Three-Component Friedel–Crafts Reaction of Indoles, Glyoxylate, and Amine under Solvent-Free and Catalyst-Free Conditions – Synthesis of (3-Indolyl)glycine Derivatives

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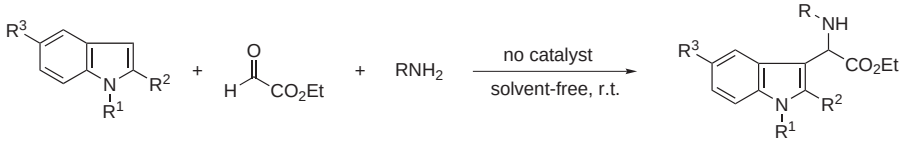
Abstract: Solvent-free and catalyst-free three-component reactions of indoles, amines, and ethyl glyoxylate gave alkylation products in good to high yields (61–93%), providing a convenient synthesis of (3-indolyl)glycine derivatives.

Key words: solvent-free, catalyst-free, indole, three-component alkylation, amine

Indolylglycines are an important class of non-proteinogenic amino acids, which are very useful building blocks for the synthesis of many biologically important compounds such as dragmacidins,[1] cephalosporin,[2] and pemedolac.[3] Several methods for the synthesis of a range of indolylglycine derivatives have appeared.[4] We have also reported a highly diastereoselective synthesis of indolylglycines by a TFA-promoted Friedel–Crafts reaction between N-substituted indoles and glyoxylate imines or chiral cyclic glyoxylate imines.[5] The Friedel–Crafts alkylation reaction is one of the most efficient methods for the construction of carbon–carbon bonds to aromatics and heteroaromatics.[6] In general, the reaction requires a stoichiometric amount or catalytic amount of Lewis acid,[7] Brønsted acid,[5] or organocatalyst,[8] as well as organic solvents. Recently, organic reactions under solvent-free conditions have attracted considerable attention[9] due to the advantages in terms of green chemistry.[10] Furthermore, recently, the development of solvent-free and multicomponent reactions is also of great concern. However, in most cases, the solvent-free reaction requires microwave or ultrasound irradiation.[11] Palmieri[12] reported a solvent-free asymmetric three-component aminoalkylation reaction for the synthesis of aminoalkylnaphthols by heating the reaction mixture at 60 °C. Herein, we would like to report our initial results on the three component Friedel–Crafts reaction of indoles, glyoxylate, and amines under solvent- and catalyst-free conditions at ambient temperature for the convenient synthesis of (3-indolyl)glycine derivatives.

As reported by Jiang,[4] the Friedel–Crafts alkylation reaction between indoles and glyoxylate imines (which is prepared by the reaction of glyoxylate with amine in CH_2Cl_2 in the presence of $MgSO_4$ for one hour), was complete in 6–72 hours in organic solvents without using an acid catalyst. Initially, we carried out the three-component reaction of indole (**1a**), ethyl glyoxylate (**2**), and aniline (**3a**) at ambient temperature without a catalyst under solvent-free conditions (Scheme 1). It was found that the yield of the reaction was dependent on the addition order of the starting materials. Although mixing **2** and **3** in situ to generate glyoxylate imine seemed to be reasonable, the reaction of **2** and **3** proceeded very fast, forming a gel too sticky to be stirred under solvent-free conditions. However, the reaction proceeded smoothly if **1a** was mixed with **3** to form a liquid mixture, **2** was then added with vigorous stirring. To our surprise, the reaction was complete within one minute to give the products, ethyl 2-(1*H*-indol-3-yl)-2-(phenylamino)acetate (**4a**) in 76% isolated yield, and **5a** in 19% yield (Figure 1) which resulted from the reaction of glyoxylate with indole. Contrary to the reaction of **1b** with **2a**, the effect of addition order on



1a–i **2**

3a, R = Ph
3b, R = $PhCH_2$
3c, R = CH_2=$CHCH_2$
3d, R = $(CH_3)_2CH$

4a–o

Scheme 1

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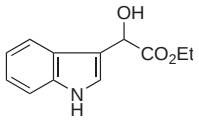


5a

Figure 1

yield is not obvious. It is most probable that three reactions occurred during the three-component reaction: in situ formation of glyoxylate imine, reaction of indole with glyoxylate, and reaction of indole with the in situ-formed glyoxylate imine. At the same time, the solvent- and catalyst-free reaction of **1a** with **2** was also examined. A reaction time of 30 minutes gave the product **5a** in 57% yield. Moreover, as soon as **2** was mixed with **3**, the reaction occurred and was complete immediately. For activated indole **1c**, the three-component reaction provided almost only aminoalkylation product **4c** in 93% yield (Table 1, entry 3). These results prove that the reaction of **2** with **3** is faster than that with **1a** and that the product of the Friedel–Crafts reaction of indole with in situ generated glyoxylate imine predominates in the solvent-free three-component reaction.

Table 1 Three-Component Friedel–Crafts Reaction of Indoles, Ethyl Glyoxylate (**2**), and Amines[a]

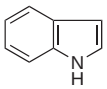
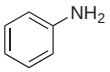
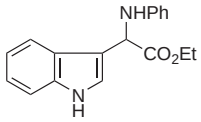
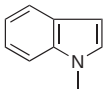
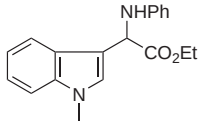
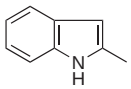
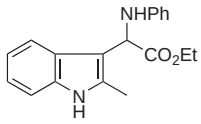
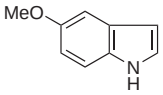
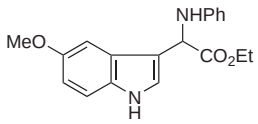
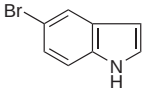
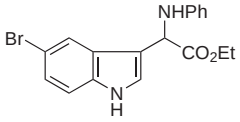
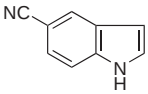
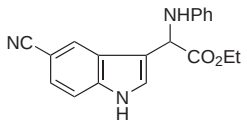
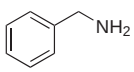
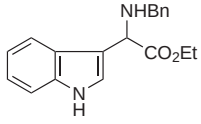
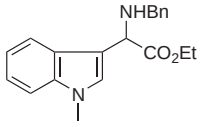
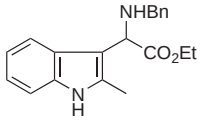
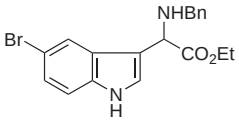
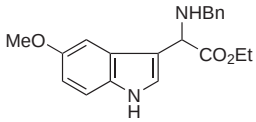
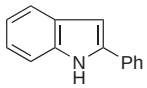
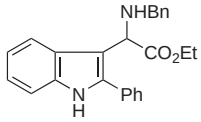
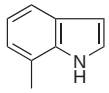
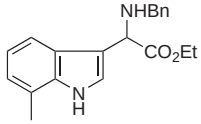
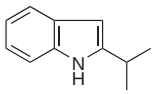
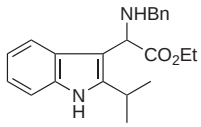
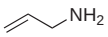
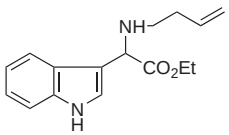
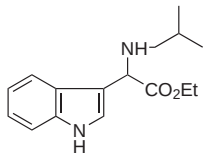
Entry	Indole	Amine	Time (min)	Product	Yield[b] (%)
1	 **1a**	 **3a**	1	 **4a**	76
2	 **1b**	**3a**	1	 **4b**	85
3	 **1c**	**3a**	1	 **4c**	93
4	 **1d**	**3a**	1	 **4d**	85
5	 **1e**	**3a**	1	 **4e**	63
6	 **1f**	**3a**	1	 **4f**	65
7	**1a**	 **3b**	30	 **4g**	80
8	**1b**	**3b**	40	 **4h**	82

Table 1 Three-Component Friedel–Crafts Reaction of Indoles, Ethyl Glyoxylate (**2**), and Amines[a] (continued)

Entry	Indole	Amine	Time (min)	Product	Yield[b] (%)
9	**1c**	**3b**	30	 **4i**	73
10	**1e**	**3b**	30	 **4j**	72
11	**1d**	**3b**	30	 **4k**	77
12	 **1g**	**3b**	30	 **4l**	63
13	 **1h**	**3b**	40	 **4m**	75
14	 **1i**	**3b**	40	 **4n**	70
15	**1a**	 **3c**	60	 **4o**	61
16	**1a**	 **3d**	4 h	 **4p**	49[c]

[a] Solvent-free and catalyst-free conditions at r.t.
[b] Isolated yield.
[c] Derivative **5a** also formed in 20% yield.

Based on the above results, various indoles **1a**–**f** were employed in the reaction with **2** and **3a** (Scheme 1) affording the corresponding products in 63–93% yield. 2-Methylindole (**1c**) showed the highest reactivity to give **4c** in excellent yield (93%). The electronic effect of the substituent on C-5 of the indole ring has an effect on the yields: electron-donating groups (such as methoxy group) gave a high yield (85%, Table 1, entry 4), while electron-withdrawing groups (Br, CN) afford relatively low yields (63–65%, Table 1, entries 5 and 6). *N*-Methylindole (**1b**) also showed good reactivity leading to **4b** in high yield (82%). When benzylamine (**3b**) was used in the three-component reaction instead of aniline (**3a**), the reaction times increased to 30–40 minutes. With a bulky group at C-2 of the indole, such as isopropyl **1i**, the reaction was complete in 40 minutes (70% yield). Allylamine **3c** exhibited lower reactivity but gave alkylated product **4o** in 61% yield. The yield of the reaction with alkylamine **3d** was low even

after a longer reaction time (49%), and was accompanied by **5a** (20% yield). It is noteworthy that ethyl 2-(1*H*-indol-3-yl)-2-(benzylamino)acetate (**4g**) was obtained in 80% yield in the three-component solvent-free and catalyst-free reaction of **1a**, **2**, and **3b** within 30 minutes. The synthesis of the same compound by the reaction of **1a** with benzylimino glyoxylate in toluene gave **4g** in 61% yield (48 h);[4] the solvent-free and catalyst-free three-component reaction represents a more convenient method.

The three-component reaction of **1a**, **2**, and **3b** was also carried out on a gram scale affording the product **4g** in 78% yield[14] (smaller scale, 80% yield). Although during the scale-up reaction under solvent-free conditions an exothermic phenomenon was observed, this did not influence the yield.

In conclusion, the solvent-free and catalyst-free three-component Friedel–Crafts alkylation of indoles, amine, and glyoxylate was developed for the convenient synthesis of (3-indolyl)glycine derivatives.

The acceleration effect in the solvent-free reaction was attributed to the concentration effect. Further mechanistic investigations are underway in this respect.

General Procedure

To a stirred mixture of indole (**1a**, 35 mg, 0.3 mmol) and aniline (**3a,** 42 μL, 0.45 mmol) ethyl glyoxylate **2** (freshly distilled; 50 mg, 0.45 mmol) was added at ambient temperature. The reaction mixture was stirred for 1 min. The crude product was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 4:1) to give ethyl 2-(1*H*-indol-3-yl)-2-(phenylamino)acetate **4a**[4] as a colorless oil (66 mg, 75%) and ethyl 2-(1*H*-indol-3-yl)-2-hydroxyacetate (**5a**, 12 mg, 19%). (3-Indolyl)glycine derivatives were characterized by ^{1}H, ^{13}C NMR, and IR spectroscopy and HRMS or elemental analysis.[13]

Acknowledgment

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(13) **4b**: colorless oil. IR: 3399, 3051, 2981, 1732, 1602, 1547, 1504, 1239, 1185, 1023 cm^{-1}. ^{1}H NMR: δ = 7.88 (d, *J* = 7.8 Hz, 1 H), 7.37–7.16 (m, 6 H), 6.77 (t, *J* = 7.3 Hz, 1 H), 6.70 (d, *J* = 8.6 Hz, 2 H), 5.44 (s, 1 H), 4.35–4.15 (m, 2 H), 3.75 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 172.7, 146.7, 137.4, 129.3, 127.7, 126.4, 122.1, 119.7, 119.6, 118.1, 113.4, 111.0, 109.6, 61.6, 54.3, 32.9, 14.2. HRMS: *m*/*z* calcd for $C_{19}H_{20}N_2O_2$ (M^+): 308.1525, found: 308.1521.
4c: colorless oil. IR: 3400, 2958, 2870, 1729, 1602, 1503, 1460, 1306, 1200, 1020 cm^{-1}. ^{1}H NMR: δ = 7.97 (s, 1 H), 7.83–7.81 (m, 1 H), 7.26–7.10 (m, 5 H), 6.74 (t, *J* = 7.2 Hz, 1 H), 6.65 (d, *J* = 7.8 Hz, 2 H), 5.30 (s, 1 H), 4.32–4.07 (m, 2 H), 2.43 (s, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 172.5, 146.7, 135.2, 133.4, 129.3, 126.8, 121.4, 119.9, 118.8, 118.0, 113.2, 110.6, 107.5, 61.5, 54.1, 14.2, 12.1. HRMS: *m*/*z* calcd for $C_{19}H_{20}N_2O_3$ (M^+): 308.1525, found: 308.1528.
4d: light yellow oil. IR: 3407, 2983, 2832, 1729, 1603, 1503, 1487, 1309, 1211, 1024 cm^{-1}. ^{1}H NMR: δ = 8.24 (s, 1 H), 7.28–7.12 (m, 5 H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.76 (t, *J* = 7.3 Hz, 1 H), 6.67 (d, *J* = 7.7 Hz, 2 H), 5.37 (s, 1 H), 4.32–4.17 (m, 2 H), 3.88 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 172.8, 154.3, 146.7, 131.6, 129.4, 126.2, 123.9, 118.2, 113.5, 112.9, 112.0, 101.1, 61.6, 55.9, 54.4, 21.1, 14.2. HRMS: *m*/*z* calcd for $C_{19}H_{20}N_2O_3$ (M^+): 324.1474, found: 324.1476.
4e: white solid; mp 123–125 °C. IR: 3409, 3381, 2985, 1710, 1602, 1506, 1455, 1314, 1270, 1021 cm^{-1}. ^{1}H NMR: δ = 8.27 (s, 1 H), 7.95 (d, *J* = 1.8 Hz, 1 H), 7.24 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.16–7.04 (m, 4 H), 6.72 (m, 1 H), 6.60 (dd, *J* = 8.6, 1.0 Hz, 2 H), 5.29 (s, 1 H), 4.26–4.08 (m, 2 H), 1.20 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 172.5, 146.4, 135.2, 129.4, 127.5, 125.4, 124.5, 122.2, 118.4, 115.3, 113.6, 113.3, 113.0, 112.1, 61.9, 54.2, 14.1. HRMS: *m*/*z* calcd for $C_{18}H_{17}N_2O_2$ (M^+): 372.0473, found: 372.0477.
4f: light yellow oil. IR: 3381, 2982, 2221, 1730, 1604, 1506, 1471, 1230, 1195, 1099 cm^{-1}. ^{1}H NMR: δ = 8.65 (s, 1 H), 8.22 (s, 1 H), 7.44–7.43 (m, 2 H), 7.36 (d, *J* = 2.0 Hz,

1 H),7.16–7.12 (m, 2 H), 6.75 (t, *J* = 7.3 Hz, 1 H), 6.63 (d, *J* = 8.1 Hz, 2 H), 5.37 (s, 1 H), 4.30–4.11 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 171.8, 146.0, 129.3, 125.7, 125.6, 125.5, 125.4, 120.5, 118.6, 113.8, 113.6, 112.4, 103.3, 62.1, 54.1, 14.1. HRMS: *m*/*z* calcd for $C_{19}H_{17}N_3O_2$ (M^+): 319.1321, found: 319.1326.

4j: white solid; mp 117–119 °C. IR: 3311, 3280, 2978, 2835, 1732, 1565, 1452, 1230, 1196, 1099 cm^{-1}. ^{1}H NMR: δ = 8.70 (s, 1 H), 7.82 (d, *J* = 1.8 Hz, 1 H), 7.35–7.22 (m, 6 H), 7.11–7.07 (m, 2 H), 4.66 (s, 1 H), 4.26–4.11 (m, 2 H), 3.86 (d, *J* = 13.0 Hz, 1 H), 3.81 (d, *J* = 13.0 Hz, 1 H), 2.60 (br s, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 173.2, 139.1, 135.0, 128.6, 128.5, 127.7, 127.4, 125.2, 124.3, 122.1, 113.2, 112.9, 112.5, 61.4, 57.2, 51.7, 14.2. HRMS: *m*/*z* calcd for $C_{19}H_{20}N_2O_2Br$ (M + H): 387.0702, found: 387.0708.

4m: light yellow oil. IR: 3409, 2979, 2932, 1729, 1592, 1495, 1450, 1187, 1025, 747 cm^{-1}. ^{1}H NMR: δ = 8.09 (s, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.36–7.22 (m, 6 H), 7.08–7.00 (m, 2 H), 4.70 (s, 1 H), 4.25–4.09 (m, 2 H), 3.84 (d, *J* = 13.0 Hz, 1 H), 3.79 (d, *J* = 13.0 Hz, 1 H), 2.46 (s, 3 H), 1.94 (s, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 173.5, 139.7, 136.0, 128.4, 128.4, 127.1, 125.7, 122.9, 122.7, 120.4, 120.1, 117.2, 113.8, 61.1, 57.6, 51.5, 16.6, 14.2. HRMS: *m*/*z* calcd for $C_{20}H_{22}N_2O_2$ (M^+): 322.1681, found: 322.1677.

4n: white solid; mp 98–99 °C. IR: 3403, 3182, 2960, 2858, 1729, 1495, 1460, 1301, 1221, 1183 cm^{-1}. ^{1}H NMR: δ = 7.97 (s, 1 H), 7.74 (d, *J* = 7.3 Hz, 1 H), 7.30–7.22 (m, 6 H), 7.13–7.07 (m, 2 H), 4.67 (s, 1 H), 4.23–4.00 (m, 2 H), 3.78 (d, *J* = 13.2 Hz, 1 H), 3.72 (d, *J* = 13.2 Hz, 1 H), 3.24–3.13 (m, 1 H), 2.20 (s, 1 H), 1.29–1.26 (m, 6 H), 1.14 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 173.2, 143.2, 140.0, 135.2, 128.3, 127.0, 126.8, 121.3, 119.8, 119.5, 110.5, 106.5, 60.9, 56.5, 51.0, 25.4, 23.2, 22.1, 14.1. HRMS: *m*/*z* calcd for $C_{22}H_{26}N_2O_2$ (M^+): 350.1994, found: 350.1999.

(14) The scale-up experiment was performed on a gram scale: To a stirred mixture of **1a** (1.0 g, 8.5 mmol) and benzylamine (**3b**; 1.43 mL, 1.4 g, 12.8 mmol), **2** (1.3 g, 12.8 mmol) was added at ambient temperature. The reaction mixture was stirred for 40 min. The crude product was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 4:1) to give ethyl 2-(1*H*-indol-3-yl)-2-(benzylamino)acetate (**4g**,[4] 2.06 g, 78%).