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Synthesis of new pyrrolo quinoline derivatives by three component reaction of quinoline, activated acetylenes and 2-chloro *N*-metyl acetoacetamide

Anvar Mirzaei*

Chemistry Department, Faculty of Science, Sanandaj Branch, Islamic Azad University, PO Box 618, Sanandaj, Iran.

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Abstract: Quinoline reacts smoothly with activated acetyleninc esters in the presence of 2-chloro *N*-metyl acetoacetamide to produce pyrrolo quinoline derivatives in moderate to good yields.

Keywords: Pyrroloquinoline, 2-Chloro *N*-metyl acetoacetamide, Activated acetylenes, Quinoline.

Introduction

Organic synthesis like any other human activity aims at achieving ideality. An ideal synthesis is one that can be performed in the most efficient and facile manner with maximum conversion. [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, straightforward 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].

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 [6-9]. As part of our current studies on the development of new routes to new heterocyclic systems [10-13], in this letter we describe a simple and efficient synthesis of functionalized 1-*H*-pyrroloquinoline derivatives.

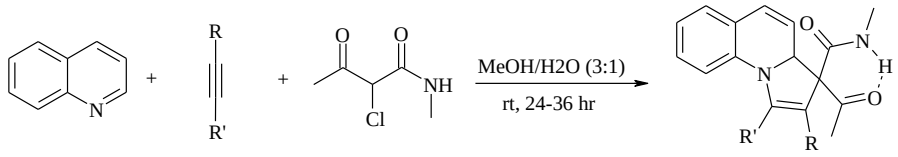
The reaction of quinoline (**1**) with activated acetylenic esters (**2**) in the presence of 2-chloro *N*-metyl acetoacetamide (**3**) proceeded smoothly in MeOH/H_2O (3:1) and was complete with in 24-36 hours. The ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of [1, 10]-dihydropyrrolo isoquinoline (**4**) in 45– 85% yields (Scheme **1**).

Results and discussion

The structures of compounds **4a-4d** were deduced from their elemental analyses and their IR, ^1H NMR, ^{13}C NMR. For example, the ^1H NMR spectrum of **4a** exhibited sex singlets (δ= 1.92, 2.97, 3.74, 3.89, 5.73 and 7.92) identified as metyl, *N*-methyl, two methoxy, methin and NH protons respectively along with multiplets for the remaining aromatic protons. The ^1H-

*Corresponding author. Tel: (+98) 871 3288661, Fax: (+98) 871 3288662, E-mail: mirzaei.anvar@gmail.com

decoupled ^{13}C NMR spectrum of **4a** showed 20 distinct resonances which further confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic amide NH, ketone and ester carbonyl bands. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**4d** were similar to those for **4a** except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.



1

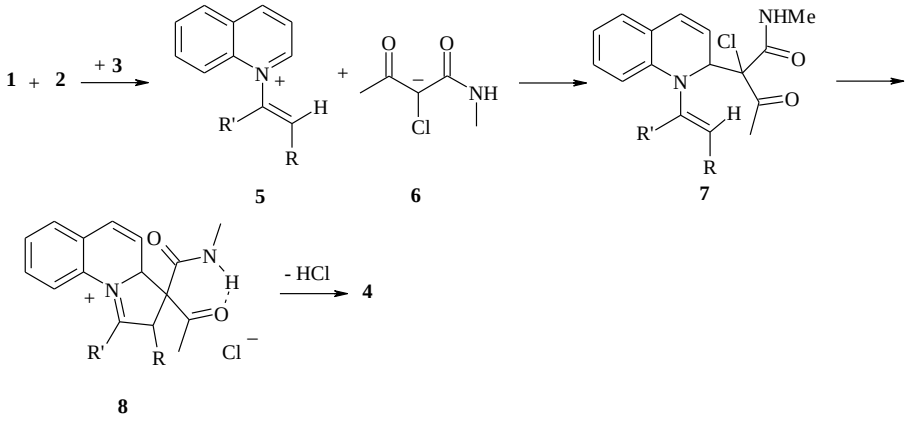
2	R'	R
a	CO_2Me	CO_2Me
b	CO_2Et	CO_2Et
c	$CO_2{}^{i}Pr$	$CO_2{}^{i}Pr$
d	$CO_2{}^{t}Bu$	$CO_2{}^{t}Bu$
e	H	CO_2Me
f	H	CO_2Et

3

4	R'	R	Yield%
a	CO_2Me	CO_2Me	85
b	CO_2Et	CO_2Et	80
c	$CO_2{}^{i}Pr$	$CO_2{}^{i}Pr$	57
d	$CO_2{}^{t}Bu$	$CO_2{}^{t}Bu$	45
e	H	CO_2Me	0
f	H	CO_2Et	0

Scheme 1: Synthesis of three-functionalized pyrrolo quinoline derivatives.

A possible mechanism for the formation of **4** is shown in (Scheme **2**). Presumably, the zwitterionic intermediate [15-16], formed from quinoline and the dialkyl acetylenedicarboxylate, is protonated by **3** to furnish intermediate **5**, which is attacked by carbanion **6**, to produce **7**. This intermediate is converted into **8** *via* intermolecular cyclization. The inermdiate **8**, is finally converted to **4** by elimination of HCl.



Scheme 2: Proposed mechanism for the formation of products.

Conclusion

In summary, we have reported a new procedure for the synthesis of biologically active pyrrolo quinoline derivatives *via* three component reaction of activated acetylenes in the presence of 2-chloro *N*-metyl acetoacetamide in moderate to good 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.

Experimental

General procedure:

All compounds were obtained from Fluka or 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; δ in 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 MeOH/H_2O (3:1) was added quinoline (2 mmol) at rt. The reaction mixture was then stirred for 24 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 (5:1) mixture as eluent to get pure product **4**.

Data:

*Dimethyl 3-acetyl-3-[(methylamino)carbonyl]-3,3a-dihydropyrrolo[1,2.a]-quinoline-1,2- dicarboxylates (**4a**)*:

Yellow powder, M. p: 172-172, 0.32 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 3350, 2950, 1749, 1710, 1688, 1141, 770. Anal. Calcd for $C_{20}H_{20}N_2O_6$ (384.38): C, 62.49; H, 5.24; N, 7.29%. Found: C, 62.55; H, 5.29; N, 7.36%. ^{1}H NMR: δ 1.92 (3H, s, Me), 2.97 (3H, s, N-Me), 3.74 (3H, s, O-Me), 3.89 (3H, s, OMe), 5.73 (1H, s, N-CH), 6.19 (1H d, ^3J = 10.0 Hz, CH), 6.60-6.65 (3H, m, CH), 6.75 (1H, d, ^3J = 7.1 Hz, CH), 7.08-7.11 (1H, m, CH), 7.92 (1H, br s, NH) ppm. ^{13}C NMR: δ 28.8 (CH_3), 30.3 (N-Me), 53.0 (OMe), 53.6 (OMe), 63.8 (CH), 69.6 (C), 117.3 (CH), 121.4 (CH), 125. 7 (C), 129.3 (C), 129.5 (CH), 129.5 (CH), 130.2 (CH), 133.1 (CH), 139.6(C), 141.0 (C), 164.7 (C=O), 166.6 (C=O), 170.1(C=O), 188.2 (C=O) ppm.

*Diethyl 3-acetyl-3-[(methylamino)carbonyl]-3,3a-dihydropyrrolo[1,2.a]-quinoline-1,2- dicarboxylates (**4b**)*:

Yellow powder, M. p: 178-180, 0.32 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 3345, 2980, 1740, 1720, 1689, 1140, 778. Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.4): C, 64.07; H, 5.87; N, 6.79%. Found: C, 64.10; H, 5.94; N, 6.98%. ^{1}H NMR: δ 0.98 (3H, t, ^3J = 6.9 Hz, CH_3), 1.09(3H, t, ^3J = 7.3 Hz, CH_3), 1.94 (3H, s, Me), 3.11 (3H, s, N-Me), 4.06 (2H, q, ^3J = 6.9 Hz, O-CH_2), 4.18 (2H, q, ^3J = 7.3 Hz, O-CH_2), 5.68 (1H, s, N-CH), 6.22 (1H d, ^3J = 9.7 Hz, CH), 6.60-6.75 (4H, m, 4CH), 7.02-7.12 (1H, m, CH), 8.03 (1H, br s, NH) ppm. ^{13}C NMR: δ 13.8 (CH_3), 14.3 (CH_3), 29.7 (CH_3), 31.6 (N-Me), 60.1 (O-CH_2), 61.4 (O-CH_2), 63.8 (CH), 68.4 (C), 115.4 (CH), 122.7 (CH), 126.1 (C), 128.8 (C), 129.4 (CH), 129.7 (CH), 130.6 (CH), 132.5 (CH), 138.9(C), 142.2 (C), 163.5 (C=O), 164.6 (C=O), 171.5(C=O), 190.3 (C=O) ppm.

*Diisopropyl 3-acetyl-3-[(methylamino)carbonyl]-3,3a-dihydropyrrolo[1,2.a]-quinoline-1,2- dicarboxylates (**4c**)*:

Brown powder, M. p: 183-186, 0.32 g, yield 57%. IR (KBr) (ν_{max}/cm^{-1}): 3330, 2985, 1741, 1719, 1680, 1170, 794. Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.5): C, 65.44; H, 6.41; N, 6.36%. Found: C, 65.70; H, 6.64; N, 6.48%. ^{1}H NMR: δ 1.29-1.34(12H, m, 4 CH_3), 2.16 (3H, s, Me), 3.26 (3H, s, N-Me), 5.12 (1H, m, O-C*H*Me_2), 5.27 (1H, m, O-C*H*Me_2), 5.54 (1H, s, N-CH), 6.35 (1H d, ^3J = 9.5 Hz, CH), 6.64-6.77 (4H, m, 4CH), 7.05-7.12 (1H, m, CH), 8.28 (1H, br s, NH) ppm. ^{13}C NMR: δ 21.5 (2CH_3), 21.8 (2CH_3), 29.9 (CH_3), 30.7 (N-Me), 63.8 (CH), 67.6 (CH), 68.4 (C), 69.1 (CH), 116.1 (CH), 123.2 (CH), 126.3 (C), 127.9 (C), 129.2 (CH), 129.8 (CH), 131.4 (CH), 132.2 (CH), 138.7(C), 141.1 (C), 163.6 (C=O), 164.8 (C=O), 171.7(C=O), 191.2 (C=O) ppm.

*Di(tet-buthy)l 3-acetyl-3-[(methylamino)carbonyl]-3,3a-dihydropyrrolo[1,2.a]-quinoline-1,2-dicarboxylates (**4d**)*:

Brown powder, M. p: 191-193, 0.21 g, yield 45%. IR (KBr) (ν_{max}/cm^{-1}): 3290, 2980, 1750, 1730, 1680, 1230, 764. Anal. Calcd for $C_{26}H_{22}N_2O_6$ (468.5): C, 66.65; H, 6.88; N, 5.98%. Found: C, 66.75; H, 6.97; N, 6.08%. ^{1}H NMR: δ 1.47 (9H, s, C*Me*$_3$), 1.52 (9H, s, C*Me*$_3$), 2.25 (3H, s, Me), 3.18 (3H, s, N-Me), 5.45 (1H, s, N-CH), 6.47 (1H d, ^3J = 9.7 Hz, CH), 6.84-6.97 (4H, m, 4CH), 7.08-7.13 (1H, m, CH), 8.41 (1H, br s, NH) ppm. ^{13}C NMR: δ 27.5 (C*Me*$_3$), 27.9 (C*Me*$_3$), 28.4 (CH_3), 31.8 (N-Me), 68.1 (C), 68.9 (CH), 78.3 (CH), 79.6 (CH), 119.2 (CH), 123.7 (CH), 125.4 (C), 126.8 (C), 129.3 (CH), 129.6 (CH), 131.7 (CH), 132.9 (CH), 138.6(C), 140.3 (C), 164.2 (C=O), 164.7 (C=O), 173.5 (C=O), 194.6 (C=O) ppm.

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