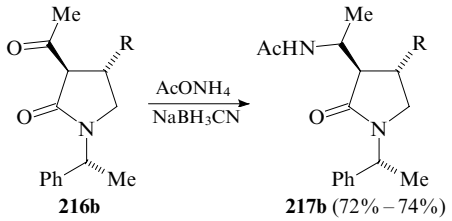
Alkoxy-substituted five- and six-membered lactams **214** were synthesized by the reaction of trifluoroacyl lactams with sulfonyl azide **215** followed by the reaction with alcohols in the presence of rhodium catalysts. The reaction proceeds through rhodium carbene intermediates.[28]



R = Me, Et, Bu^t, cyclo-C_5H_9, Bn; n = 1, 2; oct is octanoate.

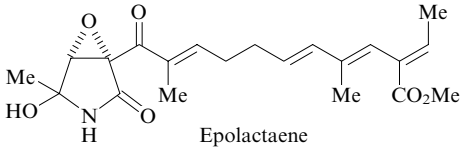
trans-3-Acetyl-4-alkylpyrrolidones **216a**,**b** can be subjected to reductive amination in the presence of the $NaBH_3CN-AcONH_4$ system. The treatment with acetic anhydride affords diastereomerically pure amides **217a**,**b**.





R = Alk.

One of α-acyl lactams, *viz*., epolactaene, was isolated from the mycellium *Penicillium* sp. BM 1689-P. This compound exhibits high physiological activity and causes apoptosis in human leukemia B cells.[168]



* * *

The data surveyed in the present review clearly show that α-acyl lactams can be prepared from commercially available lactams, have considerable synthetic potential and are useful starting reagents for the synthesis of various compounds, including biologically active substances.

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