Transformations of Methyl 2-(2,2-Disubstituted-ethenyl)amino-3-dimethylaminopropenoates. The Synthesis of Methyl 1-Heteroaryl-1*H*-imidazole-4-carboxylates

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Transformations of intermediates **4**, prepared from methyl 2-(2,2-disubstituted-ethenyl)amino-3-dimethylaminopropenoates **2** and sterically hindered heteroarylamines **3**, into methyl 1-heteroaryl-1*H*-imidazole-4-carboxylates **7** are described.

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The synthesis of imidazole derivatives has been of great interest in the last century and therefore numerous methods have been designed [1a]. However, there is no single widely applicable method for the synthesis of this heterocyclic system. The common synthetic methods are divided into those which build up the imidazole ring from acyclic precursors, and transformations of other heterocyclic systems [1b,c].

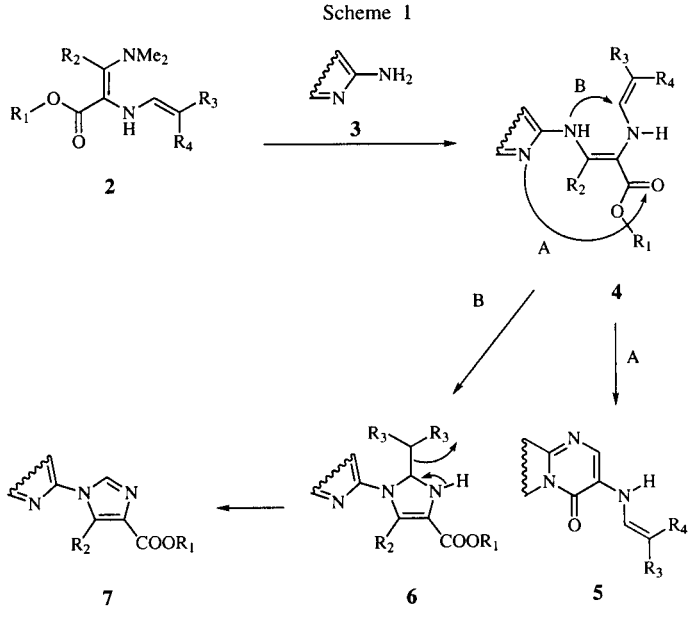
There has been only a limited number of syntheses described in the literature in which the acyclic precursors containing C-N-C-C-N structural element have been used [1]. In this connection, cyclisations of α-acylaminoamidines [2-5], α-acylaminothiocarboxylic acid amides [6], α-acylaminocarboxylic acid amides [7,8], hydrazones [9], *N*-substituted derivatives of α-aminocarbonitriles [10,11], *N*-substituted 1,2-diaminoalkenes [12-17], and bis amides of oxalic acid [18-20] have been reported.

Recently, we have prepared alkyl 2-(2,2-disubstituted-ethenyl)amino-3-dimethylaminopropenoates and related compounds and used them as reagents for preparation of many heterocyclic systems, including 2*H*-pyran-2-ones and fused pyran-2-ones, fused pyridinones and pyrimidinones [21-35].

We have observed earlier that in the reaction of methyl 2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminopropenoate (**2a**), methyl 2-[2,2-bis(acetyl)ethenyl]-amino-3-dimethylaminopropenoate (**2b**) [27], methyl 2-(2-acetyl-2-benzyloxycarbonylethenyl)amino-3-dimethylaminopropenoate (**2c**) [22] and methyl 2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminobut-2-enoate (**2d**) [31] with heterocyclic amines, having the amino group attached at α-position in regard to the ring nitrogen atom, the corresponding azolo- and azinopyrimidinones **5** have been formed.

However, when the compounds **2** and 2-amino-6-methylpyridine (**3a**) or 2-amino-4-chlorobenzothiazole (**3b**) were heated in glacial acetic acid for several hours methyl 1-(6-methylpyridin-2-yl)-1*H*-imidazole-4-carboxylate (**7a**), methyl 1-(4-chlorobenzothiazol-2-yl)-1*H*-imidazole-4-carboxylate (**7b**) and its 5-methyl derivative **7c** were formed. The reaction can be explained in the following manner. In the reaction between propenoate derivatives **2** and heterocyclic amines **3** the intermediates **4** are formed. They can in principle cyclize in two different manners. Normally, cyclization occurs according to the path A to give fused pyrimidinones **5** as observed earlier [22,23,25,27,29,31]. On the other hand, when the cyclisation to a ring nitrogen atom is sterically hindered due to the presence of a substituent at position 6 in a pyrimidine ring or at position 4 in a benzothiazole ring, the cyclisation occurs according to path B to give 1-heteroaryl-1*H*-imidazole-4-carboxylates **7** (Scheme1).

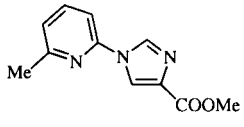
Scheme 1



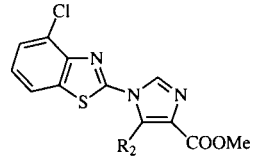
1	2	R_1	R_2	R_3	R_4	Yield of **2** (%)	Reference
a	**a**	Me	H	COOEt	COOEt	98	This paper
b	**b**	Me	H	COMe	COMe	98	27
c	**c**	Me	H	COOBn	COMe	98	22
	d	Me	Me	COOEt	COOEt	75	31

The structure of new compounds were determined by elemental analyses for C, H and N, and with ^{1}H nmr spectra.

The reaction represents a novel method for the preparation of methyl 1-heteroaryl-1*H*-imidazole-4-carboxylates. However, the method is limited only to those heteroarylamines in which the cyclization can not occur to ring nitrogen atom, due to the steric hindrance.



7a



7b R_2 = H
c R_2 = Me

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on Bruker Avance DPX 300 spectrometer with tetramethylsilane as the internal standard, mass spectra on AutoSpecQ spectrometer and elemental analyses for C, H and N on a Perkin-Elmer CHN Analyser 2400.

The following compounds were prepared according to the procedures described in the literature: **1a** [31], **1b** [27], **1c** [22], **2b** [27], **2c** [22] and **2d** [31].

Methyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminopropenoate (**2a**).

A suspension of methyl *N*-[2,2-bis(ethoxycarbonyl)ethenyl]-glycinate (**1a**, 100 mmoles, 25.92 g) and dimethylformamide dimethyl acetal (150 mmoles, 22.5 ml) in acetonitrile (40 ml) was heated under reflux for 4 hours. Volatile components were evaporated *in vacuo* and ethyl acetate was added for crystallisation. The precipitate was collected by filtration and recrystallized from ethyl acetate to give **2a** in 98% yield, mp 62-64°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.17 and 1.22 (t, COOEt), 2.98 (s, NMe_2), 3.68 (s, COOMe), 4.05 and 4.13 (q, COOEt), 7.29 (s, H_3), 7.68 (d, C*H*NH), 9.49 (d, NH); J_{Et} = 7.2 Hz, J_{CHNH} = 14.3 Hz.

Anal. Calcd. for $C_{14}H_{22}N_2O_6 \cdot {}^1/_2H_2O$ [36]: C, 51.86; H 6.92; N, 8.92. Found: C, 52.00; H, 7.17; N, 8.66.

Synthesis of 1-Heteroaryl-1*H*-imidazole-4-carboxylates **7**.

General Procedure.

A suspension of propenoate (or butenoate) **2** (1 mmole) and heterocyclic amine **3** (1 mmole) in glacial acetic acid (3-4 ml) was heated under reflux for several hours. Volatile components were evaporated *in vacuo*, crystallized from an appropriate solvent and purified by recrystallization. The following compounds were prepared by this method:

Methyl 1-(6-Methylpyridin-2-yl)-1*H*-imidazole-4-carboxylate (**7a**).

This compound was prepared from 2-amino-6-methylpyridine (**3a**) and compound **2b**, 3 hours, 20% yield; from 2-amino-6-methylpyridine (**3a**) and compound **2c**, 2.5 hours, 36% yield; mp 180-183° (toluene); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.53 (s, 6'-Me), 3.81 (s, COOMe), 7.31 (d, H'$_5$), 7.74 (d, H'$_3$), 7.92 (dd, H'$_4$), 8.60 and 8.61 (d, H_2, H_5); J_{H2H5} = 1.5 Hz, $J_{H5'H4'}$ 7.5 Hz, $J_{H3'H4'}$ = 8.1 Hz.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.05; N, 19.13. Found: C, 60.58; H, 5.05; N, 19.13.

Methyl 1-(4-Chlorobenzothiazol-2-yl)-1*H*-imidazole-4-carboxylate (**7b**).

This compound was prepared from 2-amino-4-chlorobenzothiazole (**3b**) and compound **2a**, 4 hours, 23% yield; mp 190-200° (ethanol/toluene 1:1); ms: M^+ = 293; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.84 (s, COOMe), 7.50 (dd, H'$_6$), 7.70 (dd, H'$_7$), 8.19 (dd, H'$_5$), 8.50 (d, H_5), 8.68 (d, H_2); $J_{H6'H7'}$ = 7.9 Hz, $J_{H5'H6'}$ = 7.9 Hz, $J_{H5'H7'}$ = 1.1 Hz, J_{H2H5} = 1.5 Hz.

Anal. Calcd. for $C_{12}H_8N_3O_2SCl$: C, 49.07; H, 2.75; N, 14.31. Found C, 48.79; H, 2.90; N, 13.99.

Methyl 1-(4-Chlorobenzothiazol-2-yl)-5-methyl-1*H*-imidazole-4-carboxylate (**7c**).

This compound was prepared from 2-amino-4-chlorobenzothiazole (**3b**) and compound **2d**, 3 hours, 30% yield; mp 176-179° (toluene/2-propanol 1:1); ms: M^+ = 307; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 2.48 (s, 5-Me), 3.72 (s, COOMe), 6.99-7.70 (m, H'$_5$, H'$_6$, H'$_7$), 9.99 (s, H_2).

Anal. Calcd. for $C_{13}H_{10}N_3O_2SCl$: C, 50.74; H, 3.28; N, 13.65. Found: C, 50.46; H, 3.10; N, 13.69.

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[36] Ethyl analogue of compound **2a** was found as a hemihydrate and its structure was confirmed by X-ray analysis [23].