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Synthesis of highly functionalized pyrroles from primary amines and activated acetylenes in water

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Abstract

Stable derivatives of pyrroles were prepared using multicomponent reactions of dialkyl acetylenedicarboxylate, primary amine and propiolate in the presence of *N*-methylimidazole in water at room temperature in good yields.

Keywords: Propiolate; Dialkyl acetylenedicarboxilates; Multicomponent reactions; *N*-methylimidazole

Water is an ideal solvent and reagent for biochemical transformations. In the past, water was not used as a solvent for synthetic organic chemistry due to the poor solubility and, in some cases, the instability of organic reagents in aqueous solutions. Now, it has been recognized that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents and often the insolubility of the final products facilitates their isolation [1,2]. Five-membered, nitrogen-containing heterocycles, such as pyrroles are important building blocks in an extensive number of biologically active compounds [3]. Pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes [4]. Polysubstituted pyrroles are molecular frameworks having immense importance in material science [5]. They have been also employed as antioxidants, antibacterial, ionotropic, antitumor, anti-inflammatory, and antifungal agents [6]. Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry [7,8]. Herein, we examined the reaction between primary alkylamine, dimethyl acetylenedicarboxylate and propiolate in the presence of catalytic amount of *N*-methylimidazole in water at room temperature. The reaction proceeded smoothly to give pyrrole derivatives **4** in good yield (Scheme 1).

The structures of compounds **4a–g** were deduced from their IR, ^{1}H and ^{13}C NMR spectra [9]. The mass spectra of these compounds displayed the molecular ion peaks at the appropriate *m/z* values. The ^{1}H and ^{13}C NMR spectroscopic data, as well as IR spectra, were in agreement with the proposed structures. For example, the ^{1}H NMR spectrum of **4a** in $CDCl_3$ exhibited five sharp singlets readily recognized as arising from methoxy (δ 3.72, 3.80, 3.92), methyl (δ 3.85), and vinyl (δ 6.78) protons. The ^{13}C NMR spectrum of **4a** exhibited 11 signals in agreement with the proposed

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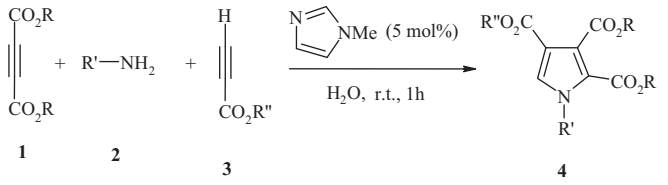
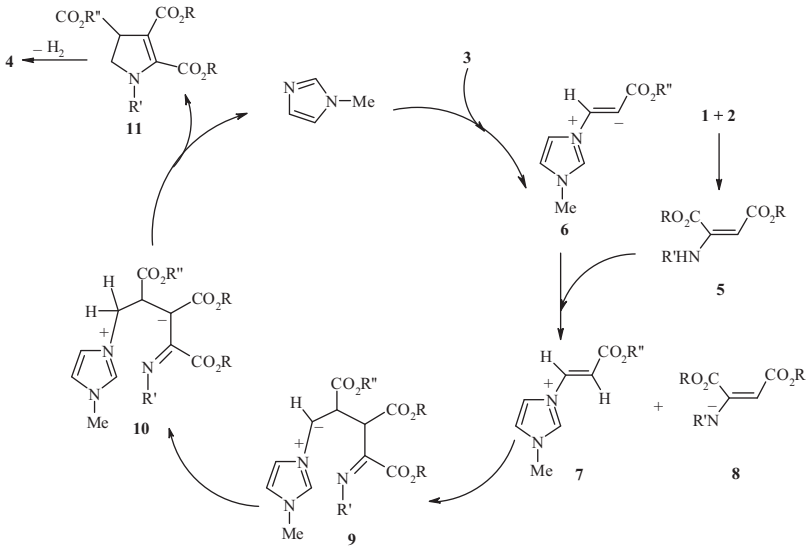


1, 2, 3, 4	R	R'	R"	Yield (%) of **4**
a	Me	Me	Me	80
b	Et	Me	Et	75
c	Me	Et	Me	78
d	Et	Et	Et	70
e	Me	Bn	Me	87
f	Me	4-Me$C_6H_4CH_2$	Me	85
g	Me	4-MeO$C_6H_4CH_2$	Me	80

Scheme 1.



Scheme 2.

structure. Presumably, the zwitterionic intermediate **6**, formed from *N*-methylimidazole and propiolate **3**, is protonated by the enaminoester **5**, generated in situ from primary amine **2** and acetylenic ester **1**, to produce intermediates **7** and **8** (Scheme 2). Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9**, which undergoes proton shifts to afford new zwitterionic intermediate **10**. Finally, intramolecular cyclization affords **11** by elimination of *N*-methylimidazole, which is converted into **4** by elimination of hydrogen [10].

In summary, we have developed a simple, one-pot synthesis of highly functionalized pyrroles from reactions of primary amines with acetylenic esters in the presence *N*-methylimidazole in water at room temperature. Short reaction times, readily available starting materials and water as the green solvent are the main advantages of this methodology.

References

[1] P.A. Grieco, Organic Synthesis in Water, Blackie Academic & Professional, Glasgow, 1998.
[2] P. Anastas, T.C. Williamson, Green Chemistry Frontiers in Benign Chemical Synthesis and Processes, Oxford University Press, New York, 1998
[3] (a) G.W. Gribble, J. Chem. Soc. Perkin Trans. 1 (2000) 1045;
(b) G.W. Gribble, J. Chem. Soc. Perkin Trans. 1 (1998) 615;
(c) A. Nobuyoshi, O. Akihiko, M. Chikara, et al. J. Med. Chem. 42 (1999) 2946;

(d) P.S. Baran, J.M. Richter, D.W. Lin, Angew. Chem. Int. Ed. 44 (2005) 609;
(e) M. Torok, M. Abid, S.C. Mhadgut, B. Torok, Biochemistry 45 (2006) 5377.

[4] R.J. Sundberg, in: A. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry, vol. 2, Pergamon, Oxford, 1996, p. 119.

[5] (a) M. Baumgarten, N. Tyutyulkov, Chem. Eur. J. 4 (1998) 987;
(b) A. Deronzier, J.C. Moutet, Curr. Top. Electrochem. 3 (1994) 159;
(c) G.A. Pagani, Heterocycles 37 (1994) 2069.

[6] (a) J. Lehuede, B. Fauconneau, L. Barrier, et al. Eur. J. Med. Chem. 34 (1999) 991;
(b) R.W. Burli, D. McMinn, J.A. Kaizerman, et al. Bioorg. Med. Chem. Lett. 14 (2004) 1253;
(c) R.W. Burli, P. Jones, D. McMinn, et al. Bioorg. Med. Chem. Lett. 14 (2004) 1259;
(d) R. Jonas, M. Klockow, I. Lues, et al. Eur. J. Med. Chem. 28 (1993) 129.

[7] D.L. Boger, C.W. Boyce, M.A. Labrili, et al. J. Am. Chem. Soc. 121 (1999) 54.

[8] C.M. Sharland, J. Singkhonrat, M.N. Ullah, et al. Tetrahedron Lett. 52 (2011) 2320.

[9] *General procedure for preparation of compounds **4a**–**g***. To a stirred solution of amine **2** (2 mmol) and acetylenic esters **1** (2 mmol) in water (5 mL), was added propiolate **3** (2 mmol) and *N*-methylimidazole (0.1 mmol) at r.t. After completion of the reaction [1 h; TLC (AcOEt/hexane 1:5) monitoring], the mixture of reaction was purified by preparative TLC on silica gel column chromatography (Merck 230-400 mesh) using *n*-hexane-EtOAc as eluent to give compound **4**. *Trimethyl 1-methyl-1H-pyrrole-2,3,4-tricarboxylate (**4a**)*. Yellow oil; yield: 0.41 g (80%). IR (KBr, cm^{-1}): 1720, 1587, 1454, 1256. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.72 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.85 (s, 3H, NMe), 3.92 (s, 3H, MeO), 6.78 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 38.2 (NMe), 52.2 (MeO), 52.8 (MeO), 53.4 (MeO), 108.2 (C), 130.2 (C), 134.2 (CH), 147.2 (C), 165.2 (C═O), 165.6 (C═O), 166.0 (C═O). MS *m/z*: 255 (M^+, 15), 240 (68), 224 (88), 31 (100). Anal. Calcd. for $C_{11}H_{13}NO_6$ (255.22): C, 51.77; H, 5.13; N, 5.49. Found: C, 51.85; H, 5.24; N, 5.58. *Triethyl 1-methyl-1H-pyrrole-2,3,4-tricarboxylate (**4b**)*. Yellow oil; yield: 0.45 g (75%). IR (KBr, cm^{-1}): 1727, 1547, 1485, 1372, 1264. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.12 (t, 3H, ^3J = 7.2 Hz, Me), 1.32 (t, 3H, ^3J = 7.3 Hz, Me), 1.42 (t, 3H, ^3J = 7.2 Hz, Me), 3.86 (s, 3H, NMe), 4.12 (q, 2H, ^3J = 7.2 Hz, CH_2O), 4.25 (q, 2H, ^3J = 7.2 Hz, CH_2O), 4.32 (q, 2H, ^3J = 7.2 Hz, CH_2O), 6.85 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (Me), 14.2 (Me), 14.5 (Me), 37.8 (NMe), 62.4 (CH_2O), 63.0 (CH_2O), 63.4 (CH_2O), 107.8 (C), 131.0 (C), 135.4 (CH), 148.2 (C), 165.2 (C═O), 165.5 (C═O), 165.8 (C═O). MS *m/z*: 297 (M^+, 20), 282 (46), 252 (82), 45 (100). Anal. Calcd. for $C_{14}H_{19}NO_6$ (297.30): C, 56.56; H, 6.44; N, 4.71. Found: C, 56.67; H, 6.52; N, 4.78. *Trimethyl 1-ethyl-1H-pyrrole-2,3,4-tricarboxylate (**4c**)*. Pale yellow oil; yield: 0.42 g (78%). IR (KBr, cm^{-1}): 1735, 1547, 1474, 1367, 1263, 1195. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.24 (t, 3H, ^3J = 7.2 Hz, Me), 3.75 (s, 3H, MeO), 3.84 (q, 2H, ^3J = 7.2 Hz, CH_2), 3.87 (s, 3H, MeO), 3.93 (s, 3H, MeO), 6.87 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 42.0 (CH_2N), 52.3 (MeO), 53.4 (MeO), 53.7 (MeO), 108.6 (C), 124.5 (CH), 129.6 (C), 147.8 (C), 163.4 (C═O), 163.7 (C═O), 164.2 (C═O). Anal. Calcd. for $C_{12}H_{15}NO_6$ (269.25): C, 53.53; H, 5.62; N, 5.20. Found: C, 53.64; H, 5.73; N, 5.28. *Triethyl 1-ethyl-1H-pyrrole-2,3,4-tricarboxylate (**4d**)*. Yellow oil; yield: 0.44 g (70%). IR (KBr, cm^{-1}): 1722, 1567, 1456, 1382, 1247. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.14 (t, 3H, ^3J = 7.4 Hz, Me), 1.18 (t, 3H, ^3J = 7.2 Hz, Me), 1.27 (t, 3H, ^3J = 7.5 Hz, Me), 1.37 (t, 3H, ^3J = 7.2 Hz, Me), 3.85 (q, 2H, ^3J = 7.2 Hz, CH_2N), 4.10 (q, 2H, ^3J = 7.4 Hz, CH_2O), 4.26 (q, 2H, ^3J = 7.5 Hz, CH_2O), 4.34 (q, 2H, ^3J = 7.5 Hz, CH_2O), 6.80 (s, 1H, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.9 (Me), 14.0 (Me), 14.3 (Me), 14.6 (Me), 38.9 (NCH_2), 62.2 (CH_2O), 62.8 (CH_2O), 63.5 (CH_2O), 108.2 (C), 126.4 (CH), 130.4 (C), 148.5 (C), 161.2 (C═O), 161.5 (C═O), 162.2 (C═O). Anal. Calcd. for $C_{15}H_{21}NO_6$ (311.33): C, 57.87; H, 6.80; N, 4.50. Found: C, 57.76; H, 6.72; N, 4.39. *Trimethyl 1-benzyl-1H-pyrrole-2,3,4-tricarboxylate (**4e**)*. Pale yellow oil; yield: 0.57 g (87%). IR (KBr, cm^{-1}): 1732, 1684, 1558, 1467, 1394, 1268. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.75 (s, 3H, MeO), 3.83 (s, 3H, MeO), 3.90 (s, 3H, MeO), 5.32 (2H, s, CH_2N), 6.84 (s, 1H, CH), 7.22 (d, 2H, ^3J = 7.2 Hz, 2CH), 7.32–7.36 (m, 3H, 3CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 48.7 (CH_2N), 52.6 (MeO), 53.2 (MeO), 53.5 (MeO), 108.2 (C), 121.4 (CH), 127.2 (C), 127.8 (2CH), 128.6 (CH), 129.4 (2CH), 135.4 (C), 145.3 (C), 163.2 (C═O), 164.3 (C═O), 164.6 (C═O). Anal. Calcd. for $C_{17}H_{17}NO_6$ (331.32): C, 61.63; H, 5.17; N, 4.23. Found: C, 61.72; H, 5.24; N, 4.30. *Trimethyl 1-(4-methylbenzyl)-1H-pyrrole-2,3,4-tricarboxylate (**4f**)*. Yellow oil; yield: 0.59 g (85%). IR (KBr, cm^{-1}): 1728, 1678, 1536, 1458, 1385, 1265. ^1H NMR (500.1 MHz, $CDCl_3$): δ 2.45 (s, 3H, Me), 3.72 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.87 (s, 3H, MeO), 5.34 (s, 2H, CH_2N), 6.87 (s, 1H, CH), 7.28 (d, 2H, ^3J = 7.6 Hz, 2CH), 7.34 (d, 2H, ^3J = 7.6 Hz, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 23.4 (Me), 48.5 (CH_2N), 52.4 (MeO), 52.8 (MeO), 53.2 (MeO), 108.2 (C), 121.5 (CH), 127.6 (C), 128.2 (2CH), 128.7 (2CH), 132.4 (C), 137.6 (C), 147.2 (C), 163.4 (C═O), 164.6 (C═O), 165.2 (C═O). Anal. Calcd. for $C_{18}H_{19}NO_6$ (345.35): C, 62.60; H, 5.55; N, 4.06. Found: C, 62.73; H, 5.64; N, 4.17. *Trimethyl 1-(4-methoxybenzyl)-1H-pyrrole-2,3,4-tricarboxylate (**4g**)*. Yellow oil; yield: 0.58 g (80%). IR (KBr, cm^{-1}): 1735, 1686, 1557, 1462, 1423, 1274. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.74 (s, 3H, MeO), 3.82 (s, 3H, MeO), 3.88 (s, 3H, MeO), 3.93 (s, 3H, MeO), 5.30 (s, 2H, CH_2N), 6.87 (s, 1H, CH), 7.32 (d, 2H, ^3J = 7.6, 2CH), 7.78 (d, 2H, ^3J = 7.6, 2CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 49.2 (CH_2N), 52.2 (MeO), 52.7 (MeO), 53.4 (MeO), 54.6 (MeO), 108.5 (C), 115.4 (2CH), 121.6 (CH), 127.3 (C), 133.4 (2CH), 134.3 (C), 146.4 (C), 158.2 (C), 163.4 (C═O), 163.8 (C═O), 164.5 (C═O). Anal. Calcd. for $C_{18}H_{19}NO_7$ (361.35): C, 59.83; H, 5.30; N, 3.88. Found: C, 59.75; H, 5.23; N, 3.79.

[10] I. Yavari, Z.S. Hossaini, M. Sabbaghan, Tetrahedron Lett. 47 (2006) 6037.