Transformations of Ethyl 3-{[1-(Alkoxycarbonyl)-2-(dimethylamino)ethenyl]amino}-2-cyanoprop-2-enoates: Synthesis of Dialkyl 3-Aminopyrrole-2,4-dicarboxylates

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The transformation of ethyl 3-{[1-(alkoxycarbonyl)-2-(dimethylamino)ethenyl]amino}2-cyanoprop-2-enoates **2** to dialkyl 3-aminopyrrole-2,4-dicarboxylates **3** in good yields is described.

Introduction. – Recently, the synthesis of pyrrole derivatives has attracted considerable interest. This heterocycle is incorporated in many natural products with biological activity, and constitutes the building block for porphyrins, chlorophylls, corrins, and bile pigments [1–6].

In view of the importance of pyrrole for various applications, great efforts have been made towards preparation of this heterocyclic system [5][7–9]. Variously substituted pyrroles have been prepared by condensation of α-aminocarbonyl compounds with 1,3-dicabonyl compunds [10–12], β-amino enones [13][14], or 3-alkoxyacroleins [15], by reaction of nitro compounds with isocyano acetates [16–21], of α-chloroaldimines with KCN [22] and α-acetoxy nitro compounds with isocyanatoacetonitrile [23].

Nucleophilic substitutions on halogen-substituted pyrroles by charged and neutral C, N, O, and S nucleophiles have been reported. They represent a versatile instrument to prepare a wide variety of functionalized pyrroles [24].

Pyrrole-2-carboxylates have been prepared from 1,3-dicarbonyl compounds and aminomalonate [11][12]25], diethyl oximinomalonate [26], various 2-amino-1,3-dicarbonyl compounds [13], 1,3-dicarbonyl compounds, and α-amino-acid derivatives [27–30], and by addition of α-amino-acid derivatives to dimethyl acetylenedicarboxylate [31][32].

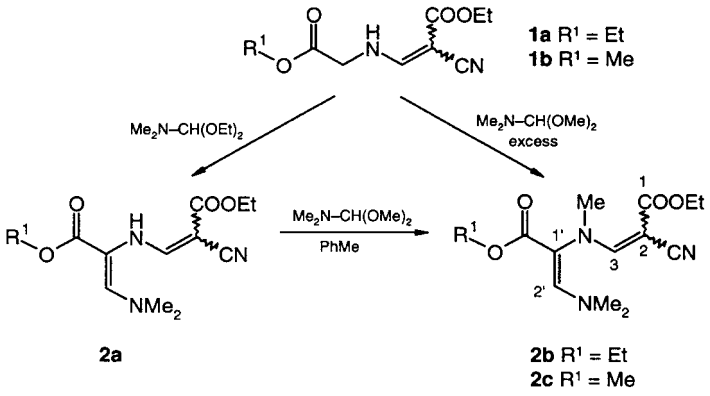
Only few examples of 3-aminopyrrole-2-carboxylates have been reported. These include the synthesis of 2-(alkoxycarbonyl)-3-ureidopyrroles derived from pyrrole-2,3-dicarboxylic acid *via Curtius* rearrangement of the 3-acyl-azide intermediate [33], and condensation of α-amino-α-cyano-acetamides with ethyl acetoacetate followed by cyclization to ethyl 3-amino-2-carboxamido-5-methylpyrrole-4-carboxylate [34]. Several alkyl 3-aminopyrrole-2-carboxylates have been obtained by the base-catalyzed cyclization of *N*-(2-cyanoethenyl)glycine esters [35]. These 3-aminopyrrole-2-carboxylates have served as intermediates in the synthesis of pyrrolo[3,2-*d*]pyrimidines (9-deazapurines), 9-deazaguanozines, and other pyrrolo[3,2-*d*]pyrimidine *C*-nucleosides [36].

Recently, substituted 2-(acylamino)-3-(dimethylamino)propenoates, masked α-formyl-α-amino-acid derivatives (for a review, see [37]), and alkyl 2-[(2,2-disubstituted-ethenyl)amino]-3-(dimethylamino)propenoates and related compounds have been used as reagents for preparation of several heterocyclic systems, including 2*H*-pyran-2-one and fused pyran-2-ones, fused pyridinones and pyrimidinones [38–43].

However, when we tried to prepare 6-amino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine by the reaction of 2-aminothiazole with 2-(2-acetyl-2-benzoylethenyl)amino-3-(dimethylamino)propenoate, ethyl 4-benzoyl-3-methylpyrrole-2-carboxylate was formed in low yield. When the reagent itself was heated in CF_3COOH, the pyrrole derivative was obtained in 65% yield. Its structure was confirmed by X-ray analysis [44].

Since the reaction represents a new synthesis of polysubstituted pyrrole-2-carboxylates, we decided to carry out further investigations. In this context, the following compounds were selected: ethyl 2-cyano-3-{[2-(dimethylamino)-1-(ethoxycarbonyl)ethenyl]amino}prop-2-enoate (**2a**) [45], ethyl 2-cyano-3-{[2-(dimethylamino)-1-(ethoxycarbonyl)ethenyl]methylamino}prop-2-enoate (**2b**), and ethyl 2-cyano-3-{[2-(dimethylamino)-1-(methoxycarbonyl)ethenyl]methylamino}prop-2-enoate (**2c**) (*Scheme 1*).

Scheme 1



2	R^1	Yield [%]	(1'*E*) / (1'*Z*) [a]	(2*E*) / (2*Z*) [a]	Ref.
a	Et	47	0 : 100	21 : 79	[45]
b	Et	86	0 : 100	11 : 89	This work
c	Me	40	0 : 100	6 : 94	This work

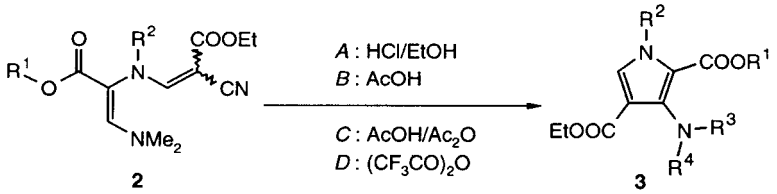
[a]) In (D_6)DMSO.

Results and Discussion. – The structure of **2a** has been already established [45]. The compounds **2b** and **2c** exist in two isomeric forms with respect to the orientation around the C(2)=C(3) bond, while the configuration around the C(1′)=C(2′) bond is always (*Z*).

The compounds **2a**–**c** were cyclized under various conditions (*Scheme 2*, *Exper. Part*). Structures of the final products were found to be dependent upon the reaction conditions. Compound **2c** afforded, when heated in EtOH in presence of HCl

(*Method A*), 3-aminopyrrole **3a**; compounds **2b** and **2c** gave in AcOH (*Method B*) 3-acetylamino derivatives **3b** and **3c**, respectively, and compounds **2a**, and **2b** led, in a mixture of AcOH and Ac_2O (*Method C*), to the corresponding 3-(diacetylamino)pyrroles **3e** and **3d**, respectively, while compounds **2a**–**c** were transformed in $(CF_3CO)_2O$ (*Method D*) into 3-[(trifluoroacetyl)amino]pyrroles **3f**–**h**.

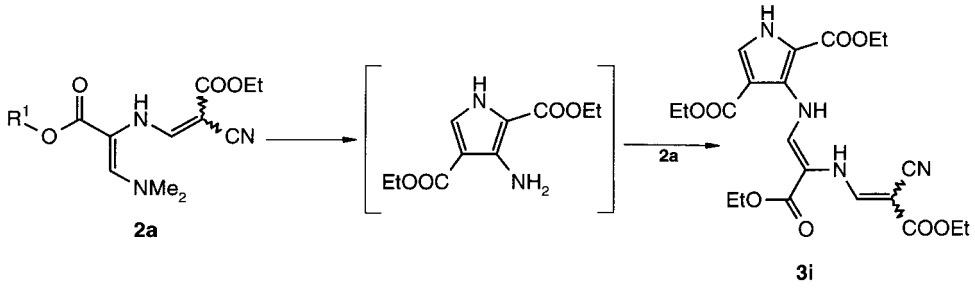
Scheme 2



Educt	*Method*	Reaction time	Product	R^1	R^2	R^3	R^4	Yield [%]
2c	*A*	5 h	**3a**	Me	Me	H	H	90
2c	*B*	2 h	**3b**	Me	Me	H	MeCO	54
2b	*B*	2 h	**3c**	Et	Me	H	MeCO	88
2b	*C*	4 h	**3d**	Et	Me	MeCO	MeCO	52
2a	*C*	5 h	**3e**	Et	H	MeCO	MeCO	68
2c	*D* (r.t.)	72 h	**3f**	Me	Me	H	CF_3CO	56
2c	*D* (Δ)	20 min	**3f**	Me	Me	H	CF_3CO	65
2a	*D* (r.t.)	24 h	**3g**	Et	H	H	CF_3CO	17
2b	*D* (r.t.)	48 h	**3h**	Et	Me	H	CF_3CO	40
2a	*B*	5 h	**3i**	Et	H	H	EtOCOC(CN)=CH–NHC(COOEt)=CH	42

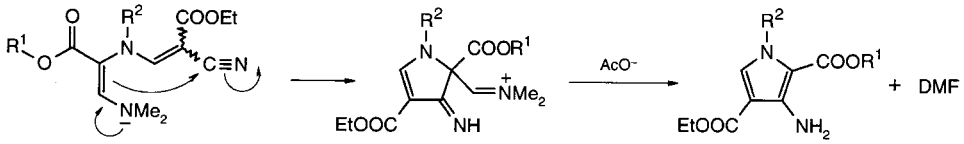
When compound **2a** was heated in glacial AcOH, the corresponding 3-aminopyrrole derivative was formed first as an intermediate, which reacted further with **2a** to give the pyrrole derivative **3i**. Since the pyrrole adduct resulting from the cyclization of **2a** is unsubstituted at N(1), the 3-amino group is less reactive for acetylation, and, therefore, substitution of the Me_2N group in a second molecule of **2a** occurred as a consequence to give **3i** (*Scheme 3*).

Scheme 3



A possible mechanism of the formation of the 3-aminopyrrole derivatives is shown in *Scheme 4*. This proposal is supported by elimination of DMF, the formation of which was observed when the reaction was followed by ^{1}H-NMR.

Scheme 4



Experimental Part

General. M.p.: *Kofler* micro hot stage. IR Spectra: *Perkin-Elmer 1310* spectrometer. ^{1}H-NMR Spectra: *Bruker Advance DPX 300* spectrometer; δ in ppm rel. to internal Me_4Si, J in Hz. MS: *AutoSpecQ* spectrometer. Elemental analyses for C, H, and N: *Perkin-Elmer CHN Analyser 2400*.

Synthesis of Starting Compounds. The compounds **1a** and **2a** were prepared according to the procedure described in [45].

Ethyl 2-Cyano-3-[(2-methoxy-2-oxoethyl)amino]prop-2-enoate (**1b**). To a suspension of methyl glycinate hydrochloride (100 mmol, 12.57 g) in EtOH (100 ml), Et_3N (100 mmol, 14 ml) and ethyl 2-cyano-3-ethoxyprop-2-enoate (100 mmol, 16.92 g) were added. The mixture was stirred for 1 h and left overnight. Volatile components were evaporated *in vacuo*, and the solid residue was recrystallized first from H_2O and then from EtOH: **1b** (95%; 55% (*Z*)). M.p. 170–174°. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.23 (*t*, *J* = 7.1, COOEt); 3.71 (*s*, COOMe); 4.09–4.21 (*m*, *J* = 7.1, *J* = 6.1, COOEt, C*H*$_2$NH); 7.75 (*d*, *J* = 14.4, (*Z*)-C*H*NH); 8.05 (*d*, *J* = 14.4, (*E*)-C*H*NH); 8.64–8.68 (*td*, *J* = 6.1, 14.4, (*E*)-NH); 9.11–9.19 (*td*, *J* = 6.1, 14.4, (*Z*)-NH). MS: 212 (M^+). Anal. calc. for $C_9H_{12}N_2O_4$ (212.21): C 50.94, H 5.70, N 13.20; found: C 50.86, H 5.65, N 13.17.

Ethyl 2-Cyano-3-{[2-(dimethylamino)-1-(ethoxycarbonyl)ethenyl](methyl)amino}prop-2-enoate (**2b**). A mixture of *ethyl 2-cyano-3-{[2-(dimethylamino)-1-(ethoxycarbonyl)ethenyl]amino}prop-2-enoate* (**2a**, 10 mmol, 2813 mg), and $(MeO)_2CHNMe_2$ (30 mmol, 4.5 ml) in toluene (25 ml) was refluxed for 5 h. Volatile components were evaporated *in vacuo*, and EtOH was added for crystallization. The precipitate was collected by filtration and recrystallized from EtOH: **2b** (86%; 100% (2*Z*), 89% (1′*E*)), M.p. 102–103°. IR 2200 (CN). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.19, 1.20 (2*t*, *J* = 7.1, 2 COOEt); 2.99 (*s*, Me_2N); 3.27 (*s*, MeN); 4.08 (*q*, 2 COOEt); 7.27 (*s*, H–C(3)); 7.97 (*s*, C*H*NMe). Anal. calc. for $C_{14}H_{21}N_3O_4$ (295.34): C 56.94, H 7.17, N 14.23; found: C 56.84, H 7.40, N 14.15.

Ethyl 2-Cyano-3-{[2-(dimethylamino)-1-(methoxycarbonyl)ethenyl](methyl)amino}prop-2-enoate (**2c**). A mixture of *ethyl 2-cyano-3-[(2-methoxy-2-oxoethyl)amino]prop-2-enoate* (**1b**, 225 mmol, 47.75 g) and $(MeO)_2CHNMe_2$ (533 mmol, 80 ml) was heated at 80° for 4 h. Volatile components were evaporated *in vacuo*. Toluene was added for cystallization. Precipitate was collected by filtration and recrystallized from toluene: **2c** (40%; 100% (2*Z*), 94% (1′*E*)). M.p. 131–133°. IR 2180 (CN). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.20 (*t*, *J* = 7.1, COOEt); 2.99 (*s*, Me_2N); 3.27 (*s*, MeN); 3.61 (*s*, COOMe); 4.13 (*q*, *J* = 7.1, COOEt); 7.29 (*s*, H–C(3)); 7.96 (*s*, C*H*NMe). MS: 281 (M^+). Anal. calc. for $C_{13}H_{19}N_3O_4$ (281.31): C 55.51, H 6.81, N 14.94; found: C 55.12, H 6.71, N 14.93.

Pyrrole Formation. Method A. Propenoate **2** (7 mmol) was suspended in EtOH/36% HCl 5:1 and heated under reflux for several h. Volatile components were evaporated *in vacuo*. 3-Aminopyrrole-2-carboxylate, which is formed as a HCl salt, was then treated with H_2O, and the free amine was collected by filtration and recrystallized from an appropriate solvent.

Method B. Propenoate **2** (1 mmol) was refluxed in glacial AcOH (3–4 ml) for several h. Volatile components were evaporated *in vacuo*, the oily residue was treated with an appropriate solvent to form a precipitate, which was collected by filtration and purified by recrystallization.

Method C. Propenoate **2** (1 mmol) was refluxed in glacial AcOH (3–4 ml), with 1–2 ml of Ac_2O, for several h. Volatile components were evaporated *in vacuo*, the oily residue was treated with an appropriate solvent to form a precipitate, which was collected by filtration and purified by recrystallization.

Method D. Propenoate **2** (1 mmol) was suspended in 1–1.5 ml of $(CF_3CO)_2O$ and stirred at r.t., until a clear soln. was obtained, or refluxed in 3 ml of $(CF_3CO)_2O$ for 20 min. Then, the mixture was cooled on ice, and MeOH was added dropwise, until all $(CF_3CO)_2O$ was transformed into CF_3COOMe. The mixture was then

cooled to $-20°$ to form a precipitate or evaporated *in vacuo*, ans then treated with an appropriate solvent. Precipitate was collected by filtration and purified by recrystallization.

Reaction times, methods, and yields are presented in *Scheme 2*, m.p. and ^{1}H-NMR data in *Table 1*, and elemental analyses in *Table 2*.

Table 1. *Melting Points, and NMR and MS Data for 3-Amino-1*H*-pyrrole-2-carboxylates* **3**

Compound	M.p. [°]	MS (M^+)	^{1}H-NMR (300 MHz, (D_6)DMSO)
3a	94–96 (EtOH)	226	1.25 (*t*, COOEt); 3.72, 3.73 (2*s*, MeN, COOMe); 4.8 (*q*, COOEt); 5.77 (br. *s*, NH_2); 7.44 (*s*, H–C(5))
3b	135–136 (EtOH)		1.21 (*t*, COOEt); 3.72, 3.81 (2*s*, MeN, COOMe); 4.13 (*q*, COOEt); 7.62 (*s*, H–C(5)); 9.21 (*s*, N*H*COMe)
3c	92–115 (i-PrOH)	282	1.23, 1.24 (2*t*, $J=7.1$, 2 COOEt); 1.96 (*s*, NHCO*Me*); 3.81 (*s*, MeN); 4.18 (2*q*, $J=7.1$, 2 COOEt); 7.61 (*s*, H–C(5)); 9.19 (*s*, N*H*COMe)
3d	68–74 (i-PrOH)		1.19, 1.20 (2*t*, $J=7.1$, 2 COOEt); 2.18 (*s*, N(CO*Me*)$_2$); 3.91 (*s*, MeN); 4.15, 4.18 (2*q*, $J=7.1$, 2 COOEt); 7.86 (*s*, H–C(5))
3e	83–65 (toluene)		1.20, 1.22 (2*t*, $J=7.1$, 2 COOEt); 2.18 (*s*, N(CO*Me*)$_2$); 4.15, 4.20 18 (2*q*, $J=7.1$, 2 COOEt); 7.64 (*d*, $J=3.4$, H–C(5)); 12.80 (*d*, $J=3.4$, NH)
3f	136–138 (CF_3COOMe)		1.22 (*t*, $J=7.1$, COOEt); 3.72 (*s*, COOMe); 3.88 (*s*, MeN); 4.15 (*q*, $J=7.1$, COOEt); 7.78 (*s*, H–C(5)); 10.82 (*s*, NHCOCF_3)
3g	120–135 (toluene)		1.22, 1.23 (2*t*, $J=7.1$, 2 COOEt); 4.1 (2*q*, $J=7.1$, 2 COOEt); 7.56 (*d*, $J=3.7$, H–C(5)); 10.80 (*s*, NHCOCF_3); 12.66 (*d*, $J=3.7$, NH)
3h	75–80 (EtOH)		1.22, 1.24 (2*t*, $J=7.1$, 2 COOEt); 3.88 (*s*, MeN); 4.15, 4.19 (2*q*, $J=7.1$, 2 COOEt); 7.78 (*s*, H–C(5)); 10.80 (*s*, NHCOCF_3)
3i	140–150 (EtOH)	462	1.17–1.32 (*m*, 4 COOEt); 4.11–4.30 (*m*, 4 COOEt); 7.50 (*d*, $J=3.7$, H–C(5)); 7.76–10.58 (*m*, 8 H, NHC*H*, N*H*CH, signals for all four possible geometric isomers); 12.30 (*d*, $J=3.7$, NH)

Table 2. *Elemental Analyses for 3-Amino-1*H*-pyrrole-2-carboxylates* **3**

Compound	Molecular formula	Mol. mass	Calc. [%]			Found [%]		
			C	H	N	C	H	N
3a	$C_{10}H_{14}N_2O_4$	226.23	53.09	6.24	12.38	52.92	6.28	12.51
3b	$C_{12}H_{16}N_2O_5$	268.27	53.73	6.07	10.44	53.57	5.76	10.48
3c	$C_{13}H_{18}N_2O_5$	282.30	55.31	6.43	9.92	55.13	6.65	10.09
3d	$C_{15}H_{20}N_2O_6$	324.33	55.55	6.22	8.64	55.20	6.49	8.66
3e	$C_{14}H_{18}N_2O_6$	310.31	54.19	5.85	9.03	53.90	5.95	9.18
3f	$C_{12}H_{13}F_3N_2O_5$	322.24	44.73	4.07	8.69	44.57	4.10	8.62
3g	$C_{12}H_{13}F_3N_2O_5$	322.24	44.73	4.07	8.69	45.06	4.31	8.83
3h	$C_{13}H_{15}F_3N_2O_5$	336.27	46.43	4.50	8.33	46.54	4.51	8.46
3i	$C_{21}H_{26}N_4O_8$	462.46	54.54	5.67	12.11	54.37	5.60	12.08

The authors wish to express their gratitude to the *Ministry of Science and Technology*, Slovenia, for their financial support.

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Received May 26, 1998