J IRAN CHEM SOC (2015) 12:389–396
DOI 10.1007/s13738-014-0495-6

ORIGINAL PAPER

Highly selective base-catalyzed ring closing Ugi-adducts from the reaction of 2-formylindole, 2-bromoacetic acid, amines and isocyanides

Morteza Shiri · Zahra Bozorgpour-Savadjani

Received: 11 February 2014 / Accepted: 24 June 2014 / Published online: 19 July 2014

Abstract The intermediate products of the Ugi reaction between indole-2-carboxaldehyde, 2-bromoacetic acid, amines and isocyanides were treated with Cs_2CO_3 in DMF to form a series of novel cyclized 1,2-dihydropyrazino[1,2-*a*]indol-3(4*H*)-ones (indole –NH cyclization) as major and piperazin-2-ones (amide –NH cyclization) as minor products.

Keywords Multicomponent condensation reactions · Indole · Base-catalyzed cyclization · Pyrazino[1,2-*a*]indolone

Introduction

Multicomponent reaction (MCR) techniques not only make the rapid construction of diverse and complex molecules possible, but also save time and costs, and reduce waste, in alignment with the principles of green chemistry [1–8]. A subtle change in the design of MCRs, followed by an efficient post-MCR transformation, can improve the diversity and complexity of organic compounds. In this context, indole derivatives in MCRs [6] gained much attention due to their different reactive sites, and the indole core being one of the most valuable scaffolds in many important natural and synthetic products [9–15]. Balalaie et al. [16] established a strategy for the one-pot syntheses of indolo[1,2-a]quinoxalinones from the Ugi reaction of aldehydes, 2-iodoaniline, 2-indole carboxylic acid, and isocyanides, followed by the copper-catalyzed intramolecular *N*-arylation in good to high yields. Zhang et al. [17] demonstrated that products from the condensation of 1*H*-indole-2-carbaldehyde, 2-iodobenzoic acid, isocyanides and amines, in a highly selective controlled manner gave three distinct sets of indole-based heterocycles under different reaction conditions. The same group in another innovative design, selectively prepared 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,7-dihydroindolo[2,3-*c*]quinolones [18]. Ivachtchenko and his co-workers established a method for the synthesis of 2,3-dihydropyrazino[1,2-a]indole-1,4-diones starting with the condensation of indole-2-carboxylic acids, ethyl pyruvate, isocyanides, and primary amines followed by cyclization [19].

Van der Eycken's group, prepared special Ugi-adducts containing indole and an alkyne motif with subsequent treatment with different gold derivatives to obtain a series of novel spiroindolines [20], azepinoindoles [21], indoloazocines [22], azepino- and azocino-[*c*,*d*]indolones [23]. Indolyl-substituted piperazinediones have been prepared starting from the Ugi reaction of *N*-protected tryptophane, amino acid esters, aldehydes and isocyanides, followed by deprotection and subsequent cyclization with the aid of MW radiation [24]. Very recently, an efficient approach to synthesize indole-fused diketopiperazines was developed by Pandey et al. [25] in which the Ugi reaction and the subsequent cyclization occurred in a one-pot reaction.

Using 2-(3-chloro-2-formyl-1*H*-indol-1-yl) acetic acid, amines and isocyanides in a Ugi three component condensation reactions involving an intramolecular cyclization strategy resulted in the preparation of indoloketopiperazine derivatives in moderate to high yields [26].

In continuation of our study on indole chemistry [6, 14, 27–30] and with the purpose to get access to a set of novel heterocyclic compounds with potential biological activity,

M. Shiri (✉) · Z. Bozorgpour-Savadjani
Department of Chemistry, Faculty of Science, Alzahra University, 1993893973 Vanak, Tehran, Iran
e-mail: mshiri@alzahra.ac.ir

we used 2-formylindole as aldehyde and bromoacetic acid as acid sources in the Ugi reaction, followed by cyclization of the intermediate under basic conditions.

Experimental section

General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Melting points are uncorrected. IR spectra were recorded on a Shimadzu infra red spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz Spectrometer in $CDCl_3$ as solvent. A Leco CHNS, model 932 was used for elemental analysis.

The synthesis of Ugi-adduct

To a stirred solution of 2-formylindole (1 mmol) and amine (1 mmol) in MeOH (5 mL), were added, bromoacetic acid (1 mmol) and then isocyanide (1 mmol) at room temperature. The reaction process was monitored by TLC. After 24 h, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using petroleum ether-EtOAc as eluent.

General procedure for the cyclization of Ugi-adducts

To a solution of Ugi-adduct (0.5 mmol) in DMF (10 mL) was added Cs_2CO_3 (1 equiv.) at room temperature. The reaction process was monitored by TLC. After 30 min, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using petroleum ether-EtOAc as eluent.

Physical and spectral data

1.1 White powder, mp 230–232 °C. FT-IR (KBr): ν_{max} = 3,323, 3,287, 3,082, 2,927, 1,653, 1,561, 712 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.00 (m, 3H), 1.25 (m, 2H), 1.57 (m, 3H), 1.79 (m, 2H), 2.27 (s, 3H), 3.59 (d, J = 11.76 Hz, 2H), 3.73 (m, 1H), 5.33 (s, 1H), 5.66 (d, J = 7.96 Hz, 1H), 6.40 (d, J = 0.96 Hz, 1H), 7.06 (t, J = 6.56 Hz, 4H), 7.15 (t, J = 7.9 Hz, 2H), 7.28 (d, J = 8.04 Hz, 1H), 7.51 (d, J = 7.88 Hz, 1H), 9.49 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 1.1, 24.7, 24.8, 25.3, 27.6, 32.7, 32.8, 49.0, 63.4, 77.2, 105.3, 111.7, 120.0, 120.6, 122.8, 127.1, 127.9, 130.4, 131.6, 136.6, 138.8, 139.3, 166.2, 168.1 ppm. CHN calculated for $C_{25}H_{28}BrN_3O_2$: C, 62.24; H, 5.85; N, 8.71, Found C, 62.18; H, 5.91; N, 8.66.

1.2 Pink–yellow powder, mp 222–224 °C. FT-IR (KBr): ν_{max} = 3,300, 3,006, 2,928, 1,650, 731 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.00 (m, 3H), 1.24 (m, 2H), 1.57 (m, 3H), 1.86 (m, 2H), 3.63 (q, 2H), 3.75 (m, 1H), 5.36 (s, 1H), 5.68 (d, J = 8.04 Hz, 1H), 6.40 (d, J = 1.2 Hz, 1H), 7.05 (m, 1H), 7.16 (m, 2H), 7.28 (m, 5H), 7.54 (d, J = 7.84 Hz, 1H), 9.47 (s, br, 1H) ppm. CHN calculated for $C_{24}H_{26}BrN_3O_2$: C, 61.54; H, 5.60; N, 8.97, Found C, 61.02; H, 5.42; N, 8.45.

1.4 White powder, mp 195–197 °C. FT-IR (KBr): ν_{max} = 3,305, 3,074, 2,928, 1,554, 720 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 (m, 3H), 1.27 (m, 2H), 1.60 (m, 5H), 3.63 (m, 2H), 3.71 (s, 4H), 5.40 (s, 1H), 5.72 (d, J = 8 Hz, 1H), 6.40 (d, J = 1.12 Hz, 1H), 6.76 (d, J = 8.88 Hz, 2H), 7.12 (m, 5H), 7.28 (d, J = 8.24 Hz, 1H), 7.51 (d, J = 7.88 Hz, 1H), 9.49 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.3, 27.6, 32.7, 32.8, 49.0, 55.5, 63.0, 105.3, 111.7, 114.9, 120.0, 120.6, 122.8, 127.1, 129.4, 131.5, 133.8, 136.6, 159.9, 166.3, 168.2 ppm. CHN calculated for $C_{25}H_{28}BrN_3O_3$: C, 60.24; H, 5.66; N, 8.43, Found C, 60.33; H, 5.51; N, 8.08.

1.5 White powder, mp 130–133 °C. FT-IR (KBr): ν_{max} = 3,264, 3,082, 2,975, 1,639, 1,562, 725 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 2.67 (s, 3H), 3.64 (q, 2H), 5.41 (s, 1H), 5.78 (s, 1H), 6.39 (s, 1H), 7.03 (t, J = 6.36 Hz, 5H), 7.11 (m, 1H), 7.25 (d, J = 8.12 Hz, 1H), 7.51 (d, J = 7.92 Hz, 1H), 9.42 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.4, 21.1, 28.6, 51.8, 55.4, 105.1, 111.6, 119.9, 120.6, 122.7, 127.1, 128.0, 130.3, 131.7, 136.6, 138.3, 139.3, 166.5, 167.9 ppm. CHN calculated for $C_{23}H_{26}BrN_3O_2$: C, 60.53; H, 5.74; N, 9.21, Found C, 60.65; H, 5.84; N, 9.32.

1.6 White powder, mp 169–171 °C. FT-IR (KBr): ν_{max} = 3,303, 3,300, 3,074, 2,933, 1,645, 1,559, 698 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 (m, 3H), 1.23 (m, 2H), 1.53 (m, 3H), 1.71 (m, 1H), 1.82 (m, 1H), 3.96 (m, 1H), 3.82 (s, 2H), 4.62 (d, J = 3.32 Hz, 2H), 5.14 (s, 1H), 5.60 (d, J = 7.92 Hz, 1H), 6.28 (s, 1H), 7.05 (d, J = 7.88 Hz, 1H), 7.16 (m, 6H), 7.24 (m, 1H), 7.48 (d, J = 7.84 Hz, 1H), 9.54 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 24.7, 24.8, 25.3, 26.7, 32.6, 32.8, 48.8, 53.1, 59.9, 105.5, 111.7, 120.0, 120.6, 122.9, 126.9, 127.1, 128.0, 128.9, 131,6, 135.2, 136.6, 166.2, 169.1, ppm. CHN calculated for $C_{25}H_{28}BrN_3O_2$: C, 62.24; H, 5.85; N, 8.71, Found C, 62.42; H, 5.54; N, 8.65.

2.1a Yellow powder, mp 239–241 °C. FT-IR (KBr): ν_{max} = 3,315, 3,063, 2,924, 1,669, 1,546 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.07 (m, 3H), 1.33 (m, 2H), 1.61 (m, 3H), 1.82 (m, 1H), 1.92 (m, 1H), 2.28 (s, 3H), 3.58 (m, 1H), 4.93 (q, 2H), 5.22 (s, 1H), 5.58 (d, J = 7.4 Hz, 1H), 6.38 (s, 1H), 7.09–7.23 (m, 7H), 7.54 (d, J = 7.88 Hz, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.1, 22.6, 24.6, 24.7, 25.3, 29.7, 32.5, 32.8, 47.1, 49.2, 63.5, 97.53,

109.1, 120.6, 120.9, 122.4, 126.7, 128.2, 129.1, 130.2, 135.7, 138.1, 138.3, 166.2, 167.1 ppm. CHN calculated for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47, Found C, 74.77; H, 6.50; N, 10.32.

2.1b Red powder, 79–81 °C. FT-IR (KBr): $\nu_{max} = 3{,}313$, 3,003, 2,924, 1,655, 1,452 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 0.78$ (m, 3H), 1.00 (m, 2H), 1.42 (m, 2H), 1.62 (m, 2H), 1.78 (m, 1H), 2.24 (s, 3H), 3.94 (q, 2H), 4.23 (m, 1H), 5.50 (s, 1H), 6.5 (s, 1H), 7.09 (m, 4H), 7.24 (m, 2H), 7.51 (d, $J = 7.84$ Hz, 1H), 8.61 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.0$, 22.7, 25.1, 25.3, 25.4, 29.4, 29.6, 29.7, 45.47, 53.1, 63.5, 100.9, 111.2, 120.3, 120.6, 122.7, 124.8, 127.7, 129.8, 131.5, 136.9, 137.4, 164.5, 165.2 ppm. CHN calculated for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47, Found C, 74.61; H, 6.84; N, 10.55.

2.2a Orange powder, mp 229–231 °C. FT-IR (KBr): $\nu_{max} = 3{,}322$, 3,061, 2,958, 1,662, 1,594 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 0.79$ (m, 1H), 1.00 (m, 4H), 1.21 (m, 2H), 1.58 (m, 3H), 1.78 (m, 1H), 3.59 (m, 1H), 4.94 (q, 2H), 5.24 (s, 1H), 5.57 (d, $J = 7.72$ Hz, 1H), 6.39 (s, 1H), 7.10–7.35 (m, 8H), 7.54 (m, 1H) ppm. CHN calculated for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84, Found C, 74.12; H, 6.42; N, 10.55.

2.2b Purple powder, mp 82–84 °C. FT-IR (KBr): $\nu_{max} = 3{,}301$, 3,057, 2,957, 1,655, 1,546 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.10$ (m, 3H), 1.32 (m, 2H), 1.61 (m, 4H), 1.89 (m, 2H), 3.94 (q, 2H), 4.23 (m, 1H), 5.54 (s, 1H), 6.51 (s, 1H), 7.05 (m, 1H), 7.16 (m, 2H), 7.26-7.37 (m, 5H), 7.50 (d, $J = 7.8$ Hz, 1H), 8.66 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 24.1, 24.3, 24.3, 28.4, 28.5, 28.6, 30.9, 44.4, 52.1, 62.41, 75.6, 99.9, 110.2, 119.3, 119.6, 121.7, 123.8, 126.3, 126.6, 128.2, 130.3, 135.9, 138.4, 163.4, 164.1 ppm. CHN calculated for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84, Found C, 74.45; H, 6.65; N, 10.09.

2.3a White powder, mp 241–243 °C. FT-IR (KBr): $\nu_{max} = 3{,}301$, 3,053, 2,924, 1,681, 1,646 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 0.77$ (m, 3H), 0.96 (m, 3H), 1.20 (m, 4H), 1.67 (m, 1H), 2.03 (s, 3H), 2.28 (s, 1H), 3.60 (m, 1H), 5.11 (m, 3H), 5.54 (d, $J = 7.96$ Hz, 1H), 6.38 (s, 1H), 7.01 (m, 1H), 7.18–7.27 (m, 7H), 7.55 (d, $J = 7.92$ Hz, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 17.5$, 24.5, 24.6, 25.3, 32.6, 32.9, 47.2, 49.2, 62.8, 97.3, 109.1, 120.6, 120.9, 122.4, 127.2, 128.1, 128.3, 128.7, 129.2, 131.2, 135.2, 135.8, 139.6, 165.9, 167.1 ppm. CHN calculated for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47, Found C, 74.65; H, 6.58; N, 10.36.

2.4a White powder, mp 255–257 °C. FT-IR (KBr): $\nu_{max} = 3{,}293$, 3,087, 2,925, 1,737, 1,656 cm^{-1}. ^{1}H-NMR (600 MHz, DMSO): $\delta = 1.09$ (m, 6H), 1.59 (m, 5H), 3.45 (m, 1H), 3.79 (s, 3H), 4.91 (d, $J = 16.98$ Hz, 1H), 5.07 (d, $J = 17.16$ Hz, 1H), 5.59 (s, 1H), 6.5 (s, 1H), 7.01 (d, $J = 8.76$ Hz, 2H), 7.11 (d, $J = 7.5$ Hz, 1H), 7.17 (t, $J = 4.47$ Hz, 3H), 7.51 (d, $J = 8.16$ Hz, 1H), 7.60 (d, $J = 7.92$ Hz, 1H), 8.38 (d, $J = 7.8$ Hz, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 18.4$, 24.0, 24.1, 24.9, 31.6, 32.1, 46.6, 47.4, 48.0, 55.3, 61.8, 96.7, 109.7, 114.3, 120.0, 120.3, 121.3, 127.7, 127.9, 130.2, 133.7, 134.9, 158.2, 165.7, 167.5 ppm. CHN calculated for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06, Found C, 72.11; H, 6.68; N, 10.19.

2.4b White powder, mp 222–224 °C. FT-IR (KBr): $\nu_{max} = 3{,}268$, 3,044, 2,923, 1,661, 1,623 cm^{-1}. ^{1}H-NMR (600 MHz, DMSO): $\delta = 1.22$ (m, 5H), 1.64 (m, 5H), 3.70 (s, 3H), 4.11 (m, 2H), 4.38 (d, $J = 17.28$ Hz, 1H), 5.47 (s, 1H), 6.45 (s, 1H), 6.86 (d, $J = 8.94$ Hz, 1H), 6.97 (m, 1H), 7.07 (m, 1H), 7.16 (d, $J = 8.88$ Hz, 2H), 7.35 (d, $J = 8.16$ Hz, 1H), 7.47 (d, $J = 7.86$ Hz, 1H), 11.21 (s, br, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 25.2$, 25.6, 28.7, 29.1, 45.5, 48.0, 48.1, 48.3, 53.0, 55.6, 63.0, 100.8, 111.9, 114.5, 119.6, 120.5, 121.9, 128.0, 128.4, 132.5, 134.5, 136.8, 158.5, 163.0, 164.3 ppm. CHN calculated for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06, Found C, 71.35; H, 6.42; N, 10.15.

2.5a Orange powder, mp 262–264 °C. FT-IR (KBr): $\nu_{max} = 3{,}295$, 3,008, 2,924, 1,691, 1,649, 745 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 2.52$ Hz, 9H), 2.29 (s, 3H), 4.93 (m, 2H), 5.14 (d, $J = 4.24$ Hz, 1H), 5.44 (s, 1H), 6.37 (d, $J = 2.96$ Hz, 1H), 7.13 (m, 7H), 7.55 (d, $J = 7.92$ Hz, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 28.4, 47.1, 52.2, 64.1, 97.3, 109.1, 120.6, 120.9, 122.3, 126.8, 128.2, 129.2, 130.2, 135.7, 138.1, 138.3, 166.1, 167.2 ppm.

CHN calculated for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19, Found C, 73.42; H, 6.54; N, 11.52.

2.6a Yellow powder, mp 29–32 °C. FT-IR (KBr): $\nu_{max} = 3{,}300$, 3,008, 2,925, 1,705, 1,660, 1,463 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (m, 3H), 1.14 (m, 2 Hz), 1.34 (m, 3H), 1.63 (m, 1H), 1.90 (m, 1H), 3.54 (m, 1H), 4.08 (d, $J = 15.16$ Hz, 1H), 4.87 (m, 3H), 5.44 (m, 2H), 6.27 (s, 1H), 7.03 (m, 2H), 7.23 (m, 6H), 7.49 (d, $J = 7.84$ Hz, 1H) ppm. CHN calculated for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47, Found C, 74.65; H, 6.47; N, 10.35.

2.6b White powder, mp 29–32 °C. FT-IR (KBr): $\nu_{max} = 3{,}281$, 3,085, 2,928, 1,653 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (m, 3H), 1.05 (m, 1H), 1.27 (m, 1H), 1.52 (m, 3H), 1.64 (m, 2H), 3.80 (m, 1H), 3.92 (m, 2H), 4.16 (m, 2H), 5.03 (s, 1H), 5.54 (d, $J = 14.8$ Hz, 1H), 6.31 (s, 1H), 7.59 (m, 2H), 7.15 (m, 2H), 7.26 (m, 5H), 8.42 (s, br, 1H) ppm. CHN calculated for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47, Found C, 74.97; H, 6.64; N, 10.55.

3a White powder, mp 234–236 °C. FT-IR (KBr): $\nu_{max} = 3{,}264$, 3,083, 2,931, 1,654, 1,561 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (m, 3H), 1.33 (m, 2H), 1.67

(m, 3H), 1.89 (m, 1H), 1.95 (m, 1H), 2.30 (s, 3H), 3.64 (d, $J = 0.6$ Hz, 2H), 3.81 (m, 1H), 5.65 (d, $J = 7.76$ Hz, 1H), 5.92 (s, 1H), 7.08 (d, $J = 8.48$ Hz, 4H), 7.17 (d, $J = 8.48$ Hz, 2H), 7.26 (m, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 24.7, 24.8, 32.7, 32.84, 48.8, 64.8, 128.6, 129.8, 129.9, 131.7, 132.6, 134.7, 136.1, 139.1, 167.3, 167.6 ppm. CHN calculated for $C_{23}H_{26}BrClN_2O_2$: C, 57.81; H, 5.48; N, 5.86, Found C, 57.77; H, 5.39; N, 5.81.

3b White powder, mp 229–231 °C. FT-IR (KBr): $\nu_{max} = 3{,}253$, 3,085, 2,930, 1,672, 1,565, 712 cm^{-1}. ^{13}C-NMR (100 MHz, DMSO): $\delta = 24.3$, 24.5, 25.0, 29.2, 32.0, 47.9, 60.5, 62.5, 63.0, 121.1, 121.4, 127.9, 128.0, 131.4, 131.8, 132.4, 132.6, 132.9, 133.7, 133.8, 137.1, 137.8, 165.3, 167.6, 168.1, 171.2 ppm. CHN calculated for $C_{22}H_{23}Br_2ClN_2O_2$: C, 48.69; H, 4.27; N, 5.16, Found C, 48.75; H, 4.31; N, 5.22.

3c White powder, mp 255–257 °C. FT-IR (KBr): $\nu_{max} = 3{,}327$, 3,080, 2,913, 1,661, 1,557, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (m, 3H), 1.34 (m, 2H), 1.87 (m, 5H), 3.65 (t, $J = 12.02$ Hz, 2H), 3.81 (m, 1H), 5.65 (d, $J = 7.8$ Hz, 1H), 5.94 (s, 1H), 7.06–7.26 (m, 8H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 24.7$, 24.8, 25.4, 27.59, 32.7, 32.8, 48.9, 64.8, 77.2, 128.6, 129.0, 129.2, 130.1, 131.7, 132.4, 134.7, 138.7, 167.1, 167.6 ppm. CHN calculated for $C_{22}H_{23}Br_2ClN_2O_2$: C, 56.97; H, 5.22; N, 6.04, Found C, 56.88; H, 5.31; N, 6.14.

3d White powder, mp 239–241 °C. FT-IR (KBr): $\nu_{max} = 3{,}275$, 3,078, 2,930, 1,655, 1,556, 737 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (m, 5H), 1.33 (m, 2H), 1.57–1.97 (m, 9H), 2.16 (s, 1H), 3.60 (m, 2H), 3.79 (m, 1H), 5.78 (m, 1H), 5.85 (s, 1H), 7.08 (m, 3H), 7.23 (m, 4H), 7.57 (m, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 17.7$, 24.6, 24.7, 25.4, 27.4, 32.7, 32.8, 48.8, 65.1, 127.2, 128.3, 129.5, 130.5, 131.1, 131.4, 131.5, 132.0, 134.9, 137.0, 137.4, 167.4, 167.7 ppm. CHN calculated for $C_{23}H_{26}BrClN_2O_2$: C, 57.81; H, 5.48; N, 5.86, Found C, 57.81; H, 5.42; N, 5.79.

3e White powder, mp 215–217 °C. FT-IR (KBr): $\nu_{max} = 3{,}268$, 3,080, 2,929, 1,659, 1,560, 714 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (m, 3H), 1.34 (m, 2H), 1.86 (m, 5H), 2.31(s, 3H), 3.63 (q, 2H), 3.82 (m, 4H), 5.55 (d, $J = 7.92$ Hz, 1H), 5.94 (s, 1H), 6.72 (m, 2H), 7.04 (m, 4H), 7.27 (m, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 24.7, 24.8, 25.4, 27.9, 32.8, 32.9, 48.7, 55.2, 65.0, 77.2, 113.7, 126.1, 129.6, 129.9, 131.7, 136.4, 138.6, 159.6, 167.0, 168.3 ppm. CHN calculated for $C_{24}H_{29}BrN_2O_3$: C, 60.89; H, 6.17; N, 5.92, Found C, 60.72; H, 6.14; N, 6.15.

3f White powder, mp 214–216 °C. FT-IR (KBr): $\nu_{max} = 3{,}263$, 3,080, 2,929, 1,651, 1,562, 714 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.0$ (m, 3H), 1.34 (m, 2H), 1.62 (m, 3H), 1.85 (m, 1H), 1.95 (m, 1H), 3.63 (q, 2H), 3.81 (m, 4H), 5.43 (d, $J = 8.12$ Hz, 1H), 6.00 (s, 1H), 6.73 (d, $J = 8.72$ Hz, 2H), 7.01 (d, $J = 8.64$ Hz, 2H), 7.28 (s, 4H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 24.7$, 24.8, 25.4, 27.4, 32.8, 48.8, 55.2, 64.5, 77.2, 114.0, 122.9, 125.6, 131.6, 132.2, 137.9, 159.8, 166.7, 168.1 ppm. CHN calculated for $C_{23}H_{26}Br_2N_2O_3$: C, 51.32; H, 4.87; N, 5.20, Found C, 51.39; H, 5.12; N, 5.02.

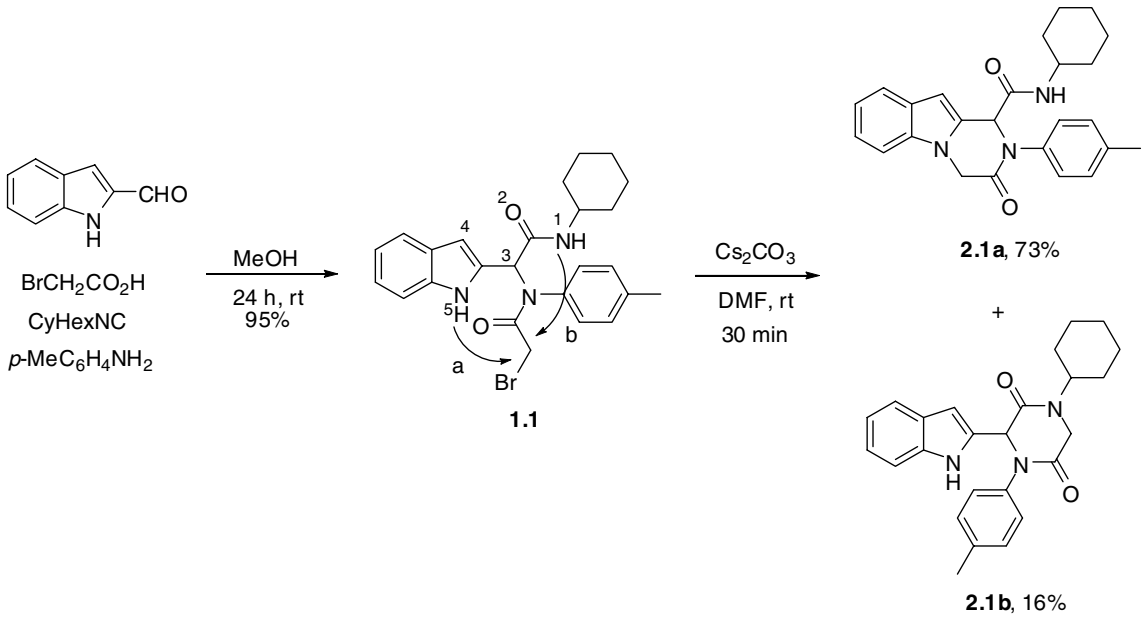
3g White powder, mp 223–225 °C. FT-IR (KBr): $\nu_{max} = 3{,}269$, 3,067, 2,934, 1,653, 1,552, 712 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (m, 3H), 1.34 (m, 2H), 1.64 (m, 3H), 1.95 (m, 3H), 2.14 (m, 2H), 3.60 (m, 2H), 3.77 (m, 4H), 5.65 (d, $J = 7.88$ Hz, 1H), 5.86 (s, 1H), 6.67 (d, $J = 8.6$ Hz, 1H), 6.82 (m, 1H), 7.03 (m, 2H), 7.22 (m, 3H), 7.63 (m, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 17.7$, 18.7, 24.7, 24.8, 25.4, 27.7, 28.1, 32.7, 32.8, 48.6, 48.7, 55.1, 55.2, 65.3, 113.5, 113.9, 125.0, 126.9, 127.2, 128.9, 129.2, 130.0, 130.6, 130.9, 131.3, 131.5, 132.0, 136.7, 137.2, 137.8, 159.7, 167.1, 167.7, 168.3 ppm. CHN calculated for $C_{24}H_{29}BrN_2O_3$: C, 60.89; H, 6.17; N, 5.92, Found C, 60.65; H, 6.14; N, 5.87.

3h White powder, mp 213–215 °C. FT-IR (KBr): $\nu_{max} = 3{,}269$, 3,014, 2,938, 1,662, 1,562, 720 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (m, 3H), 1.33 (m, 2H), 1.92 (m, 5H), 3.65 (q, 2H), 3.79 (m, 7H), 5.52 (d, $J = 7.92$ Hz, 1H), 5.97 (s, 1H), 6.71 (d, $J = 9$ Hz, 5H), 7.01 (d, $J = 8.64$ Hz, 2H), 7.26 (m, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 24.7$, 24.8, 25.4, 27.9, 32.8, 32.9, 48.7, 55.2, 55.3, 64.7, 77.2, 113.7, 114.0, 126.1, 131.4, 131.5, 131.7, 159.4, 159.6, 167.3, 168.3 ppm. CHN calculated for $C_{24}H_{29}BrN_2O_4$: C, 58.90; H, 5.97; N, 5.72, Found C, 58.78; H, 6.15; N, 5.63.

3i White powder, mp 242–244 °C. FT-IR (KBr): $\nu_{max} = 3{,}266$, 3,076, 2,927, 1,653, 1,557, 741 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (m, 3H), 1.26 (m, 2H), 1.55 (m, 3H), 1.79 (m, 2H), 2.21 (s, 6H), 3.57 (q, 2H), 3.74 (m, 1H), 5.45 (d, $J = 7.88$ Hz, 1H), 5.83 (s, 1H), 6.93 (s, 7H), 7.19 (s, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 21.2, 24.7, 24.8, 25.4, 27.9, 32.7, 32.8, 48.7, 65.6, 77.2, 129.15, 129.6, 129.8, 130.2, 131.2, 136.65, 138.4, 138.6, 167.0, 168.2 ppm. CHN calculated for $C_{24}H_{29}BrN_2O_2$: C, 63.02; H, 6.39; N, 6.12, Found C, 63.15; H, 6.55; N, 6.27.

3j White powder, mp 235–237 °C. FT-IR (KBr): 3,265, 3,077, 2,926, 1,658, 1,557, 715 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (m, 3H), 1.37 (m, 5H), 1.85 (m, 1H), 1.95 (m, 1H), 2.30 (s, 3H), 3.63 (m, 2H), 3.81 (m, 1H), 5.42 (d, $J = 7.88$ Hz, 1H), 5.99 (s, 1H), 7.01 (m, 4H), 7.31 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 24.7, 24.8, 25.4, 27.4, 32.7, 32.8, 48.9, 65.0, 77.2, 122.8, 129.4, 130.2, 130.6, 132.1, 138.0, 138.8, 166.7, 168.0 ppm. CHN calculated for $C_{23}H_{26}Br_2N_2O_2$: C, 52.89; H, 5.02; N, 5.36, Found C, 52.95; H, 5.14; N, 5.51.

3k White powder, mp 242–244 °C. FT-IR (KBr): $\nu_{max} = 3{,}270$, 3,079, 2,929, 1,656, 1,558, 703 cm^{-1}.



Scheme 1 Ugi reaction and selective cyclization of **1.1** to **2.1a** and **2.1b**

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 3H), 1.05 (m, 2H), 1.53 (m, 5H), 2.19 (s, 3H), 3.58 (m, 2H), 3.75 (m, 1H), 5.45(d, J = 7.76 Hz, 1H), 5.86 (s, 1H), 6.92 (s, 4H), 7.12 (m, 5H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.1, 24.7, 24.8, 25.4, 27.8, 32.7, 32.8, 48.8, 65.66, 77.2, 128.6, 129.0, 129.1, 130.2, 130.3, 130.3, 130.9, 138.5, 139.2, 166.9, 168.1, 168.2 ppm. CHN calculated for $C_{23}H_{27}BrN_2O_2$: C, 62.31; H, 6.14; N, 6.32, Found C, 62.23; H, 6.16; N, 6.27.

Results and discussion

In the first step, the reaction of indole-2-carboxaldehyde, 2-bromoacetic acid, 4-methylaniline and cyclohexyl isocyanide was set up (Scheme 1). The Ugi-adduct **1.1** was isolated in 88 % yield. This is quite exceptional since it has five nucleophilic positions which can potentially perform an intramolecular attack on the electrophilic –CH_2-Br group (numbered 1–5 in Scheme 1). In the second step, treatment of compound **1.1** with Cs_2CO_3 in DMF (the reaction is completed at room temperature during 30 min), afforded 1,2-dihydropyrazino[1,2-*a*]indol-3(4*H*)-one **2.1a** in 73 % and piperazin-2-one **2.1b** in 16 % yield. It should be noted one-pot strategy gave a messy reaction.

The possibility of a reaction by other weak bases such as $NaHCO_3$, Na_2CO_3 and K_2CO_3 was also explored, but after 48 h the reaction had not been completed and most of the starting material was recovered. It is noteworthy that using chloroacetic acid instead of bromoacetic acid in this two-step reaction gave lower overall yield.

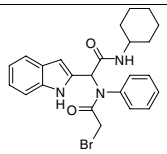
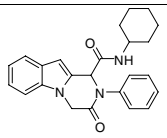
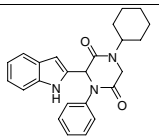
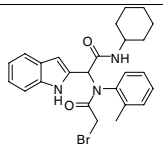
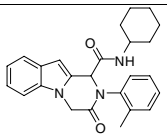
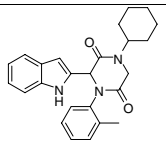
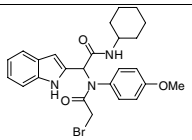
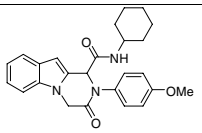
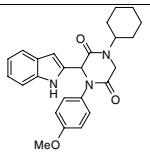
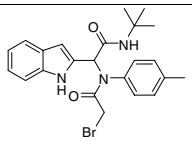
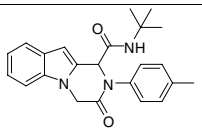
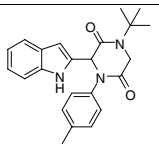
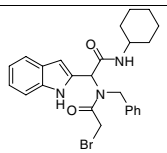
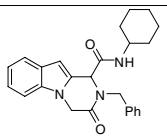
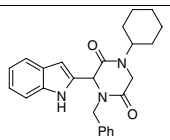
To evaluate the scope and limitations of the reaction, different Ugi-adducts were synthesized in good to excellent yields, followed by the subsequent cyclization reaction (See Scheme 1 and Table 1). Using aniline as alternative amine gave the diamide intermediate **1.2** and final product **2.2a** in 82 % and compound **2.2b** in 16 % yield (Table 1, entry 1). The *o*-toluidine derivative **1.3** gave pyrazino[1,2-*a*]indolone **2.3a** in 55 % yield with trace amounts of **2.3b**, but the *para*-anisidine derivative **1.4** yielded both products **2.4a** and **2.4b,** respectively, in 59 and 10 % yield in the presence of cesium carbonate (Table 1, entries 2 and 3). It is interesting to note that **1.3** and **2.3a** are isolated as a mixture of diastereomers, due to the restricted rotation of the *ortho*-methyl benzene group. The fact that **2.3a** is obtained as a 83:17 mixture of diastereomers suggests that one of the diastereomers (major product) is most possibly both the kinetically as well as thermodynamically determined product.

Ugi product **1.5** containing *tert*-butyl as a bulky group gave only 62 % corresponding cyclic product **2.5a** (Table 1, entry 4). Benzylamine, as a candidate for alkyl amines, adequately followed the same trend both in terms of the Ugi reaction and subsequent cyclization (Table 1, entry 5).

The apparent reason for the difference in the yields for **2.1a** and **2.1b** (and the corresponding reactions in Table 1) is the stronger acid character of the indole N–H proton (cyclization route a) in comparison to the amide N–H proton (cyclization route b).

We also attempted to use benzaldehyde derivatives instead of 2-formylindole in the Ugi coupling. For instance, the reactions of 4-chloro-, methoxy-, and

Table 1 Cyclization of Ugi-adduct in the presence of Cs_2CO_3

Run	Ugi-adduct[a] (Isolated yield %)	Pyrazinoindole[b]	Isolated yield (%)	Piperazin-2-one	Isolated yield (%)
1	 **1.2** (88)	 **2.2a**	82	 **2.2b**	17
2	 **1.3**[c] (81)	 **2.3a**[d]	55	 **2.3b**	trace
3	 **1.4** (78)	 **2.4a**	59	 **2.4b**	10
4	 **1.5** (68)	 **2.5a**	62	 **2.5b**	trace
5	 **1.6** (91)	 **2.6a**	50	 **2.6b**	14

[a] Ugi-adducts were synthesized from the reaction of 2-formylindole (1 equiv.), amine (1 equiv.), bromoacetic acid (1 equiv.) and isocyanide (1 equiv.) in MeOH at room temperature after 24 h

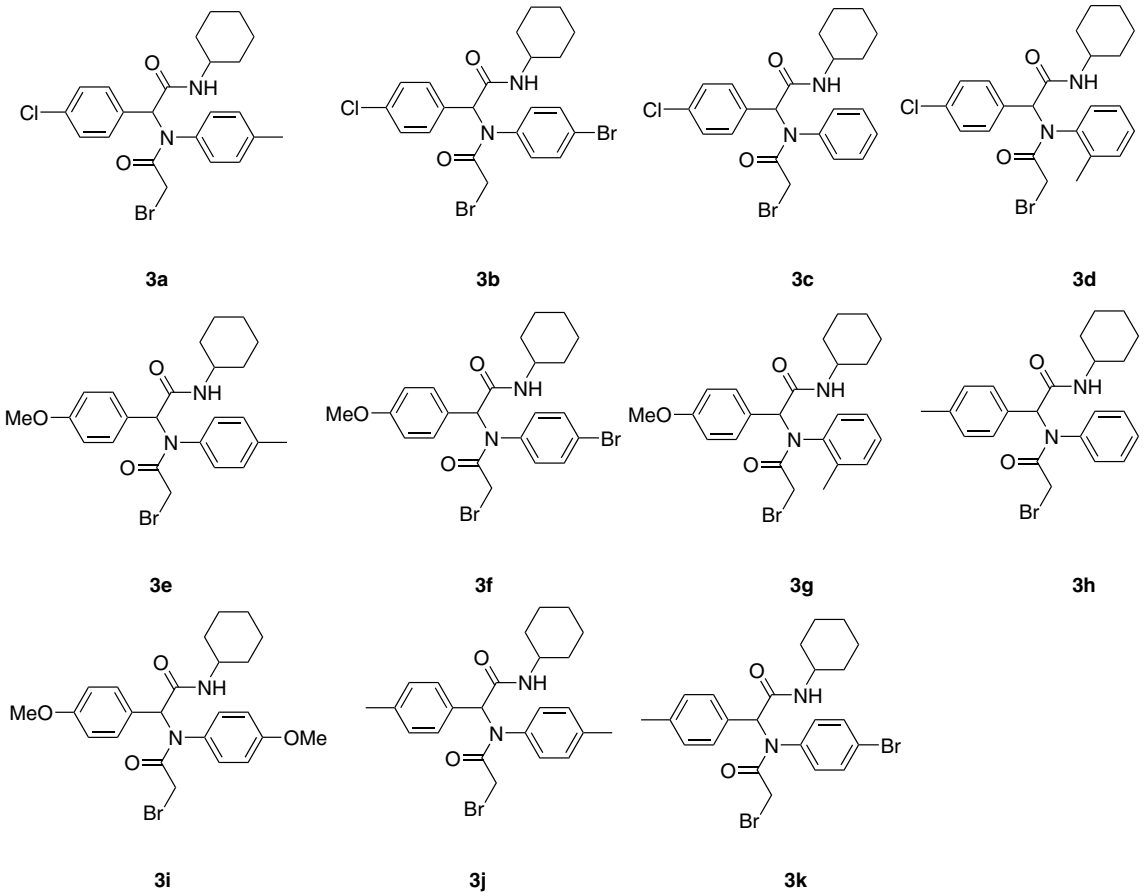
[b] Ugi-adduct (0.5 mmol), Cs_2CO_3 (0.5 mmol) and 10 mL DMF at room temperature

[c] Compound **1.3** is obtained as a 50:50 mixture of diastereomers (detected by NMR)

[d] Compound **2.3a** is obtained as a 83:17 mixture of diastereomers (detected by NMR)

methyl-benzaldehyde, as aldehyde sources, aniline, *o*- and *p*-toluidine, *p*-anisidine and *p*-bromoaniline as amine sources, and bromoacetic acid and cyclohexyl isocyanide gave the wide range of corresponding Ugi compounds **3a–3k**. Unexpectedly, these compounds remained unchanged in the presence of Cs_2CO_3 in DMF at room temperature, even after 24 h (Scheme 2). Raising the temperature of the reaction gave a mixture of unidentified compounds. It is worth mentioning that the similar Ugi-adducts (Cl instead of Br) in ethanolic potassium hydroxide solution under ultrasonic conditions properly underwent cyclization to form 2,5-diketopiperazines [31].

The structures of all new compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and CHN analysis. For example the ^{1}H NMR spectra clearly demonstrated the removing of N–H in indole for **2.1a** and N–H in amide for **2.1b**. Diastereotopic protons in CH_2 at α-position of carbonyl for both **2.1a** and **2.1b** are split as quartet and appeared in 4.93 ppm (J = 16.77, 12.06 Hz) and 3.93 ppm (J = 16.90, 24.44 Hz), respectively. Proton of CO–NH- appears as doublet in 5.58 ppm (J = 7.40 Hz) for **2.1a** and the N–H of indole appears as singlet at 8.61 ppm for **2.1b**. The two related carbonyl groups in both **2.1a** and **2.1b** show two carbon peaks at 167.1 and 166.2 ppm in



Scheme 2 Benzaldehyde derivatives of Ugi-adducts which were unreactive at room temperature in the presence of Cs_2CO_3

the ^{13}C NMR spectra for **2.1a** and two peaks at 165.2 and 164.5 ppm for **2.1b**. Three sp^3 carbon atoms which are adjacent to nitrogen appear in 63.6, 49.2 and 47.1 ppm for **2.1a** and 63.6, 49.2 and 47.1 ppm for **2.1b**. The indole N–H in **2.1a** and the amide N–H in **2.1b** show FT-IR peaks at 3,313 and 3,315 cm^{-1}, respectively. The infrared spectra also confirmed the existence of C=O in both **2.1a** and **2.1b** with absorptions at 1,655 and 1,669 cm^{-1}, respectively.

Conclusion

In conclusion, we observed that 2-formylindole, bromoacetic acid, cyclohexyl isocyanide and amines combined to form a series of novel Ugi-adducts, which in the presence of Cs_2CO_3 in DMF at room temperature, selectively undergo cyclization. This leads to the formation of 1,2-dihydropyrazino[1,2-*a*]indol-3(4*H*)-ones as major and 2,5-diketopiperazines as minor products. Although 2,5-diketopiperazines were obtained in low yields, this class of compounds exhibits highly important applications in medicinal chemistry [32].

Acknowledgments We thank Alzahra University and Iran National Science Foundation (INSF) for financial support to our research group. We thank the Catalysis and Peptide Research Unit (http://cpru.ukzn.ac.za/Homepage.aspx) at UKZN for assistance with the NMR analysis of these compounds.

References

1. J. Zhu, H. Bienaymé, Multicomponent reactions (Wiley, Weinheim, 2005)
2. A. Dömling, Y. Huang, Synthesis 2859 (2010)
3. A. Shaabani, A. Maleki, A. Rezayan, A. Sarvary, Mol. Divers. **15**, 41 (2011)
4. S. Sadjadi, M.M. Heravi, Tetrahedron **67**, 2707 (2011)
5. A.V. Ivachtchenko, Y.A. Ivanenkov, V.M. Kysil, M.Y. Krasavin, A.P. Ilyin, Russ. Chem. Rev. **79**, 787 (2011)
6. M. Shiri, Chem. Rev. **112**, 3508 (2012)
7. A. Dömling, W. Wang, K. Wang, Chem. Rev. **112**, 3083 (2012)
8. C. Simon, T. Constantieux, J. Rodriguez, Eur. J. Org. Chem. 4957 (2004)
9. J.A. Joule, in Science of Synthesis, Houben–Weyl methods of molecular transformations, ed. by E. J. Thomas George vol. 10, Chapter 10.13 (Thieme Verlag: Stuttgart, 2000)
10. M. Bandini, A. Eichholzer, Angew. Chem. Int. Ed. **48**, 9608 (2009)

11. G. Bartoli, G. Benciveni, R. Dalpozzo, Chem. Soc. Rev. **39**, 4449 (2010)
12. G.R. Humphrey, J.T. Kuethe, Chem. Rev. **106**, 2875 (2006)
13. S. Cacchi, G. Fabrizi, Chem. Rev. **105**, 2873 (2005)
14. M. Shiri, M.A. Zolfigol, H.G. Kruger, Z. Tanbakouchian, Chem. Rev. **110**, 2250 (2010)
15. Heterocyclic scaffolds II: reactions and applications of indoles, in Topics in heterocyclic chemistry, vol. 26, ed. by G.W. Gribble (Springer, Berlin, 2010)
16. S. Balalaie, M. Bararjanian, S. Hosseinzadeh, F. Rominger, H.R. Bijanzadeh, E. Wolf, Tetrahedron **67**, 7294 (2011)
17. L. Zhang, F. Zhao, M. Zheng, Y. Zhai, H. Liu, Chem. Commun. **49**, 2894 (2013)
18. L. Zhang, F. Zhao, M. Zheng, Y. Zhai, J. Wang, H. Liu, Eur. J. Org. Chem. 5710 (2013)
19. S. Tsirulnikov, M. Nikulnikov, V. Kysil, A. Ivachtchenko, M. Krasavin, Tetrahedron Lett. **50**, 5529 (2009)
20. S.G. Modha, A. Kumar, D.D. Vachhani, J. Jacobs, S.K. Sharma, V.S. Parmar, L. Van Meervelt, E.V. Van der Eycken, Angew. Chem. Int. Ed. **51**, 9572 (2012)
21. A. Kumar, D.D. Vachhani, S.G. Modha, S.K. Sharma, V.S. Parmar, E.V. Van der Eycken, Eur. J. Org. Chem. 2288 (2013)
22. S.G. Modha, D.D. Vachhani, J. Jacobs, L. Van Meervelt, E.V. Van der Eycken, Chem. Commun. **48**, 6550 (2012)
23. A. Kumar, Z. Li, S.K. Sharma, V.S. Parmar, E.V. Van der Eycken, Chem. Commun. **49**, 6803 (2013)
24. C.R.B. Rhoden, B. Westermann, L.A. Wessjohann, Synthesis 2077 (2008)
25. S. Pandey, S. Khan, A. Singh, H.M. Gauniyal, B. Kumar, P.M.S. Chauhan, J. Org. Chem. **77**, 10211 (2012)
26. M. Ghandi, N. Zarezadeh, A. Taheri, Tetrahedron Lett. **53**, 3353 (2012)
27. M. Shiri, M.A. Zolfigol, M. Pirveysian, R. Ayazi-Nasrabadi, H.G. Kruger, T. Naicker, I. Mohammadpoor-Baltork, Tetrahedron **68**, 6059 (2012)
28. M.A. Zolfigol, P. Salehi, M. Shiri, A. Sayadi, A. Abdoli, K. Niknam, H. Kolvari Keypour, M. Rezaeivala, Mol. Divers. **12**, 203 (2008)
29. M.A. Zolfigol, P. Salehi, M. Shiri, Z. Tanbakouchian, Catal. Commun. **8**, 173 (2007)
30. M. Shiri, M.A. Zolfigol, T. Faal-Rastegar, H.G. Kruger, J. Iran. Chem. Soc. **11**, 85 (2014)
31. S. Marcaccini, R. Pepino, M.C. Pozo, Tetrahedron Lett. **42**, 2727 (2001)
32. A.D. Borthwick, Chem. Rev. **112**, 3641 (2012)