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Efficient Synthesis of [6-Chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]-acetic Acid, a Novel COX-2 Inhibitor

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Abstract: The synthesis of 6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-ylacetic acid (**1**), a selective cyclooxygenase 2 (COX-2) inhibitor, is described. The synthesis relied on a novel indole formation that involved an alkylation/1,4-addition/elimination/isomerization cascade. It was demonstrated that the entire sequence from sulfonamide **13** and bromoketone **14** to the desired indole (**1**) could be executed in a single pot.

6-Chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-ylacetic acid (**1**, Figure 1) was identified at Pfizer Global Research and Development as a selective COX-2 inhibitor for the potential treatment of pain and inflammatory-related disorders.[1,2] A synthesis amenable to multi-kilogram scale was desired for this 6-chloroindole. Herein, we present a practical and efficient synthesis of the desired target, which includes a one-pot synthesis of the desired indole nucleus.

The proposed retrosynthesis of **1** involved the elimination of a leaving group on nitrogen followed by isomerization to generate the indole (Scheme 1). The desired dihydroindole **2** could be obtained by a Michael addition to an α,β-unsaturated ester **3** by a deprotonated ketoaniline, which would result from the alkylation of a protected aniline **4** with an α-haloketone **5**.[3] Ideally, the protecting group used in the alkylation could be eliminated in the last step. This strategy proved to be successful for a variety of substrates.[4]

The first task was the identification of a suitable synthesis of **4**. The Discovery synthesis used a Wittig olefination of nitroaldehyde **6** to obtain the desired alkene according to the known procedure.[5] Since we could not identify a commercial source of the starting aldehyde for large-scale synthesis, it was prepared from the corresponding nitrotoluene derivative **7**. Following Coe's procedure,[6] the methyl group was oxidized using DMF dimethyl acetal to the dimethylenamine **8**. While the enamine could be isolated, it was more convenient to oxidize it directly to the aldehyde **9** using aqueous $NaIO_4$ in near-quantitative yield (Scheme 2).

A superior alternative that avoided the elevated temperature reaction, high-energy intermediates, and the Wittig reaction was also identified (Scheme 3). 2-Chloro-5-bromonitrobenzene **10** was submitted to a Heck reaction with ethyl acrylate leading to the desired cinnamate **11** in 95% yield. The nitro group could be chemoselectively reduced with iron in the presence of ammonium chloride affording the aniline **12** in 94% yield. Finally, the sulfonamide **13** could be accessed under standard methods in high yield. A sulfonamide was selected as a protecting group because of some precedence for its use as a leaving group in the formation of an indole.[7] Interestingly, the Heck reaction did not proceed on the

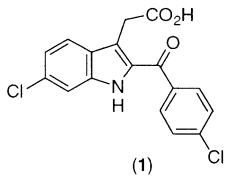
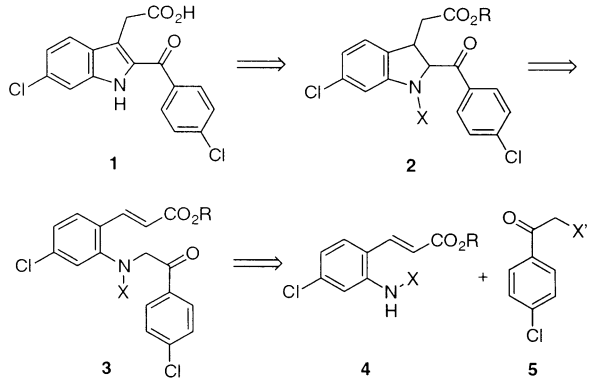
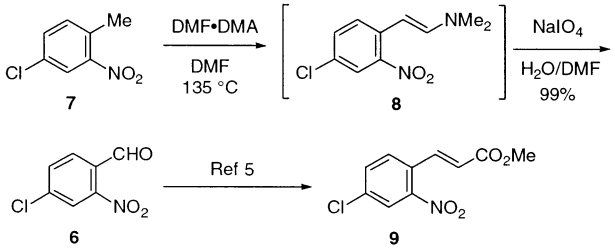


FIGURE 1. Synthetic target **1**.

SCHEME 1



SCHEME 2



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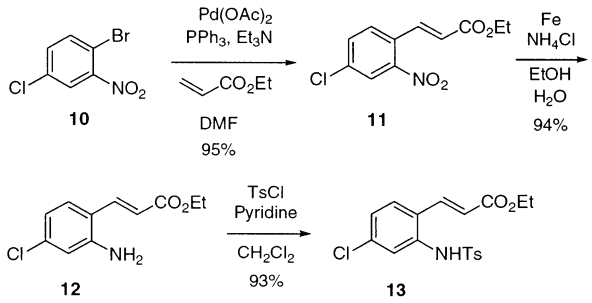
SCHEME 3

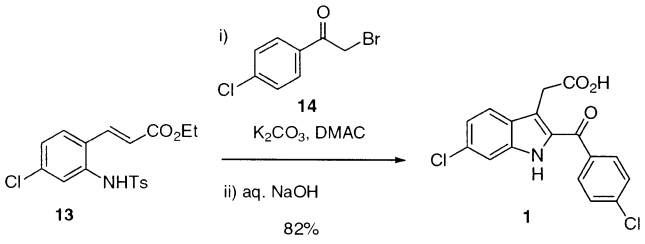


sulfonamide analogous to **10** (obtained from a reduction with Raney-nickel and hydrazine[8] and treatment with TsCl).

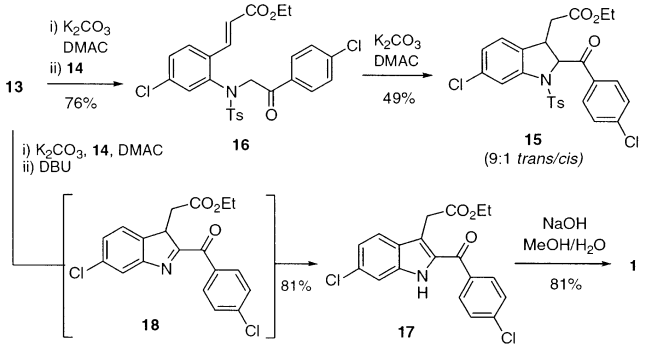
The next challenge was the formation of the indole. The classical procedure for the preparation of this heterocycle is the Fisher indole synthesis.[9] Recently, a number of new synthetic methods have been published on the topic.[10−14] Our approach begins with the alkylation of sulfonamide **13**. Several solvents and bases were evaluated, and K_2CO_3 in dimethyl acetamide (DMAC) proved to be the optimal combination. Both the α-bromo and α-chloro ketones were investigated, and it was found that while the reaction took only a few minutes with the bromide, it necessitated over a day with the chloride. When sulfonamide **13** was treated with 1.1 equiv of bromo ketone **14** and 2.0 equiv of K_2CO_3 in DMAC, the sulfonamide was rapidly alkylated and the Michael reaction proceeded to provide the dihydroindole **15** in less than 30 min. However, elimination of the toluenesulfinic acid was slow under these conditions. This was circumvented by addition of a stronger base, such as 1 N NaOH, to the reaction mixture, which allowed for the elimination and isomerization to the indole to proceed as well as for the hydrolysis of the ethyl ester to the desired target. The isolation of the product in pure form proved to be straightforward. The sodium salt of **1** is very water soluble such that once the hydrolysis of the ester was completed, the reaction mixture was extracted with methyl *tert*-butyl ether (MTBE), which allowed for removal of the DMAC and other organic materials. The aqueous layer was acidified to pH 1 with HCl, and carboxylic acid **1** was extracted with EtOAc. After concentration of the extracts, the product was crystallized in ^{i}PrOH/H_2O to afford **1** in 82% yield (Scheme 4).

The indole formation proceeds through several intermediates, most of which could be observed and even isolated by modifying the reaction conditions. For instance, if the potassium salt of sulfonamide **13** was first prepared, the alkylated product **16** could be isolated in 76% yield. Furthermore, if this product was resubmitted to K_2CO_3 in DMAC, the dihydroindole **15** could be

SCHEME 4



SCHEME 5



isolated as a 9:1 mixture of trans and cis isomers. Finally, if the entire reaction was performed in K_2CO_3 in DMAC and DBU was added in place of NaOH, indole **17** was isolated in 81% yield. The ethyl ester could then easily be cleaved to the carboxylic acid **1** using NaOH in MeOH and water. The only intermediate that was never observed is imine **18**, which must rapidly isomerize to the indole (Scheme 5).

An efficient preparation of 6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-ylacetic acid (**1**) has been demonstrated. The route implemented relied on a novel indole formation, which involves four tandem reactions. The precursor to this sequence, acrylate **13**, can be prepared efficiently through a Heck reaction. This synthesis is amenable to the preparation of a variety of indoles since the three components (an aniline, a Michael acceptor, and an α-haloketone) are all easily accessible.[4]

Experimental Section

General Methods. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Silica gel chromatography was carried out with J. T. Baker 40 mm silica gel according to Still's procedure.[15] Thin-layer chromatography was performed with EM Separations Technology silica gel F_{254}, and HPLC was performed with a Hewlett-Packard Series 1100 using a Puresil C_{18} column (4.6 × 150 mm) and 50/50 or 80/20 CH_3CN/H_2O mobile phase. Melting points were measured in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured in $CDCl_3$ unless otherwise indicated. Coupling constants (*J*) are reported in hertz. IR spectra were recorded as thin films on NaCl plates unless otherwise indicated.

2-Nitro-4-chlorobenzaldehyde (6). A solution of 2-nitro-4-chlorotoluene (**7**) (25.0 g, 122 mmol) and DMF·DMA (48.6 mL, 366 mmol) was heated at 135 °C (external oil bath temperature) for 11 h. The reaction mixture was cooled to room temperature and added dropwise to a 20 °C solution of $NaIO_4$ (78.0 g, 365

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mmol) in water (250 mL) and DMF (125 mL).[16] After 3 h, the crude reaction mixture was filtered, and the solids were washed with toluene (250 mL). The filtrate was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with water (3 × 250 mL) and concentrated to an oil. Hexanes (30 mL) were added, and the desired product was crystallized. The solid was filtered to afford 2-nitro-4-chlorobenzaldehyde (**6**) (22.4 g, 99% yield), which was identical to the reported ^{1}H NMR spectrum.[17]

3-(4-Chloro-2-nitrophenyl)acrylic Acid Ethyl Ester (11). To 2-chloro-5-bromonitrobenzene (**10**) (30.0 g, 127 mmol), $Pd(OAc)_2$ (285 mg, 1.27 mmol), and PPh_3 (666 mg, 2.54 mmol) in DMF (360 mL) were added Et_3N (24.7 mL, 178 mmol) and ethyl acrylate (138 mL, 1.27 mol). The reaction was stirred at 87 °C for 10 h, cooled to room temperature, and poured into a separatory funnel containing toluene (300 mL). The mixture was washed with 1 N HCl (300 mL) and water (2 × 200 mL). The organic extracts were concentrated to an oil that was crystallized in hexanes (60 mL). The solid was filtered to afford 3-(4-chloro-2-nitrophenyl)acrylic acid ethyl ester (**11**) (30.8 g, 95%): mp = 64−65 °C; ^{1}H NMR (300 MHz) δ 1.38 (t, 3H, J = 7.2), 4.32 (q, 2H, J = 7.2), 6.39 (d, 1H, J = 15.9), 7.60−7.67 (m, 2H), 8.04−8.09 (m, 2H); ^{13}C NMR (100 MHz) δ 14.14, 60.96, 123.86, 125.01, 128.94, 130.06, 133.51, 136.08, 138.43, 165.41; IR 1715, 1523, 1291, 1046 cm^{-1}. Anal. Calcd for $C_{11}H_{10}ClNO_4$: C, 51.68; H, 3.94; N, 5.48. Found: C, 51.68; H, 4.17; N, 5.25.

3-(4-Chloro-2-aminophenyl)acrylic Acid Ethyl Ester (12). To 3-(4-chloro-2-nitrophenyl)acrylic acid ethyl ester (**11**) (10.8 g, 42.2 mmol) in EtOH (151 mL) and H_2O (43 mL) were added iron powder (325 mesh) (7.10 g, 127 mmol) and NH_4Cl (1.35 g, 25.2 mmol). The reaction was stirred at 85 °C for 1 h, cooled to room temperature, and filtered through Celite. The filter cake was washed with toluene (200 mL), and the filtrate was concentrated to a low volume (∼50 mL), diluted with toluene (150 mL), and washed with H_2O (2 × 100 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to a solid that was triturated with hexanes (25 mL). The solid was filtered to afford 3-(4-chloro-2-aminophenyl)acrylic acid ethyl ester (**12**) (8.71 g, 91%): mp = 69−71 °C; ^{1}H NMR (300 MHz) δ 1.36 (t, 3H, J = 7.2), 4.08 (bs, 2H), 4.29 (q, 2H, J = 7.2), 6.35 (d, 1H, J = 15.7), 6.72−6.77 (m, 2H), 7.29−7.36 (m, 1H), 7.75 (d, 1H, J = 15.7); ^{13}C NMR (75 MHz) δ 14.33, 60.59, 116.18, 118.30, 118.53, 119.09, 129.21, 136.77, 138.85, 146.37, 167.08. IR 3389, 3347, 3240, 2987, 1698, 1627, 1319, 1185, 796 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.63; H, 5.41; N, 6.21.

3-[4-Chloro-2-(4-toluenesulfonylamino)phenyl]acrylic Acid Ethyl Ester (13). To 3-(2-amino-4-chlorophenyl)acrylic acid ethyl ester (**12**) (18.0 g, 79.8 mmol) in CH_2Cl_2 (144 mL) were added pyridine (9.04 mL, 112 mmol) and *p*-TsCl (16.0 g, 83.9 mmol). The reaction was stirred at room temperature for 18 h and poured into 1 N HCl (150 mL). The layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and concentrated. Hexanes was added to the resulting solid and filtered to afford 3-[4-chloro-2-(4-toluenesulfonylamino)phenyl]-acrylic acid ethyl ester (**13**) (28.3 g, 93%): mp = 124−127 °C; ^{1}H NMR (300 MHz) δ 1.35 (t, 3H, J = 7.2), 2.40 (s, 3H), 4.27 (q, 2H, J = 7.2), 6.12 (dd, 1H, J = 15.9, 0.9), 7.20−7.39 (m, 4H), 7.39 (d, 1H, J = 8.6), 7.48−7.53 (m, 2H), 7.62 (d, 2H, J = 8.3); ^{13}C NMR (75 MHz) δ 15.50, 22.79, 62.24, 122.48, 127.98, 128.49, 129.34, 129.50, 131.05, 136.82, 137.00, 137.73, 138.93, 145.55, 167.59; IR 3214, 1694, 1631, 1318, 1167 cm^{-1}. Anal. Calcd for $C_{18}H_{18}ClNO_4S$: C, 56.91; H, 4.78; N, 3.69. Found: C, 57.10; H, 5.08; N, 3.70.

[6-Chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic Acid (1). To a solution of 3-[4-chloro-2-(4-toluenesulfonylamino)-phenyl]acrylic acid ethyl ester (**13**) (13.0 g, 34.2 mmol) in DMAC (120 mL) were added K_2CO_3 (9.45 g, 68.4 mmol) and 2′-bromo-4-chloroacetophenone (**14**) (8.78 g, 37.6 mmol). The reaction was stirred at room temperature for 15 min. NaOH (1 N, 130 mL) was added, and the reaction mixture was heated to 100 °C for 8 h. The reaction mixture was cooled to room temperature, poured into a separatory funnel, and washed with MTBE (2 × 200 mL). The aqueous layer was acidified to pH 1 with 6 N HCl and was extracted with EtOAc (150 mL). The solvent was removed under reduced pressure, and to the resulting oil were added ^{i}PrOH (24 mL) and water (48 mL). A solid precipitated, and the slurry was stirred 12 h. The solid was filtered, washed with water, and dried to provide [6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic acid (**1**) (9.73 g, 82%): mp 181−183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 2H), 7.08 (dd, 1H, J = 8.5, 1.9), 7.42 (d, 1H, J = 1.9), 7.60 (d, 2H, J = 8.5), 7.62−7.73 (m, 3H), 11.74 (bs, 1H), 12.22 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.74, 113.25, 118.00, 121.93, 123.96, 127.69, 130.10, 131.30, 132.02, 133.59, 138.02, 138.37, 138.58, 173.20, 188.29; IR 3314, 1710, 1700, 1618, 1522, 1323, 1227, 1093, 941 cm^{-1}. Anal. Calcd for $C_{17}H_{11}Cl_2NO_3$: C, 58.64; H, 3.18; N, 4.02. Found: C,58.58; H, 3.22; N, 3.93.

3-[4-Chloro-2-(*N*-chlorophenyl)-2-oxoethyl]-*N*-(4-toluenesulfonylamino)]acrylic Acid Ethyl Ester (16). To a solution of 3-[4-chloro-2-(4-toluenesulfonylamino)phenyl]acrylic acid ethyl ester (**13**) (3.00 g, 7.90 mmol) in DMAC (15.0 mL) were added K_2CO_3 (2.18 g, 15.8 mmol) and 2′-bromo-4-chloroacetophenone (**14**) (2.03 g, 8.69 mmol). The reaction was stirred for 30 min, poured into 1 N HCl (30 mL), and extracted with MTBE (2 × 30 mL). The organic extracts were dried over $MgSO_4$, filtered, concentrated to a low volume. Hexanes was added and a solid precipitated. The precipitate was filtered to provide 3-[4-chloro-2-*N*-(4-chlorophenyl)-2-oxoethyl]-*N*-(4-toluenesulfonylamino)]acrylic acid ethyl ester (**16**) (3.19 g, 76%): mp = 162−165 °C; ^{1}H NMR (300 MHz) δ 1.38 (t, 3H, J = 7.2), 2.47 (s, 3H), 4.28 (q, 2H, J = 7.2), 5.00 (bs, 2H), 6.23 (d, 1H, J = 16.0), 7.29−7.36 (m, 4H), 7.47 (d, 2H, J = 8.7), 7.54 (d, 1H, J = 8.4), 7.59 (d, 2H, J = 8.3), 7.74 (d, 1H, J = 16.0), 7.88 (d, 2H, J = 8.7); ^{13}C NMR (75 MHz) δ 14.33, 21.62, 57.72, 60.66, 112.49, 120.69, 128.07, 129.21, 129.58, 129.70, 131.22, 132.80, 133.83, 134.80, 135.84, 138.55, 139.28, 140.38, 144.46, 166.02, 191.70; IR 1720, 1698, 1590, 1338, 1313, 1179, 1161, 1089 cm^{-1}. Anal. Calcd for $C_{26}H_{23}Cl_2NO_5S$: C, 58.65; H, 4.35; N, 2.63. Found: C, 58.74; H, 4.56; N, 2.72.

***cis*- and *trans*-[6-Chloro-2-(4-chlorobenzoyl)-1-(4-toluenesulfonyl)-2,3-dihydro-1*H*-indol-3-yl]acetic Acid Ethyl Ester (15).** To 3-[4-chloro-2-(*N*-chlorophenyl)-2-oxoethyl]-*N*-(4-toluenesulfonylamino)]acrylic acid ethyl ester (**16**) (1.00 g, 1.88 mmol) in DMAC (5.0 mL) was added K_2CO_3 (0.520 g, 3.76 mmol). The reaction mixture was stirred for 4 h, poured in 1 N HCl (30 mL) and extracted with MTBE (2 × 30 mL). The organic extracts were dried with $MgSO_4$, filtered, and concentrated. The resulting solid was purified by chromatography on silica gel (EtOAc/hexanes 20/80) to provide [6-chloro-2-(4-chlorobenzoyl)-1-(4-toluenesulfonyl)-2,3-dihydro-1*H*-indol-3-yl]acetic acid ethyl ester (**15**) as a 1:9 mixture of cis and trans isomers (0.488 g, 49%). Some of the ^{1}H NMR (300 MHz) significant signals are: δ 1.09 (t, J = 7.2), 1.19 (t, J = 7.2), 2.44 (s), 5.40 (d, J = 4.0), 5.99 (d, J = 9.7), 6.92 (dd, J = 8.1, 1.1), 7.04 (dd, J = 8.1, 1.9), 7.52 (d, J = 8.4), 7.57 (d, J = 1.9), 7.73 (d, J = 8.3), 7.99 (d, J = 8.6). LC−MS analysis was performed on the mixture of diastereoisomers and indicated to products with identical mass of 531 (M + H$^+$).

[6-Chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic Acid Ethyl Ester (17). To a solution of 3-[4-chloro-2-(4-toluenesulfonylamino)phenyl]acrylic acid ethyl ester (**13**) (3.00 g, 7.90 mmol) in DMAC (15.0 mL) were added K_2CO_3 (2.18 g, 15.8 mmol) and 2′-bromo-4-chloroacetophenone (**14**) (2.03 g, 8.69 mmol). The reaction was stirred for 30 min, and DBU (3.54 mL, 23.7 mmol) was added. The reaction mixture was stirred 1 h, poured into 1 N HCl (30 mL), and extracted with MTBE (2 × 30 mL). The organic extracts were dried with $MgSO_4$, filtered, and concentrated to provide a solid that was stirred in a mixture of MTBE and hexanes to afford [6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic acid ethyl ester (**17**) (2.42 g, 81%): mp = 186−188 °C;

(16) The quench of this reaction is exothermic but can be controlled. The internal temperature did not rise above 26 °C when it was performed in a flask placed in a 20 °C bath.

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^{1}H NMR (300 MHz) δ 1.27 (t, 3H, J = 7.1), 3.80 (s, 2H), 4.11 (q, 2H, J = 7.1), 7.15 (ddd, 1H, J = 8.5, 1.7, 0.5), 7.28−7.30 (m, 1H), 7.48 (d, 2H, J = 8.3), 7.54−7.57 (m, 1H), 7.77 (d, 2H, J = 8.3), 9.16 (bs, 1H); ^{13}C NMR (75 MHz) δ 15.42, 32.29, 62.45, 113.27, 117.60, 122.99, 123.23, 127.85, 130.12, 131.77, 133.61, 137.86, 138.13, 140.10, 172.45, 188.25; IR 3305, 1732, 1618, 1323 cm^{-1}. Anal. Calcd for $C_{19}H_{15}Cl_2NO_3$: C, 60.65; H, 4.02; N, 3.72. Found: C, 60.70; H, 3.97; N, 3.71.

[6-Chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic Acid (1) from 17. To a solution of [6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic acid ethyl ester (**17**) (200 mg, 0.532 mmol) in MeOH (2 mL) and water (0.8 mL) was added NaOH (137 mg, 3.43 mmol). The reaction mixture was stirred for 24 h and was concentrated to a low volume. Water (4 mL) was added, and the material was transferred to a separatory funnel and was washed with CH_2Cl_2 (5 mL). The aqueous layer was acidified to pH 1 with 1 N HCl and was extracted with EtOAc (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford [6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-yl]acetic acid (**1**) (150 mg, 81%). The ^{1}H NMR spectrum was identical with the one obtained for the compound prepared by the method described earlier.

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