Transformations of Alkyl 2-(2,2-Disubstituted-ethenyl)amino-3-dimethylaminoprop-2-enoates: Synthesis of Alkyl 3,4-Disubstituted- and Alkyl 1-Acyl-3,4-disubstituted Pyrrole-2-carboxylates

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Received 14 May 1998; revised 14 August 1998

Dedicated to Professor Henk van der Plas, Wageningen, on the occasion of his 75th birthday

Abstract: Alkyl 3,4-disubstituted pyrrole-2-carboxylates were obtained by cyclization of alkyl 2-(2,2-disubstituted-ethenyl)amino-3-(dimethylamino)prop-2-enoates in acidic media, while in the presence of acyl chlorides alkyl 1-acyl-3,4-disubstituted pyrrole-2-carboxylates were formed.

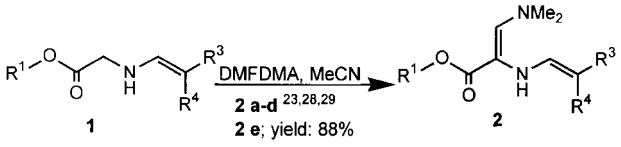
Key words: alkyl substituted pyrrole-2-carboxylates, alkyl 1-acyl substituted pyrrole-2-carboxylates, nitogen hetrocycles

Recently, considerable interest has been shown in the synthesis of pyrrole derivatives. This heterocycle is incorporated in many natural products which posses biological properties and constitute the building block for porphyrins, chlorophylls, corrins and bile pigments.[1–6] In view of the importance of pyrroles for various applications, a large number of papers have been published on the preparation of this heterocyclic system.[5,7–9]

Pyrrole-2-carboxylates have been prepared from 1,3-dicarbonyl compounds and aminomalonate,[10–12] diethyl oximinomalonate,[13] various 2-amino-1,3-dicarbonyl compounds,[14] 1,3-dicarbonyl compounds and α-amino acid derivatives,[15–18] and by addition of α-amino acids derivatives to dimethyl acetylenedicarboxylate.[19–20] Recently, substituted 2-acylamino-3-dimethylaminopropenoates, masked α-formyl-α-amino acid derivatives,[21] and alkyl 2-(2,2-disubstituted-ethenyl)amino-3-(dimethylamino)prop-2-enoates and related compounds as reagents for the preparation of several heterocyclic systems, including 2*H*-pyran-2-one and fused pyran-2-ones, fused pyridinones and pyrimidinones, [22–26] have been described.

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-benzoyl-1-ethenyl)amino-3-(dimethylamino)propenoate, ethyl 4-benzoyl-3-methylpyrrole-2-carboxylate was formed in low yield. When the reagent itself was heated in trifluoracetic acid the pyrrole derivative was obtained in 65% yield whose structure was confirmed by X-ray analysis.[27]

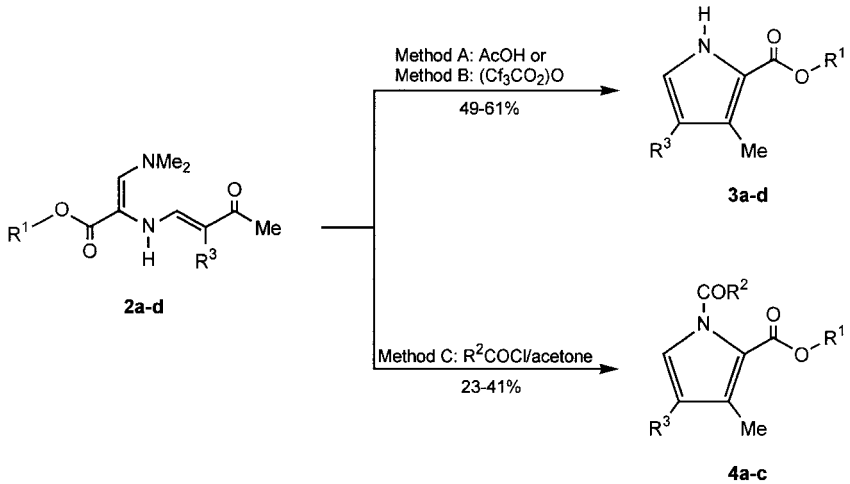
Since the reaction represents a new synthesis of polysubstituted pyrrole-2-carboxylates we investigated the reactions of alkyl 2-[(2-acyl-3-oxobut-1-enyl)amino]propenoates **2a**,[28] **2b**,[23] **2c**,[23] **2d**,[29] and methyl 2-(2-ethoxycarbonyl-2-phenylethenyl)amino-3-(dimethylamino)prop-2-enoate (**2e**), prepared from methyl *N*-(2-ethoxycarbonyl-2-phenylethenyl)glycinate (**1e**) and *N,N*-dimethylformamide dimethyl acetal (DMFDMA)] (Scheme 1).



1,2 **a)** R^1 = Me, R^3= COMe, R^4= COMe
b) R^1= Me, R^3= COOBn, R^4= COMe
c) R^1= Me, R^3= COOMe, R^4= COMe
d) R^1= Et, R^3= COOEt, R^4= COMe
e) R^1= Me, R^3= COOEt, R^4= Ph

Scheme 1

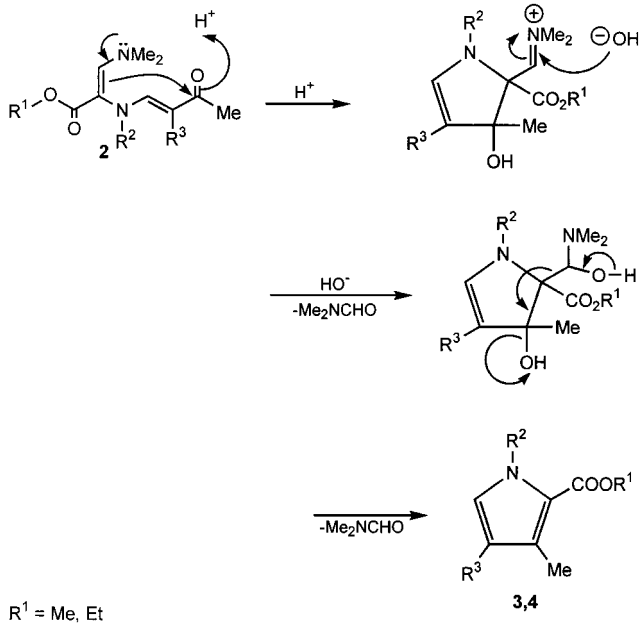
Compounds **2a–e** were cyclized under various conditions: by heating in anhydrous acetic acid (Method A), in tri-



Scheme 2

fluoroacetic anhydride at room temperature or heating at 40 °C (Method B), or in acetone in the presence of an acyl chloride at reflux or room temperature (Method C) to give 3,4-disubstituted **3a–d** and 1-acyl-3,4-trisubstituted pyrrole-2-carboxylates **4a–c**, respectively (Scheme 2, Tables 1 and 2).

The formation of the pyrrole derivatives can be explained by the mechanism shown on Scheme 3 which is also supported experimentally. Namely, when the reaction of **3a** was followed by ^{1}H NMR spectroscopy, the formation of dimethylformamide as the side product was observed.



Scheme 3

This reaction failed with **2e** and the expected methyl 3-hydroxy-4-phenylpyrrole-2-carboxylate was not formed.

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on Bruker Avance DPX 300 spectrometer with TMS as the internal standard, IR spectra on a Perkin-Elmer 1600 spectrometer (KBr pellets), 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 literature: **2a**,[28] **2b**,[23] **2c**,[23] **2d**.[29]

Methyl *N*-(2-Ethoxycarbonyl-2-phenylethenyl)glycinate (1e)

A mixture of ethyl phenylacetate (63 mmol, 10 mL) and *tert*-butyloxy-bis(dimethylamino)methane (65 mmol, 13 mL) in toluene (20 mL) was refluxed for 3.5 h. Volatile components were evaporated in vacuo and methyl glycinate hydrochloride (63 mmol, 7.91 g) in glacial AcOH (15 mL) was added and the mixture was heated under reflux for another 2 h. Then volatile components were evaporated and propan-2-ol (5 mL) was added for initiating the crystallization. The precipitate was collected by filtration and recrystallized from EtOH to give **1e** in 45% yield [100% (*E*)-configuration]; mp 74–76 °C.

Anal. Found: C, 63.45; H, 6.62; N, 5.29. $C_{14}H_{17}NO_4$ requires: C, 63.87; H, 6.51; N, 5.32.

^{1}H NMR (DMSO-d_6/TMS): δ = 1.18 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.67 (s, 3 H, CO_2CH_3), 4.11 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.15 (d, 2 H, J = 6.0 Hz, CH_2), 7.05 (d, 1 H, J = 13.3 Hz, C*H*NH), 7.21–7.27 (m, 5 H, C_6H_5), 8.32 (td, 1 H, J = 13.3, 6.0 Hz, NH).

Methyl 2-[2-Ethoxycarbonyl-2-phenylethenyl]amino-3-(dimethylamino)prop-2-enoate (2e)

A mixture of **1e** (15 mmol, 3.95 g) and DMFDMA (45 mmol, 7 mL) in DMF (15 mL) was heated at 80 °C for 5 h. Volatile components were evaporated in vacuo to yield 4.20 g (88%) of **2e** [100% (2*Z*,1'*E*)-configuration]. This compound was used in further experiments without purification.

MS: m/z = 318 (M^+).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.27 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.05 [s, 6 H, $N(CH_3)_2$], 3.68 (s, 3 H, CO_2CH_3), 4.21 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.78 (d, 1 H, J = 12.7 Hz, C*H*NH), 7.21 (s, 1 H, H-3), 7.18–7.42 (m, 5 H, C_6H_5), 8.82 (d, 1 H, J = 12.7 Hz, NH).

Pyrroles 3, 4; General Procedure

Method A: Propenoate **2** (1 mmol) was heated in glacial AcOH (3–4 mL) under reflux for several hours. Volatile components were evaporated in vacuo, the oily residue was triturated with an appropriate solvent to form a precipitate, which was collected by filtration and purified by recrystallization. (Tables 1 and 2).

Method B: Propenoate **2** (1 mmol) was suspended in trifluoracetic anhydride (TFAA) (1–1.5 mL) and stirred at r.t., until a clear solution was obtained. After that, the mixture was cooled in an ice bath and MeOH (2–3 mL) was added dropwise, until all TFAA was destroyed. The mixture was then cooled to –20 °C to form a precipitate, or evaporated in vacuo and then triturated with an appropriate solvent. The precipitate was collected by filtration and purified by recrystallization (Tables 1 and 2).

Table 1 Compounds **3** and **4** Prepared

Reactant(s)	Reaction Conditions	Method	Product	R^1	R^2	R^3	Yield (%)	mp (°C) (solvent)
2a; **(2a)**	reflux, 5 h; (r.t., 10 min)	A; (B)	**3a**	Me	–	COMe	45; (54)	128–131 (toluene)
2b; **(2b)**	reflux, 3.5 h; (r.t., 10 min)	A; (B)	**3b**	Me	–	CO_2Bn	51; (61)	>300 (CF_3CO_2Me)
2c	r.t., 10 min	B	**3c**	Me	–	CO_2Me	49	124–127 (CF_3CO_2Me)
2d	r.t., 10 min	B	**3d**	Et	–	CO_2Et	60	79–80 (EtOH)
2a + MeCOCl	reflux, 2 h	C	**4a**	Me	Me	COMe	41	77 (EtOH)
2a + PhCOCl	r.t., 2 h	C	**4b**	Me	Ph	COMe	23	125–126 (toluene)
2b + MeCOCl	reflux, 2.5 h	C	**4c**	Me	Me	CO_2Bn	34	69–70 (EtOH)

Table 2 Spectroscopic Data of Compounds **3** and **4**

Product[a]	IR (KBr) ν (cm^{-1})	MS (M^+) *m/z*	^{13}C NMR (75 MHz, DMSO-d_6/TMS) δ	^1H NMR (300 MHz, DMSO-d_6/TMS) δ, *J* (Hz)
3a	3241, 1722, 1645, 1561	181	12.25 (3-CH_3), 28.97 (CO*C*H_3), 51.93 (OCH_3), 121.18, 125.05, 128.78 and 130.31 (Pyrrole), 162.07 (*C*O_2Me), 194.61 (*C*OMe)	2.34 (s, 3 H, $COCH_3$), 2.44 (s, 3 H, 3-CH_3), 3.79 (s, 3 H, CO_2CH_3), 7.74 (d, 1 H, *J* = 3.5, H–5), 12.05 (d, 1 H, *J* = 3.5, NH)
3b	3350, 1715, 1684, 1593	273	11.93 (3-CH_3), 51.98 (OCH_3), 65.48 (Ph*C*H_2), 115.75, 121.06, 128.56, 128.68, 128.80, 129.29, 129.68 and 137.59 (Pyrrole, Ph), 161.84 and 164.44 (C=O)	2.51 (s, 3 H, 3-CH_3), 3.79 (s, 3 H, CO_2CH_3), 5.24 (s, 2 H, C*H*$_2$Ph), 7.29–7.45 (m, 5 H, C_6H_5), 7.51 (d, 1 H, *J* = 3.4, H–5), 12.21 (d, 1 H, *J* = 3.4, NH)
3c	3252, 1704	197	11.85 (3-CH_3), 51.54 and 51.98 (OCH_3), 115.81, 120.92, 128.61 and 129.60 (Pyrrole), 161.87 and 165.14 (C=O)	2.49 (s, 3 H, 3-CH_3), 3.71 and 3.79 (s, 6 H, CO_2CH_3), 7.45 (d, 1 H, *J* = 3.4, H), 12.16 (d, 1 H, *J* = 3.4, NH)
3d	3292, 1716, 1668	225	11.87 (3-CH_3), 15.12 (2×OCH_2CH_3), 50.91 and 60.58 (OCH_2CH_3), 116.11, 121.12, 128.45 and 129.37 (Pyrrole), 161.49 and 164.71 (C=O)	1.26 and 1.30 (t, 6 H, *J* = 7.1, $CO_2CH_2CH_3$), 2.49 (s, 3 H, 3-CH_3), 4.18 and 4.25 (q, 4 H, *J* = 7.1, $CO_2CH_2CH_3$), 7.43 (d, 1 H, *J* = 3.4, H–5), 12.09 (d, 1 H, *J* = 3.4, NH)
4a	3244, 1716, 1681, 1645	224[b]	11.62 (3-CH_3), 23.71 and 29.03 (CO*C*H_3), 51.97 (OCH_3), 121.20, 125.67, 128.48 and 131.56 (Pyrrole), 162.10 and 162.78 (*C*O_2Me, N*C*OMe), 194.61 (*C*OMe)	2.25 (s, 3 H, 4-$COCH_3$), 2.43 (s, 3 H, 3-CH_3), 2.65 (s, 3 H, $NCOCH_3$), 3.75 (s, 3 H, CO_2CH_3), 8.35 (s, 1 H, H–5)
4b	3110, 1715	285	12.18 (3-CH_3), 29.19 (CO*C*H_3), 52.49 (OCH_3), 125.36, 129.06, 130.07, 130.61, 131.60, 132.76, 133.52 and 135.32 (Pyrrole, C_6H_5), 161.37 and 168.68 (*C*O_2Me, N*C*OPh), 194.93 (*C*OMe)	2.34 (s, 3 H, $COCH_3$), 2.41 (s, 3 H, 3-CH_3), 3.48 (s, 3 H, CO_2CH_3), 7.58–7.64 and 7.72–7.80 (m, 5 H, C_6H_5), 8.23 (s, 1 H, H–5)
4c	3350, 3126, 1742, 1712, 1580	274[b]	11.33 (3-CH_3), 23.77 (CO*C*H_3), 52.98 (OCH_3), 66.21 (Ph*C*H_2), 117.32, 123.50, 128.56, 128.76, 129.30, 129.35, 130.29, and 137.11 (Pyrrole, C_6H_5), 162.61, 163.70 and 169.52 (C=O)	2.27 (s, 3 H, 3-CH_3), 2.63 (s, 3 H, $NCOCH_3$), 3.75 (s, 3 H, CO_2CH_3), 5.29 (s, 2 H, C*H*$_2$Ph), 7.34–7.47 (m, 5 H, C_6H_5) 8.11 (s, 1 H, H-5)

[a] Satisfactory microanalyses obtained for all compounds: C ± 0.40, H ± 0.40, N ± 0.25.
[b] MH^+.

Method C: Propenoate **2** (1 mmol) was suspended in acetone (3–4 mL), then the appropriate acyl chloride (0.5–1 mL) was added and the reaction mixture was heated under reflux, for several hours (Table 1) or stirred at r.t. The mixture was then cooled to –20 °C and left until a precipitate was formed, or evaporated in vacuo and then tritutated with an appropriate solvent. Precipitate was collected by filtration and purified by recrystallization. (Tables 1 and 2).

Acknowledgement

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

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