I.A.U. Karaj Branch

Journal of Applied Chemical Research, 9, 3, 27-31 (2015)

Journal of Applied Chemical Research
www.jacr.kiau.ac.ir

Three Component Syntheses of Pyrrolo Imidazole Derivatives in the Presence of N-methyl imidazole, Activated Acetylenes and Phenylsulfonylacetophenone

Anvar Mirzaei

Chemistry Department, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran.

(Received 06 Dec. 2014; Final version received 14 Feb. 2015)

Abstract

Because of the significant role in biological processes in living cells and the diverse types of physiological activities, heterocyclic compounds are in focus of intense investigations by academic, industry and applied-oriented chemists. Considerably, ascientific renaissance of heterocycles during the last decades is closely related to the development of multicomponent approaches to their synthesis. Multicomponent methodology is fundamentally different from two-component or sequential processestogether with other innovative synthetic methods like microwave- and ultrasonic assisted reactions offer some new possibilities in constructing heterocyclic systems with high level of molecular diversity and complexity. Among them Imidazoles are quite important reagents in modern heterocyclic chemistry, and their reactions with electrophiles are the most widespread and facile synthetic approach for obtaining diverse heterocyclic systems containing Imidazolemoiety. An interest on these heterocycles is attributed to their known biological activities: analgesics, cardiovascular vasodilators, calcium channel blocking agents, potassium channel inhibitors, apoptosis-inducers, and so on. In this research, N-methyl imidazole reacts smoothly with dialkylacetylenedicarboxylates in the presence of phenylsulfonyl acetone to produce pyrroloimidazole derivatives in good yields.

Keywords: *Pyrrolo imidazole, Phenylsulfonyl acetone, Activated acetylenes, N-methyl imidazole.*

Introduction

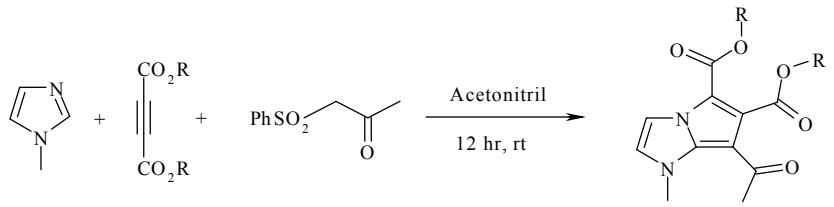
The development of simple synthetic routs for widely used organic compounds from readily available reagents is one of the major tasks

***Corresponding author:** P.O. Box: 618, E-mail: mirzaei.anvar@gmail.com..*

in organic synthesis [1]. Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straight forward reaction design and the opportunity to construct target compounds by the of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple, since all the organic reagents employed are consumed and are incorporated into the target compound. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug like' molecules [2].

In other hand, Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural products, many of which exhibit useful biological activity [3-4]. The reaction of nucleophiles, nitrogen-containing heterocycles in particular, with activated acetylenes has been the subject of significant research [5]. An old example is the interesting reaction between pyridine and dimethyl acetylenedicarboxylate (DMAD) in methanol, in which the corresponding indolizine-1,2,3-tricarboxylate is isolated [6-7]. As part of our current studies on the development of new routes to new heterocyclic systems [8-11], in this letter we describe a simple and efficient synthesis of functionalized 1-*H*-pyrrolo[1,2-*a*]imidazole derivatives.

The reaction of *N*-methyl imidazole (**1**) with dialkylacetylenedicarboxylates (**2**) in the presence of Phenylsulfonylacetophenone (**3**) proceeded smoothly in Acetonitril and was complete within a few hours. The ^{1}H and ^{13}C NMR spectra of the crud products clearly indicated the formation of dialkyl-7-acetyl-1-methyl-1*H*-1-pyrrolo[1,2-*a*] imidazole-5,6-dicarboxylates (**4**) in 80– 89% yields(Scheme **1**).



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

2, 4	R	Yield % of 4
a	Me	89
b	Et	86
c	^{i}Pro	80

Scheme 1. Synthesis of three-functionalized pyrrolo imidazole derivatives.

Experimental

General procedure

All compounds were obtained from Flukaor Merck and were used without further purification.IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C- NMR spectra: Bruker DRX- 500 AVANCE instrument; in $CDCl_3$ at 500, 125 MHz, respectively; δin ppm. Elemental analyses (C, H, N)were performed with a Heraeus CHN-O-Rapid analyser.

*Typical procedure for preparation of (**4**)*

To a stirred solution of **2** (2 mmol) and **3** (2 mmol) in **3** mL MeCN was added N-methyl imidazole (2 mmol) at rt. The reaction mixture was then stirred for 12 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) flash column chromatography using *n*-hexane–EtOAc (8:1) mixture as eluent to get pure product **4**.

*Dimethyl-7-acetyl-1-methyl-1H-1-pyrrolo [1,2-a]imidazole-5,6-dicarboxylates (**4a**)*

Yellow oil, 0.27 g, yield 89%. IR (KBr) (ν_{max}/ cm^{-1}): 1739, 1714, 1703, 1590, 1280, 929, 766, 688. Anal.Calcd for $C_{13}H_{14}N_2O_5$ (278.62): C, 56.11; H, 5.07; N, 10.07%. Found: C, 56.19; H, 5.09; N, 10.35%. ^{1}H NMR: δ 2.25 (3H, s, Me), 3.63 (3H, s, N-Me), 3.85 (3H, s, OMe), 3.96 (3H, s, OMe), 6.95 (1H, d, ^{3}J=3.5 Hz, CH), 7.56 (1 H, ^{3}J=3.5 Hz, 1 CH)ppm. ^{13}C NMR: δ 27.9 (CH_3), 37.5 (N-Me), 52.3 (OMe), 58.8 (OMe), 106.0 (CH), 108.4 (C), 116.6 (C), 127.4 (CH), 128.9 (C), 142.3 (C), 161.5 (C=O), 164.8 (C=O), 196.3 (C=O) ppm.

*Diethyl-7-acetyl-1-methyl-1H-1-pyrrolo [1,2-a] imidazole-5,6-dicarboxylates (**4b**)*

Yellow oil, 0.26 g, yield 86%.IR (KBr) (ν_{max}/ cm^{-1}): 1728, 1716, 1703, 15906, 1284, 1029, 788, 687.Anal.Calcd for $C_{15}H_{18}N_2O_5$ (306.36): C, 58.82; H, 5.92; N, 9.15%. Found: C, 59.01; H, 5.96; N, 9.35%. ^{1}H NMR: δ 1.25 (3H, t, ^{3}J =7.6 Hz, Me), 1.49 (3H, t, ^{3}J =7.2 Hz, Me), 2.31 (3H, s, Me),3.59(3H, s, N-Me), 3.80 (2H, q, ^{3}J =7.6 Hz, OCH2),4.30 (2H, q, ^{3}J =7.2 Hz, OCH_2), 6.98 (1H, d, ^{3}J=3.7 Hz, CH), 7.52 (1 H, ^{3}J=3.7 Hz, 1 CH) ppm. ^{13}C NMR: δ 14.8 (Me), 15.1 (Me), 28.5 (Me), 37.8 (N-Me), 62.1 (OCH_2), 62.5 (OCH_2), 105.4 (CH), 108.6 (C), 116.1 (C), 127.7 (CH), 129.3 (C), 141.4 (C), 160.7 (C=O), 164.6 (C=O), 191.9 (C=O) ppm.

*Diisopropyl-7-acetyl-1-methyl-1H-1-pyrrolo [1,2-a]imidazole-5,6-dicarboxylates (**4c**)*

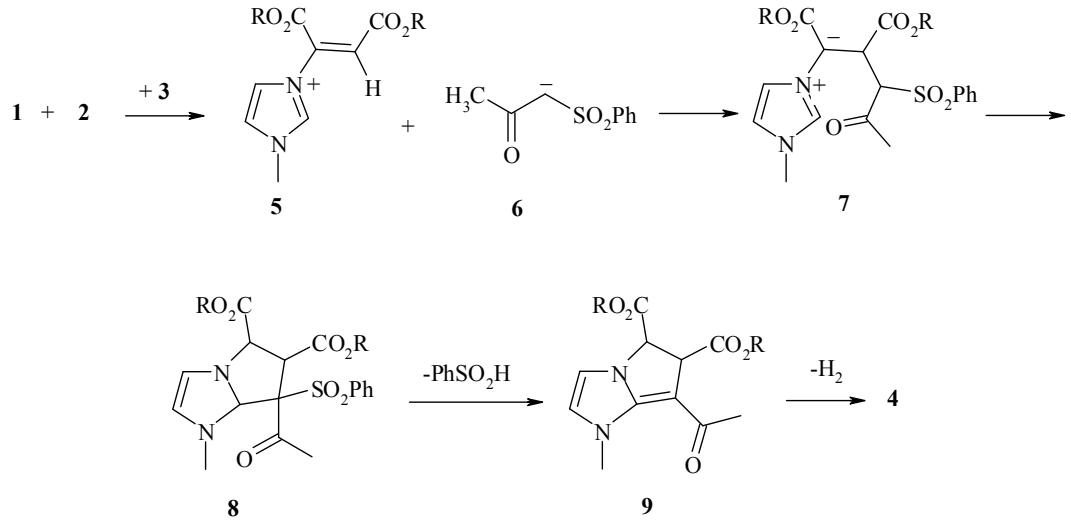
Red oil, 0.26 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 1724, 1711, 1708, 1580, 12910, 945, 785, 676.Anal.Calcd for $C_{17}H_{22}N_2O_5$ (334.37): C, 61.07; H, 6.63; N, 8.38%. Found: C, 61.22; H, 6.69; N, 8.49%. ^{1}HNMR: δ1.22 (6H, d, ^{3}J = 6.9 Hz, 2 CH_3), 1.29 (6H, d, ^{3}J = 6.7 Hz, 2 CH_3), 2.32 (CH_3), 3.51 (3H, s, N-Me), 4.98 (1H, m, CH), 5.09 (1H, m, CH), 7.05 (1H, d, ^{3}J=3.5 Hz, CH), 7.59 (1 H, 3J=3.5 Hz, 1 CH) ppm. ^{13}C NMR*:* δ 21.7 (2 CH_3), 22.78 (2 CH_3),

28. 2 (CH_3), 36.1 (N-Me), 68.9 (CH), 69.3 (CH), 107.1 (CH), 108.9 (C), 116.7 (C), 126.4 (CH), 129.1 (C), 143.0 (C), 161.3 (C=O), 164.4 (C=O), 191.4 (C=O) ppm.

Results and discussion

The structures of compounds **4a-4c** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR. For example, the ^{1}H NMR spectrum of **4a** exhibited foursinglets (δ= 2.25, 3.63, 3.85 and 3.96) identified as metyl, *N*-methyl and two methoxy protons, along with two doublets for the remaining alkenes' protons. The 1Hdecoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances which further confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic ketone and ester carbonyl bands. The ^{1}H NMR and ^{13}C NMR spectra of **4b–4c** were similar to those for 4a except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

A possible mechanism for the formation of **4** is shown in (Scheme **2**). Presumably, the zwitterionic intermediate [12-14], formed from *N*-methyl imidazole and the dialkylacetylenedicarboxylate, is protonated by 3 tofurnish intermediate **5**, which is attacked by carbanion 6, to produce **7**. This intermediate is converted into **8** via a 1,3-proton shift and cyclization. The intermediate **9**, produced by elimination of $PhSO_2H$.This intermediate is finally converted to **4** by aromatizationthrough elimination of H_2.



Scheme 2: Proposed mechanism for the formation of products.

Conclusion

To sum up, we have reported a new procedure for the synthesis of biologically active pyrrolo imidazole derivatives via three component reaction of activated acetylenes in the presence of phenylsulfonyl acetone in good to excellent yield. The functionalized bridged head N-Heterocycles reported in this

research may be considered as potentially useful intermediates because they possess atoms with different oxidation states. The present procedure has the advantage that not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

References

[1]V. Poel, G. Guilaumet, M. Viaud, *Tetrahedron Lett.,* 43, 1205 (2002).

[2] J. Zhu, H. Bienaymé, In: Multicomponent Reactions, Wiley-VCH: Weinheim, NY, 1-197 (2005).

[3] J. Swinbourne, H. Hunt, G.Klinkert, A*dv. Heterocycl. Chem*., 23, 103 (1978).

[4] I. Hermecz, L. Vasvari, P. Matyus, In: Comprehensive Heterocyclic Chemistry, Pergamon Press: London, Vol. 8, Chapter 23, 563–595 (1996).

[5] R. Acheson, N. Elmore, *Adv. Heterocycl. Chem.,* 23, 263 (1978).

[6]R. Acheson, G. Taylor, *Proc. Chem. Soc*., 186 (1959).

[7] R. Acheson, G. Taylor,*J. Chem. Soc*., 1691(1960).

[8] A. Mirzaei, Z. Hossaini, M. Sabbaghan, *Iran. J. O. C.*,35, 168 (2009).

[9] A. Mirzaei, *Iran. J.O.C.*,5, 971 (2013).

[10] A. Mirzaei, *Iran. J.O.C.*,5, 1085 (2013).

[11] A. Mirzaei, *Iran. J.O.C.*,5, 1153 (2013).

[12] R. Huisgen, R. Grashey, H. Knupfer, R. Kunz,*Chem. Ber*., 97, 1085 (1964).

[13] R. Huisgen, M. Morikawa, K. Herbig, E. Brunn, *Chem. Ber*., 100, 1094 (1967).

[14] E. Winterfeldt, D. Schumann, H. Dillinger, *Chem. Ber*., 102, 1656 (1969).