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A three-component, intramolecular Ugi reaction toward unique indoloketopiperazines

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ABSTRACT

2-(3-Chloro-2-formyl-1*H*-indol-1-yl) acetic acid, as a bifunctional formyl-acid, is prepared in three steps. This compound undergoes a one-pot, four-center, three-component Ugi reaction with primary amines and alkyl isocyanides. A series of novel substituted indoloketopiperazine derivatives are obtained in moderate to high yields.

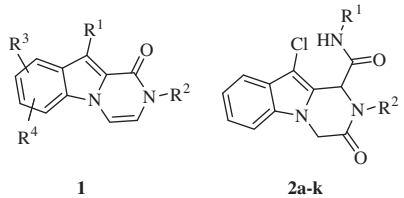
Multicomponent reactions (MCRs)[1] and isocyanide-based multicomponent reactions (IMCRs)[2] have emerged as efficient and powerful tools for the synthesis of highly complex natural and diverse drug-like compounds. The most popular IMCR is probably the Ugi reaction, in which a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in a one-pot manner to afford an N-substituted acyl aminoamide containing four independently varying groups in one reaction.[3] Utilization of bifunctional reagents, in which the participating functional groups of two components of the U-4CR are present in one structure, is another strategy to increase scaffold diversity.[4]

The indole nucleus is an important subunit present in many biologically active natural products.[5] Compounds possessing an indole moiety show antitumor activity,[6] and vesication to human skin.[7] Due to their binding with high affinity to many receptors, substituted indoles have been referred to as privileged structures.[8] On the other hand, piperazines, and their keto analogues are among the most important backbones in drug discovery.[9] Piperazines are a class of compounds which are present in molecules involved in the regulation of a wide variety of biological processes.[10]

The known antidepressant,[11] anti-inflammatory[12] and anti-obesity[13] properties of pyrazino-indoles along with the documented antitumor activity of compound **1**, especially against colon and lung tumors (Fig. 1),[14] prompted us to undertake a study on the synthesis of fused tricyclic scaffolds **2a–k** as the respective analogues of **1**, in which the bioactive ketopiperazine motif is fused with an indole moiety. As part of our interest in Ugi reactions,[15] herein, we describe the synthesis of a new series of fused indoloketopiperazines via the four-center, three-component Ugi reaction of 2-(3-chloro-2-formyl-1*H*-indol-1-yl)acetic acid (**3**) with various amines and isocyanides.

The aldehyde-acid **3** chosen for this study was synthesized according to the procedure presented in Scheme 1. Initially, 3-chloro-1*H*-indole-2-carbaldehyde (**4**) was synthesized using a previously reported procedure.[16] Subsequent treatment of **4** with methyl chloroacetate in the presence of K_2CO_3 in refluxing MeCN for 6 h afforded methyl 2-(3-chloro-2-formyl-1*H*-indol-1-yl)acetate (**5**) in 90% yield.[17] Transformation of **2** into acid **3** was then carried out in methanolic NaOH at room temperature in 85% yield over 4 h.[18]

In a model experiment, formyl-acid **3** was treated with *p*-toluidine and *tert*-butyl isocyanide. The reaction proceeded smoothly and was complete within 4 h at 40 °C, affording **2a** in 90% yield (Scheme 2).[19]



1 **2a-k**

Figure 1. The known anti-colon and lung tumors pyrazinoindoles (**1**) and the unique indoloketopiperazines **2a–k** as the respective analogues.

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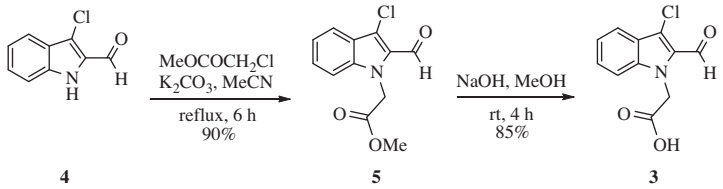
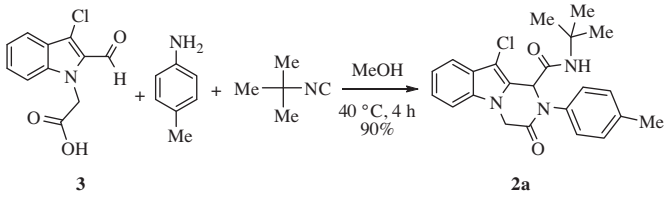


Scheme 1. Synthesis of formyl acid **3**.



Scheme 2. Synthesis of indoloketopiperazine **4a**.

The structure of **2a** was confirmed on the basis of analytical data.[19] For example, the mass spectrum of **2a** displayed the molecular ion peak at 409. The IR spectrum displayed characteristic absorption bands at 3310 and 1684 cm^{-1} due to N–H and C=O stretching vibrations, respectively. The ^1H NMR spectrum of **2a** displayed singlets at δ 1.33 (9H, s, CMe_3) and δ 2.42 (3H, s, Me) along with a singlet at δ 5.32 (1H, s, NCOCHN) and an AB quartet at δ 5.05 (2H, J = 16.5 Hz, NCH_2CO), representing the ketopiperazine ring protons. This reaction demonstrated that substituted indoloketopiperazine derivatives could be prepared through a four center, three-component condensation (3CC) Ugi reaction.

Subsequent reaction of various amines and commercially available 1,1,3,3-tetramethylbutyl, *tert*-butyl, or cyclohexyl isocyanides under the described conditions afforded the indoloketopiperazines **2a–k** in moderate to high yields (Table 1).[20]

As has been rationalized in Scheme 3, it is conceivable that the initial event is the formation of iminium ion **6** from the amine, and formyl-acid **3** followed by activation of the imine by the carboxylic acid. Subsequent addition of the nucleophilic isocyanide to the activated iminium species followed by trapping of the nitrilium intermediate by the carboxylate affords the iminolactone **7**. The irreversible acyl transfer step (Mumm rearrangement) associated with the Ugi reaction finally gives the desired indoloketopiperazines **2a–k**.

In conclusion, using a bifunctional starting material containing an aldehyde and carboxylic acid functional group in Ugi 3CC reactions leads to a variety of novel heteroaryl-fused substituted indoloketopiperazine derivatives **2a–k**. The method offers several advantages including moderate to high yields of products and an easy experimental work-up procedure. These new structures broaden the scaffolds accessible through Ugi reactions, and many of them may represent interesting pharmacophores.

Table 1
Structures and yields of compounds **2a–k** obtained from 3CC Ugi reactions

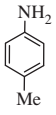
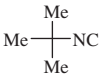
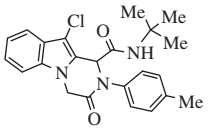
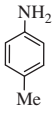
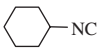
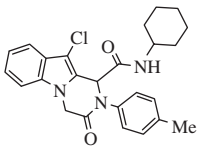
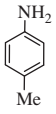
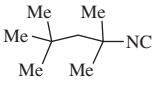
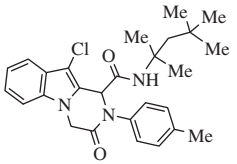
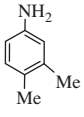
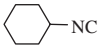
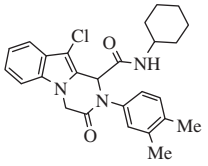
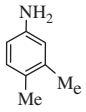
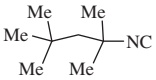
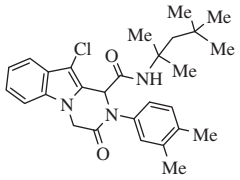
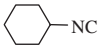
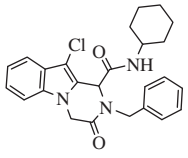
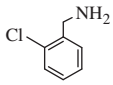
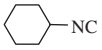
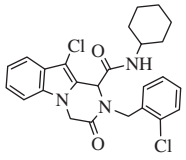
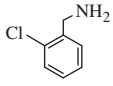
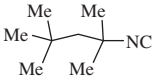
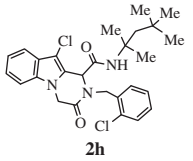
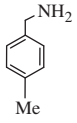
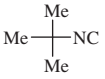
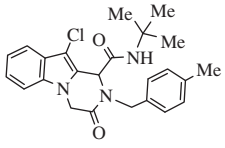
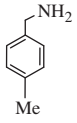
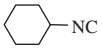
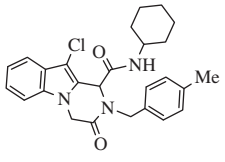
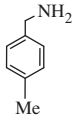
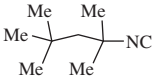
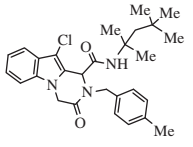
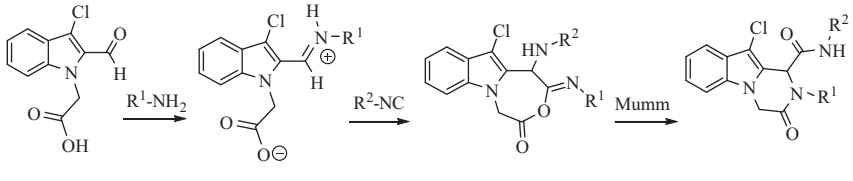
Entry	R^1NH_2	R^2NC	Product	Time (h)	Yield (%)
1			 **2a**	4	90
2			 **2b**	4	83
3			 **2c**	4	89
4			 **2d**	4	85

Table 1 (*continued*)

Entry	R^1NH_2	R^2NC	Product	Time (h)	Yield (%)
5			 **2e**	4	87
6			 **2f**	8	73
7			 **2g**	10	60
8			 **2h**	10	65
9			 **2i**	6	90
10			 **2j**	6	88
11			 **2k**	6	92



3 6 7 2a-k

Scheme 3. Proposed mechanism for the formation of **2a**–**k**.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.090. These data include MOL files and InChiKeys of the most important compounds described in this article.

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17. Preparation of methyl 2-(3-chloro-2-formyl-1*H*-indol-1-yl)acetate (**5**). To a solution of **4** (2.68 g, 15 mmol) in MeCN (30 mL) were added methyl chloroacetate (1.65 g, 15.2 mmol) and K_2CO_3 (2.10 g, 15 mmol) and the mixture was heated at reflux for 6 h. The resulting solid was filtered, and the filtrate concentrated under reduced pressure to afford 3.39 g (90%) of **5**. Brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (3H, s, O*Me*), 5.35 (2H, s, CH_2CO_2), 7.24–7.35 (2H, m, Ar), 7.53 (1H, t, J = 7.2 Hz, Ar), 7.82 (1H, d, J = 7.7 Hz, Ar), 10.19 (1H, s, CO*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.9 (CH_2CO_2), 5.26 (O*Me*), 109.9, 120.8, 122.0, 124.4, 124.6, 128.7, 129.2, 138.4 (C-Ar), 168.7 (C=O), 181.2 (C=O); IR (KBr) υ: 1741 cm^{-1}; MS (EI) m/z: 253 (M$^+$ [^{37}Cl], 32), 251 (M$^+$ [^{35}Cl], 100), 236 (24), 222 (28), 216 (6), 204 (12), 192 (59), 177 (14), 164 (15), 123 (20%). Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.20; H, 3.98; N, 5.51.
18. Preparation of 2-(3-chloro-2-formyl-1*H*-indol-1-yl)acetic acid (**3**). To a stirred solution of methyl 2-(3-chloro-2-formyl-1*H*-indol-1-yl)acetate (**5**) (3.76 g, 15 mmol) in MeOH (15 mL), a solution of NaOH (0.72 g, 18 mmol) in H_2O (7 mL) was added dropwise. The mixture was stirred for 4 h at rt (TLC monitoring). After evaporation of the volatiles, the mixture was diluted with H_2O (4 mL), and the pH of the reaction mixture adjusted to pH 3–4 with 5% aqueous HCl solution. Filtration of the mixture and recrystallization of the solid from EtOH afforded 3.02 g (85%) of **3**. Pale-red solid: mp 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (2H, s, CH_2CO_2H), 7.15 (1H, t, J = 7.5 Hz, Ar), 7.23 (1H, d, J = 8.2 Hz, Ar), 7.36 (1H, t, J = 7.5 Hz, Ar), 7.64 (1H, d, J = 8.2 Hz, Ar), 10.03 (1H, s, CO*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.3 (CH_2CO_2H), 110.6, 120.9, 122.2, 124.4, 124.7, 128.9, 129.2, 138.8 (C-Ar), 170.5 (C=O), 181.3 (C=O); IR (KBr) υ: 2482–2955, 1754 cm^{-1}; MS (EI) m/z: 239 (M$^+$ [^{37}Cl], 17), 237 (M$^+$ [^{35}Cl], 55), 192 (100), 164 (41), 128 (35), 123 (90%). Anal. Calcd for $C_{11}H_8ClNO_3$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.49; H, 3.41; N, 6.14.
19. Representative procedure for the preparation of compound **2a**: A solution of formyl-acid **3** (0.24 g, 1.0 mmol), toluidine (1.0 mmol) and *tert*-butyl isocyanide (1.0 mmol) in MeOH (3 mL) was stirred at 40 °C for 4–10 h. After completion of the reaction as indicated by TLC, the precipitate was filtered and recrystallized from EtOH to give *N-tert-butyl-10-chloro-3-oxo-2-p-tolyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole-1-carboxamide* (**2a**) as a white solid (0.37 g, 90%); mp 251–253 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (9H, s, CMe_3), 2.42 (3H, s, *Me*), 5.05 (2H, AB-q, J = 16.5 Hz, NCH_2CO), 5.32 (1H, s, NCOC*H*N), 5.82 (1H, br s, NH), 7.26 (2H, d, J = 8.3 Hz, Ar), 7.30 (2H, d, J = 8.3 Hz, Ar), 7.38–7.44 (3H, m, Ar), 7.38 (1H, d, J = 7.9 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2 (*Me*), 28.5 (CMe_3), 46.9 (NCH_2CO), 52.5 (CMe_3), 62.0 (NCOCHN), 99.9, 109.4, 118.4, 121.2, 123.4, 124.9, 125.4, 126.9, 130.3, 134.0, 138.1, 138.4 (C-Ar), 165.8 (C=O), 165.9 (C=O); IR (KBr) υ: 3310, 1684 cm^{-1}; MS (EI) m/z: 411 (M$^+$ [^{37}Cl], 2), 409 (M$^+$ [^{35}Cl], 6), 374 (9), 309 (100), 281 (38), 167 (29), 149 (90), 57 (26%). Anal. Calcd for $C_{23}H_{24}ClN_3O_2$: C, 67.39; H, 5.90; N, 10.25. Found: C, 67.77; H, 5.90; N, 10.30.
20. *10-Chloro-N-cyclohexyl-2-(3,4-dimethylphenyl)-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-a]indole-1-carboxamide* (**2d**): White solid (0.38 g, 85%); mp 254–256 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07–1.92 (10H, m, $5CH_2$ of cyclohexyl), 2.27 (6H, s, 2*Me*), 3.66–3.72 (1H, m, C*H*NH of cyclohexyl), 5.02 (2H, AB-q, J = 16.5 Hz, NCH_2CO), 5.39 (1H, s, NCOC*H*N), 6.29 (1H, d, J = 8.1 Hz, N*H*), 7.06 (1H, d, J = 8.0 Hz, Ar), 7.11 (1H, s, Ar), 7.20 (1H, d, J = 8.0 Hz, Ar), 7.23–7.32 (3H, m, Ar), 7.62 (1H, d, J = 7.9 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5 (*Me*), 19.9 (*Me*), 24.5 ($2CH_2$), 25.3 (CH_2), 32.5 (CH_2), 32.9 (CH_2), 47.0 (NCH_2CO), 49.3 (*C*HNH of cyclohexyl), 61.5 (NCOCHN), 100.0, 109.4, 118.4, 121.2, 123.5, 124.2, 124.8, 125.3, 128.0, 130.8, 134.0, 137.1, 138.2, 138.4 (C-Ar), 165.8 (C=O), 166.1 (C=O); IR (KBr) υ: 3307, 1683 cm^{-1}; MS (EI) m/z: 451 (M$^+$ [^{37}Cl], 2), 449 (M$^+$ [^{35}Cl], 6), 414 (8), 323 (100), 295 (29), 144 (11), 55 (14%). Anal. Calcd for $C_{26}H_{28}ClN_3O_2$: C, 69.40; H, 6.27; N, 9.34. Found: C, 69.43; H, 6.20; N, 9.39. *10-Chloro-2-(4-methylbenzyl)-3-oxo-N-(2,4,4-trimethylpentan-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole-1-carboxamide* (**2k**). Cream solid (0.44 g, 92%); mp 196–198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (9H, s, CMe_3), 1.33 and 1.34 (6H, 2s, CMe_2), 1.69 (2H, AB-q, J = 15.0 Hz, CCH_2C), 2.38 (3H, s, *Me*), 4.16 (1H, d, J = 15.1 Hz, C*H*HPh), 4.94 (2H, AB-q, J = 16.6 Hz, NCH_2CO), 5.00 (1H, s, NCOC*H*N), 5.34 (1H, d, J = 15.1 Hz, CH*H*Ph), 5.72 (1H, br s, NH), 7.20 (4H, s, Ar), 7.25–7.35 (3H, m, Ar), 7.62 (1H, d, J = 7.9 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1 (*Me*), 28.6 (CMe_2), 29.4 (CMe_2), 31.2 (CMe_3), 31.5 (CCH_2C), 46.5 (NCH_2CO), 49.0 (CH_2Ph), 51.7 (CMe_3), 56.4 (CMe_2), 56.9 (NCOCHN), 100.0, 109.3, 118.3, 121.1, 123.4, 124.7, 125.3, 128.4, 129.6, 132.0, 133.9, 137.8 (C-Ar), 165.0 (C=O), 165.9 (C=O); IR (KBr) υ: 3356, 1691 cm^{-1}; MS (EI) m/z: 480 (M$^+$, 4), 444 (9), 323 (80), 105 (100), 57 (49%). Anal. Calcd for $C_{28}H_{34}ClN_3O_2$: C, 70.06; H, 7.14; N, 8.75. Found: C, 70.04; H, 6.86; N, 8.90.