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REVIEW

Heterocyclizations of *β*-alkoxy, *β*-diaminoalkyl, and related *β*-functionalized enones (enals) with *NCN*-binucleophiles

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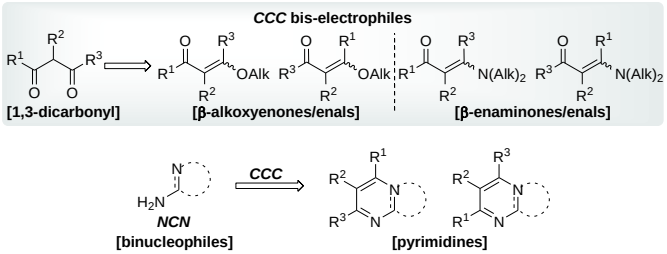
Abstract: This review provides a detailed survey of the present literature data on *β*-alkoxyvinyl- and *β*-enaminocarbonyl compounds as *CCC bis*-electrophiles in reactions with the common *NCN*-binucleophiles. The focus is put mostly on the reactions leading to low-molecular-weight and functionalized pyrimidines as the products that are of special interest as building blocks for drug discovery.

Keywords: heterocycles; pyrimidines; enones; *bis*-electrophiles; binucleophiles.

Introduction

It is well-known that pyrimidines and their fused derivatives are the most abundant heterocycles in marketed drugs and natural compounds, such as nucleic acids and numerous alkaloids [1-4]. A general approach toward their synthesis (the so-called “principal pyrimidine synthesis”) includes the use of 1,3-dicarbonyl compounds as *CCC bis*-electrophiles in heterocyclizations with *NCN* binucleophiles [5-10]. Due to the strong electrophilic nature of dicarbonyl compounds, they sometimes possess high reactivity and consequent limited stability. In turn, this results in problems with chemo- and regioselectivity, lowered yields of the products, as well as limited accessibility of some of the target heterocycles. This is especially true for the case of the simplest representatives bearing no additional substituents or decorated with the smallest alkyl substituents at the azine core.

To address the above issues, *β*-alkoxyvinyl- and *β*-enaminocarbonyl compounds have been developed as the synthetic equivalents of classical 1,3-dicarbonyl *CCC bis*-electrophiles with a push-pull reactivity (Scheme 1). In addition to increased stability and the possibility to synthesize the simplest and the least substituted functionalized heterocycles [11-15], these building blocks provide increased chemo- and regioselectivity with diminished side processes, as well as improved yields of the condensation product [16-23]. The synthesis of these *bis*-electrophiles can be achieved starting from 1,3-dicarbonyl compounds [16, 24-26] or alkoxyvinyl acetylenes [27], by reaction of ketals with acylating agents [28, 29], acylation of vinyl ethers [29-31], the Heck-type palladium-catalyzed carbonylation of vinyl ethers in the presence of aryl iodides and carbon monoxide [32, 33], and other methods.



Scheme 1. *β*-Alkoxyvinyl- and *β*-enaminocarbonyl compounds as the synthetic equivalent of 1,3-dicarbonyl compounds.

This review provides a comprehensive analysis of heterocyclizations of *β*-alkoxyvinyl- and *β*-enaminocarbonyl compounds with *NCN* binucleophiles, focusing mainly on the synthesis of low-molecular-weight and functionalized heterocycles as the target products. First, reactions of various *bis*-electrophile types with the classi-

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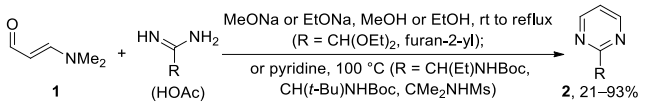
cal acyclic *NCN* binucleophiles (e.g. amidines, guanidines, thiuronium salts, etc.) are discussed. Then, heterocyclizations with aminoheterocycles leading to fused pyrimidines are covered.

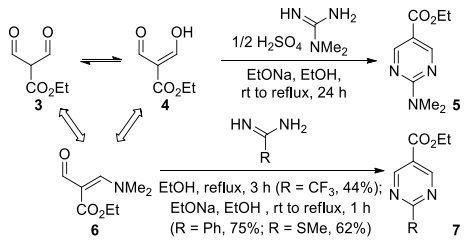
β-Alkoxy- and *β*-diaminoalkyl enals

Parent *β*-enaminal **1** was evaluated as a convenient reagent for the preparation of 2-substituted pyrimidines **2** by reactions with amidines bearing acetal [34], furan-2-yl [35], or aminoalkyl moieties (Scheme 2) [36].



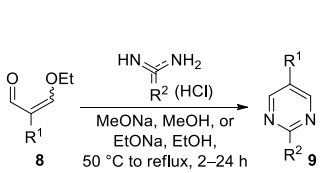
Scheme 2. Synthesis of 2-substituted pyrimidines **2**.

Taking into account the fact that *β*-enamino carbonyl compounds can generate the corresponding dicarbonyl compounds upon alkaline hydrolysis [37], the chemical behavior of *α,β*-unsaturated carbonyl compounds bearing a leaving group at the *β*-position can be modelled by the tautomerization of 2-formyl-3-oxopropanoate (**3**) into 3-hydroxyacrylate **4** that reacts with *N,N*-dimethylguanidine to give 2,5-disubstituted pyrimidine **5** (Scheme 3). Ethyl 3-(dimethylamino)-2-formyl acrylate (**6**) is a stable synthetic equivalent of both **3** and **4** and undergoes heterocyclization with amidines or isothiourea to give pyrimidine-5-carboxylates **7** [25, 38].



Scheme 3. Heterocyclizations of 3-(dimethylamino)-2-formyl acrylate **6**.

Reactions of the corresponding *β*-alkoxyenals are represented by *α*-alkyl-substituted derivatives **8**, which provided 2,5-disubstituted pyrimidines **9** by treatment with amidines [39-42], guanidine [41], urea [43], and thiourea [43] (Scheme 4).

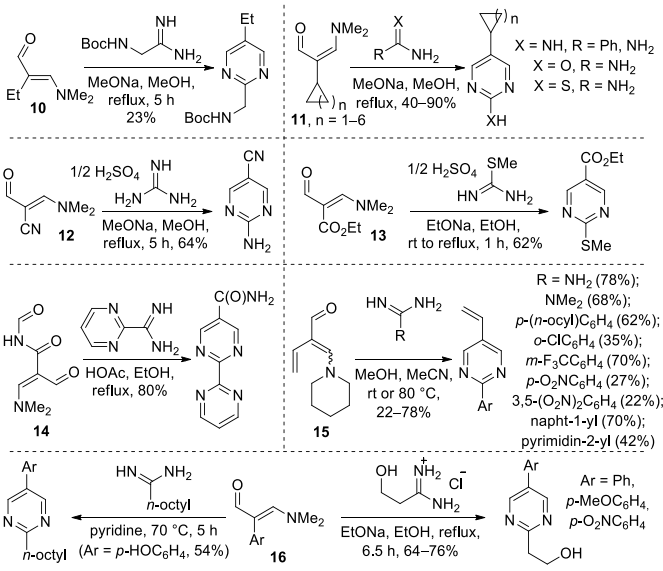


R^1 = Me: R^2 = NH_2 (40%), Ph (62%), *p*-MeC_6H_4 (67%), CH_2NHBoc (75%);
R^1 = *n*-heptyl, R^2 = Me (15%);
R^1 = *n*-octyl, R^2 = *p*-HOC_6H_4 (44%);
R^1 = *n*-decyl, R^2 = *p*-HOC_6H_4 (49%);
R^1 = *n*-dodecyl, R^2 = *p*-HOC_6H_4 (54%);
R^1 = *n*-dodecyl, R^2 = *m*-HOC_6H_4 (63%);
R^1 = *s*-Bu, R^2 = O(H) (7%);
R^1 = *s*-Bu, R^2 = S(H) (72%).

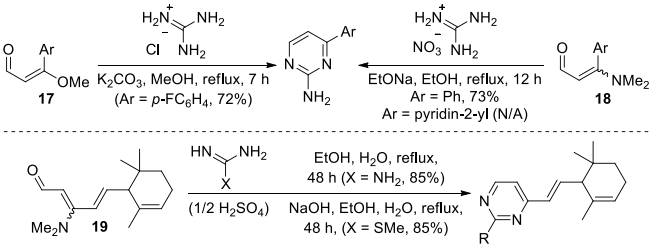
Scheme 4. Heterocyclizations of α-alkyl-substituted *β*-alkoxyenals **8**.

A wide range of *β*-enaminals bearing an *α*-substituent have been reported, including compounds with alkyl **10** [40, 44, 45], cycloalkyl **11** [46], nitrile **12** [47-51], imide **13** [52], ester groups **14** [38], chorine [53], and other moieties (Scheme 5). Formyldiene **15** was used as a versatile reagent for the synthesis of a series of 5-vinylpyrimidines [54]. 5-(Het)aryl-substituted pyrimidines could be prepared by using aryl-substituted enones **16** [53, 55-57] or those decorated with thiohetaryl groups [58].

On the contrary, heterocyclizations of *β*-aryl-substituted alkoxyenals **17** [59] and enaminals **18** [60] have been scarcely reported providing limited examples of 2,4-disubstituted pyrimidine synthesis (Scheme 6). This substitution pattern was also represented by enaminal **19** [61-63].



Scheme 5. Heterocyclizations of *α*-substituted *β*-enaminals.

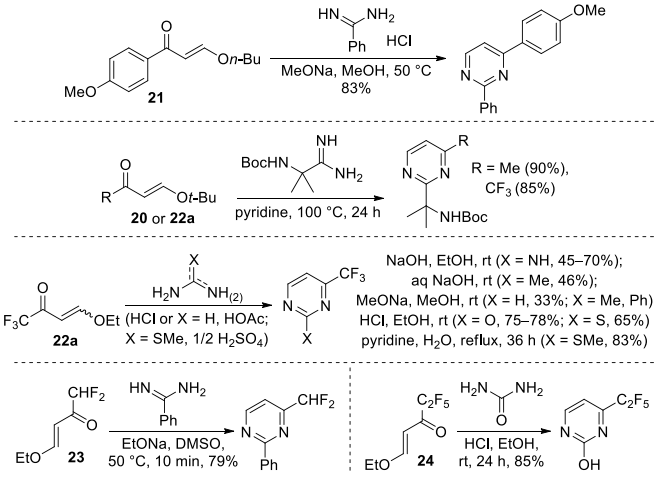


Scheme 6. Heterocyclizations of *β*-substituted enals **17**–**19**.

Usual *β*-alkoxy- and *β*-diaminoalkyl enones

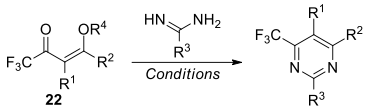
One more type of *β*-alkoxy-*α,β*-unsaturated carbonyl compounds is represented by a few examples of alkyl- **20** [36] and aryl-substituted **21** *β*-alkoxyenones (Scheme 7) [32]. The most well-studied compound for this category is CF_3-substituted derivative **22a** [64-66], which might be due to its chemical accessibility and the importance of the corresponding fluorinated heterocyclic products to medicinal chemistry. The known examples included the reaction of **22a** with guanidine [67, 68], urea [67, 69], thiourea [67], isothiourea [70], formamidine [69] acetamidine, and benzamidine [71]. The variability of substituents and heterocyclization conditions of trifluoro-4-alkoxybut-3-en-2-ones **22** for the synthesis of 4-CF_3-substituted pyrimidines is summarized in Table 1 [29, 66-69, 72-79].

Analogous transformations included the condensation of CHF_2-substituted analog **23** with benzamidine [80] and C_2F_5-substituted compound **24** – with urea [81] (Scheme 7). Prominent examples of using **22a**, **23**, and *β,β*-dimethoxyenones **25** and **26** included reactions with amidine **27** for the synthesis of 4-(di)trifluoromethylpyrimidines **28** and **29** (Scheme 8) [82]. Related 2-(ethoxymethylene)-4,4,5,5-tetrafluoro-3-oxopentenoate **30** was used for the preparation of tetrafluoroethylpyrimidine **31** (Scheme 9) [75, 76]. In turn, using 5-aminotetrazole could result in either 2-aminopyrimidines [83] or 2-azidopyrimidines [76].

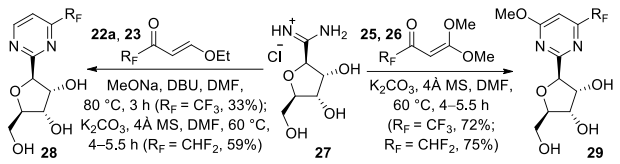


Scheme 7. Heterocyclizations of *β*-alkoxyenones **20-24**.

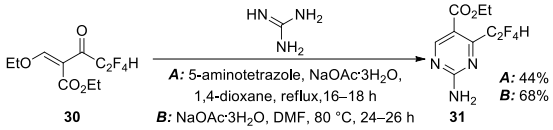
Table 1. Heterocyclizations of CF_3-substituted *β*-alkoxyenones 37.



R^1	R^2	R^3	R^4	Conditions	%
H	H	NH_2	Et	NaOH, EtOH	70 [84]
CO_2Et	H	NH_2	Et	aminotetrazole, 1,4-dioxane, $NaOAc·3H_2O$, reflux, 16-18 h	38 [83]
CO_2Et	H	NH_2	Et	$NaOAc·3H_2O$, DMF, 80 °C, 24-26 h	60 [83]
CO_2Et	H	NMe_2	Et	EtONa, EtOH, reflux, 1 h	70 [85]
H	CH_2N_3	SMe	Me	Na_2CO_3, H_2O, rt, 3 h	75 [86]
H	$(CH_2)_2CO_2Me$	Me	Me	trichloro-isocyanuric acid, EtOH, rt, 30 min.	59 [87]
		Ph			62 [87]
		SMe			52 [87]
H	H	2-amino-benzo-thiazo-lyl	Et	H_2O, reflux, 24 h	65 [88]
H	Me		Me/Et		75 [88]
Me	H		Me/Et		88 [88]
H	Ph		Me		80 [88]
H	*p*-$MeOC_6H_4$		Me		70 [88]
H	*p*-MeC_6H_4		Me		60 [88]
H	*p*-BrC_6H_4		Me	H_2O, reflux, 8 h	80 [88]
H	*p*-FC_6H_4		Me		70 [88]
H	thien-2-yl		Me		60 [88]

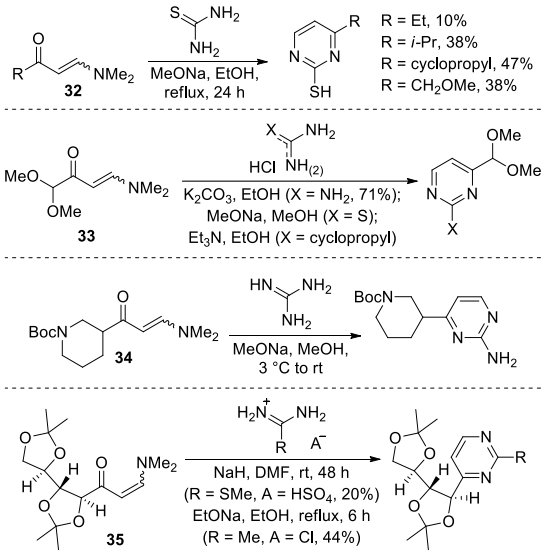


Scheme 8. Synthesis of (*β*-D-ribofuranosyl)-4-(di)trifluoromethylpyrimidines.



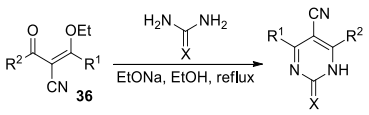
Scheme 9. Preparation of tetrafluoroethyl-substituted pyrimidine **31**.

Representative examples of *β*-amino-substituted *α,β*-unsaturated ketones included derivatives decorated with (cyclo)alkyl **32** [89], acetal **33** [90, 91], piperidine **34** [58, 92], and bis-1,3-dioxolane **35** [93] moieties (Scheme 10).



Scheme 10. Heterocyclizations of 4-(dimethylamino)but-3-en-2-ones **32-35**.

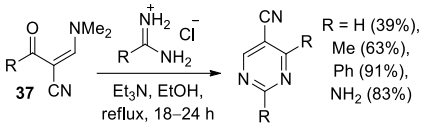
Table 2. Reactions of acylated *β*-alkoxyacrylonitriles **36**.



R^1	R^2	X	Yield, %
Me	Me	S	N/A[a]
Me	Et	S	50
Me	*n*-Pr	S	15
Me	*i*-Pr	S	42
Et	Et	S	61
Ph	Ph	S	N/A[a]
Et	Et	O	10
Me	Et	NH_2	52
Et	Et	NH_2	50
Et	Et	Me	56

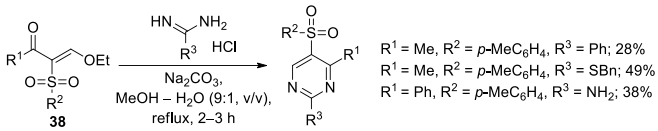
[a] Yield was not given.

α-Acylacrylonitriles **36** reacted with (thio)urea or guanidine to form the corresponding tetrasubstituted (thio)pyrimid-2-ones or 2-aminopyrimidines (Table 2) [94]. Analogous transformations have been reported for the case of cyano-substituted enaminones **37** (Scheme 11).



Scheme 11. Heterocyclizations of α-acyl-β-(dimethylamino)-acrylonitriles **37**.

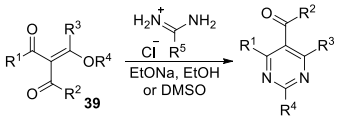
The scope of β-alkoxyenones with electron-withdrawing substituents at the α-position also includes sulfones **38**, which reacted with benzamidine, isothiourea, and guanidines to give the corresponding 5-sulfonylpyrimidines in moderate yields (Scheme 12) [95].



Scheme 12. Reactions of α-sulfonyl-β-ethoxyenones **38**.

Reactions of enones bearing an additional carbonyl or alkoxycarbonyl moiety at the α-position [6, 8, 10, 17, 96-98] with nucleophiles typically proceeded at the more electrophilic ketone carbonyl group. Representative examples included reactions of 2-carbonyl-3-ethoxyacrylates **39** with urea, acetamidine, and trifluoroacetamidine described

Table 3. Heterocyclizations of β-alkoxyenones **39** bearing an additional carbonyl moiety at the α-position.



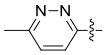
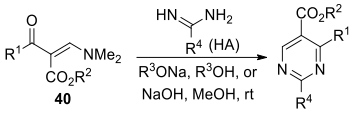
R^1	R^2	R^3	R^4	R^5	Yield, %
CF_3	OEt	H	Et	thien-2-yl	89
CF_3	OEt	H	Et		74
CF_3	OEt	H	Et	O(H)	45
CF_3	OEt	H	Et	Me	55
CF_3	OEt	H	Et	CF_3	39
C_2F_5	OEt	H	Et	O(H)	66
Ph	OEt	H	Et	O(H)	65
thien-2-yl	OEt	H	Et	O(H)	51
n-Pr	OEt	H	Et	O(H)	72
Et	OEt	H	Et	O(H)	81
Me	OEt	H	Et	O(H)	88
Me	OEt	H	Et	CF_3	58
Me	Me	H	Et	pyridine-4-yl	87
Me	Me	H	Et	SMe	70
Me	OEt	H	Et	Ph (flow synthesis)	80 [101]
Me	OEt	H	Et	NH_2	85 [102]
Me	OEt	H	Et	S	86 [49]
Me	OEt	Me	Et	*o*-$MeOC_6H_4$	73
Me	OEt	Me	Et	cyclobutyl	82
Me	OMe	Me	Me	4-*t*-BuC_6H_4	N/A [103]
Me	OMe	Me	Me	CF_3 (no base, MeOH, acetone)	44 [104]

Table 4. Heterocyclizations of β-enaminones **40** bearing an alkoxycarbonyl moiety at the α-position.



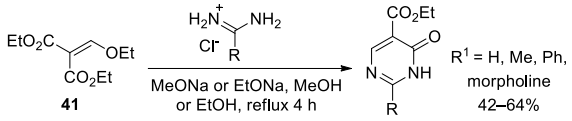
R^1	$R^2 = R^3$	R^4	Yield %
Me	Me (Et)	H	50 [105]
Et	Et		45 [106]
Me	Me	Me	85 [105]
Me	Et		65 [107]
Et	Et		67 [107]
n-Pr	Et		62 [107]
i-Pr	Et		85 [107]
n-Bu	Et		N/A [108]
i-Bu	Et		N/A [108]
CH_2cyclopropyl	Et		N/A [108]
CH_2cyclopentyl	Et		N/A [108]
cyclopentyl	Et		N/A [108]
cyclopentyl	Et		N/A [108]
t-Bu	Et		88 [107]
CH_2OMe	Et		64 [107]
Ph	Et		68 [107]
Bn	Me		13 [107]
p-FC_6H_4	Et		61 [109]
(*N*-Ph-pyrrolid-2-on)-4-yl	Me		50 [110]
Et	Et	*n*-Pr	87 [111]
Me	Et	Ph	68 [107]
			80 [112]
Et	Me		73 [112]
Et	Et		71 [107]
n-Pr	Et		80 [107]
i-Pr	Et		60 [107]
t-Bu	Et		75 [107]
CH_2OMe	Et		67 [107]
Bn	Me		22 [107]
Ph	Et		72 [107]
m-$O_2NC_6H_4$	Et		91 [113]
p-$O_2NC_6H_4$	Et		86 [113]
(*N*-Ph-pyrrolid-2-on)-4-yl	Me		65 [110]
m-$O_2NC_6H_4$	Et	*p*-ClC_6H_4	84 [113]
p-$O_2NC_6H_4$	Et		76 [113]
Et	Et	*p*-HOC_6H_4	86 [114]
Me	Et	NH_2	81 [107]
Et	Et		74 [107]
n-Pr	Et		73 [107]
i-Pr	Et		70 [107]
t-Bu	Et		81 [107]
Bn	Et		37 [107]
CH_2OMe	Et		66 [107]
Ph	Et		80 [107]
			(84 [109])
p-FC_6H_4	Et		N/A [115]
m-$O_2NC_6H_4$	Et		51 [113]
H	Et	NMe_2	59 [85]
Me	Et		87 [85]
CH_2OMe	Me		70 [85]
Et	Et		85 [85]
и-Pr	Et		86 [85]
i-Pr	Et		82 [85]
m-Bu	Et		72 [85]
Bn	Me		41 [85]
Ph	Et		86 [85]
CO_2Et	Et		41 [85]
Ph	Et	SMe	77 [109]
5-Me-thien-2-yl	Et (Me)		50 [56]
p-FC_6H_4	Et	*p*-$ClC_6H_4CH_2S$	66 [109]

[a] Et_3N, EtOH was used instead of sodium alkoxide or alkali

for the synthesis of 2,4-disubstituted 5-carboxylates or the corresponding ketones (Table 3) [25, 94, 99, 100]. Notably, it is possible to apply the continuous flow synthesis conditions to the reaction of enones for bezamidine [101].

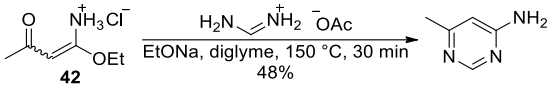
A wide range of analogous enaminones **40** easily accessible through DMFDMA-mediated condensation reactions has been also used for the preparation of pyrimidines (Table 4).

A promising chemotype of pyrimidine-5-carboxylates could be obtained from 2-(alkoxymethylene)malonate **41** that was involved in reactions with formamidine [108], acetamidine [108], benzamidine [112], and morpholine-derived guanidine [108] (Scheme 13).



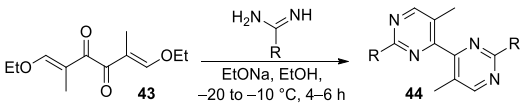
Scheme 13. Heterocyclizations of ethyl 2-(alkoxymethylene)malonates (**41**).

One more interesting example included the reaction of alkoxyenone **42** bearing a non-protected *β*-amino group, which provided an access to 4-aminopyrimidines (Scheme 14) [116].



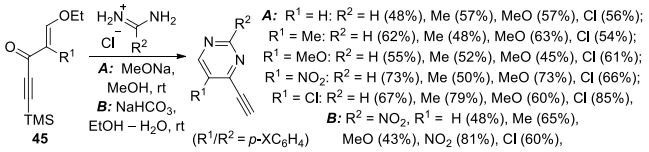
Scheme 14. Heterocyclization of 4-amino-4-ethoxybut-3-en-2-one hydrochloride (**42**).

Also, bis-alkoxyvinyl ketone **43** was converted into the corresponding 4,4'-bipyrimidines **44** in moderate yield via the condensation with amidines or isothiourea (Scheme 15) [117].



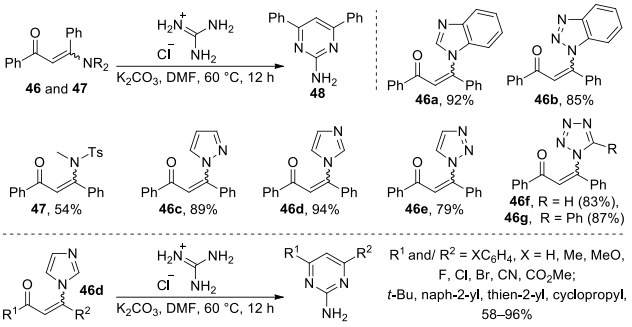
Scheme 16. Double heterocyclization into 4,4'-bipyrimidines **44**

Heterocyclization of enones **45** bearing a silylated alkyne moiety with aromatic amidines was disclosed as a good method for the synthesis of a wide range of alkynylpyrimidines (Scheme 17) [118]. This transformation could be also carried out without desilylation. However, the predominant formation of ethyl 2-(4-nitrophenyl)acetate (up to 50% yield) was observed upon the typical reaction conditions for the case of the nitro-substituted derivatives **45**.



Scheme 17. Heterocyclizations of 5-(trimethylsilyl)penten-4-yn-3-ones **45**.

Aside from the common dialkylamino moiety, screening of a range of azolyl and *N*-tosyl enones **46** and **47**, respectively, in the model reaction with guanidine for the preparation of pyrimidines **48** revealed that the best-leaving groups is imidazolyl moiety (Scheme 18) [119]. The reaction of a series of imidazole-1-yl enones **46d** with *NCN* nucleophiles was suitable to give pyrimidines in good to excellent yields.



Scheme 18. Reaction of azolyl and *N*-tosyl enones **46** and **47**.

β-Alkoxyvinyl- and *β*-enamino *α*-ketoesters

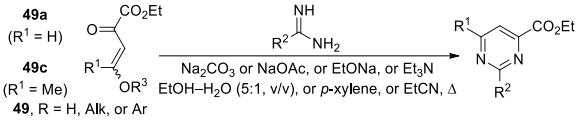
Using *β*-alkoxyvinyl *α*-ketoesters (synthetic equivalents of acyl pyruvates) as the *CCC* bis-electrophiles was studied as a multipurpose method for the preparation of the simplest pyrimidine-4-carboxylates. The presence of the ester functional group at the low-molecular-weight pyrimidine core provides an entry towards readily accessible building blocks relevant to medicinal chemistry. Despite the wide synthetic potential and stability of *β*-alkoxyvinyl *α*-ketoesters, their use in the known literature procedures had long been limited by non-optimized reactions of **49** with *S*-methyl- and *S*-benzyl thiouronium salts [28], acetamide, 2-methylbenzimidamide, and guanine, leading to the formation of di- and trisubstituted pyridine-4-carboxylates [120-123] (Table 5). However, good to high yields of products were obtained with *β*-aryl-substituted enones **49**, while reactions of simplest derivative **49a** and *β*-methylated derivative **49c** typically provided pyrimidines in low yields.

Screening for the optimal conditions of the heterocyclization reaction was initially performed for the synthesis of ethyl 2,6-diphenylpyrimidine-4-carboxylate ($R^1 = R^2 = Ph$): the highest yield was achieved using Na_2CO_3 as a base [28]. These reaction conditions were extended to synthesize a series of 2-methylthiopyrimidines **50** (Scheme 19). When the reactions were carried out in the presence of NaOH, hydrolysis of oxobutenoate **49** was observed.

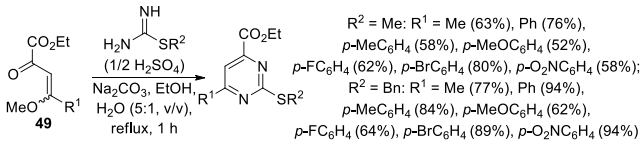
The reactivity of *β*-alkoxyvinyl *α*-ketoesters **49a-c** as *CCC bis*-electrophiles in condensation reactions with 15 representative amidines, *S*-methylthiuronium salt, and guanidines was recently disclosed by our group (Scheme 20) [13]. A typical procedure relied on heating reagents in MeCN at 70 °C in the presence of K_2CO_3 for 2 h (Method A), which was suitable only for the most reactive *β*-methylated enone **49c**. The corresponding pyrimidines were synthesized in good to high yields. In turn, heating of

the starting compounds in the presence of Et_3N in 1,4-dioxane at 100 °C for 48 h (Method B) worked well for the parent enone **49a** and the least reactive derivative **49b**, as well as for methyl, cyclopropyl, and *p*-chlorophenyl-substituted amidines with low reactivity, and provided higher yields of the corresponding pyrimidines. However, method B proved to be ineffective in all experiments with formamidine acetate and could not be used for chloromethyl-substituted amidine due to the side alkylation of Et_3N.

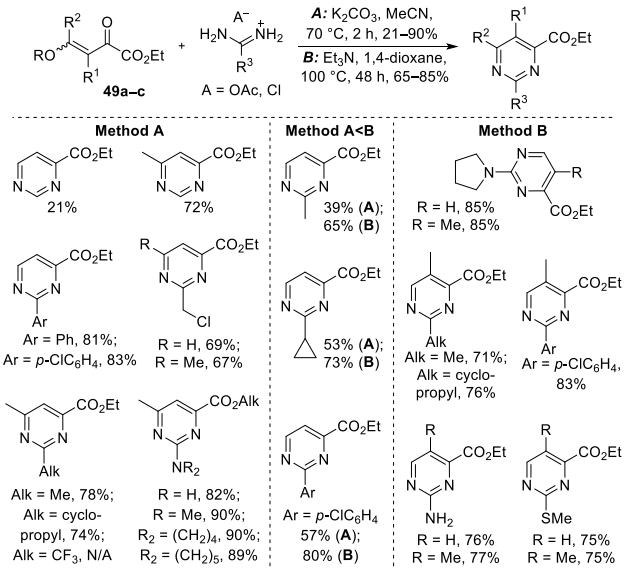
Table 5. Heterocyclizations of *β*-alkoxyvinyl *α*-ketoesters **49**.



R^1	R^2	R^3	Conditions	Yield %
Me	SMe	Me	1 M Na_2CO_3,	63 [28]
Ph			EtOH, H_2O (5:1, v/v)	76 [28]
p-MeC_6H_4			reflux, 1 h.	58 [28]
p-$MeOC_6H_4$				52 [28]
p-FC_6H_4			Ratio	62 [28]
p-BrC_6H_4			*CCC* / *NCN* / base =	80 [28]
p-$O_2NC_6H_4$			1 : 2 : 2	58 [28]
Me	SBn	Me	1 M Na_2CO_3,	77 [28]
Ph			EtOH, H_2O (5:1, v/v)	94 [28]
p-MeC_6H_4			reflux, 1 h.	84 [28]
p-$MeOC_6H_4$				62 [28]
p-FC_6H_4			Ratio	64 [28]
p-BrC_6H_4			*CCC* / *NCN* / base =	89 [28]
p-$O_2NC_6H_4$			1 : 1.2 : 1.2	94 [28]
H	Me	Et	N/A	N/A [120]
H	*o*-tolyl	Et	NaOAc, *p*-xylene, reflux, 36 h	36 [74]
H	NH_2	Et	Et_3N, EtCN, 100 °C, 24 h	27 [123]



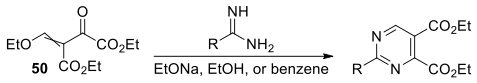
Scheme 19. Synthesis of 2-methylthiopyrimidine-4-carboxylates.



Scheme 20. The reactivity pattern of *β*-alkoxyvinyl α-ketoesters **49a-c**.

Moreover, heterocyclization reactions of 2-(ethoxymethylene)-3-oxosuccinate **50** for the synthesis of 2-substituted pyrimidine-4,5-dicarboxylates have been widely studied (Table 6); EtONa in EtOH was typically used.

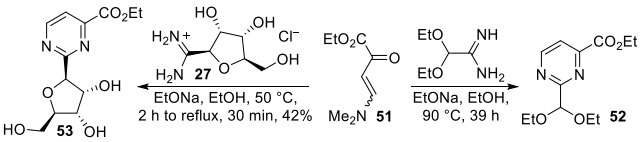
Table 6. Heterocyclizations of 2-(methylene)-3-oxosuccinate **50**.



R	Conditions	Yield, %
NH_2	EtONa, EtOH, 1.5 h, 0 °C to rt.	57 [124]
OH	neat, heat	70[a] [124]
H	benzene, reflux, 2.5 h	68 [125]
H		37 [126]
Me		N/A[b] [127]
Et		40 [126]
CH_2OH		29 [126]
n-pentyl		51 [126]
Ph		85 [126]
m-MeC_6H_4	EtONa, EtOH, 0 °C to rt, 5 h	76 [126]
p-ClC_6H_4	(overnight)	93 [126]
p-$O_2NC_6H_4$		84 [126]
p-$MeOC_6H_4$		53 [126]
napht-2-yl		53 [126]
pyridin-2-yl		87 [126]
furan-2-yl		89 [126]
thien-2-yl		90 [126]

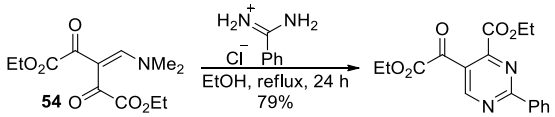
[a] The intermediate diethyl ureidomethylene oxaloacetate was isolated with pyrimidine, the overall yield is given [b] Yield was not reported.

Enaminone **51** bearing an additional ester group also proved to be a good reagent for the preparation of pyrimidines (Scheme 21); representative examples included acetal **52** [128-130] and 2-(*β-D*-ribofuranosyl)pyrimidine **53** (via the condensation of **27**) [131].



Scheme 21. Synthesis of pyrimidines **52** and **53**.

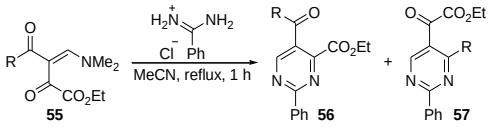
The scope of reported enones included derivative **54** [132, 133] decorated with two glyoxylate moieties (Scheme 22) and other polycarbonyl enones **55**. An interesting study revealed that their condensation with *NCN* binucleophiles, e.g. benzamidine, could occur at both competing carbonyl groups and, therefore, could result in the formation of pyrimidine-4-carboxylate **56** (the major or the only product in most cases) or pyrimidine-5-glyoxylate **57** (Table 7) [134]. The observed regioselectivity could be explained by the more electrophilic nature of the carbonyl group adjacent to the ester moiety as compared to the benzoyl-type fragment, with an exception of CF_3-substituted ketone moiety.



Scheme 22. Heterocyclization of bis-glyoxylate-derived enone **54**.

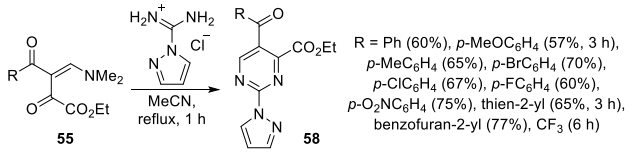
This trend was confirmed in other works describing the use of 1*H*-pyrazole-1-carboximidamide for the regioselective synthesis of biaryl derivatives **58** (Scheme 23) [135].

Table 7. Regioselectivity in heterocyclizations of enaminone **55**.



R	Ratio **56** : **57**	Yield, %[a]
Ph	10:1[b]	84
p-MeC_6H_4	1:0	86
p-$MeOC_6H_4$	1:0	78
p-BrC_6H_4	5:1	81
p-ClC_6H_4	10:1	72
p-FC_6H_4	1:0	82
p-$O_2NC_6H_4$	2:1	78
thien-2-yl	1:0	70
benzofuran-2-yl	3:1	81
CF_3	0:1	50

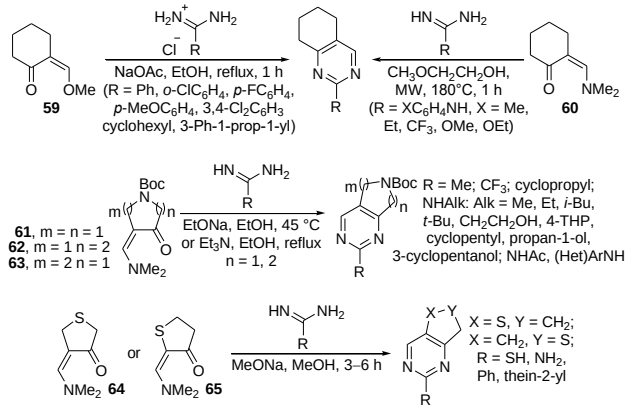
[a] Yield is given for both regioisomers [b] Reverse regioselectivity has been also reported [132, 133].



Scheme 23. 2-(1*H*-Pyrazol-1-yl)pyrimidine-4-carboxylates **58**.

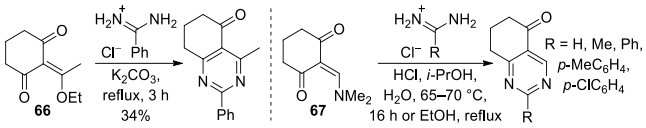
Cyclic *β*-alkoxy- and *β*-diaminoalkyl enones

An important chemotype is presented by pyrimidines fused with saturated rings that can be obtained by reactions of amidines with cycloalkanones bearing an exocyclic double bond, *e.g.* 2-(methoxymethylene)cyclohexan-1-one (**59**) [136] or analogous enaminone **60** [137-144] (Scheme 24).



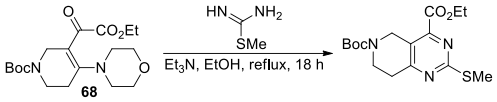
Scheme 24. Heterocyclizations of (hetera)cycloalkanone derivatives **59**-**65**.

Promising derivatives could be obtained from saturated heterocyclic ketones, *i.e.* pyrrolidone **61** [145, 146], isomeric piperidones **62** and **63** [145, 147], thiolanones **64** and **65** [148], *etc.* [149]. Enones **66** [26] and **67** [150, 151] derived from dihydroresorcinol provide an entry to fused pyrimidines with carbonyl group (Scheme 25). Other transformations included the use of substituted cyclic diketones [150, 152, 153] in reactions with amidines [150, 154] and guanidines [150, 153-155].



Scheme 25. Heterocyclizations of 2-methylene-cyclohexane-1,3-diones **66** and **67**.

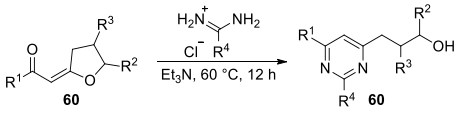
Tetrahydropyridine-derived glyoxylate **68** with an *endocyclic* C=C bond was used for the preparation of functionalized fused pyrimidine by the reaction with isothiourea (Scheme 26) [156]. Heterocyclizations of 3-acetyl-2-methoxycyclohepta-2,4,6-trienone [157, 158] or 2-oxo-2*H*-pyran-5-carbaldehyde [159] bearing the *β*-alkoxyenone motif have also been reported.



Scheme 26. Heterocyclization of tetrahydropyridine-derived glyoxylate **68**.

Interesting results can be obtained with enones where a push-pull-type alkoxide motif is a part of a cyclic system, which results in recyclization of the enone system upon the reaction with *NCN* binucleophile. A prominent example of cyclic *β*-alkoxyenones with an exocyclic C=C bond reactivity included recyclizations of tetrahydrofuranyl enones **69** with acetamidine or formamidine that resulted in the formation of γ-hydroxypropyl moieties at the C(4)-position of pyrimidine (Table 8) [160].

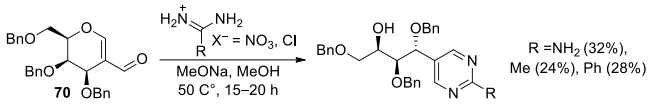
Table 8. Recyclization of tetrahydrofuranyl enones **69**.



R^1	R^2	R^3	R^4	Yield, %
Ph	H	H	Me	41
Ph	H	H	Ph	60
Ph	H	H	NH_2	56
Ph	H	Me	Me	47
Ph	H	Me	Ph	50
Ph	H	Et	Me	42
Ph	H	Et	Ph	57
Ph	Me	H	Me	41
Ph	Me	H	Ph	45
Ph	Et	H	Ph	55
Ph	CH_2Cl	H	Ph	85
Ph	CH_2Br	H	Ph	79
Me	CH_2Br	H	Ph	91
Me	CH_2OH	H	Ph	88

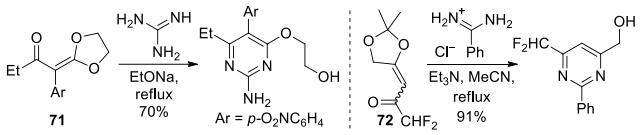
In turn, a sugar-derived enone, *i.e.* 2-formylgalactal **70** [161], reacted with amidines and guanidine to give interesting C(5)- functionalized pyrimidines (Scheme 27). Analogous transformations were reported for the case of

PMB-protected analogues [162,163], as well as *p*-Me- and *p*-Cl-substituted bezamidines [164]. It should be noted that aminoalkyl-substituted pyrimidines could be obtained in the same manner from the corresponding enaminones [165].



Scheme 27. Recyclizations of 2-formylgalactal **70** [161].

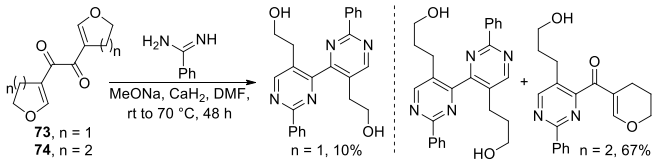
An interesting type of enone recyclizations in the presence of *NCN* binucleophiles could be observed for 1,3-dioxolane-containing enone **71** decorated with exocyclic C=C double bond at the C(2)-position (Scheme 28) [33].



Scheme 28. Recyclizations of 1,3-dioxolane-containing enones.

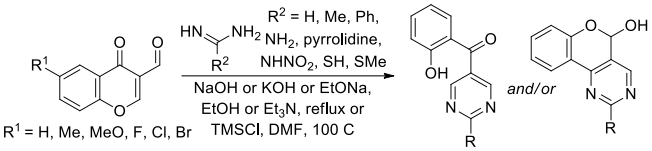
This transformation resulted in 2-((2-aminopyrimidin-4-yl)oxo)ethanol with hydroxyethyl ether fragment derived from the dioxolane cycle. If the alkenyl fragment was located at the C(4) position of 1,3-dioxolane core, *e.g.* in enone **72**, pyrimidinyl methanols were formed (Scheme 28) [150, 151].

The use of cyclic dienones with an endocyclic C=C double bond is used to synthesize 5,5'-bipyrimidines with hydroxyalkyl substituents [117]. In particular, five-membered dienone **73** reacts with benzamidine to form 5,5'-bis(2-hydroxyethyl)pyrimidine in low yield, while the six-membered homolog **74** was converted to 5.5'-bis(2-hydroxypropyl)pyrimidine in 67% yield alongside with formation of a monoheterocyclization product (Scheme 29).



Scheme 29. Synthesis of 5,5'-bipyrimidines from **73** and **74**.

3-Formylchromone **75** is known to react via recyclization with amidines [166-169], guanidines [166, 168, 170, 171], thiourea [171], 2-methylisothiourea [172], carbonohydrazonic diamides [173] to give pyrimidines decorated with the salicylic moiety or the corresponding cyclic fused hemiacetal products [172, 174] (Scheme 30). Moreover, the reactions of 3-formylchromone with amidoximes were used for the instant preparation of pyrimidine-*N*-oxides [175-178]. The scope of this type of heterocyclization was extended to derivatives substituted by benzene ring [179], the corresponding ketochromones [180], di- and trifluoromethyl ketones [181, 182], glyoxylate [183], which all underwent recyclization with *NCN* binucleophiles [182]. Aside from the common reaction conditions for the heterocyclization with *NCN* binucleophiles, which typically relied on using alkali or alcoholates (rarely, K_2CO_3 or Et_3N) as bases, significant synthetic advances were achieved by using TMSCl in DMF, which was disclosed in a series of papers by Volochnyuk, Ryabukhin, and co-workers [184-188].



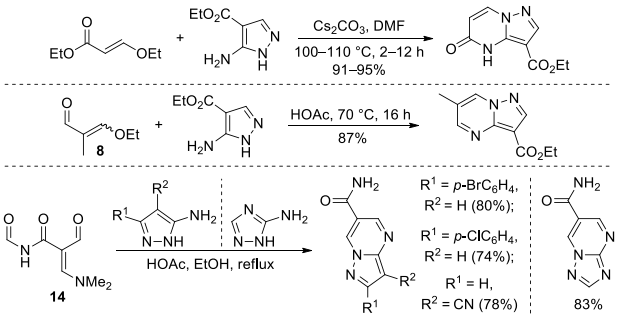
Scheme 30. Recyclizations of 3-formylchromones **75**.

Recyclization of carbonyl-substituted 4*H*-chromenes and 1*H*-benzo[*f*]chromenes by the treatment with amidines and guanidines has also been reported [189]. In addition to the two-component condensations, three-component reactions, *i.e.* Biginelli pyrimidine synthesis, are also common for these substrates [190-192].

Heterocyclizations with aminoheterocycles

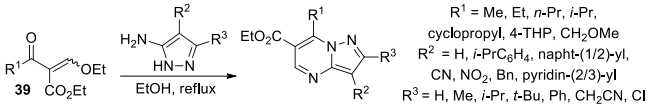
Electron-rich aminoheterocycles, *i.e.* *N*-unsubstituted aminopyrazoles, amino-1,2,4-triazoles, 1*H*-benzimidazole-2-amine, 2-amino-1*H*-imidazoles, aminouracyls, etc., react with *CCC* bis-electrophiles analogously to acyclic *NCN* binucleophiles providing fused heteroaromatic pyrimidines. In particular, 3-formylchromones mentioned just above were studied in such heterocylizations [193].

The simplest open-chain enones have been widely studied in these reactions and used for the preparation of fused pyrimidines by reactions with aminoheterocycles. Starting from the reaction of ethyl 3-ethoxyacrylate with ethyl 5-amino-1*H*-pyrazole-4-carboxylate [194, 195], the scope of known transformations included reaction of the simplest derivative **8** [196] or 3-(dimethylamino)-*N*,2-diformylacrylamide **14** [52] (Scheme 31).



Scheme 31. Reactions of *β*-alkoxyenones with 5-aminopyrazoles.

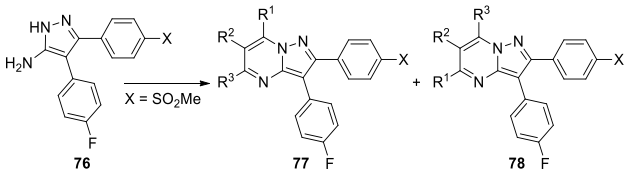
In turn, most of the known transformations relied on using enones derived from ketoesters **39** (Scheme 32) [197-203] that were subjected to heterocylizations with (3)5-aminopyrazoles (mostly substituted by alkyl, aryl, halogen, nitrile and nitro groups), or diazo diaminopyrazoles [204, 205]. Other reported reactions included enones derived from malonates **41** [206-208] or cyanoacetates **36** [208-214], haloalkyl enones **22-24**, and their analogs [206, 215-220], and functionalized derivatives bearing sulfonyl [221] or alkynyl [222] groups.

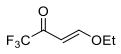
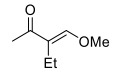
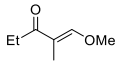
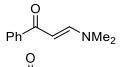
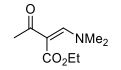
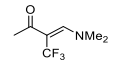
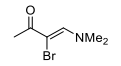
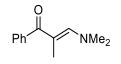


Scheme 32. Reactions of enones derived from ketoesters **39**.

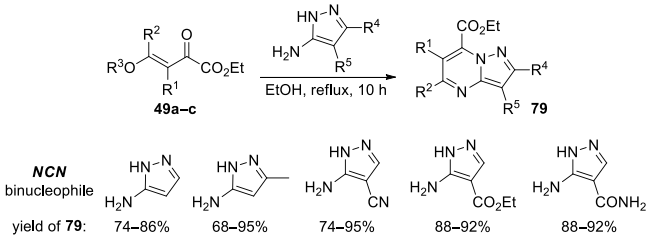
Notably, in most cases, the condensation reaction proceeded in a regioselective manner. However, the reaction of diaryl-substituted 5-aminopyrazoles **76** was not regioselective for most examples of *β*-alkoxyenones or the corresponding enaminones (Table 9) and resulted in the formation of two regioisomers **77** (major) and **78** (minor) [223].

Table 9. Formation of regioisomers **77** and **78**.



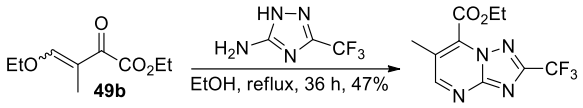
Reagent	Conditions	Yield, %	Ratio
	piperidine, EtOH, reflux, 18 h	46	1:0
	piperidine, EtOH, reflux, 1-18 h	45	9:1
		36	9:1
		35	1:0
	HOAc, EtOH, reflux, 1 h	80	1:0
		36	4:1
	HBr, EtOH, reflux, 1 h	31	7:3
	HCl, EtOH, reflux, 1-18 h	51	1:0

Nevertheless, the reactions of simplest *β*-alkoxyvinyl ketoesters **49a–c** with 5-aminopyrazoles proceeded regioselectively to give the corresponding pyrazolo[1,5-*a*]pyrimidine-7-carboxylates **79** in high yields (Scheme 33) [12]. The formation of the second possible regioisomer was not observed, in contrast to the similar non-regioselective condensation with acetylpyruvate known from the literature.



Scheme 33. Regioselective synthesis of pyrazolo[1,5-*a*]pyrimidine-7-carboxylates **79** from the simplest *β*-alkoxyvinyl ketoesters **49**.

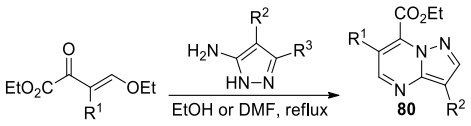
Condensation of enones **49a–c** with 5-amino-1*H*-1,2,4-triazoles as *NCN* binucleophiles led to the formation of complex mixtures of products in most cases, except enone **49b** (Scheme 34).



Scheme 34. A representative reaction of **49b** with 5-aminotriazole.

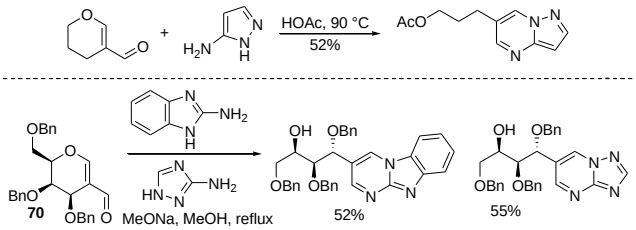
Synthesis of dicarboxylates, ketocarboxylates, and related derivatives **80** from 3-acetyl- or 3-ethoxycarbonylenones also proceeded regioselectively in a short reaction time (Table 10) [223].

Table 10. Synthesis of pyrazolo[**1**,5-*a*]pyrimidine-7-carboxylates **80**.



R^1	R^2	Conditions	Yield, %
C(O)Me	CN	EtOH, reflux, 5 min	100
C(O)Me	$C(O)NH_2$	EtOH, reflux, 5 min	98
C(O)Me	C(O)NHMe	EtOH, reflux, 8 min	64
CO_2Et	CN	EtOH, reflux, 5 min	92
CO_2Et	$C(O)NH_2$	EtOH, reflux, 5 min	95
CO_2Et	C(O)NHMe	EtOH, reflux, 9 min	92

As for the case of symmetric amidines, (thio)ureas, and guanidines, recyclization reactions of 2-formylgalactal **70** [161] as well as the parent 3,4-dihydro-2*H*-pyran-5-carbaldehyde have been reported (Scheme 35) [224].

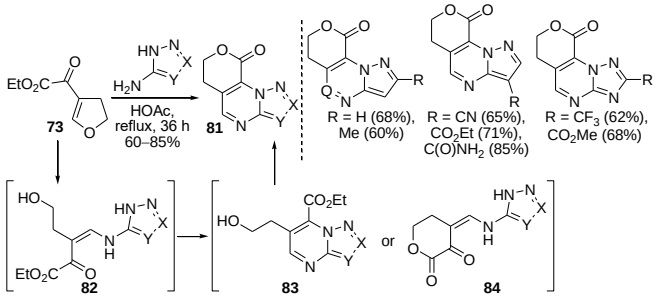


Scheme 35. Recyclization reactions of cyclic enones with amino-heterocycles in the preparation of fused pyrimidines.

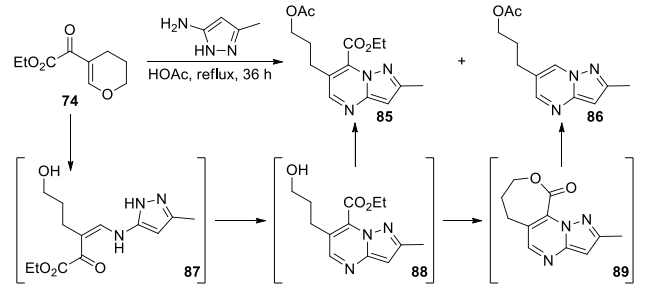
Heterocyclizations of *N*-unsubstituted 5-aminopyrazoles were also performed with cyclic enones **73** and **74**. The process proceeded regioselectively to give the tricyclic products, *i.e.* pyrazolo[1,5-*a*]pyrimidines **81** with an additional lactone cycle (Scheme 36) [11]. This result could be explained by the formation of enaminones **82** followed by intramolecular heterocyclization into hydroxyethyl pyrimidine **83** and the lactonization reaction by the attack of the hydroxyl group at the ester moiety. The derivative **84** also was considered as a possible intermediate that could be transformed into **81**.

In contrast to five-membered enone **73**, the condensation reactions of six-membered counterpart **74** did not lead to the formation of homologous seven-membered lactones under similar conditions. Instead, the formation of

pyrazolo[1,5-*a*]pyrimidines **85** and **86** in a ratio of 3:1 was observed (Scheme 37). In particular, bicyclic derivative **85** was formed from enaminone **87** formed in the first stage, which subsequently underwent acetylation of the hydroxy group of **88** with HOAc at high temperatures of the reaction mixture. The formation of **86** could be explained by ring-opening, acylation, and partial decarboxylation of the intermediate seven-membered lactone **88**.

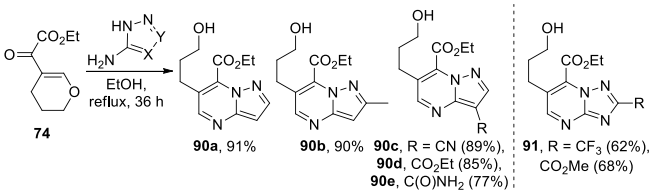


Scheme 36. Synthesis of tricyclic pyrazolo [1,5-*a*]pyrimidines **81**.



Scheme 37. Reaction of enone **74** with 5-aminopyrazole.

To prevent the side reactions observed for the case of **74**, reactions with aminoazoles were carried out by refluxing in EtOH, which enabled the selective synthesis of the corresponding pyrazolo[1,5-*a*]pyrimidines **90** and [1,2,4]triazolo[1,5-*a*] pyrimidines **91** in high yields (Scheme 38). In all cases discussed above, the heterocyclization proceeded regioselectively: only C-7 carboxylates (or the corresponding δ-lactones) were formed.



Scheme 38. Synthesis of pyrazolo[1,5-*a*]pyrimidines **90** and [1,2,4]triazolo[1,5-*a*] pyrimidines **91**.

Conclusions

In this review, heterocyclizations of *β*-alkoxyvinyl and *β*-enamino carbonyl compounds as *CCC* bis-electrophiles with common *NCN* binucleophiles leading to pyrimidine derivatives are covered. It is shown that in most cases, the reaction is very efficient and demonstrates remarkable regioselectivity, even with substrates bearing additional functional groups or fluorinated substituents. With most cyclic bis-electrophiles, recyclization typically occurs, whereas with aminoheterocycles as the *NCN* binucleophiles, fused pyrimidine derivatives can be obtained. It is clear therefore that *β*-alkoxyvinyl- and *β*-enaminocarbonyl compounds are important synthetic equivalents of *β*-dicarbonyl compounds in the pyrimidine synthesis, opening access to functionalized derivatives useful as building blocks for medicinal chemistry and natural compound analogs.

Notes

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The authors declare no conflict of interest.

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Гетероциклізації *β*-алкокси-, *β*-діаміноалкіл- та споріднених *β*-функціоналізованих енонів (еналів) з *NCN*-бінуклеофілами

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Резюме: Огляд присвячений обговоренню наявних літературних даних щодо *β*-алкоксивініл- та *β*-енамінокарбонільних сполук як *CCC-біс*-електрофілів у реакціях із класичними *NCN*-бінуклеофілами. Основна увага приділяється реакціям, що призводять до утворення низькомолекулярних та функціоналізованих піримідинів як продуктів, що є особливо цікавими як будівельні блоки для створення лікарських засобів.

Ключові слова: гетероцикли; піримідини; енони; *біс*-електрофіли; бінуклеофіли.