Synthesis of Heterocycles from Alkyl 3-(Dimethylamino)propenoates and Related Enaminones

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1. Introduction

For more than a century, 1,3-dicarbonyl compounds and their derivatives have been some of the most versatile and frequently employed C_3 synthons in organic, especially heterocyclic, synthesis. They are starting materials or key intermediates in the preparation of furans, pyrans, pyrroles, pyrazoles, pyridines, pyrimidines, and their fused analogues. A wide variety of simple 1,3-dicarbonyl compounds are nowadays commercially available. However, α-formyl acetates (3-hydroxypropenoates) are usually unstable. For synthetic purposes, they have to be prepared by formylation and then used in situ or stored and used in the form of more stable derivatives, such as acetals, mercaptals, enol ethers, enethiol ethers, and enamines. Examples of stable derivatives of α-formyl acetates are 2-substituted alkyl 3-(dimethylamino)propenoates and related enaminones (Figure 1).

Several α-carbon-substituted β-(dimethylamino)-enones with general formula **A** have been prepared previously by condensation of active methylene compounds, such as 1,3-diketones or β-keto esters, with reactive *N*,*N*-dimethylformamide (DMF) derivatives. They have been most frequently used in the synthesis of heterocycles, such as pyrazoles, isoxazoles, pyrimidines, and others (Figure 2).[1]

On the other hand, there has been, until recently, no report on the preparation of α-nitrogen- and α-oxygen-substituted 3-(dimethylamino)propenoates. In 1975, Yamato and Okumura reported the preparation of several other alkyl 2-(aroylamino)-3-(*N*,*N*-disubstituted-amino)propenoates with methyl 2-(ben-

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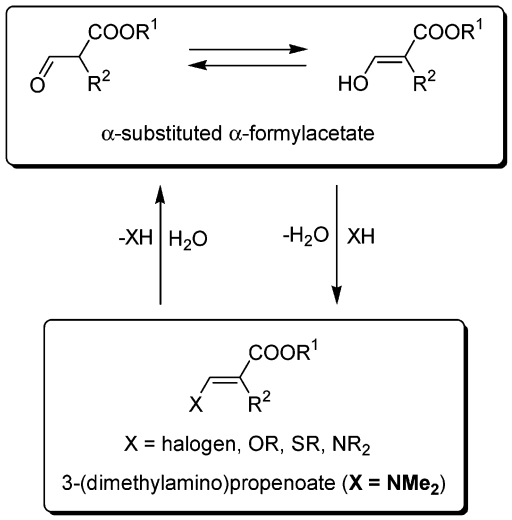
Branko Stanovnik was born in Slovenia in 1938. He received his diploma in chemistry in 1960 and his Ph.D. in organic chemistry at the University of Ljubljana in 1964. He became an Associate Professor at that university in 1967 and Full Professor in 1972. He was a postdoctorate fellow with the National Research Council in Canada and a Visiting Professor in the United States and Australia. He is a member of many advisory boards and societies and the author of over 500 papers, reviews, and books. His research interests lie in the synthesis and transformations of heterocyclic chemistry, asymmetric synthesis, and natural products derived from amino acids.

Jurij Svete was born in Ljubljana, Slovenia, in 1962. He received his diploma in chemistry in 1986 and his Ph.D. in 1990 under the supervision of Professor Stanovnik. After his Ph.D., he continued to work as a researcher with Professor Stanovnik's group. In 1997 he spent one year as a Humbold Fellow at the University of Stuttgart, Germany, working with Professor Jäger on the synthesis of iminopolyols from furan–nitrile oxide cycloadducts. In 1996, he became an Assistant Professor at the University of Ljubljana and an Associate Professor in 2001. His research interests include the synthesis of heterocyclic compounds with emphasis on chiral functionalized heterocycles containing an amino acid, peptide, amino alcohol, polyol, and related structural motifs.

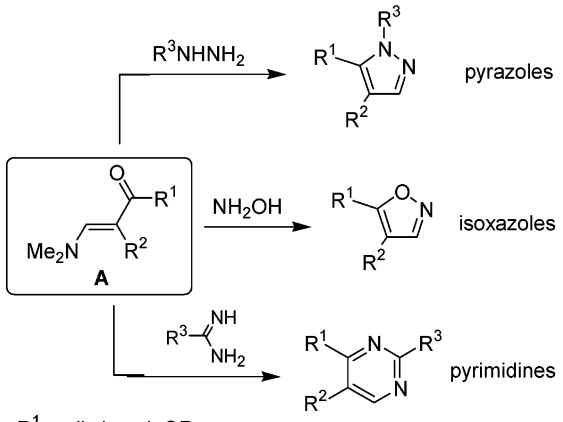
zoylamino)-3-(dimethylamino)propenoate (**3a**) as the representative. They used propenoate **3** as the reagent for the preparation of *N*-benzoyl-α,*β*-dehydrotryptophane ester **4** by dimethylamine substitution with indole. However, their further attempts to prepare *N*-benzoyltryptophan ester **5** by catalytic hydrogenation were unsuccessful. The configuration around the C═C double bond was not determined (Scheme 1).[2]

In the mid 1980s, we began research in the field of transformations of primary heteroarylamines **6** into 3-(heteroarylamino)-2,3-dehydroalanine derivatives **8** including peptides, via 4-[(heteroarylamino)methylidene]-5(4*H*)-oxazolones **7** as the key intermediates



R^1 = alkyl
R^2 = alkyl, (hetero)aryl, acyl, OR, OCOR, NHR, NHCOR

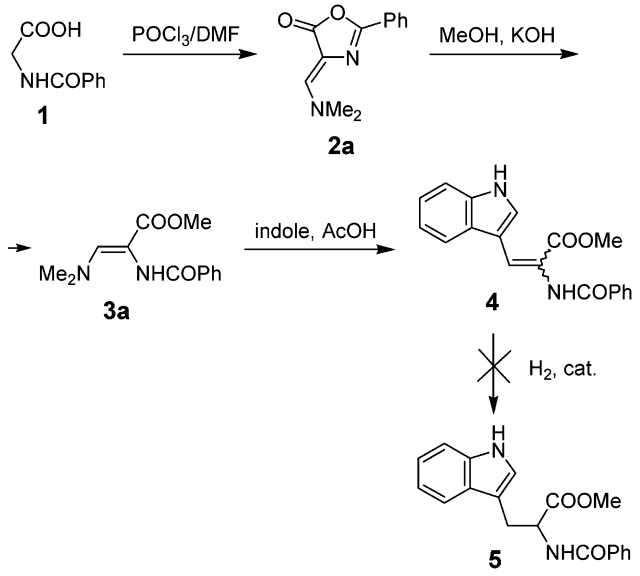
Figure 1. 3-(Dimethylamino)propenoates as masked α-formyl acetates.



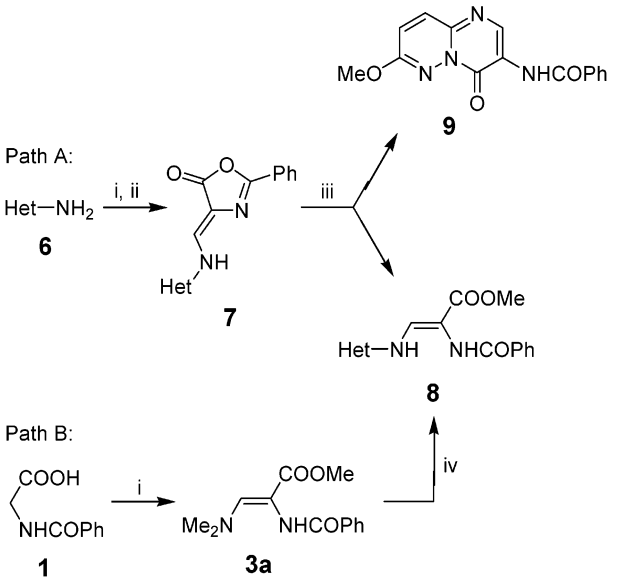
R^1 = alkyl, aryl, OR
R^2 = acyl, CN

Figure 2. *β*-(Dimethylamino)enones as precursors for heterocycles.

Scheme 1



Scheme 2[a]



[a] Reaction conditions: (i) DMFDMA, toluene, reflux; (ii) hippuric acid, Ac_2O, 70 °C; (iii) MeONa, MeOH, rt; (iv) Het-NH_2, HCl (1 equiv), EtOH, reflux.

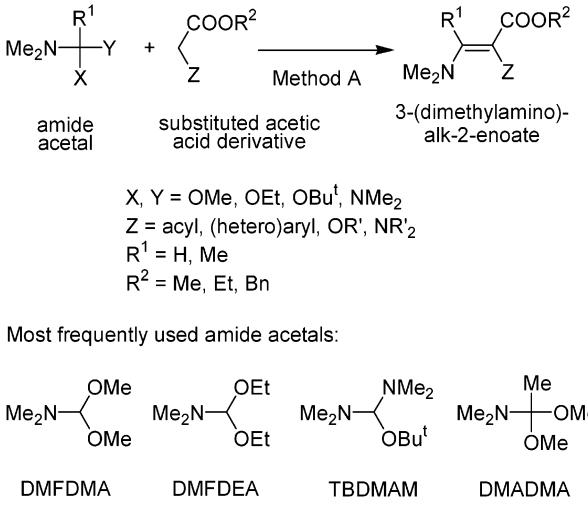
(path A).[3−5] Similarly, 3-heteroaryl-2,3-dehydroalanine derivatives were obtained from heterocyclic compounds with an active methylene group at the α-position with respect to the ring nitrogen atom.[6] Because, in some cases, the propenoates cyclized into fused pyrimidones **9** under the basic conditions employed, we looked for alternative methods for the preparation of dehydroalanine esters **8**. It turned out that methyl 2-(benzoylamino)-3-(dimethylamino)propenoate (**3a**), obtained upon reaction of hippuric acid (**1**) with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), undergoes facile acid-catalyzed vinylogous dimethylamine substitution with heteroarylamines **6** to afford dehydroalanine esters **8** selectively and in good yields (path B). An additional advantage of this method was that it was not limited to primary amines (Scheme 2).[4]

Encouraged by these results, we started an extensive study on the chemistry of various 2-substituted alkyl 3-(dimethylamino)propenoates, which have shown versatile synthetic potential, especially in heterocyclic synthesis.[7−12]

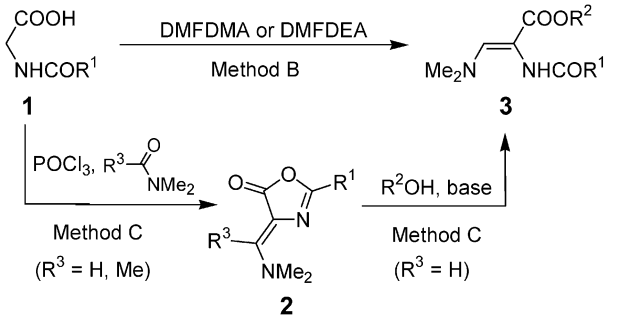
2. Preparation of 2-Substituted Alkyl 3-(Dimethylamino)propenoates and Related Enaminones

2-Substituted alkyl 3-(dimethylamino)propenoates are generally and most conveniently prepared by condensation between an α-substituted acetic acid ester and an amide acetal (method A). Commercially available amide acetals (given in increasing order of reactivity), *N*,*N*-dimethylacetamide dimethyl acetal (DMADMA), *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), *N*,*N*-dimethylformamide diethyl acetal (DMFDEA), and *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent, TBDMAM), are usually employed. They react with a variety of α-substituted acetic acid esters, such as *β*-keto esters

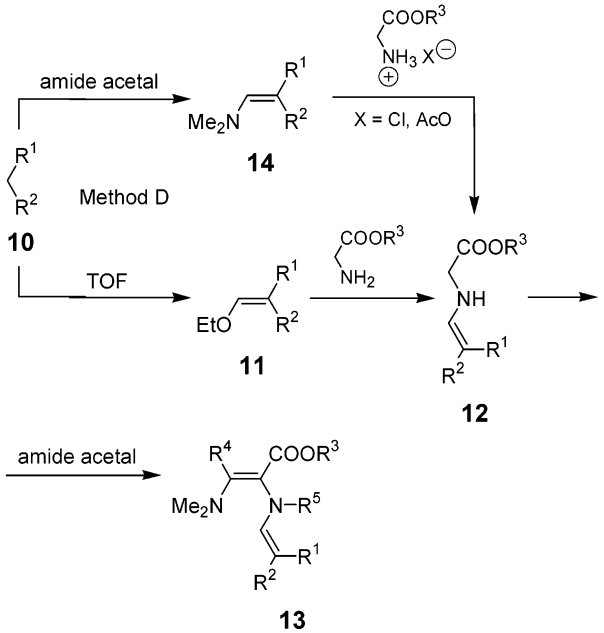
Scheme 3. Preparation of Alkyl 3-(Dimethylamino)propenoates and Analogues by Condensation between Substituted Acetic Acid Ester and Amide Acetal (Method A)



Scheme 4. Preparation of Alkyl 2-(Acylamino)-3-(dimethylamino)propenoates from *N*-Acylglycines (Methods B and C)

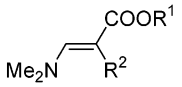


Scheme 5. Preparation of Alkyl 2-[(2,2-Disubstituted-vinyl)amino]-3-(dimethylamino)propenoates 13 (Method D)



(α-acyl acetates), (hetero)aryl acetates, *N*-protected glycinates, and *O*-protected glycolates. In most cases, the condensation is carried out in anhydrous toluene

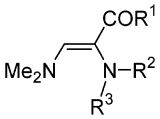
Table 1. Examples of 2-Alkyl-, 2-Aryl-, 2-Heteroaryl-, and 2-Acyl-3-(dimethylamino)propenoates 14



14a–u

compd	R^1	R^2	method	amide acetal employed	ref
14a	Et	CH_2COOEt	A	TBDMAM	13
14b	Et	Ph	A	TBDMAM	14
14c	Et	pyridin-2-yl	A	DMFDMA	15
14d	Me	1*H*-indol-3yl	A	TBDMAM	16
14e	Et	1*H*-indol-3-yl	A	TBDMAM	16
14f	Me	COMe	A	DMFDMA	17, 18
14g	Et	COMe	A	DMFDMA	19−21
14h	Et	COEt	A	DMFDMA	19
14i	Et	$COCH_2CH_2CH_3$	A	DMFDMA	19
14j	Et	$COCH(CH_3)_2$	A	DMFDMA	19
14k	Et	$COC(CH_3)_3$	A	DMFDMA	19
14l	Me	$COCH_2Ph$	A	DMFDMA	19
14m	CH_2Ph	COMe	A	DMFDMA	17
14n	Et	COPh	A	DMFDMA	22
14o	Me	COOMe	A	DMFDMA	23
14p	Et	COOEt	A	DMFDMA	24
14q	Et	COCOOEt	A	DMFDMA	25
14r	Et	4-fluorobenzoyl	A	DMFDMA	22
14s	Me	CH_2OMe	A	DMFDMA	26
14t	Me	$(CH_2)_2COOMe$	A	DMFDMA	26
14u	Et	$(CH_2)_3COOEt$	A	DMFDMA	26

Table 2. 2-Acylamino-3-(dimethylamino)propenoates 3



3a–s

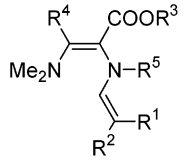
compd	R^1	R^2	R^3	method	amide acetal employed	ref
3a	OMe	H	COPh	B, C	DMFDMA	2, 4
3b	OMe	H	COMe	B, C	DMFDMA	27
3c	OEt	H	COMe	C		28
3d	OMe	H	$CO-C_6H_4-Cl(2)$	C		29
3e	OMe	H	$CO-C_6H_4-Cl(3)$	B	DMFDMA	30
3f	OMe	H	$CO-C_6H_4-Cl(4)$	C		29
3g	OMe	H	$CO-C_6H_4-Me(4)$	C		29
3h	OMe	H	$CO-C_6H_4-OMe(3)$	B	DMFDMA	30
3i	OMe	H	$CO-C_6H_4-OMe(4)$	C		29
3j	OMe	H	CO−CH=CHPh	C		31
3k	OEt	H	CO−CH=CHPh	B	TBDMAM	31
3l	OMe	H	$CO-CH=CH-C_6H_3-Cl_2(2,6)$	C		31
3m	OMe	H	$CO-CH=CH-C_6H_4-Me(4)$	C		31
3n	OMe	H	$CO-CH=CH-C_6H_4-OMe(2)$	C		31
3o	OMe	Me	$COCF_3$	B	DMFDMA	27
3p	OMe	H	COOtBu	A	TBDMAM	32
3q	OMe	H	COOBn	A	TBDMAM	33
3r	OEt		CO−C_6H_4−CO (phthaloyl)	A	TBDMAM	34
3s	Me	H	NHCOPh	A	DMFDMA	35

at 90−110 °C. This method is the most general and can be applied in the synthesis of all types of 2-substituted 3-(dimethylamino)propenoates (Scheme 3).[1,7−12]

Despite the general applicability of method A, some alternative and more or less closely related variations have also been developed. An example is the synthesis of alkyl 2-(acylamino)-3-(dimethylamino)propenoates **3** from *N*-acylglycines **1**. They can be transformed into propenoates, either in one step by treatment with excess DMFDMA or DMFDEA (method B) or in two steps by reaction with a mixture of $POCl_3$ and DMF (Vilsmeier reagent) to give the 4-[(dimethylamino)methylidene]-5(4*H*)-oxazolone derivative **2**, followed by base-catalyzed ring opening with an alcohol (method C) (Scheme 4).[2,4,7−11]

Alkyl 2-[(2,2-disubstituted-vinyl)amino]-3-(dimethylamino)propenoates **13** have been prepared in three steps starting from an active methylene compound **10** by treatment with triethyl orthoformate (TOF) or with an amide acetal to give the enol ether **11** or

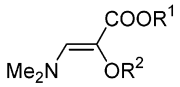
Table 3. Alkyl 2-(Vinylamino)-3-(dimethylamino)-propenoates 13



13a–z

compd	R^1	R^2	R^3	R^4	R^5	method	amide acetal employed in final step	ref
13a	COOMe	COOMe	Et	H	H	D	TBDMAM	36
13b	COOEt	COOEt	Me	H	H	D	DMFDMA	23
13c	COOEt	COOEt	Et	H	H	D	DMFDMA	37
13d	COOEt	COOEt	Me	Me	H	D	DMADMA	38
13e	COOEt	COPh	Me	H	H	D	DMFDMA	39
13f	COOEt	COPh	Et	H	H	D	DMFDMA	39
13g	COOEt	COMe	Et	H	H	D	DMFDMA	40
13h	COOMe	COMe	Me	H	H	D	DMFDMA	17
13i	COOMe	COMe	Me	Me	H	D	DMADMA	14
13j	COOBn	COMe	Me	H	H	D	DMFDMA	17
13k	COOBn	COMe	Me	Me	H	D	DMADMA	14
13l	COOEt	CN	Et	H	H	D	DMFDEA	41
13m	COOEt	CN	Me	H	Me	D	DMFDMA	42
13n	COOEt	CN	Et	H	Me	D	DMFDMA	42
13o	COPh	COPh	Et	H	H	D	DMFDEA	43
13p	COMe	COPh	Et	H	H	D	DMFDMA	44
13q	COMe	COMe	Me	H	H	D	DMFDMA	45
13r	CN	pyridin-2-yl	Me	H	H	D	DMFDMA	46
13s	CN	pyridin-2-yl	Et	H	H	D	DMFDMA	46
13t	COOEt	pyridin-2-yl	Me	H	H	D	DMFDMA	47
13u	COOEt	pyridin-2-yl	Et	H	H	D	DMFDMA	47
13v	COOEt	Ph	Me	H	H	D	DMFDMA	14
13w	1,3-dioxocyclohex-2-ylidene		Me	H	H	D	DMFDMA	48
13x	5,5-dimethyl-1,3-dioxocyclo-hex-2-ylidene		Me	H	H	D	DMFDMA	48
13y	2,4,6-trioxoperhydro-pyrimidin-5-ylidene		Me	H	H	D	DMFDMA	49
13z	1,3-dimethyl-2,4,6-tri-oxoperhydropyrimidin-5-ylidene		Me	H	H	D	DMFDMA	49

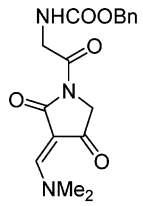
Table 4. 2-(Substituted-hydroxy)-3-(dimethylamino)-propenoates 15[50]



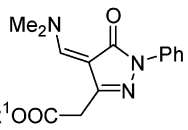
15a–d

compd	R^1	R^2	method	amide acetal employed
15a	Me	COPh	A	TBDMAM
15b	Et	COPh	A	TBDMAM
15c	Me	CH_2Ph	A	TBDMAM
15d	Me	Ph	A	TBDMAM

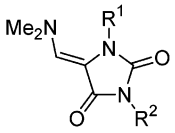
Table 5. Heterocyclic Analogues of 2-Substituted 3-(Dimethylamino)propenoates 2 and 16−23



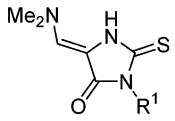
16 (Type A)



17a,b (Type B)

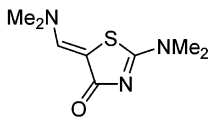


18a-d (Type C)

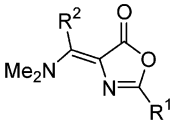


19a-d (Type D)

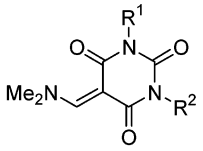
20a-d (Type E)



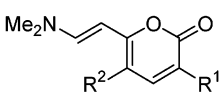
21 (Type F)



2a-k (Type G)



22a,b (Type H)



23a,b (Type I)

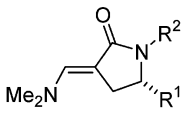
compd	type	R^1	R^2	gen method	amide acetal employed	ref
16	A			A	DMFDMA	51
17a	B	Me		A	DMFDMA	52
17b	B	Et		A	DMFDMA	52
18a	C	H	H	A	TBDMAM	53
18b	C	H	Me	A	DMFDMA	53
18c	C	Me	H	A	TBDMAM	54
18d	C	Me	Me	A	DMFDMA	54
19a	D	Et		A	TBDMAM	54
19b	D	$CH_2CH{=}CH_2$		A	TBDMAM	54
19c	D	Ph		A	TBDMAM	54
19d	D	4-Me-C_6H_4−		A	TBDMAM	54
20a	E	Et	-	A	DMFDMA	54
20b	E	$CH_2CH{=}CH_2$		A	DMFDMA	54
20c	E	Ph		A	DMFDMA	54
20d	E	4-Me-C_6H_4−		A	DMFDMA	54
21	F			A	TBDMAM	54
2a	G	Ph	H	C		2
2b	G	Me	H	C		27
2c	G	2-Cl-C_6H_4	H	C		29
2d	G	4-Cl-C_6H_4	H	C		29
2e	G	4-Me-C_6H_4	H	C		29
2f	G	4-MeO-C_6H_4	H	C		29
2g	G	CH=CHPh	H	C		31
2h	G	CH=CH−C_6H_3−Cl_2(2,6)	H	C		31
2i	G	CH=CH−C_6H_4−Me(4)	H	C		31
2j	G	CH=CH−C_6H_4−OMe(2)	H	C		31
2k	G	Ph	Me	C		55
22a	H	H	H	A	DMFDMA	49
22b	H	Me	Me	A	DMFDMA	49
23a	I	NHCOPh	COMe	A	DMFDMA	56
23b	I	NHCOPh	COOEt	A	DMFDMA	56

enaminone **14** followed by substitution of the ethoxy or dimethylamino group with alkyl glycinate to afford the *N*-(substituted-vinyl)-protected glycine ester **12**. Treatment of **12** with an amide acetal leads to alkyl 2-[(2,2-disubstituted-vinyl)amino]-3-(dimethylamino)-propenoates **13** (method D) (Scheme 5).[8−11]

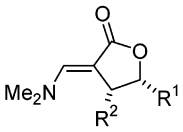
Types of 2-substituted alkyl 3-(dimethylamino)-propenoates **3**, **13**−**32**, methods of preparation and amide acetals employed are given in Tables 1−7.

Important and synthetically useful analogues of 3-(dimethylamino)propenoates are 2-substituted alkyl

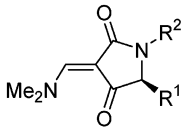
Table 6. Chiral Cyclic Analogues of 2-Substituted 3-(Dimethylamino)propenoates 24−28



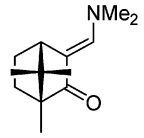
24a-c (Type A)



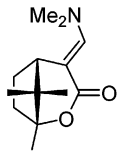
25a-c (Type B)



26a,b (Type C)



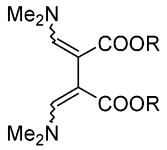
27 (Type D)



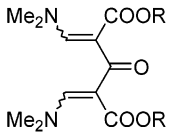
28 (Type E)

compd	type	R^1	R^2	method	amide acetal employed	ref
24a	A	COOMe	COOtBu	A	TBDMAM	57
24b	A	COOMe	COPh	A	TBDMAM	58
24c	A	CH_2OCOPh	COPh	A	TBDMAM	59
25a	B	COOMe	H	A	TBDMAM	57
25b	B	CH_2OCOPh	H	A	TBDMAM	57, 60
25c	B	H	NHCOOBn	A	TBDMAM	61
26a	C	CH_2Ph	COOtBu	A	DMFDMA	51
26b	C	CH_2Ph	COOBn	A	DMFDMA	51
27	D			A	TBDMAM	62
28	E			A	TBDMAM	63

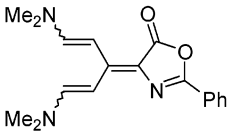
Table 7. 3-(Dimethylamino)propenoate Analogues with Two (Dimethylamino)methylidene Structural Elements 29−32



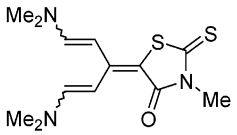
29 (Type A)



30a,b (Type B)



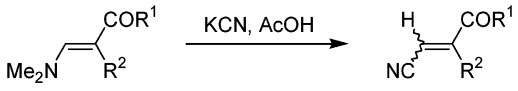
31 (Type C)



32 (Type D)

compd	type	R	method	amide acetal employed	ref
29	A	Et	A	TBDMAM	13
30a	B	Me	A	DMFDMA	64
30b	B	Et	A	DMFDMA	64
31	C		A	DMFDMA	65
32	D		A	TBDMAM	65

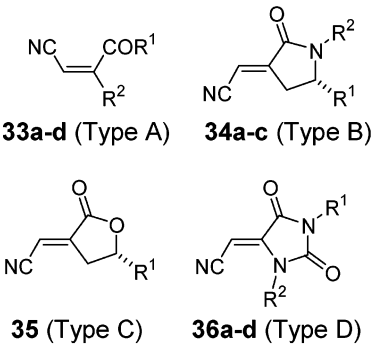
Scheme 6



3, 18, 24, 25 **33-36**

3-cyanopropenoates **33**−**36**, which are available upon treatment of 3-(dimethylamino)propenoates **3**, **18**, **24**, and **25** with potassium cyanide in acetic acid (Scheme 6; Table 8).

Table 8. 2-Substituted Alkyl 3-Cyanopropenoates and Their Chiral Analogues 33−36



compd	type	precursor	R^1	R^2	ref
33a	A	**3b**	OMe	NHCOMe	66
33b	A	**3a**	OMe	NHCOPh	66
33c	A	**3n**	OMe	$NHCOOCH_2Ph$	10
33d	A	**3p**	Me	NHCOPh	67
34a	B	**24a**	COOMe	COOtBu	68
34b	B	**24b**	COOMe	COPh	58
34c	B	**24c**	CH_2OCOPh	COPh	10−12
35	C	**25a**	COOMe		69
36a	D	**18a**	H	H	70
36b	D	**18b**	Me	H	70
36c	D	**18b**	Me	COMe	70
36d	D	**18b**	Me	COPh	70

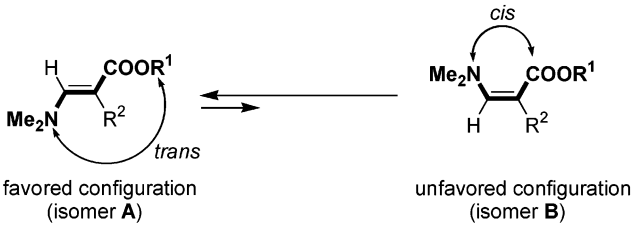


Figure 3.

3. Structure of 2-Substituted Alkyl 3-(Dimethylamino)propenoates and Related Enaminones

The structures of many 3-(dimethylamino)propenoates, their analogues, and dimethylamine substitution products with *N*- and *C*-nucleophiles have been determined by X-ray analysis and various NMR techniques. In most cases, the substituent at C-3 (e.g., the dimethylamino group) was found to be oriented *trans* with respect to the ester group or analogous structural element at C-1 (isomer **A**). So far, only a few examples of propenoates with the opposite configuration around the C=C double bond, where the substituent at C-3 and the ester group are *cis* oriented (isomer **B**), have been found (Figure 3). X-ray structural determinations for several propenoates have been made (Table 9).

In solution, propenoates can exist in (*Z*)- and/or (*E*)-isomeric form with respect to the C=C double bond. Various NMR techniques, such as NOESY, ROESY, and HMBC techniques, were used for structure determination of 3-(dimethylamino)propenoates and their analogues in $CDCl_3$ and DMSO-d_6 solution. Structures of several propenoates have been solved by NOESY and ROESY techniques on the basis of characteristic NOE between the substituents around

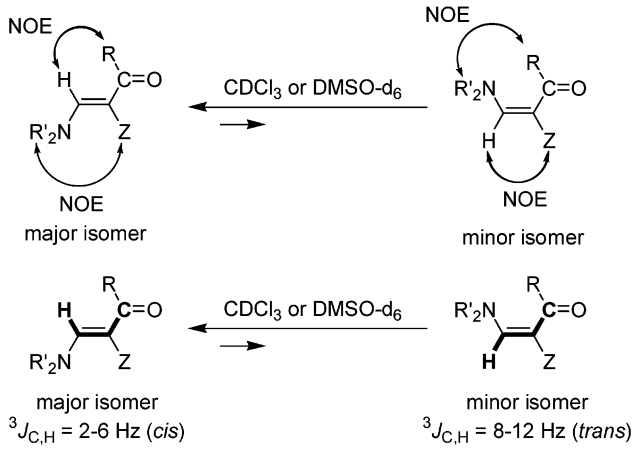


Figure 4. Determination of configuration and/or isomerization around the C=C double bond in solution by NOESY, ROESY, and HMBC techniques.

the C=C double bond. On the other hand, the HMBC correlation technique has been found to be the most reliable for the determination of the configuration around the C=C double bond in α,β-unsaturated carbonyl compounds, because the (*Z*)- and the (*E*)-isomeric forms can be differentiated on the basis of the long-range heteronuclear $^{13}C-^{1}H$ coupling constants. Generally, the magnitude of the coupling constants $^3J_{C-H}$ for nuclei with (*Z*)-orientation around the C=C double bond are smaller (2−6 Hz) than those for the (*E*)-oriented ones (8−12 Hz).[74−77] Similar coupling constants have also been observed in 3-(dimethylamino)propenoates and related compounds (Figure 4).[32,34,54,58,62,69,78]

NMR structural studies (NOESY, ROESY, and HMBC techniques) showed that, even in solution, the majority of 3-(dimethylamino)propenoates exist as single isomers. In most cases, the dimethylamino group or another substituent at position 3 was found to be *trans* oriented with respect to the ester group, and only a few examples of propenoates with the opposite configuration have been found (Table 10).

In some cases, conformational and configurational equilibria have been established. For compound **3b** two sets of signals in ratios of 91:9 and 77:23, assigned to rotamers with respect to the partial double bond C(1)=C(2), have been found in both $CDCl_3$ and DMSO-d_6 solution.[77] Compound **3q** exists as a single isomer in $CDCl_3$ solution, whereas in DMSO-d_6 a mixture of two rotamers in a ratio of 77:23 was observed.[33] NMR studies on alkyl 2-(2-acyl-2-alkoxycarbonylethenyl)amino-3-(dimethylamino)-propenoates and 2-(2-alkoxycarbonyl-2-cyanoethenyl)-amino-3-(dimethylamino)propenoates **13f**,**h**,**j**,**m**,**n** have shown that in solution there is an equilibrium between the (2*Z*,2′*E*)- and (2*Z*,2′*Z*)-forms. Compounds **13f**,**h**,**j**,**m**,**n** exist in the *Z*-form concerning the orientation around the C=C double bond to which both amino groups are attached. The isomerization arises from the orientation around the other C=C double bond.[17,42,77] Ethyl 2-(2-cyano-2-ethoxycarbonylethenyl)amino-3-(dimethylamino)propenoate **13l** exists in DMSO-d_6 solution in an equilibrium among the **13l**, **13l′**, and **13l″** forms.[38] Propenoates **62a**−**d** exist in

Table 9. X-ray Structures of 2-Substituted Alkyl 3-(Dimethylamino)propenoates and Their Analogues

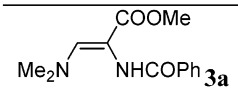
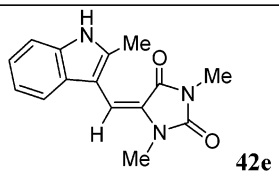
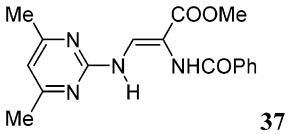
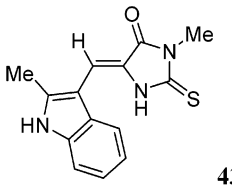
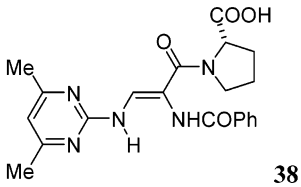
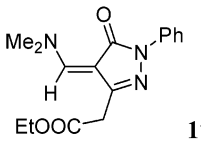
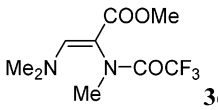
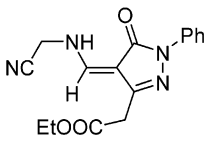
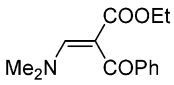
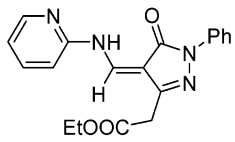
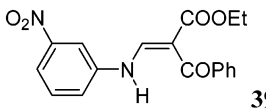
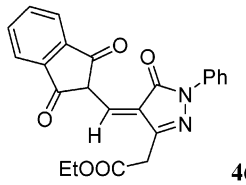
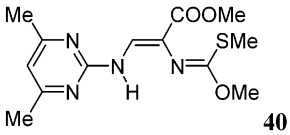
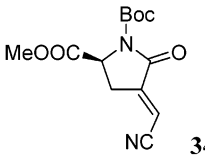
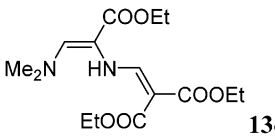
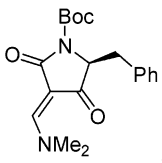
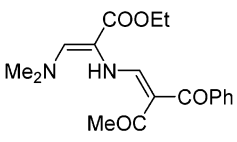
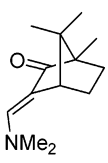
Compound	Ref.	Compound	Ref.
 **3a**	71	 **42e**	54
 **37**	71	 **43f**	53
 **38**	71	 **17b**	52
 **3o**	27	 **44**	52
 **14n**	72	 **45**	52
 **39**	72	 **46**	52
 **40**	72	 **34a**	68
 **13c**	37	 **26a**	51
 **13p**	44	 **27**	62

Table 9 (Continued)

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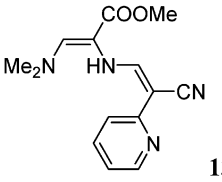
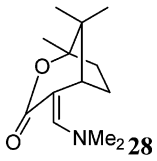
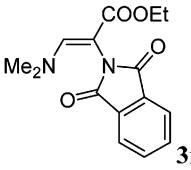
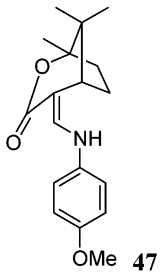
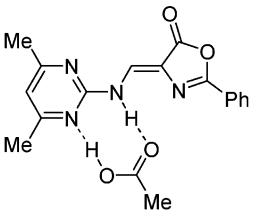
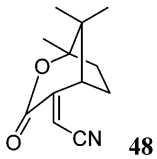
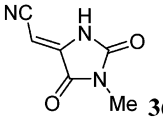
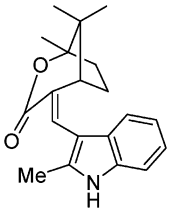
 **13r**	46	 **28**	63
 **3r**	34	 **47**	63
 **41**	73	 **48**	63
 **36b**	70	 **49**	63

DMSO-d_6 solution as mixtures of the major (*Z*)-isomers and the minor (*E*)-isomers.[34] On the other hand, equilibrium between the major (*E*)-isomers and the minor (*Z*)-isomers has been established for compounds **42e**,**q** in DMSO-d_6 solution. In this case, predominant formation of otherwise usually unfavorable major isomer with *cis*-orientation between the carbonyl group and the substituent at the position 3 might be attributed to steric reasons, most probably due to repulsion of the two methyl groups in the case of the minor (*Z*)-isomer (Table 11).[54]

Although the 3-(substituted-amino)propenoates could also exist in the imino tautomeric form, the imino tautomers have so far not been observed in the 3-alkylamino and 3-(hetero)arylaminopropenoate series. Exceptions are 3-hydrazino-substituted propenoates, for which the equilibrium between the enhydrazino and the hydrazono tautomeric form have been established by NMR. Such examples are ethyl 3-[(6-substituted-pyridazin-3-yl)hydrazino)-2-phthalimidopropenoates **63a**,**b**, which exist in DMSO-d_6 solution as mixtures of the major enehydrazino tautomers **63a**,**b** and the minor hydrazono tautomers **63′a**,**b**.[34] In the case of propenoates **64a**,**b**, derived from 3-[(*E*)-dimethylamino)methylidene]-D-(+)-camphor (**27**) and hydrazinopyridazines, equilibrium among three isomeric forms **64a**,**b**, **64′a**,**b**, and **64″a**,**b** was established in DMSO-d_6 solution, whereas in $CDCl_3$ solution, compounds **64** exist as mixtures of diastereomeric hydrazones **64′a**,**b** and **64″a**,**b** (Table 12).[62]

4. Typical Reactivity of Alkyl 3-(Dimethylamino)-propenoates and Related Enaminones

3-(Dimethylamino)propenoates are polyfunctional compounds possessing both electrophilic and nucleophilic properties. Typical electrophilic positions are C-3 (the dimethylaminomethylene group) and C-1 (the ester group) with the reactivity order C-3 > C-1. These chemical properties have been used to substitute the dimethylamino group by nucleophiles such as amines without affecting other groups. With dinucleophiles, reaction with the ester group can follow, furnishing cyclic products. On the other hand, propenoates exhibit enamine character toward electrophiles. A typical nucleophilic position is C-2, which can be nitrosated and/or cyclized intramolecularly

Table 10. NMR Structural Studies on 2-Substituted Alkyl 3-(Dimethylamino)alk-2-enoates and Their Analogues

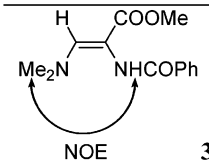
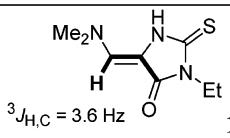
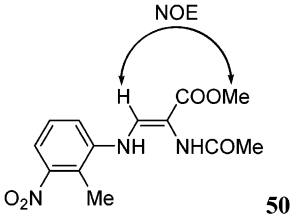
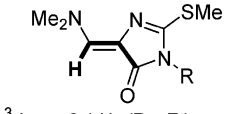
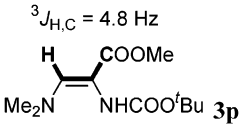
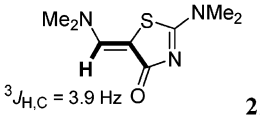
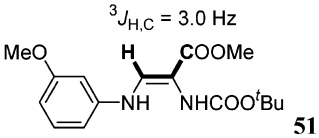
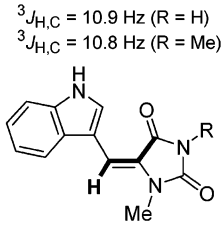
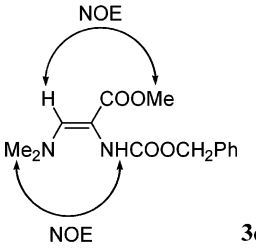
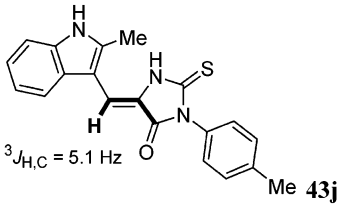
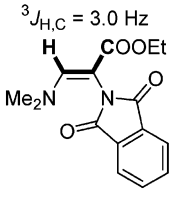
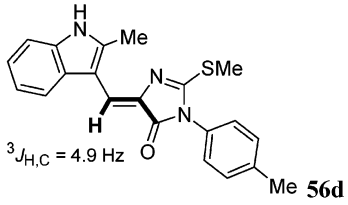
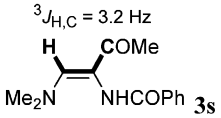
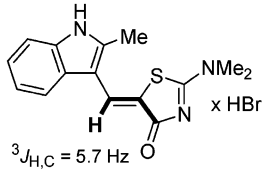
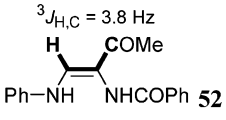
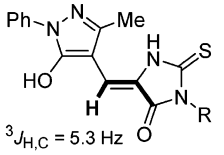
Compound	Ref.	Compound	Ref.
 **3a**	77	 **19a**	54
 **50**	77	 **20a,d**	54
 **3p**	32	 **21**	54
 **51**	32	 **42a,p**	54
 **3q**	33	 **43j**	54
 **3r**	34	 **56d**	54
 **3s**	35	 **57**	54
 **52**	35	 **58a,c**	78

Table 10 (Continued)

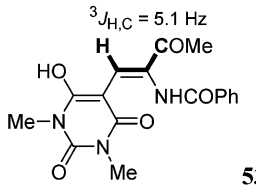
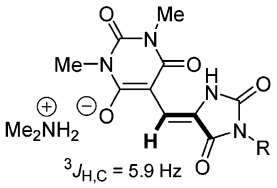
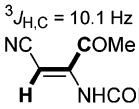
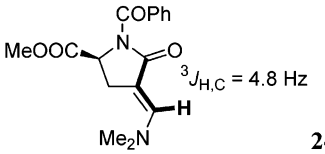
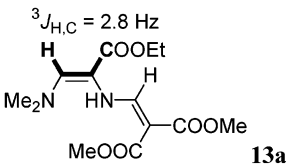
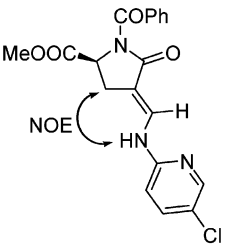
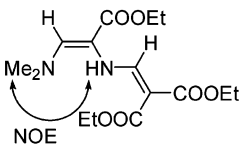
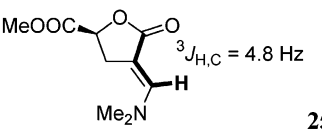
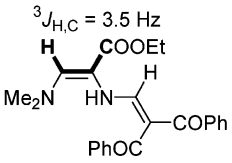
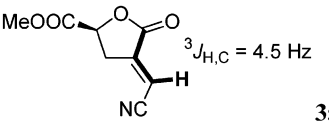
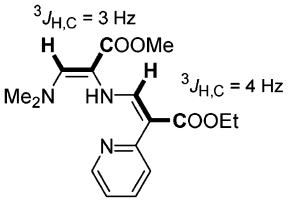
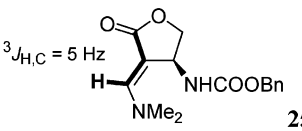
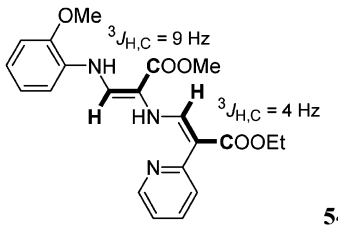
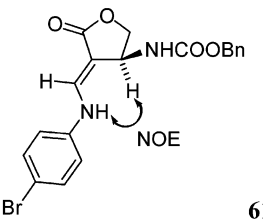
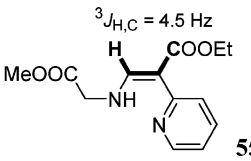
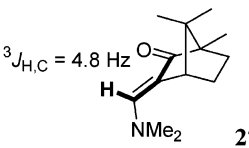
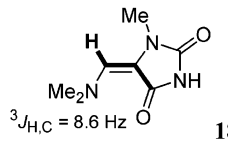
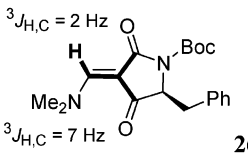
Compound	Ref.	Compound	Ref.
 **53**	35	 **59a,b**	78
 **33d**	67	 **24b**	58
 **13a**	36	 **60**	79
 **13c**	77	 **25a**	69
 **13o**	43	 **35**	69
 **13t**	47	 **25c**	61
 **54**	47	 **61**	61
 **55**	47	 **27**	62
 **18c**	54	 **26a**	51

Table 11. NMR Structural Studies on Isomerization of 2-Substituted Alkyl 3-(Dimethylamino)propenoates and Their Analogues in Solution

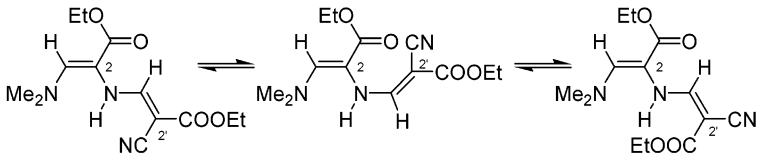
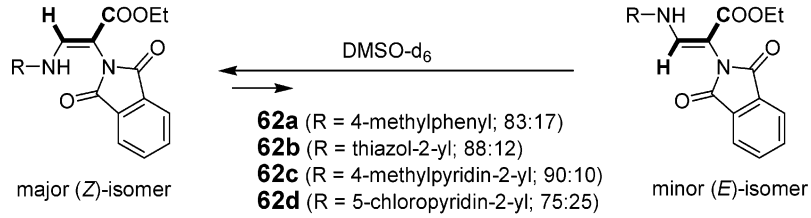
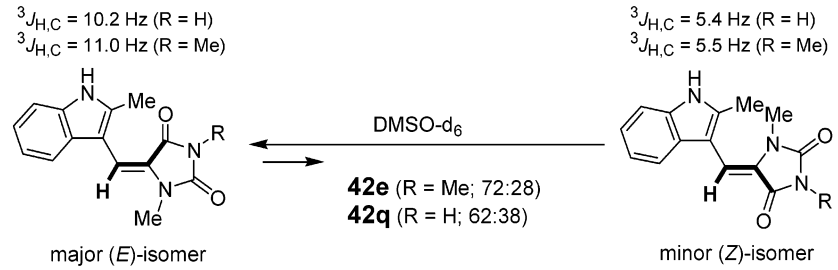
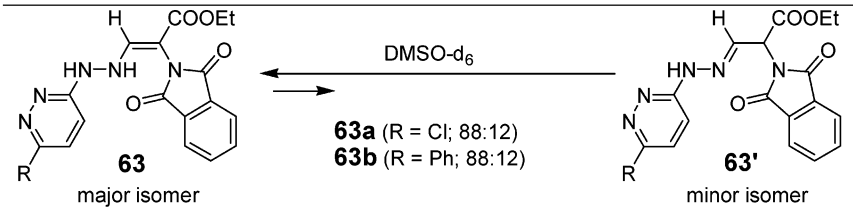
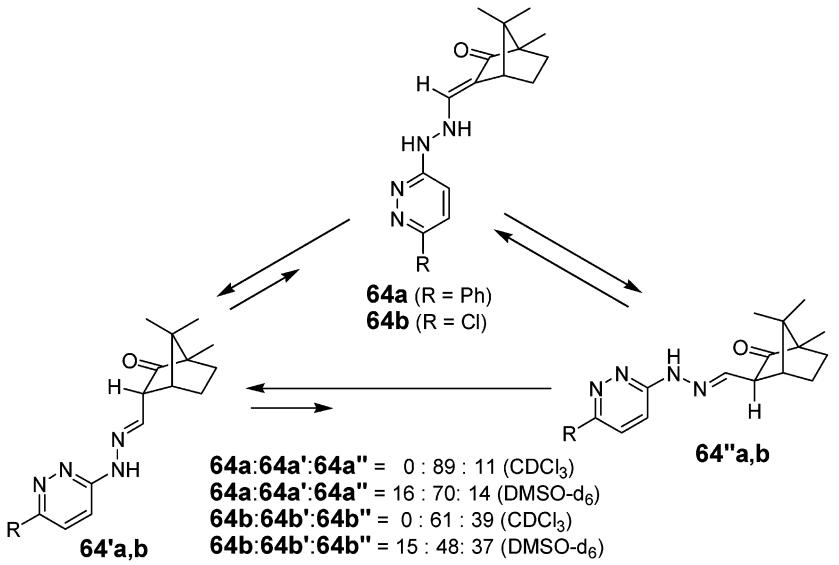
Compound	Ref.
	77
	33
 **13f** (R^1 = Et, R^2 = COPh, R^3 = Et, R^4 = H; 50:30 in DMSO-d_6, >95:5 in $CDCl_3$) **13h** (R^1 = Me, R^2 = COMe, R^3 = Me, R^4 = H; 88:12 in DMSO-d_6) **13j** (R^1 = CH_2Ph, R^2 = COMe, R^3 = Me, R^4 = H; 87:13 in DMSO-d_6) **13m** (R^1 = Et, R^2 = CN, R^3 = R^4 = Me; 94:6 in DMSO-d_6) **13n** (R^1 = Et, R^2 = CN, R^3 = Et, R^4 = Me; 89:11, in DMSO-d_6)	17,42,77
 **13l** 43% *anti* (2Z,2'E) **13l'** 36% *syn* (2Z,2'E) **13l''** 21% *anti* (2Z,2'Z)	41
	34
	54

Table 12. Enehydrazine−Hydrazone Isomerization of 3-(Hydrazino)propenoates 63, 64

Compound	Ref.
	34
	62

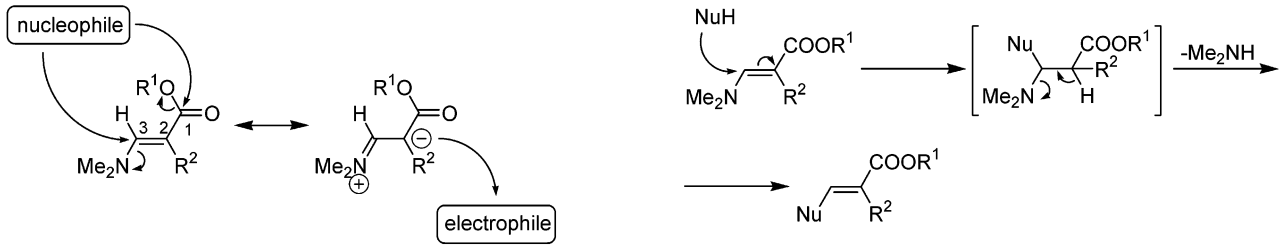


Figure 5.

Figure 6. Dimethylamine substitution reactions of 3-(dimethylamino)propenoates with *N*- and *C*-nucleophiles.

with a carbonyl or nitrile group in the substituent R^2 to give pyrroles or 1,2,4-oxadiazoles (Figure 5).[7−12]

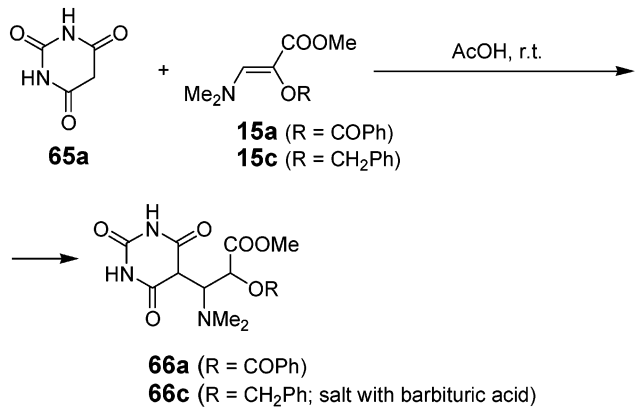
4.1. Reactions with Nucleophiles

3-(Dimethylamino)propenoates react with a variety of *O*-, *N*-, and *C*-nucleophiles to give the dimethylamine substitution products. A typical reaction with *O*-nucleophile is hydrolysis of 3-(dimethylamino)propenoates to 3-hydroxypropenoates. Typical reactive *N*-nucleophiles are primary and secondary aliphatic, aromatic, and heteroaromatic amines, whereas in the *C*-nucleophile series, treatment with active methylene compounds, such as 1,3-dicarbonyl compounds and their cyclic analogues, indole derivatives, heteroarylacetic acid derivatives, and hydrogen cyanide, gives the substitution products (see sections 5.1.1−5.1.3 and 5.3.1). Reactions are acid-catalyzed and, most probably, they proceed by an addition−elimination mechanism (Figure 6).[7−12,32,34,35,47−49,52−54,60−62,66−70,78,80]

Namely, in the reaction of propenoates **15a**,**c** with barbituric acid (**65a**), the intermediate adducts **66a**,**c** have been isolated (Scheme 7).[50]

With dinucleophiles, reaction with the ester group can follow, furnishing cyclic products. Typical dinucleophiles are hydrazine derivatives and primary heteroarylamines with the amino group attached at the α-position with respect to the ring nitrogen atom

Scheme 7



(*N*,*N*-dinucleophiles), (α-heteroaryl)acetic acid derivatives (*C*,*N*-dinucleophiles), and 1,3-dicarbonyl compounds and their cyclic analogues (*C*,*O*-dinucleophiles). Also, these reactions are acid-catalyzed and are usually carried out in acetic acid. Selectivity is controlled by reaction conditions: under mild conditions (20−80 °C), the dimethylamine substitution products are formed, whereas upon heating at 90−120 °C further cyclization takes place to give pyrazoles, pyridones, pyrimidones, 2*H*-pyran-2-ones, and their fused analogues (see sections 5.2.3, 5.2.4, 5.2.8, 5.2.9, 5.2.11, 5.2.12, and 5.3.2) (Figure 7).[7−12,32,34,35,60,67]

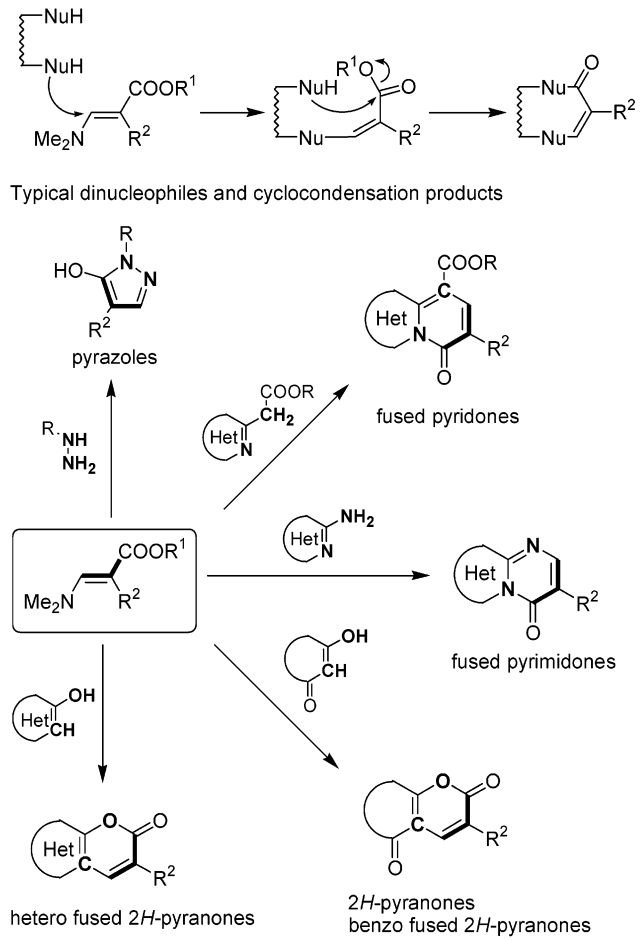


Figure 7. Reactions of 3-(dimethylamino)propenoates with ambident nucleophiles.

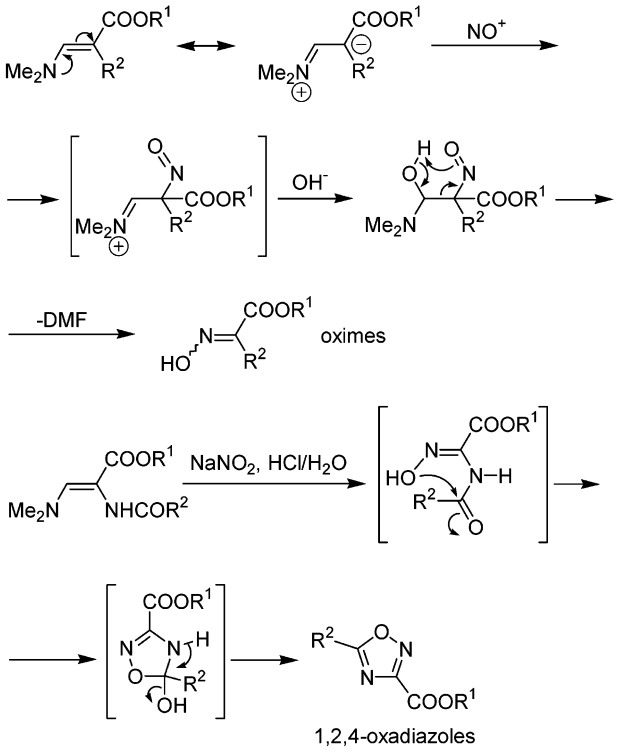


Figure 8. Reactions of 3-(dimethylamino)propenoates with nitrous acid.

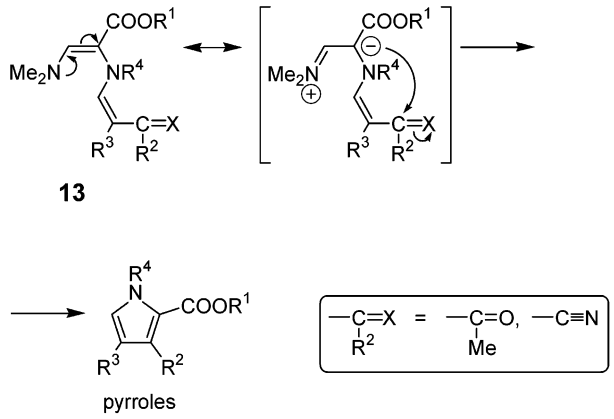


Figure 9. Intramolecular cyclization of alkyl 3-(dimethylamino)-2-[(2,2-disubstituted-vinyl)amino]propenoates **13**.

4.2. Reactions with Electrophiles

Despite deactivation by conjugated carbonyl group, propenoates still exhibit enamine character (position C-2) toward electrophiles. Thus, reaction of 3-(dimethylamino)propenoates with nitrous acid leads to oximes as the primary products. The transformation could be explained by the addition of nitrous acid to C-2 of the propenoate followed by elimination of DMF. In the case of 2-(acylamino)-3-(dimethylamino)-propenoates, the so-formed oxime cyclizes spontaneously to furnish 1,2,4-oxadiazoles (see sections 5.2.6 and 5.3.3) (Figure 8).[8−12,29,31,57]

Alkyl 3-(dimethylamino)-2-[(2,2-disubstituted-vinyl)amino]propenoates **13** undergo acid-catalyzed intramolecular cyclization by attack of the nucleophilic C-2 to the carbonyl group or cyano group attached to the side chain, to afford the pyrrole derivatives (see section 5.2.2) (Figure 9).[9−11,14,42,44,46]

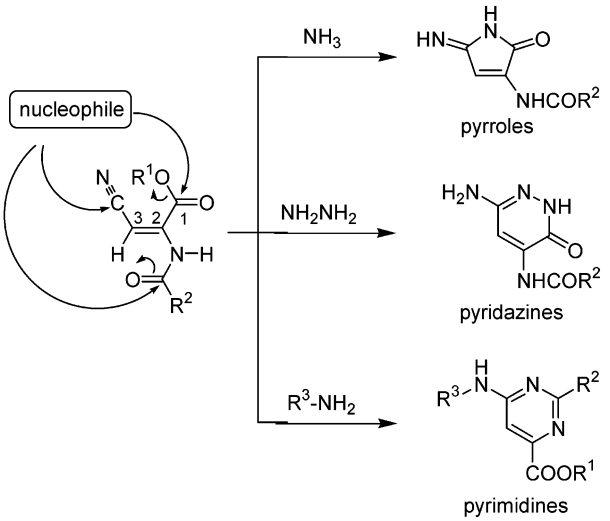


Figure 10. Reactions of 2-(acetylamino)-3-cyanopropenoates and analogues with nucleophiles.

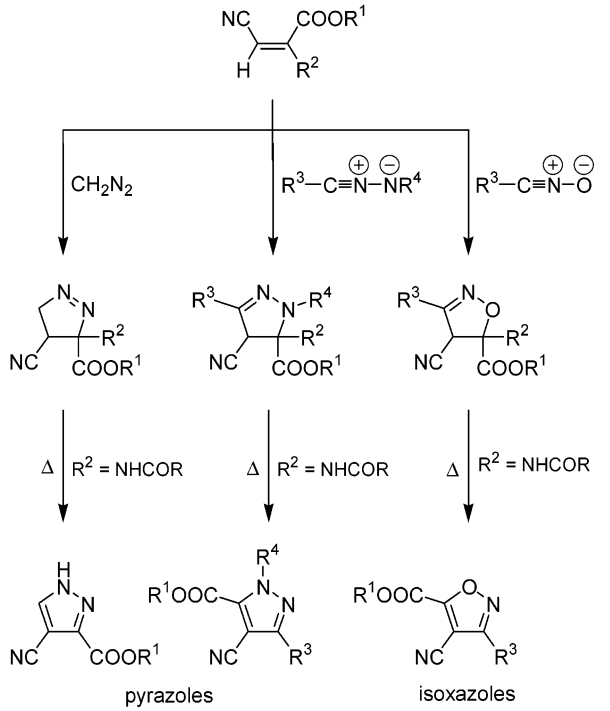


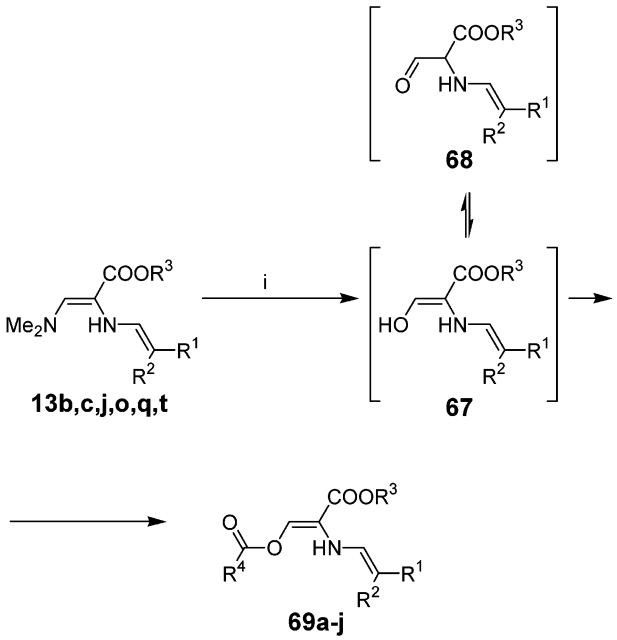
Figure 11.

4.3. Reactions of 2-Substituted 3-Cyanopropenoates

Alkyl 2-(acylamino)-3-cyanopropenoates, obtained upon acid-catalyzed treatment of the parent dimethylamino compounds with potassium cyanide (see section 2), are also useful reagents in heterocyclic synthesis. They possess three electrophilic sites, with the following order of reactivity: CN > $COOR^1$ ~ $NHCOR^2$. In reactions with nucleophiles, cyclocondensation can involve cyano and ester group to give pyrroles (see section 5.2.2) and pyridazines (see section 5.2.10) or cyano and acylamino groups to give pyrimidines (see section 5.2.11) (Figure 10).[9−12,66]

On the other hand, 2-substituted 3-cyanopropenoates can be used as dipolarophiles in 1,3-dipolar cycloaddition reactions with diazomethane, nitrile oxides, nitrile imines, and azomethine imines to furnish pyrazole (see section 5.2.4) and isoxazole derivatives (see section 5.2.3) (Figure 11).[9−12,67−70]

Scheme 8[a]



[a] Reaction conditions: (i) R^4COCl (excess), acetone, reflux.

5. Synthetic Applications

5.1. Synthesis of Alkyl α,β-Disubstituted Propenoates

5.1.1. Synthesis of α-Amino-β-hydroxypropenoates as Dehydroserine Analogues

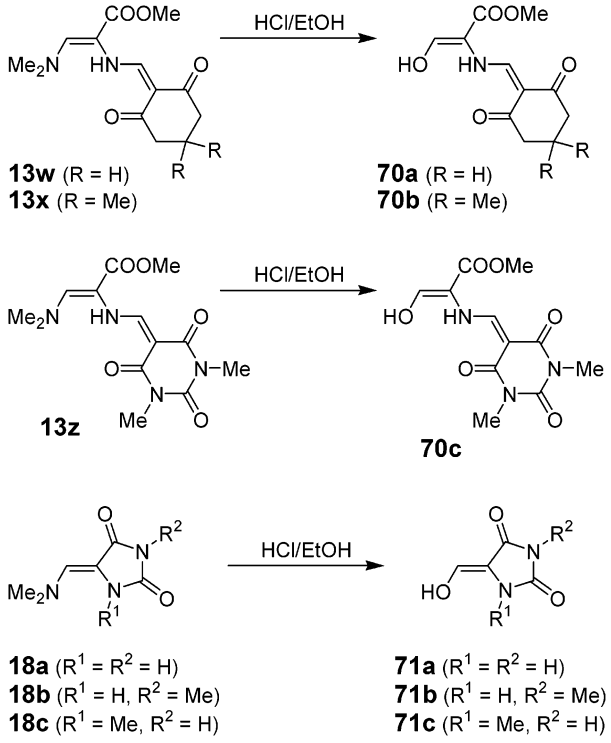
Various α,β-disubstituted propenoic acid derivatives can be prepared from 2-substituted alkyl 3-(dimethylamino)propenoates by acid-catalyzed dimethylamine substitution with various *O*-, *N*-, and *C*-nucleophiles (see section 4.1). In the *O*-nucleophile series, reaction with water (hydrolysis) takes place, where the dimethylamino group is substituted by the hydroxy group. Until now, dimethylamine substitution with an alkoxy group has not been observed. Usually, hydrolysis of (dimethylamino)propenoates takes place in the absence of a suitable *N*- or *C*-nucleophile. For example, 2-[(2,2-disubstituted-ethenyl)amino]-3-(dimethylamino)propenoates **13b**,**c**,**j**,**o**,**q**,**t** in the presence of acyl chlorides are converted primarily into *N*-acylpyrrole-2-carboxylates (see section 5.2.2).[14,42] However, when the reaction is carried out in refluxing acetone in the presence of a large excess of acyl chloride, 3-(acyloxy)-2-[(2,2-disubstituted-ethenyl)amino]propenoates **69a**−**j** are formed in 12−91% yields via the corresponding aldehyde **68** and enol **67** intermediates, followed by acylation with acyl chloride (Scheme 8; Table 13).[80]

Furthermore, when 3-(dimethylamino)propenoates **13w**,**x**,**z** were hydrolyzed with a solution of HCl in ethanol, the corresponding 3-hydroxypropenoates **70a**−**c** were obtained in 27−85% yields. Similarly, hydantoin-derived enamines **18a**−**c** were converted into enols **71a**−**c** in 55−98% yields (Scheme 9).[48]

Table 13. Alkyl 3-Acyloxy-2-[(2,2-disubstituted-ethenyl)amino]propenoates 69a−j Prepared[80]

compd	R^1	R^2	R^3	R^4	yield (%)
69a	COOEt	COOEt	Me	4-Me-C_6H_4	30
69b	COMe	COMe	Me	4-Me-C_6H_4	23
69c	COOBn	COMe	Me	Ph	12
69d	COOBn	COMe	Me	4-Me-C_6H_4	47
69e	COOBn	COMe	Me	4-Cl-C_6H_4	17
69f	COOEt	COOEt	Et	4-Me-C_6H_4	43
69g	COPh	COPh	Et	4-Me-C_6H_4	33
69h	COOEt	pyridin-2-yl	Me	4-Cl-C_6H_4	91
69i	COOEt	pyridin-2-yl	Me	Ph	77
69j	COOEt	pyridin-2-yl	Me	4-Me-C_6H_4	80

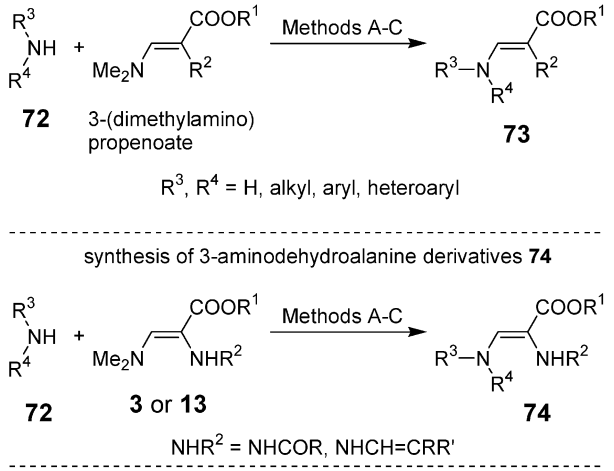
Scheme 9



5.1.2. Synthesis of α-Substituted β-Aminopropenoates and β-Aminodehydroalanine Derivatives

2-Substituted alkyl 3-(dimethylamino)propenoates undergo acid-catalyzed dimethylamine substitution with various primary and secondary alkyl-, aryl-, and heteroarylamines **72** to give β-aminopropenoic acid derivatives **73**. This substitution reaction is one of the most general reactions of 3-(dimethylamino)-propenoates. Usually, dimethylamine substitution with alkyl-, aryl-, and heteroarylamines is carried out in acetic acid (method A) or in ethanol or methanol in the presence of 1 equiv of 37% hydrochloric acid (method B). Alternatively, the amine hydrochloride can be used instead of an equimolar mixture of free amine and hydrochloric acid (method C). In this manner, a number of various types of α-substituted β-aminopropenoates and analogues have been prepared.[4,7−12,32,34,52,60,79,81−87] For example, the use of 2-(acylamino)-3-(dimethylamino)propenoates **3** and 2-(vinylamino)-3-(dimethylamino)propenoates **13** as reagents enables a one-step preparation of *N*-protected β-alkylamino, β-arylamino, and β-heteroaryl-

Scheme 10[a]



[a] Method A, R^3R^4NH, AcOH, 20−120 °C; method B, R^3R^4NH, 37% HCl (aq, 1 equiv), EtOH, or MeOH, 20−80 °C; method C, $R^3R^4NH \times$ HCl, EtOH, or MeOH, 20−80 °C.

Table 14. Some Examples of β-Aminodehydroalanine Derivatives 74 Prepared from 2-(Acylamino)- and 2-(Vinylamino)-3-(dimethylamino)propenoates[a]

NHR^2	method	ref
NHCOMe	A−C	27
NHCOPh	A−C	4, 88
NHCOOBn	A, B	83
NHBoc	B, C	32
N-phthaloyl	B	34
NHCH=C(pyridin-2-yl)COOMe	A	47
NHCH=C(pyridin-2-yl)COOEt	A	47, 85
NHCH=C(pyridin-2-yl)CN	A	86
NHCH=C(COOEt)COMe	A	40
$NHCH=C(COOEt)_2$	A	37

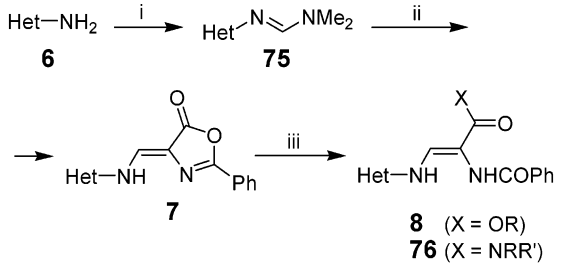
[a] R^1 = Me, Et; NR^3R^4 = anilino, 2-hydroxyanilino, 4-hydroxyanilino, 2-nitroanilino, 3-nitroanilino, 4-nitroanilino, 2,4-dinitroanilino, 2-methyl-3-nitroanilino, 2-methylanilino, 3-methylanilino, 4-methylanilino, 2,4-dimethylanilino, 3-carboxyanilino, 4-carboxyanilino, 4-ethoxycarbonylanilino, 2-aminoanilino, 2-benzoylanilino, 3-benzoylanilino, naphthylamino, isoxazol-3-ylamino, 5-methylisoxazol-3-ylamino, thiazol-2-ylamino, 4-chlorobenzothiazol-2-ylamino, 1*H*-[1,2,4]triazol-3-ylamino, 3-phenyl[1,2,4]thiadiazol-5-ylamino, pyridin-2-ylamino, 5-chloropyridin-2-ylamino, 4-methylpyridin-2-ylamino, 6-methylpyridin-2-ylamino, quinolin-2-ylamino, pyrimidin-2-ylamino, 4-methylpyrimidin-2-ylamino, 4,6-dimethylpyrimidin-2-ylamino, 4-chloro-6-methylpyrimidin-2-ylamino, pyridazin-3-ylamino, 6-chloropyridazin-3-ylamino, pyrazinylamino, pyrrolidinyl-1, piperidinyl-1, piperazin-1,4-diyl, benzylamino, 4-methoxybenzylamino, methoxycarbonylmethylamino, ethoxycarbonylmethylamino.

amino-α,β-dehydroalanine esters **74**, usually in good yields (Scheme 10; Table 14).[4,27,32,34,37,40,47,83,85,86,88]

Alternatively, α-benzoylamino-β-heteroarylamino-α,β-dehydroalanine esters **8** (X = OR) and amides **76** including peptides can be prepared via the corresponding 4-heteroarylaminomethylidene-2-phenyl-5(4*H*)-oxazolones **7**, which are available in two steps from primary heteroarylamines **6** (Scheme 11).[3−5,89]

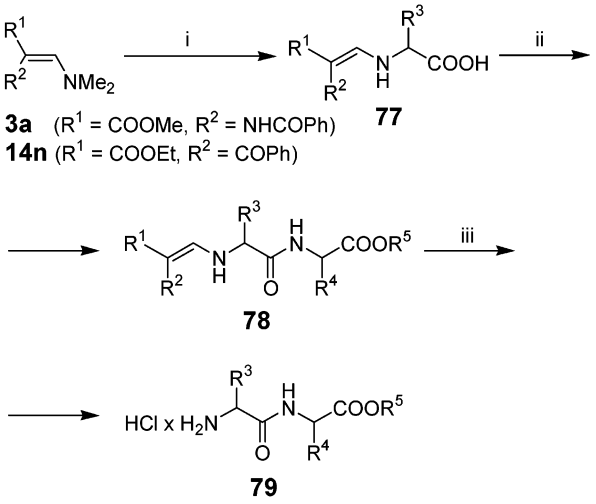
Dimethylamine substitution with amino acids and their derivatives leads to *N*-(2,2-disubstituted-vinyl)-protected amino acids. The 3-(dimethylamino)propenoates **3a** and **14n** can be recommended as reagents for the protection of the amino group of amino acids to afford enamines **77**. These *N*-blocked amino acids were coupled with various amino acid esters to

Scheme 11[a]



[a] Het = 2-methoxycarbonylpyridin-3-yl, 3-nitropyridin-2-yl, 5-nitropyridin-2-yl, 3,5-dibromopyridin-2-yl, isoxazol-3-yl, 5-methylisoxazol-3-yl, 6-chloropyridazin-3-yl, pyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,6-dimethylpyrimidin-4-yl, 4,6-dimethylpyrimidin-2-yl, 4-chloro-6-methylpyrimidin-2-yl, 5-ethoxycarbonyl-2-methylthiopyrimidin-4-yl, pyrazinyl, 3-methoxycarbonylpyrazin-2-yl, [1,2,4]benzothiazol-4-yl. X = OMe, OEt, NH_2, NEt_2, $NHNH_2$ ($\rightarrow N_3$), NHCH(R)COOH. Reaction conditions: (i) DMFDMA, toluene, reflux; (ii) hippuric acid, Ac_2O, 70 °C; (iii) *N*- or *O*-nucleophile (HX, X = OR, NHR, NR_2, $NHNH_2$), base, 20−80 °C.

Scheme 12[a]



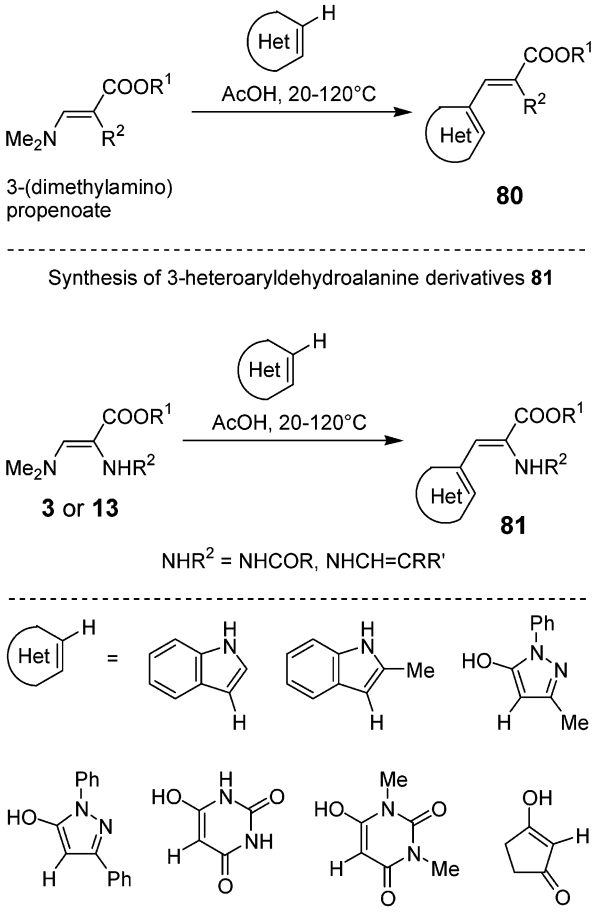
[a] Reaction conditions: (i) amino acid, AcOH, 70−80 °C; (ii) amino acid ester, *N*,*N*−dicyclohexylcarbodiimide, CH_2Cl_2; (iii) for R^1 = COOMe and R^2 = NHCOPh, hydrazine monohydrochloride or hydroxylamine hydrochloride, MeOH, reflux; for R^1 = COOEt and R^2 = COPh, 2-amino-4,6-dimethylpyrimidine hydrochloride, EtOH, reflux.

furnish dipeptides **78**. The removal of the *N*-protecting group was achieved with hydrazine monohydrochloride or hydroxylamine hydrochloride or, for R^1 = NHCOPh and R^2 = Me, with 2-amino-4,6-dimethylpyrimidine hydrochloride. Peptide esters **79** have also been employed for the preparation of tri-, tetra-, and pentapeptides with protected N termini (Scheme 12).[89,90]

5.1.3. Synthesis of β-Heteroarylpropenoates and β-Heteroaryldehydroalanine Esters

Substitution with, mainly heterocyclic, *C*-nucleophiles, such as indoles and (hetero)cyclic analogues of 1,3-dicarbonyl compounds, affords *β*-heteroarylpropenoates **80**. Typically, derivatives of indole, barbituric acid, and 1-phenyl-5(4*H*)-pyrazolone are used as *C*-nucleophiles, and the reactions are carried out in acetic acid. When 2-(acylamino)-3-(dimethylamino)propenoates **3** and 2-(vinylamino)-3-(dimethylamino)propenoates **13** are used, substitution leads to the formation of 3-heteroaryl-2,3-dehydroalanine derivatives **81** (Scheme 13).[7−11,34,35,50,52,53,85,86,91]

Scheme 13[a]



[a] NHR^2 = NHCOPh, *N*-phthaloyl, NHCH=C(pyridin-2-yl)COOEt, NHCH=C(pyridin-2-yl)CN, OCOPh.

Scheme 14

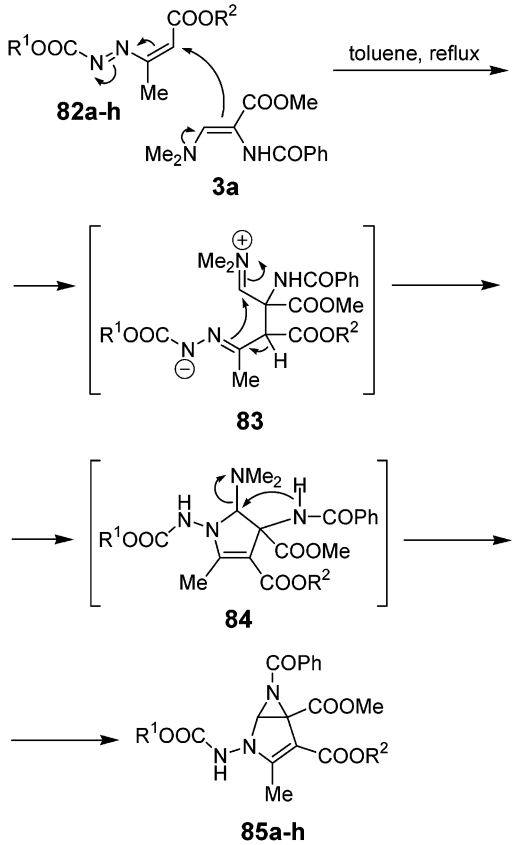
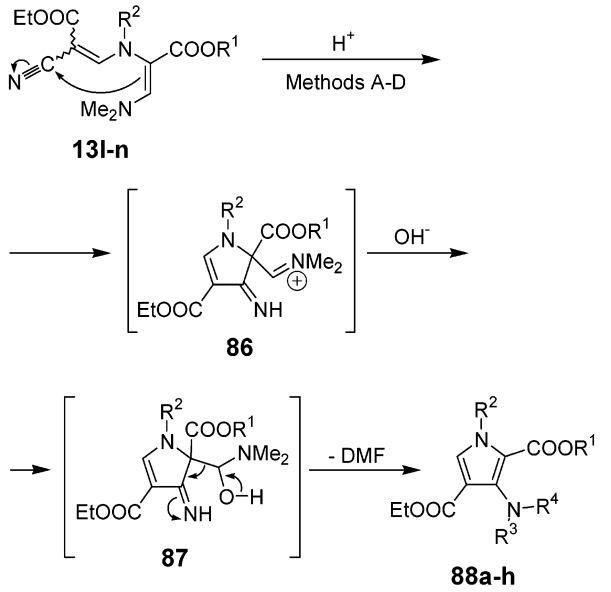


Table 15. 2,6-Diazabicyclo[3.1.0]hexenes 85a−h Prepared from Azadienes 82a−h and Propenoate 3a[95]

compd	R^1	R^2	yield (%)
85a	Me	Me	70
85b	Et	Et	56
85c	*t*-Bu	Me	65
85d	*t*-Bu	benzyl	51
85e	benzyl	Me	56
85f	benzyl	Et	54
85g	*p*-methoxybenzyl	Me	61
85h	*p*-methoxybenzyl	Et	66

Scheme 15[a]



[a] Methods: A, HCl, EtOH; B, AcOH; C, AcOH, Ac_2O; D, $(CF_3CO)_2O$.

Table 16. Dialkyl 3-Aminopyrrole-2,4-dicarboxylates 88a−h Prepared[42]

compd	method	R^1	R^2	R^3	R^4	yield (%)
88a	A	Me	Me	H	H	90
88b	B	Me	Me	H	MeCO	54
88c	B	Et	Me	H	MeCO	88
88d	C	Et	Me	MeCO	MeCO	52
88e	C	Et	H	MeCO	MeCO	68
88f	D	Me	Me	H	CF_3CO	56
88g	D	Et	H	H	CF_3CO	65
88h	D	Et	Me	H	CF_3CO	40

5.2. Synthesis of Heterocyclic Systems

5.2.1. Synthesis of Fused Aziridines

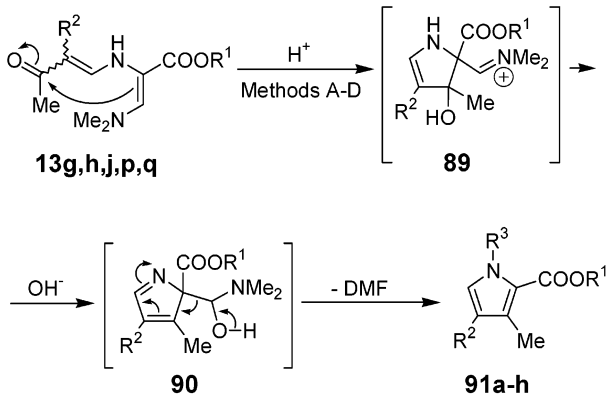
A simple and convenient synthesis of highly protected aziridines fused to pyrroline rings **85a−h** is represented by addition of 1,2-diaza-1,3-butadienes **82a−h**[92−94] to methyl 2-(benzoylamino)-3-(dimethylamino)propenoate (**3a**).[3] Addition leads to the formation of zwitterionic hydrazine intermediate **83**. In this example, 3-(dimethylamino)propenoate **3a** exhibits enamine character toward the terminal carbon of the heterodiene system (Scheme 14; Table 15).[95]

5.2.2. Synthesis of Pyrroles and Fused Pyrroles

Propenoates **13l−n** undergo acid-catalyzed intramolecular cyclization to afford 3-aminopyrrole-2,4-dicarboxylates **88a−h** in 40−90% yields. Depending on the acid used, the 3-amino group can be acylated (Scheme 15; Table 16).[42]

Pyrrole-2-carboxylates have been prepared from 1,3-dicarbonyl compounds and aminomalonate,[96,97] diethyl oximinomalonate,[98] various 2-amino-1,3-di-

Scheme 16[a]

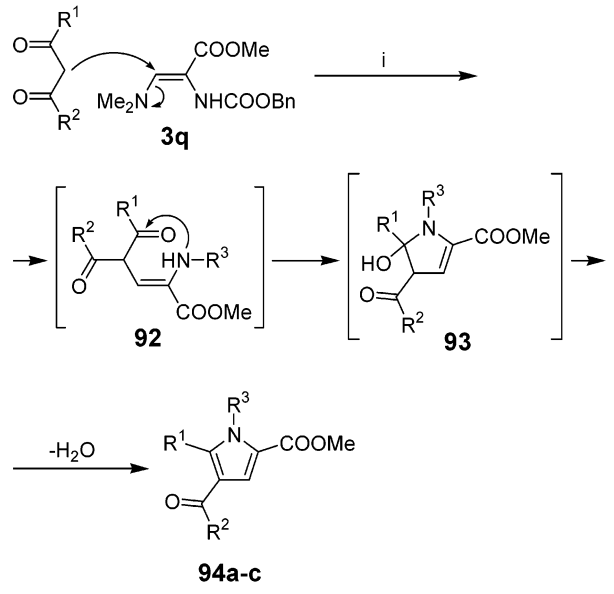


[a] Methods: A, AcOH; B, CF_3COOH; C, $(CF_3CO)_2O$; D, R^3Cl, acetone.

Table 17. Alkyl 2-Pyrrolecarboxylates 91a−h Prepared

compd	method	R^1	R^2	R^3	yield (%)	ref
91a	B	Et	COPh	H	65	44
91b	A, C	Me	COMe	H	45	14
91c	D	Me	COMe	COMe	41	14
91d	D	Me	COMe	COPh	23	14
91e	C	Me	COOMe	H	49	14
91f	C	Et	COOEt	H	60	14
91g	C	Me	COOBn	H	61	14
91h	D	Me	COOBn	COMe	34	14

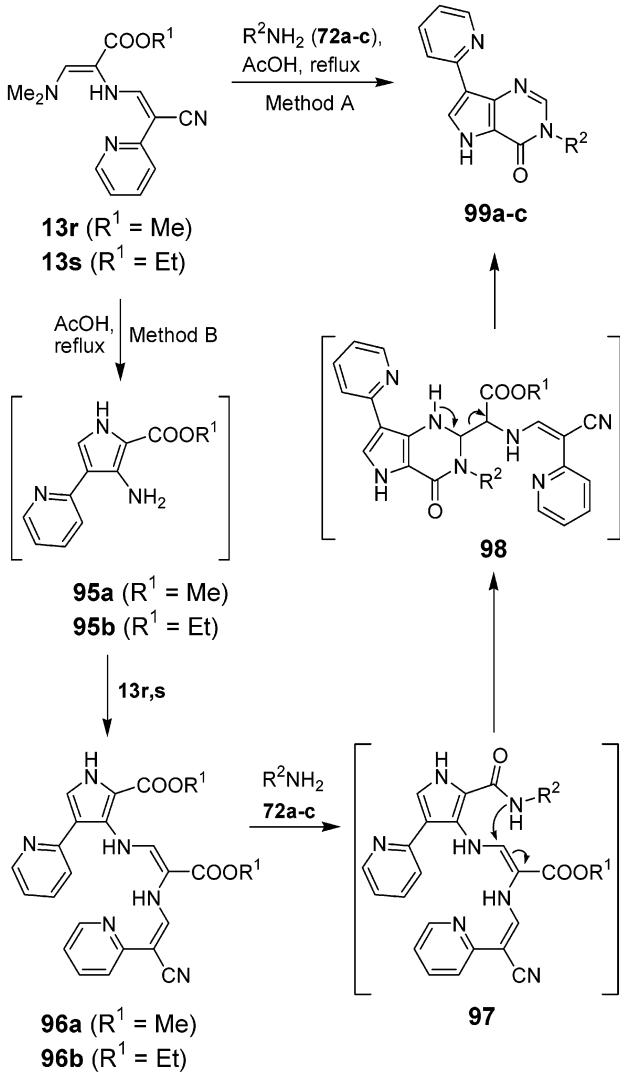
Scheme 17[a]



Compound	R^1	R^2	R^3
94a	Me	Me	H
94b	Me	Ph	H
94c	Me	Me	$COOCH_2Ph$

[a] Reaction conditions: (i) AcOH, reflux (N−R^3, N−COOBn → N−H).

Scheme 18



Reaction	R^1	R^2	Method	Yield (%)
13r→96a	Me		B	33
13s→96b	Et		B	29
13r→99a	Me	benzyl	A	42
13s→99a	Et	benzyl	A	36
96a→99a	Me	benzyl	B	34
13r→99b	Me	4-methoxybenzyl	A	32
13s→99b	Et	4-methoxybenzyl	A	27
13r→99c	Me	methyl	A	25

carbonyl compounds,[99] 1,3-dicarbonyl compounds, and α-amino acid derivatives[100−103] and by the addition of α-amino acid derivatives to dimethyl acetylenedicarboxylate.[104,105] We found that heating the propenoate **13p** in CF_3COOH gives the pyrrole **91a** in 65% yield.[44] The reaction has been extended to the propenoates **13g**,**h**,**j**,**q**. Under various conditions pyrrole-2-carboxylates **91b**−**h** were obtained (Scheme 16; Table 17).[14]

From compound **3q** and 1,3-diketones 5-substituted pyrrole-2-carboxylates **94a**−**c** can be prepared (Scheme 17).[33]

Alkyl 2-[2-cyano-2-(pyridin-2-yl)ethenyl]amino-3-(dimethylamino)propenoates **13r** and **13s** were transformed by heating in acetic acid to compounds **96a** and **96b** in 33 and 29% yields, respectively. The formation of these compounds can be explained by cyclization of **13r** and **13s** into 3-amino-4-(pyridin-2-yl)pyrrole-2-carboxylates **95a** and **95b** according to the scheme reported earlier for the formation of other 4-substituted 3-aminopyrrole-2-carboxylates[42] followed by the reaction with the starting compound in

Scheme 19

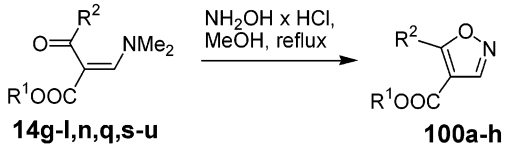
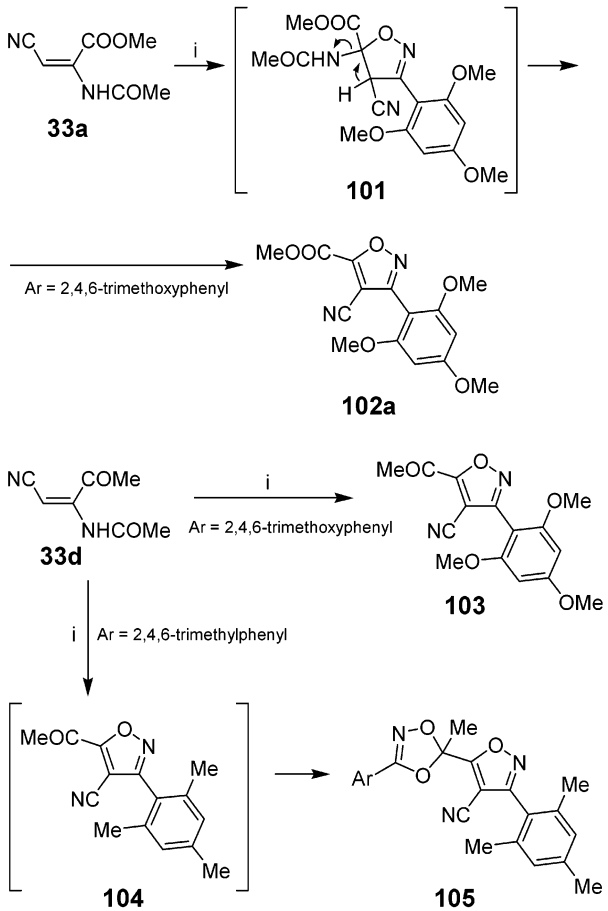


Table 18. Isoxazole-4-carboxylates 100a−k Prepared from Alkyl 2-Acyl-3-(dimethylamino)propenoates 14g−l,n,q,s−u[107]

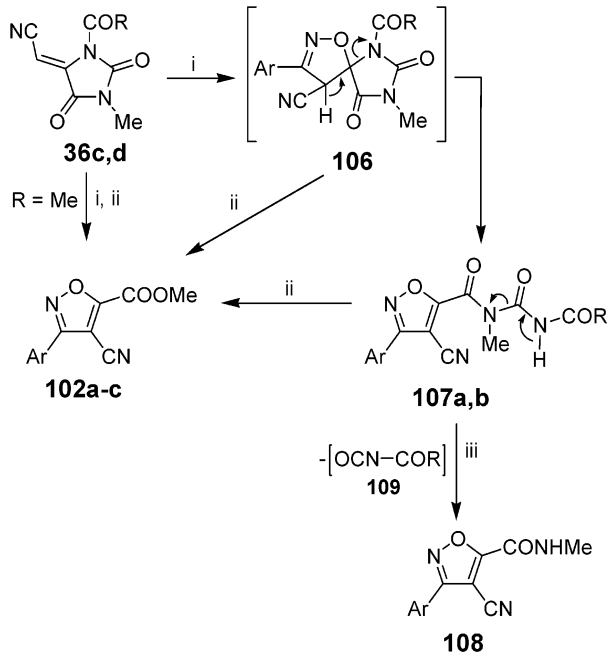
reaction	R^1	R^2	yield (%)
14g → 100a	Et	Me	84
14h → 100b	Et	Et	76
14i → 100c	Et	1-propyl	68
14j → 100d	Et	2-propyl	82
14k → 100e	Et	*t*-Bu	87
14l → 100f	Me	CH_2Ph	74
14n → 100g	Et	Ph	90
14q → 100h	Et	COOEt	70
14s → 100i	Me	CH_2OMe	76
14t → 100j	Me	$(CH_2)_2COOMe$	85
14u → 100k	Et	$(CH_2)_3COOMe$	72

Scheme 20[a]



[a] Reaction conditions: (i) Ar−C≡N^+−O^-, CH_2Cl_2, or $CHCl_3$, reflux; Ar = 2,4,6-trimethoxyphenyl and 2,4,6-trimethylphenyl.

Scheme 21[a]



Reaction	R	Ar	Yield (%)
36c→106	Me	2,4,6-trimethoxyphenyl	20
36d→107a	Ph	2,4,6-trimethoxyphenyl	66
36d→107b	Ph	2,4,6-trimethylphenyl	62
107b→108	Ph	2,4,6-trimethylphenyl	76
106→102a	Me	2,4,6-trimethoxyphenyl	69
107a→102a	Ph	2,4,6-trimethoxyphenyl	88
36c→102a	Me	2,4,6-trimethoxyphenyl	57
36c→102b	Me	2,4,6-trimethylphenyl	80
36c→102c	Me	2,6-dichlorophenyl	45

[a] Reaction conditions: (i) Ar–C≡N$^+$–O$^-$,$CHCl_3$, rt reflux; (ii) column chromatography, silica gel, $CHCl_3$/MeOH (99:1); (iii) Et_3N, CH_2Cl_2, reflux.

which the dimethylamino group is substituted by aminopyrrole derivative to give products **96a** and **96b**. By further treatment of **96a** with benzylamine **72a** in acetic acid, compound **99a** was obtained in 34% yield. When propenoate **13r** was heated with primary aliphatic amines **72a**–**c** in acetic acid, pyrrolo[3,2-*d*]pyrimidin-4-ones **99a**–**c** were obtained in 42, 32, and 25% yields, respectively (Scheme 18).[46]

5.2.3. Synthesis of Isoxazoles

Treatment of alkyl 2-acyl-3-(dimethylamino)propenoates **14g**–**l**,**n**,**q**,**s**–**u** with hydroxylamine hydrochloride in methanol leads to 5-substituted isoxazole-4-carboxylates **100a**–**k** (Scheme 19; Table 18).[106,107]

Methyl 3-(2,4,6-trimethoxyphenyl)-4-cyanoisoxazole-5-carboxylate (**102a**)[66] and 5-acetyl-3-(2,4,6-trimethoxyphenyl)-4-cyanoisoxazole (**103**)[67] were obtained upon 1,3-dipolar cycloaddition of 2,4,6-trimethoxybenzonitrile oxide to methyl 2-(acetylamino)-3-cyanopropenoate (**33a**) and 2-(benzoylamino)-4-cyano-2-oxobut-3-ene (**33d**), respectively. Reaction proceeds via 1,3-dipolar cycloaddition to produce the dihydroisoxazole intermediate, such as **101**, from which the amide moiety is eliminated to give the isoxazole derivative. Interestingly, in the reaction of 2-(benzoylamino)-4-cyano-2-oxobut-3-ene (**33d**) with 2,4,6-trimethylbenzonitrile oxide, biscycloadduct **105** was formed (Scheme 20).[67]

Similarly, cycloadditions of benzonitrile oxides to 1-acyl-5-[(*Z*)-cyanomethylidene]-3-methyl-imidazolidine-2,4-diones **36c**,**d** resulted in the formation of 3-aryl-4-cyanoisoxazole-5-carboxylic acid derivatives **108** and **102a**–**c**. Thus, in refluxing chloroform, formation of ureides **107a**,**b** was observed in most cases. In the presence of a base, elimination of acyl isocyanate **109** took place to afford *N*-methylcarboxamide **108**. When isolation of products was carried out by column chromatography on silica gel with a mixture of chloroform and methanol as eluent, methyl isoxazole-5-carboxylates **102a**–**c** were obtained (Scheme 21).[70]

5.2.4. Synthesis of Pyrazoles

2-Acyl-3-(dimethylamino)propenoates and related enamino ketones react with hydrazine derivatives to afford 1,4,5-trisubstituted pyrazole derivatives. Reaction proceeds by initial dimethylamine substitution followed by condensation to the acyl group.[19,108–110] Various 1-alkyl-, 1-aryl-, and 1-heteroaryl substituted pyrazole-4-carboxylates **111a**–**q** were prepared in this manner from 2-acyl-3-(dimethylamino)propenoates **14g**–**l**,**n**,**q** (Scheme 22; Table 19).[19,109,110]

Upon reaction of ethyl (*E*)-4-(dimethylamino)-2-oxobut-3–enoate (**112**)[25,110] with pyridazinylhydra-

Scheme 22

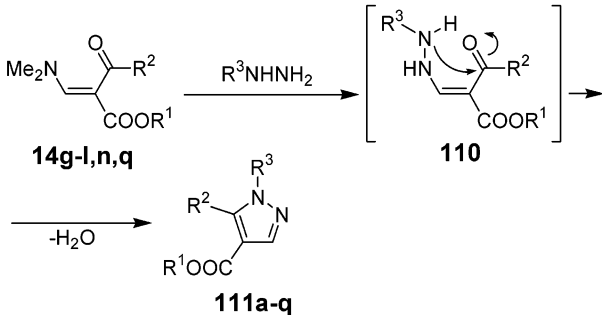
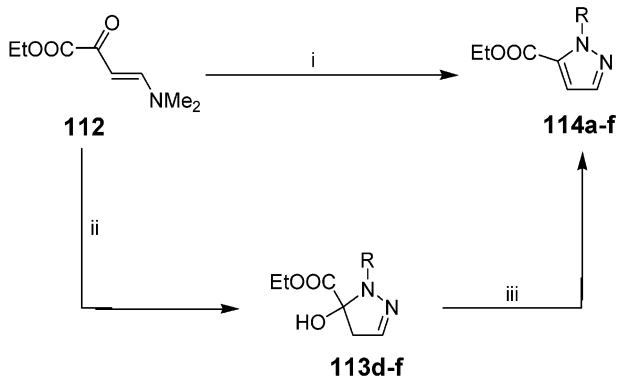


Table 19. Pyrazole-4-carboxylates 111a–q from 2-Acyl-3-(dimethylamino)propenoates 14g–l,n,q and Their Analogues[19,109,110]

reaction	R^1	R^2	R^3	yield (%)	ref
14q → 111a	Et	COOEt	H	56	110
14q → 111b	Et	COOEt	Ph	86	110
14g → 111c	Et	Me	Ph	96	19
14g → 111d	Et	Me	*t*-Bu	88	109
14h → 111e	Et	Et	Ph	89	19
14i → 111f	Et	*n*-Pr	Ph	95	19
14j → 111g	Et	*i*-Pr	Ph	93	19
14k → 111h	Et	*t*-Bu	Ph	68	19
14n → 111i	Et	Ph	Ph	83	19
14l → 111j	Me	CH_2Ph	Ph	87	19
14q → 111k	Et	COOEt	4-nitrophenyl	36	110
14q → 111l	Et	COOEt	6-chloropyridazin-3-yl	29	110
14q → 111m	Et	COOEt	6-phenylpyridazin-3-yl	37	110
14q → 111n	Et	COOEt	pyrimidin-2-yl	89	110
14q → 111o	Et	COOEt	imidazo[1,2-*b*]pyridazin-6-yl	48	110
14q → 111p	Et	COOEt	1,2,4-triazolo[4,3-*b*]-pyridazin-6-yl	44	110
14q → 111q	Et	COOEt	tetrazolo[1,5-*b*]pyridazin-6-yl	70	110

Scheme 23[a]



Compound	R	Yield (%)	
		113	**114**
114a	H	-	76
114b	Ph	-	9
114c	4-nitrophenyl	-	72
113d	6-chloropyridazin-3-yl	78	-
114d	1,6-dihydro-6-oxopyridazin-3-yl	-	75
113e, **114e**	6-phenylpyridazin-3-yl	95	88
113f, **114f**	imidazo[1,2–*b*]pyridazin-6-yl	47	69

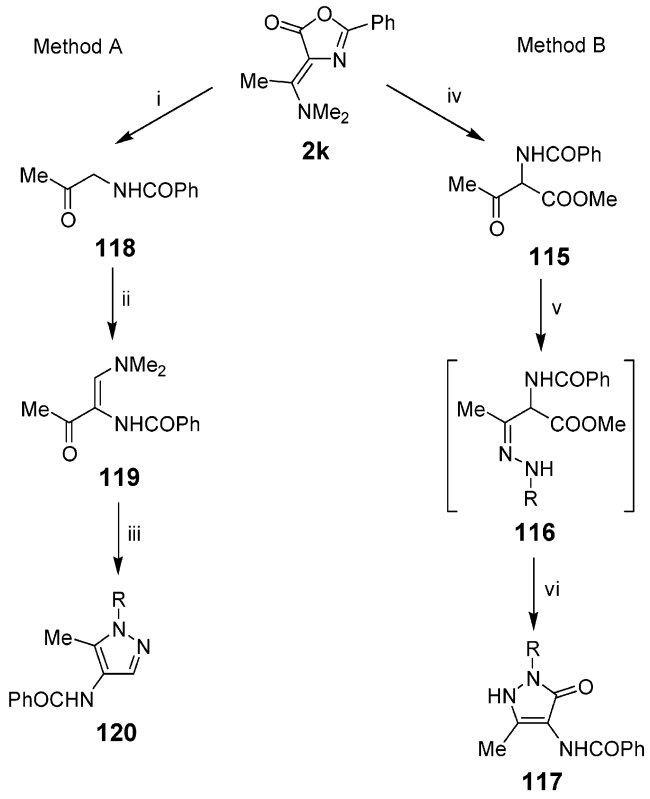
[a] Reaction conditions: (i) $RNHNH_2 \times HCl$, MeOH, or EtOH, 20−60 °C (R = H, aryl); (ii) $RNHNH_2 \times HCl$, EtOH, rt (R = heteroaryl); (iii) AcOH, reflux.

zines in ethanol at room temperature, ethyl 4,5-dihydro-5-hydroxy-1*H*-pyrazole derivatives **113** were formed as stable intermediates in the pyrazole ring formation. Aromatization of dihydropyrazoles was achieved in refluxing acetic acid to afford pyrazoles **114a**−**f** (Scheme 23).[110]

Alkyl 2-(acylamino)-3-oxobutanoates, for example, **115**, have been prepared by acylation with acyl chlorides of lithio dianions of alkyl hippurates prepared at −78 °C with lithium diisopropylamide in tetrahydrofuran. Compounds such as **115** found use as intermediates in the synthesis of heterocyclic amino acids related to furanomycin and steptolutine.[111−113] However, the ester **115** has been obtained in only 28% yield.[113] On the other hand, oxazolone **2k** can be prepared from hippuric acid and *N*,*N*-dimethylacetamide in the presence of phosphorus oxychloride in 93% yield.[55] Hydrolysis with hydrochloric acid in methanol gives ester **115** in 53% yield. Alternatively, compound **115** was obtained from hippuric acid in a one-pot procedure in 60% yield.[55] Transformation with various hydrazines afforded the pyrazolones **117a**,**d**−**m**,**o**. In some cases, the intermediate hydrazones **116** were isolated (method B).[55] On the other hand, upon prolonged heating of **2k** in a 5:1 mixture of methanol and 37% hydrochloric acid, 1-(benzoylamino)-2-propanone (**118**) is obtained in 58% yield. Treatment of propanone **118** with DMFDMA furnishes (*Z*)-3-(benzoylamino)-4-(dimethylamino)-2-oxo-3-butene (**119**) in 74% yield. This reagent was then used for the preparation of 1-substituted 4-(benzoylamino)-5-methyl-1*H*-pyrazoles **120** (method A) (Scheme 24; Table 20).[35]

1,3-Dipolar cycloaddition of diazomethane to methyl 2-(acylamino)-3-cyanopropenoates **33a**,**b** under mild conditions leads to dihydropyrazole derivatives

Scheme 24[a]



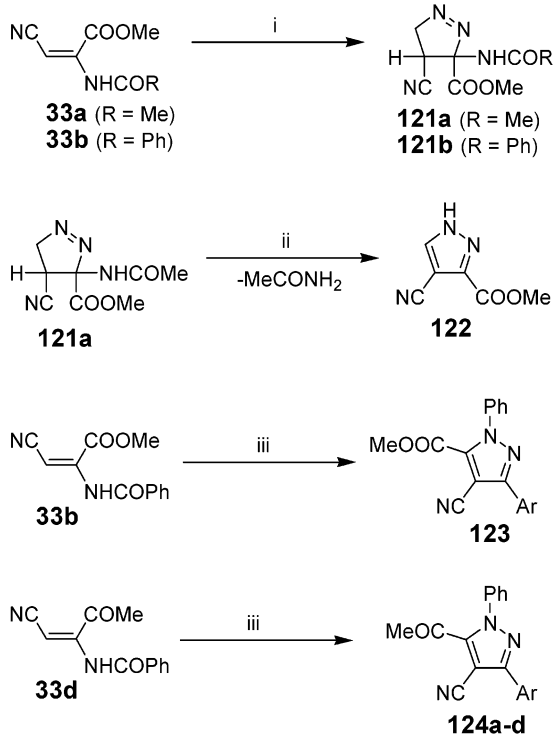
[a] Reaction conditions: (i) MeOH, 37% HCl (aq, 15 equiv), reflux; (ii) DMFDMA, toluene, reflux; (iii) $R-NHNH_2$, EtOH, 37% HCl (aq, 1 equiv), rt; (iv) MeOH, 37% HCl (aq, ∼10 equiv), reflux; (v) $RNHNH_2$, MeOH, reflux; (vi) Et_3N, MeOH, reflux.

Table 20. Pyrazoles 117 and 120 Prepared from 4-(Dimethylamino)ethylidene-5(4*H*)-oxazolone 2k[35,55]

		yield (%)	
compd	R	**117**	**120**
117a, **120a**	H	60	65
120b	Me		54
120c	$PhCH_2$		63
117d	3-hydroxybenzyl	65	
117e	Ph	39	
117f, **120f**	4-carboxyphenyl	31	44
117g, **120g**	4-nitrophenyl	85	70
117h	pyridin-2-yl	62	
117I	6-methylpyridazin-3-yl	62	
117j, **120j**	6-chloropyridazin-3-yl	77	20
117k	6-phenylpyridazin-3-yl	48	
117l	pyrimidin-2-yl	78	
117m, **120m**	1,2,4-triazolo[4,3-*b*]pyridazin-6-yl	71	20
120n	3-methyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl		59
117o, **120o**	3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl	38	36

121a,**b**. Heating of dihydropyrazole **121a** in refluxing xylene resulted in elimination of acetamide to produce methyl 4-cyano-1*H*-pyrazole-3-carboxylate (**122**). Similarly, treatment of propenoate **33b** with *N*-phenyl-2,4,6-trimethoxybenzohydrazonoyl chloride in refluxing chloroform in the presence of triethylamine gave methyl 4-cyano-1-phenyl-3-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole-5-carboxylate (**123**). In the same manner, 5-(acylisoxazole)-4-carbonitriles **124a**−**d** were prepared from benzonitrile imines and (*E*)-3-(benzoylamino)-4-cyano-2-oxobut-3-ene (**33d**) in dichloromethane (Scheme 25).[66,67]

Scheme 25[a]



Compound	Ar	Yield (%)	Ref.
121a	-	86	[66]
121b	-	58	[66]
122	-	79	[66]
123	phenyl	81	[66]
124a	4-chlorophenyl	75	[67]
124b	4-methylphenyl	53	[67]
124c	4-methoxyphenyl	71	[67]
124d	phenyl	61	[67]

[a] Reaction conditions: (i) CH_2N_2, Et_2O, −20 °C; (ii) xylene, reflux; (iii) Ar−C(Cl)═N−NHPh, Et_3N, $CHCl_3$, or CH_2Cl_2, reflux.

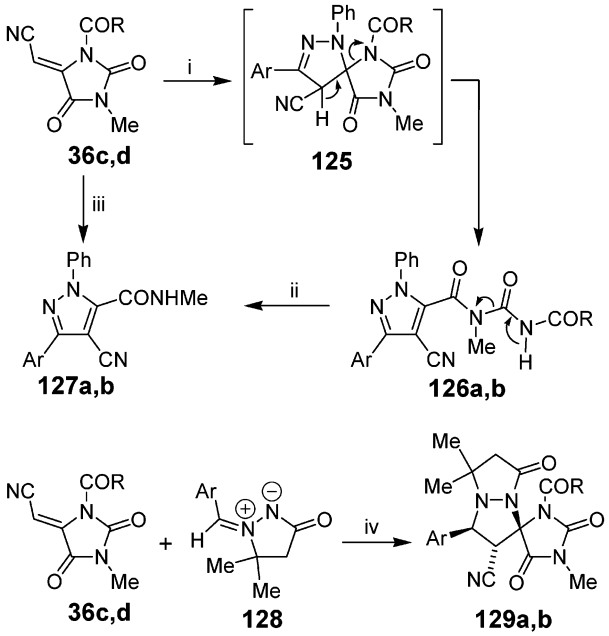
1-Phenyl-3-aryl-4-cyano-1*H*-pyrazole-5-carboxylic acid derivatives **127a**,**b** were formed when 1-acyl-5-[(*Z*)-cyanomethylidene]-3-methylimidazolidine-2,4-diones **36c**,**d** were treated with nitrile imines formed in situ. At room temperature in the presence of silver oxide, the ureides **126** were formed, whereas in the presence of triethylamine in refluxing dichloromethane, pyrazole-5-(*N*-methyl)carboxamides **127** were obtained. Upon treatment of **36c**,**d** with (*Z*)-5,5-dimethyl-1-(2,4,6-trimethoxybenzylidene)-3-pyrazolidinone-1-azomethine imine (**128**) in refluxing 1,4-dioxane under microwave irradiation, spiropyrazolidines **129a**,**b** were obtained (Scheme 26).[70]

5.2.5. Synthesis of Imidazoles

Usually, 3-(dimethylamino)propenoates and heterocycles with an amino group in the α-position with regard to the ring nitrogen atom react to give fused pyrimidones (see section 5.2.11).[7−12] However, when compounds **13b**,**d**,**j**,**q**,**r**,**t** were heated for several hours with 2-amino-6-methylpyridine, 2-amino-4-chlorobenzothiazole, or 3-amino-5-methylisoxazole in glacial acetic acid, the imidazoles **131a**−**d** were formed. Formation of the pyrimidones occurs according to path A (see sections 4.1 and 5.2.11). Alternatively, when the cyclization is sterically hindered due to the presence of a substituent adjacent to the ring nitrogen of heterocyclic amine, the cyclization occurs according to path B, giving imidazoles **131a**−**d** (Scheme 27).[23,85,86]

Methyl 1-aryl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylates were also obtained as side products in intramolecular cyclizations of methyl 3-(arylamino)-2-(benzoylamino)but-2-enoates (see section 5.2.12).

Scheme 26[a]



Reaction	R	Ar	Yield (%)
36c→126a	Me	4-chlorophenyl	85
36d→126b	Ph	4-chlorophenyl	81
126a→127a	Me	4-chlorophenyl	74
36c→127a	Me	4-chlorophenyl	40
36d→127b	Ph	4-methylphenyl	27
36c→129a	Me	2,4,6-trimethoxyphenyl	66
36d→129b	Ph	2,4,6-trimethoxyphenyl	41

[a] Reaction conditions: (i) Ar−C(Cl)═N−NHPh, Ag_2O, CH_2Cl_2, rt; (ii) Et_3N, CH_2Cl_2, reflux; (iii) Ar−C(Cl)═N−NHPh, Et_3N, CH_2Cl_2, reflux; (iv) 1,4-dioxane, microwave (1000 W), reflux.

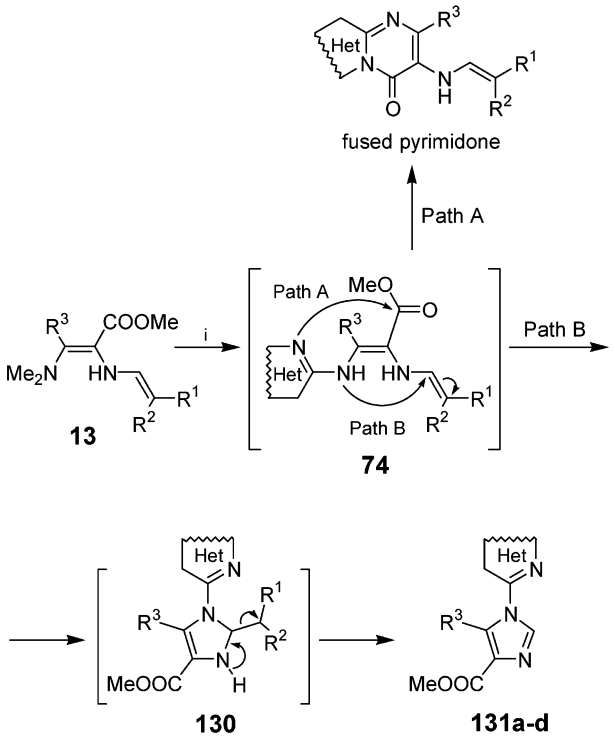
5.2.6. Synthesis of 1,2,4-Oxadiazoles

Treatment of propenoate **3a** at 0 °C in aqueous hydrochloric acid with sodium nitrite gave the 1,2,4-oxadiazole **133a** in 78% yield. Similarly, the propenoates **3b**,**d**,**f**,**g**,**i**,**k**,**n** were transformed into 1,2,4-oxadiazoles **133b**−**h** in 38−78% yields. This transformation, which can also be carried out as a one-pot synthesis, proceeds via the α-oximino esters **132** which, in some instances, have been isolated (Scheme 28).[29,31]

5.2.7. Synthesis of Fused 1,2,4-Triazoles

The most convenient methods for the preparation of 1,2,4-triazolo[4,3-*x*]azines are (a) cyclocondensation of α-hydrazinoazines with carboxylic acid derivatives (method A) and (b) oxidative cyclization of hydra-

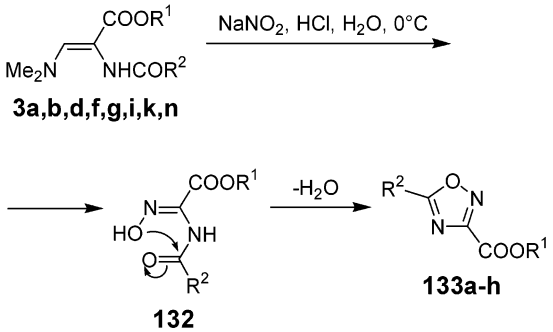
Scheme 27[a]



Reaction	R^3	Het	Yield (%)	Ref
13j→131a	H	6-methylpyridin-2-yl	36	23
13q→131a	H	6-methylpyridin-2-yl	20	23
13b→131b	H	4-chlorobenzothiazol-2-yl	23	23
13t→131b	H	4-chlorobenzothiazol-2-yl	67	85
13d→131c	Me	4-chlorobenzothiazol-2-yl	30	23
13r→131d	H	5-methylisoxazol-3-yl	20	86
13t→131d	H	5-methylisoxazol-3-yl	37	85

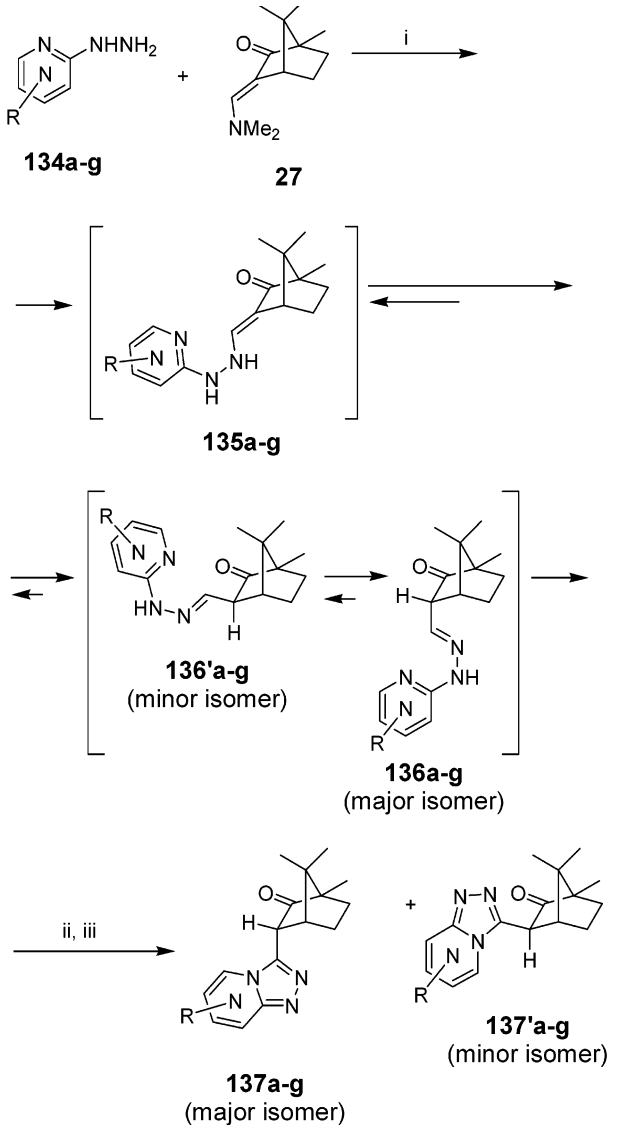
[a] Reaction conditions: (i) Het-NH_2, AcOH, reflux.

Scheme 28



Reaction	R^1	R^2	Yield (%)	Ref.
3a→133a	Me	Ph	78	29
3d→133b	Me	2-chlorophenyl	67	29
3f→133c	Me	4-chlorophenyl	71	29
3g→133d	Me	4-methylphenyl	69	29
3i→133e	Me	4-methoxyphenyl	68	29
3n→133f	Me	2-methoxystyryl	38	31
3k→133g	Et	styryl	70	31
3b→133h	Me	Me	60	29

Scheme 29[a]



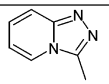
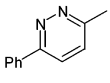
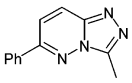
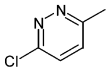
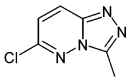
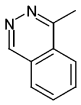
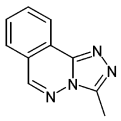
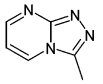
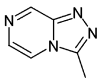
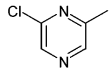
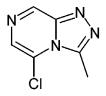
[a] Reaction conditions: (i) MeOH, HCl, rt; (ii) Br_2, MeOH, AcONa, rt; (iii) chromatographic purification.

zones derived from aldehydes and α-hydrazinoazines (method B).[114] Because 3-(dimethylamino)propenoates are actually enamine-masked aldehydes, they can also be used for the preparation of triazolo[4,3-*x*]azines by method B. In this manner, several (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones **137a**−**g** were prepared stereoselectively in two steps from (1*R*,4*R*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**27**) via coupling with hydrazinoazines (**134a**−**g**) to afford the intermediate enehydrazines **135a**−**g**, in equilibrium with hydrazones **136a**−**g**, followed by oxidative cyclization with methanolic bromine (Scheme 29; Table 21).[62]

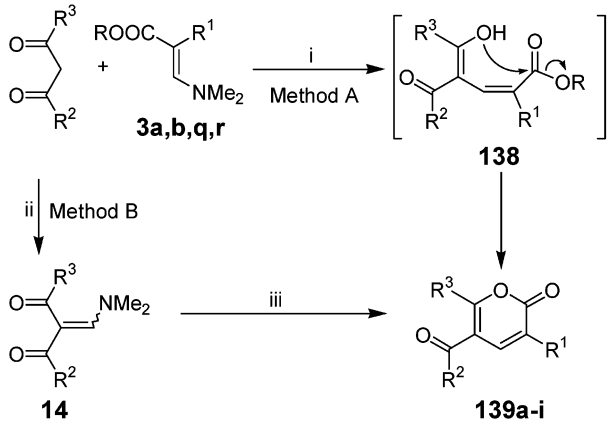
5.2.8. Synthesis of Pyranones and Fused Pyranones

From 2-(acylamino)-3-(dimethylamino)propenoates **3a**,**b**,**q**,**r** and 1,3-diketones or *β*-keto esters 2*H*-pyran-2-ones **139a**−**i** were synthesized via intermediates **138** (method A).[7−12,21,27,33,34] Alternatively, pyranones **139a**−**d** can also be obtained from enaminones **14**, prepared in situ from the corresponding 1,3-dicarbo-

Table 21. Hydrazinoazines 134a−g, Enehydrazines 135a−g, Hydrazones 136a−g, and Fused 1,2,4-Triazoles 137a−g[62]

Compound	Heteroaryl Residue		Yield (%)		D.e. (%)	
	134–136 →	137	136	137	136	137
134a–137a			-	37	-	68
134b–137b			51	79	78	84
134c–137c			48	71	22	94
134d–137d			-	61	-	92
134e–137e			-	42	-	84
134f–137f			-	59	-	72
134g–137g			-	60	-	94

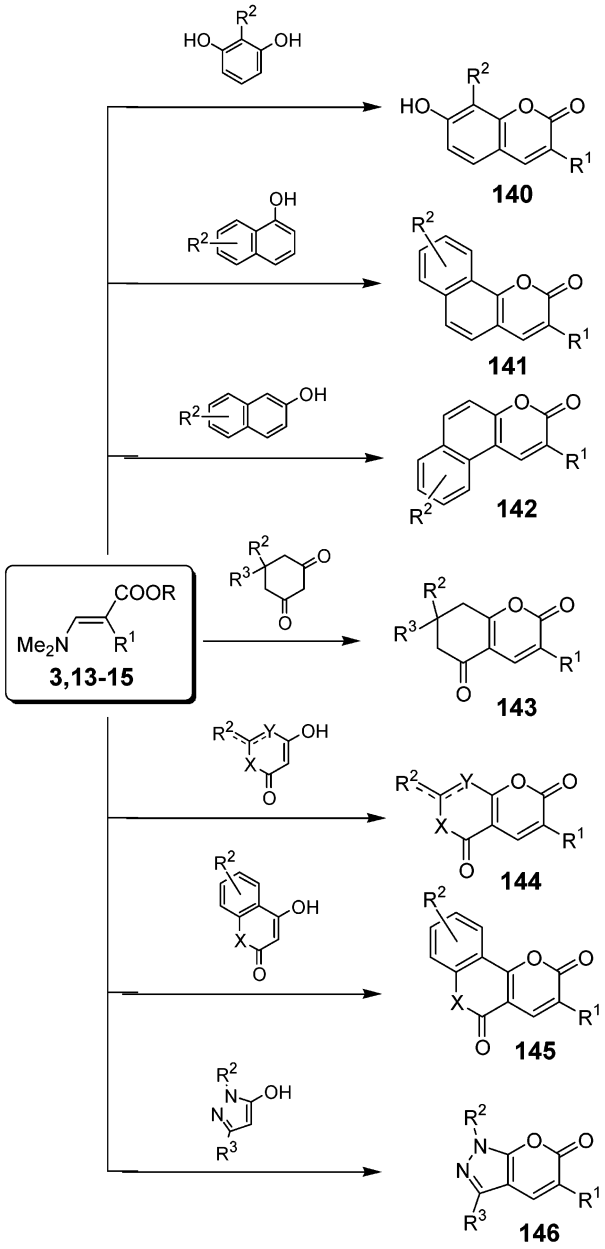
Scheme 30[a]



Compound	R^1	R^2	R^3	Method	Ref
139a	NHCOPh	Me	Me	A, B	21
139b	NHCOPh	Ph	Me	A, B	21
139c	NHCOPh	OEt	Me	A, B	21
139d	NHCOPh	OEt	Ph	A, B	21
139e	NHCOMe	Ph	Me	A	27
139f	NHCOOBn	OMe	Me	A	33
139g	NHCOOBn	OEt	Ph	A	33
139h	NHCOOBn	OBn	Me	A	33
139I	N-phthaloyl	OEt	Me	A	34

[a] Reaction conditions: (i) AcOH, reflux; (ii) DMFDMA, toluene, reflux; (iii) hippuric acid, Ac_2O, 100 °C.

Scheme 31



nyl compounds and dimethylformamide dimethyl acetal (DMFDMA) and hippuric acid in acetic anhydride (method B) (Scheme 30).[21]

Similarly, fused 2*H*-pyran-2-ones **140**−**146** were prepared from 3-(dimethylamino)propenoates **3**, **13**−**15**, and carbocyclic and heterocyclic analogues of 1,3-dicarbonyl compounds (Scheme 31; Table 22).[7−12,17,27,32−34,36−41,43,45,50,82,85,86,115−119]

5.2.9. Synthesis of Pyridines and Fused Pyridines

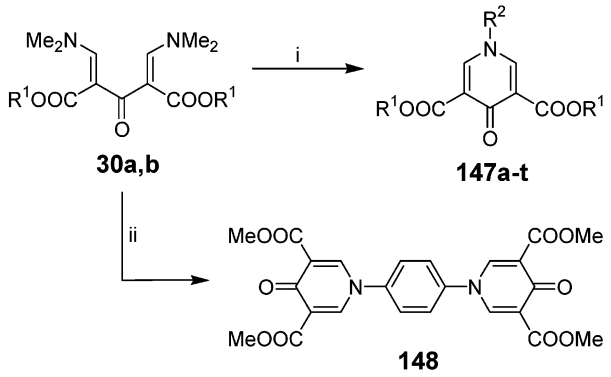
Dialkyl 1,5-bis(dimethylamino)-3-oxo-penta-1,4-diene-2,4-dicarboxylates **30a**,**b**, available from dialkyl acetone-1,3-dicarboxylates and DMFDMA, react with primary aliphatic, aromatic, and heteroaromatic amines to give 1,4-dihydropyridine derivatives as double dimethylamine substitution products **147a**−**t** in 17−94% yields. In the reaction of **30a** with *p*-phenylenediamine, both amino groups reacted to give compound **148** in 57% yield (Scheme 32; Table 23).[64]

Table 22. Fused 2*H*-Pyran-2-ones 140−146 Prepared from 3-(Dimethylamino)propenoates 3, 13−15, and Carbocyclic and Heterocyclic Analogues of 1,3-Dicarbonyl Compounds[a]

compd	R^2	R^3	X	Y	ref
140a	H				27, 33, 50, 115
140b	Me				17, 27, 33, 37, 38, 40, 50, 116
141a	H				27, 33, 40, 50, 116, 117
141b	OH				117
142a	H				27, 33, 39, 50, 117
142b	6-OH				27, 40, 82
142c	9-OH				115
142d	10-OH				27, 33, 40, 82, 115, 116
143a	H	H			17, 33, 34, 38, 39, 41, 45, 85, 86, 116, 117
143b	Me	Me			17, 27, 33, 34, 38, 39, 40, 41, 43, 45, 85, 86, 116, 117
144a	Me		O	CH	32, 33, 34, 36, 39, 40, 43, 50, 85, 86, 116
144b	H		NH	CH	27, 33, 34, 36, 39, 40, 50, 116
144c	OH		NH	N	27, 33, 118
144d	=O		*N*-Me	*N*-Me	27, 33, 50, 118
144e	Me		NH	N	27, 116
144f	=S		NH	NH	27
145a			O		37, 40, 43, 85, 86
145b	8-OH		O		27, 50, 117
145c	8-Me		O		50
145d			*N*-Me		27, 43, 116, 119
145e			*N*-Ph		27, 43, 50
146a	Ph	Me			33, 50, 82, 118
146b	Ph	Ph			27, 33, 118

[a] R^1 = COOEt, NHCOMe, NHCOPh, $NHCOOCH_2Ph$, NH-Boc, *N*-phthaloyl, $NHCH{=}C(COOMe)_2$, $NHCH{=}C(COOEt)_2$, NHCH=C(CN)COOMe, NHCH=C(COMe)COOMe, NHCH=C(COMe)-$COOCH_2Ph$, NHCH=C(COPh)COOEt, OCOPh, NH-CH=C(pyridin-2-yl)CN, NHCH=C(pyridin-2-yl)COOEt, OCH_2-Ph, OPh.

Scheme 32[a]



[a] Reaction conditions: (i) MeOH or EtOH, $R^2{-}NH_2$, reflux; (ii) MeOH, 4-aminoaniline, reflux.

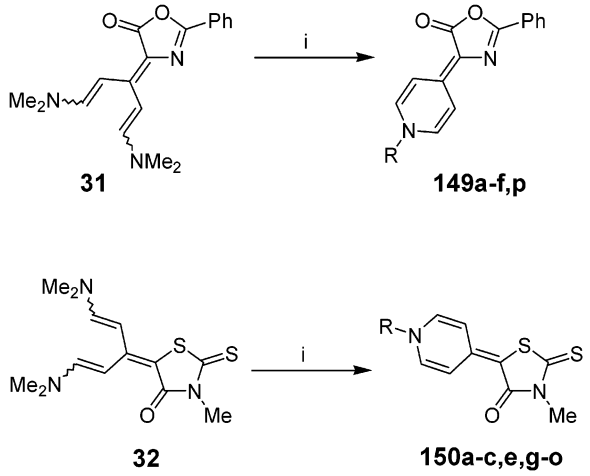
In the same manner, 4-heteroarylidene substituted 1,4-dihydropyridine derivatives **149a**−**f**,**p** and **150a**−**c**,**e**,**g**−**o** were prepared in good yields from primary amines and 4-{3-(dimethylamino)-1-[2-(dimethylamino)vinyl]prop-2-enylidene}-2-phenyl-5(4*H*)-oxazolone (**31**) and 5-{3-(dimethylamino)-1-[2-(dimethylamino)vinyl]prop-2-enylidene}-3-methyl-2-thioxothiazolidin-4-one (**32**) (Scheme 33; Table 24).[65]

Compounds **149a**,**b**,**f** were transformed with hydrazine hydrate into 3-amino-4*H*-imidazol-4-ones **151a**−**c** in 31−75% yields, whereas upon treatment of **149a**,**b**,**d**−**f** with sodium methoxide or sulfuric acid in methanol methyl (1,4-dihydropyridin-4-ylidene)-acetates **152a**−**e** were obtained. Catalytic hydrogenation of **152b** in formic acid in the presence of Pd−C afforded methyl (1-benzylpiperididin-4-yl)acetate (**153**) in 48% yield, whereas by catalytic hydrogenation in

Table 23. Dialkyl 1-Substituted 1,4-Dihydro-4-oxopyridine-3,5-dicarboxylates 147a−t[64]

compd	R^1	R^2	yield (%)
147a	Me	H	34
147b	Et	H	60
147c	Me	*i*-propyl	17
147d	Et	$-NHCH_2CH_2OH$	21
147e	Et	1-hydroxybut-2-yl	28
147f	Et	CH_2COOEt	33
147g	Et	NH_2	34
147h	Et	Ph	62
147I	Et	4-methylphenyl	92
147j	Et	4-hydroxymethylphenyl	86
147k	Et	2-aminophenyl	77
147l	Me	4-hydroxyphenyl	76
147m	Me	3-bromophenyl	75
147n	Et	3,4-methylenedioxyphenyl	94
147o	Et	5-methylisoxazol-3-yl	63
147p	Et	thiazol-2-yl	34
147q	Et	pyridin-2-yl	66
147r	Et	6-methylpyridin-2-yl	73
147s	Et	6-aminopyridin-2-yl	53
147t	Et	pyrimidin-2-yl	28

Scheme 33[a]

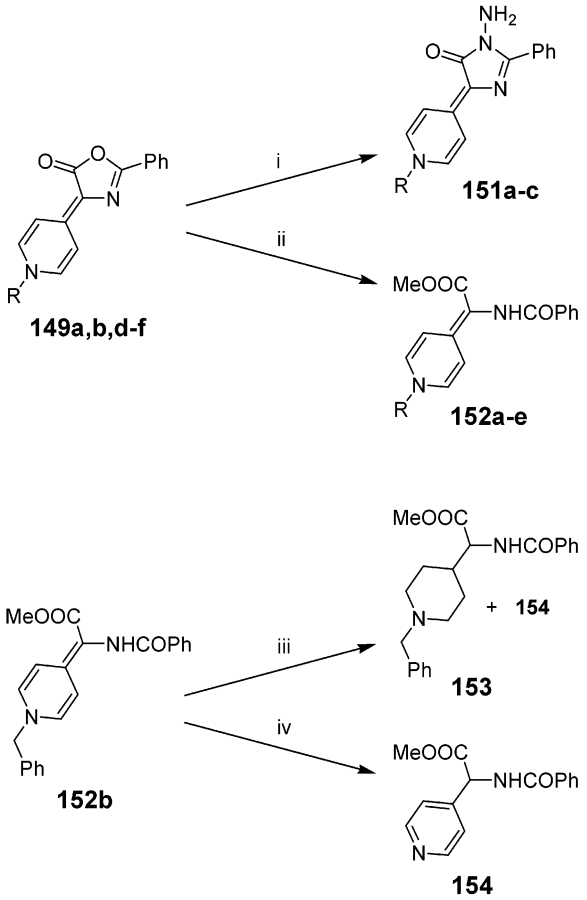


[a] Reaction conditions: (i) $R{-}NH_2 \times HCl$, EtOH, reflux.

Table 24. 4-Heteroarylidene-Substituted 1,4-Dihydropyridines 149 and 150[65]

		yield (%)	
compd	R	**149**	**150**
149a, **150a**	Me	56	78
149b, **150b**	CH_2Ph	71	94
149c, **150c**	2-hydroxyethyl	75	90
149d	cyclohexyl	72	
149e, **150e**	Ph	53	83
149f	4-methylphenyl	75	
150g	4-fluorophenyl		93
150h	3-nitrophenyl		56
150I	pyridin-2-yl		48
150j	5-chloropyridin-2-yl		32
150k	isoxazol-3-yl		43
150l	thiazol-2-yl		66
150m	benzothiazol-2-yl		43
150n	CH_2COOMe		47
150o	CH_2COOEt		50
149p	NH_2	19	

Scheme 34[a]



Compound	R	Yield (%)	
		151	**152**
151a, 152a	Me	75	66
151b, 152b	CH_2Ph	53	99
151c, 152c	4-methylphenyl	31	38
152d	cyclohexyl		74
152e	Ph		91

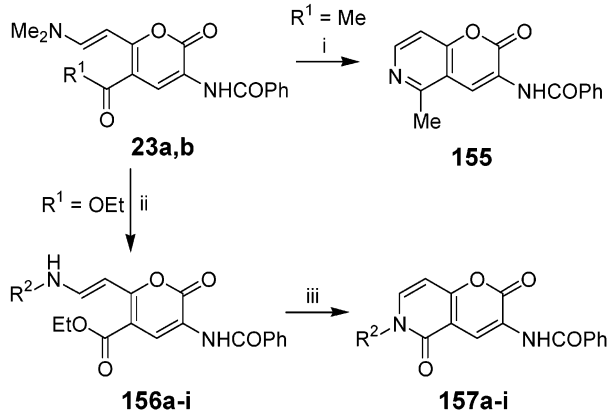
[a] Reaction conditions: (i) hydrazine hydrate, reflux; (ii) MeOH, MeONa, rt, or MeOH, H_2SO_4, reflux; (iii) H_2, 10%Pd−C, HCOOH, rt; (iv) $HCOONH_4$, 10%Pd−C, MeOH, reflux.

the presence of ammonium formate and Pd−C only debenzylation took place to furnish methyl *N*-benzoyl-α-(pyridin-4-yl)glycinate (**154**) almost quantitatively (Scheme 34).[65]

Reaction of primary amines with 5-acyl-3-(benzoylamino)-6-[2-(dimethylamino)vinyl]-2*H*-pyran-2-ones **23a**,**b** leads to 2*H*-pyrano[3,2-*c*]pyridine derivatives. Treatment of **23a** with ammonium acetate in acetic acid gave 3-(benzoylamino)-5-methyl-2*H*-pyrano-[3,2-*c*]pyridin-2-one (**155**) in 86% yield.[120] On the other hand, reaction of **23b** with alkyl- and arylamine hydrochlorides in ethanol under reflux gave the substitution products **156**. Further cyclization of compounds **156** into 5,6-dihydro-2*H*-pyrano[3,2-*c*]-pyridin-2,5-diones **157** was achieved by treatment with sodium ethoxide in ethanol at room temperature (Scheme 35).[56]

Treatment of 3-(dimethylamino)propenoates **3**, **13**, and **14** with 2-pyridineacetic acid derivatives, such as methyl and ethyl pyridineacetate and pyridine-

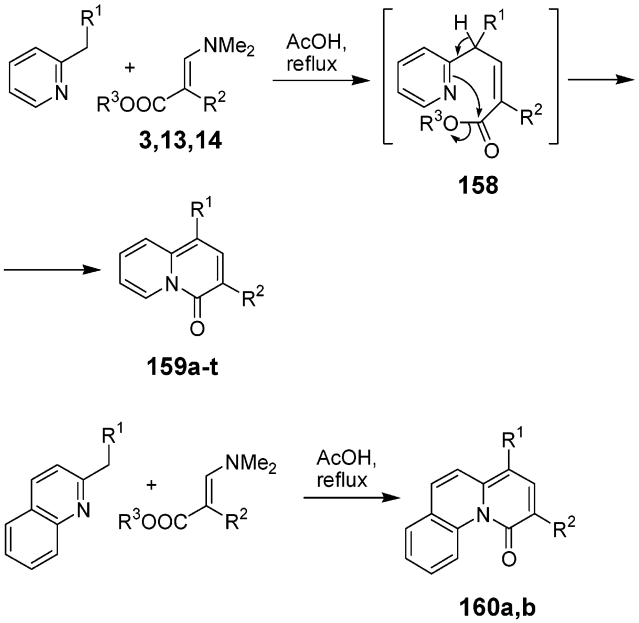
Scheme 35[a]



Compound	R^2	Yield (%)	
		156	**157**
156a, 157a	CH_2COOEt	52	68
156b, 157b	CH_2Ph	75	72
156c, 157c	4-nitrobenzyl	89	62
156d, 157d	phenyl	86	48
156e, 157e	3-nitrophenyl	89	61
156f, 157f	4-methoxyphenyl	87	63
156g, 157g	4-methylphenyl	92	43
156h, 157h	4-bromophenyl	89	62
156i, 157i	pyrimidin-2-yl	72	47

[a] Reaction conditions (i) NH_4OAc, AcOH, reflux; (ii) $R^2-NH_2 \times HCl$, EtOH, reflux; (iii) EtONa, EtOH, rt.

Scheme 36



acetonitrile, in refluxing acetic acid affords 1,3-disubstituted 4*H*-quinolizin-4-ones **159**. Similarly, reaction with methyl 2-quinolineacetate leads to 1,3-disubstituted 4*H*-benzo[*f*]quinolizin-4-ones **160** (Scheme 36; Table 25).[7−12,28,32,34,85,121]

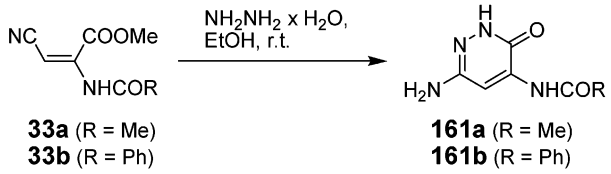
5.2.10. Synthesis of Pyridazines

Methyl 2-(acetylamino)-3-cyanopropenoate (**33a**) and its benzoyl analogue **33b** react with hydrazine

Table 25. 1,3-Disubstituted 4*H*-Quinolizin-4-ones 159 and 160 Prepared

reaction	R^1	R^2	R^3	yield (%)	ref
13q → 159a	CN	NHCH=C(COMe)$_2$	Me	37	45
13c → 159b	CN	NHCH=C(COOEt)$_2$	Et	61	116
13a → 159c	CN	NHCH=C(COOMe)$_2$	Et	95	36
13l → 159d	CN	NHCH=C(CN)COOEt	Et	85	41
13e → 159e	CN	NHCH=C(COPh)COOEt	Me	84	39
13o → 159f	CN	NHCH=C(COPh)$_2$	Et	79	43
13g → 159g	CN	NHCH=C(COMe)COOEt	Et	61	40
13j → 159h	CN	NHCH=C(COMe)−COOCH$_2$Ph	Me	41	17
13t → 159i	CN	NHCH=C(pyridin-2-yl)−COOEt	Me	53	85
14p → 159j	CN	COOEt	Et	84	82
3p → 159k	CN	NHCOMe	Me	86	32
3c → 159k	CN	NHCOMe	Et	74	28
3a → 159l	CN	NHCOPh	Me	99	121
3p →159m	CN	NHCOOtBu	Me	73	32
3q→ 159n	CN	NHCOOCH$_2$Ph	Me	96	33
3r → 159o	CN	*N*-phthaloyl	Et	62	34
13c → 159p	COOEt	NHCH=C(COOEt)$_2$	Et	10	116
13g → 159q	COOEt	NHCH=C(COMe)COOEt	Et	13	40
3c → 159r	COOEt	NHCOMe	Et	42	28
3a → 159s	COOMe	NHCOPh	Me	55	121
14p → 159t	COOEt	COOEt	Et	64	82
3q → 159u	COOEt	NHCOOCH$_2$Ph	Me	46	33
3r → 159v	COOEt	*N*-phthaloyl	Et	58	34
13f → 160a	COOMe	NHCH=C(COPh)COOEt	Et	28	39
3a → 160b	COOMe	NHCOPh	Me	22	121
14p → 160c	COOMe	COOEt	Et	22	82

Scheme 37



33a (R = Me)
33b (R = Ph)

161a (R = Me)
161b (R = Ph)

hydrate in ethanol to afford 4-(acylamino)-6-amino-2*H*-pyridazin-3-ones **161a** and **161b** in 62 and 81% yield, respectively (Scheme 37).[66]

5.2.11. Synthesis of Pyrimidines and Fused Pyrimidines

Formation of pyrimidines can take place when 3-(dimethylamino)propenoates are treated with N−C−N-synthons, such as amidines and their analogues. For example, various 4-arylpyrimidine-5-carboxylates **162a**−**j** were prepared in 23−84% yields from ethyl 2-benzoyl-3-(dimethylamino)propenoate (**14n**) and its 4-fluoro analogue (**14r**) and amidine derivatives (Scheme 38).[22]

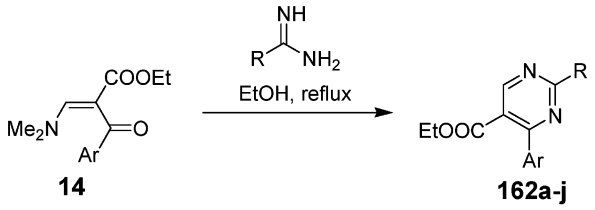
(*Z*)-3-(Benzoylamino)-4-(dimethylamino)-2-oxo-3-butene (**3s**), prepared in two steps from 4-[1-(dimethylamino)ethylidene]-2-phenyl-5(4*H*)-oxazolone (**2k**),[35] was used as reagent for the preparation of pyrimidines. Treatment of **3s** with amidines, guanidine, and 3-amino-5-mercapto-1*H*-1,2,4-triazole as guanidine-like compound in ethanol in the presence of sodium carbonate furnished pyrimidine derivatives **163** and **164** in 16−82% yields (Scheme 39).[67]

The formation of substituted fused pyrimidones from 2-substituted 3-(dimethylamino)propenoates **3**, **13**−**15**, and heterocyclic α-amino compounds takes place in refluxing acetic acid. Under these conditions, the cyclization of intermediates, 2-substituted 3-heteroarylaminopropenoates **73** or **74**, takes place to give the fused pyrimidines **165**−**172** with a bridgehead nitrogen atom (Scheme 40; Table 26).[7−12,27,28,32,34,36−38,40,41,43,45,82,83,85,86,122−126]

However, sterically hindered amines, for example, 2-amino-6-methylpyridine, or compounds with electronegative substituents attached to the heterocyclic ring, such as 5-nitro- or 3,5-dibromopyridines, and some isoxazoles do not cyclize under these conditions. Only the corresponding 3-aminopropenoates **73** and **74** were isolated (see section 5.1.2).

6-Aminopyrimidine-4-carboxylic acid derivatives **174** and **175** were prepared by treatment of methyl 2-(acylamino)-3-cyanopropenoates **33a**,**b** with methylamine and benzylamine. In this reaction, primary aliphatic amines add to the cyano group to give the

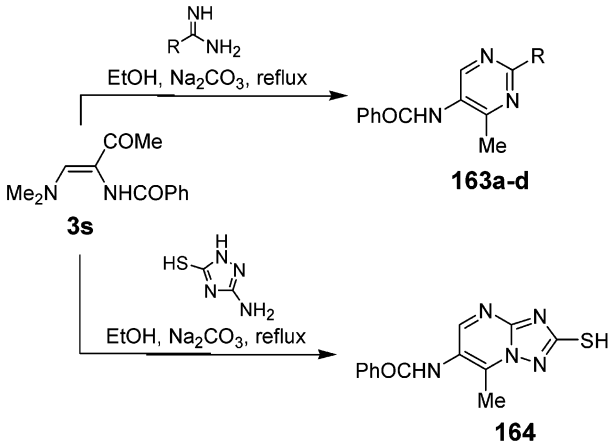
Scheme 38



14 **162a-j**

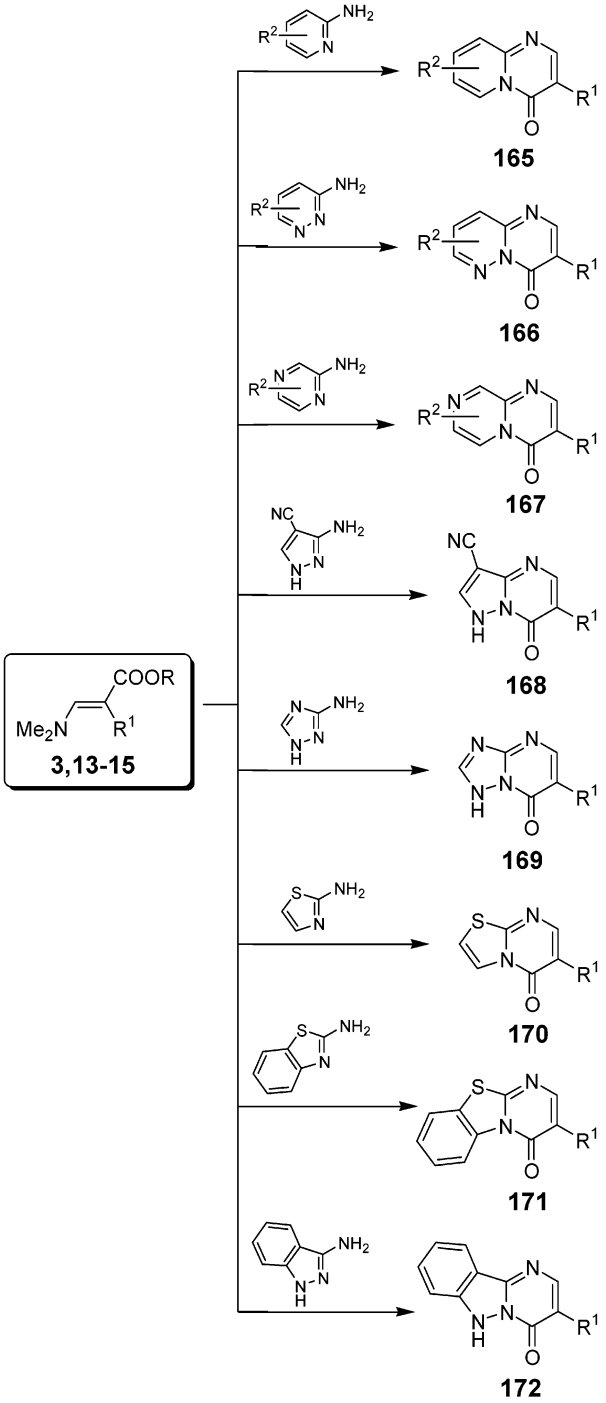
Compound	Ar	R	Yield (%)
162a	phenyl	NH_2	84
162b	phenyl	SMe	77
162c	phenyl	phenyl	49
162d	phenyl	SCH_2-C_6H_4-Cl (*p*)	83
162e	phenyl	SCH_2-C_6H_4-Cl (*p*)	66
162f	4-fluorophenyl	H	35
162g	4-fluorophenyl	NMe_2	37
162h	4-fluorophenyl	$NHCH_2CONH_2$	23
162l	4-fluorophenyl	NHPh	39
162j	4-fluorophenyl	Me	61

Scheme 39



Compound	R	Yield (%)
163a	phenyl	55
163b	3-nitrophenyl	45
163c	4-aminocarbonylphenyl	16
163d	NH_2	82
164	-	56

Scheme 40



amidine intermediates **173**, which cyclizes into the pyrimidine derivatives **174a**−**c**. Thus, from **33a** and methylamine in methanol, methyl pyrimidine-4-carboxylate **174a** was obtained in 40% yield. On the other hand, treatment of propenoates **33a**,**b** with benzylamine in ethanol afforded pyrimidine-4-(*N*-benzyl)carboxamides **175a**,**b** in 38 and 47% yields, respectively (Scheme 41).[66]

5.2.12. Synthesis of Oxazolo[4,5-c]quinolines

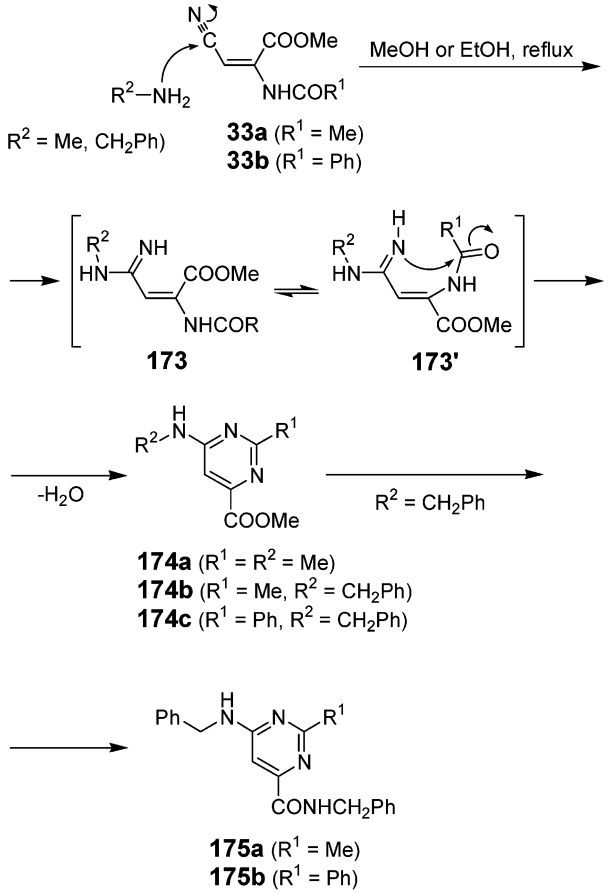
[1,3]Oxazolo[4,5-*c*]quinoline derivatives **178a**−**c** were obtained in 13−65% yields upon heating of methyl 3-(arylamino)-2-(benzoylamino)but-2-enoates **176a**−**c**, available from methyl 2-(benzoylamino)-3-oxobutanoate (**115**) and anilines, in PPA at 130−140 °C. 1-Aryl-1*H*-imidazole-4-carboxylates **179a**−**c** were formed as side product in low yields. Heating of methyl 3-[(3-bromophenyl)amino]-2-(benzoylamino)-

Table 26. Fused Pyrimidones 165−172 Prepared (Table of Substituents)[a]

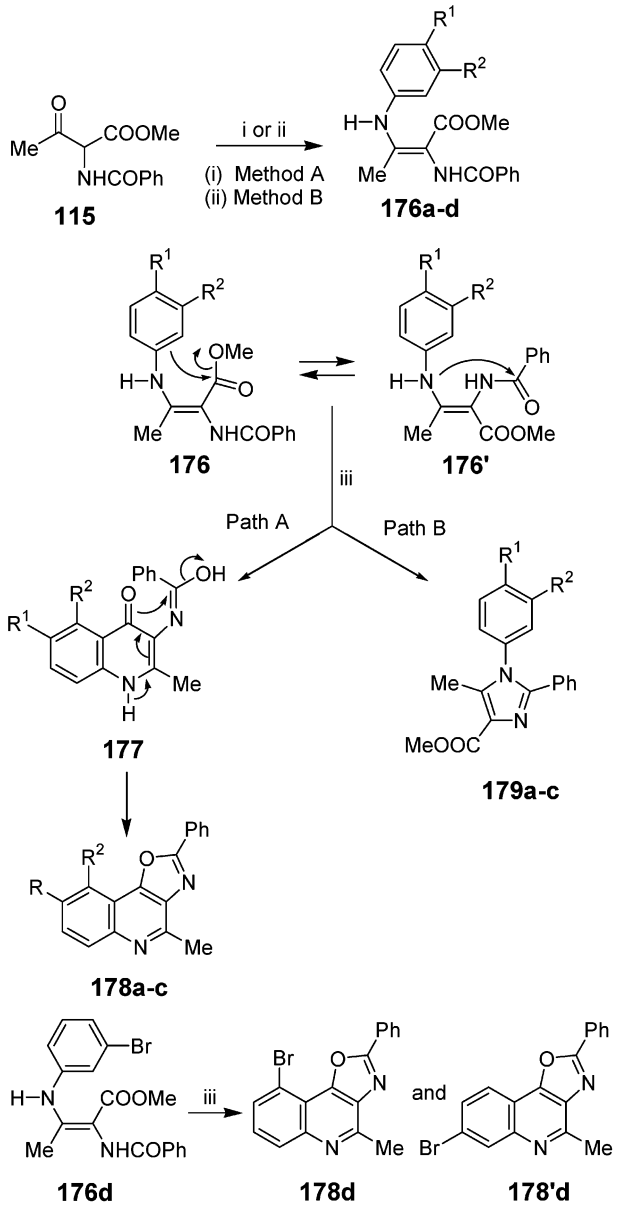
compd	R^2	ref
165a	H	17, 27, 32, 34, 36−38, 40, 41, 43, 45, 82, 83, 85, 86, 122
165b	8-Me	17, 27, 28, 34, 37, 38, 40, 41, 45, 82, 83, 85, 86, 122, 123
165c	9-Me	28, 82, 83
165d	7-Cl	17, 36, 37, 38, 40, 41, 43, 45, 83, 85, 86, 123, 124
165e	9-OH	36, 38, 40, 85, 86
166a	H	28, 83
166b	7-Cl	83, 122
166c	7-OH	125
166d	7-Ph	125
166e	7-Cl-9-Me	125
166f	7,8-di-Ph-9-CN	125
167a	H	83, 122
167b	8-OH	122
168		122
169		27, 83, 122
170		17, 27, 32, 34, 36, 37, 38, 40, 41, 43, 83, 86, 126
171		36, 38, 45, 86
172		37, 82

[a] R^1 = NHCOMe, NHCOPh, $NHCOOCH_2Ph$, *N*-phthaloyl, COOEt, NHCH=C(COOMe)$_2$, NHCH=C(COOEt)$_2$, NHCH=C(COMe)$_2$, NHCH=C(COPh)$_2$, NHCH=C(CN)COOMe, NHCH=C(COMe)COOMe, NHCH=C(COMe)-$COOCH_2Ph$, NHCH=C(COPh)COOEt.

Scheme 41



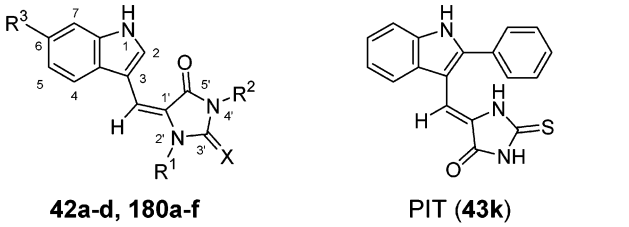
Scheme 42[a]



Compound	R^1	R^2	Yield (%)	
			178	**179**
176a–179a	H	H	20	14
176b–179b	OMe	H	13	9
176c–179c	F	H	65	32

[a] Reaction conditions. (i) Ar−NH_2, benzene, PTSA (cat.), reflux, Dean−Stark (method A); (ii) Ar−NH_2, EtOH, PTSA (cat.), reflux (method B); (iii) PPA, 130−140 °C, then chromatographic separation.

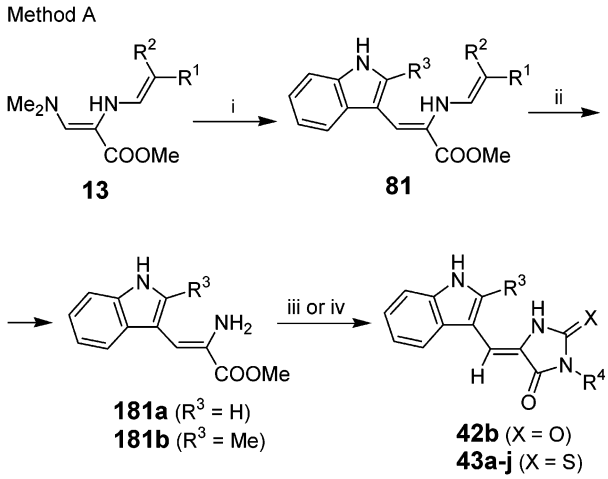
but-2-enoate (**176d**) in PPA afforded two isomeric oxazolo[4,5-*c*]quinolines **178d** and **178′d** in 14 and 24% yield, respectively. The formation of the products **178** and **179** can be explained in the following way. The cyclization of compounds **176** can take place between the methoxycarbonyl group and the aromatic ring at the ortho position with regard to the amino group to form 3-benzoylamino substituted 4-oxo-1,4-dihydroquinoline intermediate **177** followed by cyclodehydration taking place between benzoylamino and potential hydroxy group at the 4-position



Compound **29**	R^1	R^2	R^3	X
180a	Me	Me	H	NH
180b	H	Me	H	NH
180c	Me	Me	H	NMe
180d	Me	Me	Br	NH
180e	H	Me	Br	NH
180f	H	Me	Br	NMe
42a	Me	Me	H	O
42b	H	H	H	O
42c	Me	Me	Br	O
42d	H	H	Br	O

Figure 12. Aplysinopsin, its naturally occurring analogues **42a−d** and **180a−f**, and synthetic analogue PIT (**43k**).

Scheme 43[a]



[a] Reaction conditions: (i) indole or 2-methylindole, AcOH, 80−90 °C, 3−10 h; (ii) hydrazine hydrate, EtOH, reflux, 2 h; (iii) urea, DMF, reflux, 2 h, or *N*,*N*′-diphenylthiourea, pyridine, reflux 2.5-3.5 h; (iv) alkyl, allyl, or aryl isothiocyanate, pyridine, reflux, 3−10 h.

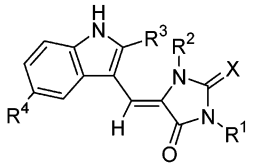
in the quinoline ring to give oxazolo[4,5-*c*]quinoline derivatives **178** (path A). The concurrent reaction is cyclization taking place between the amino group attached to the aromatic ring and the carbonyl group of the benzoylamino group to give imidazole derivatives **179** (path B).[127] Just recently, it has been observed that heating of compounds **176** in anisole under reflux leads to selective formation of imidazoles **179** (Scheme 42).[128]

5.3. Synthesis of Functionalized Heterocyclic Compounds and Natural Product Analogues

5.3.1. Synthesis of Aplysinopsin Analogues

Aplysinopsin (**180a**) (Figure 12) has been isolated from the sponge *Aplysinopsis reticulata* of the Australia Great Barrier Reef[129] and from *Verongia spen-*

Table 27. Aplysinopsin Analogues 42 and 43 Prepared According to Methods A and B

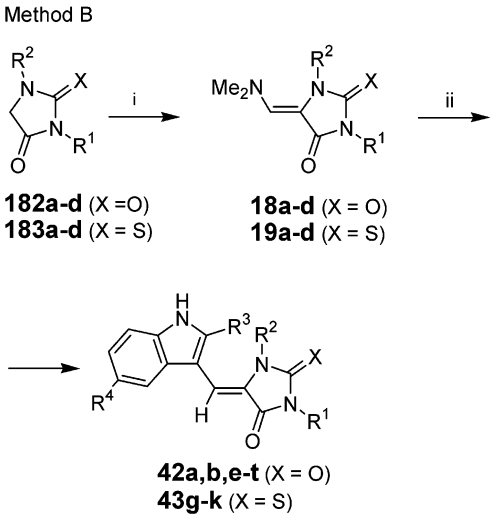


42 (X = O), **43** (X = S)

compd	R^1	R^2	R^3	R^4	X	method	yield[a] (%)	*Z*:*E*	ref
42a	Me	Me	H	H	O	B	65	0:100	54
42b	H	H	H	H	O	A	65	>95:5	53
42b	H	H	H	H	O	B	48	>95:5	53
42e	Me	Me	Me	H	O	B	61	28:72	54
42f	Me	Me	H	H	O	B	78	0:100	141
42g	Me	Me	H	Br	O	B	35	0:100	141
42h	Me	Me	Ph	H	O	B	10	0:100	141
42i	Me	H	Me	H	O	B	60	>95:5	53
42j	H	H	H	Br	O	B	45	92:8	141
42k	H	H	Me	H	O	B	65	>99:1	53
42l	H	H	Ph	H	O	B	68	100:0	141
42m	Me	H	H	H	O	B	42	>95:5	53
42n	Me	H	Ph	H	O	B	46	100:0	141
42o	Me	H	H	Br	O	B	40	>95:5	141
42p	H	Me	H	H	O	B	58	0:100	54
42q	H	Me	Me	H	O	B	81	38:62	54
42r	H	Me	H	Br	O	B	38	0:100	54
42s	H	Me	H	F	O	B	69	0:100	54
42t	H	Me	Ph	H	O	B	14	0:100	141
43a	Me	H	H	H	S	A	42	>95:5	53
43b	Et	H	H	H	S	A	28	92:8	53
43c	allyl	H	H	H	S	A	25	94:6	53
43d	Ph	H	H	H	S	A	61	80:20	53
43e	4-Me-C_6H_4	H	H	H	S	A	10	92:8	53
43f	Me	H	Me	H	S	A	96	>99:1	53
43g	Et	H	Me	H	S	A	39	>99:1	53
43g	Et	H	Me	H	S	B	15	100:0	54
43h	allyl	H	Me	H	S	A	40	>99:1	53
43h	allyl	H	Me	H	S	B	48	100:0	54
43i	Ph	H	Me	H	S	A	78	>99:1	53
43i	Ph	H	Me	H	S	B	79	100:0	54
43j	4-Me-C_6H_4	H	Me	H	S	A	58	>99:1	53
43j	4-Me-C_6H_4	H	Me	H	S	B	77	100:0	54
43k	H	H	Ph	H	S	B	55	100:0	141

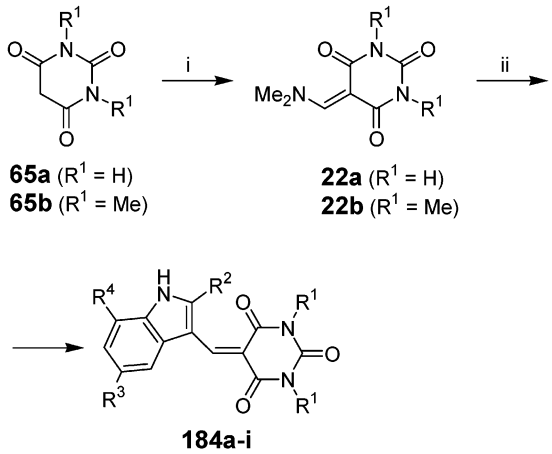
[a] Yields of the last step are given.

Scheme 44[a]



[a] Reaction conditions (i) TBDMAM or DMFDMA, acetonitrile, or DMF; (ii) indole derivative, AcOH, or 2-phenylindole, HCl, *i*-PrOH.

Scheme 45[a]



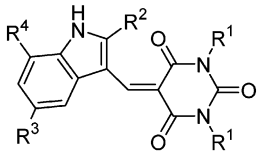
[a] Reaction conditions: (i) TBDMAM or DMFDMA, acetonitrile, or DMSO; (ii) indole derivative, AcOH, 90−100 °C (method A) or 2-phenylindole, HCl, *i*-PrOH, reflux (method B).

gelii.[130] Some other derivatives, such as 2′-demethylaplysinopsin **180b**, have been isolated from the marine sponge *Dercitus* spp.,[131] 2′-demethyl-3′-methylaplysinopsin **180c** and 3′-deimino-3′-oxoaplysinopsin **42a** from dendrophylliid coral *Tubastraea* spp.,[132,133] 3′-deimino-2′,4′-bis(demethyl)-3′-oxoaplysinopsin **42b** from *Leptopsammia pruvoti*,[132] 6-bromoaplysinopsins derivatives **180d**−**f** from *Dendrophyllia* spp.,[133] **42c** from *Dercitus*,[132] and **42d** from *Leptopsammia pruvoti*.[132] Some of these compounds display biological activities, such as specific cytotoxicity for cancer cells[130] and neurotransmission effects.[134] Recently, 5-[(2-phenyl-1*H*-indol-3-yl)methylidene]-2-thiooxoimidazolidin-4-one (PIT) (**43k**), a synthetic analogue of aplysinopsin (**180a**), has been tested against several cancer cell lines.[135]

Synthetic approaches toward aplysinopsin-type structures involve base-catalyzed condensation of a 3-formyl indole derivative with a five-membered ring containing an α-methylene carbonyl structural element, such as hydantoin, thiohydantoin, or creatinine derivatives.[131−133,136] However, poor yields, purification difficulties, and formation of mixtures of *Z* and *E* isomers are generally encountered in these procedures. These inconveniences have been circumvented by the introduction of a tandem Staudinger/aza-Wittig reaction followed by electrocyclic ring closure.[137] In this context the aplysinopsin skeleton has been prepared from iminophosphoranes, obtained from 3-formylindole in four steps, followed by the reaction with methyl isocyanate to form the corresponding carbodiimide. This has been cyclized by treatment with nitrogen-containing reagents, such as ammonia, aliphatic amines, and hydrazines to give aplysinopsin derivatives.[138] Also, some highly effective methods for the synthesis of azacarboline and azaaplysinopsin mimic structures from heterocumulenes[139] and from alumina-supported heterocumulenes[140] have been reported.

Recently, two simple and efficient approaches to the (*Z*)-aplysinopsin skeleton have been developed employing methyl 2-(2,2-disubstituted-ethenyl)amino-

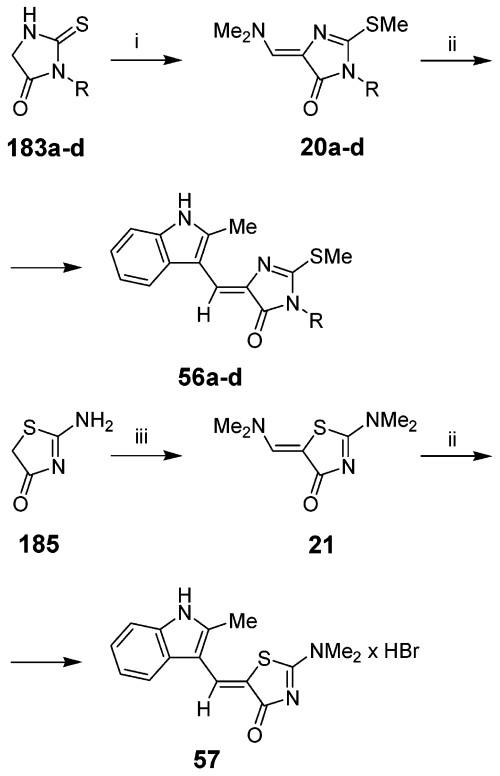
Table 28. Pyrimidinetrione Analogues of Aplysinopsins 184a−i



compd	R^1	R^2	R^3	R^4	method	yield[a] (%)	ref
184a	H	H	H	H	A	73	49
184b	H	Me	H	H	A	85	49
184c	H	Ph	H	H	B	76	141
184d	H	H	Br	H	A	69	49
184e	H	H	H	Et	A	56	49
184f	Me	H	H	H	A	73	49
184g	Me	Ph	H	H	B	46	141
184h	Me	H	Br	H	A	29	49
184i	Me	H	H	Et	A	11	49

[a] Yields of the last step are given.

Scheme 46[a]

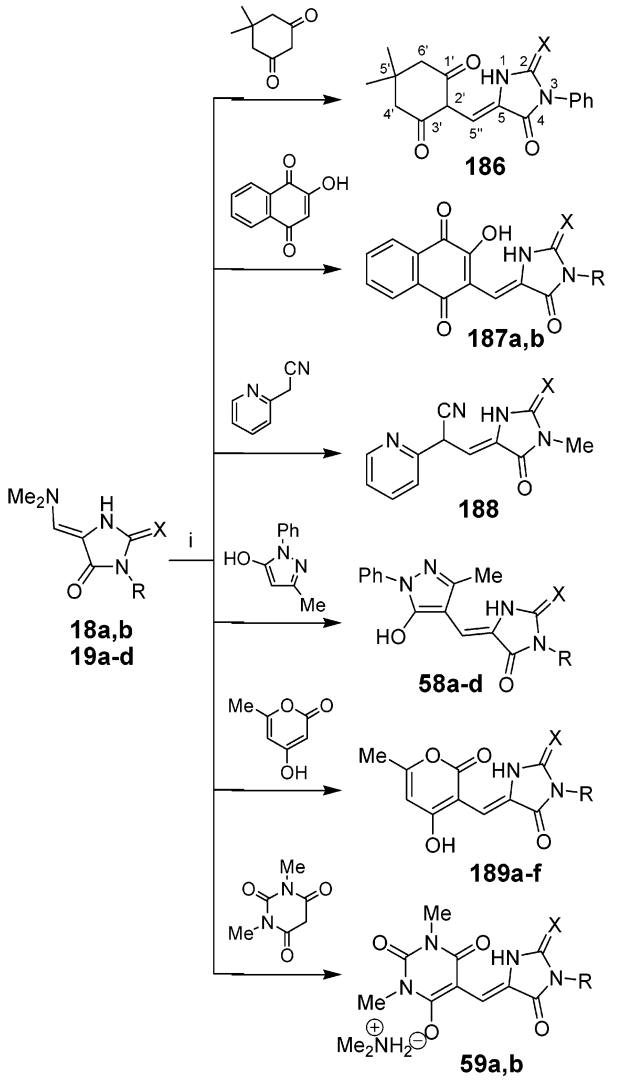


Compound	R	Yield[a] (%)
56a	Et	7
56b	allyl	48
56c	Ph	14
56d	4-Me-C_6H_4	65
57	-	48

[a] Yields of the last step are given. Reaction conditions: (i) DMFDMA, acetonitrile, or DMF, reflux; (ii) 2-methylindole, AcOH, HBr, 20−50 °C; (iii) TBDMAM, DMF, reflux.

3-(dimethylamino)propenoates **13** and 5-[(dimethylamino)methylidene]hydantoin derivatives **18** and **19** as starting compounds. Both methods are stereoselective and can afford various types of aplysinopsin analogues in moderate or good overall yields. The first method (method A) is a three-step synthesis, in

Scheme 47[a]

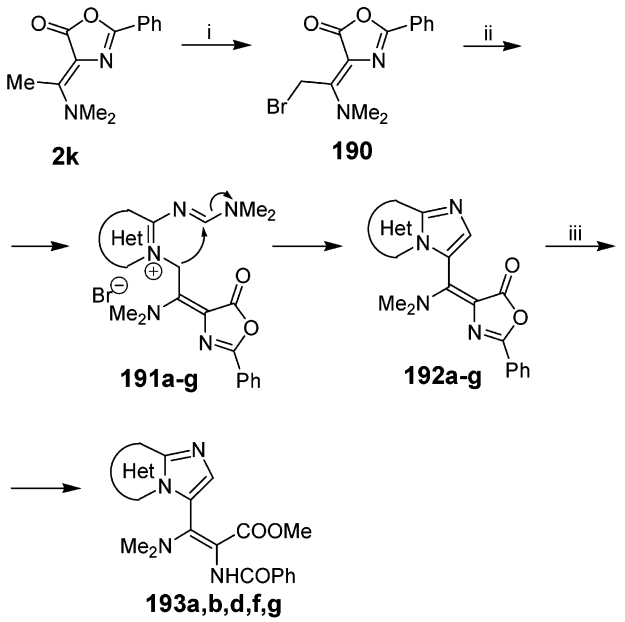


Compound	R	X	Yield (%)
186	-	S	36
187a	H	O	56
187b	Me	O	84
188	Me	O	43
58a	H	O	43
58b	Me	O	50
58c	Et	S	78
58d	Ph	S	50
189a	H	O	51
189b	Me	O	71
189c	Et	S	76
189d	allyl	S	56
189e	Ph	S	82
189f	4-Me-C_6H_4	S	65
59a	H	O	52
59b	Me	O	66

[a] Reaction conditions: (i) AcOH, reflux.

which methyl 2-(2,2-disubstituted-ethenyl)amino-3-(dimethylamino)propenoates **13** react with indole or 2-methylindole. Substitution occurs at position 3 of the indole skeleton to give 2-(2,2-disubstituted-ethenyl)amino-3-(1*H*-indol-3-yl)propenoates **81** in 22−58% yields. The unsaturated side chain can be easily removed from the amino group by treatment with

Scheme 48[a]



Compound	Het	Yield (%)	
		192	193
191a–193a	imidazo[1,2-*a*]pyridin-3-yl	69	70
191b–193b	7-methylimidazo[1,2-*a*]pyridin-3-yl	57	95
191c–193c	8-nitroimidazo[1,2-*a*]pyridin-3-yl	14	
191d–193d	6-chloroimidazo[1,2-*a*]pyridin-3-yl	80	29
191e–193e	imidazo[1,2-*b*]pyridazin-3-yl	25	
191f, 192f	6-chloroimidazo[1,2-*b*]pyridazin-3-yl	81	
193f	6-methoxyimidazo[1,2-*b*]pyridazin-3-yl		82
191g–193g	imidazo[1,2-*b*]thiazol-3-yl	70	84

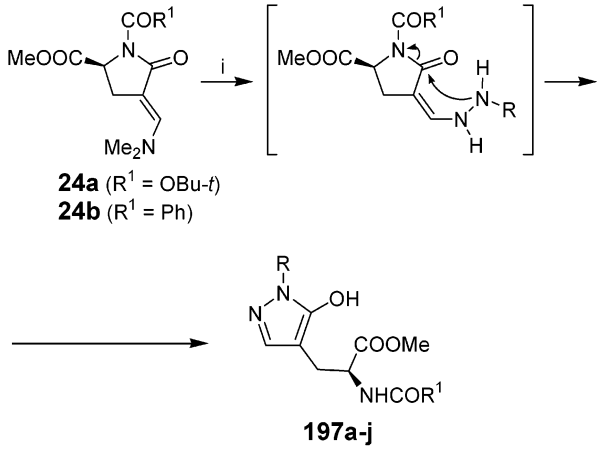
[a] Reaction conditions: (i) Br_2, $CHCl_3$, reflux; (ii) *N*,*N*-dimethyl-*N*′-heteroarylformamidine, MeCN, or DMF, reflux; (iii) MeOH/MeONa, rt.

hydrazine to give methyl 2-amino-3-(1*H*-indol-3-yl)-propenoates **181a**,**b** in 57−87% yields. By treatment of **181a** with urea, 3′-deimino-2′,4′-bis(demethyl)-3′-oxoaplysinopsin (**42b**) is formed in 65% yield. Compounds **181** heated with an isothiocyanate derivative in pyridine for several hours give thioaplysinopsin derivatives **43a**−**j** in 10−96% yields. Compounds **43d** and **43i** can be also obtained from **181a** and **181b** by treatment with 1,3-diphenyl thiourea in 45 and 78% yield, respectively (Scheme 43; Table 27).[53]

The second method (method B) is a two-step synthesis. In this case, hydantoin derivatives **182** are transformed with *tert*-butoxybis(dimethylamino)-methane (Bredereck's reagent) or *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) into the corresponding (*Z*)-5-[(dimethylamino)methylidene]imidazolidine-2,4-diones **18a**−**d**. Compounds **18** react further with indole derivatives to give aplysinopsin derivatives **42a**,**b**,**e**−**t** in 10−81% yields.[53,141] Similarly, thiooxo analogues of aplysinopsin **43g**−**k** were prepared in two steps from thiohydantoins **183** via 3-substituted (*Z*)-5-[(dimethylamino)methylidene]-2-thiooxoimidazolidin-4-ones **19a**−**d** (Scheme 44; Table 27).[54,141]

In the same manner, pyrimidinetrione analogues of aplysinopsins **184a**−**i** were prepared from 5-[(di-

Scheme 49[a]

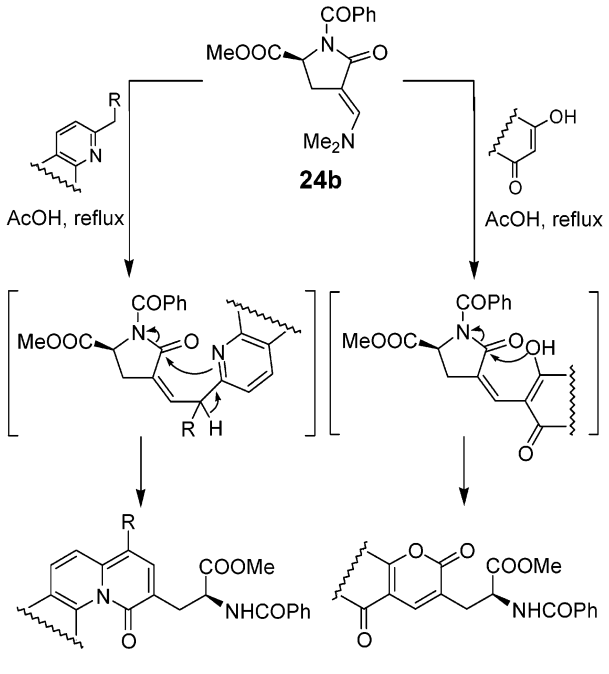


[a] Reaction conditions: (i) R−$NHNH_2$, AcOH, reflux (method A); R−$NHNH_2$, AcOH, 80 °C (method B); NH_2NH_2 × HCl, EtOH, 20 °C, 2 h (method C).

Table 29. (*S*)-*N*-Acyl-3-(1-substituted-5-hydroxy-1*H*-pyrazol-4-yl)alanine Methyl Esters 197a−j[156]

compd	R	R^1	method	yield (%)
197a	H	OBu-*t*	C	47
197b	benzyl	Ph	A	73
197c	4-nitrophenyl	Ph	A	69
197d	pyridin-2-yl	Ph	A	87
197e	6-chloropyridazin-3-yl	OBu-*t*	B	50
197f	6-chloropyridazin-3-yl	Ph	B	72
197g	6-hydroxypyridazin-3-yl	Ph	A	84
197h	6-phenylpyridazin-3-yl	Ph	A	88
197I	pyrimidin-2-yl	Ph	A	62
197j	1,2,4-triazolo[4,3-*b*]pyridazin-6-yl	Ph	A	41

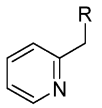
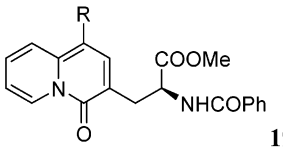
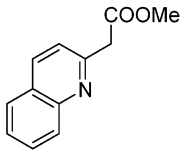
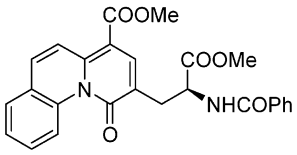
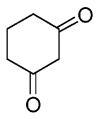
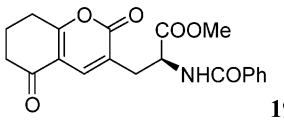
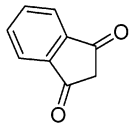
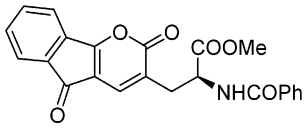
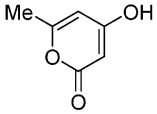
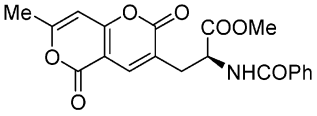
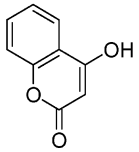
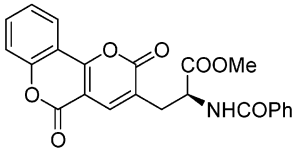
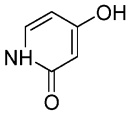
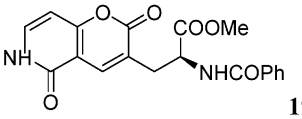
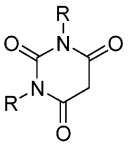
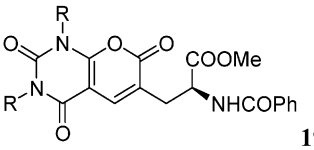
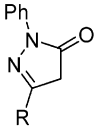
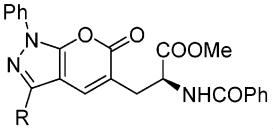
Scheme 50



methylamino)methylidene]pyrimidine-2,4,6-triones **22a**,**b** and various substituted indoles (Scheme 45; Table 28).[49,141]

Further examples of the formation of aplysinopsin analogues **56a**−**d** and **57** are represented by the

Table 30. (*S*)-*N*-Benzoyl-3-(4-oxo-4*H*-quinolizin-3-yl)- (198a−d) and (*S*)-*N*-Benzoyl-3-(2-oxo-2*H*-pyran-3-yl)alanine Methyl Esters (199a−i)[155]

1,3-Dinucleophile	Heteroarylalanine Ester	Yield (%)
	 **198a–c**	68 (**198a**, R = COOMe) 90 (**198b**, R = COOEt) 71 (**198b**, R = CN)
	 **198d**	71
	 **199a**	59
	 **199b**	84
	 **199c**	82
	 **199d**	93
	 **199e**	80
	 **199f,g**	69 (**199f**, R = H) 76 (**199g**, R = Me)
	 **199h,i**	51 (**199h**, R = Ph) 49 (**199i**, R = Me)

reaction of 2-methylindole with dimethylaminomethylidene derivatives of some five-membered heterocycles, such as compounds **20a**−**d** and **21** (Scheme 46).[54]

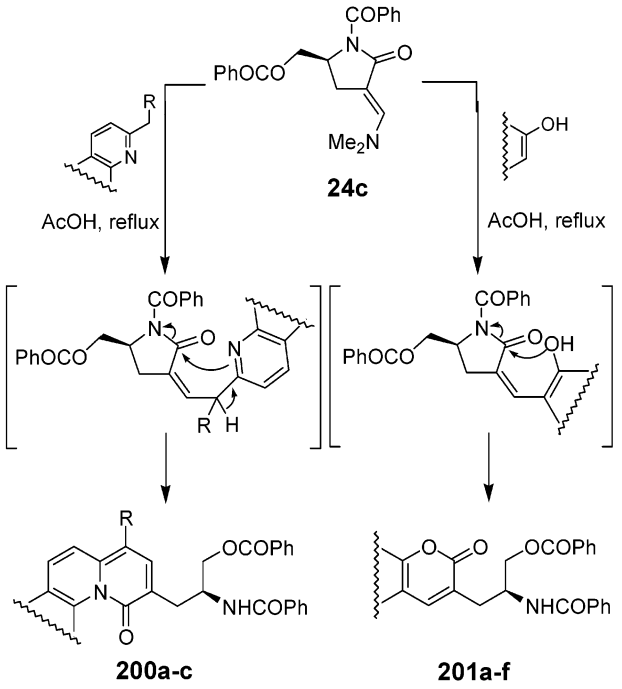
As an extension in this field, the stereoselective synthesis of 3-substituted 5-[(*Z*)-heteroarylmethylidene]imidazolidine-2,4-diones and 5-[(*Z*)-heteroarylmethylidene]-2-thiooxoimidazolidin-4-ones as novel aplysinopsin analogues, having the indole moiety replaced by various carbocyclic and heterocyclic system, was developed. In this connection, compounds **18a**,**b** and **19a**−**d** were treated with carbocyclic and heterocyclic *C*-nucleophiles in acetic acid under reflux to give the corresponding isomerically pure substitution products **58**, **59**, and **186**−**189** in 36−84% yields. Compounds **59a**,**b** were obtained in the form of dimethylammonium salts (Scheme 47).[78]

Fused imidazoles with the imidazole ring connected by a methylidene bridge to an oxazolone system as azaaplysinopsin analogues were prepared in two steps by treatment of the oxazolone **2k** with bromine in boiling chloroform. The brominated oxazolone **190** was then treated with various *N*,*N*-dimethyl-*N*′-heteroarylformamidines in acetonitrile or DMF. When the reaction was allowed to stand at room temperature in DMF for 12 h, the quarternary salts **191** were formed. With the exception of the compound **191f** the intermediate salts **191a**−**e**,**g** were not isolated. On heating, the intermediate salts **191** cyclized to the fused imidazoazoles and imidazoazines **192a**−**g**. Compounds **192a**,**b**,**d**,**f**,**g** have been treated with sodium methoxide in methanol to give propenoates **193a**,**b**,**d**,**f**,**g** in 29−95% yields (Scheme 48).[55]

5.3.2. "Ring Switching" Synthesis of 3-Heteroarylalanine, 3-Heteroarylalaninol, 3-(Heteroaryl)lactic Acid, and 3-Heteroarylpropane-1,2-diol Derivatives

In the past few decades, several synthetic methods for the preparation of 3-heteroarylalanines have been developed due to their occurrence in nature, biological activity, and synthetic applicability.[142] Among various synthetic approaches, transformations of commercially available α-amino acids, such as serine, aspartic acid, and glutamic acid, found a wide applicability in the preparation of 3-heteroarylalanines.[143−151] Recently, Young and co-workers reported the synthesis of 3-(pyrazolyl)-, 3-(isoxazolyl)-, and 3-(pyrimidinyl)alanines from (*S*)-3-formylpyroglutamic acid derivatives, using a ring switching strategy.[152−154] On the other hand, our previous study on the chemistry of polyfunctionalized alkyl 2-substituted 3-(dimethylamino)propenoates showed that this type of compound can serve as a versatile, simple, and efficient synthetic tool for the preparation of a variety of heterocyclic systems, α,*β*-dehydro-α-amino acid derivatives, and peptides, as well as *N*-protecting reagents in the peptide synthesis.[7−12] In this connection, we introduced 5-substituted (*S*)-1-acyl-3-[(*E*)-(dimethylamino)methylidene]pyrrolidin-2-ones **24** and (*S*)-3-[(*E*)-(dimethylamino)methylidene]tetrahydrofuran-2-ones **25**, which can be prepared in two steps from commercially available precursors.[57−60] Analogously to acyclic alkyl 3-(dimethylamino)propenoates,

Scheme 51

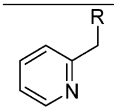
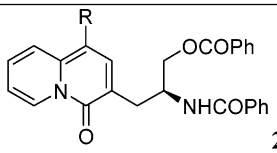
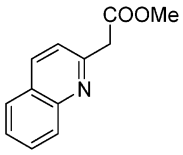
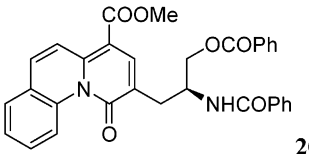
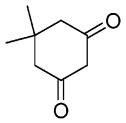
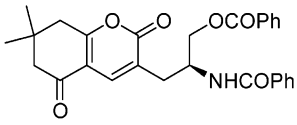
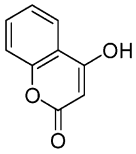
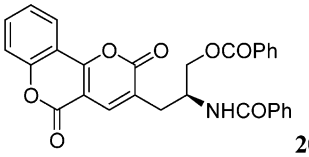
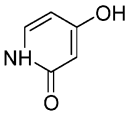
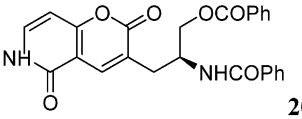
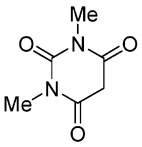
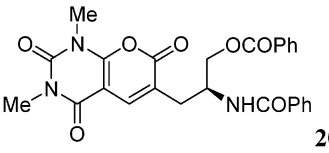
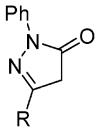
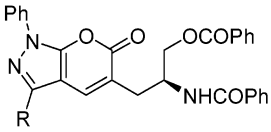


enamino lactams **24** and lactones **25** show ambident 1,3-dielectrophilic behavior, due to electrophilic reactive sites at positions *C*(3′)-NMe_2 and *C*(2)═O with the following order of reactivity: *C*(3′)-NMe_2 > *C*(2)═O. Therefore, the reaction of compounds **24** and **25** with ambident 1,2- and 1,3-dinucleophiles results in the cleavage of the lactone or lactam ring with the "simultaneous" formation of another heterocyclic system and concurrent release of α-amino- or α-hydroxy acid or *β*-aminoalcohol moiety side chain. According to the results of Young and co-workers[152−154] and according to our previous observations in the acyclic 3-(dimethylamino)propenoate series,[7−12] the ring switching transformations (see also section 4.1) proceed predominantly via initial substitution of the dimethylamino group, followed by attack to the ring carbonyl group to afford compounds **196**. This proposed reaction pathway is supported by isolation of the intermediates **195**. Under mild conditions, dimethylamine substitution products **195** are formed exclusively when enamino lactams **24** and lactones **25** are treated with various nucleophiles (Figure 13, path B).[79]

(*S*)-1-Acyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-ones **24a**,**b** are transformed into the corresponding 3-heteroarylalanine derivatives **197**−**199** by reaction with 1,2- and 1,3-dinucleophiles such as hydrazines, aminoazines, (pyridin-2-yl)acetic acid derivatives, and 1,3-dicarbonyl compounds and their carbocyclic and heterocyclic analogues. The reaction proceeds via a ring switching mechanism. Thus, the substitution of the dimethylamino group takes place first, followed by the second attack of a dinucleophile to the ring carbonyl group, resulting in simultaneous cleavage of the pyrrolidinone ring and the formation of (*S*)-3-heteroarylalanine esters **197**−**199**.[155,156]

Among various types of heteroarylalanines, the synthesis of 3-pyrazolylalanines has attracted con-

Table 31. *O*-Benzoyl-2-(benzoylamino)-3-heteroaryl-1-propanols 200a−c and 201a−f[59]

1,3-Dinucleophile	*O*-Benzoyl-2-benzoylamino-3-heteroaryl-1-propanol	Yield (%)
	 **200a,b**	24 (**200a**, R = COOEt) 30 (**200b**, R = CN)
	 **200c**	30
	 **201a**	27
	 **201b**	52
	 **201c**	37
	 **201d**	32
	 **201e,f**	22 (**201e**, R = Ph) 24 (**201f**, R = Me)

siderable attention. (*S*)-3-(1-Pyrazolyl)alanine has been isolated from the seed of *Citrullus vulgaris* and is so far the only naturally occurring amino acid with a pyrazolyl residue.[157−162] It was also used as constituent of highly potent renine inhibitors.[163,164] (*S*)-1-*tert*-Butoxycarbonyl- (**24a**) and (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**24b**) are transformed with various hydrazines in refluxing acetic acid into the corresponding (*S*)-*N*-acyl-3-(1-substituted-5-hydroxy-1*H*-4-pyrazolyl)alanine methyl esters **197a**−**j** in 41−88% yields. In the reaction of lactam **24b** with 6-chloro-3-hydrazinopyridazine also the substitution of chloro by a hydroxy group takes place to give (*S*)-*N*-benzoyl-3-[5-hydroxy-1-(6-hydroxypyridazin-3-yl)-1*H*-pyrazol-4-yl]alanine methyl ester (**197g**). However, at 80 °C (*S*)-*N*-benzoyl-3-[1-(6-chloropyridazin-3-yl)-5-hydroxy-1*H*-pyrazol-4-yl]alanine methyl ester (**197f**) is formed. On the other hand, treatment of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**24a**) with hydrazines under acidic conditions results in decomposition of the reagent **24a** rather than in the formation of pyrazolylalanine esters. However, reaction of **24a** with hydrazine hydrochloride in ethanol at room temperature, as well as reaction with (6-chloropyridazin-3-yl)hydrazine in acetic acid at 80 °C, gives the corresponding (*S*)-*N*-*tert*-butoxycarbonyl-3-(5-hydroxy-1*H*-pyrazol-4-yl)- (**197a**) and (*S*)-*N*-*tert*-butoxycarbonyl-3-[1-(6-chloropyridazin-3-yl)-5-hydroxy-

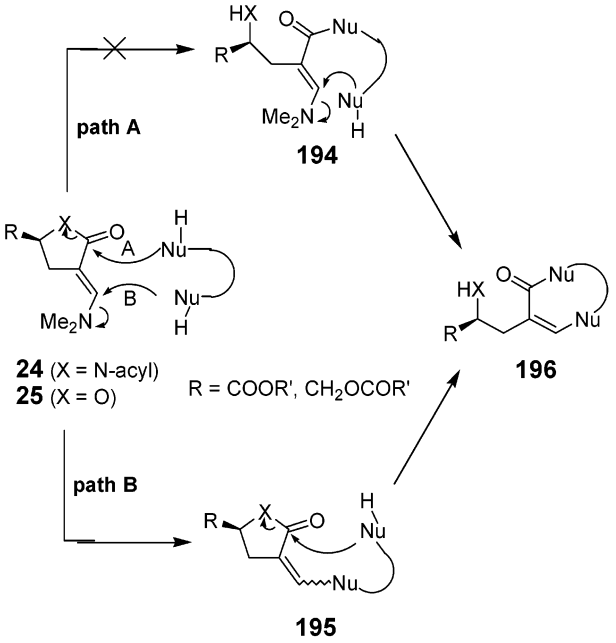


Figure 13. Proposed mechanism for ring switching transformation of **24** and **25** with dinucleophiles.

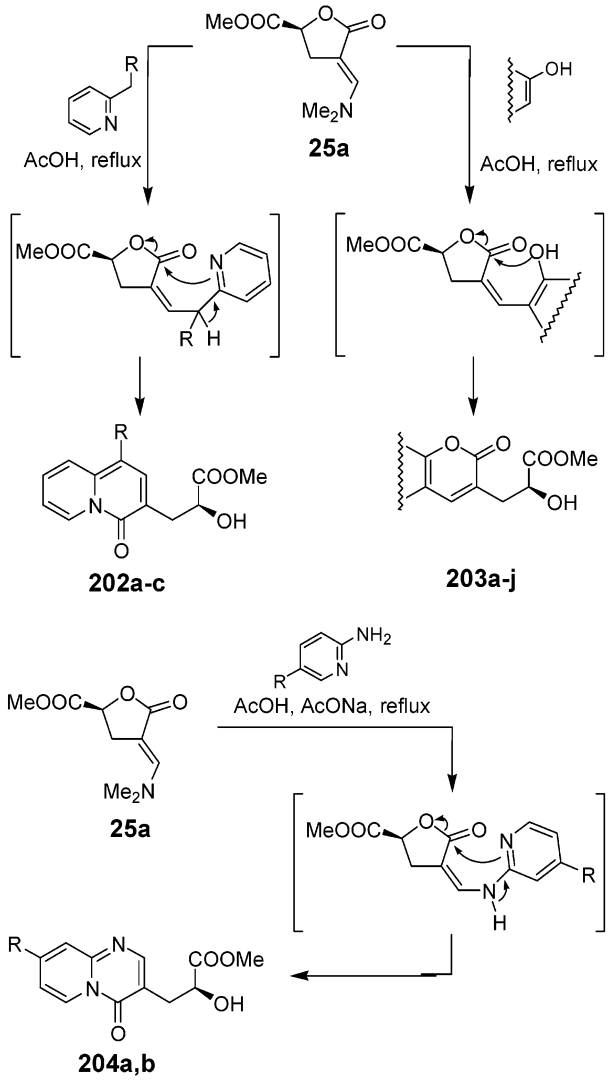
1*H*-pyrazol-4-yl]alanine methyl ester (**197e**), respectively (Scheme 49; Table 29).[156]

(*S*)-1-Benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**24b**) has also been successfully employed for the preparation of (*S*)-*N*-benzoyl-3-(quinolizin-3-yl)- **198** and (*S*)-*N*-benzoyl-3-(2-oxo-2*H*-pyran-3-yl)alanine esters **199**. For this purpose, the lactam **24b** is treated with 1,3-dinucleophiles such as alkyl 2-(pyridin-2-yl)acetates or 2-(pyridin-2-yl)acetonitrile and 1,3-dicarbonyl compounds and their carbocyclic and heterocyclic analogues to give the corresponding quinolizinyl **198a**−**d** and 2-oxo-2*H*-pyranyl substituted alanine esters **199a**−**i** in 49−93% yields (Scheme 50; Table 30).[155]

Chiral β-aminoalcohols and their derivatives found a wide applicability in the synthesis of optically active compounds, especially as chiral building blocks, chiral auxiliaries, and resolving agents.[165,166] As a consequence, numerous chiral synthons of this type are commercially available, usually in both enantiomeric forms. In this connection, a one-step synthesis of 3-heteroaryl substituted (*S*)-*O*-benzoyl-2-benzoylamino-1-propanols **200** and **201** has been developed from easily available (*S*)-1-benzoyl-5-benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene]pyrrolidin-2-one (**24c**). Treatment of **24c** with ambident *C*,*N*- and *C*,*O*-1,3-dinucleophiles, such as 2-(pyridin-2-yl)- and 2-(quinolin-2-yl)acetic acid derivatives, carbocyclic and heterocyclic 1,3-dicarbonyl compounds, and their analogues in refluxing acetic acid, affords (*S*)-*O*-benzoyl-2-(benzoylamino)-3-heteroaryl-1-propanols **200a**−**c** and **201a**−**f**. Because the precursor **24c** is easily available and because only one step is required for further transformation into the aminoalcohols **200** and **201**, this method could be convenient for a simple preparation of 3-(heteroaryl)-alaninols, although the yields are usually rather low (Scheme 51; Table 31).[59]

Chiral hydroxy acids, such as lactic acid, malic acid, mandelic acid, tartaric acid, and their derivatives,

Scheme 52



found a wide applicability in asymmetric synthesis, especially as chiral synthons, chiral auxiliaries, and resolving agents. However, much less attention has been paid to the synthesis and utilization of heteroaryl substituted α-hydroxy acid derivatives. Analogously to the ring switching synthesis of heteroarylalanines and heteroarylalaninols, 3-heteroaryl substituted lactic acid esters **202**−**204** can be prepared in one step from methyl (*S*)-3-[(*E*)-(dimethylamino)methylidene]-2-oxotetrahydrofuran-5-carboxylate (**25a**), available in two steps from (*S*)-2-oxotetrahydrofuran-5−carboxylic acid.[57,167] Lactone **25a** affords, upon treatment with various ambident 1,3-dinucleophiles in refluxing acetic acid, the corresponding methyl (*S*)-3-(4-oxo-4*H*-quinolizin-3-yl)- (**202a**−**c**), methyl 3-(2-oxo-2*H*-pyran-3-yl)- (**203a**−**j**), and methyl (*S*)-3-(4-oxo-4*H*-pyridino[1,2-*a*]pyrimidin-3-yl)lactates (**204a**, **b**) upon treatment with 2-(pyridin-2-yl)acetic acid derivatives, 1,3-dicarbonyl compounds and their analogues, and substituted 2-aminopyridines, respectively (Scheme 52; Table 32).[84,168]

O-Benzoyl (*S*)-3-heteroarylpropane-1,2-diols **205**−**207** were prepared by ring switching methodology from (*S*)-5-benzoyloxymethyl-3-[(*E*)-(dimethylamino)-methylidene]tetrahydrofuran-2-one (**25b**) upon acid-catalyzed treatment with 2-pyridineacetic acid de-

Table 32. Methyl (*S*)-3-(4-Oxo-4*H*-quinolizin-3-yl)- (202a−c), (*S*)-3-(2-Oxo-2*H*-pyran-3-yl)- (203a−j), and (*S*)-3-(4-Oxo-4*H*-pyridino[1,2-*a*]pyrimidin-3-yl)lactates (204a,b)[84,168]

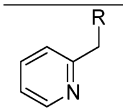
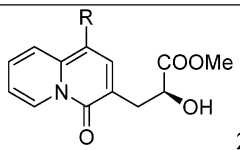
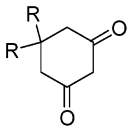
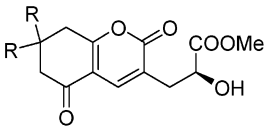
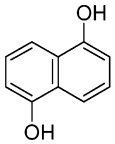
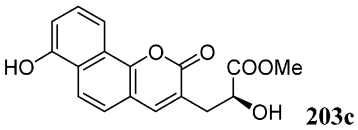
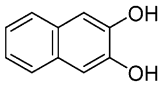
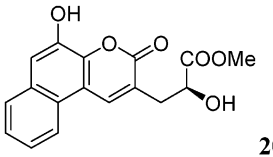
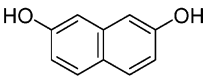
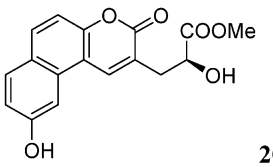
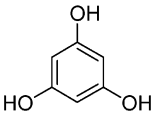
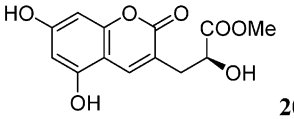
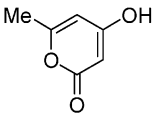
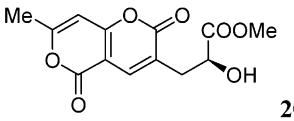
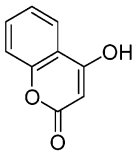
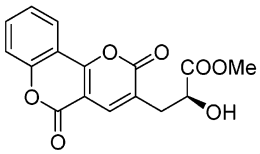
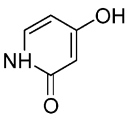
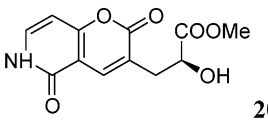
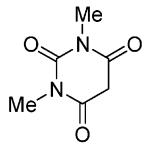
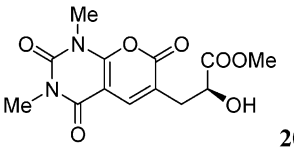
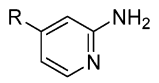
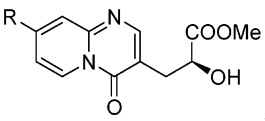
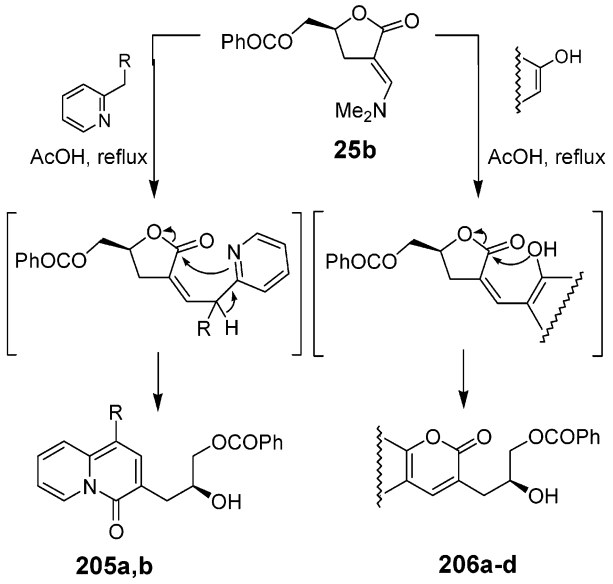
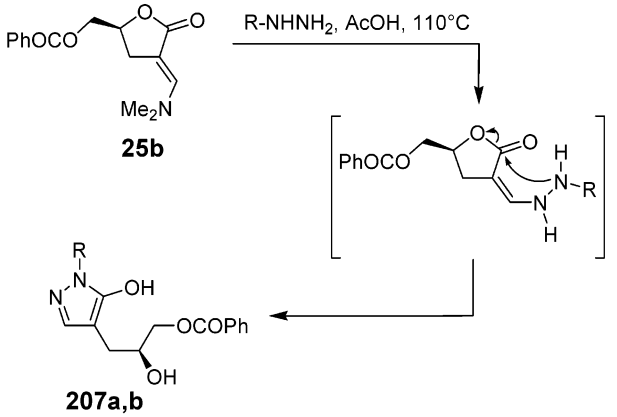
1,3-Dinucleophile	Methyl Heteroaryllactate	Yield (%)	Ref.
	 **202a–c**	43 (**202a**, R = COOMe) 35 (**202b**, R = COOEt) 45 (**202c**, R = CN)	84
	 **203a,b**	20 (**203a**, R = H) 64 (**203b**, R = Me)	168
	 **203c**	27	168
	 **203d**	28	168
	 **203e**	13	168
	 **203f**	31	168
	 **203g**	65	168
	 **203h**	81	168
	 **203i**	64	168

Table 32 (Continued)

1,3-Dinucleophile	Methyl Heteroaryllactate	Yield (%)	Ref.
	 **203j**	30	168
	 **204a,b**	19 (**204a**, R = H) 15 (**204b**, R = Me)	84

Scheme 53





rivatives, 1,3-dicarbonyl compounds and their analogues, and heteroarylhydrazines in 14−81% yields (Scheme 53; Table 33).[60]

5.3.3. Synthesis of Heterocyclic Analogues of Dipeptides

Chiral cyclic analogues of 3-(dimethylamino)propenoates have been employed as key intermediates in the synthesis of mono- and bicyclic heterocycles with a dipeptide structural element. Types of heterocyclic analogues of dipeptides are given in Figure 14.

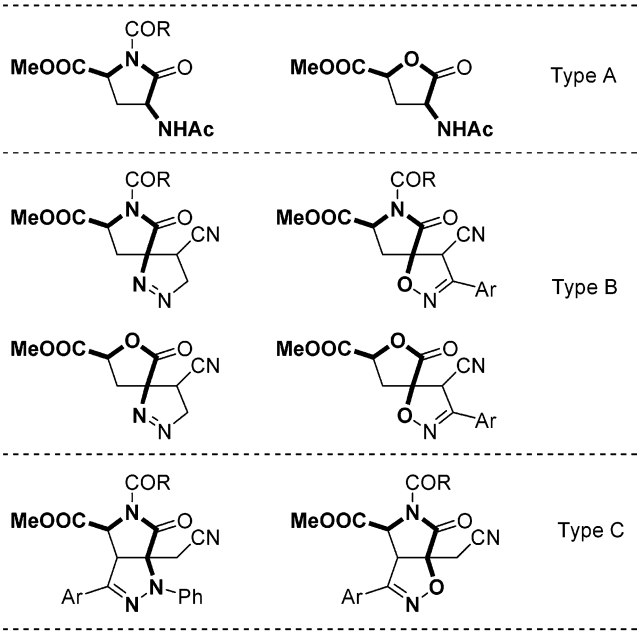
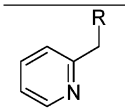
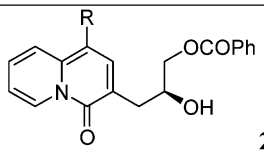
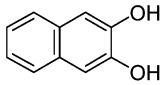
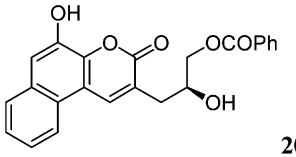
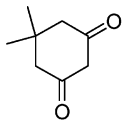
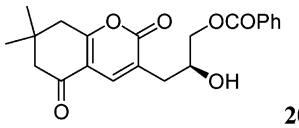
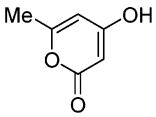
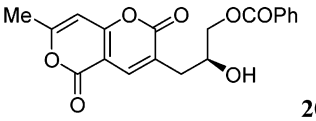
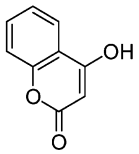
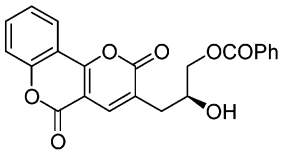
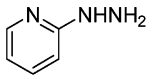
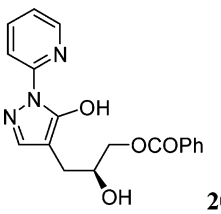
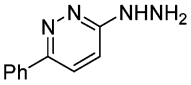
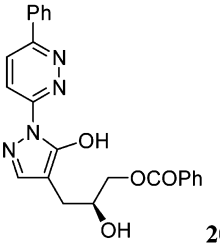


Figure 14.

Heterocyclic dipeptide analogues of type A with the pyrrolidin-2-one and tetrahydrofuran-2-one scaffold have been obtained by stereoselective α-amination of (5*S*)-substituted 1-acylpyrrolidin-2-ones **208** and tetrahydrofuran-2-ones **209**. Treatment with TBDMAM afforded 3-(dimethylamino)methylidene derivatives **24a**,**b** and **25a**,**b**, which were nitrosated to give the α-oximino compounds **210a**−**d**. Finally, catalytic hydrogenation in a mixture of acetic acid and acetic anhydride furnished 5-substituted (3*S*,5*S*)-3-(acetylamino)pyrrolidin-2-ones **211a**,**b**, (3*S*,5*S*)-3-(acetylamino)tetrahydrofuran-2-ones **211c**,**d**, and their (3*R*,5*S*)-epimers. In most cases, stereoselectivity of hydrogenation was high (>80% de). Isomerically pure compounds **211a**−**d** were obtained upon crystallization or chromatographic purification (Scheme 54; Table 34).[57]

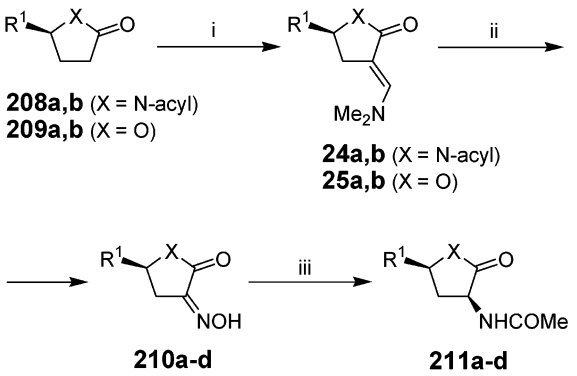
Peptidomimetics of type B with spiro-connected heterocyclic rings were obtained by 1,3-dipolar cycloadditions of diazomethane and stable nitrile oxides to methyl (*S*)-3-[(*E*)-cyanomethylidene]pyrrolidinone-5-carboxylates **34a**,**b** and methyl (*S*)-3-[(*E*)-cyanomethylidene]tetrahydrofuranone-5-carboxylate (**35**).

Table 33. 1-*O*-Benzoyl (*S*)-3-Heteroarylpropane-1,2-diols Prepared[60]

Dinucleophile	3-Heteroarylpropane-1,2-diol	Yield (%)
	 **205a,b**	18 (**205a**, R = COOEt) 46 (**205b**, R = CN)
	 **206a**	14
	 **206b**	81
	 **206c**	33
	 **206d**	37
	 **207a**	19
	 **207b**	32

1,3-Dipolar cycloadditions of diazomethane to **34a**,**b** furnished (4*S*,5*S*,8*S*)-triazaspiro[4.4]non-1-en-6-ones **212a**,**b** together with the (4*R*,5*R*,8*S*)-isomers **213a**,**b**. Methyl (4*S*,5*S*,8*S*)-7-oxa-1,2-diazaspiro[4.4]non-1-en-6-one **216** and its (4*R*,5*R*,8*S*)-isomer **217** were prepared from **35** and diazomethane. Diastereoselectivity of these cycloadditions is poor. However, isomerically pure compounds **212a**,**b**, **213a**,**b**, **216**, and **217** are obtained upon crystallization of isomeric mixtures or chromatographic separation using medium-pressure liquid chromatography (MPLC). Similarly, compounds **34a**,**b** react with 2,4,6-trimethoxybenzonitrile oxide in refluxing chloroform to give the major isomers (4*R*,5*S*,8*S*)-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-one derivatives **214a**,**b** and the minor isomers **215a**,**b**. Interestingly, treatment of **35** with benzonitrile oxides under the same reaction conditions led to the formation of racemic cycloadducts **218a**−**c** together with the minor isomers **219a**−**c**. Minor isomers **213b**, **215a**,**b**, and **219a**−**c** were not isolated in isomerically pure form (Scheme 55; Table 35).[58,68,69]

Scheme 54[a]



[a] Reaction conditions: (i) *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), toluene, 90−100 °C; (ii) HCl, $NaNO_2$, H_2O, 0 °C; (iii) H_2, Pd−C, AcOH−Ac_2O, 20−60 °C, 1 bar, then crystallization or chromatogtaphic separation.

Table 34. Stereoselective Amination of 5-Substituted γ-Lactones and γ-Lactams[57]

compd	R	X	yield (%) 210	yield (%) 211	de (%)
208a, **24a**, **210a**, **211a**	CO_2Me	*N*-COPh	79	45	50
208b, **24b**, **210b**, **211b**	CO_2Me	*N*-Boc	79	44	86
209a, **25a**, **210c**, **211c**	CO_2Me	O	78	58	82
209b, **25b**, **210d**, **211d**	$PhCO_2CH_2$	O	81	56	86

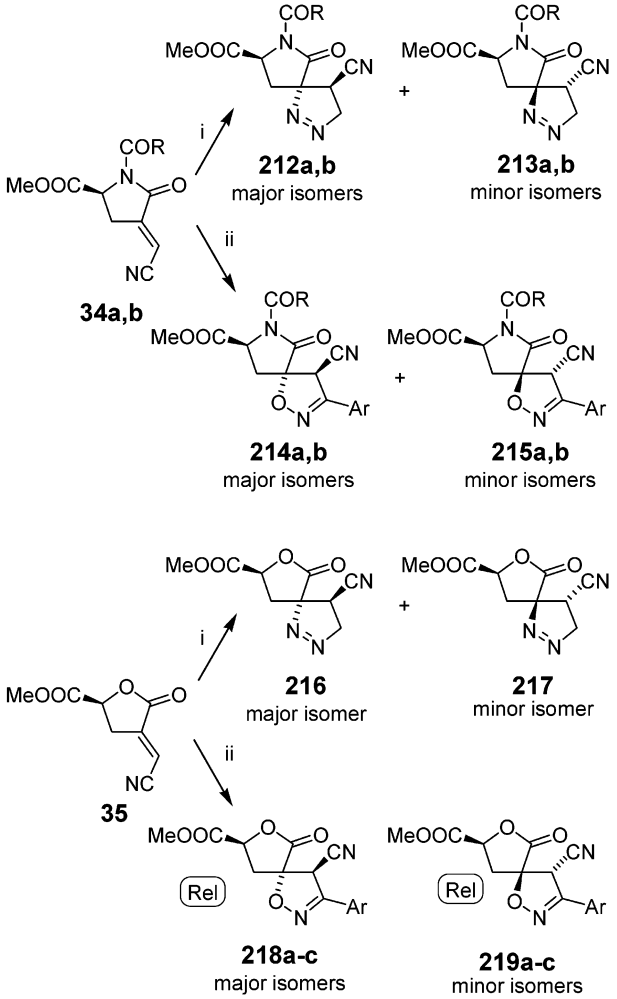
Type C peptidomimetics were obtained upon base-catalyzed cycloadditions of nitrile imines and nitrile oxides to methyl (*S*)-1-acyl-3-[(*E*)-cyanomethylidene]-pyrrolidin-2-one-5-carboxylates **34a**,**b**. Thus, reactions of *N*-phenylbenzonitrile imines and 2,4,6-trimethoxybenzonitrile oxide with **34a**,**b**, performed in the presence of triethylamine, afforded racemic pyrrolo[3,4-*c*]pyrazoles **221a**−**d** and pyrrolo[4,3-*d*]isoxazoles **222a**,**b** in 56−97% de. Most probably, these base-catalyzed cycloadditions proceed via initial isomerization of optically active dipolarophile into racemic (*RS*)-1-acyl-3-(cyanomethyl)-1,2-dihydro-2-oxo−5*H*-pyrrole-5-carboxylate **220**, which then undergoes 1,3-dipolar cycloaddition. This reaction pathway is supported by the isolation of the racemic dipolarophile **220a** (Scheme 56; Table 36).[58,68]

5.4. Synthesis and Transformations of Heterocyclic Amines and Diazonium Salts Derived Thereof

Pyrans and their fused derivatives,[169] quinolizines,[170] and azino[1,2-*x*]pyrimidines[171,172] are significant classes of heterocyclic compounds and constituents of various important naturally occurring and synthetic compounds. For example, 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have been recently studied as fluorescent probes for hypoxic cells in solid tumors.[173] They have been prepared, either in three steps by condensation of substituted 2-aminopyridines with ethyl 3-ethoxy-2-nitropropenoate followed by cyclization in polyphosphoric acid and reduction of the nitro group[174] or by hydrolysis of 3-benzoylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in concentrated hydrochloric acid in yields below 30%.[175]

On the other hand, utilization of alkyl 2-benzyloxycarbonylamino- **3q** 2-phthaloylamino- **3r** and

Scheme 55[a]



[a] Reaction conditions: (i) CH_2N_2, Et_2O, −10 °C, then MPLC or crystallization; (ii) Ar−C≡N^+−O^-, $CHCl_3$, reflux, then MPLC or crystallization.

Table 35. Dipeptide Analogues 212−214 and 216−218 of Type B

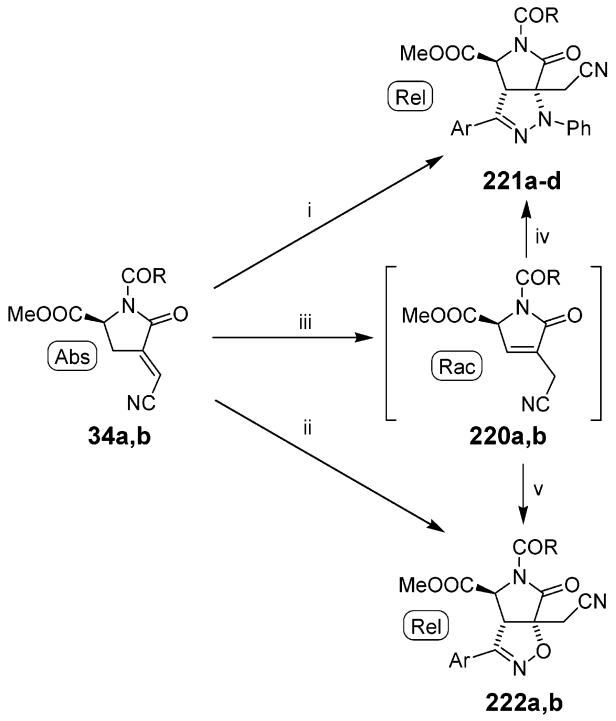
compd	R	Ar	yield (%)	se (%)	ref
212a	OtBu		28	20	68
213a	OtBu		25	*a*	68
212b	Ph		42	38	68
214a	OtBu	2,4,6-tri-MeO-C_6H_2	44	30	68
214b	Ph	2,4,6-tri-MeO-C_6H_2	44	20	58
216			43	24	69
217			24	*a*	69
218a		2,4,6-tri-Me-C_6H_2	27	32	69
218b		2,4,6-tri-MeO-C_6H_2	25	34	69
218c		2,6-di-Cl-C_6H_4	48	34	69

[a] Minor isomer.

2-(2,2-disubstituted-ethenyl)amino-3-(dimethylamino)propenoates **13** made 3-amino substituted 2*H*-pyran-2-ones and their fused derivatives, 4*H*-quinolizin-4-ones, and 4*H*-azino[1,2-*x*]pyrimidin-4-ones available in two steps and good yields from the corresponding ambident nucleophiles (see also sections 5.2.8, 5.2.9, and 5.2.11).[17,33,34,36,38,41,43,83,124,125]

Propenoates **13a**−**z** contain two enamine moieties, which differ considerably with respect to their reactivity toward nucleophiles. The 3-(dimethylamino)-propenoate group is more reactive and was therefore

Scheme 56[a]



[a] Reaction conditions: (i) Ar−C(Cl)═NNHPh, CH_2Cl_2, Et_3N, reflux, then crystallization; (ii) Ar−C≡N^+−O^-, $CHCl_3$, Et_3N, reflux, then crystallization; (iii) basic alumina, CH_2Cl_2, rt; (iv) Ar−C(Cl)═NNHPh, CH_2Cl_2, Ag_2O, reflux, then crystallization; (v) Ar−C≡N^+−O^-, $CHCl_3$, reflux, then crystallization.

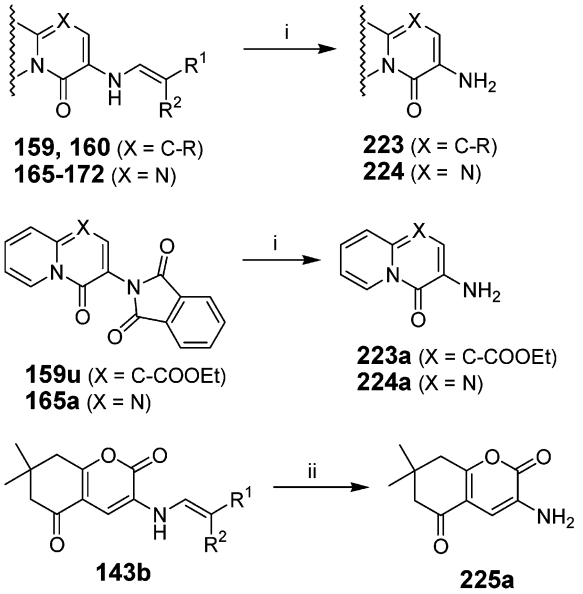
Table 36. Pyrrolo[3,4-*c*]pyrazoles 221a−d and Pyrrolo[4,3-*d*]isoxazoles 222a,b Prepared[58,68]

compd	R	Ar	yield (%)	de (%)	ref
221a	OtBu	Ph	39	84	68
221b	Ph	Ph	47	61	58
221c	OtBu	4-Cl-C_6H_4	66	86	68
221d	Ph	4-Cl-C_6H_4	36	56	58
222a	OtBu	2,4,6-tri-MeO-C_6H_2	60	82	68
222b	Ph	2,4,6-tri-MeO-C_6H_2	58	86	58

used for the construction of various heterocycles (see section 5.2). The remaining enamine group, the (2,2-disubstituted-1-ethenyl)amino group, can be regarded as an ethenyl-protected amino group. The removal of the ethenyl group of compounds **159**, **160**, and **165**−**172** with excess hydrazine hydrate in refluxing ethanol gave amines **223** and **224** without considerable decomposition of the heterocyclic part of the molecules (method A).[17,36,38,41,43,124] This deprotection method was also employed for the preparation of 3-aminoquinolizin-4-one **223a** and 3-aminopyridino[1,2-*a*]pyrimidin-4-one **224a** from the corresponding *N*-phthaloyl-protected derivatives **159u** and **165a**, respectively.[34] For the preparation of the 3-amino-2*H*-pyran-2-ones **139**−**146**, the strongly nucleophilic deprotecting reagent hydrazine hydrate turned out to be inappropriate, because opening of the pyranone ring occurrs. In two instances, however,[17,43] diethylamine in refluxing ethanol (method B) was successfully employed for the preparation of the pyranone **225a** from **143b** (Scheme 57).

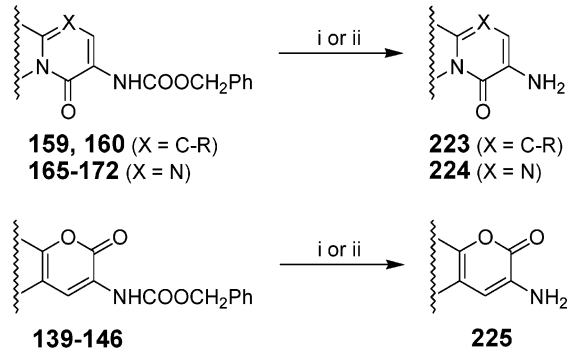
The benzyloxycarbonyl protecting group, introduced by **3n**, is easily removed by catalytic transfer

Scheme 57[a]



[a] Reaction conditions: (i) $NH_2NH_2 \times H_2O$, EtOH, reflux (method A); (ii) Et_2NH, EtOH, reflux (method B).

Scheme 58[a]

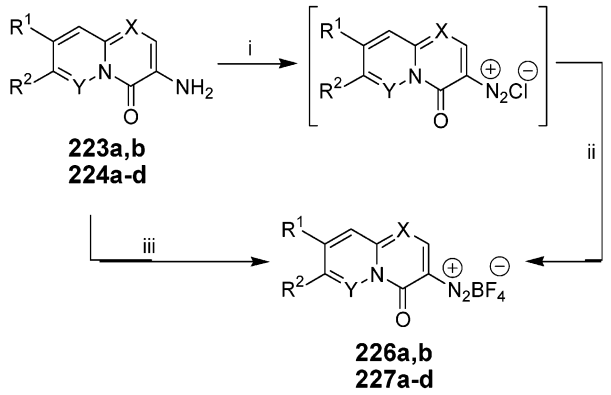


[a] Reaction conditions: (i) cyclohexene, EtOH, 10% Pd−C, reflux (method C); (ii) 33% HBr−AcOH, 40 °C (method D).

hydrogenation reaction (method C).[33] Simple catalytic hydrogenation can cause partial saturation of endocyclic double bonds, especially in the quinolizine **223** and azino[1,2-*x*]pyrimidine **224** series.[28] Removal of the benzyloxycarbonyl group was also achieved with hydrogen bromide in acetic acid (method D)[83,125] according to the procedure used in peptide chemistry.[176] For laboratory scale preparation of heteroarylamines **223**−**225** in the form of their hydrobromide salts, the latter method proved to be the most practical, especially because all of these systems are quite stable under acidic conditions (Scheme 58).[177]

Nitrosation of 3-amino-4-oxo-4*H*-quinolizines **223a**,**b**, 3-amino-4-oxo-4*H*-pyridino[1,2-*x*]pyrimidines **224a**,**b**, and 3-amino-4-oxo-4*H*-pyrimidino[1,2-*x*]pyridazines **224c**,**d** followed by treatment with fluoroboric acid afforded the corresponding stable diazonium salts **226a**,**b** and **227a**−**d** in high yields. Nitrosation of amines **223a**,**b** and **224a**,**c**,**d** was carried out in aqueous medium at ∼0 °C, followed by addition of 50% fluoroboric acid,[125,178,179] whereas 8-methyl-4-oxo-4*H*-pyridino[1,2-*a*]pyrimidin-3-diazonium tetrafluoroborate (**227b**) was prepared from the parent amine **224b** upon treatment with *tert*-butyl nitrite and

Scheme 59[a]

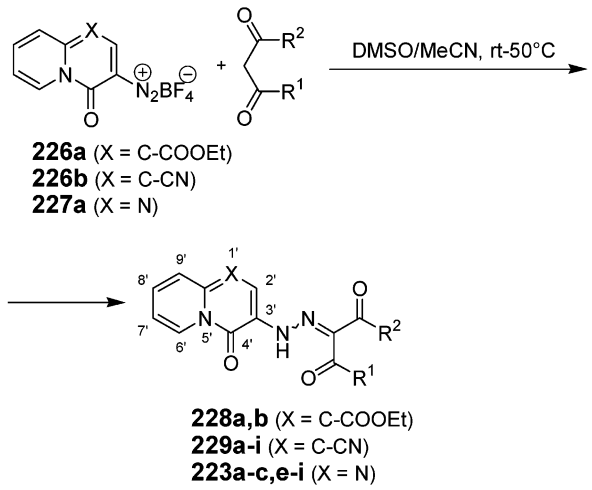


[a] Reaction conditions: (i) $NaNO_2$ (aq), HCl, H_2O, 0 °C; (ii) 50% HBF_4 (aq), 0 °C (method A); (iii) $BF_3 \times Et_2O$, *t*-BuO−N=O, CH_2Cl_2, −15 °C (method B).

Table 37. 4-Oxo-4*H*-quinolizine- 226a,b and 4-Oxo-4*H*-azino[1,2-*x*]pyrimidin-3-diazonium Tetrafluoroborates 227a−d

compd	X	Y	R^1	R^2	method	yield (%)	ref
226a	C−COOEt	CH	H	H	A	84	179
226b	C−CN	CH	H	H	A	86	179
227a	N	CH	H	H	A	82	178
227b	N	CH	Me	H	B	95	178
227c	N	N	H	H	A	70	125
227d	N	N	H	Ph	A	83	125

Scheme 60



boron trifluoride ethyl etherate in anhydrous dichloromethane at −15 °C (Scheme 59; Table 37).[178]

Coupling of diazonium tetrafluoroborates **226a**,**b** and **227a** with various 1,3-dicarbonyl compounds in DMSO or acetonitrile at 20−50 °C afforded hydrazones **228**−**230** in 55−96% yields (Scheme 60; Table 38).[180]

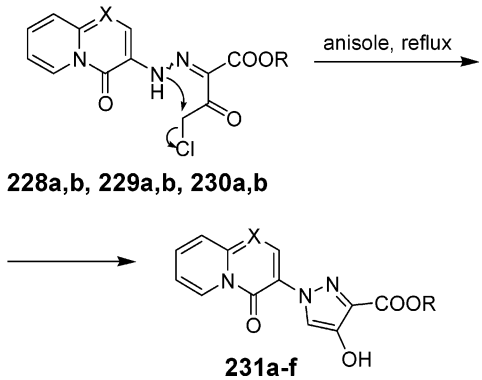
Heating of hydrazones **228a**,**b**, **229a**,**b**, and **230a**,**b**, derived from alkyl 4-chloro-3-oxobutanoates, in anisole under reflux afforded the corresponding alkyl 1-heteroaryl-4-hydroxy-1*H*-pyrazole-3-carboxylates **231a**−**f** in 87−96% yields (Scheme 61).[180]

By treatment of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-**227a**,**b** and 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine-3-diazonium tetrafluoroborates **227c**,**d** with primary alcohols at 40−90 °C 1-heteroaryl-1*H*-1,2,3-triazole-

Table 38. *N*-Heteroarylhydrazones 228−230 Prepared from Heteroaryldiazonium Tetrafluoroborates and 1,3-Dicarbonyl Compounds[180]

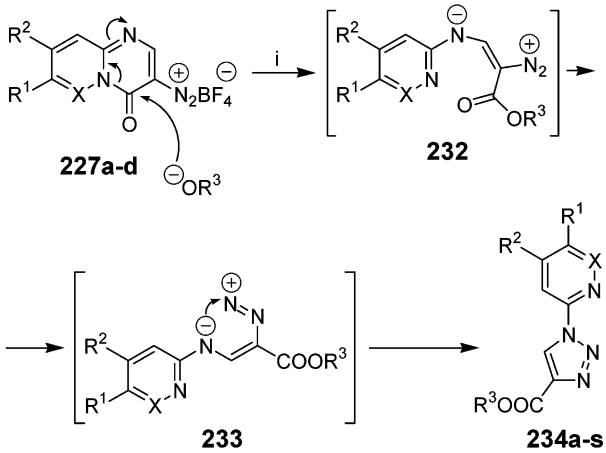
	1,3-dicarbonyl residue		yield (%)		
compd	R^1	R^2	**228**	**229**	**230**
228a−230a	CH_2Cl	OMe	64	72	61
228b−230b	CH_2Cl	OEt	55	60	60
229c, **230c**	Me	Ph		66	72
229d	Me	COOEt		61	
229e, **230e**	Me	Me		89	78
229f, **230f**	Ph	Ph		91	62
229g, **230g**	1,3-cyclohexanedione			96	96
229h, **230h**	5,5-dimethylcyclohexane-1,3-dione			90	62
229i, **230i**	*N*,*N*-dimethylbarbituric acid			90	79

Scheme 61



Compound	X	R	Yield (%)
231a	C–CN	Me	89
231b	C–CN	Et	87
231c	C–COOEt	Me	96
231d	C–COOEt	Et	88
231e	N	Me	88
231f	N	Et	90

Scheme 62[a]



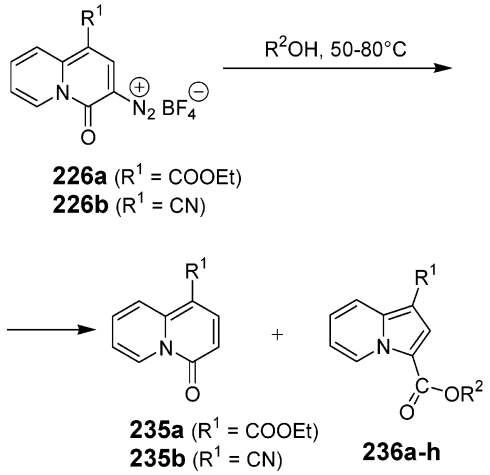
[a] Reaction conditions: (i) R^3−OH (R = alk-1-yl), 50−80 °C.

4-carboxylates **234a**−**s** were obtained. The formation of products can be explained by the nucleophilic attack of an alcohol to the carbonyl group at the 4-position, followed by cleavage of the C(4)−N(5) bond to give intermediates **232**. Isomerization around the C(2)=C(3) double bond and ring closure of the dia-

Table 39. 1-Heteroaryl-1*H*-1,2,3-triazole-4-carboxylates 234a−s

reaction	X	R^1	R^2	R^3	yield (%)	ref
227a + MeOH → **234a**	CH	H	H	Me	70	178
227a + EtOH → **234b**	CH	H	H	Et	51	178
227a + *n*-PrOH → **234c**	CH	H	H	*n*-Pr	57	178
227a + *n*-BuOH → **234d**	CH	H	H	*n*-Bu	56	178
227a + *n*-PeOH → **234e**	CH	H	H	*n*-pentyl	60	178
227b + MeOH → **234f**	CH	H	Me	Me	42	178
227b + EtOH → **234g**	CH	H	Me	Et	30	178
227b + *n*-PrOH → **234h**	CH	H	Me	*n*-Pr	42	178
227b + *n*-BuOH → **234i**	CH	H	Me	*n*-Bu	41	178
227b + *n*-PeOH → **234j**	CH	H	Me	*n*-pentyl	30	178
227c + MeOH → **234k**	N	H	H	Me	64	125
227c + EtOH → **234l**	N	H	H	Et	30	125
227c + *n*-PrOH → **234m**	N	H	H	*n*-Pr	33	125
227c + *n*-BuOH → **234n**	N	H	H	*n*-Bu	33	125
227d + MeOH → **234o**	N	Ph	H	Me	66	125
227d + EtOH → **234p**	N	Ph	H	Et	23	125
227d + *n*-PrOH → **234q**	N	Ph	H	*n*-Pr	31	125
227d + *n*-BuOH → **234r**	N	Ph	H	*n*-Bu	34	125
227d + *n*-PeOH → **234s**	N	Ph	H	*n*-pentyl	34	125

Scheme 63



zonium group to the former N(1) atom gave 1*H*-1,2,3-triazole derivatives **234a**−**s** (Scheme 62; Table 39).[125,178]

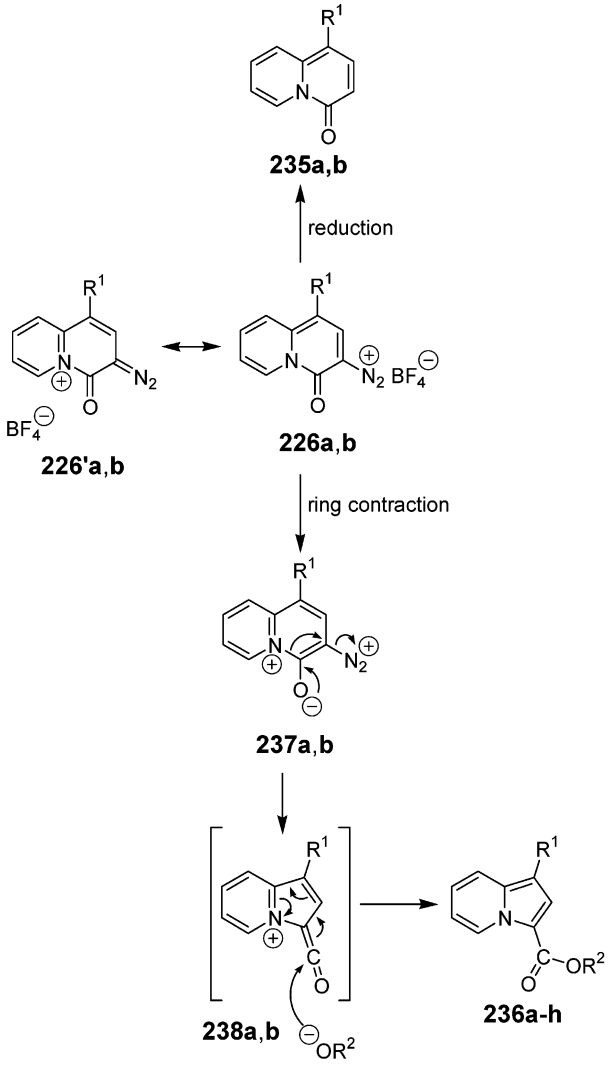
On the other hand, treatment of 1-substituted 4-oxo-4*H*-quinolizine-3-diazonium tetrafluoroborates **226a**,**b** with anhydrous alcohols, such as methanol, ethanol, 1-propanol, and 2-propanol, at 50−80 °C gave mixtures of 3-unsubstituted 4*H*-quinolizin-4-ones **235a**,**b** and alkyl indolizine-3-carboxylates **236a**−**h**. In most cases, selectivity of these transformations was dependent upon the type of alcohol employed. Thus, heating of **226a**,**b** in methanol and 1-propanol afforded the corresponding methyl and *n*-propyl indolizine-3-carboxylates **236a**,**c**,**e**,**g**, whereas treatment of **226a**,**b** with 2-propanol under reflux gave the corresponding dediazonized 4*H*-quinolizin-4-one **235a**,**b** as the major products. When the reaction was performed in ethanol, both products, 4*H*-quinolizin-4-ones **235a**,**b** and ethyl indolizine-3-carboxylates **236b**,**f**, respectively, were obtained in similar yields (Scheme 63; Table 40).[179]

Apparently, two competitive reactions took place when heteroaryldiazonium salts **226** were heated in alcohols: (a) dediazoniation (reduction) to 3-unsubstituted quinolizinones **235** and (b) ring contraction

Table 40. Experimental Data for Reactions of Diazonium Salts 226a,b with Alcohols[179]

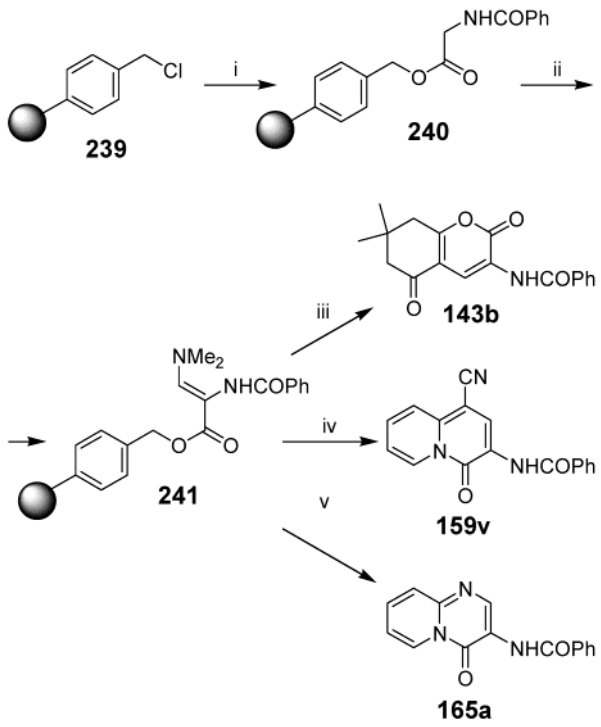
reaction	solvent	R^1	R^2	*T* (°C)	time (h)	yield (%) **235**	yield (%) **236**
226a → **235a** + **236a**	MeOH	COOEt	Me	60	15	8	57
226a → **235a** + **236b**	EtOH	COOEt	Et	50	7	49	38
226a → **235a** + **236c**	*n*-PrOH	COOEt	*n*-Pr	60	7	11	42
226a → **235a** + **236d**	*i*-PrOH	COOEt	*i*-Pr	reflux	8	85	
226b → **235b** + **236e**	MeOH	CN	Me	60	5	25	53
226b → **235b** + **236f**	EtOH	CN	Et	60	6	35	44
226b → **235b** + **236g**	*n*-PrOH	CN	*n*-Pr	70	8	23	50
226b → **235b** + **236h**	*i*-PrOH	CN	*i*-Pr	70	7	69	25
226b → **235b** + **236h**	*i*-PrOH	CN	*i*-Pr	reflux	12	73	7.5

Scheme 64



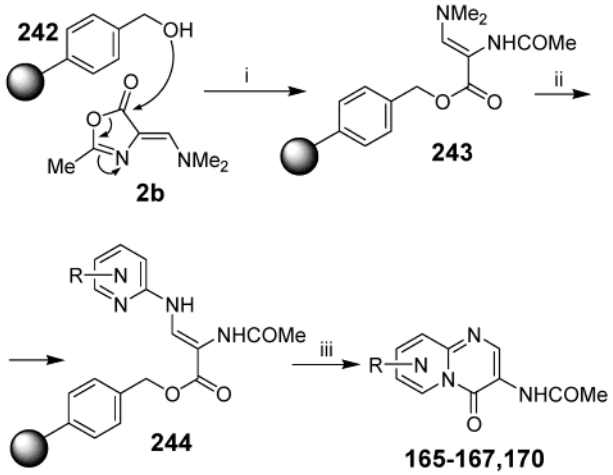
(rearrangement) to indolizines **236**. Reduction of diazonium salts **226** with alcohols at elevated temperatures was not surprising, because closely related reductions in aryldiazonium series, in most cases with ethanol as the reducing agent, have been well documented in the literature.[181,182] On the other hand, formation of indolizine derivatives **236** can formally be regarded as aza-Wolff rearrangement.[183] Recently reported calculations in 6,6-fused heterocycles with a bridgehead nitrogen atom support the existence of α-diazocarbonyl mesomeric structures **226′**,[184] thus making the carbenoid rearrangement mechanism feasible (Scheme 64).[179]

Scheme 65[a]



[a] Reaction conditions: (i) hippuric acid, Cs_2CO_3, DMF, 200 °C; (ii) DMFDEA, DMF, 180 °C (MW); (iii) dimedone, AcOH, 180 °C; (iv) (pyridin-2-yl)acetonitrile, AcOH, 180 °C; (v) 2-aminopyridine, AcOH, 180 °C. All reactions were carried out under microwave irradiation.

Scheme 66[a]

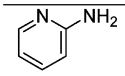
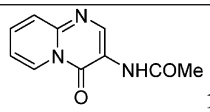
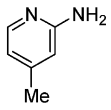
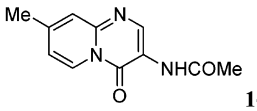
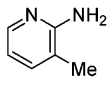
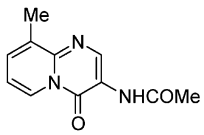
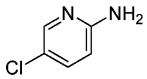
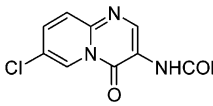
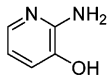
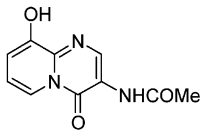
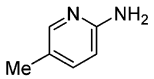
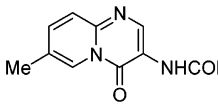
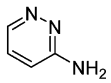
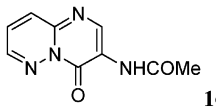
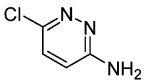
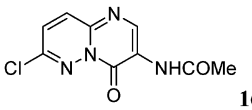
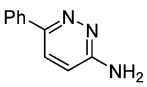
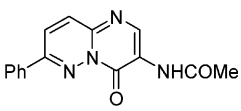
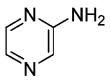
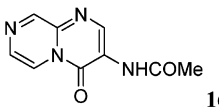
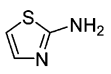
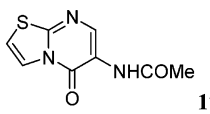


[a] Reaction conditions: (i) toluene, *t*-BuOK, 18-crown−6, rt; (ii) aminoazine, AcOH, 50 °C; (iii) AcOH, 100 °C.

5.5. Utilization of Alkyl 3-(Dimethylamino)-propenoates in Combinatorial Synthesis

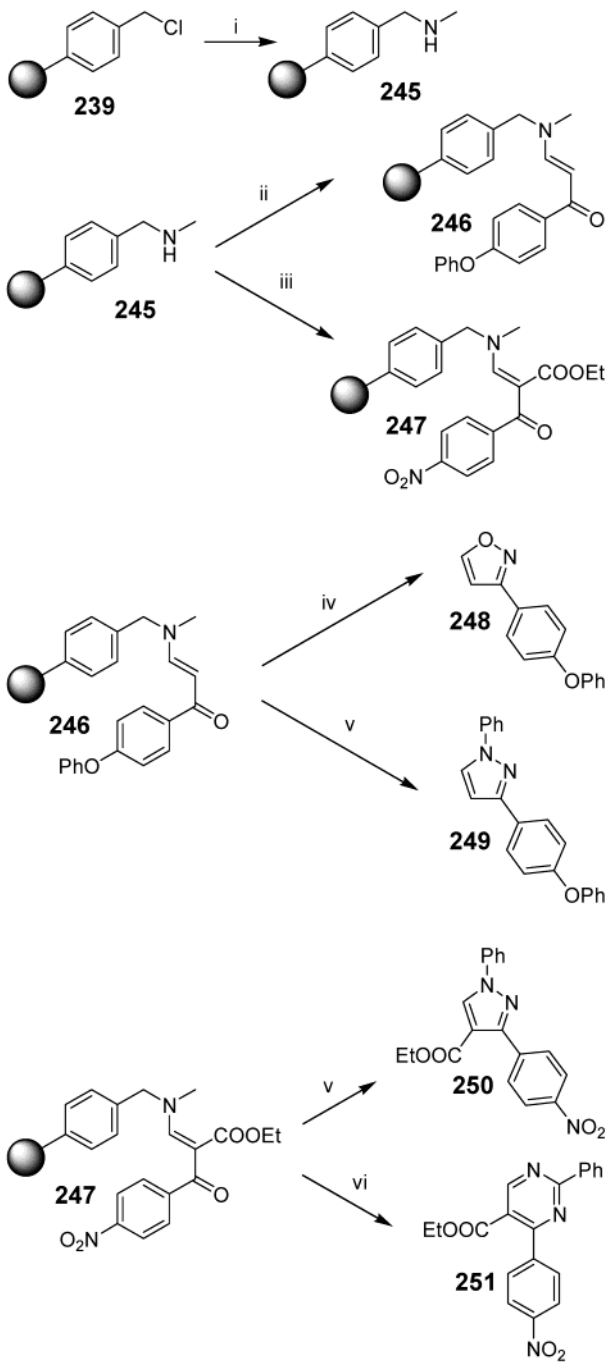
Just recently, solid phase synthesis of 3-amino-propenoates and 3-aminopropenones as synthons for combinatorial synthesis of heterocycles has been reported. Polymer-bound 2-(benzoylamino)-3-(dimethylamino)propenoate **241** was prepared in two steps by loading the Merrifield resin **239** with *N*-benzoylglycine in DMF at 200 °C to give compound **240**, followed by treatment with DMFDEA. Heating of polymer-bound propenoate **241** with dimedone, (pyridin-2-yl)acetonitrile, and 2-aminopyridine afforded 3-(benzoylamino) substituted benzopyranone

Table 41. 3-Acetylaminoazino[1,2-*x*]pyrimidin-4-ones 165−167 and 170 Prepared via Polymer-Bound Propenoate 243[186]

Amine	Product	Yield (%)[a]
	 **165a**	85
	 **165b**	79
	 **165c**	84
	 **165d**	24
	 **165e**	63
	 **165f**	88
	 **166a**	50
	 **166b**	24
	 **166d**	48
	 **167a**	10
	 **170**	11

[a] Overall yield calculated on the loading capacity of Wang resin employed (Fluka, 1.1 mmol/g).

Scheme 67[a]

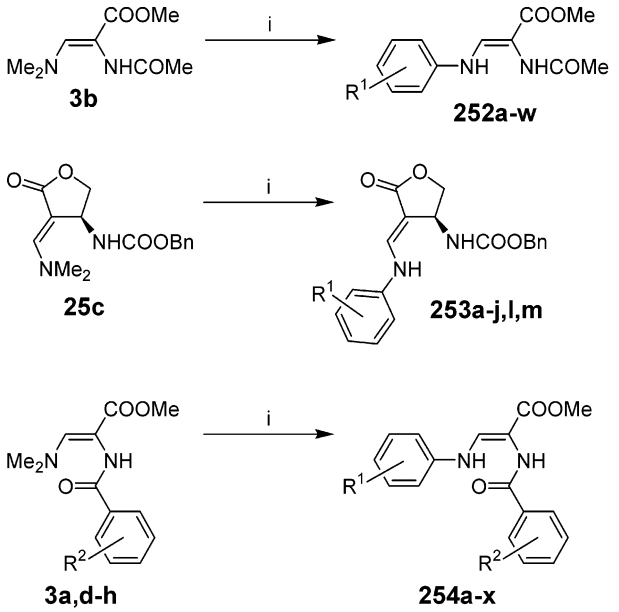


[a] Reaction conditions: (i) $MeNH_2$, H_2O, 150 °C; (ii) DMFDEA, 4-phenoxyacetophenone, DMF, 150 °C; (iii) DMFDEA, ethyl (4-nitrobenzoyl)acetate, DMF, 150 °C; (iv) $NH_2OH \times HCl$, EtOH, 180 °C; (v) $PhNHNH_2$, AcOH, or EtOH, 180 °C; (vi) benzamidine hydrochloride, KOH, DMF, 180 °C. All reactions were carried out under microwave irradiation.

143b, quinolizin-4-one **159v**, and 4*H*-pyridino[1,2-*a*]-pyrimidin-4-one **165a**, respectively (Scheme 65).[185]

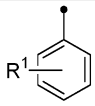
Similarly, a library of 3-acetylaminoazino[1,2-*x*]-pyrimidin-4-ones **165**−**167** and **170** was synthesized: Wang resin **242** was treated with 4-(dimethylamino)methylidene-2-methyl-5(4*H*)-oxazolone (**2b**) to give the polymer-bound 2-(acetylamino)-3-(dimethylamino)propenoate **243**, which reacted with excess aminoazines in acetic acid at ∼50 °C to afford polymer-bound dimethylamine substitution products

Scheme 68[a]



[a] Reaction conditions: (i) $Ar-NH_2 \times HCl$, $EtOH-H_2O$ (1:1), rt.

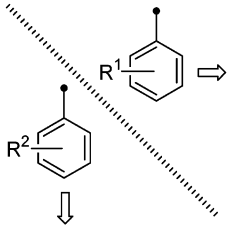
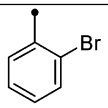
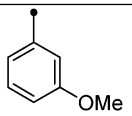
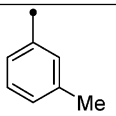
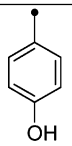
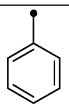
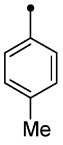
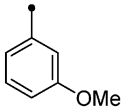
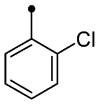
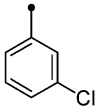
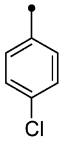
Table 42. Methyl 2-(Acetylamino)-3-arylamino-propenoates 252[186] and α-Arylaminomethylidene-β-benzyloxycarbonyl-amino-γ-butyrolactones 253[61] Prepared by Parallel Solution Phase Approach

compd		yield (%) 252	yield (%) 253
252a, **253a**	phenyl	73	89
252b, **253b**	2-methylphenyl	88	45
252c, **253c**	3-methylphenyl	90	76
252d, **253d**	4-methylphenyl	78	88
252e, **253e**	2-methoxyphenyl	79	77
252f, **253f**	3-methoxyphenyl	94	62
252g, **253g**	4-methoxyphenyl	87	73
252h, **253h**	2-bromophenyl	81	71
252i, **253i**	3-bromophenyl	92	70
252j, **253j**	4-bromophenyl	100	74
252k	2-hydroxyphenyl	82	
252l, **253l**	3-hydroxyphenyl	62	94
252m, **253m**	4-hydroxyphenyl	91	46
252n	2-aminophenyl	81	
252o	3-nitrophenyl	96	
252p	4-nitrophenyl	72	
252q	4-carboxy-2-hydroxyphenyl	79	
252r	3-benzoylphenyl	77	
252s	4-phenylazophenyl	95	
252t	4-fluorophenyl	72	
252u	3-chloro-4-fluorophenyl	93	
252v	2,6-dimethylphenyl	63	
252w	1-naphthyl	78	

244. Finally, compounds **244** were heated in acetic acid at 100 °C to furnish 3-acetylaminoazino[1,2-*x*]-pyrimidin-4-ones **165**−**167** and **170** (Scheme 66; Table 41).[186]

In the previously mentioned solid phase approaches, the propenoates were bound to the polymer support via the ester linkage. In another approach, the benzyl chloride handle of the Merrifield resin **239** was first transformed into the benzyl methylamine handle to give the resin **245**. A three-component reaction between the resin **245**, DMFDMA, and 4-phenoxyacetophenone gave the polymer-bound pro-

Table 43. 2-(Aroylamino)-3-(arylamino)propenoates 254a−x Combinatorial Library Prepared by Solution Phase Approach[30]

	Compound/Yield (%)			
				
	**254a**/81	**254b**/84	**254c**/89	**254d**/70
	**254e**/77	**254f**/88	**254g**/91	**254h**/84
	**254i**/81	**254j**/91	**254k**/89	**254l**/87
	**254m**/82	**254n**/77	**254o**/80	**254p**/79
	**254q**/75	**254r**/91	**254s**/82	**254t**/78
	**254u**/81	**254v**/91	**254w**/85	**254x**/83

penone **246**. A related propenone **247** was prepared from **245** and ethyl 4-nitrobenzoyl acetate. Treatment of **246** and **247** with hydroxylamine, phenylhydrazine, and benzamidine furnished the corresponding isoxazole **248**, pyrazole **249**, **250**, and pyrimidine derivative **251** (Scheme 67).[185]

On the other hand, a series of methyl 2-(acetylamino)-3-(hetero)arylaminopropenoates **252** were prepared in 62−100% yields by parallel solution phase synthesis from aromatic amines hydrochlorides and methyl 2-(acetylamino)-3-(dimethylamino)propenoate (**3b**) in aqueous ethanol at room temperature.[186] In the same manner, a library of 12 α-arylaminomethylidene-*β*-benzyloxycarbonylamino-*γ*-butyrolactones **253a**−**j**,**l**,**m** was synthesized from propenoate **25c** in 45−94% yields (Scheme 68; Table 42).[61] In the case of dimethylamine substitution products, the solution phase synthesis is advantageous to the solid phase approach, because the products precipitate from the reaction mixtures and can be isolated, mostly in analytically pure form, simply upon filtration, washing, and thorough drying. Due to its simplicity, this method was extended on preparation of the combinatorial library of 24 2-(aroylamino)-3-arylaminopropenoates **254a**−**x** in 70−91% yields by varying four anilines and six propenoates (Scheme 68; Table 43).[30]

6. Conclusion

In this review we demonstrate how a series of 2-substituted 3-(dimethylamino)propenoates and related enaminones as masked α-formyl-α-substituted acid derivatives and ketones, including chiral ana-

logues, has been developed into a group of versatile reagents for the preparation of 2,3-disubstituted propenoates and numerous monocyclic and fused heterocyclic systems with an α-amino acid or other related structural element incorporated into the newly formed heterocyclic system. Most of these reagents are accessible from easily or commercially available starting materials. Their applicability has been extended to the preparation of some natural products and their analogues, 3-heteroarylalanines, alaninols, lactic acid esters, diols, and heterocyclic compounds with incorporated dipeptide structural element. The broad synthetic methodology and elaborated experimental techniques allow their application in the preparation of small libraries of these types of compounds by combinatorial approach.

7. References

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