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A Convenient Method for the Synthesis of Indole-3-acetic Acids

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Abstract: *Starting from the corresponding indoles, indole-3-acetic acids were synthesized through indole-3-glyoxylic acids, followed by hydrazone formation with p-toluenesulfonhydrazide, then reduction of the hydrazones with sodium borohydride.*

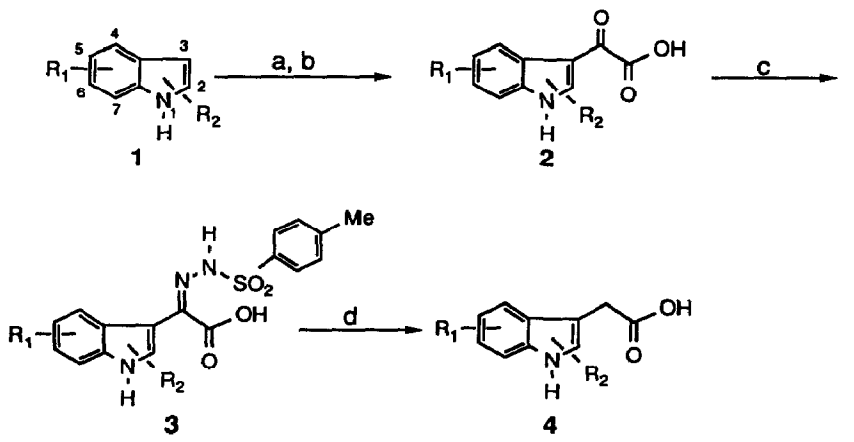
Indole-3-acetic acid and its derivatives have attracted considerable attention due to their demonstrated plant-growth regulating properties[1] and anti-inflammatory activities.[2] The general approaches for the synthesis of indole-3-acetic acids include: (a) Fischer indole ring closure in the presence of an acid at elevated temperature;[3] (b) alkylation of indoles with α-haloacetic acids or their corresponding esters[4] or α-hydroxyacetic acid,[5] as well as ethyl α-azidoacetate;[6] and (c) chemical[7] or enzymatic[8] hydrolysis of indole-3-acetonitriles which are synthesized from the corresponding indoles via three- to four-step procedures. All of these methods involve the use of strong acids or bases at elevated temperatures for a prolonged period of time except for the enzymatic hydrolysis. The harsh reaction conditions employed in these methods make their application unsuitable for the synthesis of indole-3-acetic acids bearing acid- or base-sensitive functional groups. In addition, a number of methods are discussed only in the patent literature; thus, detailed experimental procedures are not readily available.

Herein we wish to report a convenient method for the preparation of indole-3-acetic acids in three steps under mild conditions starting from the corresponding indoles. The overall yields were relatively low (14-38%); however, the mild conditions of this method make it very attractive for the synthesis of indole-3-acetic acids with potentially labile functional groups.

The synthetic method started with the preparation of indole-3-glyoxylic acids (**2**) according to a literature procedure with minor modification.[9] The indoles, dissolved in anhydrous ethyl ether, were reacted with oxalyl chloride at 0 °C for 20 min. The mixture was then treated with saturated sodium bicarbonate under reflux for 30 min to afford indole-3-glyoxylic acids (Scheme 1, Table 1, **2a-f**). All of the indoles employed were commercially available except for 5,7-dibenzyloxy-indole, which was prepared according to a literature procedure.[10]

The crude indole-3-glyoxylic acids (**2a-f**) were pure enough to be used for the next step. The hydrazone formation was achieved by treating indole-3-glyoxylic acids with *p*-toluene-sulfonhydrazide in refluxing methanol (Scheme 1). ^{1}H NMR spectra of the crude reaction mixture showed that the indole-3-glyoxylic acids were almost completely converted into the hydrazones after 8 h. These hydrazones were characterized by ^{1}H NMR, MS, and HRMS (Fab$^+$). Methanol was removed and the residue was treated with sodium borohydride in

tetrahydrofuran (THF) under reflux for 10 h to produce 30 to 40% yield of indole-3-acetic acids (Table 1,**4a-f**).



a. Oxalyl chloride, anhydrous ether, 0 °C, 20 min; b. Saturated aqueous $NaHCO_3$, reflux 30 min; c. Methanol, *p*-toluenesulfonhydrazide, reflux 8 h; d. $NaBH_4$, THF, reflux 10 h.

Scheme 1

Table 1 Preparation of Indole-3-glyoxylic acids (2) and Indole-3-acetic acids (4)

entry	R_1	R_2	2,[a]	Yield (%)	4,[b]	Yield (%)[c]
1	H	H	**a**	98	**a**	39
2	2-Me	H	**b**	98	**b**	39
3	5-Me	H	**c**	97	**c**	38
4	5-Br	H	**d**	40[d]	**d**	42
5	5-OCH_2Ph	H	**e**	97	**e**	37
6	5-OCH_2Ph	7-OCH_2Ph	**f**	78	**f**	33

a. **2a** is commercially available from Aldrich and **2b** is a known compound;[11] **2c-2f** were characterized by ^1H NMR, MS, and HRMS;[12] b. Compounds **4a,b,d** are commercially available from Aldrich; **4c**[3c] and **4e**[13] are known compounds and the spectroscopic data were identical with the literature values; Compound **4f** was fully characterized by ^1H NMR, ^{13}C NMR, IR, MS, and HRMS.[12] c. The yields were based on the conversion of **2** to **4**; d. Not optimized, 56% of 5-bromoindole was recovered.

Attempts were made to synthesize 5-nitroindole-3-acetic acid. However, 5-nitroindole failed to react with oxalyl chloride to form 5-nitroindole-3-glyoxylic acid under the reaction conditions employed. Conceivably, the strong electron-withdrawing effect of the nitro substituent prevents the oxalylation of 5-nitroindole under such mild conditions. This effect also explains the low yield observed for the oxalylation of 5-bromoindole (Table 1, **2d**). These results suggest that this method may not be suitable for preparation of indole-3-acetic acids with strong electron-withdrawing substituents.

In conclusion, we have developed a convenient method for the synthesis of indole-3-acetic acids. The method involves three steps starting from indoles, and the mildness of the reaction conditions is a major feature of this method.

GENERAL PROCEDURE

Indole-3-glyoxylic acids (2a-f). To a two-necked 50 mL flask containing the indole (4 mmol) in anhydrous ether (18 mL) a solution of oxalyl chloride (4 mmol) in anhydrous ether (0.64 mL) at 0 °C under an argon atmosphere was added dropwise over 10 min. The mixture was stirred for an additional 10 min; an orange precipitate formed. A saturated aqueous solution of sodium bicarbonate (6 mL) was added with caution. The mixture was heated to reflux for 30 min, cooled and acidified with 10% HCl, resulting in the precipitation of the indole-3-glyoxylic acid. The solid was filtered and dried. The crude acids, except for 5-bromoindole-3-glyoxylic acid, were pure enough for the next step. For 5-bromoindole-3-glyoxylic acid, a different workup condition was used. Before the acidification with 10% HCl, dichloromethane was used to extract the remaining unreacted 5-bromoindole. After that, the rest of the procedure was identical to that described above.

Indole-3-acetic acids (4a-f). An indole-3-glyoxylic acid (1 mmol) prepared above was mixed with *p*-toluenesulfonhydrazide (1.5 mmol) in methanol (23 mL) and refluxed under argon for 8 h. Methanol was removed under reduced pressure. The residue was dissolved in anhydrous tetrahydrofuran (THF) (23 mL) followed by addition of $NaBH_4$ (21.4 mmol). The mixture was allowed to reflux for 10 h under argon. After cooling, glacial acetic acid (6 mL) was added to destroy any remaining $NaBH_4$ and also to acidify the mixture. The whole mixture was passed quickly through a short silica gel column (THF:hexanes 1:1). Solvents were removed under reduced pressure and the crude product was further purified by column chromatography [silica gel, eluting with ethyl acetate:hexanes (1:1) and THF:hexanes (1:1)].

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REFERENCES AND NOTES

1. (a) Thimann, K. V. In *Hormone Action in the Whole Life of Plants;* University of Massachusetts Press: Amherst, 1977, pp. 29-70. (b) Engvild, K. C. *Phytochem.* **1986**, *25*, 781-791.
2. (a) Shen, T.-Y.; Winter, C. A. In *Advances in Drug Research*; Harper, N. J.; Simmonds, A. B., Eds.; Academic Press: New York, 1977; Vol. 12, pp. 89-245. (b) Boltze, K. H.; Brendler, O.; Jacobi, H.; Opitz, W.; Raddatz, S.; Seidel, P. R.; Vollbrecht, D. *Arzneim. Forsch.* **1980**, *30*, 1314-1325.

3. (a) Fox, S. W.; Bullock, M. W. *J. Am. Chem. Soc.* **1951**, *73*, 2756-2759. (b) Bullock, M. W.; Fox, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 5155-5157. (c) Ilic, N.; Klaic, B.; Magnus, V.; Vikic-Topic, D.; Gacs-Baitz, E. *Croat. Chem. Acta* **1991**, *64*, 79-88.
4. (a) Cai, Y.; Du, R. *Jinan Daxue Xuebao* **1990**, *11*, 52-55. (b) Avramenko, V. G.; Pershin, G. N.; Mushulov, P. I.; Makeeva, O. O.; Eryshev, B. Y.; Shagalov, L. B.; Suvorov, N. N. *Khim. Farm. Zh.* **1970**, *4*, 15-18. (c) Shagalov, O. U.S. Patent 3,320,281, 1967.
5. Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1963**, *28*, 1246-1248.
6. Badger, G. M.; Christie, B. J.; Rodda, H. J.; Pryke, J. M. *J. Chem. Soc.* **1958**, 1179-1184.
7. (a) Leonte, C.; Sauciuc, A.; Carp, E. RO. Patent 640061, 1978. (b) Delvigs, P.; McIsaac, W. M.; Taborsky, R. G. *J. Biol. Chem.* **1965**, *240*, 348-350. (c) DeGraw, J.; Goodman, L. *J. Org. Chem.* **1962**, *27*, 1728-1730.
8. Klempier, N.; de Raadt, A.; Griengl, H.; Heinisch, G. *J. Heterocycl. Chem.* **1992**, *29*, 93-95.
9. Kline, T. B; Benington, F.; Morin, R. D.; Beaton, J. M. *J. Med. Chem.* **1982**, *25*, 908-913.
10. (a) Sinhababu, A. K.; Borchardt, R. T. *J. Am. Chem. Soc.* **1989**, *111*, 2230-2233. (b) Lee, F. G. H.; Dickson, D. E.; Suzuki, J.; Zirnis, A.; Manian, A. A. *J. Heterocycl. Chem.* **1973**, *10*, 649-654.
11. Sanna, G. *Gazz. Chim. Ital.* **1931**, *61*, 60-74.
12. **2c**: ^{1}H NMR (300 MHz, d_6-acetone) δ 2.42 (s, 3 H, CH_3), 7.11 (dd, *J* = 8.2, 1.2 Hz, 1 H, H-7), 7.43 (d, *J* = 8.2 Hz, 1 H, H-6), 8.10 (s, 1 H, H-4), 8.67 (d, *J* = 3.3 Hz, 1 H, H-2), 11.30 (br, H-1); EIMS, m/e 203 (M^+), 158, 130; HRMS, $C_{11}H_9NO_3$ requires m/e 203.0582. Found 203.0578. **2d**: ^{1}H NMR (300 MHz, d_6-acetone) δ 7.41 (dd, *J* = 8.4, 2.0 Hz, 1 H, H-7), 7.54 (d, *J* = 8.4 Hz, 1 H, H-6), 8.44 (d, *J* = 2.0 Hz, 1 H, H-4), 8.72 (d, *J* = 6.3 Hz, 1 H, H-2), 11.61 (br, 1 H, H-1); EIMS, m/e 269 (M^++2), 267, 224, 222, 197, 195; HRMS, $C_{10}H_6BrNO_3$ requires m/e 266.9531. Found 266.9521. **2e**: ^{1}H NMR (300 MHz, d_6-acetone) δ 5.18 (s, 2 H, OCH_2), 7.01 (dd, *J* = 8.7, 2.4 Hz, 1 H, H-7), 7.20-7.55 (m, 6 H, ArH), 7.92 (d, *J* = 2.4 Hz, 1 H, H-4), 8.64 (s, 1 H, H-2), 11.45 (br, 1 H, H-1); EIMS, m/e 295 (M^+), 250, 223, 91; HRMS, $C_{17}H_{13}NO_4$ requires m/e 295.0845. Found 295.0840. **2f**: ^{1}H NMR (300 MHz, d_6-acetone) δ 5.13 (s, 2 H, OCH_2), 5.25 (s, 2 H, OCH_2), 6.71 (d, *J* = 2.1 Hz, 1 H, H-4 or H-6), 7.24-7.54 (m, 11 H, ArH), 8.55 (s, 1 H, H-2), 11.60 (br, 1 H, H-1); EIMS, m/e 329, 91; HRMS (FAB+), $C_{24}H_{20}NO_5$ (M+1) requires m/e 402.1341. Found 402.1356. **4f**: IR ($CDCl_3$) 3450 (br s) (OH), 1700 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 2 H, CH_2CO_2), 5.07 (s, 2 H, OCH_2), 5.14 (s, 2 H, OCH_2), 6.54 (d, *J* = 1.8 Hz, 1 H, H-4 or H-6), 6.76 (d, *J* = 1.8 Hz, 1 H, H-4 or H-6), 7.13 (d, *J* = 2.5 Hz, 1 H, H-2), 7.22-7.60 (m, 10 H, Ph), 8.27 (br s, 1 H, H-1); ^{13}C NMR (300 MHz, $CDCl_3$) δ 31.1, 70.3, 70.9, 93.8, 96.3, 108.1, 122.3, 123.2, 125.5, 127.8, 127.9, 128.2, 128.5, 128.6, 136.7, 137.5, 145.7, 154.2, 176.5; EIMS, m/e 387 (M^+), 341, 205, 91; HRMS, $C_{24}H_{21}NO_4$ requires m/e 387.1471. Found 387.1467.
13. ^{1}H NMR, Sadtler Standard Spectra, 1972, Vol. 21, 13777M.

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