Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 1219–1222
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

A solvent-free synthesis of 1,2,3,5-tetrasubstituted pyrroles from enaminones and α-haloketones

Issa Yavari *, Maryam Ghazvini, Leila Azad, Tayebeh Sanaeishoar

Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran

Received 3 March 2011
Available online 18 July 2011

Abstract

A simple synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives from the reaction of enaminone with α-haloketones, under solvent-free conditions, is described.

Keywords: 1*H*-Pyrrole; Enaminone; α-Haloketone; 1,3-Dicarbonyl compound; Solvent-free

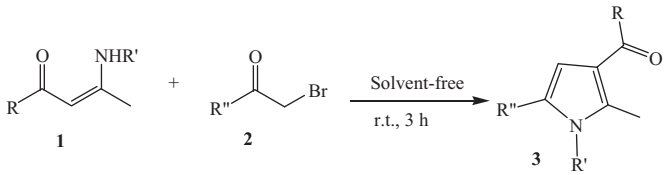
Simple *N*-heterocycles received considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores [1]. Of these heterocycles, the synthesis, reactions, and biological activities of pyrrole derivatives stand as an area of research in heteroaromatic chemistry, and this structural motif appears in a large number of pharmaceutical agents and natural products [2]. Accordingly, many strategies have been developed for the preparation of pyrroles [3–7]. Despite these new developments, the classical Paal-Knorr [8] reaction remains the most attractive method for the synthesis of pyrroles [9]. Enaminones were employed in several new preparations of the pyrrole derivatives [9,10]. As a part of our current studies on the development of new routes in pyrrole synthesis [10–14], we wish to report a convenient catalyst-free synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives from the reaction of enaminone with α-haloketones, under solvent-free conditions (Scheme 1).

1. Experimental

Enaminones **1** were prepared by known methods [15] and α-haloketones **2** were obtained from Merck; IR spectra: Shimadzu IR-460 spectrometer; ^{1}H- and ^{13}C NMR spectra: Bruker DRX-300AVANC instrument; in $CDCl_3$ at 300 MHz and 75 MHz, respectively, *(* in ppm *J* in Hz; EI-MS (70 eV): Finningan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer.

* Corresponding author.
E-mail address: yavarisa@modares.ac.ir (I. Yavari).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2011.05.026



	R	R'	R"	Yiled (%) of **3**
a	OEt	*n*-Bu	4-Br-C_6H_4	89.2
b	OEt	*n*-Bu	CO_2Et	91.0
c	OEt	*n*-Bu	4-MeO-C_6H_4	93.4
d	OEt	*c*-Hexyl	CO_2Et	88.2
e	OEt	*c*-Hexyl	4-MeO-C_6H_4	85.0
f	OEt	*c*-Hexyl	4-Br-C_6H_4	74.1
g	OEt	Bn	CO_2Et	94.3
h	OEt	Bn	4-MeO-C_6H_4	65.3
i	OEt	Bn	4-Br-C_6H_4	83.2
j	Me	Bn	CO_2Et	71.1
k	Me	Bn	4-MeO-C_6H_4	69.0
l	Me	Bn	4-Br-C_6H_4	76.1

Scheme 1.

*1.1. Typical procedure for the preparation of compounds **3***

A mixture of enaminone **1** (2 mmol) and the α-haloketone **2** (2 mmol) was stirred at r.t. After completion of the reaction (about 3 h); TLC (AcOEt/hexane 2:1)], the reaction mixture was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/AcOEt 4:1].

*1.1.1. Ethyl 5-(4-bromophenyl)-1-butyl-2-methyl-1H-pyrrole-3-carboxylate (**3a**)*

Pale yellow oil; 0.66 g (89.2%). IR: 1689, 1429, 1388, 1270 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, J = 7.3 Hz, Me), 1.16 (m, 2H, CH_2), 1.35 (t, 3H, J = 7.1 Hz, Me), 1.51 (m, 2H, CH_2), 2.61 (s, 3H, Me), 3.84 (t, 2H, J = 7.7 Hz, CH_2N), 4.28 (q, 2H, J = 7.1 Hz, CH_2O), 6.55 (s, 1H, CH), 7.22 (d, 2H, J = 7.7 Hz, 2 CH), 7.53 (d, 2H, J = 7.7 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (Me), 13.9 (Me), 14.9 (Me), 20.1 (CH_2), 33.1 (CH_2), 44.3 (CH_2N), 59.7 (CH_2O), 110.5 (CH), 112.5 (C), 121.9 (C), 131.2 (2 CH), 132.0 (2 CH), 132.5 (C), 134.1 (C), 137.1 (C), 165.9 (CO). MS (EI, 70 eV): *m/z* (%) 365 (M^++2, 10), 363 (M^+, 9), 336 (23), 334 (100), 322 (20), 320 (17). Anal. Calcd. for $C_{18}H_{22}BrNO_2$ (364.28): C, 59.35; H, 6.09; N, 3.85%. Found: C, 59.68; H, 6.13; N, 3.69%.

*1.1.2. Diethyl 1-butyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3b**)*

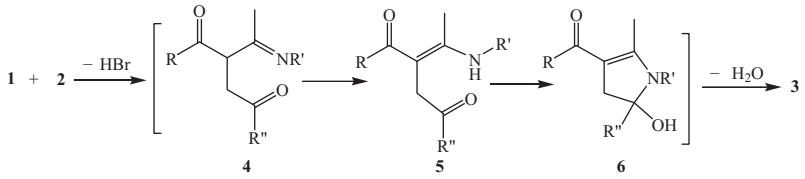
Yellow oil; 0.51 g (91.0%). IR: 1691, 1401, 1393, 1289 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, J = 7.3 Hz, Me), 1.32 (m, 8H, 2 Me, CH_2), 1.68 (m, 2H, CH_2), 2.38 (s, 3H, Me), 3.79 (t, 2H, J = 7.2 Hz, CH_2N), 4.28 (m, 4H, 2 CH_2O), 7.10 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1 (Me), 14.0 (Me), 14.6 (Me), 14.7 (Me), 20.1 (CH_2), 33.0 (CH_2), 47.2 (CH_2N), 60.4 (CH_2O), 60.6 (CH_2O), 113.6 (C), 115.3 (C), 126.1 (CH), 134.9 (C), 164.6 (CO), 165.9 (CO). MS (EI, 70 eV): *m/z* (%) 281 (M^+, 7), 252 (100), 238 (19). Anal. Calcd. for $C_{15}H_{23}NO_4$ (281.35): C, 64.03; H, 8.24; N, 4.98%. Found: C, 63.88; H, 8.11; N, 4.89%.

*1.1.3. Ethyl 1-butyl-5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (**3c**)*

Yellow oil; 0.58 g (93.4%). IR: 1697, 1373, 1244, 1189 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, 3H, J = 7.2 Hz, Me), 1.17 (m, 2H, CH_2), 1.35 (t, 3H, J = 7.1 Hz, Me), 1.51 (m, 2H, CH_2), 2.66 (s, 3H, Me), 3.83 (m, 2H, CH_2N), 3.86 (s, 3H, MeO), 4.72 (q, 2H, ^3J 7.1, CH_2O), 6.49 (s, 1H, CH), 6.94 (d, 2H, ^3J 8.6, 2 CH), 7.26 (d, 2H, ^3J 8.6, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (Me), 13.9 (Me), 14.9 (Me), 20.1 (CH_2), 33.1 (CH_2), 44.2 (CH_2N), 55.6 (MeO), 56.9 (CH_2O), 109.6 (CH), 112.0 (C), 114.2 (2 CH), 126.0 (C), 131.1 (2 CH), 133.5 (C), 136.3 (C), 159.4 (C), 166.1 (CO). MS (EI, 70 eV): *m/z* (%) 315 (M^+, 11), 286 (100), 272 (22). Anal. Calcd. for $C_{19}H_{25}NO_3$ (315.41): C, 72.35; H, 7.99; N, 4.44%. Found: C, 71.88; H, 7.86; N, 4.39%.

*1.1.4. Diethyl 1-cyclohexyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3d**)*

Yellow oil; 0.54 g (88.2%). IR: 1681, 1311, 1265, 1209 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33–1.35 (m, 6H, 2 Me), 1.27–2.00 (m, 10H, 5 CH_2), 2.04 (s, 3H, Me), 3.66 (m, 1H, CHN), 4.28–4.62 (m, 4H, 2 CH_2O), 7.28 (s. 1H, CH).



Scheme 2.

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (Me), 14.0 (Me), 14.3 (Me), 24.9 (CH_2), 29.3 (2 CH_2), 31.1(2 CH_2), 54.4 (CH_2O), 55.1 (CH_2O), 57.8 (CHN), 112.2 (C), 115.9 (C), 126.1 (CH), 133.9 (C), 164.6 (CO), 165.9 (CO). MS (EI, 70 eV): *m/z* (%) 307 (M^+, 12), 224 (100). Anal. Calcd. for $C_{17}H_{25}NO_4$ (307.38): C, 66.43; H, 8.20; N, 4.56%. Found: C, 66.88; H, 8.09; N, 4.51%.

*1.1.5. Ethyl 1-cyclohexyl-5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (**3e**)*

Yellow oil; 0.58 g (85.0%). IR: 1700, 1319, 1255, 1222 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–2.07 (m, 10H, 5 CH_2), 1.26 (t, 3H, J = 7.1 Hz, Me), 2.71 (s, 3H, Me), 3.72 (m, 1H, CHN), 3.91 (s, 3H, MeO), 4.12 (q, 2H, J = 7.1 Hz, CH_2O), 6.31 (s, 1H, CH), 6.98 (d, 2H, J = 8.8 Hz, 2 CH), 7.23 (d, 2H, J = 8.8 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (Me), 14.4 (Me), 25.4 (CH_2), 26.5 (2 CH_2), 32.4 (2 CH_2), 55.0 (MeO), 57.7 (CH_2O), 58.8 (CHN), 110.1 (CH), 112.5 (C), 113.9 (2 CH), 131.0 (C), 131.7 (2 CH), 132.4 (C), 135.7 (C), 159.8 (C), 165.2 (CO). MS (EI, 70 eV): *m/z* (%) 341 (M^+, 8), 258 (100). Anal. Calcd. for $C_{21}H_{27}NO_3$ (341.44): C, 73.87; H, 7.97; N, 4.10%. Found: C, 73.58; H, 8.09; N, 3.96%.

*1.1.6. Ethyl 5-(4-bromophenyl)-1-cyclohexyl-2-methyl-1H-pyrrole-3-carboxylate (**3f**)*

Yellow oil; 0.57 g (74.1%). IR: 1717, 1345, 1258, 1227 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14–2.07 (m, 10H, 5 CH_2), 1.24 (t, 3H, J = 7.1 Hz, Me), 2.73 (s, 3H, Me), 4.10 (m, 1H, CHN), 4.21 (q, 2H, J = 7.1 Hz, CH_2O), 6.40 (s, 1H, CH), 7.31 (d, 2H, J = 8.3, 2 CH), 7.63 (d, 2H, J = 8.3 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (Me), 14.3 (Me), 25.4 (CH_2), 26.4 (2 CH_2), 32.4 (2 CH_2), 58.0 (CH_2O), 58.9 (CHN), 110.8 (CH), 112.9 (C), 121.6 (C), 131.8 (2 CH), 132.1 (2 CH), 132.8 (C), 135.1 (C), 136.7 (C), 165.0 (CO). MS (EI, 70 eV): *m/z* (%) 391 (M^++2, 10), 389 (M^+, 9), 308 (100), 306 (23). Anal. Calcd. for $C_{20}H_{24}BrNO_2$ (390.31): C, 61.54; H, 6.20; N, 3.59%. Found: C, 62.05; H, 6.41; N, 3.64%.

2. Results and discussion

The reaction of enaminones (**1**) and α-haloketones (**2**) proceeds at room temperature after 12 h to produces (**3**) in good yields (Scheme 1). The structures of compounds (**3a–3l**) were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ showed one singlet for methyl (δ 2.61), together with characteristic multiplets for the butyl ethoxy groups, one singlet signal (δ 6.55) for methine and two doublet (δ 7.22, 7.53) for the aromatic proton. The ^{13}C NMR spectrum of **3a** showed 16 signals in agreement with the proposed structure. Partial assignments of these resonances are given in Section 1. The ^{1}H- and ^{13}C NMR spectra of **3b–3l** are similar to those of **3a** except for the alkyl and aryl substituents, which exhibit characteristic signals in the appropriate regions of the NMR spectra.

A plausible rationalization may be advanced to explain the product formation (Scheme 2). Presumably, the enaminone **1** attacks α-haloketones **2** and undergoes HBr elimination to produce **4**. Elimination of water from intermediate **6** leads to product **3**.

In conclusion, we report a simple synthesis of 1,2,3,5-tetrasubstituted pyrroles from the reaction of enaminone with α-haloketones, under solvent-free conditions. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The procedure described here provides an acceptable method for the preparation of new derivatives of 1*H*-pyrrole.

References

[1] G.W. Gribble, in: A.R. Katrizky, C.W. Ree, E.F. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol. 2, Elsevier, Oxford, 1996, p. 207.

[2] G.P. Bean, in: R.A. Jones (Ed.), Pyrroles, Part II, The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles, Wiley, New York, 1990, p. 105.
[3] T.L. Gilchrist, J. Chem. Soc., Perkin Trans. 1 (2001) 2491.
[4] H.S.P. Rao, S. Jothilingam, Tetrahedron Lett. 42 (2001) 6595.
[5] H. Xue, T. Ma, L. Wang, G. Liu, Chin. Chem. Lett. 21 (2010) 1291.
[6] B. Zuo, J.X. Chen, M.C. Liu, et al. Chin. Chem. Lett. 20 (2009) 423.
[7] S.Z. Yuan, J. Liu, L. Xu, Chin. Chem. Lett. 21 (2010) 664.
[8] R.J. Sundberg, in: A.R. Katrizky, C.W. Ree, E.F. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, Pergamon Press, Oxford, 1996, p. 149.
[9] G. Kaupp, J. Schmeyers, A. Kuse, et al. Angew. Chem. Int. Ed. Engl. 38 (1999) 2896.
[10] I. Yavari, M. Anary-Abbasinejad, F. Nasiri, et al. Mol. Divers 9 (2005) 209.
[11] I. Yavari, M. Sabbaghan, Synthetic Commun. 37 (2007) 1791.
[12] I. Yavari, H. Djahaniani, Tetrahedron Lett. 47 (2006) 2953.
[13] I. Yavari, E. Kowsari, Synlett (2008) 897.
[14] I. Yavari, Z. Hossaini, M. Sabbaghan, Tetrahedron Lett. 49 (2008) 844.
[15] A.R. Khosropour, M.M. Khodaei, M. Kookhazadeh, Tetrahedron Lett. 45 (2004) 1725.