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ORIGINAL PAPER

Synthesis of functionalized 1,2-dihydroisoquinolines via one-pot reaction of isoquinoline, alkyl propiolate, and 1,3-diketones

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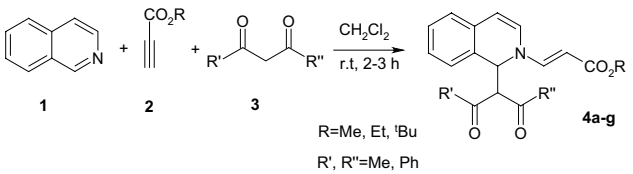
Abstract The three-component reaction between alkyl propiolates, isoquinoline, and 1,3-diketones, proceeded to give functionalized 1,2-dihydroisoquinolines in good yields in the absence of any catalysts under mild reaction conditions.

Graphical abstract



Keywords Organic acids · Isoquinoline · 1,2-Dihydroisoquinolines · Alkyl propiolate · Multicomponent reaction

Introduction

The prominence of 1,2-dihydroisoquinoline as a basic scaffold in many natural products and biologically active molecules [1–3] has promoted considerable efforts toward their synthesis [4–8]. Significant efforts continue to be given to the development of new 1,2-dihydroisoquinoline-based structures and new methods for their construction. For instance, recently it was reported that 1,2-dihydroisoquinoline skeletons could be obtained through the direct addition of various carbon pronucleophiles to *ortho*-alkynylaryl aldimines catalyzed by Lewis acid [4, 5]. The scaffold also could be generated from isoquinolines via multicomponent reaction [6–12].

The rich chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. Aromatic *N*-heterocycles are known to form zwitterions with activated acetylenes such as dimethyl acetylenedicarboxylate (DMAD) [13]. It has been shown that these types of zwitterions can be trapped by a variety of organic acids [14–17]. In this Letter, we wish to report a synthesis of 1,2-dihydroisoquinolines via the three-component reaction of isoquinoline, alkyl propiolate, and CH-acids, under mild reaction conditions (Scheme 1).

Experimental

The reagents and solvents used in this work were obtained from Aldrich and Fluka and were used without further purification. Melting points were determined using Electrothermal-9100 apparatus in open glass capillaries. IR spectra, in cm^{-1}, were recorded on a Shimadzu IR-460 spectrometer using potassium bromide pellets. ^{1}H and ^{13}C NMR spectra were obtained at 500.1 and 125.7 MHz with a Bruker DRX-500 Avance instrument in $CDCl_3$, δ in ppm and J in Hz, and TMS used as an internal standard. MS spectra were measured at Finnigan-MAT-8430 mass spectrometer at 70 eV, in m/z (rel. %). Elemental analyses were performed using Heraeus CHN-O-Rapid analyzer.

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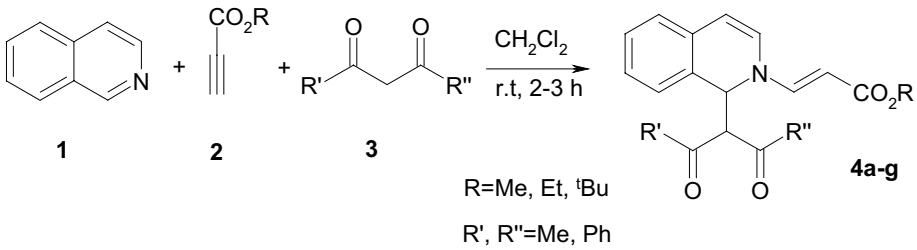
Scheme 1 Synthesis of 1,2-dihydroisoquinolines derivatives **4**



General procedure for the synthesis of 1,2-dihydroisoquinolines 4

To a stirred solution of the acetylenic ester (2 mmol) and the 1,3-diketones (2 mmol) in 10 mL of CH_2Cl_2 was added 0.26 g of isoquinoline (2 mmol) at r.t. After completion of the reaction (2–3 h), as indicated by TLC (AcOEt/hexane, 1:2), the solvent was removed under reduced pressure and the viscous residue was purified by column chromatography on silica gel (Merck 230-400 mesh) using hexane-AcOEt (2:1) as eluent to afford pure title compounds.

(E)-Methyl 3-(1-(2,4-dioxopentan-3-yl)isoquinolin-2(1H)-yl)acrylate (**4a**) Orange crystals; Mp: 98–100 °C, 0.56 g, yield 90 %. IR (KBr) (ν_{max}/cm^{-1}): 1732 (C=O), 1730 (C=O), 1697 (C=O), 1608, 1159, 1204, 761. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.73 (3 H, s, Me), 2.13 (3 H, s, Me), 3.62 (3 H, s, MeO), 4.40 (1 H, d, ^3J 8.9 Hz, CH), 5.02 (1 H, d, ^3J 13.5 Hz, CH), 5.49 (1 H, d, ^3J 7.8 Hz, CH), 6.04 (1 H, d, ^3J 7.3 Hz, CH), 6.33 (1 H, d, ^3J 7.4 Hz, CH), 6.97 (1 H, d, ^3J 7.5 Hz, CH), 7.06 (1 H, d, ^3J 7.5 Hz, CH), 7.08 (1 H, t, ^3J 7.6 Hz, CH), 7.18 (1 H, t, ^3J 7.6 Hz, CH), 7.37 (1 H, d, ^3J 13.6 Hz, CH). ^{13}C NM: δ 30.3 (Me), 32.1 (Me), 51.1 (CH), 51.2 (MeO), 69.4 (CH), 92.4 (CH), 110.9 (CH), 125.1 (CH), 126.8 (CH), 127.6 (CH), 128.2 (CH), 128.6 (CH), 129.3 (C), 130.4 (C), 147.5 (CH), 168.5 (C=O), 200.4 (C=O), 201.1 (C=O). EI-MS: *m/z* (%) = 313 (M^+, 5), 298 (18), 270 (25), 228 (40), 214 (45), 129 (65), 99 (78), 85 (52), 59 (24), 43 (100). Anal. Calcd. for $C_{18}H_{19}NO_4$ (313.35): C, 68.99; H, 6.11; N, 4.47 %. Found: C, 68.90; H, 6.10; N, 4.50 %.

(E)-Ethyl 3-(1-(2,4-dioxopentan-3-yl)isoquinolin-2(1H)-yl)acrylate (**4b**) Orange crystals; Mp: 72–74 °C, 0.58 g, yield 89 %. IR (KBr) (ν_{max}/cm^{-1}): 1730 (C=O), 1727 (C=O), 1698 (C=O), 1604, 1157, 1202, 781. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (3 H, t, ^3J 7.5 Hz, Me), 1.81 (3 H, s, Me), 2.20 (3 H, s, Me), 4.14 (2 H, ABX_3 system, CH_2O), 4.37 (1 H, d, ^3J 8.9 Hz, CH), 5.02 (1 H, d, ^3J 13.5 Hz, CH), 5.46 (1 H, d, ^3J 7.8 Hz, CH), 6.09 (1 H, d, ^3J 7.3 Hz, CH), 6.39 (1 H, d, ^3J 7.4 Hz, CH), 6.91 (1 H, d, ^3J 7.5 Hz, CH), 7.03 (1 H, d, ^3J 7.5 Hz, CH), 7.06 (1 H, t, ^3J 7.6 Hz, CH), 7.21 (1 H, t, ^3J 7.6 Hz, CH), 7.44 (1 H, d, ^3J 13.6 Hz, CH). ^{13}C NM: δ 14.6 (Me), 30.2 (Me), 32.1 (Me), 52.1 (CH), 59.6 (MeO), 69.2 (CH), 92.9 (CH), 110.9 (CH), 125.1 (CH), 126.8 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 129.2 (C), 130.5 (C), 147.2 (CH), 168.1 (C=O), 200.4 (C=O), 201.2 (C=O). EI-MS: *m/z* (%) = 327 (M^+, 3), 298 (26), 284 (29), 254 (40), 228 (49), 129 (76), 99 (100), 73 (52), 43 (56). Anal. Calcd. for $C_{19}H_{21}NO_4$ (327.37): C, 69.71; H, 6.47; N, 4.28 %. Found: C, 69.80; H, 6.40; N, 4.25 %.

(E)-tert-Butyl 3-(1-(2,4-dioxopentan-3-yl)isoquinolin-2(1H)-yl)acrylate (**4c**) Orange crystals; Mp: 83–85 °C, 0.60 g, yield 85 %. IR (KBr) (ν_{max}/cm^{-1}): 1730 (C=O), 1729 (C=O), 1701 (C=O), 1600, 1160, 1200, 782. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (9 H, s, C*Me*$_3$), 1.79 (3 H, s, Me), 2.19 (3 H, s, Me), 4.42 (1 H, d, ^3J 8.9 Hz, CH), 5.03 (1 H, d, ^3J 13.5 Hz, CH), 5.55 (1 H, d, ^3J 7.8 Hz, CH), 6.04 (1 H, d, ^3J 7.3 Hz, CH), 6.37 (1 H, d, ^3J 7.4 Hz, CH), 6.97 (1 H, d, ^3J 7.5 Hz, CH), 7.02 (1 H, d, ^3J 7.5 Hz, CH), 7.10 (1 H, t, ^3J 7.6 Hz, CH), 7.21 (1 H, t, ^3J 7.6 Hz, CH), 7.32 (1 H, d, ^3J 13.6 Hz, CH). ^{13}C NM: δ 28.4 (C*Me*$_3$), 30.2 (Me), 32.2 (Me), 59.9 (CH), 69.1 (CH), 79.1 (*C*Me$_3$), 79.3 (CH), 94.9 (CH), 110.4 (CH), 125.1 (CH), 126.8 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 130.5 (C), 146.5 (CH), 167.5 (C=O), 200.5 (C=O), 201.3 (C=O). EI-MS: *m/z* (%) = 355 (M^+, 6), 312 (22), 298 (38), 256 (25), 254 (47), 226 (43), 127 (45), 101 (65), 99 (58), 57 (100), 43 (46). Anal. Calcd. for $C_{21}H_{25}NO_4$ (355.43): C, 70.96; H, 7.09; N, 3.94 %. Found: C, 69.90; H, 7.05; N, 3.90 %.

(E)-Methyl 3-(1-(2,3-dioxo-1,3-diphenylpropan-3-yl) isoquinolin-2(1H)-yl)acrylate (**4d**) Orange crystals; Mp: 135–137 °C, 0.76 g, yield 87 %. IR (KBr) (ν_{max}/cm^{-1}): 1692 (C=O), 1680 (C=O), 1595 (C=O), 1144, 751. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70 (3 H, s, MeO), 5.06 (1 H, d, ^3J 11.2 Hz, CH), 6.08 (1 H, d, ^3J 8.5 Hz, CH), 6.10 (1 H, d, ^3J 7.2 Hz, CH), 6.21–6.23 (2 H, m, 2 CH), 6.99 (1 H, t, ^3J 7.3 Hz, CH), 7.10–7.12 (3 H, m, 3 CH), 7.28 (2 H, t, ^3J 7.7 Hz, CH), 7.41 (2 H, t, ^3J 7.5 Hz, 2 CH), 7.43 (1 H, d, ^3J 7.3, CH), 7.49 (1 H, t, ^3J 7.4, CH), 7.53 (1 H, t, ^3J 7.5, CH), 7.62 (2 H, d, ^3J 7.6 Hz, 0.2 CH), 7.91 (2 H, d, ^3J 7.6 Hz, 2 CH). ^{13}C NM: δ 50.8 (MeO), 57.8 (CH), 61.4 (CH), 92.4 (CH), 110.8 (CH), 125.2 (CH), 125.4 (CH), 126.8 (CH), 127.2 (C), 127.4 (C), 127.6 (CH), 127.8 (CH), 128.6 (2 CH), 128.7 (CH), 128.9 (2 CH), 129.0 (2 CH), 129.1 (2 CH), 129.2 (CH), 129.4 (C), 130.4 (C), 147.9 (CH), 168.5 (C=O), 192.5 (C=O), 193.0 (C=O). EI-MS: *m/z* (%) = 437 (M^+, 4), 422 (15), 378 (36), 352 (28), 332 (41), 227 (56), 223 (70), 214 (58), 129 (69), 105 (100), 77 (52),

59 (24). Anal. Calcd. for $C_{28}H_{23}NO_4$ (437.49): C, 76.87; H, 5.30; N, 3.20 %. Found: C, 76.80; H, 5.40; N, 3.15 %.

(E)-Ethyl 3-(1-(2,3-dioxo-1,3-diphenylpropan-3-yl)isoquinolin-2(1H)-yl)acrylate (**4e**) Orange crystals; Mp: 114–116 °C, 0.74 g, yield 82 %. IR (KBr) (ν_{max}/cm^{-1}): 1690 (C=O), 1684 (C=O), 1599 (C=O), 1140, 750. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3 H, t, ^3J 7.1 Hz, CH_3), 4.15 (2 H, ABX_3 system, CH_2O), 5.08 (1 H, d, ^3J 11.2 Hz, CH), 6.04 (1 H, d, ^3J 8.5 Hz, CH), 6.13 (1 H, d, ^3J 7.2 Hz, CH), 6.20–6.22 (2 H, m, 2 CH), 6.98 (1 H, t, ^3J 7.3 Hz, CH), 7.09–7.13 (3 H, m, 3 CH), 7.26 (2 H, t, ^3J 7.7 Hz, CH), 7.39 (2 H, t, ^3J 7.5 Hz, 2 CH), 7.42 (1 H, d, ^3J 7.3 Hz, CH), 7.50 (1 H, t, ^3J 7.4 Hz, CH), 7.53 (1 H, t, ^3J 7.5 Hz, CH), 7.62 (2 H, d, ^3J 7.6 Hz, 2 CH), 7.92 (2 H, d, ^3J 7.6 Hz, 2 CH). ^{13}C NMR: δ 14.8 (Me), 58.2 (CH_2O), 59.8 (CH), 61.8 (CH), 93.3 (CH), 111.2 (CH), 125.2 (CH), 125.3 (CH), 126.9 (CH), 127.3 (C), 127.5 (C), 127.7 (CH), 127.8 (CH), 128.6 (2CH), 128.7 (CH), 128.9 (2 CH), 129.0 (2 CH), 129.1 (2 CH), 129.2 (CH), 129.5 (C), 130.9 (C), 148.2 (CH), 168.5 (C=O), 192.9 (C=O), 193.0 (C=O). EI-MS: *m/z* (%) = 451 (M^+, 3), 422 (18), 378 (29), 352 (42), 346 (62), 241 (38), 228 (65), 223 (45), 129 (59), 123 (38), 105 (100), 73 (36). Anal. Calcd. for $C_{29}H_{25}NO_4$ (451.51): C, 77.14; H, 5.58; N, 3.10 %. Found: C, 77.10; H, 5.50; N, 3.14 %.

(E)-tert-Butyl 3-(1-(2,3-dioxo-1,3-diphenylpropan-3-yl) isoquinolin-2(1H)-yl)acrylate (**4f**) Orange crystals; Mp: 125–127 °C, 0.76 g, yield 80 %. IR (KBr) (ν_{max}/cm^{-1}): 1697 (C=O), 1680 (C=O), 1589 (C=O), 1144, 753. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (9 H, s, CMe_3), 5.07 (1 H, d, ^3J 11.2 Hz, CH), 6.08 (1 H, d, ^3J 8.5 Hz, CH), 6.12 (1 H, d, ^3J 7.2 Hz, CH), 6.20–6.23 (2 H, m, 2 CH), 6.91 (1 H, t, ^3J 7.3 Hz, CH), 7.09–7.12 (3 H, m, 3 CH), 7.28 (2 H, t, ^3J 7.7 Hz, 2 CH), 7.32 (2 H, t, ^3J 7.5 Hz, 2 CH), 7.41 (1 H, d, ^3J 7.3, CH), 7.48 (1 H, t, ^3J 7.4 Hz, CH), 7.51 (1 H, t, ^3J 7.5, CH), 7.60 (2 H, d, ^3J 7.6, 2 CH), 7.91 (2 H, d, ^3J 7.6 Hz, 2 CH). ^{13}C NMR: δ 28.6 (CMe_3), 58.4 (CH), 61.6 (CH), 80.1 (CMe_3), 94.1 (CH), 112.2 (CH), 125.3 (CH), 125.4 (CH), 126.9 (CH), 127.3 (C), 127.5 (C), 127.7 (CH), 127.8 (CH), 128.6 (2 CH), 128.7 (CH), 128.9 (2CH), 129.0 (2 CH), 129.1 (2CH), 129.2 (CH), 129.4 (C), 130.7 (C), 147.4 (CH), 168.3 (C=O), 196. (C=O), 193.0 (C=O). EI-MS: *m/z* (%) = 479 (M^+, 4), 422 (11), 378 (31), 374 (40), 352 (18), 269 (35), 223 (40), 164 (41), 129 (48), 127 (78), 105 (100), 57 (54). Anal. Calcd. for $C_{31}H_{29}NO_4$ (479.57): C, 77.64; H, 6.10; N, 2.92 %. Found: C, 77.60; H, 6.15; N, 3.00 %.

(E)-Methyl 3-(1-(2,3-dioxo-1-phenylbutan-2-yl)isoquinolin-2(1H)-yl)acrylate (**4g**) Orange crystals; Mp: 115–117 °C, 0.62 g, yield 83 %. IR (KBr) (ν_{max}/cm^{-1}): 1723 (C=O), 1684 (C=O), 1599 (C=O), 1142, 753. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.21 (3 H, s, Me), 3.67 (3 H, s, MeO), 4.47 (1 H, d, ^3J 8.2 Hz, CH), 5.09 (1 H, d, ^3J 13.5 Hz, CH), 5.41 (1 H, d, ^3J 7.6 Hz, CH), 6.08 (1 H, d, ^3J 7.3 Hz, CH), 6.23 (1 H, d, ^3J 7.2 Hz, CH), 6.94 (1 H, d, ^3J 7.6 Hz, CH), 7.06 (1 H, d, ^3J 7.5 Hz, CH), 7.11 (1 H, t, ^3J 7.6 Hz, CH), 7.16 (1 H, t, ^3J 7.6 Hz, CH), 7.26 (2 H, t, ^3J 7.7 Hz, 0.2 CH), 7.37 (1 H, d, ^3J 13.6 Hz, CH), 7.43 (H, t, ^3J 7.5 Hz, CH), 7.62 (2 H, d, ^3J 7.7 Hz, 0.2 CH), ^{13}C NMR: δ 31.4 (Me), 51.6 (MeO), 52.9 (CH), 67.6 (CH), 92.3 (CH), 110.4 (CH), 125.1 (CH), 125.3 (CH), 126.2 (CH), 126.7 (CH), 127.3 (C), 127.8 (CH), 128.1 (2CH), 128.3 (CH), 128.9 (2CH), 129.2 (C), 130.5 (C), 147.6 (CH), 168.4 (C=O), 200.2 (C=O), 203.6 (C=O). EI-MS: *m/z* (%) = 375 (M^+, 5), 332 (15), 316 (28), 290 (42), 270 (28), 129 (61), 105 (100), 77 (58), 59 (38), 43 (25). Anal. Calcd. for $C_{23}H_{21}NO_4$ (375.43): C, 73.58; H, 5.64; N, 3.73 %. Found: C, 73.63; H, 5.61; N, 3.76 %.

Table 1 Synthesis of 1,2-dihydroisoquinolines **4a–g** (Scheme 1)

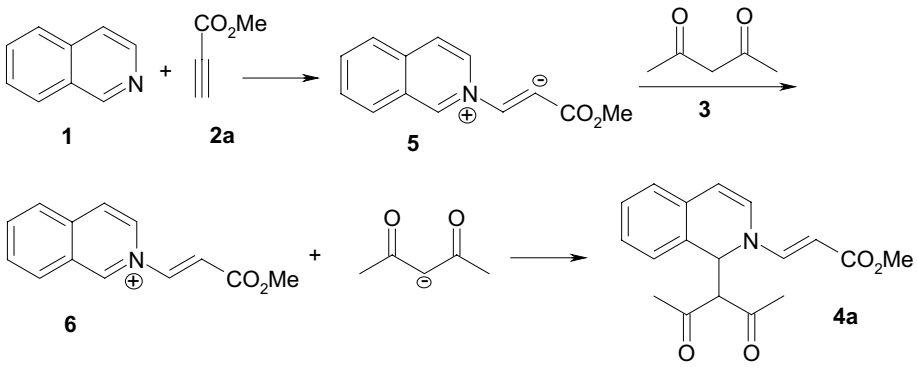
Entry	Products	R	R′	R″	Yield (%)[a]
1	**4a**	Me	Me	Me	90
2	**4b**	Et	Me	Me	89
3	**4c**	t-Bu	Me	Me	85
4	**4d**	Me	Ph	Ph	87
5	**4e**	Et	Ph	Ph	82
6	**4f**	t-Bu	Ph	Ph	80
7	**4g**	Me	Ph	Me	83

[a] Isolated yields

Results and discussion

The reaction between isoquinoline and alkyl propiolates in the presence of acetylacetone, dibenzoylmethane and benzoylacetone at ambient temperature in CH_2Cl_2 led to functionalized isoquinolin-2(1*H*)-yl)but-2-enedioates **4a**–**4g** in high yields (Table 1). The structures of compounds **4a**–**4g** were deduced from their ^{1}H-NMR, ^{13}C-NMR and IR spectra. The mass spectra of these compounds displayed, in each case, the molecular ion peak at the appropriate *m/z* values. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed three singlets for methyl and methoxy (*δ* 1.73, 2.13, 3.62) and four doublets (*δ* 4.40, 5.02, 5.49, and 7.37) for the methine and vinylic protons along with aromatic moiety. The ^{13}C NMR spectrum of **4a** exhibited 18 signals in agreement with the proposed structure. As an example, a tentative mechanism for the formation of **4a** is proposed in Scheme 1. It is conceivable that the initial event is the formation of **5** from isoquinoline and methyl propiolate which is subsequently protonated by acetylacetone to produce **6** (Scheme 2). Intermediate **6** is attacked by the conjugate base of the CH-acid to generate **4a**.

Scheme 2 Proposed mechanism for the formation of compound **4a**



Conclusion

In conclusion, we have developed a convenient route to functionalized isoquinolin-2(1*H*)-yl)but-2-enedioates from the reaction of isoquinoline with activated acetylenes in the presence of acetylacetone or dibenzoylmethane. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The present method may be considered as a practical route for the synthesis of functionalized dihydro-isoquinolin-ring systems.

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