Iranian Journal of Organic Chemistry Vol. 5, No. 1 (2013) 971-973

Facile three component preparation of new indolizine derivatives

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Received: November 2012; Revised: December 2012; Accepted: December 2012

Abstract: pyridine reacts smoothly with phenylsulfonyl acetone in the presence of dialkyl acetylenedicarboxylates to produce indolizine derivatives in good to excellent yields.

Keywords: Indolizine, Phenylsulfonyl acetone, Phenylsulfonyl acetophenone Activated acetylenes, Isoquinoline.

Introduction

Bridgehead nitrogen heterocycles are important natural products [1]. Among those Pyrrolo[1,2-*a*]pyridine, known as indolizine, and its dreviatives are found in many alkaloids [2-4]. These natural and many synthetic indolizine derivatives have been found to have a variety of biological activity [5-10]. As a result, indolizine derivatives have now become important target compounds in developing new pharmaceuticals for the treatment many diseases [11-12].

Also they are important as potential central nervous system depressants, calcium entry blockers, cardiovascular and antimycobacterial agents, spectral sensitizers and novel dyes [13-15].

In the course of our research program on the facile synthesis of heterocycles using multi component reaction in mild conditions [16-17], herein we report the results of our studies involving the reactions of zwitterions derived from quinoline (**1**) and dialkyl acetylenedicarboxylates **2** in the presence of phenylsulfonyl acetone (**3**), which constitutes a synthesis of three-functionalized inolizine derivatives **4** (Scheme **1**).

Under similar reaction conditions, activate acetylenes reacts with isoquinoline and quinoline in the presence of phenylsulfonyl acetone to produce compounds **6** and **8** (Scheme **2**).

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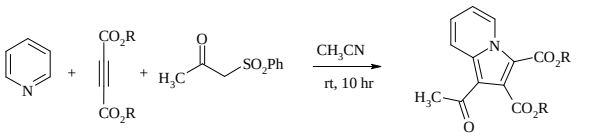


1	2	R	3
	a	CO_2Me	
	b	CO_2Et	
	c	$CO_2{}^tBu$	

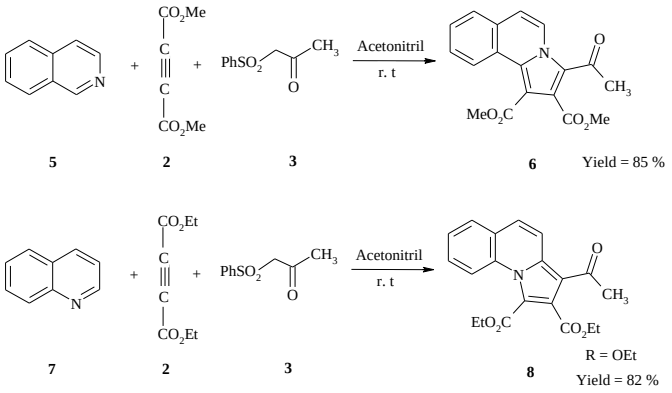
4	R	Yield (%)
a	CO_2Me	89
b	CO_2Et	86
c	$CO_2{}^tBu$	75

Scheme 1: Synthesis of three-functionalized inolizine derivatives.

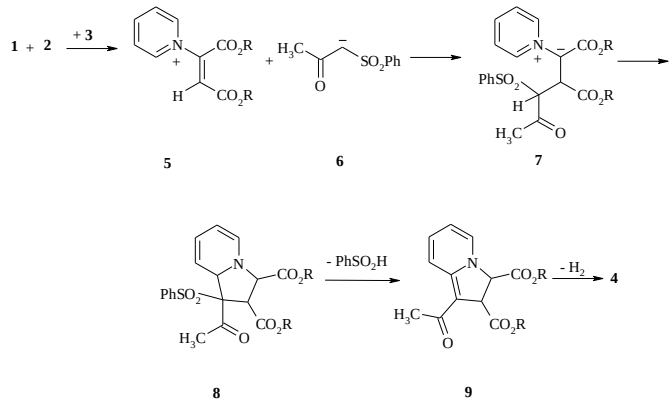
The structures of compounds **4a-4c**, **6** and **8** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR. For example, the ^{1}H NMR spectrum of **4a** exhibited two singlets (δ= 3.93 and 3.98) identified as methoxy protons, along with multiplets for the remaining aromatic protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 12 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. We have similar pattern in spectrum of **6** and **8**.

A possible mechanism for the formation of **4** is shown in (Scheme **3**). Presumably, the zwitterionic intermediate [18-20] formed from isoquinoline 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* a 1,3-proton shift and cyclization. The inermdiate **9**, produced by elimination of $PhSO_2H$, is finally converted to **4** by aromatization.



Scheme 2: Synthesis of other inolizine derivatives by isoquinoline and quinoline.



Scheme 3: Proposed mechanism for the formation of products.

Conclusion

In summary, we have reported a new procedure (**4a-4c**, **6** and **8**) for the synthesis of biologically active indolizine derivatives *via* three component reaction of activated acetylenes and isoquinoline in the presence of phenylsulfonyl acetone in good to excellent yield.

Experimental

General procedure:

All compounds were obtained from Fluka and were used without further purification. M.p. Electrothermal-9100 apparatus. 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 MeCN was added pyridine (2 mmol) at rt. The reaction mixture was then stirred for 10 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 1-acetyl-2,3-indolizinedicarboxylate (**4a**):*

Pale yellow powder, mp 195–197 °C, 0.29 g, yield 89%. IR (KBr) (νmax/cm^{-1}): 1730 , 1693, 1597, 1480, 11149, 929, 764, 687. MS, m/z (%): 250 (4), 246 (970), 231 (80), 214 (93), 77 (100). Anal. Calcd for $C_{14}H_{15}NO_5$ (375.25): C, 61.09; H, 4.76; N, 5.09%. Found: C, 61.15; H, 4.85; N, 5.18%. ^{1}H NMR: δ 2.67 (3H, s, Me), 3.41 (3H, s, OMe), 3.92 (3H, s, OMe), 7.19 (1H, dd, ^3J=8.02, 4 Hz, CH), 7.55-7.57 (1 H, m, 1 CH), 8.05- 8.06 (1H,m, 1CH), 9.46 (1 H, d, ^3J = 6.9 Hz, CH) ppm. ^{13}C NMR: δ 28.2 (CH_3), 51.2 (OMe), 59.6 (OMe), 113.8 (CH), 117.92 (CH), 119.4 (C), 122.8 (CH), 128.8 (C), 136.2 (CH), 139.1 (C), 142.7 (C), 163.6 (C=O), 166.7 (C=O), 197.2 (C=O) ppm.

*Diethyl 1-acetyl-2,3-indolizinedicarboxylate (**4b**):*

Pale yellow crystals, mp 196–198 °C, 0.26g, yield 86%. IR (KBr) (νmax/cm^{-1}): 1720, 1718, 1710, 1601, 1217, 725. MS, m/z (%): 303 (M, 3), 242 (40), 214 (50), 187 (100), 157 (50), 77 (60), 51 (30). Anal. Calcd for $C_{16}H_{17}NO_5$ (303.31): C, 63.36; H, 5.65; N, 4.62%. Found: C, 63.55; H, 5.59; N, 4.72%. ^{1}H NMR: δ 1.36 (3H, t, ^3J =7.2 Hz, Me), 1.57 (3H, t, ^3J =7.6 Hz, Me), 3.50 (2H, q, ^3J =7.6 Hz, OCH_2), 4.30 (2H, q, ^3J =7.2 Hz, OCH_2), 6.87 (1H, d, ^3J=8.50 Hz, CH), 7.26-7.29 (1 H, m, CH), 8.50 (1H, d, ^3J=7.3 Hz, 2CH), 9.50 (1H, d, ^3J=7.2 Hz, CH) ppm. ^{13}C NMR: δ 13.7 (Me), 14.0 (Me), 27.3 (Me), 61.2 (OCH_2), 62.3 (OCH_2), 118.8 (CH), 118.7 (C), 120.2 (CH), 120.6 (C), 127.3 (CH), 129.7 (C), 132.3 (C), 136.7 (CH), 160.1 (C=O), 163.3 (C=O), 200.8 (C=O) ppm.

Di(^{t}*butyl) 1-acetyl-2,3-indolizinedicarboxylate (**4c**):*

Yellow crystals, mp 200–203 °C, 0.27 g, yield 75%. IR (KBr) (νmax/cm^{-1}): 17282 (C=O), 1731 (C=O), 1692 (C=O), 1616, 1366, 1210. MS, m/z (%): 359 (M, 2), 298 (18), 187 (60), 157 (30), 77 (100). Anal. Calcd for $C_{24}H_{27}NO_5$ (359.41): C, 66.84; H, 7.01; N, 3.90%. Found: C, 66.79; H, 7.12; N, 3.78%. ^{1}H NMR: δ 1.18 (9H, s, CMe_3), 1.25 (9H, s, CMe_3), 7.01 (1H, d, ^3J=7.3 Hz, CH), 7.50-7.51 (1 H, m, 1 CH), 8.35 (1 H, d, ^3J = 7.2 Hz, CH), 9.12 (1H, d, ^3J=7.2 Hz, CH) ppm. ^{13}C NMR: δ 25.5 (CMe_3), 27.3 (CMe_3), 80.6 (CMe_3), 81.2 (CMe_3), 116.8 (CH), 118.5 (CH), 120.5 (C), 121.6 (C),

127.4 (CH), 128.9 (C), 132.6 (C), 136.2 (CH), 162.1 (C=O), 163.4 (C=O), 197.8 (C=O) ppm.

*Dimethyl 1-acetylpyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (**6**):*

Pale yellow powder, mp 189–191 °C, 0.27 g, yield 85%. IR (KBr) (νmax/cm^{-1}): 1733 (C=O), 1699 (C=O), 1698 (C=O), 1645, 1210. MS, m/z (%): 325 (M, 2), 264 (90), 185 (60), 140 (80), 112 (90), 77 (100). Anal. Calcd for $C_{18}H_{15}NO_5$ (325.31): C, 66.46; H, 4.65; N, 4.31%. Found: C, 66.59; H, 4.58; N, 4.20%. ^{1}H NMR: δ 2.62 (Me), 3.93 (3H, s, OMe), 3.97 (3H, s, OMe), 7.19 (1H, d, ^3J=7.5 Hz, CH), 7.56-7.59 (2H, m, 2CH), 7.70-7.72 (1H, m, 1CH), 8.53 (1H, t, ^3J = 7.9 Hz, CH), 9.20 (1H, t, ^3J =7.5 Hz, CH). ^{13}C NMR: δ 30.2 (Me), 52.1 (OMe), 52.9 (OMe), 115.8 (CH), 118.9 (C), 123.7 (CH), 124.3 (C), 125.6 (CH), 127.1 (C), 127.2 (CH), 128.0 (CH), 129.2 (CH), 129.6 (C), 132.0 (C), 136.5 (CH), 160.5 (C=O), 166.3 (C=O), 197.5 (C=O) ppm.

*Diethyl 3-acetylpyrrolo[1,2-a]quinoline-1,2-dicarboxylate (**8**):*

Pale yellow crystals, mp 189–191 °C, 0.29 g, yield 82%. IR (KBr) (νmax/cm^{-1}): 2929, 1743 (C=O), 1700 (C=O), 1677 (C=O), 1639, 1452, 1120, 1398, 418. MS, m/z (%): 353 (M, 2), 292 (42), 185 (60), 140 (39), 112 (88), 77 (100). Anal. Calcd for $C_{20}H_{2119}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96%. Found: C, 68.21; H, 5.50; N, 3.88%. ^{1}H NMR: δ 1.22 (3H, t, ^3J =7.1 Hz, Me), 1.37 (3H, t, ^3J =7.2 Hz, Me), 4.12 (2H, q, ^3J =7.2 Hz, OCH_2), 4.40 (2H, q, ^3J =7.1 Hz, OCH_2), 7.15 (1H, d, ^3J =7.6 Hz, CH), 7.47-7.59 (2H, m, 2CH), 7.81 (1H, t, ^3J =8.17.5 Hz, CH), 8.50 (1H, d, ^3J =7.9 Hz, CH), 9.220 (1H, d, ^3J =7.65 Hz, CH) ppm. ^{13}C NMR: δ 13.8 (Me), 14.1 (Me), 29.3 (Me), 61.1 (OCH_2), 63.9 (OCH_2), 115.6 (CH), 118.7 (C), 123.6 (CH), 124.7 (C), 125.6 (CH), 127.0 (C), 127.2 (CH), 128.02 (CH), 129.1 (CH), 129.5(C), 131.9 (C), 134.2 (CH), 160.1 (C=O), 164.3 (C=O), 197.4 (C=O) ppm.

Acknowledgement

The author is grateful to Islamic Azad University, Sanandaj Branch for financial support of this work.

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