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A novel three-component reaction for the synthesis of 1,2-dihydroisoquinolines via the reaction of isoquinoline and isocyanides with strong CH-acids in water

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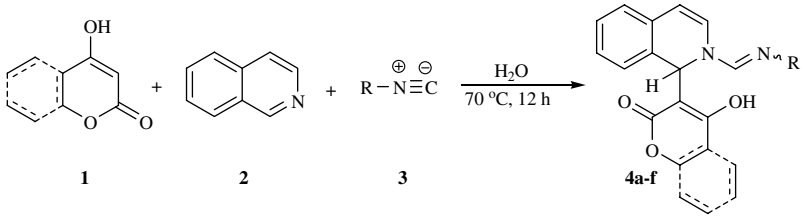
Abstract—A straightforward and efficient method for the synthesis of 1,2-dihydroisoquinolines via the one-pot, three-component reaction of an isocyanide, isoquinoline and a strong CH-acid in water without using any catalyst at 70 °C is reported. The method offers several advantages including high yields of products and an easy work-up procedure.

1. Introduction

Water is an ideal solvent and reagent for biochemical transformations. In the past, water was not used as a solvent for synthetic organic chemistry due to the poor solubility and, in some cases, the instability of organic reagents in aqueous solutions. Now, it has been recognized that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents and often the insolubility of the final products facilitates their isolation.[1,2]

The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds.[3–7] In particular, 1,2-dihydroisoquinolines act as delivery systems that transport drugs through the otherwise highly impermeable blood–brain barrier.[8–11] These compounds also exhibit sedative,[12] antidepressant,[13,14] antitumour and antimicrobial activity.[15–17] For the functionalization of quinoline, isoquinoline and related aromatic amines, the Reissert reaction has remained one of the most powerful tools.[18–20] The reaction can be considered as a multi-component reaction, where adducts are formed from an azine, an acyl chloride and sodium cyanide via an *N*-acyliminium intermediate.

As part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and our interest in isocyanide-based multi-component reactions,[21–28] herein we describe an efficient synthesis of 1,2-dihydroisoquinolines **4** via the reaction of CH-acids **1** with isoquinoline **2** and isocyanide **3** in water at 70 °C (Scheme 1).



Scheme 1. Synthesis of 1,2-dihydroisoquinolines via the one-pot, three-component reaction of isocyanides, isoquinoline and CH-acids.

Keywords: 1,2-Dihydroisoquinoline; Isoquinoline; Isocyanide; Multi-component reactions.
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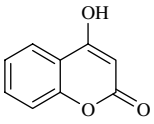
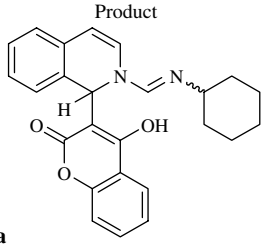
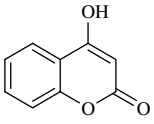
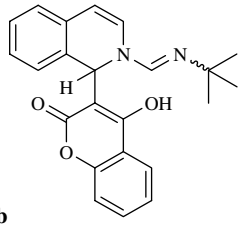
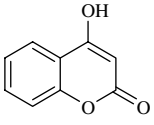
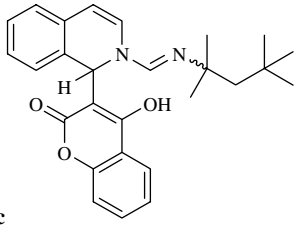
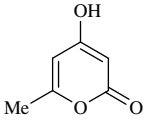
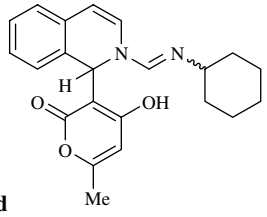
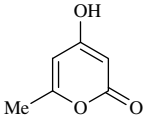
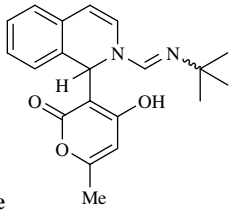
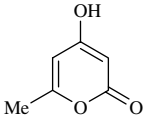
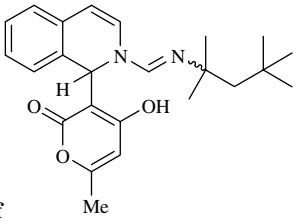
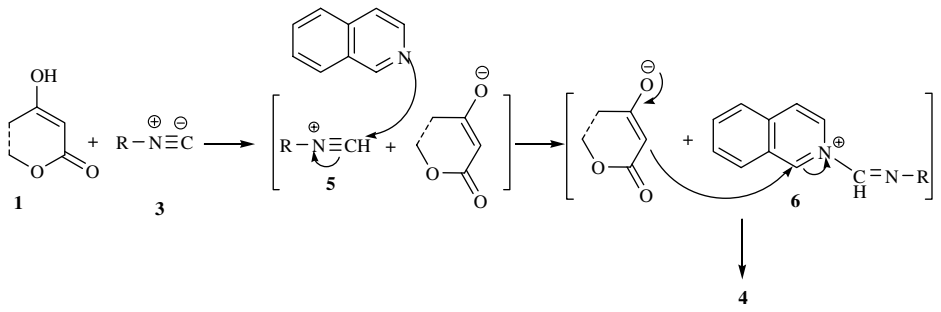
As indicated in Table 1, CH-acids, isoquinoline and isocyanides undergo a smooth 1:1:1 addition reaction in water at 70 °C to produce 1,2-dihydroisoquinolines. The structures of the products were deduced from their IR, mass, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

The ^{1}H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring ($\delta = 1.12$–1.89 ppm), a multiplet for the N–C*H* cyclohexyl proton ($\delta = 2.98$ ppm), two doublets for the N–CH=C*H* ($\delta = 6.15$ ppm, $^3J_{HH} = 7.4$ Hz) and N–C*H*=CH ($\delta = 6.85$ ppm, $^3J_{HH} = 7.4$ Hz) protons, a singlet for the N–CH=N ($\delta = 6.61$ ppm) proton, a multiplet for the aromatic protons ($\delta = 6.89$–

Table 1. Synthesis of 1,2-dihydroisoquinoline derivatives in water

Entry	CH-acid	R	Product	Yield (%)
1		Cyclohexyl	 **4a**	99
2		*tert*-Butyl	 **4b**	95
3		1,1,3,3-Tetramethyl-butyl	 **4c**	78
4		Cyclohexyl	 **4d**	62
5		*tert*-Butyl	 **4e**	62
6		1,1,3,3-Tetramethyl-butyl	 **4f**	59



Scheme 2. Proposed mechanism.

8.15 ppm), and two broad singlets for the N–C*H* isoquinoline ring and OH of the enolic tautomer ($\delta = 8.00$ ppm and 11.96 ppm) protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 25 distinct resonances, partial assignment of these resonances is given in Section 2.

The rationale for the formation of the products is shown in Scheme 2. It is conceivable that the initial event is the formation of acid–base complex **5** from the isocyanide and the activated CH-acid. Complex **5** activates the isocyanide functional group sufficiently for further nucleophilic attack by isoquinoline to produce intermediate **6**. Finally, nucleophilic attack of the conjugated base of the CH-acid on **6** affords product **4**.[29]

In conclusion, we have described a new and successful strategy for the convenient synthesis of 1,2-dihydroisoquinolines via a one-pot, three-component condensation reaction of a CH-acid, isoquinoline and an isocyanide in water at 70 °C. The method offers several advantages including high yields of products and an easy experimental work-up procedure.

2. Experimental

2.1. Typical procedure for the preparation of 3-(2-((cyclohexylimino)methyl)-1,2-dihydroisoquinolin-1-yl) chroman-2,4-dione (4a)

To a magnetically stirred solution of isoquinoline (0.13 g, 1 mmol) and 4-hydroxycoumarin (1 mmol) in H_2O (3 mL) was added cyclohexyl isocyanide (1 mmol) and the reaction heated for 12 h at 70 °C. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2:1), the reaction mixture was filtered and washed with water (2 × 10 mL) and the solid residue was crystallized from ethyl acetate to afford **4a** as colourless crystals (0.39 g, yield 99%); mp 194–196 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2929, 2856, 1682, 1657, 1603, 1508, 1453. MS, *m*/*z* (%): 401 (M^++1, 5), 329 (15), 287 (20), 265 (99), 243 (25), 222 (45), 183 (98), 155 (100), 128 (100), 67 (30), 39 (50). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.12–1.89 (10H, m, 5CH_2 of cyclohexyl), 2.98 (1H, m, CH–N of cyclohexyl), 6.15 (1H, d, $^{3}J_{HH} = 7.4$ Hz, N–CH=C*H*), 6.61 (1H, s, N–CH=N), 6.85 (1H, d,$^{3}J_{HH} = 7.4$ Hz, N–C*H*=CH), 6.89–8.15 (8H, m, H-Ar), 8.00 (1H, br s, N–CH), 11.96 (1H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.23, 24.31, 24.62, 31.99, 33.41 (C-cyclohexyl), 53.02 (CH–N of cyclohexyl), 57.53 (N–CH), 101.56 (CO–*C*=COH), 112.21, 116.09, 121.51, 123.03, 124.96, 125.64, 126.00, 126.90, 126.93, 127.35, 129.36, 131.25, 132.61, 153.07 (C-Ar, N–*C*H=*C*H), 154.15, 164.31, 174.18 (*C*O–C=*C*OH, 1C=N). Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.82; H, 5.95; N, 7.05.

2.2. 3-(2-((*tert*-Butylimino)methyl)-1,2-dihydroisoquinolin-1-yl)chroman-2,4-dione (4b)

Colourless crystals (0.35 g, yield 95%); mp 176–178 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2966, 1657, 1649, 1507, 1451. MS, *m*/*z* (%): 374 (M^+, 3), 344 (15), 288 (15), 209 (10), 183 (20), 155 (70), 121 (70), 92 (50), 64 (25), 44 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.22 (9H, s, C(CH_3)$_3$), 6.21 (1H, d, $^{3}J_{HH} = 8.0$ Hz, N–CH=C*H*), 6.62 (1H, s, N–CH=N), 6.71–5.15 (9H, m, N–C*H*=CH, H-Ar), 7.93 (1H, br s, N–CH), 11.86 (1H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.92 (C(*C*H$_3$)$_3$), 53.01 (*C*(CH$_3$)$_3$), 55.81 (N–CH), 101.79 (CO–*C*=COH), 112.55, 116.15, 121.49, 123.00, 125.10, 125.58, 125.96, 126.92, 127.26, 127.57, 129.60, 131.19, 132.50, 150.51 (C-Ar, N–*C*H=*C*H), 154.24, 164.41, 173.98 (*C*O–C=*C*OH, 1C=N). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.70; H, 5.96; N, 7.53.

2.3. 3-(2-((2,4,4-Trimethylpentan-2-ylimino)methyl)-1,2-dihydroisoquinolin-1-yl)chroman-2,4-dione (4c)

Colourless crystals (0.33 g, yield 78%); mp 149–151 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2952, 1669, 1601, 1509, 1451. MS, *m*/*z* (%): 430 (M^+, 3), 155 (75), 121 (78), 92 (60), 64 (30), 44 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.92 (9H, s, C(CH_3)$_3$), 1.30 (3H, s, C(CH_3)$_2$), 1.39 (3H, s, C(CH_3)$_2$), 1.65 (1H, d, $^{3}J_{HH} =$ 14.2 Hz, CH_2), 1.77 (1H, d, $^{3}J_{HH} = 14.2$ Hz, CH_2), 6.18–7.74 (11H, m, N–C*H*=C*H*, N–C*H*=N,H-Ar), 8.15 (1H, br s, N–CH), 12.16 (1H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.45 (C(*C*H$_3$)$_2$), 19.35 (C(*C*H$_3$)$_2$), 31.22 (C(*C*H$_3$)$_3$), 31.63 (CH_2), 53.56 (N–CH), 54.15 (*C*(CH$_3$)$_3$), 59.41 (*C*(CH$_3$)$_2$), 101.66 (CO–*C*=COH), 113.21, 116.21, 121.49, 122.78, 125.08, 125.46, 126.13, 126.40, 127.13, 127.79, 129.38, 131.08,

132.47, 149.86 (C-Ar, N–CH=CH), 154.26, 163.86, 173.74 (*C*O–C=*C*OH, 1C=N). Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 75.21; H, 7.14; N, 6.38.

2.4. 3-(2-((Cyclohexylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-6-methyl-3*H*-pyran-2,4-dione (4d)

Colourless crystals (0.22 g, yield 62%); mp 181–191 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2927, 2856, 1688, 1633, 1488, 1451. MS, *m*/*z* (%): 365 (M^++1, 2), 284 (5), 257 (5), 129 (100), 101 (30), 98 (35), 67 (50), 55 (25), 43 (35), 39 (35). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.17–1.96 (10H, m, 5CH_2 of cyclohexyl), 2.10 (3H, s, C*H*$_3$–C=CH), 2.92 (1H, m, CH–N of cyclohexyl), 5.76 (1H, s, CH_3–C=C*H*), 6.08 (1H, d, $^3J_{HH} = 7.4$ Hz, N–CH=C*H*), 6.38 (1H, s, N–CH=N), 6.83 (1H, d, $^3J_{HH} = 7.2$ Hz, H-Ar), 6.88 (1H, d, $^3J_{HH} = 7.4$ Hz, N–C*H*=CH), 6.95–7.08 (3H, m, H-Ar), 7.99 (1H, br s, N–C*H*), 11.96 (1H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 19.85 (3H, s, CH_3), 24.40, 24.47, 24.64, 32.31, 33.14 (C-cyclohexyl), 52.49 (CH–N of cyclohexyl), 57.50 (N–CH), 101.12 (CO–*C*=COH), 106.79, 112.03, 124.87, 126.07, 126.80, 126.87, 127.23, 129.44, 132.62, 153.05 (C-Ar, CH_3–*C*=*C*H, N–*C*H=*C*H), 160.36, 164.65, 178.25 (*C*O–C=*C*OH, 1C=N). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.45; H, 6.60; N, 7.72.

2.5. 3-(2-((*tert*-Butylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-6-methyl-3*H*-pyran-2,4-dione (4e)

Colourless crystals (0.20 g, yield 62%); mp 188–190 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2971, 1678, 1642, 1492, 1448. MS, *m*/*z* (%): 339 (M^++1, 100), 240 (15), 170 (10), 129 (100), 130 (100), 129 (100), 102 (25), 57 (50), 41 (20). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.25 (9H, s, C(CH_3)$_3$), 2.09 (3H, s, C*H*$_3$–C=CH), 5.76 (1H, s, CH_3–C=C*H*), 6.13 (1H, d, $^3J_{HH} = 6.8$ Hz, N–CH=C*H*), 6.39 (1H, s, N–CH=N), 6.91–7.03 (5H, m, N–C*H*=CH, H-Ar), 7.85 (1H, br s, N–CH), 12.04 (1H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 19.83 (*C*H$_3$–C=CH), 28.88 (C(*C*H$_3$)$_3$), 52.43 (*C*(CH$_3$)$_3$), 55.66 (N–CH), 101.33 (CO–*C*=COH), 106.79, 112.25, 125.05, 125.94, 126.75, 126.38, 127.49, 129.69, 132.54, 153.64 (C-Ar, CH_3–*C*=*C*H, N–*C*H=*C*H), 160.44, 165.84, 178.15 (*C*O–C=*C*OH, 1C=N). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.81; H, 6.60; N, 8.20.

2.6. 3-(2-((2,4,4-Trimethylpentan-2-ylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-6-methyl-3*H*-pyran-2,4-dione (4f)

Colourless crystals (0.23 g, yield 59%); mp 127–130 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2961, 1668, 1605, 1509. MS, *m*/*z* (%): 395 (M^++1, 80), 129 (100), 130 (90), 129 (95), 102 (30), 57 (50). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.97 (9H, s, C(CH_3)$_3$), 1.38 (3H, s, C(CH_3)$_2$), 1.42 (3H, s, C(CH_3)$_2$), 1.66 (1H, d, $^3J_{HH} = 14.7$ Hz, CH_2), 1.78 (1H, d, $^3J_{HH} = 14.7$ Hz, CH_2), 2.07 (3H, s, C*H*$_3$–C=CH), 5.73 (1H, s, CH_3–C=C*H*), 6.12 (1H, d, $^3J_{HH} = 6.8$ Hz, N–CH=C*H*), 6.42 (1H, s, N–CH=N), 6.66–7.11 (5H, m, N–C*H*=CH, H-Ar), 7.66 (1H, br s, N–CH), 12.45 (1H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 19.84 (*C*H$_3$–C=CH), 28.18 (C(*C*H$_3$)$_2$), 29.82 (C(*C*H$_3$)$_2$), 31.31 (C(*C*H$_3$)$_3$), 31.69 (CH_2), 53.16 (N–CH), 54.19 (*C*(CH$_3$)$_3$), 59.28 (*C*(CH$_3$)$_2$), 101.03 (CO–*C*=COH), 106.49, 113.02, 124.91, 126.20, 126.37, 127.02, 127.65, 129.44, 132.52, 149.78 (CH$_3$–*C*=*C*H, C-Ar, N–*C*H), 160.57, 165.00, 177.93 (*C*O–C=*C*OH, 1C=N). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.56; H, 7.60; N, 7.00.

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