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Synthesis of 1,2-dihydroisoquinolin derivatives *via* the multicomponent reaction between OH-acids, acetylenic esters and isoquinolin

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Abstract: An efficient synthesis of 1,2-dihydroisoquinoline derivatives *via* one-pot reaction between acetylenic esters, isoquinoline and OH- acids is described.

Keywords: isoquinoline; dialkyl acetylenedicarboxylate, multicomponent reaction.

Introduction

The frequent occurrence of the 1-substituted isoquinoline nucleus in alkaloids and in a number of physiologically active compounds has led to considerable interest in the synthesis of variously functionalized and saturated representatives of this type of compounds [1,2]. As a privileged scaffold, 1,2-dihydroisoquinoline is found in many natural products and pharmaceuticals that exhibit remarkable biological activities. Significant efforts continue to be given to the development of new 1,2-dihydroisoquinoline-based structures and new methods for their construction 3-6]. Multicomponent reactions (MCRs) are economically and environmentally advantageous because multistep syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library syntheses, thus are finding increasing use in the discovery process for new drugs and agrochemicals [7-13]. In this paper, as part of our ongoing studies on the multicomponent area [13-15], we present an efficient synthesis of 1,2-dihydroisoquinoline derivatives, using commercially available starting materials in good yields.

Result and discussion

The reaction of isoquinoline **1** and activated esters **2** with OH-acids **3**, in CH_2Cl_2 and at room temp., produced 1,2-dihydroisoquinoline derivatives **4** in good yields (Scheme **1**). As indicated in Scheme **1**, isoquinoline **1**, activated acetylenes **2**, and naphthols **3** undergo a smooth 1:1:1 addition reaction to produced 1,2-dihydroisoquinolines **4** in 70–94% yields without any catalyst added and in a neutral condition (Scheme **1**).

The structures of compounds **1a-1i** were apparent from their mass spectra, which displayed in each case, the molecular ion peak at the appropriate *m/z* values. The ^{1}H- and ^{13}C-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^{1}H NMR spectrum of **1a** in acetone showed three singlet for methoxy (δ 3.50), OH (δ 9.21) and CHN (δ 6.88) and an AX system for vinylic (δ 5.24 and 7.63) protons along with the aromatic moiety. The ^{13}C NMR spectrum of **1a** exhibited twenty three signals in agreement with the proposed structure.

Although we have not established the mechanism of our reaction in an experimental manner, a possible explanation is proposed in Scheme **2**. It is conceivable that, the reaction involves the initial formation of a 1,3-dipolar intermediate **5** between isoquinoline and the acetylenic compounds, which reacts with OH-acids to produce **4**.

Conclusion

In summary, we reported an efficient method for the synthesis of 1,2-dihydroisoquinoline derivatives. The advantages of our work are as follows: (1) the reaction is performed under neutral condition, (2) no catalyst is

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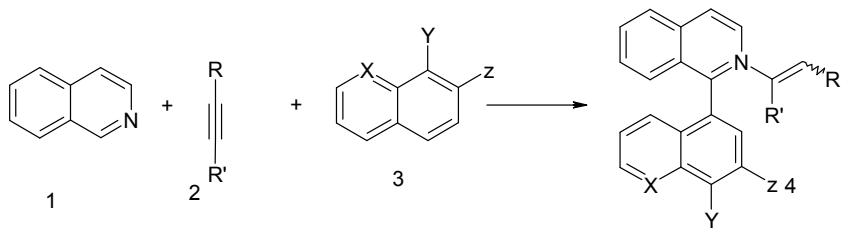
required for this reaction, and (3) the simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

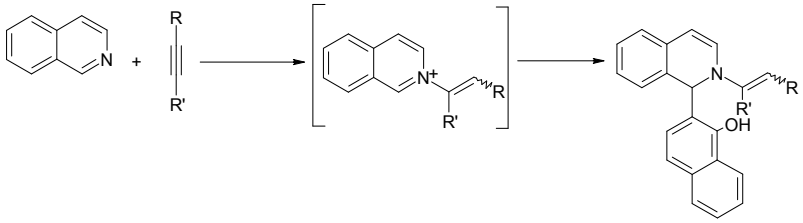


2	R	R'
a	CO_2Me	H
b	CO_2Et	H
c	CO_2Me	CO_2Me

3	X	Y	Z
a	CH	OH	H
b	CH	H	OH
c	N	OH	H

4	R	R'	X	Y	Z	Yield %
a	CO_2Me	H	CH	OH	H	70
b	CO_2Et	H	CH	OH	H	74
c	CO_2Me	CO_2Me	CH	OH	H	80
d	CO_2Me	H	CH	H	OH	80
e	CO_2Et	H	CH	H	OH	75
f	CO_2Me	CO_2Me	CH	H	OH	85
g	CO_2Me	H	N	OH	H	95
h	CO_2Et	H	N	OH	H	85
i	CO_2Me	CO_2Me	N	OH	H	70

Scheme 1:



Scheme 2:

Experimental

All chemicals were obtained from *Merck* and were used without further purification. Mp: Electrothermal-9100 apparatus. IR spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra: *Bruker DRX-500 Avance* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; δ in ppm, J in hertz.

General procedure for the production of copmpound 4a

To a magnetically stirred solution of methyl propiolate **2a** and OH-acid **3a** (2 mmol) in CH_2Cl_2 was added isoquinoline **1** (2 mmol) and the reaction was stirred for 12 h at r.t. After completion of the reaction, as indicated by TLC, the reaction mixture was purified using column chromatography with the mixture of Ethyl acetate:*n*-Hexane (1:4) as an eluent to afford Compound **4a**.

Compound **4a**: White powder, mp: 170-172ºC, yield: 0.25 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 3322 (OH), 1685 (C=O), 1606, 1412, 1371. ^{1}H-NMR (500 MHz, Acetone-d_6): δ 3.50 (3 H, s, OMe), 5.24 (1 H, d, ^3J = 13.4 Hz, CH), 5.85 (1 H, d, ^3J = 7.6 Hz, CH), 6.88 (1 H, s, CH), 6.94 (1 H, d, ^3J = 7.7 Hz, CH), 7.03 (1 H, t, ^3J = 7.2 Hz, CH), 7.08 (2 H, m, CH), 7.35 (1 H, d, ^3J = 7.6 Hz, CH), 7.38 (1 H, d, ^3J = 8.6 Hz, CH), 7.45 (1 H, t, ^3J = 7.0 Hz, CH), 7.54 (1 H, d, ^3J = 7.9 Hz, CH), 7.59 (1 H, d, ^3J = 8.5 Hz, CH), 7.63 (1 H, d, ^3J = 13.4 Hz, CH), 7.77 (1 H, d, ^3J = 8.0 Hz, CH), 8.37 (1 H, d, ^3J = 8.5 Hz, CH), 9.21 (1 H, s, OH) ppm. ^{13}C-NMR (125 MHz, Acetone-d_6): δ

50.6 (OMe), 55.4 (CH-N), 91.5 (CH), 105.5 (CH), 122.3 (CH), 122.5 (CH), 124.7 (C), 125.2 (C), 125.6 (CH), 126.4 (CH), 126.5 (C), 126.9 (CH), 127.3 (CH), 127.8 (CH), 128.4 (CH), 128.8 (CH), 130.0 (C), 133.5 (CH), 135.1 (CH), 138.3 (C), 146.8 (C), 148.0 (CH), 168.7 (C=O) ppm.

Compound 4b: Pale yellow powder, mp: 167-169ºC, yield: 0.27g (74%). IR (KBr) (ν_{max}/cm^{-1}): 3320 (OH), 1681 (C=O), 1602, 1410, 1370. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.10 (3 H, t, ^3J = 7.1 Hz, CH_3), 3.95 (2 H, q, ^3J = 7.1 Hz, CH_2), 5.21 (1 H, d, ^3J = 13.5 Hz, CH), 5.85 (1 H, d, ^3J = 7.7 Hz, CH), 6.87 (1 H, s, CH), 6.94 (1 H, d, ^3J = 7.7 Hz, CH), 7.02 (1 H, t, ^3J = 7.7 Hz, CH), 7.08 (2 H, m, 2CH), 7.35 (2 H, m, 2CH), 7.44 (1 H, d, ^3J = 6.9 Hz, CH), 7.51 (1 H, t, ^3J = 7.0 Hz CH), 7.57 (1 H, d, ^3J = 7.0 Hz, CH), 7.63 (1 H, d, ^3J = 13.4 Hz, CH), 7.76 (1 H, d, ^3J = 8.0 Hz, CH), 8.36 (1 H, d, ^3J = 8.5 Hz, CH), 9.22 (1 H, s, OH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.74 (CH_3), 55.3 (CH-N), 59.5 (OCH_2), 91.9 (CH), 105.4 (CH), 122.2 (CH), 122.5 (CH), 125.2 (C), 125.6 (CH), 125.8 (C), 126.4 (CH), 126.5 (C), 126.8 (CH), 127.3 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 130.0 (C), 132.8 (C), 133.5 (CH), 135.1 (CH), 146.9 (C), 147.9 (CH), 168.3 (C=O) ppm.

Compound 4c: Brown oil, yield: 0.33 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 3415 (OH), 1718 (C=O), 1715 (C=O), 1585, 1372. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.51 (3 H, s, OMe), 3.96 (3 H, s, OMe), 5.26 (1 H, s, OH), 5.47 (1 H, s, CH), 5.90 (1 H, d, ^3J = 7.8 Hz, CH), 6.58 (1 H, d, ^3J = 7.8 Hz, CH), 6.78 (1 H, s, CH), 7.01 (2 H, m, 2CH), 7.08 (1 H, t, ^3J = 7.5 Hz, CH), 7.36 (4 H, m, 4CH), 7.63 (1 H, d, ^3J = 8.5 Hz, CH), 7.68 (1 H, d, ^3J = 7.7 Hz, CH), 8.06 (1 H, d, ^3J = 8.0 Hz, CH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 53.2 (OMe), 53.4 (OMe), 55.7 (CH-N), 90.6 (CH), 107.9 (CH), 120.7 (CH), 122.0 (CH), 124.0 (CH), 124.2 (CH), 124.3 (C), 124.9 (CH), 125.7 (CH), 126.1 (CH), 126.5 (CH), 126.8 (C), 127.6 (CH), 127.7 (CH), 127.8 (C), 128.1 (CH), 132.6 (C), 134.1 (C), 145.3 (C), 149.6 (C), 165.5 (C=O), 167.9 (C=O) ppm.

Compound **4d**: Yellow powder, mp: 165-167ºC, yield: 0.28 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 3330 (OH), 1680 (C=O), 1610, 1410, 1371. ^{1}H-NMR (500 MHz, Acetone-d_6): δ 3.51 (3 H, s, OMe), 5.20 (1 H, d, ^3J = 13.5 Hz, CH), 6.02 (1 H, d, ^3J = 7.5 Hz, CH), 6.90 (1 H, s, CH), 6.91 (1 H, d, ^3J = 7.9 Hz, CH), 7.03 (1 H, t, ^3J = 7.2 Hz, CH), 7.10 (2 H, m, CH), 7.35 (1 H, d, ^3J = 7.5 Hz, CH), 7.46 (1 H, d, ^3J = 8.6 Hz, CH), 7.50 (1 H, t, ^3J = 7.0 Hz, CH), 7.53 (1 H, d, ^3J = 7.7 Hz, CH), 7.59 (1 H, d, ^3J = 8.5 Hz, CH), 7.81 (1 H, d, ^3J = 13.5 Hz, CH), 7.92 (1 H, d, ^3J = 8.0 Hz, CH), 8.50 (1 H, d, ^3J = 8.5 Hz, CH), 9.22 (1 H, s, OH) ppm. ^{13}C-NMR (125 MHz, Acetone-d_6): δ 51.0 (OMe), 55.0 (CH-N), 91.7 (CH), 105.3 (CH), 122.3 (CH), 122.5 (CH), 124.5 (C), 125.1 (C), 125.8 (CH), 126.3 (CH), 126.7 (C), 126.9 (CH), 127.3 (CH), 127.8 (CH), 128.4 (CH), 128.8 (CH), 131.0 (C), 133.3 (CH), 135.1 (CH), 139.1 (C), 146.8 (C), 148.0 (CH), 168.0 (C=O) ppm.

Compound 4e: Yellow powder, mp: 160-163ºC, yield: 0.27g (75%). IR (KBr) (ν_{max}/cm^{-1}): 3320 (OH), 1685 (C=O), 1602, 1408, 1370. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.10 (3 H, t, ^3J = 7.2 Hz, CH_3), 3.95 (2 H, q, ^3J = 7.2 Hz, CH_2), 5.25 (1 H, d, ^3J = 13.5 Hz, CH), 5.65 (1 H, d, ^3J = 7.6 Hz, CH), 6.91 (1 H, s, CH), 6.94 (1 H, d, ^3J = 7.6 Hz, CH), 7.05 (1 H, t, ^3J = 7.7 Hz, CH), 7.09 (2 H, m, 2CH), 7.41 (2 H, m, 2CH), 7.44 (1 H, d, ^3J = 6.9 Hz, CH), 7.51 (1 H, t, ^3J = 7.1 Hz CH), 7.56 (1 H, d, ^3J = 7.1 Hz, CH), 7.63 (1 H, d, ^3J = 13.5 Hz, CH), 7.74 (1 H, d, ^3J = 8.0 Hz, CH), 8.31 (1 H, d, ^3J = 8.5 Hz, CH), 9.15 (1 H, s, OH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.8 (CH_3), 55.3 (CH-N), 59.7 (OCH_2), 91.5 (CH), 105.4 (CH), 122.0 (CH), 123.5 (CH), 125.2 (C), 125.7 (CH), 125.9 (C), 126.4 (CH), 126.5 (C), 126.9 (CH), 127.3 (CH), 127.5 (CH), 128.4 (CH), 128.7 (CH), 130.0 (C), 132.5 (C), 133.1 (CH), 135.1 (CH), 146.9 (C), 147.8 (CH), 168.0 (C=O) ppm.

Compound **4f:** Yellow oil, yield: 0.35 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 3420 (OH), 1716 (C=O), 1714 (C=O), 1580, 1370. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.52 (3 H, s, OMe), 3.91 (3 H, s, OMe), 5.31 (1 H, s, OH), 5.60 (1 H, s, CH), 5.90 (1 H, d, ^3J = 7.8 Hz, CH), 6.59 (1 H, d, ^3J = 7.8 Hz, CH), 6.78 (1 H, s, CH), 7.00 (2 H, m, 2CH), 7.08 (1 H, t, ^3J = 7.5 Hz, CH), 7.36-7.45 (4 H, m, 4CH), 7.63 (1 H, d, ^3J = 8.5 Hz, CH), 7.81 (1 H, d, ^3J = 7.7 Hz, CH), 8.00 (1 H, d, ^3J = 8.0 Hz, CH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 53.3 (OMe), 53.5 (OMe), 55.7 (CH-N), 90.1 (CH), 107.5 (CH), 120.7 (CH), 122.0 (CH), 124.1 (CH), 124.2 (CH), 124.5 (C), 124.9 (CH), 125.8 (CH), 126.1 (CH), 126.1 (CH), 126.9 (C), 127.5 (CH), 127.7 (CH), 127.8 (C), 128.0 (CH), 132.6 (C), 134.1 (C), 145.3 (C), 149.6 (C), 166.1 (C=O), 167.7 (C=O) ppm.

Compound **4g:** Colorless crystals, mp: 143-145ºC, yield: 0.68 (95%). IR (KBr) (ν_{max}/cm^{-1}): 3365 (OH), 1695 (C=O), 1596, 1416, 1373. ^{1}H-NMR: δ 3.61 (3 H, s, MeO), 5.28 (1 H, d, ^3J = 13.4 Hz, CH), 5.78 (1 H, d, ^3J = 7.6 Hz, CH), 6.60 (1 H, d, ^3J = 7.6 Hz, CH), 6.75 (1 H, s, CH), 7.02 (2 H, m, 2 CH), 7.12 (1 H, t, ^3J = 7.4 Hz, CH), 7.20 (1 H, d, ^3J = 8.7 Hz, CH), 7.35 (1 H, d, ^3J= 7.5 Hz, CH), 7.39 (1 H, m, CH), 7.57 (1 H, d, ^3J = 13.4 Hz, CH), 7.60 (1 H, d, ^3J = 8.6 Hz, CH), 8.05 (1 H, d, ^3J = 8.2 Hz, CH), 8.79 (1 H, d, ^3J = 4.2 Hz, CH), 9.87 (1 H,

s, OH). ^{13}C-NMR: 50.8 (MeO), 54.5 (CH-O), 91.1 (CH), 105.3 (CH), 118.9 (CH), 121.8 (CH), 124.7 (C), 124.8 (CH), 125.8 (CH), 126.8 (CH), 127.3 (CH), 127.8 (CH), 127.9 (CH), 128.8 (C), 130.8 (C), 131.8 (CH), 136.2 (CH), 137.6 (C), 145.9 (C-O), 147.1 (CH), 147.9 (C), 169.0 (C=O).

Compound **4h:** White powder, mp: 139-141ºC, yield: 0.63 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 3335 (OH), 1687 (C=O), 1594, 1555, 1488, 1373. ^{1}H-NMR: δ 1.12 (3 H, t, ^3J = 7.0 Hz, Me), 3.92-4.02 (2 H, m, (AB)X_3 system, CH_2O), 5.23 (1 H, d, ^3J = 13.5 Hz, CH), 5.88 (1 H, d, ^3J = 7.7 Hz, CH), 6.79 (1 H, s, CH), 6.98 (1 H, d, ^3J = 7.7 Hz, CH), 7.10-7.16 (3 H, m, CH), 7.35 (1 H, d, ^3J = 8.7 Hz, CH), 7.39 (1 H, d, ^3J = 7.6 Hz, CH), 7.54-7.63 (1 H, m, CH), 7.65-7.73 (2 H, m, CH), 8.24 (1 H, d, ^3J = 8.2 Hz, CH), 8.56 (1 H, d, ^3J = 4.2 Hz, CH), 9.79 (1 H, s, OH). ^{13}C-NMR: 14.7 (Me), 55.2 (CH-N), 59.5 (CH_2O), 92.2 (CH), 105.5 (CH), 119.8 (CH), 123.0 (CH), 125.7 (CH), 125.9 (C), 126.2 (C), 127.3 (CH), 127.9 (CH), 128.6 (CH), 128.9 (C), 130.1 (C), 132.8 (CH), 132.9 (CH), 136.8 (CH), 138.9 (C), 147.2 (C-O), 147.8 (CH), 149.5 (CH), 168.2 (C=O).

Compound **4i:** White powder, mp: 147-149ºC, yield: 0.58 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 3360 (OH), 1698 (C=O), 1695 (C=O), 1597, 1425, 1344. ^{1}H-NMR: δ 3.65 (3 H, s, MeO), 3.75 (3 H, s, MeO), 5.56 (1 H, s, CH), 6.02 (1 H, d, ^3J = 5.9 Hz, CH), 6.34 (1 H, dd, ^3J = 9.6 Hz, ^3J = 5.9 Hz, CH), 6.53 (1 H, d, ^3J = 9.6 Hz, CH), 7.07 (1 H, t, ^3J = 7.1 Hz, CH), 7.10-7.14 (2 H, m, 2 CH), 7.18 (1 H, d, ^3J = 5.9, CH), 7.23-7.26 (2 H, m, 2 CH), 7.42 (1 H, dd, ^3J = 8.2 Hz, ^4J = 4.2 Hz, CH), 8.07 (1 H, dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, CH), 8.79 (1 H, dd, ^3J = 9.1 Hz, ^4J = 1.5 Hz, CH), 9.56 (1 H, s, OH). ^{13}C-NMR: δ 51.2 (MeO), 52.7 (MeO), 58.6 (NCH), 99.0 (CH), 118.3 (CH), 120.3 (CH), 121.4 (C), 121.9 (CH), 123.3 (CH), 124.2 (CH), 125.2 (CH), 126.4 (C), 127.0 (CH), 127.7 (CH), 127.9 (C), 128.3 (CH), 135.9 (CH), 137.8 (C), 138.0 (C), 146.2 (C), 148.2 (CH), 151.9 (C), 165.3 (C=O), 166.9 (C=O).

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