Efficient and Flexible Access to Polysubstituted Pyrroles

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Abstract: A series of polysubstituted pyrroles **3** have been synthesized very efficiently in two or three steps starting from primary amines **1**. The key-step of this process is the bromocyclisation of δ-enaminoesters **2**. The chemoselectivity of the reaction could depend on the nature of the solvent.

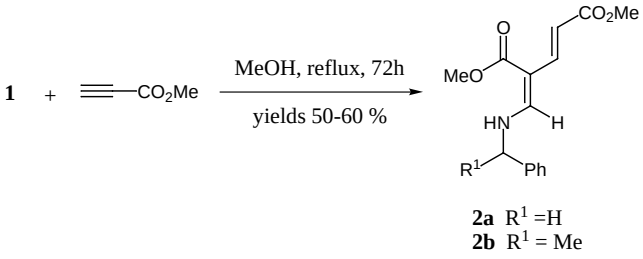
Key words: pyrroles, δ-enaminoesters, β-enaminoesters, bromocyclisation, amines

Pyrroles are heterocycles of great importance because of their presence in numerous natural products such as heme, chlorophyll, vitamin B_{12} or enzymes like the various cytochromes.[1] In addition, polysubstituted pyrroles are molecular frameworks of many biologically active compounds and have emerged as chemotherapeutic agents.[2] Although there is a number of potentially useful methods, (for example the well known Knorr reaction),[3] many synthetic designs for these ring systems continue to be developed.[4]

This paper describes a facile and flexible regioselective synthesis of 2,4-dicarbonylated substituted pyrroles **3** in two or three steps, starting from primary amines **1** (Scheme 1). The key-step involves the bromocyclisation of δ-enaminoesters **2** with *N*-bromosuccinimide (NBS).

The preparation of derivatives **2** has been achieved by two different procedures.[5] The first one allowed, in a one-pot procedure, the stereoselective synthesis of δ−enaminoester **2a**,**b** by refluxing amines **1** (R^1 = H or Me) with methyl propiolate in methanol (Scheme 2). The *Z*-configuration of the double bond α to the nitrogen atom is assumed on grounds of earlier work.[6] The *E*-configuration of the second double bond is based upon the coupling (15.5 Hz) of the ethylenic hydrogen atoms.

The δ-enaminoester **2c-f** were prepared stereoselectively via a two-step procedure:[7] i) condensation between amines **1** and methyl acetoacetate or 2,4-pentanedione led to β-enaminoester **4c-e** and β-enaminoketone **4f** respectively ii) addition of methyl propiolate[8] to these adducts **4c-f** afforded δ-enaminoester **2c-f** in a diastereomerically pure form (Scheme 3).[9]



2a R^1 =H
2b R^1 = Me

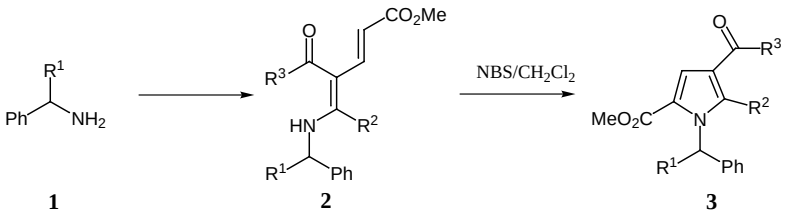
Scheme 2

Six examples of the conversion of δ-enaminoesters **2** to various substituted pyrroles are listed in Table 1. The reactions were performed by adding NBS to a solution of substrates **2** in dichloromethane at 0 °C.[10] The reactions were completed in 5 minutes, the solvent evaporated and the residue purified by chromatography on silica gel.

Table 1 Reaction of δ-enaminoesters 2 with NBS (Scheme 1)

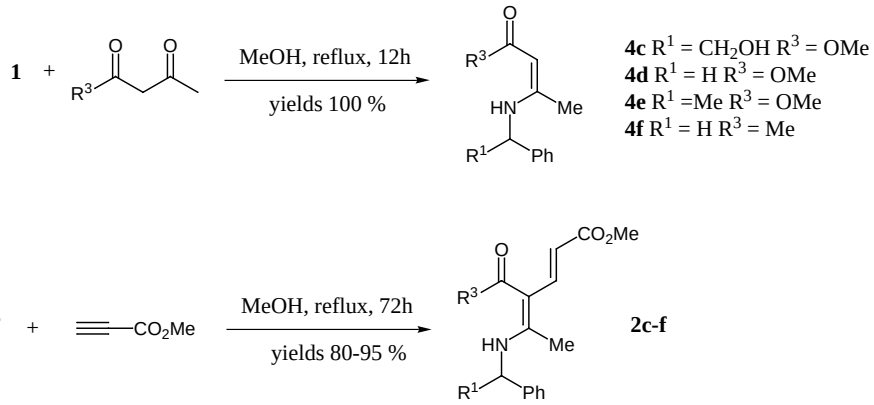
Entry	R^1	R^2	R^3	Products	Yield (%)
1	H	H	OMe	**3a**	51
2	Me	H	OMe	**3b**	5
3	CH_2OH	Me	OMe	**3c**	81
4	H	Me	OMe	**3d**	96
5	Me	Me	OMe	**3e**	89
6	H	Me	Me	**3f**	95

The products were usually obtained as solids.[11] This method gives very good results when R^2 is a methyl group (Table 1, entries 3-6). In contrast, when R^1 and R^2 are hydrogen atoms, pyrrole **3a** is formed in moderate yield (Table 1, entry 1). Moreover, when R^2 = H and when R^1 = Me as in substrate **2b** only traces of pyrrole **3b** could be observed in the ^{1}H NMR spectrum of the crude mixture (Table 1, entry 2). In this case compound **5b** was obtained in good yield.[12]

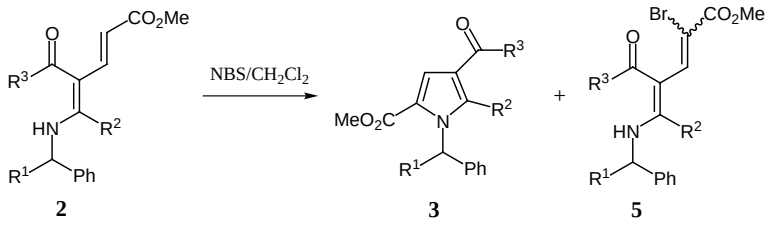


1 **2** **3**

Scheme 1



Scheme 3



Scheme 4

Similar brominated products **5** were detected by ^{1}H NMR as by-products in the reaction of NBS in dichloromethane with all others substrates **2a**,**c-f**. These compounds 5 were not isolated and led slowly (3-24 h) to pyrroles **3a**,**c-f** (Scheme 4).[13]

In order to enhance the yield of formation of pyrrole **2b**, we examined the influence of various solvents on the chemoselectivity of this reaction (Table 2). For this purpose, a solution of δ-enaminoester **2b** in various solvents was added at room temperature to 1.2 equivalent of NBS. Reactions were completed within a period of 5 minutes. The solvents were then evaporated and the ratio of the products **3b** / **5b** were determined by ^{1}H NMR of the crude material.

Table 2 Solvent effect on the reaction of δ-enaminoester 2b with NBS (Scheme 4)

Entry	Solvents	Ratio **3b** / **5b**	Yield(%)[a]
1	CH_2Cl_2	5/95	100
2	$CHCl_3$	<5/95	100
3	THF	<5/95	100
4	DMSO	<5/95	90
5	*t*-BuOH	<5/95	95
6	MeOH	>95/5	100
7	wet DMSO	50/50	85

[a] Combined yields determined by ^{1}H NMR

A dramatic solvent effect has been observed. Product **5b** is formed chemoselectively in all solvents (Table 2, entries 1-5) except in methanol (Table 2, entry 6) which promotes the exclusive formation of pyrrole **3b**; a wet DMSO medium (Table 2, entry 7) shows the same effect, albeit to a lesser extent. These results are in agreement with a nucleophilic external addition of the solvent on an intermediate imminium. The resulting α-bromo-δ-aminoester would then cyclize to furnish, after elimination of methanol (Table 2, entry 6) or water (Table 2, entry 7), the expected pyrrole **3b**. Research aimed at elucidating this intriguing question is currently underway.

In summary, it appears that this synthetic two- or three-step sequence starting from commercially avalaible primary amines is straightforward and flexible for the preparation of 2,4-dicarbonylated pyrroles. This procedure does not require harsh reaction conditions or difficult to handle reagents, offers high yields and can be easily scaled up to the preparation of gram quantities of pyrroles.

We currently investigate the use of pyrroles **3b,c,e** in asymmetric synthesis in order to prepare polysubstituted chiral non racemic pyrroles and pyrrolidines.

References and Notes

(1) Yates, F.S. In *Comprehensive Heterocyclic Chemistry*; Boulton, A.J.; McKillop, A., Eds.; Pergamon: Oxford **1984**; *2*, 511. Jones, R.A. In *Pyrroles, Part II, The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*; J. Wiley and Sons, New York **1992**.

(2) Di Santo, R.; Costi, R.; Artico, M.; Massa, S.; Lampis, G.; Deidda, D.; Pompei, R. *Bioorg. Med. Chem. Lett.* **1998**, *6*, 2931. Ragno, R.; Marshall, G.R.; Di Santo, R.; Costi, R.; Massa, S.; Rompei, R.; Artico, M. *Bioorg. Med. Chem. Lett.* **2000**, *8*, 1423.
(3) Knorr, L. *Justus Liebigs Ann. Chem.* **1886**, *236*, 290.
(4) Shiraishi, H.; Nishitani, T.; Nishihara, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron.* **1999**, *55*, 13957. Franc, C.; Denone, F.; Cuisinier, C.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 4555. Liu, J., Yang, Q.; Mak, T.C.; Wong, H.N.C. *J. Org. Chem.* **2000**, *65*, 3587. Katritzky, A.R.; Huang, T.; Voronkov, M.V.; Wang, M.; Kolb, H. *J. Org. Chem.* **2000**, *65*, 8819. Dieter, R.K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283. Fejes, I.; Toke, L.; Blasko, G.; Nyerges, M.; Pak, C. S. *Tetrahedron.* **2000**, *56*, 8545. Aelterman, W.; De Kimpe, N.; Tyvorskii, V.; Kulinkovich, O. *J. Org. Chem.* **2001**, *66*, 53.
(5) Similar β-enaminodiester have already been described with addition of additives: a) Caballero, E.; Madrigal, B.; Medarde, M.; Puebla, P.; Honores, Z. *Ach. Mod. Chem.* **1998**, *135*, 457. b) Khan, M.A.; Adams, H. *Tetrahedron Lett.* **1999**, *40*, 5389.
(6) Stoit, A.R.; Pandit, U.K. *Tetrahedron* **1988**, *44*, 6187. Compound **2a** was already described. Lee, C-H.; Kohn, H. *J.Heterocycl.Chem.* **1990**, 2107.
(7) General Procedure for the Synthesis of δ-Enaminoesters **2c-e**. To a solution of amines **1** (10 mmol) in MeOH (50 mL) was added methyl acetoacetate (12 mmol). The reaction was refluxed for 6 h and then allowed to reach room temperature. At this stage, methyl propiolate (20 mmol) was added and the mixture refluxed for 2 days. After evaporation of the solvent, the residue was recrystallized in MeOH. δ-Enaminoesters **2c-e** were obtained as white solids. Selected data for compound **2d**. mp: 106 °C. ^{1}H NMR (250 MHz, $CDCl_3$) 2.26 (s, 3H), 3.73 (s, 3H), 3.78 (s, 3H), 4.57 (d, *J* = 6Hz, 2H), 6.10 (d, *J* = 15.7Hz, 1H), 7.31 (m, 5H), 7.76 (d, *J* = 15.7Hz 1H), 10.9 (lt, NH). ^{13}C NMR (63 MHz, $CDCl_3$) 16.1, 47.8, 50.8, 50.9, 93.8, 110.1, 126.8, 127.8, 129.0, 137.0, 140.6, 166.4, 169.8, 170.8.
(8) The introduction of a methyl group on δ-enaminoester **2** was not possible. Treatment of β-enaminoester **4** with an excess of ethyl butynoate left the starting material unchanged.
(9) The *Z*-configuration of the double bond in dichloromethane is assumed on grounds of earlier work, see ref 6. Moreover, in a solvent such as DMSO, which is known to break intramolecular hydrogen bonds, we have observed for δ-enaminoester **2b** a mixture of the two *Z*- and *E*-diastereoisomers (ratio *Z*/*E* = 77/23).
(10) General procedure for the synthesis of pyrroles **3a,c-f**. To a solution of δ-enaminoester **2a,c-f** (1 mmol) in dichloromethane (10 mL) at 0 °C was added portion wise *N*-bromosuccinimide (1.2 mmol). After 15 min at this temperature the solvent was evaporated and the crude mixture purified by chromatography on silica gel.
(11) Selected data for compound **3d**. ^{1}H NMR (250 MHz, $CDCl_3$) 2.52 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 5.67 (s, 2H), 6.94 (m, 2H), 7.28 (m, 3H), 7.45 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) 11.3, 48.1, 51.0, 51.2, 112.7, 119.7, 121.4, 125.8, 127.3, 128.7, 137.0, 142.4, 162.0, 165.6. mp: 97 °C. MS: m/e (relative intensity) 287 (70%), 255 (26%), 196 (12%), 91 (100%). IR (chloroform) 1697, 1555, 1493 cm^{-1}. Anal. Calcd. For $C_{16}H_{17}NO_4$ C, 66.89; H, 5.96; N, 4.88. Found C, 66.78; H, 6.10; N, 4.72.
(12) Selected data for compound **5b**. mp: 83 °C. ^{1}H NMR (250 MHz, $CDCl_3$) 3.75 (s, 3H), 3.82 (s, 3H), 4.52 (d, *J* = 5.7Hz, 2H), 7.35 (m, 5H), 8.30 (s, 1H), 8.61 (d, *J* = 13.5Hz, 1H) 9.53 (m, NH). ^{13}C NMR (63 MHz, $CDCl_3$) 51.2, 53.0, 53.4, 92.6, 100.7, 127.5, 128.2, 129.0, 136.4, 137.4, 155.6, 164.5, 169.2.
(13) The ratio **3c-f**/**5c-f** were determined by ^{1}H NMR measurements of the crude material. The ratios **3c-f**/**5c-f** are > 9/1. Compounds **5c-f** were quantitatively transformed into pyrroles **3c-f** within 24 hours at room temperature in $CDCl_3$.

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