I.A.U. Karaj Branch

Journal of Applied Chemical Research, 9, 3, 97-102 (2015)

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

Water as the Green Media for the Synthesis of Isoquinoline Derivatives

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(Received 05 Dec. 2014; Final version received 15 Feb. 2015)

Abstract

An efficient synthesis of isoquinoline-2,3-dicarboxylates is described via one-pot reactions of isoquinoline and alkyl bromids with dialkyl acetylenedicarboxylates in water at 70 °C. The mild reaction conditions and high yields of the products exhibit the good synthetic advantage of these methods.

Keywords: *Water, One-pot reactions; Isoquinoline, phenacyl bromids.*

Introduction

Multicomponent reactions (MCRs), with three or more reactants merge in a one-pot method to provide a single product, have be converted into gradually more popular during the last decade [1-7]. They are efficiently and environmentally valuable because multi-step syntheses generate large amounts of waste mainly due to complex isolation procedures often including costly, toxic, and unsafe solvents after each step. Bridgehead nitrogen heterocycles are of fascination because they compose a main class of natural and non-natural products, many of which display valuable biological activity [8-10]. The isoquinoline frame is set up in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [11]. Thus, as part of a related study on multicomponent reactions, we wish to report a simple synthesis of functionalized pyrrolo[2,1-a]isoquinolines. The reaction of isoquinoline **1** and dialkyl acetylenedicarboxylate **2** in the presence of phenacyl bromides **3** proceeds smoothly in water at 70 °C to produce pyrrolo[2,1-a] isoquinoline **4** in excellent yields (Scheme 1).

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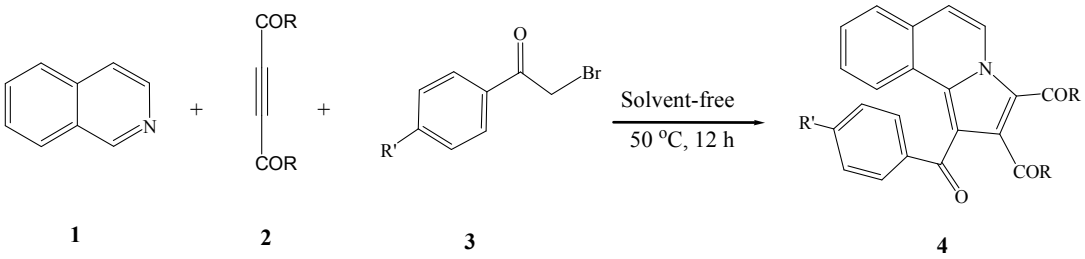


1 2 3 4

2, 3, 4	R	R'	Yield (%) of **4**
a	OMe	MeO	80
b	OEt	MeO	75
c	C_6H_5	MeO	70
d	OMe	Br	75
e	OEt	Br	75

Scheme 1. Reactions of isoquinoline and dialkyl acetylenedicarboxylate in the presence of phenacyl bromides.

Experimental

Dibenzoylacetylene was prepared by a known procedure [12, 13]. Other chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and are 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. ^{1}H, and $_{13}$C spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 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 mixture of primary amine 1 (2 mmol) and alkyl propiolate 2 (2 mmol) in water (5 mL) was added oxalyl chloride 3 (2.5 mmol) at room temperature. The reaction mixture was then stirred for 6 h. After completion of the reaction [TLC (AcOEt/hexane 1:7) 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-(4-methoxybenzoyl)pyrrolo [2,1-a] isoquinoline-2,3-dicarboxylate (**4a**)*

Pale yellow crystals, yield: 80%, m.p. 112-114 °C. IR (KBr): ν = 1729, 1713, 1697 and 1534 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): 3.62

(MeO), 3.93 (3 H, s, MeO), 3.98 (3 H, s, MeO), 6.52 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 6.75 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 6.93 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.00-7.07 (4 H, m, 4 CH), 7.13-7.20 (2 H, m, 2 CH), 8.22 (1 H, d, $^3J_{HH}$ = 7.8 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.3 (MeO), 53.3 (MeO), 53.8 (MeO), 105.7 (C), 108.9 (CH), 113.8 (CH), 113.9 (2 CH), 115.4 (C), 123.6 (CH), 124.7 (CH), 126.6 (C), 126.9 (CH), 128.0 (CH), 130.1 (C), 130.5 (C), 131.3 (2 CH), 131.5 (2 C), 160.6 (C=O), 163.9 (C), 164.2 (C=O), 192.3 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 417 (M^+, 20), 386 (68), 310 (100), 107 (100), 31 (84).

*Diethyl 1-(4-methoxybenzoyl)pyrrolo[2,1-a] isoquinoline-2,3-dicarboxylate (***4b***)*

Yellow powder, yield: 75%, m.p. 142-144 °C. IR (KBr): ν = 1722, 1715, 1700 and 1579 cm^{-1}. 1H NMR (500 MHz, $CDCl_3$): ν = 0.95 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH3), 1.40 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.92 (3 H, s, MeO), 4.02 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.43 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.86 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 6.52 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 6.76 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.02-7.06 (4 H, m, 4 CH), 7.19 (2 H, t, $^3J_{HH}$ = 7.5 Hz, 2 CH), 8.23 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.8 (Me), 14.0 (Me), 55.6 (MeO), 62.7 (CH_2O), 66.4 (CH_2O), 105.7 (C), 108.6 (CH), 113.8 (C), 113.9 (2 CH), 123.6 (CH), 124.2 (CH), 124.7 (CH), 126.8 (CH), 128.0 (CH), 130.2 (C), 130.5 (C), 131.4 (2 CH), 131.5 (2 C), 132.5 (C), 161.2 (C=O), 163.7 (C=O), 164.0 (C), 199.0 (C=O) ppm.

*Dibenzoyl 1-(4-methoxybenzoyl)pyrrolo [2,1-a]isoquinoline-2,3-dicarboxylate (***4c***)*

Yellow powder, yield: 70%, m.p. 188-190 °C. IR (KBr): ν = 1715, 1710, 1690 and 1548 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): ν = 3.85 (3 H, s, MeO), 7.15 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.30 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.38 (5 H, m, 5 CH), 7.50 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.53 (1 H, t, $^3J_{HH}$ = 7.4 Hz, CH), 7.62 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.64 (4 H, m, 4 CH), 7.74 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 8.05 (1 H, t, $^3J_{HH}$ = 7.9 Hz, CH), 8.12 (1 H, d, $^3J_{HH}$ = 7.9 Hz, CH), 9.24 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 53.4 (MeO), 118.0 (2 CH), 120.5 (2 C), 121.2 (C), 122.5 (CH), 123.4 (CH), 124.5 (C), 125.6 (CH), 126.5 (CH), 128.4 (CH), 129.3 (2 CH), 129.5 (CH), 129.7 (2 CH), 130.6 (2 CH), 130.8 (C), 131.2 (2 CH), 131.5 (2 CH), 134.5 (CH), 134.8 (C), 135.0 (CH), 137.5 (C), 139.0 (C), 139.5 (C), 142.4 (C), 189.8 (C=O), 192.2 (C=O), 193.8 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 509 (M+, 25), 380 (84), 129 (48), 107 (100), 77 (100).

*Dimethyl 1-(4-bromobenzoyl)pyrrolo[2,1-a] isoquinoline-2,3-dicarboxylate (***4d***)*

Pale yellow crystals, yield: 75%, m.p. 104-106 °C. IR (KBr): ν = 1729, 1716, 1705 and 1657 cm^{-1}.1H NMR (500.13 MHz, $CDCl_3$): ν

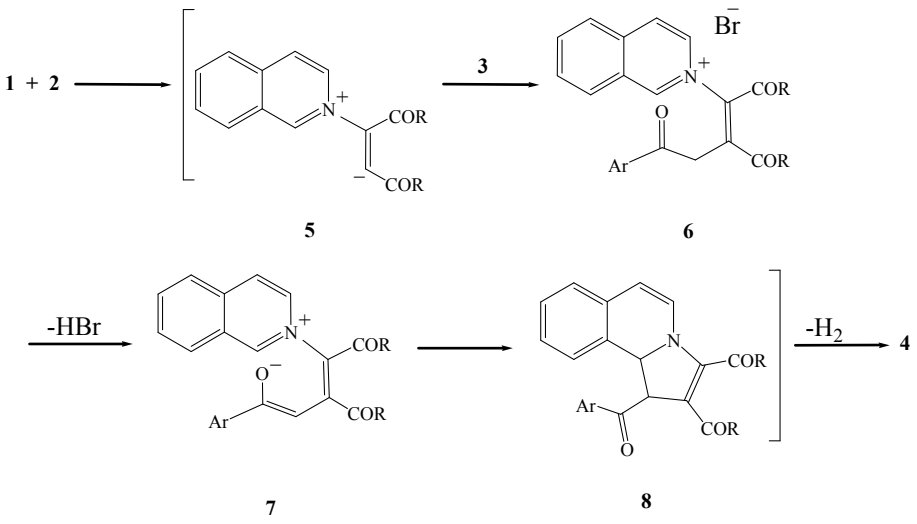
= 3.53 (3 H, s, CH_3O), 3.98 (3 H, s, CH_3O), 5.89 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 6.51 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 6.68 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.02-7.21 (3 H, m, 3 CH), 7.72 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 8.10 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 53.4 (MeO), 53.9 (MeO), 105.3 (C), 109.1 (CH), 123.4 (CH), 124.0 (CH), 124.9 (CH), 127.1 (CH), 128.3 (CH), 129.0 (C), 130.2 (C), 130.4 (2 CH), 131.2 (C), 131.4 (C), 131.9 (C), 132.2 (2 CH), 135.8 (C), 145.7 (C), 161.5 (C=O), 164.0 (C=O), 193.4 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 466 (M+, 15), 435 (68), 312 (48), 129 (84), 154 (100), 31 (84).

*Diethyl 1-(4-bromobenzoyl)pyrrolo[2,1-a] isoquinoline-2,3-dicarboxylate (***4e***)*

Yellow powder, yield: 75%, m.p. 145-147 °C. IR (KBr): ν = 1727, 1710, 1708 and 1630 cm^{-1}. ^{1}H NMR (500.13 MHz, $CDCl_3$): ν = 1.37 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.45 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.42 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.46 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 6.31 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.03-7.05 (2 H, m, 2 CH), 7.19 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.41 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.58 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.61-7.65 (2 H, m, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1 (CH_3), 14.2 (CH_3), 62.5 (OCH_2), 62.7 (OCH_2), 105.3 (C), 109.1 (CH), 123.4 (CH), 124.0 (CH), 124.9 (CH), 127.1 (CH), 128.3 (CH), 129.0 (C), 130.2 (C), 130.4 (2 CH), 131.2 (C), 131.4 (C), 131.9 (C), 132.2 (2 CH), 135.8 (C), 145.7 (C), 161.5 (C=O), 164.0 (C=O), 191.5 (C=O) ppm.

Results and discussion

Isoquinoline reacts with the electron deficient acetylenic compound **2** in the presence of phenacyl bromids in water at 70 °C. 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. The mass spectrum of **4a** displayed the molecular ion peak (M^+) at m/z = 417, which are confirmed the 1:1:1 adduct of isoquinoline, dimethyl acetylenedicarboxylate (DMAD) and 4-methoxy phenacyl bromid. The 1H NMR spectrum of **4a** showed three methoxy groups (δ = 3.62, 3.93 and 3.98), along with multiplets at δ = 6.52-8.22 for the aromatic moiety. The 13C NMR spectrum of **4a** showed 24 different resonances in agreement with the proposed structure. Although we have not established the mechanism of the reaction between isoquinoline and activated acetylenes in the presence of phenacyl bromids in an experimental manner, a possible explanation is proposed in Scheme 2. The first step may involve addition of isoquinoline to the activated acetylenic ester and formation of the 1:1 adducts **5**. Subsequent nucleophilic attack of **5** to phenacyl bromides yields the 1:1:1 adducts **6**, which is converted to **4** by elimination of hydrogen.



Scheme 2. Proposed mechanism for the formation of **4**.

Conclusions

In conclusion, we have developed a convenient and one-pot method for preparing stabilized pyrrolo[2,1-a]isoquinolines. The present method carries the advantage that these reactions are performed in weter and the substrates can be reacted without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

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