Catalyst-free, Solvent-promoted and Scalable Multicomponent Synthesis of 3-Aminoalkylated Indoles *via* a Mannich-type Reaction

Jian-Fei Cao, Yan-Li Chen, Zhi Guan, and Yan-Hong He

School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, P. R. China

Reprint requests to Dr. Zhi Guan or Dr. Yan-Hong He. Fax: +86-23-68254091.
E-mail: guanzhi@swu.edu.cn (Zhi Guan) or heyh@swu.edu.cn (Yan-Hong He)

Z. Naturforsch. **2014**, *69b*, 721 – 727 / DOI: 10.5560/ZNB.2014-3313
Received November 14, 2013

A catalyst-free, solvent-promoted and scalable three-component Mannich-type reaction of indoles, aromatic aldehydes and secondary amines for the synthesis of 3-(1-dialkylaminoalkyl)-1*H*-indoles has been developed. The protocol provided a mild, simple and highly atom-economic alternative to prepare the title compounds, and the corresponding products could be obtained in good to excellent yields in most cases.

Key words: Solvent-promoted, Scalable, Multicomponent Synthesis, 3-Aminoalkylated Indoles

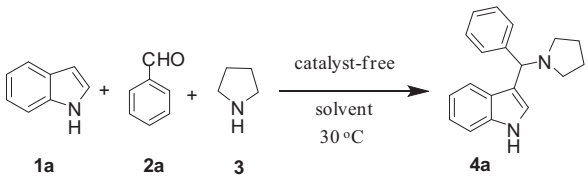
Introduction

Indole is probably the most ubiquitous motif in nature [1]. A large number of natural and synthetic indole derivatives have been found a venerable value in pharmaceutical and medical applications since they are able to bind with high affinity to many receptors [2 – 8]. Among them, 3-substituted indole derivatives have attracted much attention due to the broad scope of their biological activities [9 – 12]. Although Friedel-Crafts alkylation of indole has been widely employed for the preparation of 3-substituted indole derivatives, the methods often suffer from drastic reaction conditions (high temperature, strong acid/base) and regioselectivity problems [13 – 15]. In recent years, some transition metal catalysts have emerged as an alternative to the conventional catalysts for Friedel-Crafts alkylation of indoles. However, most of the substrates were limited to electron-neutral or electron-deficient alkenes [16 – 26]. The Mannich reaction is another straightforward and powerful tool employed in the synthesis of alkylated indoles [27], especially in the synthesis of indoles by aminoalkylation. Mannich reactions of aldehydes, primary amines, and indoles catalyzed by carboxylic acids in water [28] and the condensation of heteroaryl amines, aromatic aldehydes, and indoles under solvent-free but thermal conditions to prepare 3-(1-dialkylaminoalkyl)-1*H*-indoles have been reported [29]. Kumar and co-workers reported L-proline-catalyzed Mannich-type reactions for the synthesis of 3-(1-dialkylaminoalkyl)-1*H*-indoles using a cyclic amine under solvent-free conditions [30]. They also reported that the aminoalkylation of *N*-substituted indoles could be carried out in good yields in water in the presence of a surfactant [31]. In the course of developing new catalysts for the synthesis of 3-aminoalkylated indoles, we unexpectedly found that these compounds could be prepared without catalyst, and that solvents had an extraordinary effect on the reaction. This catalyst-free approach offers a less expensive and much simpler method for 3-amino-alkylated indoles, and the procedure is also scalable. Therefore, we wish to report this catalyst-free, one-pot, three-component reaction in this article.

Results and Discussion

Initial studies were undertaken using indole, pyrrolidine and benzaldehyde in a model reaction without catalyst in different solvents. As shown in Table 1, solvents had a remarkable effect on the reaction. When the reaction was carried out in toluene, THF, 1,4-dioxane, *n*-butyl acetate, isopropyl ether, DMSO, MTBE, $CHCl_3$, or MeCN at 30 °C, the desired product **4a** was only obtained in low yields of 11 – 46 % (Table 1, entries 3 – 13). However, polar protic solvents

Table 1. Solvent and temperature screening for the catalyst-free three-component reaction[a].



Entry	Solvent	Yield[b] (%)
1	MeOH	93
2	EtOH	75
3	Toluene	45
4	THF	31
5	1,4-Dioxane	15
6	*n*-Butyl acetate	13
7	Isopropyl ether	34
8	H_2O	45
9	DMSO	24
11	MTBE	11
12	$CHCl_3$	37
13	MeCN	46
14	MeOH (25 °C)	87
15	MeOH (35 °C)	88

[a] Reaction conditions: benzaldehyde (1.0 mmol), indole (1.0 mmol) and pyrrolidine (1.0 mmol) in solvent (1.0 mL) at 30 °C for 72 h; [b] isolated yield after silica gel chromatography.

(MeOH and EtOH) obviously promoted the reaction, and good yields of 93 % and 75 % were obtained, respectively (Table 1, entries 1 and 2). H_2O as a polar protic solvent did not give a good result, probably due to the poor solubility of substrates (Table 1, entry 8). Thus, we selected methanol as the optimal solvent for our further study. We then investigated the model reaction in MeOH at 25 °C, which gave the product in a yield of 87 % (Table 1, entry 14). The reaction at 35 °C provided the product **4a** in a yield of 88 %, but a by-product was observed (Table 1, entry 15). In comparison with the reaction at 30 °C which provided the product in a better yield of 93 % (Table 1, entry 1), we chose 30 °C as the optimal temperature for the reaction.

The time-course of this reaction was also investigated (Fig. 1). The reaction was relatively fast in the initial 24 h, and after that the reaction rate decreased markedly. A good yield of 93 % was obtained after 72 h, and prolonging the reaction time to 84 h did not increase the yield.

To further optimize the reaction conditions, we examined the effect of solvent volume on the model reaction in MeOH at 30 °C (Table 2). The best yield of

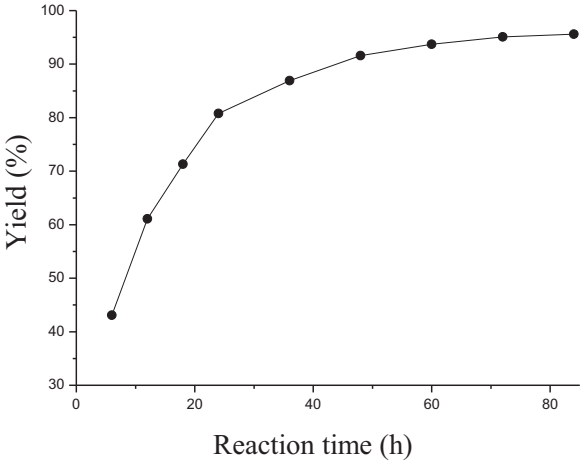


Fig. 1. Time *vs.* yield curve of the catalyst-free, three-component reaction in MeOH. Reaction conditions: benzaldehyde (1.0 mmol), indole (1.0 mmol), pyrrolidine (1.0 mmol) in MeOH (1.0 mL) at 30 °C.

Table 2. Solvent volume screening and the scale-up of the model reaction[a].

Entry	MeOH (mL)	Yield[b] (%)
1	2.0	88
2	1.5	89
3	1.2	91
4	1.0	93
5	0.7	95
6	0.5	93
7	0.4	90
8 (scale-up)[c]	7.0	86

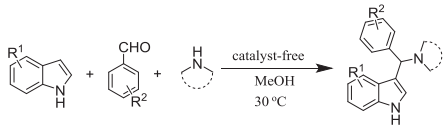
[a] Reaction conditions: benzaldehyde (1.0 mmol), indole (1.0 mmol) and pyrrolidine (1.0 mmol) in MeOH at 30 °C for 72 h; [b] isolated yield after silica gel chromatography; [c] benzaldehyde (10.0 mmol), indole (10.0 mmol) and pyrrolidine (10.0 mmol) in MeOH at 30 °C for 72 h.

95 % was obtained in 0.7 mL MeOH on a 1.0 mmol scale (Table 2, entry 5). When the solvent volume was more than or less than 0.7 mL, lower yields were obtained. Thus, we chose 0.7 mL MeOH as an optimal solvent volume for 1.0 mmole of substrate.

Next, we attempted to scale up this catalyst-free, one-pot, three-component reaction. When the model reaction was scaled up to 10.0 mmol under the optimized conditions, it worked smoothly giving product **4a** in a good yield of 86 % (Table 2, entry 8).

Finally, various structurally diverse aldehydes, indoles and secundary amines were tested under optimized reaction conditions to explore the scope and generality of this methodology. As is shown in Table 3,

Table 3. Scope of the catalyst-free, three-component reaction[a].



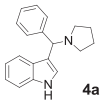
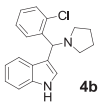
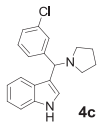
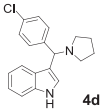
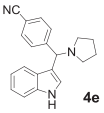
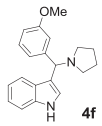
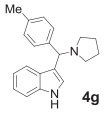
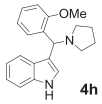
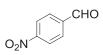
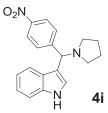
Entry	Aldehyde	Indole	Amine	Product	Yield (%)[b]
1				 **4a**	95
2				 **4b**	97
3				 **4c**	91
4				 **4d**	95
5				 **4e**	92
6				 **4f**	92
7				 **4g**	85
8				 **4h**	88
9				 **4i**	86

Table 3. (Continued.)

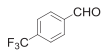
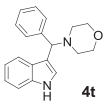
Entry	Aldehyde	Indole	Amine	Product	Yield (%)[b]
10				**4j**	90
11				**4k**	92
12				**4l**	86
13				**4m**	90
14				**4n**	96
15				**4o**	99
16				**4p**	97
17				**4q**	93
18				**4r**	31
19				**4s**	28

Table 3. (Continued.)

Entry	Aldehyde	Indole	Amine	Product	Yield (%)[b]
20				 **4t**	35

[a] Reaction conditions: benzaldehyde (1.0 mmol), indole (1.0 mmol) and secondary amine (1.0 mmol) in MeOH (0.7 mL) at 30 °C for 72 h; [b] isolated yield after silica gel chromatography.

when pyrrolidine was used as a secondary amine, activated, unactivated and deactivated indoles reacted with aromatic aldehydes bearing either electron-donating or electron-withdrawing groups affording the corresponding products in good to excellent yields of 85 – 99 % (Table 3, entries 1 – 17). However, when dimethylamine, piperidine or morpholine was used as a secondary amine, benzaldehyde and indole gave the corresponding products in low yields of 28 – 35 % (Table 3, entries 18 – 20). The position of the substituents on the benzaldehyde seems to have little effects on the yields (Table 3, entries 2 – 4).

In conclusion, we have developed a catalyst-free, three-component Mannich-type reaction for the preparation of 3-(1-dialkylaminoalkyl)-1*H*-indoles under mild reaction conditions. Solvents had a remarkable effect on the reaction, and the polar protic solvent MeOH gave the best results. The procedure is simple and scalable. Using Mannich-type reactions of aldehydes, amines and indoles through the loss of a molecule of water to prepare 3-aminoalkylated indoles was highly atom-economic. Moreover, in this procedure just a 1 : 1 : 1 molar ratio of the three reactants was sufficient to obtain good yields in most cases, which makes the methodology a rather attractive process for the synthesis of 3-aminoalkylated indoles.

Experimental Section

General information

All reagents were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (100 – 200 mesh), eluting with ethyl acetate and petroleum ether. Thin layer chromatography was carried out using Haiyang GF254 silica gel TLC plates. NMR spectra were recorded at 300 MHz or 400 MHz with $CDCl_3$ as solvent. Chemical shifts are expressed in ppm with TMS as internal standard, and coupling constants are reported in Hz. High-resolution mass spectra (Varian 7.0T FTICR-MS) were obtained by use of ESI ionization sources.

General procedure for the catalyst-free three-component reaction for the synthesis of 3-amino alkylated indoles

The aldehyde (1.0 mmol), secondary amine (1.0 mmol), indole (1.0 mmol), and MeOH (0.7 mL) were sequentially added into a round-bottom flask to form a clear yellow solution. The resultant mixture was stirred at 30 °C for 72 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel flash column chromatography with petroleum ether-ethyl acetate as eluent to give the desired product.

*3-(Phenyl(pyrrolidin-1-yl)methyl)-1H-indole (**4a**)*

– ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 8.42 (s, 1H, NH), 7.77 (d, J = 7.6 Hz, 1H, ArH), 7.54 (d, J = 7.6 Hz, 2H, Ph), 7.23 (d, J = 7.3 Hz, 3H, Ph), 7.11 (m, 4H, ArH), 4.62 (s, 1H, CH), 2.57 (d, J = 9.6 Hz, 4H, NCH_2C), 1.77 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 144.40 (s), 136.08 (s), 128.21 (s), 127.73 (s), 126.60 (s), 122.10 (s), 121.80 (s), 119.69 (s), 119.32 (s), 111.08 (s), 68.00 (s), 53.75 (s), 23.52 (s). – HRMS ((+)-ESI): m/z = 277.1699 (calcd. 276.1703 for $C_{19}H_{30}N_2$, $[M+H]^+$). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.26 min.

*3-((2-(Chlorophenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4b**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.19 (s, NH), 8.00 – 7.89 (m, 2H, ArH), 7.31 – 7.21 (m, 4H, Ph), 7.11 (m, 3H, ArH), 5.17 (s, 1H, CH), 2.57 (d, J = 5.9 Hz, NCH_2C), 1.84 – 1.70 (m, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 141.25 (s), 136.03 (s), 132.92 (s), 129.48 (d, J = 12.3 Hz), 127.51 (s), 126.95 (s), 126.53 (s), 122.82 (s), 121.93 (s), 120.11 (s), 119.51 (s), 118.02 (s), 111.08 (s), 63.02 (s), 53.53 (s), 23.61 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.41 min.

*3-((3-Chlorophenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4c**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.12 (s, 1H, NH), 7.83 (d, J = 7.9 Hz, 1H, Ph), 7.57 (t, J = 1.7 Hz, 1H, Ph), 7.50 – 7.41 (m, 1H, Ph), 7.34 (d, J = 8.0 Hz, 1H), 7.25 – 7.00 (m, 5H, ArH), 4.59 (s, 1H, CH), 2.55 (d, J = 6.8 Hz, 4H, NCH_2C), 1.81 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 146.67 (s), 136.14 (s), 134.03 (s), 129.53 (s), 127.76 (s), 126.78 (s), 126.32 (s), 125.89 (s), 122.09 (d, J = 6.3 Hz), 119.63 (d, J = 11.4 Hz), 118.81 (s), 111.18 (s), 67.55 (s), 53.68 (s), 23.58 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.50 min.

*3-((4-Chlorophenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4d**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.21 (s, 1H, NH), 7.77 (d, J = 7.8 Hz, 1H, ArH), 7.45 (d, J = 8.4 Hz, 2H, ArH), 7.27 – 7.04 (m, 6H, ArH), 4.56 (s, 1H, CH), 2.56 – 2.42 (m, 4H, NCH_2C), 1.75 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 143.00 (s), 136.14 (s), 132.09 (s), 129.07 (s), 128.40 (s), 126.30 (s), 122.05 (s), 119.61 (d, J = 18.9 Hz), 111.23 (s), 67.34 (d, J = 3.3 Hz), 53.70 (s), 23.58 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 6.97 min.

*4-((1H-Indol-3-yl)(pyrrolidin-1-yl)methyl)benzonitrile (**4e**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.09 (s, 1H, NH), 7.81 (d, J = 7.9 Hz, 1H, NH), 7.69 (d, J = 8.2 Hz, 2H, ArH), 7.58 – 7.55 (m, 2H, ArH), 7.35 (d, J = 8.1 Hz, 1H, Ph), 7.22 – 7.10 (m, 3H, Ph), 4.66 (s, 1H), 2.53 (d, J = 5.0 Hz, 4H, NCH_2C), 1.85 – 1.76 (m, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 150.11 (s), 136.22 (s), 132.21 (s), 128.32 (s), 127.10 (s), 126.05 (s), 122.22 (d, J = 6.4 Hz), 119.70 (d, J = 7.4 Hz), 119.16 (s), 118.16 (s), 111.29 (s), 110.15 (s), 67.72 (s), 53.53 (s), 23.59 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 8.82 min.

*3-((3-Methoxyphenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4f**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.03 (s, 1H, NH), 7.85 (d, J = 7.9 Hz, 1H, ArH), 7.33 – 7.07 (m, 7H, ArH), 6.70 (m, 1H, ArH), 4.56 (s, 1H, CH), 3.77 (s, 3H, OMe), 2.54 (d, J = 3.4 Hz, 4H, NCH_2C), 1.84 – 1.70 (m, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 159.54 (s), 146.28 (s), 136.15 (s), 129.19 (s), 126.57 (s), 122.02 (d, J = 34.1 Hz), 120.25 (s), 119.77 (s), 119.32 (d, J = 11.6 Hz), 113.51 (s), 111.80 (s), 111.15 (s), 68.04 (s), 55.19 (s), 53.79 (s), 23.59 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 11.37 min.

*3-(Pyrrolidin-1-yl(p-tolyl)methyl)-1H-indole (**4g**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.13 (s, 1H, NH), 7.80 (d, J = 7.8 Hz, 1H, Ph), 7.42 (d, J = 8.0 Hz, 2H, Ph), 7.29 – 7.23 (m, 1H, Ph), 7.20 – 7.04 (m, 5H, ArH), 4.57 (s, 1H, CH), 2.61 – 2.45 (m, 4H, NCH_2C), 2.27 (s, 3H, Me), 1.77 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 128.83 (s), 127.55 (s), 121.77 (s), 119.76 (s), 119.26 (s), 110.94 (s), 67.68 (s), 53.71 (s), 23.49 (s), 21.01 (s). – HRMS ((+)-ESI): m/z = 290.1857 (calcd. 291.1856 for $C_{20}H_{22}N_2$, $[M+H]^+$). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 6.90 min.

*3-((2-Methoxyphenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4h**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.22 (s, 1H, NH), 7.90 – 7.74 (m, 2H, Ph), 7.26 – 7.16 (m, 2H, Ph), 7.14 – 7.03 (m, 3H, ArH), 6.91 (d, J = 0.9 Hz, 1H, ArH), 6.79 (dd, ^1J = 0.84, ^2J = 8.2, 0.9 Hz, 1H, ArH), 5.19 (s, 1H, CH), 3.79 (s, 3H, OMe), 2.57 (d, J = 6.0 Hz, 4H, NCH_2C), 1.76 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 156.41 (s), 135.98 (s), 128.63 (s), 127.23 (s), 126.90 (s), 122.54 (s), 121.62 (s), 120.72 (s), 119.96 (s), 119.16 (s), 111.00 (s), 110.66 (s), 58.93 (s), 55.52 (s), 53.66 (s), 23.62 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.46 min.

*3-((4-Nitrophenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4i**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.19 – 8.10 (m, 3H, ArH), 7.86 – 7.71 (m, 3H, ArH), 7.36 – 7.09 (m, 4H, ArH, 4.72 (s, 1H, CH), 2.54 (d, J = 2.7 Hz, 4H, NCH_2C), 1.87 – 1.77 (m, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 152.20 (s), 146.57 (s), 136.22 (s), 128.26 (s), 125.98 (s), 123.68 (s), 122.26 (d, J = 14.5 Hz), 119.74 (d, J = 14.5 Hz), 118.10 (s), 111.28 (s), 53.51 (s), 23.60 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 6.49 min.

*3-(Pyrrolidin-1-yl(4-(trifluoromethyl)phenyl)methyl)-1H-indole (**4j**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.11 (s, 1H, NH), 7.82 (d, J = 7.9 Hz, 1H, ArH), 7.67 (d, J = 8.1 Hz, 2H, ArH), 7.51 (s, 2H, ArH), 7.31 (d, J = 8.0 Hz, 1H, ArH), 7.20 – 7.08 (m, 3H), 4.64 (s, 1H, CH), 2.52 (d, J = 6.0 Hz, 4H, NCH_2C), 1.78 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 148.60 (s), 136.18 (s), 128.86 (s), 128.54 (s), 127.88 (s), 126.20 (s), 125.64 (s), 125.23 (q, J = 3.8 Hz), 122.93 (s), 122.11 (d, J = 9.2 Hz), 119.68 (d, J = 9.0 Hz), 118.76 (s), 111.19 (s), 67.68 (s), 53.64 (s), 23.58 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 9.32 min.

*4-Chloro-3-((3-chlorophenyl)(pyrrolidin-1-yl)methyl)-1H-indole (**4k**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.43 (s, 1H, NH), 7.54 (s, 1H, ArH), 7.44 (d, J = 7.1 Hz, 2H, ArH), 7.19 (m, 4H, Ph), 7.05 – 7.00 (m, 1H, ArH), 5.40 (s, 1H, CH), 2.55 (d, J = 22.4 Hz, 4H, NCH_2C), 1.77 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 146.90 (s), 137.21 (s), 133.97 (s), 129.46 (s), 128.26 (s), 126.70 (d, J = 14.0 Hz), 125.73 (s), 124.32 (s), 123.12 (s), 122.24 (s), 121.11 (s), 119.26 (s), 110.11 (s), 65.64 (s), 53.89 (s), 23.49 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.70 min.

*4-Chloro-3-(phenyl(pyrrolidin-1-yl)methyl)-1H-indole (**4l**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.92 (s, 1H, NH), 7.54 (d, J = 7.3 Hz, 2H, Ph), 7.33 (d, J = 2.1 Hz, 1H, Ph), 7.23 (m, 2H, Ph), 7.14 (t, J = 7.3 Hz, 1H, ArH), 7.09 – 6.93 (m, 3H, ArH), 5.44 (s, 1H, CH), 2.57 (td, J = 9.3, 2.8 Hz, 4H, NCH_2C), 1.76 (d, J = 13.8 Hz, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 144.77 (s), 137.23 (s), 128.31 (d, J = 12.2 Hz), 126.66 (s), 125.86 (s), 124.37 (s), 123.29 (s), 122.07 (s), 121.00 (s), 119.84 (s), 110.07 (s), 66.20 (s), 53.99 (s), 23.51 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 8.85 min.

*5-Methoxy-3-(phenyl(pyrrolidin-1-yl)methyl)-1H-indole (**4m**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.20 (s, 1H, NH), 7.56 – 7.48 (m, 2H, Ph), 7.30 – 7.20 (m, 3H, Ph), 7.17 – 7.06 (m, 3H, ArH), 6.79 (dd, ^1J = 2.4, ^2J = 8.8, 2.4 Hz, 1H, ArH), 4.53 (s, 1H, CH), 3.83 (s, 3H, OMe), 2.63 – 2.43 (m, 4H, NCH_2C), 1.75 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 153.75 (s), 144.43 (s), 131.35 (s), 128.27 (s), 127.72 (s), 126.93 (s), 126.65 (s), 123.02 (s), 118.97 (s), 111.73 (d, J = 5.0 Hz), 101.87 (s), 68.09 (d, J = 2.9 Hz), 55.97 (d, J = 5.0 Hz), 53.77 (s), 23.58 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.92 min.

*4-((5-Methoxy-1H-indol-3-yl)(pyrrolidin-1-yl)methyl)-benzonitril (**4n**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.21 (s, 1H, NH), 7.63 (t, J = 10.2 Hz, 2H, Ph), 7.51 (d, J = 8.3 Hz, 2H, Ph), 7.26 – 7.09 (m, 3H, ArH), 6.83 (dd, ^1J = 2.36, ^2J = 8.8 Hz, 1H, ArH), 4.57 (s, 1H, CH), 3.85 (s, 3H, OMe), 2.50 (d, J = 6.0 Hz, 4H, NCH_2C), 1.77 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 153.94 (s), 150.08 (s), 132.20 (s), 131.41 (s), 128.22 (s), 126.45 (s), 123.08 (s), 119.18 (s), 117.68 (s), 111.92 (d, J = 3.2 Hz), 110.07 (s), 101.84 (s), 67.74 (d, J = 2.8 Hz), 53.51 (s), 23.59 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 9.57 min.

*4-((7-Methyl-1H-indol-3-yl)(pyrrolidin-1-yl)methyl)-benzonitrile (**4o**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.06 (s, 1H, NH), 7.66 (m, 3H, ArH), 7.53 (d, J = 8.3 Hz, 2H, ArH), 7.26 – 7.18 (m, 1H, ArH), 7.07 – 6.95 (m, 2H, ArH), 4.64 (s, 1H, CH), 2.52 (d, J = 6.9 Hz, 4H, NCH_2C), 2.45 (s, 3H, Me), 1.79 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 135.71 (s), 132.20 (s), 128.26 (s), 125.51 (s), 122.79 (s), 121.85 (s), 120.46 (s), 119.96 (s), 119.16 (s), 117.32 (s), 110.10 (s), 67.81 (d, J = 3.2 Hz), 53.55 (s), 23.57 (s), 16.63 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 8.15 min.

*7-Methyl-3-(phenyl(pyrrolidin-1-yl)methyl)-1H-indole (**4p**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.01 (s, 1H, NH), 7.66 (d, J = 7.9 Hz, 1H, ArH), 7.57 – 7.50 (m, 2H, ArH), 7.29 – 7.21 (m, 3H, ArH), 7.17 – 7.11 (m, 1H, ArH), 7.04 – 6.92 (m, 2H, ArH), 4.59 (s, 1H, CH), 2.62 – 2.47 (m, 4H, NCH_2C), 2.41 (s, 3H, Me), 1.78 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 144.26 (s), 135.61 (s), 128.23 (s), 127.70 (s), 126.62 (s), 126.00 (s), 122.42 (s), 121.73 (s), 120.23 (s), 119.68 (d, J = 12.0 Hz), 117.44 (s), 68.15 (s), 53.80 (s), 23.56 (s), 16.64 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 6.56 min.

*5-Bromo-3-(phenyl(pyrrolidin-1-yl)methyl)-1H-indole (**4q**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.45 (s, 1H, NH), 7.97 (s, 1H, Ph), 7.51 (d, J = 7.4 Hz, 2H, ArH), 7.29 – 7.14 (m, 4H, Ph), 7.08 (m, 2H, ArH), 4.51 (s, 1H, CH), 2.51 (d, J = 6.1 Hz, 4H, NCH_2C), 1.76 (s, 4H, CH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 144.04 (s), 134.69 (s), 128.41 (s), 128.18 (s), 127.64 (s), 126.87 (s), 124.70 (s), 123.35 (s), 122.15 (s), 119.00 (s), 112.68 (d, J = 11.2 Hz), 68.00 (s), 53.84 (s), 23.55 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.01 min.

*1-(1H-Indol-3-yl)-N,N-dimethyl-1-phenylmethanamine (**4r**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.30 – 8.13 (m, 1H, NH), 7.72 (d, J = 7.7 Hz, 1H, ArH), 7.38 – 7.27 (m, 6H, ArH), 7.24 – 7.16 (m, 2H, ArH), 7.12 (d, J = 7.0 Hz, 1H, ArH), 4.68 (s, 1H, CH), 2.39 (2×s, 6H, Me). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 142.10 (s), 136.07 (s), 131.02 (s), 129.57 (s), 128.38 (s), 127.98 (d, J = 8.8 Hz), 126.99 (s), 126.74 (s), 122.71 (s), 121.99 (s), 119.51 (d, J = 1.6 Hz), 116.98 (s), 111.17 (s), 69.21 (s), 44.14 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.45 min.

*3-(Phenyl(piperidin-1-yl)methyl)-1H-indole (**4s**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.07 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H, ArH), 7.49 (d, J = 7.2 Hz, 2H, Ph), 7.31 – 7.22 (m, 3H, Ph), 7.15 (m, 2H, ArH), 7.06 (m, 2H, ArH), 4.69 (s, 1H, CH), 2.42 (s, 4H, NCH_2C), 1.56 (m, 4H, NCH_2C, CH_2C), 1.41 (d, J = 5.0 Hz, 2H, CH_2). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 126.47 (s), 121.80 (s), 120.39 (s), 119.26 (s), 110.97 (s), 68.58 (s), 52.81 (s), 26.29 (s), 24.70 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 9.31 min.

*4-((1H-Indol-3-yl)(phenyl)methyl)morpholine (**4t**)*

– ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 8.08 (s, 1H, NH), 7.91 (d, J = 7.9 Hz, 1H, ArH), 7.52 (d, J = 7.5 Hz, 2H, Ph), 7.31 – 7.25 (m, 3H, Ph), 7.19 – 7.09 (m, 4H, ArH), 4.61 (s, 1H, CH), 3.72 (s, 4H, CCH_2O), 2.48 (d, J = 4.2 Hz, 4H, NCH_2C). – ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 142.45 (s), 136.33 (s), 128.32 (s), 128.16 (d, J = 28.0 Hz), 126.77 (s), 126.48 (s), 122.75 (d, J = 4.1 Hz), 122.02 (s), 120.22 (s), 119.52 (s), 117.12 (s), 111.10 (s), 68.85 (d, J = 5.3 Hz), 67.31 (s), 52.45 (s). – HPLC (Hypersil (NH_2) column, 25 °C, 254 nm, hexane-2-propanol 4 : 1): t_R = 7.92 min.

Supporting information

The spectra and chromatograms of **4a**–**4t** are given as Supporting Information available online (DOI: 10.5560/ZNB.2013-3313).

Acknowledgement

Financial support from the National Natural Science Foundation of China (no. 21276211) and the Doctoral Foundation of Southwest University (SWU112019) are gratefully acknowledged.

[1] G. R. Humphrey, T. J. Kuethe, *Chem. Rev.* **2006**, *106*, 2875 – 2911.
[2] R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, **1970**.
[3] R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**.
[4] W. Gul, M. T. Hamann, *Life Sci.* **2005**, *78*, 442 – 453.
[5] M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73 – 103.
[6] M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.* **2000**, *17*, 175 – 191.
[7] M. Shiri, *Chem. Rev.* **2012**, *112*, 3508 – 3549.
[8] D. A. Horton, Bourne, G. T. Smythe, *Chem. Rev.* **2003**, *103*, 893 – 930.
[9] B. Jiang, C. G. Yang, J. Wang, *J. Org. Chem.* **2001**, *66*, 4865 – 4869.
[10] H. Zhang, R. C. Larock, *Org. Lett.* **2001**, *3*, 3083 – 3086.
[11] M. Sakagami, M. Muratake, M. Natsume, *Chem. Pharm. Bull.* **1994**, *42*, 1393 – 1398.
[12] T. Fukuyama, X. Chen, *J. Am. Chem. Soc.* **1994**, *116*, 3125 – 3126.
[13] F. Andreanti, R. Andrisano, C. D. Case, M. Tramontini, *J. Chem. Soc.* **1970**, 1157 – 1161.
[14] S. Nunomoto, Y. Kawakami, Y. Yamashita, H. Takeuchi, S. Eguchi, *J. Chem. Soc., Perkin Trans. 1* **1990**, 111 – 114.
[15] Z. Zhang, X. Wang, R. A. Widenhoefer, *Chem. Commun.* **2006**, *35*, 3717 – 3719.
[16] T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903 – 2915.
[17] S. Yamazaki, Y. Iwata, *J. Org. Chem.* **2006**, *71*, 739 – 743.
[18] H. Yang, Y.-T. Hong, S. Kim, *Org. Lett.* **2007**, *9*, 2281 – 2284.
[19] G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2003**, *68*, 4594 – 4597.
[20] Y.-X. Jia, S.-F. Zhu, Y. Yang, Q.-L. Zhou, *J. Org. Chem.* **2006**, *71*, 75 – 80.
[21] M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *J. Org. Chem.* **2002**, *67*, 5386 – 5389.
[22] I. Komoto, S. Kobayashi, *Org. Lett.* **2002**, *4*, 1115 – 1118.
[23] J. S. Yadav, B. V. S. R. Reddy, K. V. Rao, G. G. K. S. N. Kumar, *Tetrahedron Lett.* **2007**, *48*, 5573 – 5576.
[24] S. Gérard, A. Renzetti, B. Lefevre, A. Fontana, P. Maria, J. Sapi, *Tetrahedron* **2010**, *66*, 3065 – 3069.
[25] A. Renzetti, E. Dardennes, A. Fontana, P. Maria, J. Sapi, S. Gérard, *J. Org. Chem.* **2008**, *73*, 6824 – 6827.
[26] F. Epifano, S. Genovese, O. Rosati, S. Tagliapietra, C. Pelucchini, M. Curini, *Tetrahedron Lett.* **2011**, *52*, 568 – 571.
[27] H. Grumbach, M. Arend, N. Risch, *Synthesis* **1996**, 883 – 887.
[28] S. Shirakawa, S. Kobayashi, *Org. Lett.* **2006**, *8*, 4939 – 4942.
[29] A. Olyaei, B. Shams, M. Sadeghpour, F. Gesmati, Z. Razaziane, *Tetrahedron Lett.* **2010**, *51*, 6086 – 6089.
[30] A. Kumar, M. K. Gupta, M. Kumar, *Green Chem.* **2012**, *14*, 290 – 295.
[31] A. Kumar, M. K. Gupta, M. Kumar, D. Saxena, *RSC Advances* **2013**, *3*, 1673 – 1678.