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An unexpected, novel, three-component reaction between isoquinoline, an isocyanide and strong CH-acids in water

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Abstract—An unexpected three-component condensation reaction between an isocyanide, isoquinoline and a strong CH-acid efficiently provides 1,2-dihydroisoquinoline derivatives in a one-pot reaction in water at 70 °C without using any catalyst.

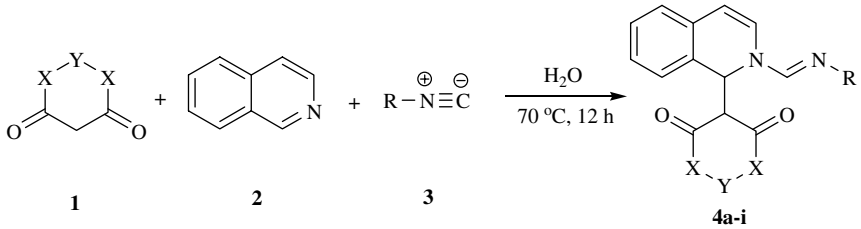
1. Introduction

The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds.[1] In particular, 1,2-dihydroisoquinoline derivatives act as delivery systems that transport drugs through the otherwise highly impermeable blood–brain barrier.[2] These compounds also exhibit sedative,[3] antidepressant,[4] antitumor, and antimicrobial activities.[5] For the functionalization of quinoline, isoquinoline and related aromatic amines, the Reissert reaction has remained one of the most powerful tools.[6] This 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.

Multi-component reactions (MCRs), due to their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry.[7] Therefore, the design of novel MCRs has attracted great attention from research groups working in areas such as drug discovery, organic synthesis and materials science. As a result, the number of new MCRs has grown rapidly.[8]

The reactivity of isocyanides or nitrogen-containing heterocycles such as isoquinoline as nucleophiles with activated alkynes in the presence of strong CH-acids is well documented.[9] The reaction generally involves the initial addition of isocyanide or isoquinoline to activated alkynes to form zwitterionic intermediates which can be trapped by various activated CH-acids. To the best of our knowledge, there has not been any report on the reaction between isocyanide and isoquinoline in the presence of activated CH-acids.

In continuation of our interest in isocyanide-based multi-component reactions,[10] we herein report a hitherto unknown three-component reaction, which affords 1,2-dihydroisoquinoline derivatives (Scheme 1).



1 2 3 4a-i

Scheme 1.

Keywords: 1,2-Dihydroisoquinoline; Isoquinoline; Isocyanide; Multi-component reactions.
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As indicated in Scheme 1 and Table 1, CH-acid **1**, isoquinoline **2** and isocyanide **3**, undergo a smooth 1:1:1 addition reaction in water at 70 °C to produce 1,2-dihydroisoquinolines **4**.

The structures of the products were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4a** consisted of two singlets for the *tert*-butyl ($\delta = 1.33$ ppm) and N–CH=N ($\delta = 5.98$ ppm) protons, respectively, two doublets for the N–CH=C*H* ($\delta = 6.09$ ppm, $^3J_{HH} = 7.5$ Hz) and N–C*H*=CH ($\delta = 6.84$ ppm, $^3J_{HH} = 7.5$) protons, a multiplet for the isoquinoline moiety ($\delta = 6.87$–7.07 ppm), a doublet for N–CH ($\delta = 8.28$ ppm, $^3J_{HH} = 13.6$ Hz), a broad singlet for the two NH groups ($\delta = 9.55$ ppm), and a doublet for the CO–CH–CO ($\delta = 11.12$ ppm, $^3J_{HH} = 13.6$ Hz) proton. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 16 distinct resonances, partial assignment of these resonances is given in the experimental section. Finally, the structure of **4a** was confirmed unambiguously by a single crystal X-ray analysis (Fig. 1).[11]

Table 1. Multi-component synthesis of 1,2-dihydroisoquinoline derivatives in water

Entry	R	X	Y	Product	Yield (%)
1	*tert*-Butyl	NH	C=O	**4a**	79
2	Cyclohexyl	NH	C=O	**4b**	80
3	Cyclohexyl	NMe	C=O	**4c**	95
4	*tert*-Butyl	NMe	C=O	**4d**	88
5	Cyclohexyl	NH	C=S	**4e**	89
6	*tert*-Butyl	NH	C=S	**4f**	81
7	Cyclohexyl	O	CMe_2	**4g**	52
8	*tert*-Butyl	O	CMe_2	**4h**	51
9	Cyclohexyl	CH_2	CMe_2	**4i**	56

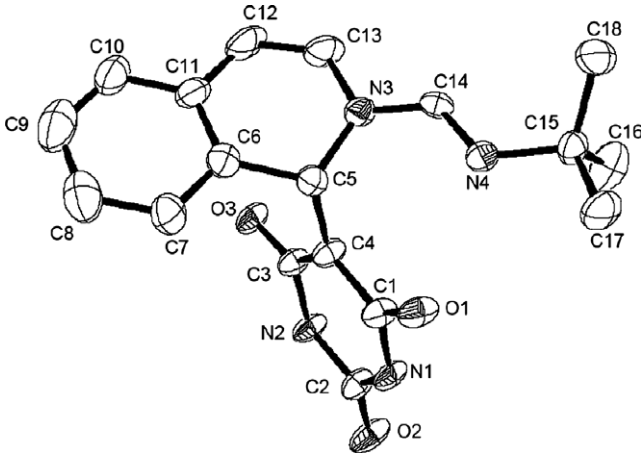


Figure 1. ORTEP representation of **4a**.

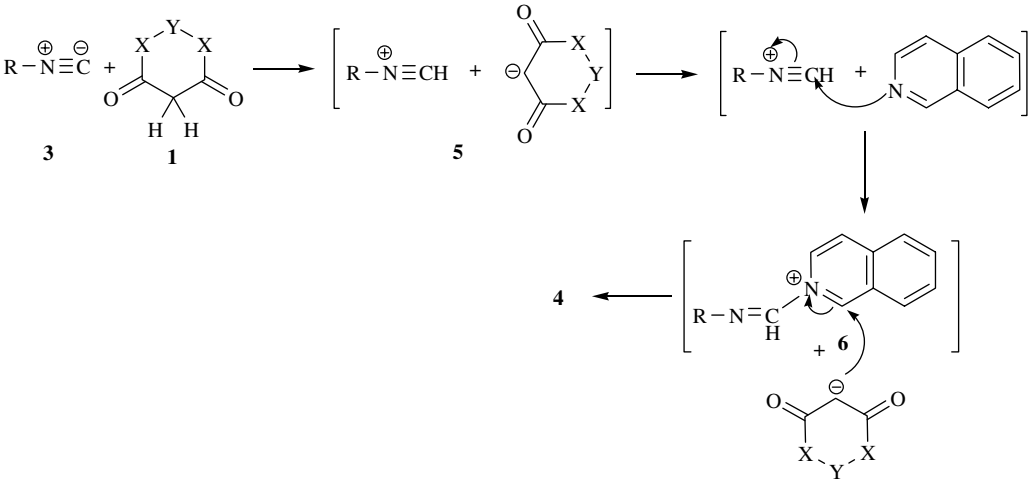
A rationale for the formation of product is shown in Scheme 2. It is conceivable that the initial event is the formation of acid–base complex **5** from the isocyanide and activated CH-acid.[12] Complex **5** activates the isocyanide functional group sufficiently for further nucleophilic attack by isoquinoline to produce intermediate **6**. Finally, nucleophilic attack of the conjugated base of the CH-acid on **6**, afforded the product **4**.

In conclusion, we have developed a new multi-component reaction capable of introducing different activated CH-acid groups into heterocyclic systems to yield 1,2-dihydroisoquinoline derivatives in water at 70 °C without a catalyst. Further reactivity studies and synthetic applications of this methodology are in progress in our laboratory.

2. Experimental

2.1. Typical procedure for the preparation of 5-(2-((*E*)-(*tert*-butylimino)methyl)-1,2-dihydroisoquinolin-1-yl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (4a)

To a magnetically stirred solution of isoquinoline (0.13 g, 1 mmol) and barbituric acid (0.16 g, 1 mmol) in H_2O (20 mL) was added *tert*-butyl isocyanide (0.08 g, 1 mmol) and the reaction was heated for 12 h at 70 °C. After completion of the reaction, as indicated



Scheme 2.

by TLC (ethyl acetate/*n*-hexane, 2:1), the reaction mixture was filtered and the residue washed with water (2×10 mL). The resulting solid was crystallized from ethyl acetate as colorless crystals (0.27 g, yield 79%); mp 189–191 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2977, 1682, 1651, 1556, 1447. MS, *m*/*z* (%): 239 (M^+-101, 2), 196 (4), 155 (4), 129 (100), 102 (35), 68 (15), 58 (35), 43 (90). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.33 (9H, s, $C(CH_3)_3$), 5.98 (1H, s, N–CH=N), 6.09 (1H, d, $^3J_{HH} = 7.5$ Hz, N–CH=C*H*), 6.84 (1H, d, $^3J_{HH} = 7.5$ Hz, N–C*H*=CH), 6.87–7.07 (4H, m, H-Ar), 8.28 (1H, d, $^3J_{HH} = 13.6$ Hz, N–CH), 9.55 (2H, br s, 2NH), 11.12 (1H, d, $^3J_{HH} = 13.6$ Hz, CO–CH–CO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 29.12 ($C(CH_3)_3$), 53.67 ($C(CH_3)_3$), 55.64 (N–CH), 89.84 (CO–*C*H–CO), 112.13, 124.84, 125.88, 126.79, 127.06, 127.39, 130.07, 133.90 (C-Ar), 151.71, 152.17, 161.14, 166.14 (3C=O, 1C=N). Anal. Calcd for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.27; H, 5.90; N, 16.18.

2.2. 5-(2-((*E*)-(Cyclohexylimino)methyl)-1,2-dihydroisoquinolin-1-yl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (4b)

Colorless crystals (0.29 g, yield 80%); mp 200–202 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2933, 2844, 1682, 1636, 1561, 1449. MS, *m*/*z* (%): 288 (M^+-78, 2), 237 (2), 129 (100), 67 (45), 45 (65). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.84–1.70 (10H, m, $5CH_2$ of cyclohexyl), 3.17 (1H, m, CH–N of cyclohexyl), 5.73 (1H, s, N–CH=N), 5.84 (1H, d, $^3J_{HH} = 7.6$ Hz, N–CH=C*H*), 6.43 (1H, d, $^3J_{HH} = 7.6$ Hz, N–C*H*=CH), 6.62–6.83 (4H, m, H-Ar), 8.11 (1H, d, $^3J_{HH} = 12.9$ Hz, N–CH), 9.32 (2H, br s, 2NH), 10.85 (1H, d, $^3J_{HH} = 12.9$ Hz, CO–CH–CO). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 24.37, 24.38, 25.01, 32.89, 32.96 (carbons of cyclohexyl), 53.82 (CH–N of cyclohexyl), 57.31 (N–CH), 89.83 (CO–*C*H–CO), 112.44, 124.89, 125.88, 126.60, 126.81, 127.46, 130.02, 133.91 (C-Ar), 152.13, 153.75, 156.13, 165.00 (3C=O, 1C=N). Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.20; H, 6.20; N, 15.02.

2.3. 5-(2-((*E*)-2-Cyclohexylvinyl)-1,2-dihydroisoquinolin-1-yl)-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (4c)

Colorless crystals (0.37 g, yield 95%); mp 192–194 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2946, 2856, 1688, 1682, 1595, 1455. MS, *m*/*z* (%): 265 (M^+-129, 45), 222 (45), 169 (20), 110 (30), 97 (40), 69 (40), 55 (70), 41 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.26–1.97 (10H, m, $5CH_2$ of cyclohexyl), 3.12 (3H, s, N–CH_3), 3.31 (1H, m, CH–N of cyclohexyl), 3.36 (3H, s, N–CH_3), 6.18 (1H, d, $^3J_{HH} = 7.5$ Hz, N–CH=C*H*), 6.29 (1H, s, N–CH=N), 6.53 (1H, d, $^3J_{HH} = 7.5$ Hz, N–C*H*=CH), 7.01–7.15 (4H, m, H-Ar), 7.63 (1H, d, $^3J_{HH} = 12.9$ Hz, N–CH), 11.50 (1H, d, $^3J_{HH} = 12.9$ Hz, CO–CH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.24, 24.38, 24.63 (carbons of cyclohexyl), 27.19, 27.98 (2N–CH_3), 32.82, 33.45 (carbons of cyclohexyl), 55.95 (CH–N of cyclohexyl), 58.70 (N–CH), 90.49 (CO–*C*H–CO), 114.56, 124.67, 125.24, 125.97, 127.19, 128.06, 128.66, 132.88 (C-Ar), 151.04, 153.23, 162.99, 164.57 (3C=O, 1C=N). Anal. Calcd for $C_{22}H_{26}N_4O_3$: C, 66.99; H, 6.64; N, 14.20. Found: C, 66.70; H, 6.53; N, 14.30.

2.4. 5-(2-((*E*)-(*tert*-Butylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (4d)

Colorless crystals (0.32 g, yield 88%); mp 183–185 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2982, 1682, 1606, 1559, 1429. MS, *m*/*z* (%): 369 (M^++1, 5), 157 (50), 129 (100), 102 (35), 84 (15), 57 (75), 42 (40). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.39 (9H, s, $C(CH_3)_3$), 3.12, 3.37 (6H, 2s, 2N–CH_3), 6.15 (1H, d, $^3J_{HH} = 7.0$ Hz, N–CH=C*H*), 6.28 (1H, s, N–CH=N), 6.52 (1H, d, $^3J_{HH} = 7.0$ Hz, N–C*H*=CH), 7.03–7.12 (4H, m, H-Ar), 7.60 (1H, d, $^3J_{HH} = 13.4$ Hz, N–CH), 11.51 (1H, d, $^3J_{HH} = 13.4$ Hz, CO–CH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 27.20, 27.94 (2N–CH_3), 29.30 ($C(CH_3)_3$), 55.71 ($C(CH_3)_3$), 55.91 (N–CH), 90.51 (CO–*C*H–CO), 114.35, 125.09, 125.17, 125.98, 127.18, 128.05, 128.67, 132.84 (C-Ar), 149.26, 153.27, 162.99, 164.42 (3C=O, 1C=N). Anal. Calcd for $C_{20}H_{24}N_4O_3$: C, 65.20; H, 6.57; N, 15.21. Found: C, 65.10; H, 6.65; N, 15.11.

2.5. 5-(2-((*E*)-(Cyclohexylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-dihydro-2-thioxopyrimidine-4,6-(1*H*,5*H*)-dione (4e)

Colorless crystals (0.34 g, yield 89%); mp 196–198 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 3171, 2931, 2856, 1687, 1647, 1598, 1516, 1428. MS, *m*/*z* (%): 313 (M^+-69, 2), 253 (95), 210 (20), 129 (100), 97 (30), 67 (55), 56 (55), 42 (90). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.28–2.06 (10H, m, $5CH_2$ of cyclohexyl), 3.56 (1H, m, CH–N of cyclohexyl), 5.99 (1H, s, N–CH=N), 6.09–7.07 (6H, m, N–CH=CH, H-Ar), 8.22 (1H, d, $^3J_{HH} = 13.4$ Hz, N–CH), 10.75 (1H, d, $^3J_{HH} = 13.4$ Hz, CO–CH–CO), 10.99 (2H, br s, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 24.35, 24.49, 24.90, 32.78, 32.89 (carbons of cyclohexyl), 53.23 (CH–N of cyclohexyl), 57.33 (N–CH), 94.02 (CO-*C*H-CO), 112.52, 124.97, 125.88, 126.56, 127.08, 127.56, 130.03, 133.03 (C-Ar), 153.84, 157.93, 160.00 (2C=O, 1C=N), 175.03 (1C=S). Anal. Calcd for $C_{20}H_{22}N_4O_2S$: C, 62.80; H, 5.80; N, 14.65. Found: C, 62.65; H, 5.88; N, 14.60.

2.6. 5-(2-((*E*)-(*tert*-Butylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-dihydro-2-thioxopyrimidine-4,6-(1*H*,5*H*)-dione (4f)

Colorless crystals (0.29 g, yield 81%); mp 210–212 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2933, 2857, 1681, 1657, 1574, 1516, 1421. MS, *m*/*z* (%): 277 (M^+-79, 75), 212 (65), 171 (45), 144 (95), 129 (100), 116 (100), 102 (90), 75 (30), 57 (90), 39 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.33 (9H, s, $C(CH_3)_3$), 5.99 (1H, s, N–CH=N), 6.08–7.06 (6H, m, N–CH=CH, H-Ar), 8.30 (1H, br s, N–CH), 10.79 (1H, br s, CO–CH–CO), 10.98 (2H, br s, 2NH). ^{13}C NMR (75 MHz,

DMSO-d_6): δ_C (ppm) 29.15 (C(CH_3)$_3$), 53.11 (C(CH_3)$_3$), 55.85 (N–CH), 94.03 (CO–CH–CO), 112.21, 124.91, 125.89, 127.00, 127.03, 127.52, 130.09, 133.05 (C-Ar), 151.86, 160.11, 162.98 (2C=O, 1C=N), 175.04 (1C=S). Anal. Calcd for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72. Found: C, 60.45; H, 5.74; N, 15.63.

2.7. 5-(2-((*E*)-(Cyclohexylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4g)

Colorless crystals (0.20 g, yield 52%); mp 189–191 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2939, 2844, 1670, 1688, 1651, 1572, 1401. MS, *m*/*z* (%): 280 (M^+−102, 3), 169 (10), 155 (6), 129 (100), 102 (50), 75 (25), 68 (30), 55 (70), 41 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.01–1.78 (10H, m, 5CH_2 of cyclohexyl), 1.64 (6H, s, 2CH_3), 3.11 (1H, m, CH–N of cyclohexyl), 6.03 (1H, s, N–CH=N), 6.08–7.15 (6H, N–CH=CH, H-Ar), 8.20 (1H, d, $^3J_{HH}$ = 11.5 Hz, N–CH), 10.89 (1H, d, $^3J_{HH}$ = 11.5 Hz, CO–CH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.22, 24.33, 24.61 (carbons of cyclohexyl), 27.59 (2CH_3), 32.36, 33.29 (carbons of cyclohexyl), 54.87 (CH–N of cyclohexyl), 57.51 (N–CH), 81.27 (CO–CH–CO), 102.23 (CH_3–C–CH_3), 112.58, 125.29, 126.20, 126.96, 127.18, 127.54, 128.85, 132.89 (C-Ar), 153.05, 162.93 (2C=O, 1C=N). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.01; H, 6.93; N, 7.11.

2.8. 5-(2-((*E*)-(*tert*-Butylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4h)

Colorless crystals (0.18 g, yield 51%); mp 210–212 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2989, 1670, 1667, 1578, 1499, 1396. MS, *m*/*z* (%): 254 (M^+−102, 3), 169 (10), 155 (5), 129 (100), 102 (55), 75 (20), 68 (35), 57 (95), 43 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.28 (9H, s, C(CH_3)$_3$), 1.65 (6H, s, 2CH_3), 6.03 (1H, s, N–CH=N), 6.15 (1H, d, $^3J_{HH}$ = 7.2 Hz, N–CH=CH), 6.92 (1H, d, $^3J_{HH}$ = 7.2 Hz, N–CH=CH), 7.02–7.15 (4H, m, H-Ar), 7.96 (1H, d, $^3J_{HH}$ = 13.7 Hz, N–CH), 11.19 (1H, d, $^3J_{HH}$ = 13.7 Hz, CO–CH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.21 (2CH_3), 29.40 (C(CH_3)$_3$), 55.02 (CH–N of cyclohexyl), 55.75 (N–CH), 81.47 (CO–CH–CO), 102.23 (CH_3–C–CH_3), 113.15, 125.41, 126.14, 126.45, 127.18, 127.72, 129.08, 132.85 (C-Ar), 151.00, 158.80 (2C=O, 1C=N). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.31; H, 6.83; N, 7.81.

2.9. 2-(2-((*E*)-(Cyclohexylimino)methyl)-1,2-dihydroisoquinolin-1-yl)-5,5-dimethylcyclohexane-1,3-dione (4i)

Colorless crystals (0.21 g, yield 56%); mp 207–209 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2939, 2844, 1670, 1688, 1651, 1572, 1401. MS, *m*/*z* (%): 378 (M^+, 5), 284 (20), 257 (75), 230 (50), 183 (20), 155 (30), 130 (100), 83 (20), 55 (45), 41 (30). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.99, 1.02 (6H, 2s, 2CH_3), 1.23–2.33 (14H, m, 7CH_2 of cyclohexyl and dimedone), 3.18 (1H, m, CH–N of cyclohexyl), 6.03 (1H, d, $^3J_{HH}$ = 7.6 Hz, N–CH=CH), 6.21 (1H, s, N–CH=N), 6.50 (1H, d, $^3J_{HH}$ = 7.6 Hz, N–CH=CH), 6.83–7.13 (4H, m, H-Ar), 7.68 (1H, br s, N–CH), 12.30 (1H, br s, CO–CH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.60, 24.63, 24.65 (carbons of cyclohexyl), 27.83, 29.61 (2CH_3), 31.62 (CH_3–C–CH_3), 33.15, 33.44 (carbons of cyclohexyl), 48.74 (2CH_2 of dimedone), 54.00 (CH–N of cyclohexyl), 58.62 (N–CH), 113.23 (CO–CH–CO), 113.36, 124.77, 125.26, 125.60, 126.60, 127.49, 128.99, 134.00 (C-Ar), 151.02 (1C=N), 193.88 (2C=O). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.05; H, 8.14; N, 7.35.

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References and notes

1. (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Pergamon Press: London, 1965; (b) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148–170; (c) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742–760; (d) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730; (e) Hansch, C. P.; Sammes, G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, 1990.
2. (a) Pop, E.; Wu, W. M.; Shek, E.; Bodor, N. *J. Med. Chem.* **1989**, *32*, 1774–1781; (b) Sheha, M. M.; El-Koussi, N. A.; Farag, H. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 47–52; (c) Mahmoud, S.; Aboul-Fadl, T.; Farag, H.; Mouhamed, A. M. I. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 573–584; (d) Prokai, L.; Prokai-Tatrai, K.; Bodor, N. *Med. Res. Rev.* **2000**, *20*, 367–416.
3. Lukevics, E.; Segal, I.; Zablotskaya, A.; Germane, S. *Molecules* **1997**, *2*, 180–185.
4. (a) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433–1454; (b) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567–3579.
5. (a) Tietze, L. F.; Rackehmann, N.; Miller, I. *Chem. Eur. J.* **2004**, *10*, 2722–2731; (b) Knjlker, H. J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173–1175; (c) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
6. (a) Scriven, E. F. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, p 65; (b) Blaskó, G.; Kerekes, P.; Makleit, S. Reissert Synthesis of Isoquinoline and Indole Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1987; Vol. 31, p 987; (c) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328.
7. Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, 1998.
8. (a) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471–1499; (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313; (c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329; (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (e) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
9. (a) Shaabani, A.; Soleimani, E.; Khavasi, H. R.; Hoffmann, R. D.; Rodewald, U. C.; Poättgen, R. *Tetrahedron Lett.* **2006**, *47*, 5493–5496; (b) Shaabani, A.; Teimouri, M. B.; Mirzaei, P.; Bijanzadeh, H. R. *J. Chem. Res. (S)* **2003**, 82–83; (c) Shaabani, A.; Soleimani, E. *Phosphorus, Sulfur*

Silicon **2006**, *181*, 2475–2482; (d) Shaabani, A.; Bazgir, A.; Tavasoli-Rad, F.; Bijanzadeh, H. R.; Razmara, F. *J. Chem. Res. (S)* **2004**, 133–134.

10. (a) Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031–3034; (b) Shaabani, A.; Teimouri, M. B.; Arab Ameri, S. *Tetrahedron Lett.* **2004**, *45*, 8409–8413; (c) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2002**, *43*, 9151–9154; (d) Shaabani, A.; Yavari, I.; Teimouri, M. B.; Bazgir, A.; Bijanzadeh, H. R. *Tetrahedron* **2001**, *57*, 1375–1378; (e) Shaabani, A.; Teimouri, M. B.; Bazgir, A.; Bijanzadeh, H. R. *Mol. Div.* **2003**, *6*, 199–206; (f) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Monatsh. Chem.* **2004**, *135*, 441–446; (g) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 2185–2188; (h) Shaabani, A.; Teimouri, M. B. *J. Chem. Res. (S)* **2003**, 732–733; (i) Shaabani, A.; Bazgir, A.; Soleimani, K.; Bijanzadeh, H. R. *J. Fluorine Chem.* **2002**, *116*, 93–95.
11. Crystal data analyses: Stoe IPDSII two-circle diffractometer, MoK_α radiation ($k = 0.71073$); $T = 298$ (2) K; Graphite monochromator; numerical absorption correction. Structure solution by direct methods using SHELXL and refinement by full-matrix least-squares on F^2 using SHELXL of the X-STEP32 crystallographic software package;[13] all nonhydrogen atoms were refined anisotropically. Crystal data for **4a**: $C_{18}H_{20}N_4O_3$, $M = 340.38$ g mol^{-1}; crystal dimensions $0.20 \times 0.10 \times 0.05$ mm^3; triclinic, space group $P\bar{1}$; $a = 11.746$ (6), $b = 12.332$ (6), $c = 16.925$ (8) Å, $\alpha = 73.99$ (4)°, $\beta = 70.09$ (4)°, $\gamma = 61.71$ (4)°, $V = 2010.3$ (17) Å^3; $Z = 4$; $F(000) = 4720$, $D_{calc} = 1.125$ g cm^{-3}; $1.89 < \theta < 29.29$; section of the reciprocal lattice: $-16 \leqslant h \leqslant 16$, $-15 \leqslant k \leqslant 16$, $-21 \leqslant l \leqslant 23$; of the 19,605 reflections that were collected, 9959 were unique with $I > 2\sigma(I)$; absorption coefficient 0.079 mm^{-1}; $R_1 = 0.1641$ for $I > 2\sigma(I)$ and $wR_2 = 0.3544$; largest peak (0.830 e Å^{-3}) and hole (-0.235 e Å^{-3}) (CCDC 628493).
12. Sung, K.; Chen, C. C. *Tetrahedron Lett.* **2001**, *42*, 4845–4848.
13. Stoe & Cie, X-STEP32, Version 1.07b: Crystallographic package; Stoe & Cie GmbH: Darmstadt, Germany, **2000**.