Bulgarian Chemical Communications, Volume 47, Number 1 (pp. 664 – 666) 2015

Multicomponent reactions of diethyl oxalate: synthesis of pyrrole derivatives in water

F. Sheikholeslami-Farahani*

Department of Chemistry, Firoozkooh Branch, Islamic Azad University, Firoozkooh, Iran

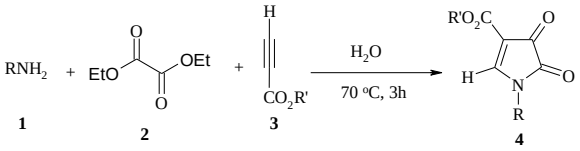
Received February 13, 2014; Revised July 21, 2014

An expert tactic for the preparation of 1H-pyrrole derivatives *via* the reaction between primary amines, alkyl propiolates and diethyl oxalate is described. Particularly, valuable features of this method include high yields of products, short reaction time, and straightforward and convenient procedure. Herein, the synthesis of substituted 1H-pyrrols was reported based on the three-component reaction of diethyl oxalate.

Keywords: Pyrrole, Alkyl propiolate, Oxalyl chloride, Primary amines, Water

INTRODUCTION

At the beginning of the new century, a move in importance in chemistry is obvious with the aim to extend environmentally gentle routes for the synthesis of numerous materials [1]. Green chemistry approaches hold out momentous potential not only for reduction of byproducts and waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies [2, 3]. More than a few biologically active synthetic compounds have five membered nitrogen containing heterocycles in their structures [4]. Among them, pyrroles are heterocycles of great importance because of their presence in frequent natural products similar to heme, chlorophyll, vitamin B12, and various cytochrome enzymes [5]. Some of the recently isolated pyrrole containing marine natural products have been found to display significant cytotoxicity and function as multidrug resistant (MDR) reversal agents [6]. Many of these biologically active compounds have appeared as chemotherapeutic agents. Also, polysubstituted pyrroles are molecular structures having immense importance in material science [7]. They have also been employed as antioxidants [8], antibacterial [9, 10] ionotropic [11, 12] antitumor [13], anti-inflammatory [14, 15] and antifungal agents [16]. Continuing our efforts directed towards the straightforward preparation of biologically active target molecules through multicomponent reactions, we performed the synthesis of some 1*H*-pyrrole derivatives *via* a three-component reaction of diethyl oxalate at 70 ^{o}C in water (Scheme 1).



1,3,4	R	R'	Yield (%) of **4**
a	Bn	Me	85
b	4-Me$C_6H_4CH_2$	Me	80
c	n-Bu	Me	87
d	Et	Et	85
e	^{t}Bu	Et	80

Scheme 1. Synthesis of compound **4**

EXPERIMENTAL

Apparatus and analysis

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. Acetylenic ester, phenacyl bromide, its derivatives and triphenylphosphine were obtained from Fluka and were used without further purification.

General procedure for the preparation of compounds 4a-e: To a stirred mixture of primary amine **1** (2 mmol) and alkyl propiolate **5** (2 mmol) in water (5 mL) diethyl oxalate **2** (2 mmol) was added at 70^{o}C. The reaction mixture was stirred for 3 h. After completion of the reaction [TLC (AcOEt/hexane 1:6) monitoring], the reaction mixture was purified by flash column chromatography on silica gel (Merck

* To whom all correspondence should be sent:
E-mail: sheikholeslamy@yahoo.com

230–400 mesh) using n-hexane–EtOAc as eluent to afford the pure compounds **4**.

Methyl-1-benzyl-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4a). White powder; 172-174 °C, yield 0.44 g (85%) IR (KBr) (ν_{max}/cm^{-1}) = 1738, 1730, 1728, 1675, 1467, 1325 cm^{-1}. MS: *m/z* (%) = 245 (M$^+$, 15), 214 (70), 91 (96), 77 (64), 31 (100),- Anal. Calcd (%) for $C_{13}H_{11}NO_4$ (245.23): C, 63.67; H, 4.52; N, 5.71. Found: C, 63.75; H, 4.63; N, 5.82. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 3.75 (3 H, s, MeO), 4.84 (1 H, d, ^2J = 11.7 Hz, CH), 5.15 (1 H, d, ^2J = 11.7 Hz, CH), 7.12 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.45 (1 H, t, ^3J = 7.8 Hz, CH), 7.68 (2 H, t, ^3J = 7.4 Hz, 2 CH), 8.65 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 47.8 (NCH_2), 52.2 (MeO), 112.2 (C), 128.5 (CH), 129.4 (2 CH), 129.8 (2 CH), 137.5 (C), 147.5 (CH), 162.4 (C=O), 163.5 (C=O), 165.7 (C=O) ppm.

Methyl-1-(4-methylbenzyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4b). White powder, 164-166 °C, yield 0.49 g (80%). IR (KBr) (ν_{max}/cm^{-1}) = 1740, 1737, 1732, 1695, 1672, 1447, 1254, 1175 cm^{-1}. MS: *m/z* (%) = 259 (M$^+$, 10), 153 (65), 105 (100), 77 (64), 31 (100). Anal. Calcd (%) for $C_{14}H_{13}NO_4$ (259.26): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.14; N, 5.53. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 2.30 (3 H, s, Me), 3.84 (3 H, s, MeO), 4.75 (1 H, d, ^2J = 12.4 Hz, CH), 5.23 (1 H, d, ^2J = 12.4 Hz, CH), 7.24 (2 H, d, ^3J = 7.9 Hz, CH), 7.32 (2 H, d, ^3J = 7.9 Hz, 2 CH), 8.74 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 20.7 (Me), 46.4 (NCH_2), 52.3 (MeO), 111.4 (C), 128.5 (2 CH), 128.7 (2 CH), 130.2 (C), 133.5 (C), 161.4 (C=O), 162.3 (C=O), 165.4 (C=O) ppm.

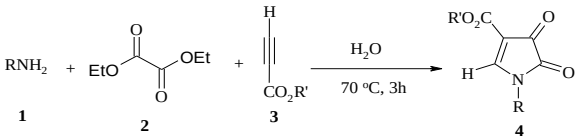
Methyl-1-(butyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4c). White powder; 145-147 °C, yield: 0.63 g (87%). IR (KBr) (ν_{max}/cm^{-1}) = 1742, 1740, 1735, 1694, 1425, 1324, 1236 cm^{-1}. Anal. Calcd (%) for $C_{10}H_{13}NO_4$ (211.22): C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.34; N, 6.73. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 0.92 (3 H, t, ^3J = 7.2 Hz, CH_3), 1.27 (2 H, m, CH_2), 1.43 (2 H, m, CH_2), 3.74 (3 H, s, MeO), 3.82-3.93 (2 H, m, NCH_2), 8.84 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 13.4 (CH_3), 18.7 (CH_2), 28.6 (CH_2), 42.5 (NCH_2), 109.4 (C), 147.3 (CH), 161.2 (C=O), 162.5 (C=O), 164.2 (C=O) ppm.

Ethyl-1-(ethyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4d). White powder; 152-154 °C (decomp.); yield 0.35 g (85%). IR (KBr) (ν_{max}/cm^{-1}) = 1738, 1735, 1728, 1425, 1229 cm^{-1}. Anal. Calcd (%) for $C_9H_{11}NO_4$ (197.19): C, 54.82; H, 5.62; N, 7.10. Found: C, 54.93; H, 5.73; N, 7.18. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.28 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.36 (3 H, t, ^3J = 7.5 Hz, CH_3), 3.68-3.82 (2 H, m, NCH_2), 4.25 (2 H, q, ^3J = 7.5 Hz, CH_2O), 8.74 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 13.4 (CH3), 13.8 (CH_3), 38.4 (NCH_2), 61.4 (CH_2O), 110.4 (C), 146.2 (CH), 161.5 (C=O), 162.3 (C=O), 164.7 (C=O) ppm.

Ethyl-1-(tert-butyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4e). White powder; 148-150 °C, yield 0.43 g (80%). IR (KBr) (ν_{max}/cm^{-1}) = 1745, 1740, 1738, 1462, 1430, 1347, 1232 cm^{-1}. Anal. Calcd (%) for $C_{11}H_{15}NO_4$ (225.24): C, 58.66; H, 6.71; N, 6.22. Found: C, 58.75; H, 6.82; N, 6.34. ^{1}H NMR (500.1 MHz, $CDCl_3$): □□= 1.34 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.48 (9 H, s, Me_3C), 4.23 (2 H, q, ^3J = 7.4 Hz, CH_2O), 8.23 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 13.7 (CH_3), 26.5 (Me_3C), 48.6 (NC), 61.4 (CH_2O), 110.7 (C), 139.8 (CH), 162.9 (C=O), 163.4 (C=O), 165.7 (C=O) ppm.

RESULTS AND DISCUSSION

Three-component reactions between primary amine 1 and diethyl oxalate 2 with alkyl propiolates 3 at 70 °C in water produce 1H-pyrrole derivatives 4 in excellent yields (Scheme 1).



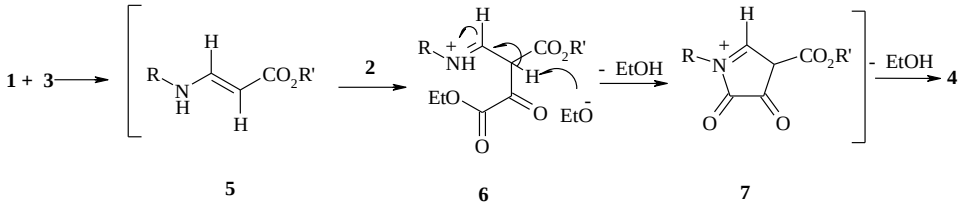
1 **2** **3** **4**

1,3,4	R	R'	Yield (%) of **4**
a	Bn	Me	85
b	4-Me$C_6H_4CH_2$	Me	80
c	n-Bu	Me	87
d	Et	Et	85
e	^{t}Bu	Et	80

Scheme 1. Synthesis of compounds **4**

The structures of compounds **4a–e** were determined on the basis of their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds show molecular ion peaks at the appropriate *m/z* values. Also, the ^{1}H NMR spectrum of **4a** exhibits two singlets at δ = 3.75 and 8.65 ppm for methoxy and methine protons, respectively. Two doublets at δ = 4.84 (d, ^2J = 11.7 Hz) and 5.15 (d, ^2J = 11.7 Hz) for CH_2 protons are registered along with signals for aromatic moiety.

On the basis of the well established chemistry of amine nucleophiles it is reasonable to assume that pyrrole derivatives **4** results from the initial addition



Scheme 2. Proposed mechanism for synthesis of **4**

of primary amines to alkyl propiolate and subsequent attack of the intermediate **5** to compound **2** producing the intermediate **6.** Intramolecular nucleophilic attack of the nitrogen to the carbonyl group in compound **6** generates compound **7** that by elimination of EtOH produces **4** (Scheme 2).

CONCLUSION

In conclusion, we reported a novel method involving primary amines and alkyl propiolates in the presence of diethyl oxalate for the synthesis of 1H-pyrrole derivatives. The advantages of our work are that the reaction is performed in water, without using a catalyst.

Acknowledgment: *This research is supported by the Islamic Azad University, Firoozkooh Branch.*

REFERENCES

1. P. Anastas, T. Williamson, Green Chemistry, Frontiers in Benign Chemical Synthesis and Procedures; Oxford Science Publications: New York, 1998.
2. G. W. V. Cave, C. L. Raston, J. L. Scott, *Chem. Commun*. 2159 (2001).
3. Z. Hossaini, F. Rostami-Charati, R. Hajinasiri, H. Jafaryan, M. Shahraki *Journal of Heterocyclic Chemistry*, **49**, 402 (2012).
4. D. Lednicer, L. A. Mitscher, In Organic Chemistry of Drug Synthesis; Wiley Interscience: New York, **1**, 226 (1977).
5. R. J. Sundberg, In Comprehensive Heterocyclic Chemistry; A. Katritzky, C. W. Rees, E. F. V. Scriven, Eds.; Pergamon: Oxford, **2**, 119 (1996).
6. H. Tao, I. Hwang, D. L. Boger, *Bioorg. Med. Chem. Lett*., **14**, 5979 (2004).
7. (a) M. Baumgarten, N. Tyutyulkov, Chem. Eur. J. 1998, 4, 987-989. (b) G. A. Pagani, *Heterocycles*, **37**, 2069 (1994).
8. J. Lehuede, B. Fauconneau, L. Barrier, M. Ourakow, A. Piriou, J. M. Vierfond, *Eur. J. Med. Chem*. **34**, 991 (1999).
9. R. W. Burli, D. McMinn, J. A. Kaizerman, W. Hu, Y. Ge, Q. Pack, V. Jiang, M. Gross, M. Garcia, R. Tanaka, H. E. Moser, *Bioorg. Med. Chem. Lett*. **14**, 1253 (2004).
10. R. W. Burli, P. Jones, D. McMinn, Q. Le, J. X. Duan, J. A. Kaizerman, S. Difuntorum, H. E. Moser, *Bioorg. Med. Chem. Lett*. **14**, 1259 (2004).
11. R. Jonas, M. Klockow, I. Lues, H. *Pruecher, H. J. Schliep, H. Wurziger, Eur*. J. Med. Chem. **28**, 129-140 (1993).
12. W. Von der Saal, J. P. Hoelck, W. Kampe, A. Mertens, B. *J. Med. Chem*. **32**, 1481-1491(1989).
13. W. A. *Denny, G.W. Rewcastle, B. C. Baguley, J*. Med. Chem. **33**, 814 (1990).
14. E. Toja, D. Selva, P. Schiatti, *J. Med. Chem.* **27**, 610 (1984).
15. V. J. Demopoulos, E. J. Rekka, *J. Pharm. Sci*. **84**,79 (1995).
16. M. Del Poeta, W. A. Schell, C. C. Dykstra, S. Jones, R. R. Tidwell, A. Czarny, M. Bajic, M. Bajic, A. Kumar, D. Boykin, J. R. Perfect, *Antimicrob. Agents Chemother*. **42**, 2495 (1998).

.

МНОГОКОМПОНЕНТНИ РЕАКЦИИ НА ДИЕТИЛ ОКСАЛАТ: СИНТЕЗА НА ПИРОЛОВИ ПРОИЗВОДНИ ВЪВ ВОДА

Ф. Шеикнолеслами-Фарахани

Катедра по химия, клон Фирузкух, Ислямски университет "Азад", Фирузкух, Иран

Постъпила на 13 февруари 2014 г.; коригирана на 21 юли, 2014 г.

(Резюме)

Описана е експертна тактика за получаване на 1H-пирол производни чрез реакция между първични амини, алкилни пропиолати и диетил оксалат. Особено ценните характеристики на този метод включват високи добиви на продукти, кратко реакционно време, ясна и удобао процедура. В тази работа е описана синтеза на заместени 1H-пироли на базата на трикомпонентна реакция на диетил оксалат