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Convenient Method of Synthesizing 3-Ethoxycarbonyl Indoles

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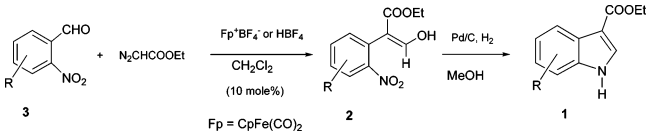
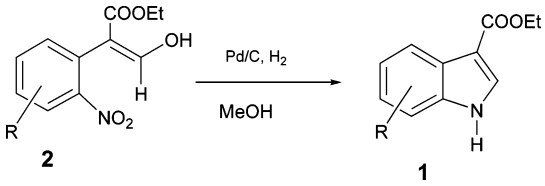


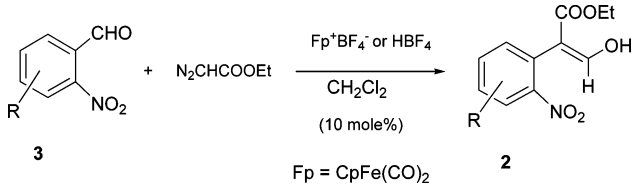
We have developed a convenient two-step procedure for the synthesis of 3-ethoxycarbonyl indoles from commercially available materials. The two-step procedure involves the synthesis of 2-aryl-3-hydroxypropenoic acid ester, followed by a catalytic reduction. This method is efficient, simple, and selective.

The indole moiety is found in numerous natural and unnatural products and is an important building block of several families of alkaloids.[1] Many of them have biological activities such as Indocin[2] (anti-inflammatory), Oncovin[1b,3] (anti-cancer), Lescol[4] (cholesterol-lowering), and Vinblastine[5] (anti-cancer). Probably the best-known compound containing the indole structure is tryptophan, which is an essential amino acid.[6] Many methods exist for the synthesis of indoles, and they vary in complexity and starting materials. The most famous synthesis is the Fischer indole synthesis.[7] One major drawback of this method is that a mixture of indoles can result from unsymmetrical ketones. Many other methods are known,[8] but very few methods for synthesizing 3-substituted indole rings are available. Here, we report a simple, convenient two-step synthesis of 3-ethoxycarbonyl indoles (**1**) from commercially available starting materials.[9]

SCHEME 1



SCHEME 2



Our method is based on the catalytic hydrogenation of 2-(2-nitroaryl)-3-hydroxypropenoic acid esters (**2**) to 3-ethoxycarbonyl indoles (**1**; Scheme 1).

The 2-(2-nitroaryl)-3-hydroxypropenoic acid esters (**2**) were prepared from 2-nitrobenzaldehydes (**3**) and ethyl diazoacetate in the presence of 10% of iron Lewis acid, $Fp^+BF_4^-$ ($Fp = Cp(CO)_2Fe$).[10] Several nitroaryl acid esters were synthesized in good yields using this iron Lewis acid. Moreover, we recently found that a simple Brønsted acid such as tetrafluoroboric acid (HBF_4) also catalyzes the reaction of 2-nitrobenzaldehydes with ethyl diazoacetate to yield the 2-nitroarylacrylic acid ester in very good yields (Scheme 2).[11] The results from both Lewis acids are summarized in Table 1. The yields of some propenoic acid esters were also improved by carrying out these reactions at a lower temperature (entries 3, 6, and 11).

The reduction of the nitro group to the amine was carried out using Pd/C in methanol under 3 atm of hydrogen for 24 h. The Pd/C was removed by filtering the crude mixture through Celite, and the indole was isolated by column chromatography and identified by ^1H and ^{13}C NMR, CHN analysis, or HRMS. The results of the reduction are listed in Table 2. The unsubstituted indole gave the best result and was isolated in 90% yield.

In our attempt to improve the yield of the indole, we tried a few different reducing agents, $SnCl_2 \cdot 2H_2O$,[12] $TiCl_3$ with ammonium acetate,[13] and ammonium formate with Pd/C.[14] When

(1) (a) Rahman, A.; Basha, A. *Indole Alkaloids*; Harwood Academic Publishers: Amsterdam, The Netherlands, 1998; p 141. (b) Gupta, R. R. *Heterocyclic Chemistry*; Springer Publishing: New York, 1999; Vol. 2, p 193.

(2) *Physicians Desk Reference*, 51st ed.; Medical Economics, Co.: Oradell, New Jersey, 1997; p 2395.

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(7) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; p 142. (b) Jones, A. R. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 334. (c) Gupta, R. R. *Heterocyclic Chemistry*; Springer Publishing: New York, 1999; Vol. 2, p 199. (d) Nakazaki, M.; Yamamoto, K. *J. Org. Chem.* **1976**, *41*, 1877.

(8) For reviews, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2848. (c) Sundberg, R. J. *Indoles*; Academic Press: San Diego, CA, 1996. (d) Moody, C. J. *Synlett* **1994**, 681. (e) Gribble, G. W. *Contemp. Org. Synth.* **1994**, 145. (f) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1.

(9) Aromatic aldehydes and ethyl diazoacetate are commercially available. Ethyl diazoacetate is also prepared in our laboratory following the known procedure: Searle, N. E. In *Organic synthesis*; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. No. IV, p 424. There is no difference in the yield of the products by using commercial ethyl diazoacetate or by using a freshly prepared one.

(10) Mahmood, S. J.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 3333.

(11) Dudley, M.; Morshed, M. M.; Brennan, C.; Islam, M. S.; Ahmad, M. S.; Atuu, M. R.; Branstetter, B.; Hossain, M. M. *J. Org. Chem.* **2004**, *69*, 7599.

(12) Faul, M. M. Tin (II) Chloride. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, p 4893.

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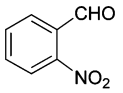
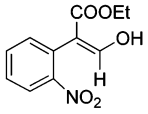
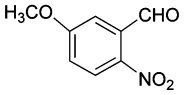
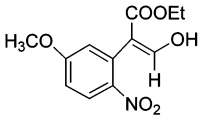
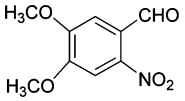
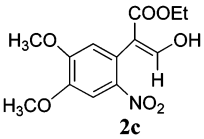
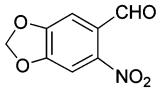
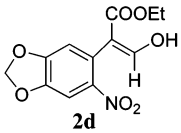
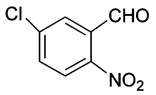
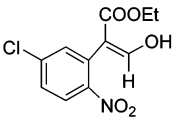
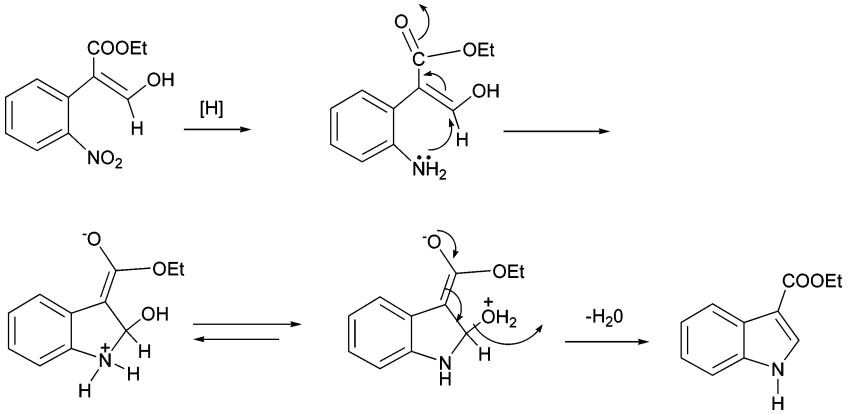
TABLE 1. Isolated Yields of 2-Aryl-3-hydroxypropenoic Acid Ester from 2-Nitrobenzaldehydes and EDA

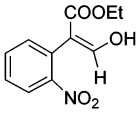
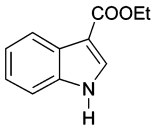
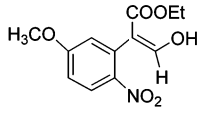
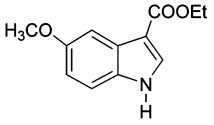
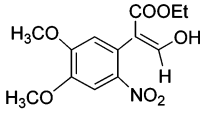
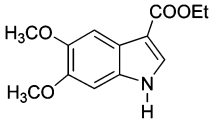
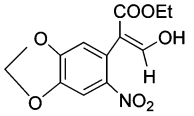
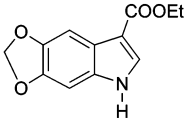
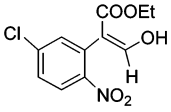
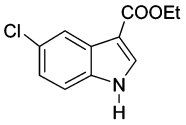
Entry	Aldehyde	Catalyst	Temp. (0^0 C)	Acid Ester	Yield (%)
1	 **3a**	$Fp^+BF_4^-$	0	 **2a**	73
2		HBF_4	0		73
3		"	-78		75
4	 **3b**	$Fp^+BF_4^-$	0	 **2b**	68
5		HBF_4	0		68
6		"	-78		75
7	 **3c**	HBF_4	-78	 **2c**	76
8	 **3d**	HBF_4	-78	 **2d**	86
9	 **3e**	Fp^+BF_4	0	 **2e**	35
10		HBF_4	0		45
11		"	-78		50

SCHEME 3



the propenoic acid esters were treated with these reducing agents, no indoles were observed. As a result of a long reaction time (24 h), we suspect some kind of polymerization during reduction lowers the yield of the indole products. We also tried adding a small amount of acetic acid during the reduction with H_2 on Pd/C to hopefully speed up the cyclization process and to minimize the polymerization. However, no change in the yield or in the reaction time was observed.

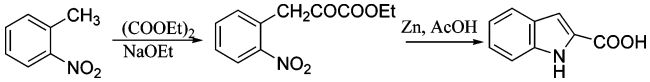
TABLE 2. Isolated Yields of 3-Ethoxycarbonyl Indoles by Reduction

Entry	Acid Ester	Indole	Yield (%)
1	 **2a**	 **1a**	90
2	 **2b**	 **1b**	62
3	 **2c**	 **1c**	76
4	 **2d**	 **1d**	86
5	 **2e**	 **1e**	66

The synthesis only requires two steps: first, the synthesis of the 2-(2-nitroaryl)-3-hydroxypropenoic acid esters and then the reduction to the corresponding indoles. Our proposed mechanism (Scheme 3) entails reduction of the nitro group and subsequent cyclization to the indole. Once the amine is formed, cyclization is spontaneous. The cyclization is similar to the methods of Reissert[15] and others[16] in that a nitro group is reduced to an amine, which then undergoes a nucleophilic attack to form a five-membered ring, followed by loss of water to form the indole ring.

The classical Reissert indole synthesis[15] involved the reductive cyclization of *o*-nitrophenylpyruvic ester to indole-2-carboxylic acid (Scheme 4). The *o*-nitrophenylpyruvic ester was synthesized from *o*-nitrotoluene and diethyl oxalate in the presence of sodium ethoxide. The cyclization provides 2-substituted indoles, whereas our method produces the indoles with an ester group at the 3 position. Our method certainly compliments the Reissert approach and could be useful in the area of heterocyclic chemistry. Work is underway using our methods to synthesize some important biologically active products containing 3-substituted indoles.

SCHEME 4



Experimental Section

HBF_4·OEt_2-Catalyzed Reaction between 2-Nitrobenzaldehyde and Ethyl Diazoacetate. To a solution of 2-nitrobenzaldehyde (0.170 g, 1.15 mmol) in freshly distilled dichloromethane (15 mL) was added HBF_4·OEt_2 (0.02 mL, 0.115 mmol) at 0 °C. Ethyl diazoacetate[9] (0.153 mL, 1.38 mmol) was diluted in 4 mL of freshly distilled dichloromethane and drawn into a gastight syringe. The diluted ethyl diazoacetate was then added to the aldehyde over a period of 6−7 h with the help of a syringe pump. The reaction mixture was allowed to stir for an additional 16 h at 0 °C and then filtered through a silica plug. The solvent was removed by rotary evaporation and products were isolated by column chromatography (silica gel, 2−10% ethyl acetate in pentane/hexane), providing ethyl 3-hydroxy-2-(2-nitrophenyl)propenate (**2a**)[17] in 73% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.93 (d, 1H, J = 13 Hz), 7.94 (d, 1H, J = 8 Hz), 7.55 (t, 1H, J = 8 Hz), 7.44 (t, 1H, J = 8 Hz), 7.23 (m, 2H), 4.12 (br q, 2H), 1.12 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.85, 162.05, 149.05, 133.16, 132.10, 129.09, 128.44, 124.69, 106.50, 61.19, 13.62. Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.68; N, 5.91. Found: C, 55.86; H, 4.60; N, 5.82.

Pd-Catalyzed Hydrogenation of Ethyl 3-Hydroxy-2-(2-nitrophenyl)propenate. A sample of ethyl 3-hydroxy-2-(2-nitrophenyl)-propenate (0.167 g, 0.702 mmol) was dissolved in 10 mL methanol, and 35 mg of Pd/C was added to the solution. The mixture was stirred under hydrogen gas at 3 atm of pressure for 24 h. The Pd/C was removed by passing the crude through a pad of Celite. The solvent was removed by rotary evaporation, and indole-3-carboxylic acid ethyl ester (**1a**)[18] was isolated in 90% yield by column chromatography (silica gel, 0−10% EtOAc in pentane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66 (br s, 1H, NH), 8.21 (m, 1H), 7.94 (d, 1H, J = 3 Hz), 7.43 (m, 1H), 7.32 (m, 2H), 4.44 (q, 2H, J = 7 Hz), 1.45 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.25, 135.99, 130.85, 125.71, 123.09, 121.92, 121.49, 111.37, 109.08, 59.74, 14.46.

Supporting Information Available: Detailed experimental procedures and compound characterizations for **1b**, **1c**, **1d**, **1e**, **2b**, and **2d** and other related information. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0601821

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