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The use of 2-(1-alkoxyalkylidene)-1,3-dicarbonyl compounds in organic synthesis †

Yu S Kudyakova, D N Bazhin, M V Goryaeva, Ya V Burgart, V I Saloutin

I Ya Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences ul. S Kovalevskoi/Akademicheskaya 22/20, 620990 Ekaterinburg, Russian Federation

The review focuses on the methods of synthesis of 2-(1-alkoxyalkylidene)-1,3-dicarbonyl compounds and their chemical transformations. The reactivity of such compounds toward various mono- and dinucleophilic reagents is considered. The potential of these compounds for synthesis of different acyclic, carbo- and heterocyclic molecules is demonstrated. Special attention is paid to the practical use of 2-(1-alkoxyalkylidene)-1,3-dicarbonyl compounds and their derivatives, which are of interest in medicine and for design of new materials.
The bibliography includes 226 references.

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I. Introduction

Compounds containing the 1,3-dicarbonyl moiety represent one of the essential 'building blocks' for solving different synthetic problems, including the synthesis of practically important molecules.[1–11] 2-(1-Alkoxyalkylidene)-1,3-dicarbonyl compounds are functionalized derivatives of 1,3-dicarbonyl compounds. The presence of the reactive alkoxyalkylidene group in the *meso* position of the 1,3-dicarbonyl moiety considerably extends the chemical possibilities of such derivatives upon their transformations into different acyclic, cyclic and heterocyclic structures widely used as physiologically active compounds and ligands. Although the data on the chemistry of 2-alkoxyalkylidene-1,3-dicarbonyl compounds have not been systematized, their use in the synthesis of bioactive fluoroquinolones[12–14] and pyrazoles[15] has reported in some reviews and monographs. When dealing with such compounds, attention should be given to the chemistry of structurally similar α,β-unsaturated ketones[16] and 2-acylcycloalkane-1,3-diones,[17] since many of their chemical transformations are similar.

This review is aimed at summarizing and scrutinizing the literature data on the synthesis and chemical transformations of 2-alkoxyalkylidene-1,3-dicarbonyl compounds, as well as on possible applications of their derivatives.

II. Synthesis of 2-(1-alkoxyalkylidene)-1,3-dicarbonyl compounds

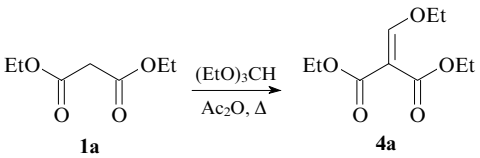
The condensation of 1,3-dicarbonyl compounds with triethyl orthoformate (less frequently, with other alkyl orthoformates) is widely used for synthesis of 2-alkoxyalkylidene-1,3-dicarbonyl derivatives.[18–55] As a 1,3-dicarbonyl component, dialkyl malonate [for example, diethyl malonate (**1a**) (Scheme 1)], 3-oxoesters **2a – m** (Scheme 2, Table 1) and 1,3-diketones **3a – d** (Scheme 3, Table 2) have been introduced into the reaction yielding the corresponding 2-alkoxyalkylidene-containing compounds **4 – 6**. For alkyl malonates exhibiting low CH-acidity, an acid catalyst (H_3PO_4, H_2SO_4 or Lewis acids) should be added.[5,20]

Yu S Kudyakova Candidate of Chemical Sciences, researcher of the Laboratory of Fluoroorganic Compounds at the IOS UB RAS. Tel. (7-343) 362 32 29, e-mail: kud@ios.uran.ru
D N Bazhin Candidate of Chemical Sciences, researcher of the same laboratory. Tel. (7-343) 362 34 25, e-mail: bazhin@ios.uran.ru
M V Goryaeva Candidate of Chemical Sciences, researcher of the same laboratory. Tel. (7-343) 362 32 29, e-mail: pmv@ios.uran.ru
Ya V Burgart Doctor of Chemical Sciences, leading researcher of the same laboratory. Tel. (7-343) 362 32 25, e-mail: burgart@ios.uran.ru
V I Saloutin Doctor of Chemical Sciences, Professor, head of the same laboratory, Deputy Director for science of the IOS UB RAS. Tel. (7-343) 374 59 54, e-mail: saloutin@ios.uran.ru
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† This review is dedicated to Academician Oleg Nikolaevich Chupakhin on the occasion of his 80th birthday.

Scheme 1

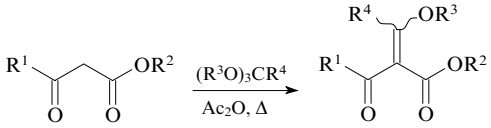


1a **4a**

Catalyst	Yield (%)	Ref.
None	49	43
$ZnCl_2$	31–98	21, 40, 41
$Zn(OAc)_2$	99	42
H_3PO_4	93	22
H_2SO_4	95	37

The formation of compounds **4**–**6** is irreversible.[1] However, without a catalyst, the reaction occurs in high yield only for fluoro derivatives **2d**,**f**,**g**,**i**–**k**, which is presumably due to the more pronounced acidic properties of their methylene group (see Table 1). In the other cases, acetic anhydride can be used, which reacts with ethyl orthoformate $(EtO)_3CH$ to give diethoxymethyl acetate $AcOCH(OEt)_2$.[3] The thermal destruction of the latter yields a more active $[(EtO)_2CR^3]^+$ cation and an acetate anion promoting the deprotonation of the methylene group of a dicarbonyl compound.

Scheme 2



2a–m **5a–n**

It has been suggested to use $BF_3 \cdot Et_2O$ as a catalyst,[22] which enables the condensation of compounds **2b**,**c** and **3a**,**b**,**d** with 1,1,1-trialkoxyethanes under mild conditions (see Table 1, 2; R^4 = Me).

Scheme 3



3a–d **6a–f**

3-Ethoxymethylidene-1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**6g**) has been synthesized by condensation of

Table 1. Products of reactions of 3-oxoesters **2** with alkyl orthoformates (see Scheme 2).

Substrate **2**	R^1	R^2	Product **5**	R^3	R^4	Conditions	Yield (%)	Ref.
a	Me	Et	**a**	Et	H	Δ	18	18
						Ac_2O, Δ	39–98	27, 28, 44–47
b	Me	Me	**b**	Me	Me	Py, AcOH, Δ	82	38
						$BF_3 \cdot Et_2O$, −10–0 °C	63	39
c	Ph	Et	**c**	Et	H	Ac_2O, Δ	38–59	29–31
			d	Et	Me	$BF_3 \cdot Et_2O$, −10–0 °C	63	39
d	CF_3	Et	**e**	Et	H	Δ	59	19, 47
						Ac_2O, Δ	64–98	32, 33, 49, 50
e	$CClF_2$	Et	**f**	Et	H	Ac_2O, Δ	88	51
f	CHF_2	Et	**g**	Et	H	Δ	57–91	48
						Ac_2O, Δ	79	51
g	CH_2F	Et	**h**	Et	H	Δ	–	48
h	C_2F_5	Et	**i**	Et	H	Ac_2O, Δ	83	47, 52
i	$H(CF_2)_2$	Et	**j**	Et	H	Δ	66	19
j	C_3F_7	Et	**k**	Et	H	Δ	57	19
k	C_6F_5	Et	**l**	Et	H	Δ	81	23
l	C_6F_4H	Et	**m**	Et	H	Ac_2O, Δ	–	34–36
m	CH_2Cl	Me	**n**	Et	H	Ac_2O, Δ	100	53

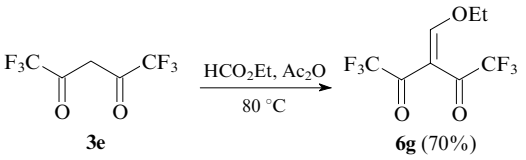
Note. The dash indicates that no yield was reported in the original reference.

Table 2. Products of reactions of 1,3-diketones **3** with alkyl orthoformates (see Scheme 3).

Substrate **3**	R^1	R^2	Product **6**	R^3	R^4	Reaction conditions	Yield (%)	Ref.
a	Me	Me	**a**	Et	H	Ac_2O, Δ	45–91	24, 25, 54, 55
			b	Et	Me	$BF_3 \cdot Et_2O$, −10–0 °C	55	39
b	Me	Ph	**c**	Et	H	Ac_2O, Δ	–	26
			d	Me	Me	$BF_3 \cdot Et_2O$, −10–0 °C	60	39
c	CF_3	Me	**e**	Et	H	Ac_2O, Δ	70	50
d	Ph	Ph	**f**	Me	Me	$BF_3 \cdot Et_2O$, −10–0 °C	52	39

hexafluoroacetylacetone (**3e**) with a formate in the presence of acetic anhydride (Scheme 4).[56]

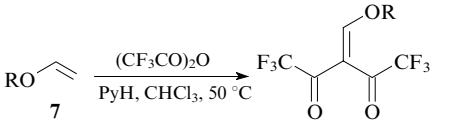
Scheme 4



3e **6g** (70%)

2-Alkoxymethylidene derivatives of hexafluoroacetylacetone **6h–j** are also obtained by bis(trifluoroacylation) of alkyl vinyl ethers **7** in the presence of a base (Scheme 5).[50, 57]

Scheme 5

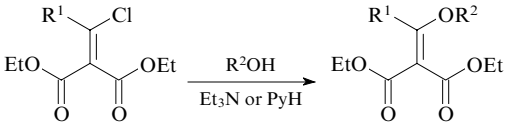


7 **6h–j** (64%–97%)

R = Bu^n (**h**), Et (**i**), Bu^t (**j**); PyH is pyridine

An alternative method of preparation of diethyl 2-(1-alkoxyalkylidene)malonates **4** is through the replacement of the halogen atom in 2-chloroalkylidenemalonates **8** under the action of an alcohol in the presence of an organic base (Scheme 6).[58, 59] An advantage of this method is the possibility of widely varying the alkoxy substituent in the target products.

Scheme 6

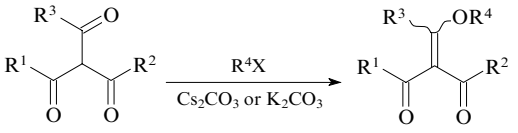


8 **4** (91%–95%)

R^1 = H, Ph; R^2 = Me, Et, Bn, Pr^i, iso-C_5H_{11}, All, Ph

Compounds **4** and **5** can be synthesized by methylation of 3,3′-tricarbonyl compounds **9** (Scheme 7) obtained by the reaction of magnesium derivatives of 1,3-dicarbonyl compounds with acyl chlorides.[60–63]

Scheme 7



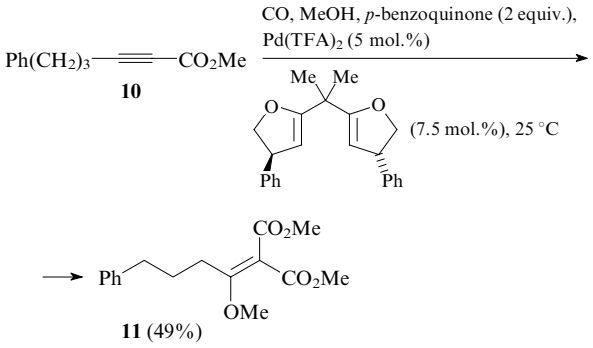
9 **4**, **5** (66%–70%)

R^4 = Me: X = OTf, OMs; R^1, R^3 = Alk; R^2 = OAlk;
R^4 = Et: X = OSO_3Et, R^1 = R^2 = OEt, R^3 = Alk

Upon alkylation of compounds **9**, unlike similar reactions of compounds **1** and **2**, an electrophilic attack occurs at the carbon atom of the keto group to give target products **4** and **5** under mild conditions and in high yields (82%–96%).[60–62, 64–67]

The Pd-catalyzed methoxycarbonylation of disubstituted alkyne **10** has been suggested as an original method of building the carbon skeleton of 2-alkoxyalkylidene-1,3-dicarbonyl compounds.[68] The reaction gives dimethyl 2-(1-methoxy-4-phenylbutylidene)malonate **11** in high yield (Scheme 8).

Scheme 8



10 **11** (49%)

TFA is trifluoroacetate

It should be noted that the most universal method of synthesis of 2-alkoxyalkylidene-1,3-dicarbonyl compounds is the condensation of alkyl orthoformates with 1,3-dicarbonyl derivatives (see Schemes 1–3).

III. Chemical transformations of 2-(1-alkoxyalkylidene)-1,3-dicarbonyl compounds

The molecules of 2-alkoxyalkylidene-1,3-dicarbonyl compounds **4–6** contain three electrophilic sites — two carbonyl groups (nonequivalent for non-symmetric compounds **5** and **6**) and the methylidene carbon atom bonded to the alkoxy substituent (Fig. 1). The conjugation of the double bond with two acceptor RC(O) groups leads to an increase in the positive charge on the methylidene carbon atom so that it becomes more electrophilic. Thus, the most predictable transformations for compounds **4–6** are reactions of addition–elimination of different nucleophilic reagents at the activated C=C bond. The use of dinucleophilic reagents can lead to subsequent cyclization involving one of the carbonyl groups. Reactions with electrophilic reagents are less typical of 2-alkoxyalkylidene-1,3-dicarbonyl compounds **4–6**.

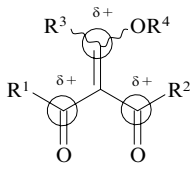


Figure 1. Charge distribution over the carbon atoms in compounds **4–6**.

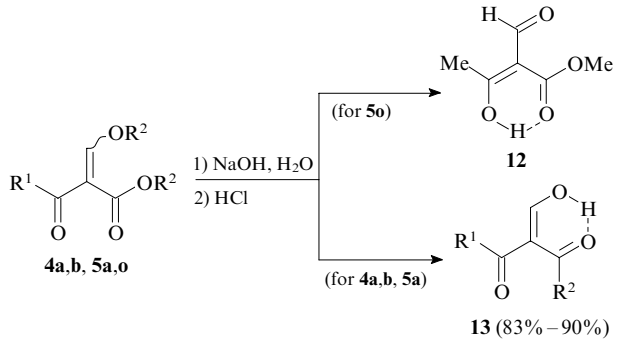
1. Reactions with O-nucleophiles

Reactions of 2-alkoxymethylidene-1,3-dicarbonyl compounds with O-nucleophiles, including water and alcohols, have been described.

In the absence of a base, water, being a weak nucleophilic reagent, reacts only with 2-ethoxymethylideneacetylacetone (**6a**).[69] A similar reaction with 2-ethoxymethylidene-1,3-dicarbonyl compounds **4** and **5** occurs in an aqueous alkaline solution (Scheme 9).[70–73] The structures of the corresponding reaction products have been assigned

to aldehyde **12**,[70] whereas ^{1}H NMR data indicate that these compounds exist in the isomeric enol form **13**.[71–73]

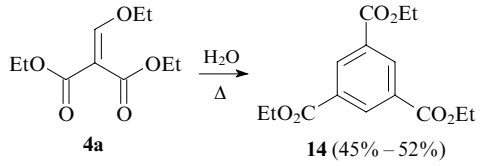
Scheme 9



R^1 = OEt, R^2 = Et (**4a**); R^1 = OMe, R^2 = Me (**4b**);
R^1 = Me: R^2 = Me (**5o**), Et (**5a**)

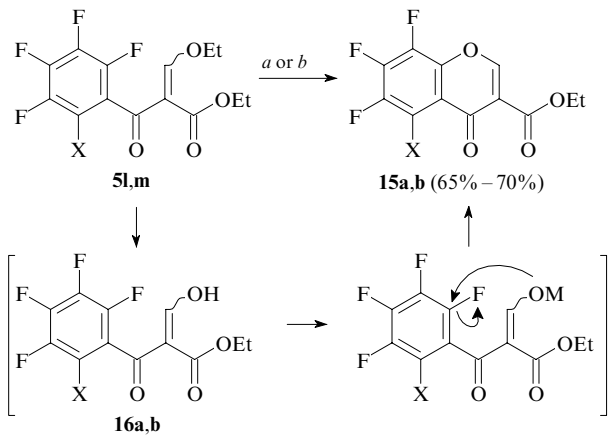
Treatment of diethyl 2-ethoxymethylidenemalonate (**4a**) with boiling water in the absence of catalysts yields triethyl benzene-1,3,5-tricarboxylate **14** (Scheme 10).[72]

Scheme 10



2-Ethoxymethylidene-substituted ethyl 2-polyfluorobenzoylacetates **5l**,**m** undergo intramolecular cyclization in boiling water to give corresponding ethyl polyfluorochromone-3-carboxylates **15a**,**b** (Scheme 11).[23,73] In these reactions, first, the ethoxy group is likely hydrolyzed to the hydroxy group to give intermediate 2-hydroxymethylidene derivatives **16a**,**b** which are then subjected to the intramolecular nucleophilic substitution of the hydroxyl group for the fluorine atom in the *ortho* position of the polyfluorophenyl substituent. It is worth noting that the same products can be obtained by the treatment with aqueous alkali at room temperature rather than with boiling water.

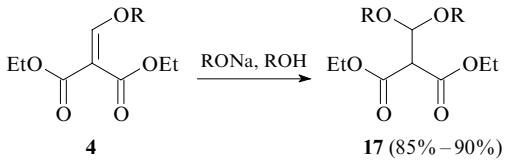
Scheme 11



M = H, Na; **15**, **16**: X = H (**a**), F (**b**);
(*a*) H_2O, Δ; (*b*) NaOH, H_2O, 20 °C

To study the reversibility of formation of 2-alkoxymethylidene-1,3-dicarbonyl compounds **5** (see Scheme 2), Jones[18] tried to combine ethanol with the ethoxymethylidene moiety. However, the reaction mass contained neither traces of triethyl orthoformate and compounds **2** nor other products. The attachment of alcohols to the double bond leading to acetals **17** becomes possible when sodium alkoxides react with 2-alkoxymethylidenemalonates **4** (Scheme 12).[38] This reaction does not occur in the case of sterically hindered alcohols (phenol and 2-propanol).

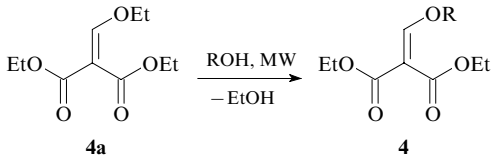
Scheme 12



R = Me, Et, Bn, iso-C_5H_{11}, All

The substitution of the ethoxy group at the C=C bond in compound **4a** by an alcohol alkoxy group containing a larger number of carbon atoms in the chain has been reported.[59] These transformations are initiated by microwave radiation (MW) (Scheme 13). The yield of the product depends on the nature of the introduced alkoxy group and increases in the series of substituents n-butyl (40%), isopentyl (41%), cyclohexyl (57%), n-octyl (80%). When phenol is used as the alcohol component (R = Ph), the reaction does not occur even in the presence of a basic catalyst (KF/Al_2O_3).

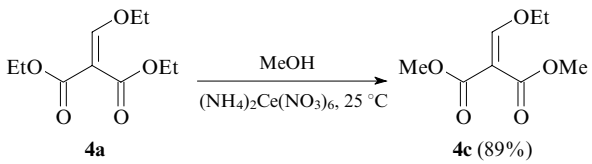
Scheme 13



R = Bu^n, iso-C_5H_{11}, cyclo-C_6H_{11}, n-C_8H_{17}

Transesterification of the ester groups in compounds **4a** on treatment with methanol occurs with retention of the methylidene moiety in the presence of ammonium hexanitrocerate(IV) (Scheme 14).[74]

Scheme 14



Thus, the reactions of 2-alkoxymethylidene derivatives **4**–**6** with O-nucleophiles occur, in most cases, through the attack of a nucleophilic species at the activated double bond, and further transformations are determined by the nature of the substituent in the initial 1,3-dicarbonyl compound.

2. Reactions with N-nucleophiles

Reactions with N-nucleophiles can be divided into two large groups depending on the involved reactive sites of 2-alkoxymethylidene-1,3-dicarbonyl compounds. The first group includes condensations of compounds **4**–**6** at the alkoxymethylidene moiety with the amino group of the nucleophile yielding 2-alkylaminomethylidene-1,3-dicarbonyl com-

pounds, and the second group includes cyclizations involving also the second site (one of the carbonyl groups) to give heterocyclic compounds.

a. Reactions with ammonia and amines

The reaction of 2-alkoxymethylidene-1,3-dicarbonyl compounds **4**–**6** with N-mononucleophiles **18** represents the first type of transformation. An amino moiety is substituted for the alkoxy group to give 2-alkylaminomethylidene derivatives **19** (Scheme 15).[14, 19, 29, 35, 75–124] Similar reactions have been accomplished with a rather wide series of primary and secondary amines, including (hetero)aromatic ones. The products of these reactions are widely used as intermediates in synthesis of biologically active compounds. The structures of such amino derivatives and information on their application with the reference list are presented in the electronic supplement to this paper.‡ In the reactions with (hetero)aromatic diamines, the use of equimolar amounts of the reactants affords the products of monocondensation at one amino group. It is worth noting that these transformations occur under mild conditions, which is favourable for the regiospecific reaction with retention of the carbonyl groups.

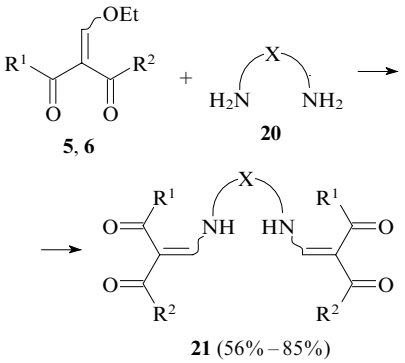
Scheme 15



4–**6** **19** (60%–100%)

The reaction of 2-ethoxymethylidene-1,3-dicarbonyl compounds **5** and **6** with diamines **20** containing remote amino groups yields bis(2-aminomethylidene-1,3-dicarbonyl compounds) **21** (Scheme 16).[125–133] The latter are the products of condensation of two molecules of the initial 2-alkoxymethylidene-1,3-dicarbonyl compounds with one diamine molecule and can be used as polydentate ligands. Ethylene- and phenylenediamines have been used as the diamine component (Table 3).

Scheme 16

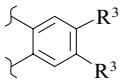
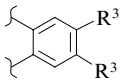
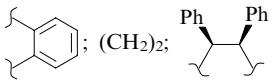


5, **6** **20** **21** (56%–85%)

It has been shown [92] that compounds **4a** can be used for selective protection of the NH_2 group in arylamines **22** in the presence of hydroxyl, sulfanyl, carboxyl or amino functional groups. When the reactants are used in equimolar amounts, the condensation occurs only at the amino group

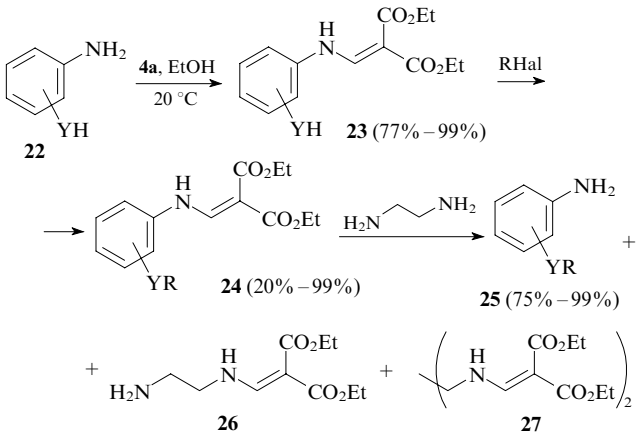
‡ Supplementrary information is available at www.uspkhim.ru

Table 3. Products of reactions of compounds **5** and **6** with diamines **20** (see Scheme 16).

R^1	R^2	X	Ref.
Me	Me	$(CH_2)_2$;  (R^3 = H, OH)	125–130
Me	OMe, OEt	$(CH_2)_2$;  (R^3 = H, $OC_{16}H_{33}$-n)	125, 126, 128, 131
CF_3, $H(CF_2)_2$, C_3F_7	OEt		81, 132, 133

to form compounds **23**. The protecting 2,2-bis(ethoxycarbonyl)vinyl group is stable to the action of bases (piperazine, NaH, KOH, K_2CO_3, Et_3N) and acidic media (10% hydrochloric acid, 10% trifluoroacetic acid in CH_2Cl_2), which enables some transformations of functional groups (alkylation, acylation, esterification). Scheme 17 shows, as an example, the alkylation reaction affording products **24**. The protecting group is removed under the action of ethylenediamine, which is a stronger nucleophile than arylamines. In addition to alkylation products **25**, diamines **26** and **27** have been isolated in trace amounts from the reaction mixture.

Scheme 17



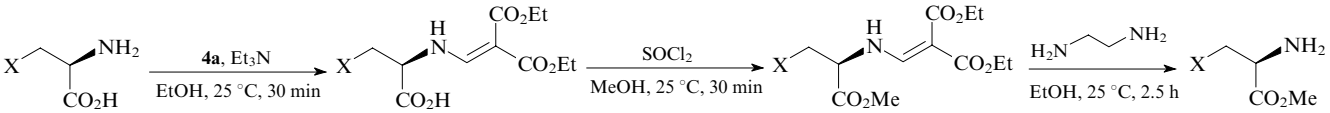
Y = S, O, C(O)O, NH; R = Me, Et, All, Ac, Bn

This protecting group is suitable for aliphatic amines and, which is especially important, for amino acids **28**. The group makes it possible to transform the carboxylic acid functionality in protected acid **29** into an ester group (compound **30**) with retention of the amino group in product **31** (Scheme 18).[92]

b. Specific features of cyclization of 2-alkylaminomethylidene-3-polyfluorobenzoylpropionates

Compounds **19** containing a polyfluorophenyl substituent are widely used in synthesis of fluorinated quinolones **32**. In this case, the NH group of the aminomethylidene moiety is substituted for the fluorine atom in the *ortho* position to the CO group (Scheme 19).[97, 103, 117] One-pot synthesis of quinolones **32** from polyfluorophenyl-substituted 2-ethoxyme-

Scheme 18

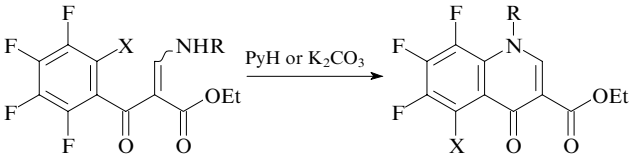


28 **29** **30** **31**

X = Pr^i, Ph, CH_2SMe

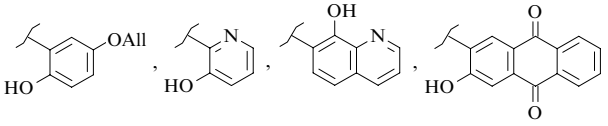
thylidene-3-oxoesters **5l**,**m** without isolation of alkylaminomethylidene intermediates **19** has been accomplished.[117]

Scheme 19



19 **32** (54%–96%)

X = F, H; R = Pr^i, 3-FC_6H_3, 3,4-$F_2C_6H_2$, (*S*)-$CHPhCH_2OH$,



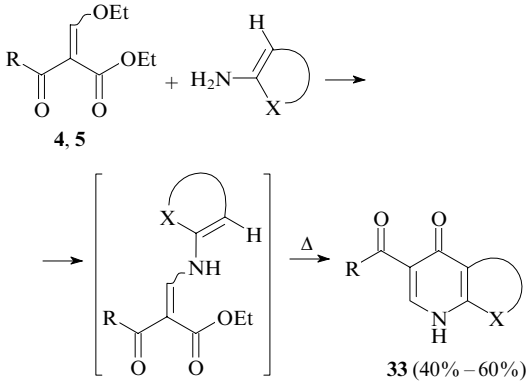
c. Specific features of reactions with (hetero)aromatic amines

The previous section (see Scheme 15) focuses on the reactions of 2-alkoxymethylidene-1,3-dicarbonyl compounds **4**–**6** with alkyl[(het)aryl]amines that yield exclusively 2-aminomethylidene-1,3-dicarbonyl derivatives **19**. In the present section, we consider reactions that occur under more severe conditions in which compounds **19** are intermediates and undergo further intramolecular transformations to form heterocyclic systems.

In particular, the reaction of 2-ethoxymethylidene derivatives **4** or **5** with (hetero)aromatic amines affords pyridinones **33** in one stage (Scheme 20, examples are listed in Table 4).[29,120,134–138] These products are a result of intramolecular cyclization (Friedel–Crafts acylation) of 2-aminomethylidene derivatives **34** obtained *in situ*. A necessary condition for such a transformation is using (het)arylamines in which at least one *ortho* position in the aromatic ring does not bear functional groups or halogen atoms. The reaction occurs under severe conditions (at temperatures above 200 °C) in an inert solvent (for example, diphenyl oxide). With asymmetric compounds **5**, cyclization occurs regiospecifically at the ethoxycarbonyl substituent.

The use of hetarylamines containing an unsubstituted pyrrole-type nitrogen atom in the *orto* position in reactions with 2-ethoxymethylidene derivatives **4**–**6** is favourable for the intramolecular acylation under milder conditions; in this case, the reaction yields heterofused pyrimidines.[139–147] For example, the cyclization of compounds **4a** and **5c** with aminoazoles **35** leads to azolopyrimidones **36** (Scheme 21).[139,142,143] In the absence of a base (conditions *a*),[140,141,144,145] the cyclocondensation of ethyl 2-ethoxymethylidene-3-oxobutanoate (**5a**) with aminoazoles occurs at the ethoxyvinylacyl moiety to give 6-ethoxycarbonyl-7-methylazolo[1,5-*a*]pyrimidines **37** (see Scheme 21). However, base-catalyzed reactions (condi-

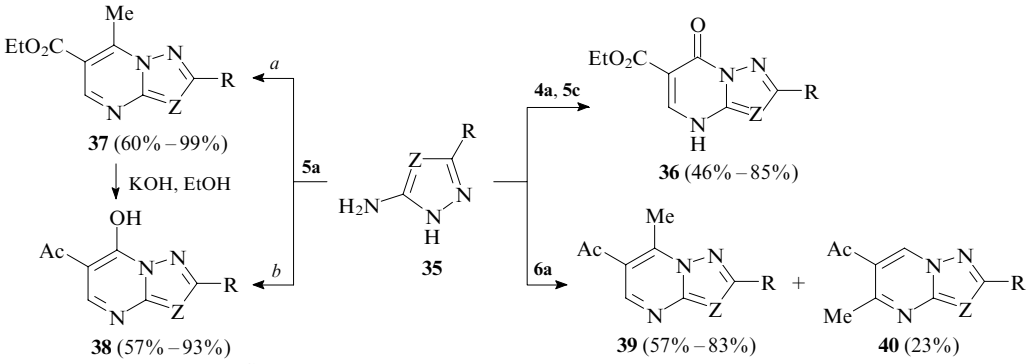
Scheme 20



4, **5** **34** **33** (40%–60%)

X = NAlk, CH; R = Alk, OAlk

Scheme 21



37 (60%–99%) **36** (46%–85%) **35** **38** (57%–93%) **39** (57%–83%) **40** (23%)

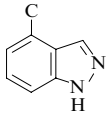
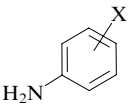
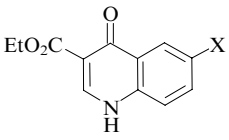
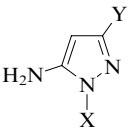
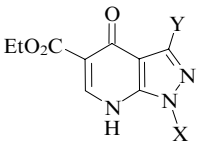
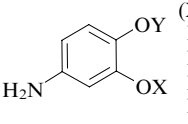
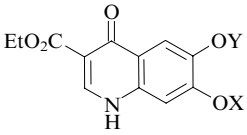
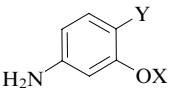
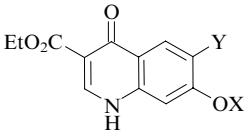
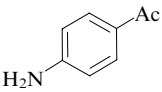
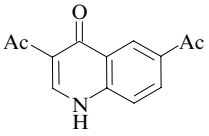
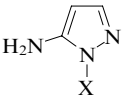
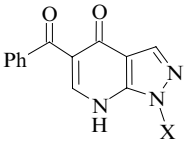
Z = N (**35**, **37**, **39**, **40**), CH (**35**–**40**),  (**35**, **36**) CCN (**35**, **37**), CMe (**35**, **39**, **40**), $CC_6H_4Pr^i$-4 (**35**, **37**); R = H, Br, Me, R = Pr^i, Bu^t, CF_3, SMe, SEt, SBn, Bn, OH, 4-Py, CH_2CN, Ph, 2-ClC_6H_4, 2-BrC_6H_4; (*a*) EtOH or AcOH, Δ; (*b*) KOH, EtOH, Δ

Table 4. Products of reactions of compounds **4a** and **5a**,**c** with (het)arylamines (see Scheme 20).

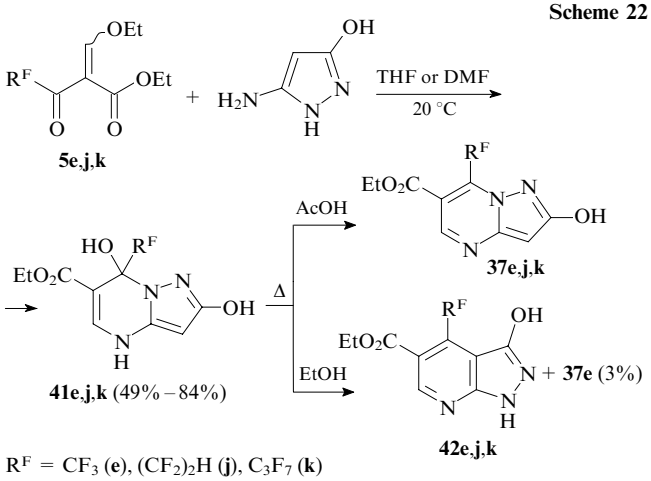
Compound	R	Amine	Product **33**	Ref.
4a	OEt	 (X = , 4-Cl, 4-OMe, 4-Bn, 3-OMe)		134
		 (X = Et, Me; Y = H, Me, Et)		135, 136
		 (X = Et, Y = n-$C_{10}H_{21}$; X = n-$C_{10}H_{21}$, Y = Et; X = Y = Bu^i; X = Bn, Y = Bu^n; X = Y = $CH_2C_3H_5$-cyclo)		137
		 (X = Me, Bn; Y = H, Br, OMe)		138
5a	Me			120
5c	Ph	 (X = $CH_2C_6H_4OMe$-4)		29

tions *b*) of compounds **5a** with aminoazoles yield 6-acetyl-7-hydroxyazolo[1,5-*a*]pyrimidines **38**, which is explained by the rearrangement of ethoxycarbonylazolopyrimidines **37** under the action of a base.[140, 144] The reaction of 3-ethoxymethylidene-2,4-pentanedione (**6a**) with aminoazoles yields, in addition to the expected 6-acetyl-5-methyl-2-methylsulfanyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**39**),[145, 146] isomeric 6-acetyl-7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**40**).[147] This compound is a result of condensation of the azole amino group at the acetyl function and of the ethoxymethylidene moiety with the less nucleophilic pyrrole nitrogen atom.

Fluorinated 2-ethoxymethylidene-1,3-dicarbonyl compounds **5e**,**j**,**k** react with 5-amino-3-hydroxypyrazole under mild conditions to give ethyl-2,7-dihydroxy-7-(polyfluoroalkyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylates **41** (Scheme 22).[143] Further transformations of products **41** occur with increasing temperature, the result depending on the solvent nature. In particular, the reaction in boiling ethanol affords substituted pyrazolo[3,4-*b*]pyridines **42**, whereas dehydration to give corresponding derivative **37** occurs in acetic acid.

Fluoroalkyl-containing compounds **5e**,**j**,**k**, unlike ethoxymethylideneacetoacetic ester (**5a**), react with aminoazoles **43** (3-amino-1,2,4-triazole, aminopyrazoles, aminoimidazole) to form dihydroazolopyrimidines (Scheme 23).[148–150] A specific feature of these heterocycles is their ability to undergo ring–chain tautomerization: in the

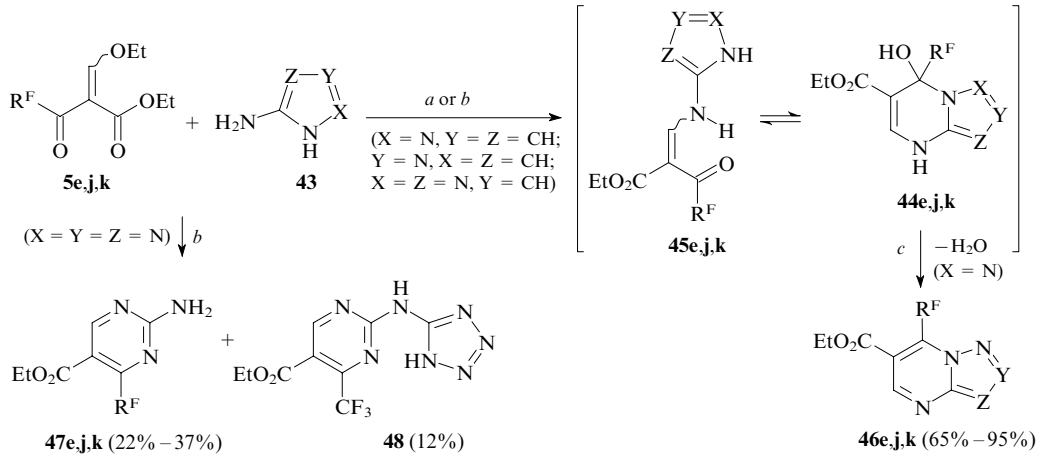
Scheme 22



R^F = CF_3 (**e**), $(CF_2)_2H$ (**j**), C_3F_7 (**k**)

solid state, they have a heterocyclic structure (**44e**,**j**,**k**), whereas in solutions they can exist in cyclic and/or open-chain forms (**45e**,**j**,**k**). Dihydroazolopyrimidines **44** with X = N (see Scheme 23) are subject to dehydration to give (polyfluoroalkyl)azolopyrimidines **46e**,**j**,**k**. The reactions of fluorinated esters **5e**,**j**,**k** with 5-aminotetrazole yield, instead of the predicted dihydrotetrazolopyrimidines, ethyl 2-amino-4-fluoroalkylpyrimidine-5-carboxylates **47e**,**j**,**k** and ethyl 2-(tetrazol-5-ylamino)-4-(trifluoromethyl)pyrimidine-5-carboxylate (**48**) *via* opening of the tetrazole ring.[150]

Scheme 23



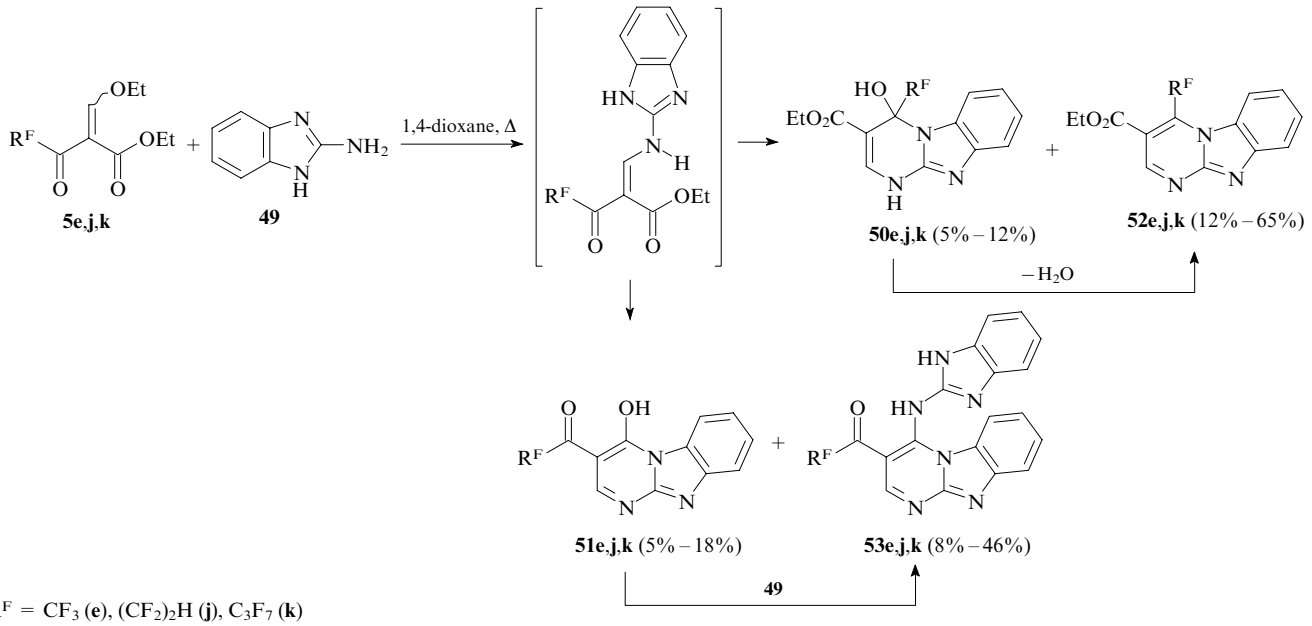
R^F = CF_3 (**e**), $(CF_2)_2H$ (**j**), C_3F_7 (**k**); (*a*) 1,4-dioxane, Δ; (*b*) 1,4-dioxane, AcONa; (*c*) AcOH, Δ

In contrast to the aminoazole reactions, cyclizations of fluorinated compounds **5e**,**j**,**k** with 2-aminobenzimidazole (**49**) carried out under similar conditions (in boiling 1,4-dioxane), are not regiospecific. They occur simultaneously *via* two pathways involving the ethoxyvinyl(polyfluoro)acyl and (ethoxyvinyl)ethoxycarbonyl moieties to give, respectively, ethyl 4-hydroxy-4-polyfluoroalkyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylates **50e**,**j**,**k** and 4-hydroxy-3-(polyfluoroacyl)benzo[4,5]imidazo-[1,2-*a*]pyrimidines **51e**,**j**,**k**. Under the reaction conditions, dihydrobenzimidazo[1,2-*a*]pyrimidines **50** are subject to dehydration resulting in ethyl 4-(polyfluoroalkyl)benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylates **52e**,**j**,**k**, while 4-hydroxy-3-polyfluoroacylbenzimidazo[1,2-*a*]-pyrimidines **51** can undergo nucleophilic substitution of the hydroxy group by the amino group of the second benzimidazole molecule to give 4-(1*H*-benzimidazol-2-ylamino)-3-polyfluoroacylbenzo[4,5]imidazo[1,2-*a*]pyrimidines **53e**,**j**,**k** (Scheme 24).[151]

It has been shown that the microwave-assisted three-component cyclization of 1-(2-thienyl)-4,4,4-trifluorobutane-1,3-dione (**3f**) and triethyl orthoformate with 5-amino-1*H*-pyrazoles **54** or 2-aminobenzimidazole (**49**) leads to pyrazolo[1,5-*a*]pyrimidines **55** or benzimidazo[1,2-*a*]pyrimidine **56**[152] (Scheme 25). It is likely that the formation of heterocycles **55** and **56** initially occurs through the condensation of the NH_2 group of the nucleophile with the trifluoroacyl moiety of 1,3-diketone **3f**, and concurrently the ethoxymethylidene group is formed which is involved in cyclization with the pyrrole nitrogen atom.

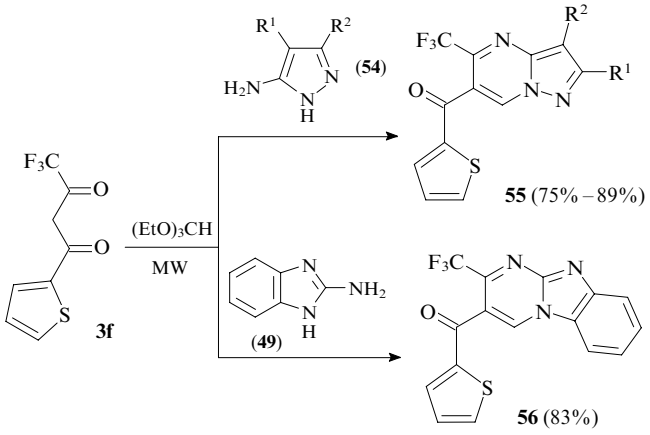
It has been shown above that, under mild conditions, the reaction of 2-ethoxymethylidene-1,3-dicarbonyl compounds with aminouracils leads to aminomethylidene derivatives **19** (see Scheme 15 and electronic supplement).[105] However, the reaction of compounds **4a** with amines **57** in boiling water in the absence of catalysts yields pyrido[2,3-*d*]-pyrimidines **58**.[153] The latter are formed by condensation of the ethoxymethylidene substituent at the 5-position of uracil **57** and

Scheme 24



R^F = CF_3 (**e**), $(CF_2)_2H$ (**j**), C_3F_7 (**k**)

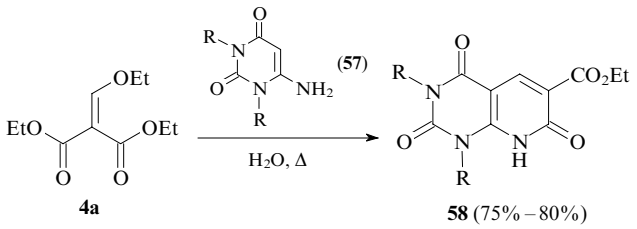
Scheme 25



R^1 = Me, Ph, 4-ClC_6H_4; R^2 = H, Ph

subsequent intramolecular cyclization with an amino group to give a lactam moiety (Scheme 26).

Scheme 26



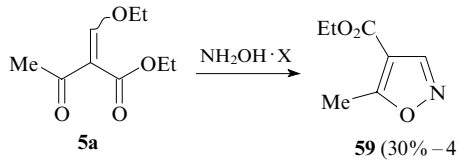
R = H, Me

The above data provide the conclusion that 2-ethoxymethylidene-1,3-dicarbonyl compounds can react with (hetero)aromatic amines to form different fused systems (see Scheme 20). The ease of their formation depends on the nature of atoms in the *ortho* position of the amine and decreases in going from X = CH to X = NH.

d. Reactions with hydroxylamine, hydrazines and thiosemicarbazides

Ethyl 2-ethoxymethylidene-3-oxobutanoate (**5a**) cyclizes with hydroxylamine at the (ethoxyvinyl)acyl moiety to give 5-methyl-4-ethoxycarbonylisoxazole (**59**), which is an intermediate for the synthesis of thienamycin and other biologically active compounds (Scheme 27).[40, 46, 154–157]

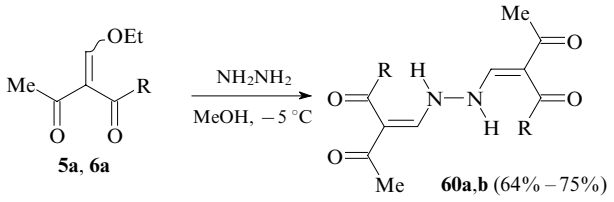
Scheme 27



X = HCl, H_2SO_4/2

At low temperature, the reaction of 2-ethoxymethylidene-1,3-dicarbonyl compounds with hydrazine yields compounds **60** — open-chain bis-condensation products (Scheme 28)[158] analogous to the products with diamines (see Scheme 16).

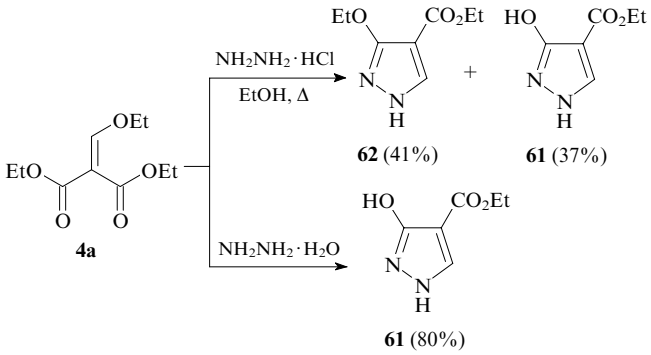
Scheme 28



R = Me (**6a**, **60a**); OEt (**5a**, **60b**)

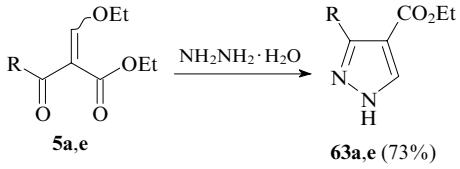
A more natural result of the reaction of 2-alkoxymethylidene derivatives with hydrazines is the formation of substituted pyrazoles. It has been recently demonstrated that different products can be obtained in the reaction of diethyl 2-ethoxymethylidenemalonate (**4a**) with hydrazine under different reaction conditions.[159] The reaction with aqueous hydrazine leads to ethyl 3-hydroxy-1*H*-pyrazole-4-carboxylate (**61**),[159, 160] whereas the reaction with hydrazine hydrochloride in boiling ethanol yields a mixture of pyrazoles **61** and **62** (Scheme 29). For pyrazole **62** to form, the condensation of hydrazine with the ethoxycarbonyl substituent of compound **4a** occurs with elimination of a water molecule, while the formation of pyrazole **61** is accompanied by ethanol elimination.

Scheme 29



2-Ethoxymethylidene-3-oxoesters **5a**,**e** regiospecifically cyclize with aqueous hydrazine at the (ethoxyvinyl)acyl moiety to give only ethyl 3-R-pyrazole-4-carboxylates **63a**,**e** (Scheme 30).[161–163]

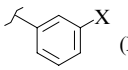
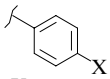
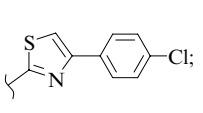
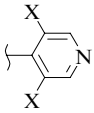
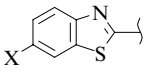
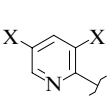
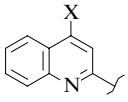
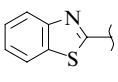
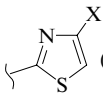
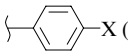
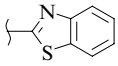
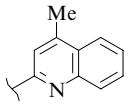
Scheme 30



R = Me (**a**), CF_3 (**e**)

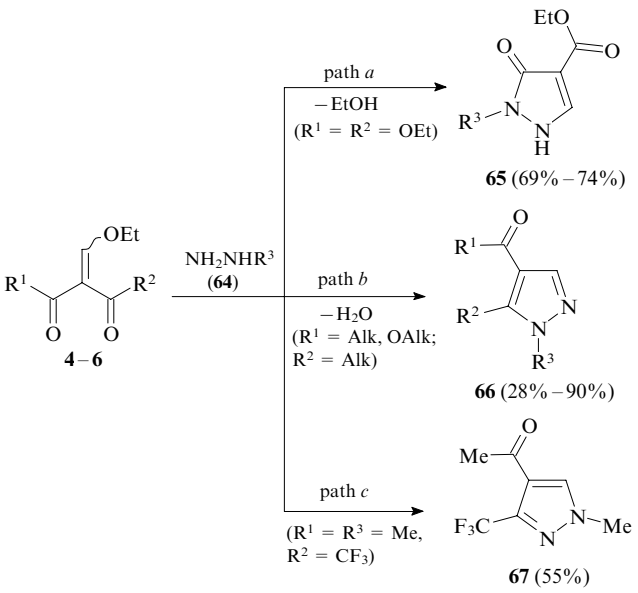
Cyclization of 2-ethoxymethylidene derivatives **4**–**6** with monosubstituted hydrazines **64** occurs through condensation of the ethoxymethylidene substituent with the free amino group of the hydrazine and one of the carbonyl groups with the secondary nitrogen atom (Scheme 31).[26, 162–172] Cyclocondensation of compounds **4a** affords 3-oxo-2,3-dihydro-1*H*-pyrazolones **65** (path *a*). Cyclization of compounds **5** and **6** involves the acyl moiety to yield pyrazoles **66** (path *b*) (Table 5). However, it has been shown that the reaction of 5,5,5-trifluoromethyl-3-

Table 5. Products of reactions of compounds **4**–**6** with hydrazines (see Scheme 31).

Structure	R^1	R^2	R^3	Ref.
65	OEt	OEt	 (X = Br, Me, NO_2)	164
66	Me, OEt	Me	CH_2CF_3, CH_2CO_2Me;  (X = H, SO_2Me, Cl, F);  Cl;  (X = H, Cl);  ;  ;  (X = H, Cl, Me);  (X = H, Cl);  (X = H, Me)	162, 163, 165–168
66	Et, Me	Et, Bn, Ph		26
66	Me, OMe, OEt	Me	Bu^i, All, $CH_2C(=CH_2)Me$	169
66	OEt	CF_3, $(CF_2)_2H$	 ;  (X = CO_2Me, CO_2Et, Ph, C_6H_4Br-4, C_6H_4Me-4);  X (X = NO_2, Br)	170, 171
67	CF_3	Me	Ph; 2-Py;  ; 	172
67	Me	CF_3	Me	165, 172

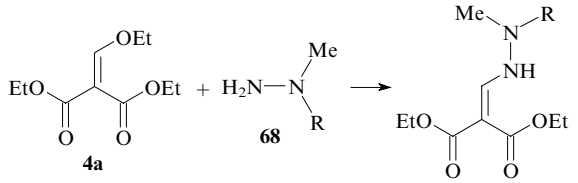
ethoxymethylidenepentanoate (**6e**) with substituted hydrazines can follow both path *b* to form 5-methyl-1-(phenyl/hetaryl)-4-trifluoroacetylpyrazoles **66** (in reactions with hydrazines with bulky substituents) and path *c* to give isomeric pyrazoles **67** (condensation with methylhydrazine).[172] The formation of products of two types is attributed to the possibility of the nucleophilic attack by the nitrogen atom on the carbonyl carbon atom of both the acyl and fluoroacyl groups.

Scheme 31



Diethyl 2-ethoxymethylidenemalonate (**4a**) reacts with N,N-disubstituted hydrazines **68** to form monocondensed products **69**, analogously to the reaction with monoamines (Scheme 32).[173]

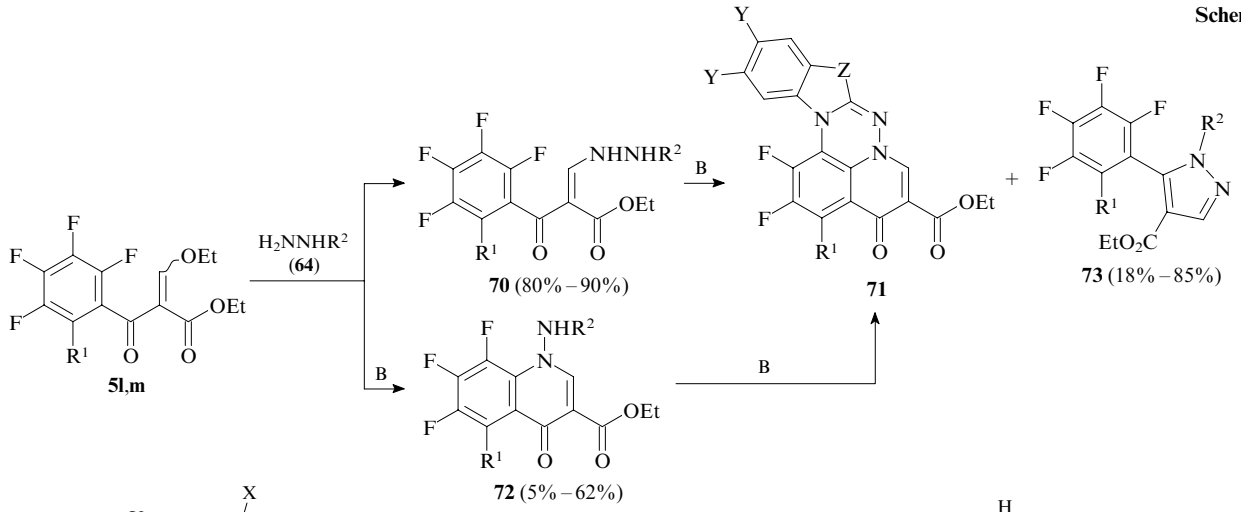
Scheme 32



R = Me, Ph

Condensation of polyfluoroaromatic 2-ethoxymethylidene-3-oxoesters **5l**,**m** with monohetarylhydrazines **64** leads to ethyl 3-(β-hydrazino)-2-(polyfluorobenzoyl)acrylates **70** (Scheme 33).[174, 175] Acrylates **70** under the action of a base — 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or potassium fluoride — can be converted into benzazolotriazinoquinolones **71** through the successive double intramolecular

Scheme 33



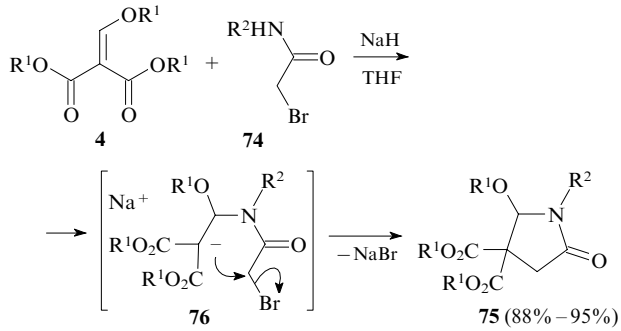
displacement of two fluorine atoms resulting in intermediate formation of quinolone **72**. Heating compounds **5l**,**m** in acetonitrile under reflux in the presence of a base directly affords pentacyclic fluoroquinolones **71**. It has been noted[174] that, in addition to polyheterocycles **72**, N-substituted pyrazoles **73** are formed under these conditions, analogously to the transformations of nonfluorinated 2-ethoxymethylidene-3-oxoesters. The yield of pyrazoles **73** varies from 18% to 85% depending on the base nature.

e. Reactions with amides and hydrazides

This section deals with reactions of 2-ethoxymethylidene derivatives with amides and hydrazides, which have weaker nucleophilic properties than the amines and hydrazines considered above.

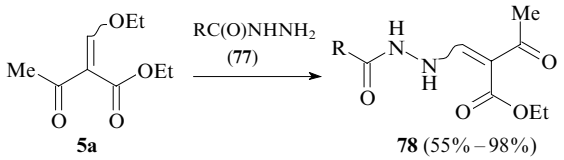
No information is available on the reactions of 2-alkoxyalkylidene-1,3-dicarbonyl compounds with amides in the absence of bases, which is due to the weak nucleophilic properties of the amide group. The use of sodium hydride as a base enables the cyclization of 2-alkoxymethylidenemalonates **4** with α-bromoacetamides **74** into pyrrolidin-2-ones **75** (Scheme 34).[176] The latter result from of the base-catalyzed addition of the amide group of a nucleophile at the methylidene moiety of diester **4** leading to carbanions **76**, which then undergo intramolecular cyclization at the electrophilic centre, the CH_2Br group.

Scheme 34



The reaction of aromatic acid hydrazides **77** with compound **5a** stops after monocondensation at the ethoxymethylidene group, whatever the substituent nature and position in the aromatic ring, to give α-formylacetoacetate aroylhydrazines **78**. According to IR spectroscopy and NMR, the latter exist in solution as a mixture of *E* and *Z* isomers, with predominance of the *E* form (90%) (Scheme 35; the product is presented as a tautomeric enehydrazine).[177, 178]

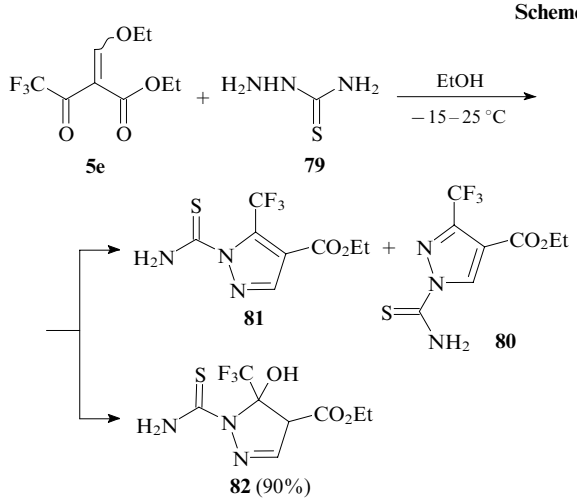
Scheme 35



The more nucleophilic thiosemicarbazide (**79**) reacts with oxoesters **5**, like substituted hydrazines, to give pyrazoles. Initially it has been believed that the reaction of ethyl 3-oxo-4,4,4-trifluoromethyl-2-ethoxymethylidenebutanoate (**5e**) with thiosemicarbazide affords a 1 : 1 mixture of isomeric 3- and 5-substituted pyrazoles **80** and **81** in a total yield of 73% (Scheme 36).[179] Later, it has been demonstrated with the use of ^{19}F and ^{13}C NMR that the reaction yields ethyl 5-hydroxy-1-thiocarbamoyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate (**82**),[180] which has higher stability owing to the effect of the electron-withdrawing fluoroalkyl group.

Polyfluorobenzoyl-containing oxoesters **5l**,**m** react with substituted hydrazines in ethanol or toluene at room temperature or on slightly heating to give benzoylacrylates **83** (Scheme 37).[181–184] Subsequent cyclization of acrylates **83** occurs on boiling or under the action of potassium carbonate or fluoride, through the intermediate formation of quinolones **84**, which are converted into fused fluoroquinolone systems **85**.

Scheme 36



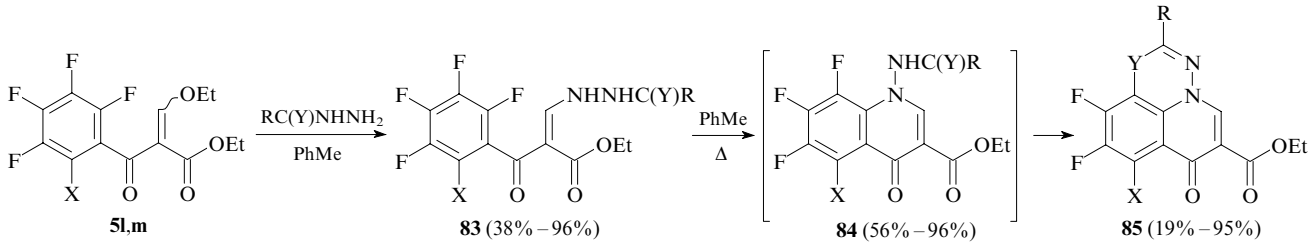
f. Reactions with urea and its derivatives

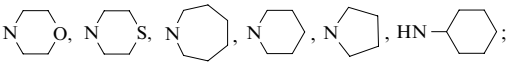
Fluoroalkyl-containing 2-ethoxymethylidene-3-oxoesters **5e**,**j**,**k** react with urea under mild conditions (DMF, room temperature) to form ethyl 3-oxo-2-(ureidomethylidene)-3-polyfluoroalkylpropionates **86** (Scheme 38, Table 6). Even upon recrystallization from ethanol, these compounds readily undergo cyclization involving the fluoroacyl moiety to form tetrahydropyrimidines **87.** Dehydration to dihydropyrimidine **88** occurs only for heptafluoropropyl-containing tetrahydropyrimidine **87** ($R^F = C_3F_7$) on boiling in acetic acid. The reactions of 2-alkoxyalkylidene-1,3-dicarbonyl compounds with urea under more severe conditions (boiling in DMF) lead to tetrahydropyrimidines **87** in one stage.[185]

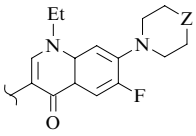
Reactions of nonfluorinated 2-alkoxymethylidene-1,3-dicarbonyl compounds with different urea derivatives give pyrimidines **89** and **90**, while no intermediate compounds **86** and **87** were observed. Pyrimidines **89** and **90** (X = OH, SH) can exist as tautomeric tetrahydropyrimidin-2-one(thiones) **88**.

Ethoxymethylidenemalonate **4a** reacts with a cyclic thiourea derivative — compound **91** — to form pyrimidothiazine **92** (Scheme 39)[193] analogously to reactions with substituted thioureas. The reaction of compounds **4a** with asymmetric cyclic guanidine **93** leads to isomeric pyrimidoquinazolines **94** and **95**, and their ratio depends on the presence of a catalyst.[193] In the absence of a catalyst, their yields are 39% and 18%, whereas in the presence of a basic catalyst [(2-dimethylaminopyridine (DMAP)], these yields are 40% and 30%, respectively. In contrast to this, the only

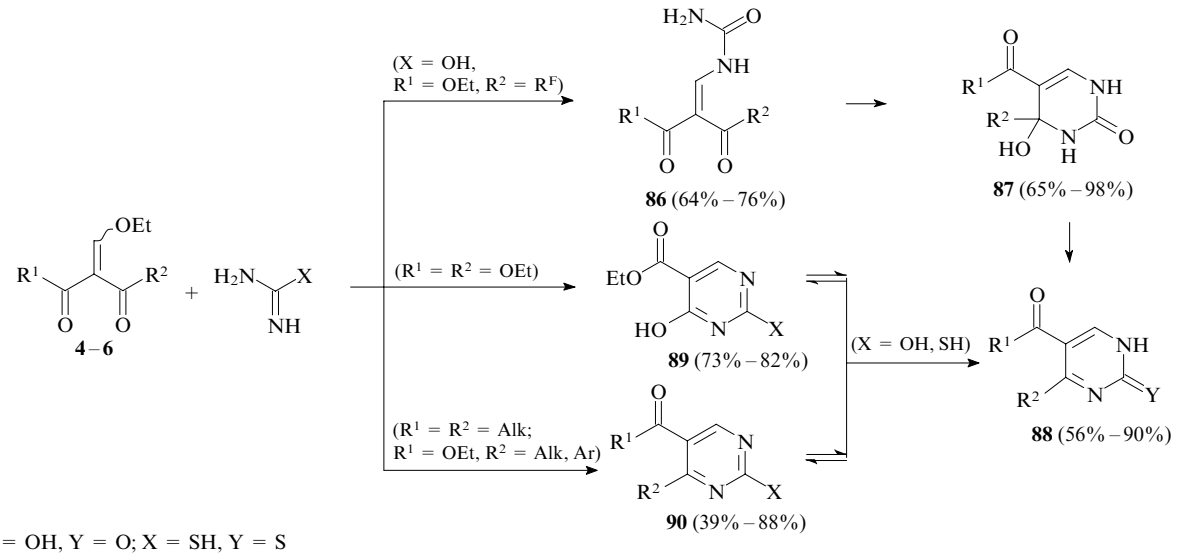
Scheme 37



X = H, F; Y = S: R = ;

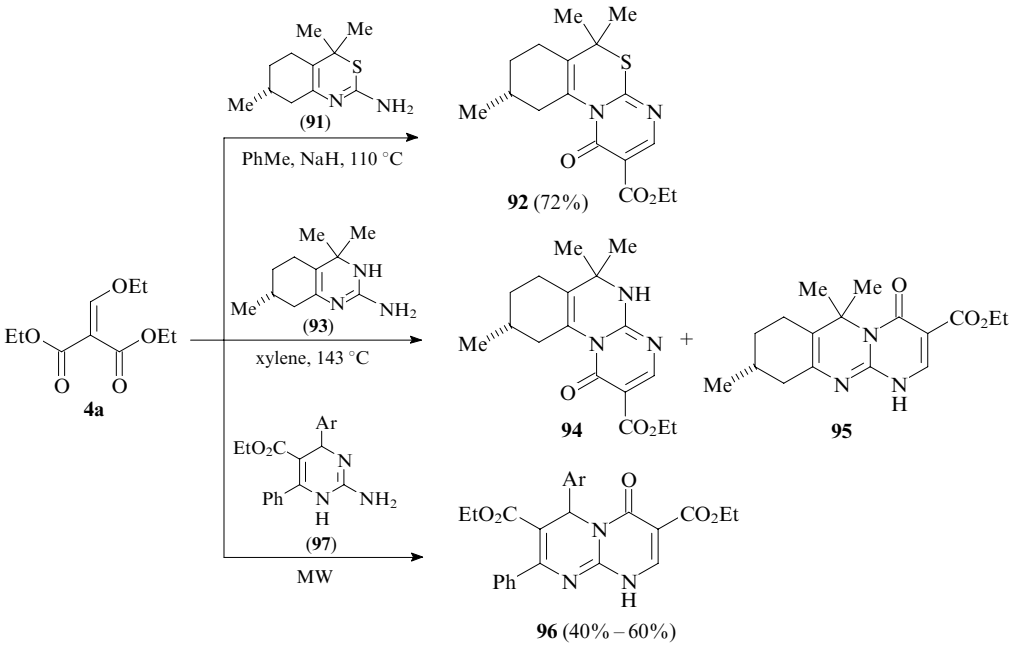
Y = O: R = 4-Py, 3-Py, 3-$O_2NC_6H_4$,  (Z = $(CH_2)_n$ (n = 0, 1, 2), O, S); Y = NH, R = Ph

Scheme 38



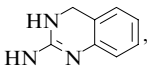
X = OH, Y = O; X = SH, Y = S

Scheme 39



Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-Th (Th is thienyl)

Table 6. Products of reactions of compounds **4**–**6** with ureas (see Scheme 38).[a]

Structure	R^1	R^2	X	Ref.
86–**88**	OEt	CF_3, $H(CF_2)_2$, C_3F_7	OH	185
89	OEt	OEt	OH	186
	OEt	OEt	H	63
	OEt	OEt		187
	OEt	OEt	NMeBn, OH	188
	OEt	OEt	SMe	189
90	Me	Me	SMe	24
	Me	Me	SH	54, 190
	Me	Me	OH	191
	OEt	Me	OH, SH, NH_2, 4-OBu^{n}C$_6$H$_4$	191, 192
	OEt	CF_3, C_2F_5, Me, Et, Pr^n, Ph	CF_3, Me, OH	27

[a] The substituents in the initial reagents are given.

regioisomeric product, diethyl 4-aryl-6-oxo-2-phenyl-6,9-dihydro-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate (**96**), has been synthesized by microwave irradiation of a mixture of compounds **4a** and ethyl 2-amino-4-aryl-6-phenyl-1,4-dihydropyrimidine-5-carboxylate (**97**).[194]

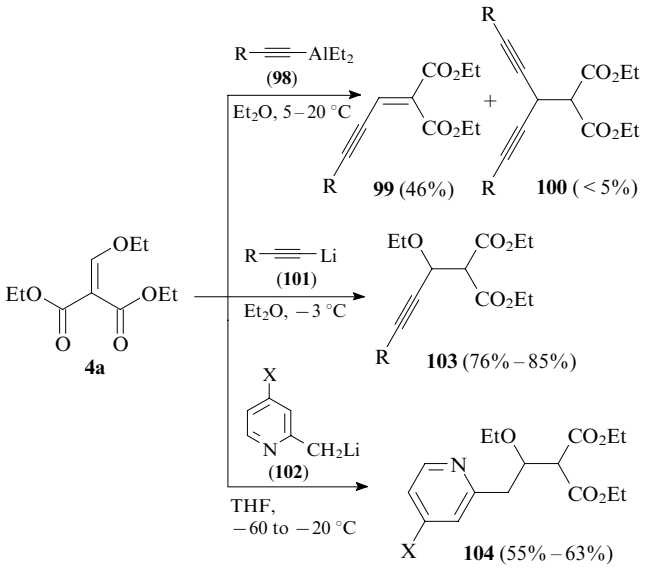
3. Reactions with C-nucleophiles

Below, we consider the reactions of 2-ethoxymethylidene-1,3-dicarbonyl compounds with carbanions that lead to the formation of a new C–C bond through the attachment of the C-nucleophile to the carbon atom of the ethoxymethylidene moiety. Organometallic compounds being donors of carboanions are used as the reagents.

It has been noted that copper acetylenides do not react with ethoxymethylidenemalonates.[195] However, lithium and aluminium acetylenides, owing to the higher polarity of the carbon–metal bond, are more reactive with respect to such compounds (Scheme 40). Aluminium acetylenides **98** react with compound **4a** with substitution for the ethoxy group at the C=C bond to give 3-substituted diethyl 2-propylidenemalonates **99**. Adducts **100**, forming in < 5% yield as a result of the addition of the second acetylenide molecule to compound **99** at the methylidene moiety, have been isolated as side products. Organolithium derivatives **101** and **102** are readily added to the activated C=C bond to give diesters **103** and **104**.[195–197]

Diester **104** can be transformed to quinolizin-4-one **105** as a result of thermal cyclization, and this transformation

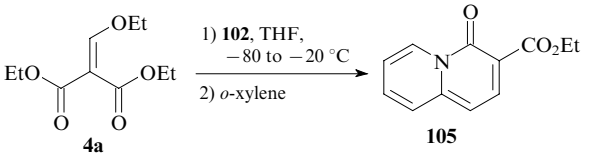
Scheme 40



R = Bu^n, Ph; X = H, Cl

can be achieved by a one-pot method — from compounds **4a** in the presence of lithium derivative **102** (Scheme 41).[198]

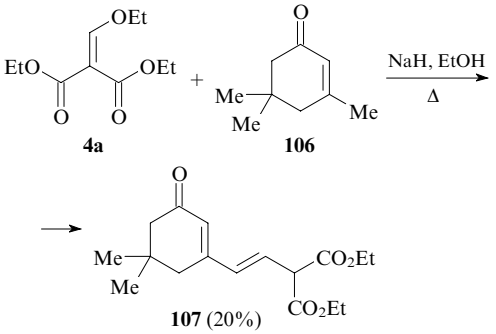
Scheme 41



For carbanions generated under the action of sodium hydride or alkoxides, there is a process of addition–elimination at the C=C bond of 2-alkoxyalkylidene-1,3-dicarbonyl compounds. Depending on the reactant structures, the resulting open-chain product can undergo subsequent intramolecular cyclization involving one of the carbonyl groups to form a (hetero)aromatic system. Cyclic products can be obtained by one-pot synthesis from 2-alkoxyalkylidene-1,3-dicarbonyl compounds.

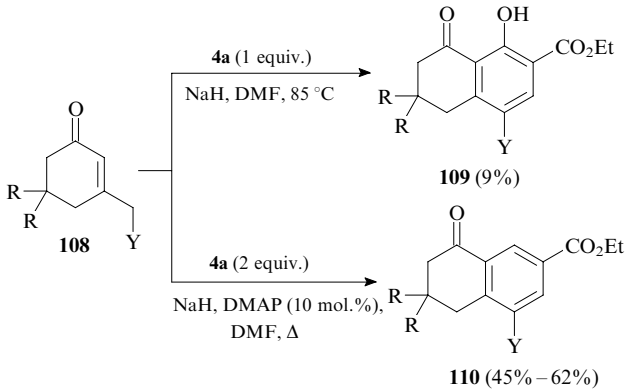
The reaction of compound **4a** with 3-methyl-2-cyclohexenone **106** in the presence of sodium hydride in ethanol leads to the substitution for the ethoxy group and formation of diethyl 2-[2-(5,5-dimethyl-3-oxocyclohexenyl)vinyl]malonate (**107**) (Scheme 42).[199]

Scheme 42



Under the action of sodium hydride, ethoxymethylidenemalonate reacts with functionalized 3-methylcyclohexenones **108** to form cyclocondensation products — diethyl 4-hydroxy-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydronaphthalene-1,3-dicarboxylates and nitriles **109**, but in low yield (Scheme 43).[199] The use of an excess of ester **4a** in the presence of 4-dimethylaminopyridine under similar conditions affords diethyl 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydronaphthalene-1,3-dicarboxylates and analogous nitriles **110** in good yield.

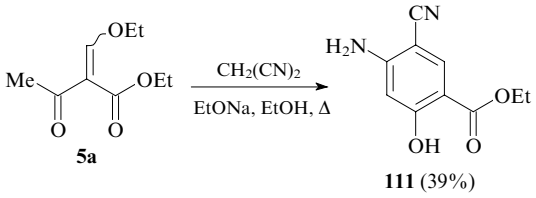
Scheme 43



R = H, Me; Y = CO_2Et, CN

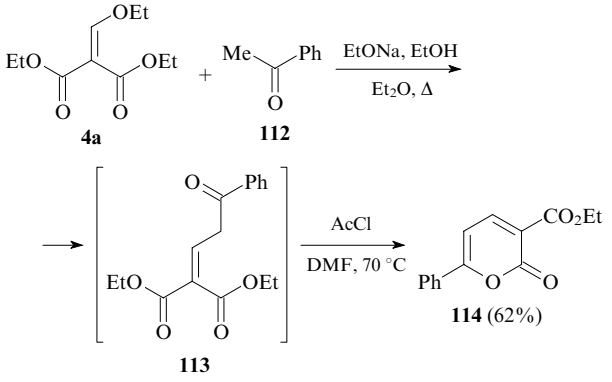
In the presence of sodium alkoxides, ethoxymethylideneacetoacetic ester **5a** is cyclized with malononitrile into ethyl 4-amino-2-hydroxy-5-cyanobenzoate (**111**) at the ethoxyvinylacyl moiety (Scheme 44).[200]

Scheme 44



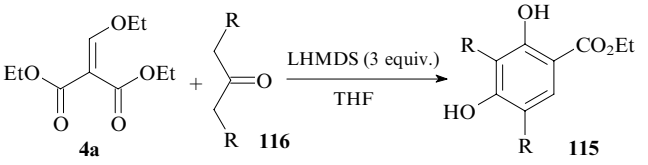
Condensation of compound **4a** with acetophenone (**112**) yields diethyl (3-oxo-3-phenylpropylidene)malonate (**113**), which undergoes intramolecular transesterification under the action of acetyl chloride to form ethyl 2-oxo-6-phenyl-2*H*-pyran-3-carboxylate (**114**) (Scheme 45).[201]

Scheme 45



The synthesis of 2,4-dialkylresorcinols **115** from ethoxymethylidenemalonate **4a** and dialkyl ketones **116** has been described.[202] For these transformations to occur, it is necessary to use 3 equiv. of a base — lithium hexamethyldisilazide (LHMDS) (Scheme 46).

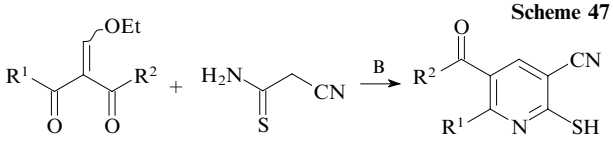
Scheme 46



R = Me (yield 88%), Et (97%), Pr^n (88%), Pr^i (47%)

Reactions of 2-ethoxymethylidene-1,3-dicarbonyl compounds **5** and **6** with thioacetamide **117** containing the methylene group activated by the nitrile substituent afford pyridines **118** (Scheme 47).[43, 203, 204] First, condensation of

Scheme 47



B is *N*-methylmorpholine, DBU, NaH;

R^2 = OEt: R^1 = Me, CH_2OEt, Ph; R^1 = CF_3: R^2 = 2-Th, Ph;

R^1 = R^2 = Me

the C-nucleophile at the ethoxymethylidene moiety takes place, and then, intramolecular cyclization occurs through the interaction of the amide group with the acyl substituent.

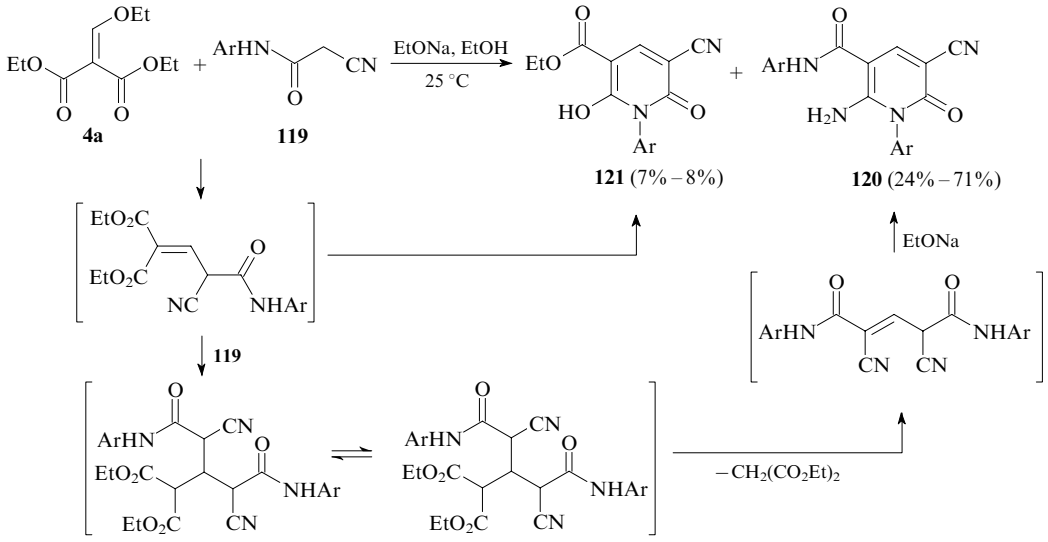
An unexpected result of condensation of compound **4a** with N-aryl-substituted cyanoacetamides **119** has been reported [205] (Scheme 48). Major products of this reaction are pyridones **120**, while cyclocondensation products, ethyl 2-hydroxy-5-cyanocarboxylates **121**, are minor components. To explain this transformation, the authors have suggested a mechanism involving successive Michael addition of two nitrile molecules at the C=C double bond of ethoxymethylidenemalonate **4a**. A specific feature of this reaction is that it involves diethyl malonate elimination, and compound **4a** thereby plays a role of the methylene group source for formation of pyridones **120** from nitriles **119**.

Trifluoromethyl-containing 2-ethoxymethylidene-1,3-dicarbonyl compounds **5e** and **6g** react with cyanoenamines **122** to form a new C–C bond yielding dienes **123** (Scheme 49). When refluxed in toluene, the latter undergo intramolecular addition of the methyl group at the trifluoroacetyl substituent, yielding 4-hydroxy-4-trifluoromethyl-1,5-cyclohexadienes **124**. The reaction of ethyl 2-ethoxymethylidene-3-oxo-4,4,4-trifluorobutanoate (**5e**) with enamines **122** on refluxing in toluene immediately leads to cyclohexadienes **125** and **126**, which are separated by column chromatography. The dehydration of cyclohexadienes **124**, **125** and **126** in toluene in the presence of *p*-toluenesulfonic acid (TsOH) or triethylamine or in chloroform with addition of several drops of thionyl chloride enables the preparation of functionalized trifluoromethylbenzenes **127**, **128** and **129** (see Scheme 49).[206]

Compounds **5** and **6** react with 1,3-bis(silyloxy)-1,3-butadienes **130** in the presence of $TiCl_4$ to give cyclization products — 4-hydroxy-1,3-benzodioates **131**–**134** (Scheme 50).[50, 55]

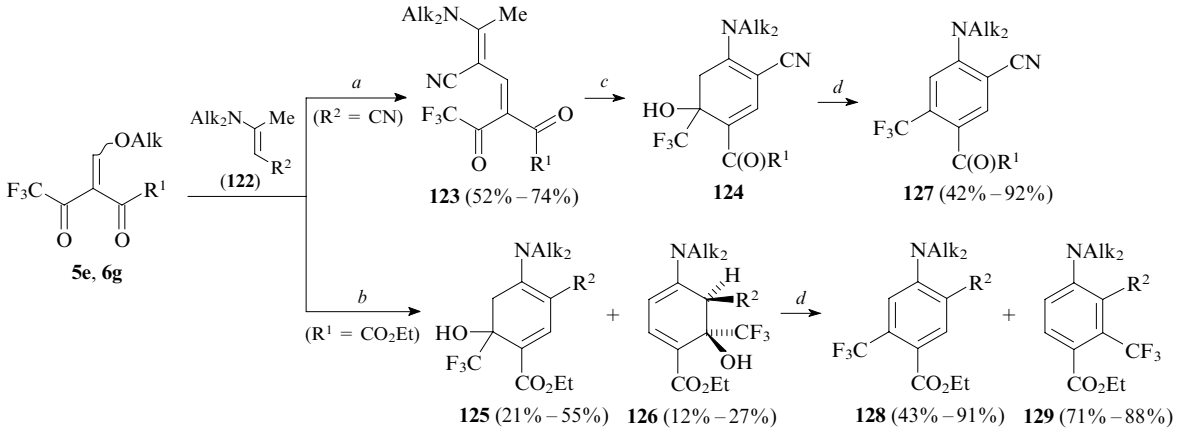
Thus, according to the HSAB principle, when there are several electrophilic sites in molecules of 2-ethoxymethylidene-1,3-dicarbonyl compounds **4**–**6**, the most preferable site for the carbanion attack is the methylene carbon atom. Reaction conditions and the nature of the organometallic compound are essential. The reaction of such compounds with functionalized C-nucleophiles results in transforma-

Scheme 48



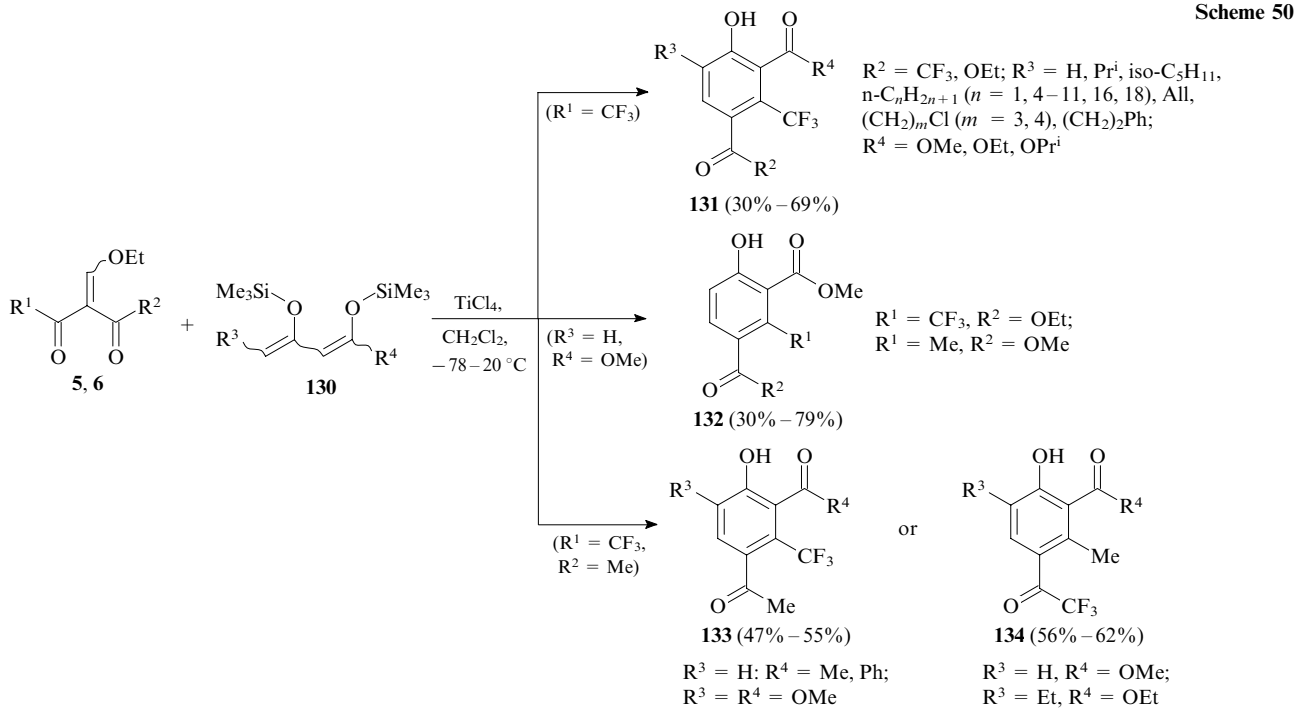
Ar = XC_6H_4 (X = 4-Me, 2-OMe, 2-Et, 3-Me, 4-F)

Scheme 49



$NAlk_2$ = $N(CH_2CH_2)_2X$ (X = CH_2, O); R^1 = CF_3, OEt; R^2 = CN, CO_2Et, Ac, Bz; (*a*) PhMe; (*b*) PhMe, Δ; (*c*) 1) PhMe, Δ; 2) Et_3N, PhMe, 60 °C; (*d*) $SOCl_2$, $CHCl_3$ or TsOH (Et_3N), PhMe

Scheme 50

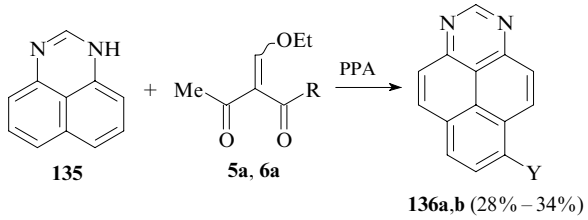


tions involving one of the carbonyl groups and yields different carbo- and heterocyclic systems.

4. Reactions with aromatic compounds

2-Ethoxymethylidene-1,3-dicarbonyl compounds can be used in the reactions of electrophilic aromatic substitution for a hydrogen atom. In particular, the reaction of compounds **5a** and **6a** with 1*H*-perimidine (**135**) in the presence of polyphosphoric acid (PPA) leads to 6-substituted 1,3-diazapyrenes **136a**,**b** (Scheme 51).[207]

Scheme 51



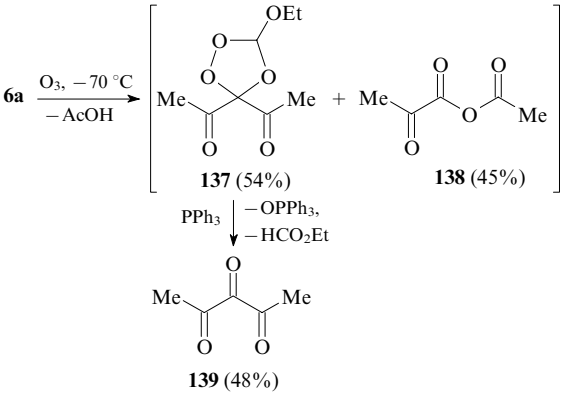
R = Me (**6a**), OEt (**5a**); Y = Me (**136a**), OH (**136b**)

It can be suggested that, first, a hydrogen atom in 1*H*-perimidine (**135**) is replaced by an electrophile according to the S_EAr mechanism, and then the intermediate undergoes cyclization involving one of the carbonyl groups. The transformations are accompanied by hydrolysis and decarboxylation of the ester group.

5. Reactions with ozone

The oxidation of ethoxymethylideneacetylacetone (**6a**) with ozone at −70 °C leads to the cleavage of the double bond, as has been demonstrated by spectral methods. Resulting ozonide **137** can undergo a rearrangement to form mixed anhydride **138**,[208] and treatment with triphenylphosphine leads to formation of acyclic 2,3,4-pentanetrione (**139**) (Scheme 52).

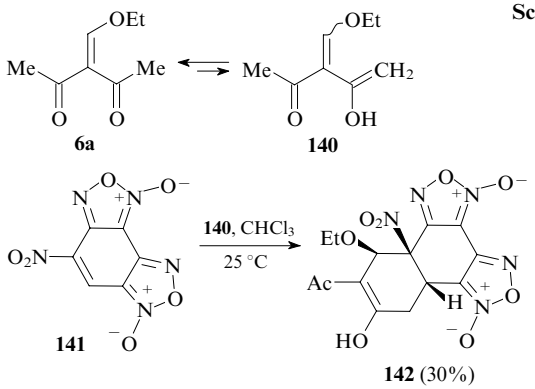
Scheme 52



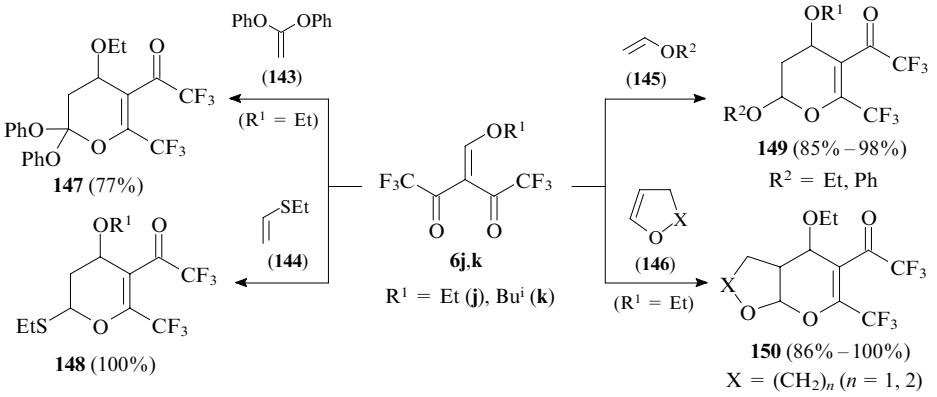
6. Interaction with dienophiles in Diels – Alder reactions

Through enolization at the acetyl group, compounds **6a** can be converted into diene tautomer **140**, which reacts as a dienophile with 4-nitrobenzodifuroxan **141** (Scheme 53).[209] As a result, compound **142** containing two furoxan rings has been synthesized.

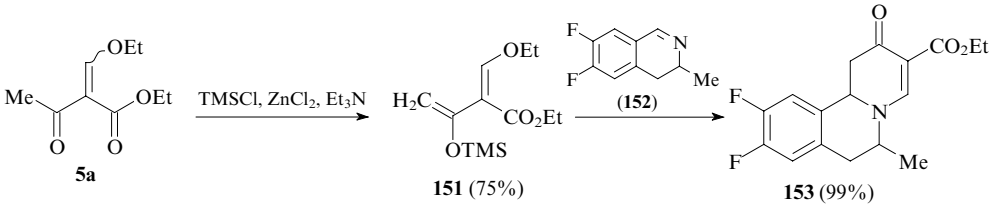
Scheme 53



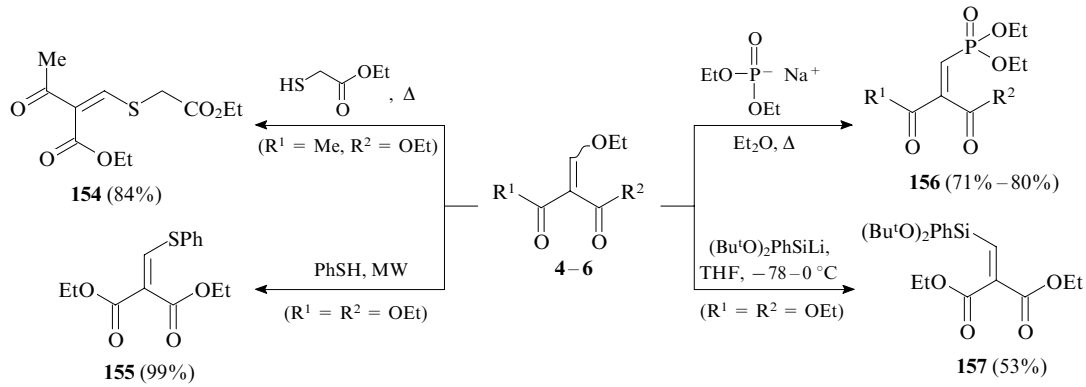
Scheme 54



Scheme 55



Scheme 56



$R^1 = R^2$ = Me, Ph, OEt; R^1 = Me, R^2 = OEt; R^1 = Me, R^2 = Ph

In the same manner, β,β-bis(trifluoroacetyl)vinyl ethers **6** react with dienophiles **143**–**146** to form pyrans **147**–**150** containing, respectively, the trifluoromethyl and trifluoroacetyl groups in the 2- and 3-positions of the ring (Scheme 54).[57]

Silylation of the enolized acetyl group in ethoxymethylideneacetoacetic ester **5a** by trimethylsilyl chloride (TMSCl) in the presence of triethylamine and $ZnCl_2$ leads to structure **151**, which is an electron-excessive carboxy-containing analogue of Danishevsky diene. Diene **151** enters into the aza-Diels–Alder reaction with 3-methyl-6,7-difluoro-3,4-dihydroisoquinoline (**152**), which yields ethyl 6-methyl-9,10-difluoro-1,6,7,11*b*-tetrahydro-2*H*-benzo[*a*]-quinolizin-2-one-3-carboxylate (**153**) (Scheme 55).[118]

7. Reactions with S-, P- and Si-Nucleophiles

In this section, we consider transformations under the action of nucleophilic agents containing heteroatoms, such as sulfur,[59] phosphorus[210] and silicon.[211] These reagents react with 2-ethoxymethylidene-1,3-dicarbonyl compounds **4**–**6** *via* the common route: regiospecifically at the ethoxymethylidene moiety with substitution for the ethoxy group at the C=C double bond to give S(P,Si)-substituted methylidene-1,3-dicarbonyl compounds **154**–**157** (Scheme 56).

IV. Application of 2-(1-alkoxyalkylidene)-1,3-dicarbonyl compounds and their derivatives

1. 2-Ethoxymethylidene-1,3-dicarbonyl compounds as precursors in synthesis of heterocyclic compounds

As already noted above, 2-alkylaminomethylidene-1,3-dicarbonyl compounds **19** (see Scheme 15), obtained by condensation of 2-ethoxymethylidene derivatives **4**–**6** with amines, are widely used as precursors in synthesis of biologically active heterocyclic compounds (see electronic supplement). Different fused heterocyclic systems can be synthesized in one stage by cyclization of compounds **4**–**6** with (hetero)aromatic amines (see Schemes 19–23) or with dinucleophiles (see Schemes 26, 27, 29–31, 33, 34, 36–39). Thus, it is evident that derivatives of this type are good

candidates for use in synthesis of heterocyclic compounds of different classes.

Special progress has been made in synthesis of quinolones. Modification of quinolone moiety has afforded new neuroleptics with high affinity to benzodiazepine receptors;[83] reversible K^+-competitive inhibitors of gastric (H^+/K^+)-ATPase (pharmaceuticals for the treatment of gastrointestinal disorders);[212] anti-infective agents;[118] novel HIV-1 integrase inhibitors;[88, 104, 134] selective platelet-derived growth factor inhibitors (see [99, 100]); ATP-competitive inhibitors of human protein kinase CK2;[93] CB_2-selective cannabinoid receptor ligands (analgesic and anti-inflammatory drugs, agents for the treatment of glioblastoma and lymphoma);[95] liver X receptor modulators (regulators of cholesterol and lipid metabolism for coronary heart disease prevention);[111] immunomodulators.[84]

Ethyl 3-(2,3,4,5-tetrafluorophenyl)-2-ethoxymethylidene-3-oxopropionate (**5m**) is one of the key intermediates for synthesis of a wide range of derivatives of polyfluorinated quinolones [14, 35, 103, 115–117, 134] and benzoxazines [213] exhibiting antibacterial [214] and antitumour [215] activity. It should be especially emphasized that some of such quinolones represent a separate group of modern synthetic antibiotics, such as cifran, ofloxacin and levofloxacin.[216, 217]

2. 2-Ethoxymethylidene-1,3-dicarbonyl compounds in synthesis of metal complexes

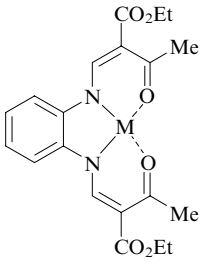
Open-chain derivatives of 2-ethoxymethylidene- and 2-alkylaminoalkylidene-1,3-dicarbonyl compounds are widely used as ligands for synthesis of different metal complexes (Refs 77, 78, 121, 122, 125–133, 158, 218–224). With the aim of searching for catalysts of organic reactions and designing magnetoactive materials based on such compounds, complexes **158**–**169** have been synthesized.

Aminomethylidene derivatives synthesized on the basis of substituted sugars [121] and steroids [220] enabled the synthesis of polynuclear complexes (for example, compound **162**) that turned out to be efficient catalysts of oxidation of di-*tert*-butylpyrocatechol to the corresponding quinone.

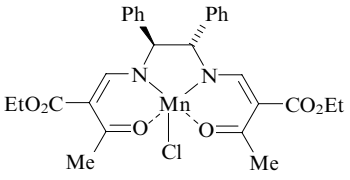
Binuclear copper complex **164** has been described, which exhibits high catalytic activity in luminol chemiluminescence.[77]

Copper complexes **165** with ligands obtained by condensation of polyfluoroalkyl-containing 2-aminomethylidene-3-oxoesters with salicylaldehyde are efficient catalysts of the radical addition of perfluoroalkyl iodides to some alkenes and alkynes.[225] Using these catalysts increases the yield of target products to 70%–91%.

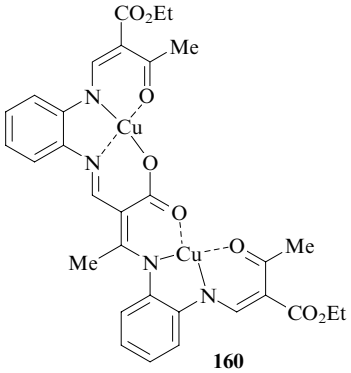
Structures 158–169



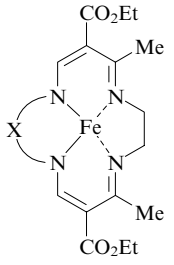
158
(M = Ni^{II}, Cu^{II})



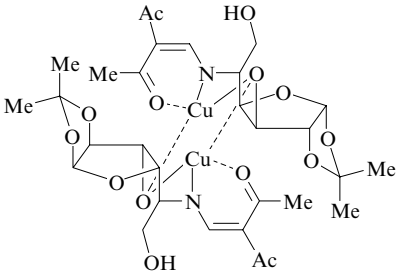
159



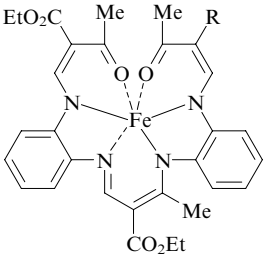
160



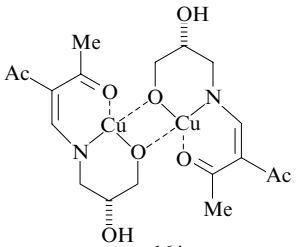
161
(X = C_2H_4, 1,2-C_6H_4)



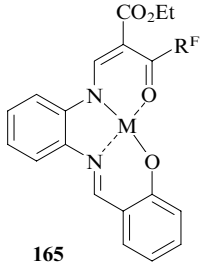
162



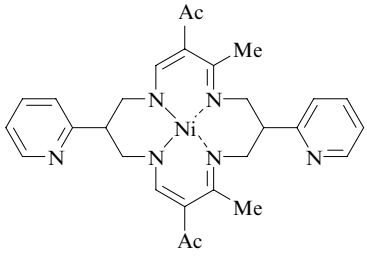
163 (R = Me, OEt)



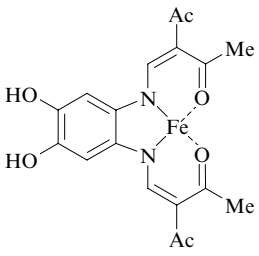
164



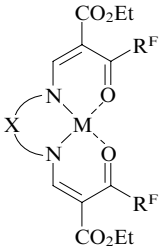
165
(R^F = CF_3, $(CF_2)_2H$, C_3F_7;
M = Ni^{II}, Cu^{II})



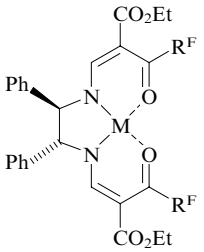
166



167



168
(X = C_2H_4, 1,2-C_6H_4;
R^F = CF_3, $(CF_2)_2H$, C_3F_7;
M = Ni^{II}, Cu^{II}, Co^{II})

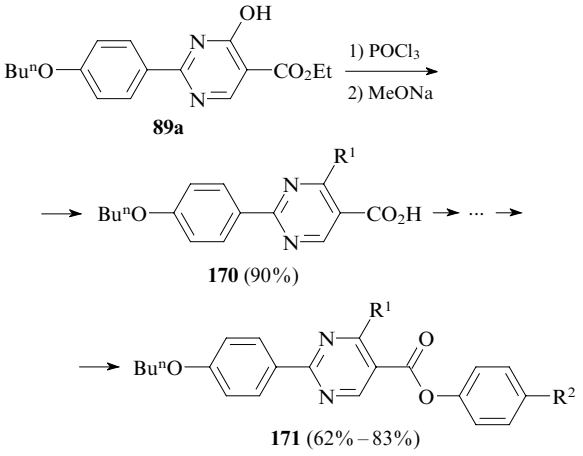


169
(R^F = CF_3, $(CF_2)_2H$, C_3F_7;
M = Ni^{II}, Cu^{II})

3. Liquid crystalline materials based on 2-ethoxymethylidene-1,3-dicarbonyl compounds

2,5-Disubstituted pyrimidine derivatives **89**, synthesized from compound **4a** by Scheme 38, are precursors of components used in liquid-crystalline materials.[192] In particular, pyrimidine **89a** has been used to synthesize acids **170** and corresponding aryl carboxylates **171** (Scheme 57). The liquid-crystalline properties of esters **171** (melting point, nematic phase range, *etc.*) essentially depend on the nature of substituents R^1 and R^2.

Scheme 57

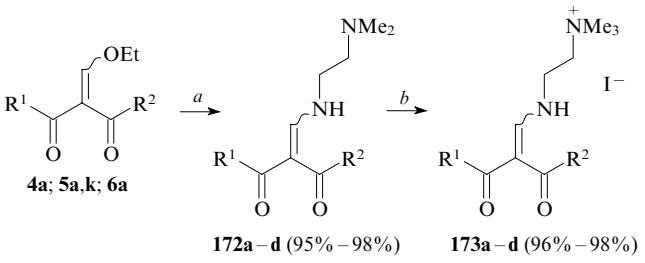


R^1 = OMe; R^2 = Am, Bn, OBu^n, CN, $CO_2C_6H_4Am$-4 (Am = n-C_5H_{11})

4. 2-Ethoxymethylidene-1,3-dicarbonyl compounds in synthesis of anti-corrosion and anti-aggregation agents

It has been shown that water-soluble quaternary ammonium salts **173a**–**d**, obtained from 2-aminomethylidene-1,3-dicarbonyl compounds **172a**–**d**, are efficient inhibitors of hydrochloric acid corrosion of carbon steel St3 (Scheme 58).[82] The best corrosion protection is provided by compounds **173a**,**b**, which have a symmetric structure of the 1,3-dicarbonyl moiety. The use of salts **173** in synthesis of cadmium and zinc sulfides makes it possible to vary the size of colloid particles in an aqueous medium.[226]

Scheme 58



172, **173**: R^1 = R^2 = Me (**a**), OEt (**b**), R^1 = OEt: R^2 = Me (**c**), C_3F_7 (**d**); (*a*) $H_2NCH_2CH_2NMe_2$, Et_2O, 25 °C; (*b*) MeI, 25–30 °C

V. Conclusions

Analysis of literature data shows that 2-alkoxyalkylidene-1,3-dicarbonyl compounds are promising building blocks for organic chemistry. Their diversity is due to a wide variety of 1,3-dicarbonyl components. The synthetic availability of such derivatives is ensured by simple methods of their synthesis.

Compounds of this class are highly reactive towards various N-, C-, O-, S-, P- and Si-containing mono- and dinucleophilic reagents, which makes it possible to design, on their basis, diverse acyclic, carbo- and heterocyclic molecules.

Unlike their 1,3-dicarbonyl precursors, 2-alkoxyalkylidene derivatives, first of all, react at the alkoxyalkylidene substituent to form open-chain products, for example, 2-alkoxyaminomethylidene-1,3-dicarbonyl compounds. The latter are of interest as complexing ligands. This field is rather promising for creation of metal complex catalysts, efficient extractants and optically and magnetically active materials.

2-Alkoxyalkylidene derivatives of 1,3-dicarbonyl compounds offer wide possibilities in synthesis of different heterocyclic systems (pyrroles, pyrans, pyrazoles, isoxazoles, pyrimidines, chromones, quinolones, azolopyridines, azolopyrimidines, *etc.*). The type of resulting heterocycle can be *a priori* determined by the structure of the dinucleophile introduced into the reaction. Especially noteworthy is the ability of similar compounds to generate poorly available functionalized carbocyclic derivatives in the reaction with C,C′-dinucleophiles. In most cases, cyclization occurs regiospecifically at one of the carbonyl groups, and its participation is caused by the nature of the dicarbonyl moiety. Development of this field is promising for synthesis of carbo- and heterocyclic molecules with different spectra of physiological action.

The cited literature data are evidence of the high synthetic potential of 2-alkoxyalkylidene-1,3-dicarbonyl compounds. Many aspects of their chemistry are still little studied. It is of interest to extend studies of nucleophilic reactions with S- and P-nucleophiles and dinucleophiles containing these heteroatoms. Almost no information is available on the reactions of 2-alkylaminoalkylidene derivatives with electrophilic reagents (for example, alkylation, acylation, etc.) aimed at synthesis of polydentate ligands with different organization of the coordination site, as well as on the synthesis of polynuclear metal complexes based on these ligands. Very promising is the chemistry of polyfluoroalkyl and especially polyfluoroaryl derivatives, which significantly differ in reactivity from the hydrocarbon analogues.

This review is intended to draw the attention of organic chemists to 2-alkoxyalkylidene-1,3-dicarbonyl compounds as readily available building blocks. Versatility of these compounds is in the possibility of targeted synthesis, on their basis, of open-chain, carbo- and heterocyclic structures essential for studies in the fields of coordination and pharmaceutical chemistry and materials science.

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