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One-pot Synthesis of Polysubstituted Indolizine Derivatives

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Abstract

An efficient approach to the synthesis of 1,2,3-trisubstituted indolizines is described via one-pot reactions of pyridine and dialkyl acetylendicarboxylate in the presence of ethyl 2-chloroacetoacetate in MeOH at room temperature. The corresponding 1, 2, 3-trisubstituted indolizines may be useful building blocks for the construction of complex indolizine derivatives.

Keywords: *Indolizines, Dialkyl acetylendicarboxylate, Pyridines, Ethyl 2-chloroacetoacetate.*

Introduction

The indolizine skeleton is present in a wide variety of natural and unnatural azacyclic compounds which possess a diverse range of biological activities, and can be considered an important scaffold for the preparation of novel pharmaceuticals [1-6].

The indolizine system has received attention with respect to its potential biological activity. They possess anti-tuberculosis [1], analgesic [7], calcium blocking [8], anti-inflammatory [9], estrogen agonist [10], antiviral [11], anticancer [12], and antioxidant [13] agents.

Several synthetic methods for the synthesis of indolizines have been reported in the literature. Some of the methods that are worth noting are the Tschitschibabin reaction [14-16], 1,3-dipolar cycloaddition reactions [17,18], intramolecular cyclisation using acetic anhydride [19], and multicomponent coupling reactions [20,21]. Additionally, many cyclisations involve metals such as silver [22], gold [23], rhodium [24], copper [25], and palladium [26] as catalysts.

However, in many cases they have drawbacks

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such as: expensive and toxic metals, extended reaction times, or high reaction temperatures providing opportunity for the further development of milder protocols. In continuation of our interest in the development of new routes to new heterocyclic systems [27-30], in this letter we found a very convenient route to indolizine core structures using MCRs reaction.

Experimental

The reagents and solvents used in this work were obtained from Aldrich and Fluka and were used without further purification. Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses for the C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. 1H, and 13C spectra were measured with a BRUKER DRX-250 AVANCE spectrometer at 250 and 62.5 respectively.^{1}H, and ^{13}C spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

*General procedure for the preparation of compounds **4a-e***

To a stirred solution of 2 (2 mmol) and 3 (2 mmol) in 3 mL, MeOH pyridine (2 mmol) was added at room temperature. The reaction mixture was then stirred for 16 h. After completion of the reaction [TLC (AcOEt/hexane 1:4) monitoring], the reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using n-hexane–EtOAc as eluent to afforded pure compounds **4**.

*Dimethyl 1-acetylindolizine-2,3-dicarboxylate (**4a**)*

Pale yellow powder, 0.24 g, yield 86%, mp 194–196 °C. IR (KBr) (ν_{max}/cm^{-1}): 1732, 1694, 1600, 1487. ^{1}H NMR (250.1 MHz, $CDCl_3$): 2.66 (3H, s, Me), 3.91 (3H, s, OMe), 3.98 (3H, s, OMe), 7.08 (1H, t, ^{3}J=7.1 Hz, CH), 7.36 (1 H, t, ^{3}J=7.6 Hz, CH), 8.37 (1H, t, ^{3}J=8.9 Hz, CH), 9.52 (1 H, d, ^{3}J = 7.2 Hz, CH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): 28.2 (Me), 52.9 (OMe), 53.6 (OMe), 103.5 (C), 112.2 (C), 117.1 (CH), 121.2 (CH), 128.1 (CH), 129.0 (CH), 129.8 (C), 139.6 (C), 161.6 (C=O), 163.7 (C=O), 197.1 (C=O) ppm. MS (EI): *m/z* (%): 275 (M^+, 4), 246 (95), 231 (80), 214 (27), 170 (23), 143 (10), 130 (8), 77 (100). Anal. Calcd for $C_{14}H_{13}NO_5$ (275.26): C, 61.09; H, 4.76; N, 5.09%. Found: C, 61.13; H, 4.84; N, 5.16%.

*Diethyl 1-acetylindolizine-2,3-dicarboxylate (**4b**)*

Pale yellow powder, 0.25 g, yield 84%, mp 192–193 °C. IR (KBr) (ν_{max}/cm^{-1}): 1724, 1718, 1712, 1601. ^{1}H NMR (250.1 MHz, $CDCl_3$): 1.36-1.46 (6 H, m, 2 CH_3), 2.66 (3H, s, Me),

4.33-4.42 (6 H, m, 2 OCH_2), 7.02 (1H, t, ^3J=7.0 Hz, CH), 7.35 (1 H, t, ^3J=7.2 Hz, CH), 8.35 (1H, d, ^3J=8.6 Hz, 2CH), 9.53 (1H, d, ^3J=7.2 Hz, CH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): 13.7 (Me), 14.1 (Me), 27.8 (Me), 61.2 (OCH_2), 62.4 (OCH_2), 103.4 (C), 112.6 (C), 117.3 (CH), 121.1 (CH), 128.1 (CH), 128.9 (CH), 129.7 (C), 139.8 (C), 161.6 (C=O), 163.6 (C=O), 198.0 (C=O) ppm. MS (EI): *m/z* (%):303 (M+, 8), 242 (45), 214 (58), 187 (100), 157 (57), 77 (65), 51 (34). Anal. Calcd for $C^{16}H^{17}NO^5$ (303.32): C, 63.36; H, 5.65; N, 4.62%. Found: C, 63.45; H, 5.58; N, 4.69%.

*Di-tert-butyl 1-acetylindolizine-2,3-dicarboxylate (***4c***)*

Yellow powder, 0.27 g, yield 76%, mp 197–199 °C. IR (KBr) (ν_{max}/cm^{-1}): 1728, 1713, 1693, 1605. ^{1}H NMR (250.1 MHz, $CDCl_3$): 1.63 (9H, s, CMe_3), 1.66 (9H, s, CMe_3), 2.67 (3H, s, Me), 7.02 (1H, d, ^3J=7.2 Hz, CH), 7.32 (1H, d, ^3J=7.0 Hz, CH), 8.35 (1 H, d, ^3J = 8.8 Hz, CH), 9.42 (1H, d, ^3J=7.2 Hz, CH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): 27.1 (CMe_3), 27.8 (Me), 28.0 (CMe_3), 81.6 (CMe_3), 82.4 (CMe_3), 104.0 (C), 113.4 (C), 117.3 (CH), 121.1 (CH), 128.3 (CH), 129.1 (CH), 129.7 (C), 139.8 (C), 161.9 (C=O), 163.5 (C=O), 198.2 (C=O) ppm. MS (EI): *m/z* (%): 359 (M^+, 6), 298 (23), 187 (64), 157 (36), 143 (10), 130 (8), 89 (8), 77 (100). Anal. Calcd for $C_{20}H_{25}NO_5$ (359.43): C, 66.84; H, 7.01; N, 3.90%. Found: C, 66.78; H, 7.10; N, 3.79%.

*Dimethyl 1-acetyl-7-methylindolizine-2,3-dicarboxylate (***4d***)*

Pale yellow powder, 0.25 g, yield 88%, mp 205-206 °C. IR (KBr) (ν_{max}/cm^{-1}): 1726, 1721, 1713, 1700, 1608. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 2.54 (3 H, s, CH_3), 2.65 (3 H, s, CH_3), 3.93 (3 H, s, OCH_3), 4.00 (3 H, s, OCH_3), 7.04 (1 H, t, ^3J = 6.8 Hz, CH), 7.36 (1 H, t, ^3J = 7.4 Hz, CH), 8.34 (1 H, d, ^3J = 8.8 Hz, CH), 9.47 (1 H, d, ^3J = 7.1 Hz, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 21.8 (Me), 28.0 (Me), 51.7 (OMe), 53.2 (OMe), 104.0 (C), 112.3 (C), 117.6 (CH), 122.1 (CH), 128.3 (CH), 131.5 (C), 132.6 (C), 140.6 (C), 161.3 (C=O), 162.9 (C=O), 197.6 (C=O) ppm. MS (EI): *m/z* (%): 289 (M^+, 4), 244 (48), 187 (94), 143 (62), 116 (58), 89 (35), 77 (100). Anal. Calcd for $C_{15}H_{15}NO_5$ (289.29): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.32; H, 5.17; N, 4.91.

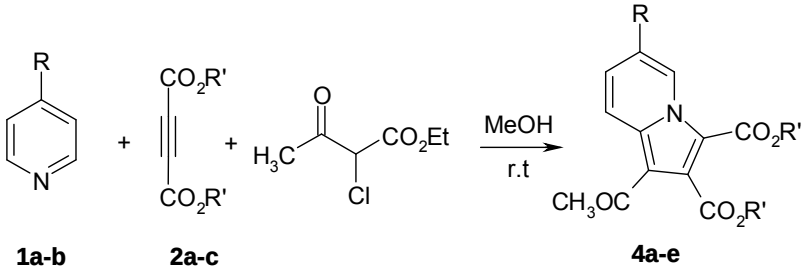
*Diethyl 1-acetyl-7-methylindolizine-2,3-dicarboxylate (***4e***)*

Yellow powder, 0.27 g, yield 85%, mp 198-199 oC. IR (KBr) (ν_{max}/cm^{-1}): 1730, 1715, 1695, 1603. ^{1}H NMR (250.1 MHz, $CDCl_3$): 1.26-1.36 (6 H, m, 2 CH_3), 2.55 (3 H, s, CH_3), 2.64 (3 H, s, CH_3), 4.34-4.43 (4 H, m, 2 OCH_2), 7.05 (1 H, d, ^3J = 7.0 Hz, CH), 7.33 (1 H, d, ^3J = 7.2 Hz, CH), 8.34 (1 H, d, ^3J = 8.6 Hz, CH), 9.49 (1 H, d, ^3J = 7.2 Hz, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 13.7 (Me), 14.0 (Me), 21.7 (Me), 27.8 (Me), 62.1 (OCH_2), 62.7 (OCH_2), 104.2 (C), 113.1 (C), 117.4 (CH), 122.4 (CH), 128.3 (CH),

131.8 (C), 132.4 (C), 141.2 (C), 160.8 (C=O), 163.2 (C=O), 198.4 (C=O) ppm. MS (EI): *m/z* (%): 317 (M^+, 6), 256 (44), 201 (100), 171 (61), 143 (46), 130 (38), 116 (6), 77 (85). Anal. Calcd for $C_{17}H_{19}NO_5$ (317.34): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.44; H, 6.10; N, 4.48.

Results and discussion

Reaction of pyridine derivatives **1a-b** with dialkyl acetylendicarboxylate **2a-c** in the presence of ethyl 2-chloroacetoacetate **3** in MeOH at room temperature led to the corresponding indolizines **4a-e** in good yields (Scheme **1**). The products were separated by column chromatography and characterized on the basis of their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of 4a in $CDCl_3$ exhibited one singlet at 2.66 ppm for methyl proton, and two singlet at 3.91 and 3.98 ppm for the methoxy groups, two doublet signals at 8.37 and 9.52 ppm and two triplet signals at 7.08 and 7.36 ppm for the aromatic region. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 14 distinct resonances which further confirmed the proposed structure.

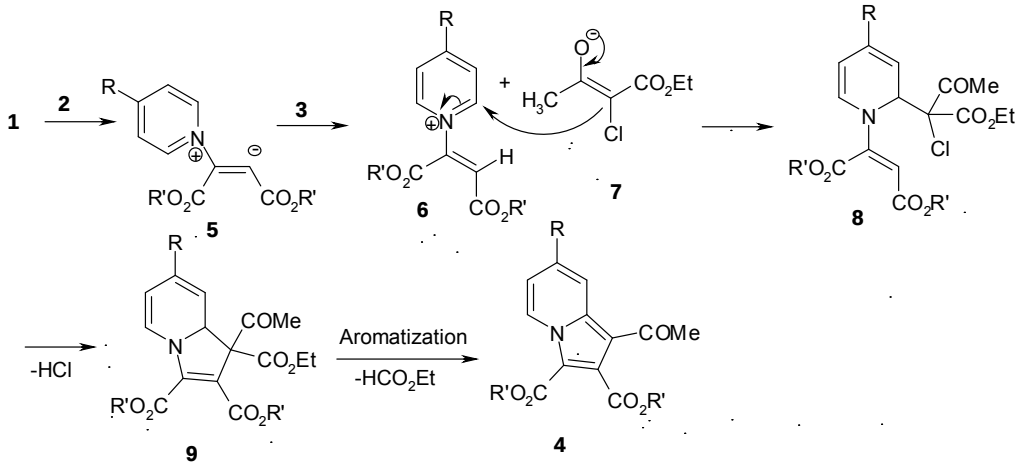


1a-b **2a-c** **4a-e**

1, 2, 4	R	R'	Yield (%) of **4**
a	H	Me	86
b	H	Et	84
c	H	^{t}Bu	76
d	Me	Me	88
e	Me	Et	85

Scheme 1. Reactions of pyridine and dialkyl acetylenedicarboxylate in the presence of ethyl 2-chloroacetoacetate.

A possible mechanism for the formation of **4** is shown in (Scheme 2). Presumably, the pyridine-acetylenedicarboxylate zwitterions intermediate **5** formed from pyridine **1** and dialkyl acetylenedicarboxylate **2**, is protonated by **3** to furnish intermediate **6**, which is attacked by carbanion **7**, to produce intermediate **8**. The subsequent cyclization of intermediate **8** followed by the elimination of the HCl leads to produced intermediate **9**. The inermdiate **9** is finally converted to **4** by elimination of HCO_2Et.



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

Conclusion

In summary, we have reported the efficient and one-pot synthesis of dialkyl 1-acetylindolizine-2,3-dicarboxylate derivatives via three component reaction of activated acetylenes and pyridine in the presence of ethyl 2-chloroacetoacetate in good yield. The mild reaction conditions and high yields of the products exhibit the good synthetic advantage of these methods.

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