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A concise synthesis of 3-hydroxyindole-2-carboxylates by a modified Baeyer–Villiger oxidation

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Abstract

Indole-2-carboxylates are converted in good yields to 3-hydroxyindole-2-carboxylates by use of a Vilsmeier–Haack/Baeyer–Villiger reaction sequence. A systematic examination of the various indole substituents revealed this route to be general in scope. © 2000 Published by Elsevier Science Ltd.

3-Hydroxyindole-2-carboxylates have been used as intermediates in the synthesis of compounds of medicinal value.[1] A common route to prepare hydroxyindoles involves the Dieckmann reaction of anthranilic acid with α-halogenoacetate.[2] Due to the numerous steps required by this approach to build this indole core, the yield is not generally higher than the 25% yield observed for the direct oxidation of 1-methylindole-2-carboxylate with lead tetraacetate.[3] Other methods, like Hawthorne's procedure, to transform a *t*-butyl 3-bromo-1-methylindole-2-carboxylate to the corresponding 3-hydroxyindole via a one pot reaction (reaction with *n*-BuLi, $(MeO)_3B$ and H_2O_2 in acetic acid) also proceed in low yields.[4] Finally, the Baeyer–Villiger oxidation of the *N*-methyl-3-formylindole-2-carboxylate has been previously reported, although this approach leads to poor yields of the corresponding alcohol.[5] To date, an efficient procedure to prepare 3-hydroxyindole-2-carboxylates from unprotected indoles is not available. As part of our medicinal chemistry research program, we required an efficient route to hydroxyindoles and we wish to report herein an improvement in the Baeyer–Villiger reaction conditions resulting in good yields of the corresponding products.

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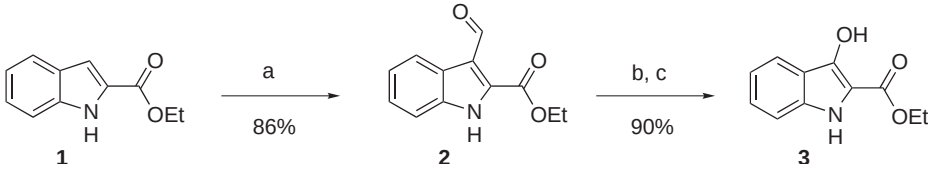
The starting 3-formylindole **2** required for our studies was easily prepared in good yield by exposing indole **1** to Vilsmeier–Haack reaction conditions (Scheme 1).[6] At the outset, we treated aldehyde **2** to reaction conditions described by Mérour (dried *m*-CPBA in CH_2Cl_2 at 5°C) originally developed to oxidize *N*-tosyl or acetyl 3-formylindoles.[5] Under these conditions, the oxidation was slow. When the reaction mixture was warmed to room temperature, a 90% yield (after hydrolysis of the 3-formyloxy intermediate) of indole **3** was obtained after 30 h. Performing the same reaction with 1 equiv. of PTSA to activate the aldehyde, a 77% yield of the Baeyer–Villiger product was realized in only 40 min. The main side product in this reaction was over oxidation of the indole moiety in approximately 15–20% yield. To avoid the formation of this undesired oxidation product, the reaction was carried out at 10°C and the efficiency of the reaction was improved to 90% (Scheme 1, Table 1, entry 1). For comparison, Mérour et al. reported a yield of 23% for the synthesis of the ethyl *N*-methyl-3-formyloxyindole-2-carboxylate.



1 2 3

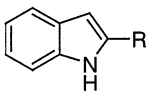
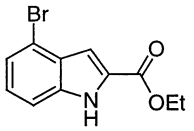
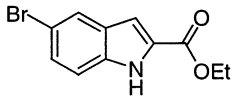
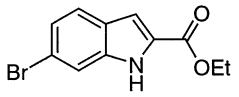
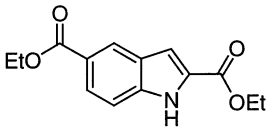
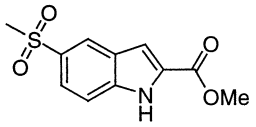
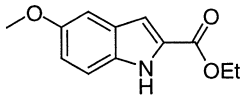
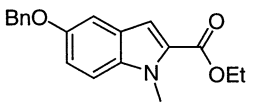
Scheme 1. Reagents and conditions: (a) $POCl_3$ (1.5 equiv.), $HCON(CH_3)C_6H_5$ (1.5 equiv.), $ClCH_2CH_2Cl$, reflux; (b) *m*-CPBA, PTSA, CH_2Cl_2, 10°C; (c) Me_2S, EtOH

Having established high yielding conditions for the oxidation of aldehyde **2** to hydroxyindole **3**, we wanted to examine the scope of this method. Table 1 summarizes the results of this indole oxidation reaction.[7] Replacement of the ester substituent with a carboxamide (Table 1, entry 1) gave similar yields of the hydroxyl product. Introduction of a bromine substituent at either the 4-, 5- or 6-position of the indole was well tolerated (Table 1, entries 2, 3 and 4).[8] Also, the presence of a second ester group on the indole did not affect the oxidation yield (Table 1, entry 5).[9] However, with a strong electron-withdrawing group such as a methylsulfone at the 5-position of the indole ring completely shut down the oxidation process (Table 1, entry 6). We speculate that this indole is too electron-poor to undergo the desired Baeyer–Villiger rearrangement.[10] On the other hand, electron-donating groups did not interfere with the efficiency of the indole oxidation (Table 1, entry 7). Likewise, both *N*-methyl or benzyloxy substituents are tolerated in this reaction (Table 1, entry 8). This last example, *N*-methyl-5-benzyloxy-3-hydroxy-indole-2-carboxylate (Table 1, entry 8), has been previously prepared according to the Hawthorne's procedure in four to five steps with an overall yield of 28%.[4] Using our method, this product is now accessible in only two steps with an overall yield of 80%.

The importance of having at least one electron-withdrawing group in the Baeyer–Villiger reaction was investigated by replacing the 2-carboxylate group of the indole with a methyl or a phenyl substituent. Exposure of these analogs to our standard reaction conditions only lead to recovery of starting material. Performing the reaction in refluxing $ClCH_2CH_2Cl$ did not improve the reaction, underscoring the importance of the 2-carboxylate substituent to the success of this reaction.

In summary, an efficient procedure has been outlined for the preparation of 3-hydroxyindole-2-carboxylates from the corresponding unprotected indole-2-carboxylates by use of a modified Vilsmeier–Haack/Baeyer–Villiger reaction sequence. Work is currently underway to further examine the scope of this indole oxidation reaction.

Table 1
Synthesis of 3-formyl and 3-hydroxyindoles

Entry	Indole	3-Formylindole[a,b] (%)	3-Hydroxyindole[b,f] (%)
1		86 (R = CO_2Et)	90 (R = CO_2Et) 86[g] (R = CONHiPr)
2		86	84
3		96	86
4		95	84
5		92[c]	84[7(b)]
6		77[c,d]	No reaction
7		85	79
8		91[c,e]	89

(a) Reactions were conducted at refluxing $ClCH_2CH_2Cl$ with 1.5 equiv. of $POCl_3$ previously mixed with 1.5 equiv. of $HCON(CH_3)C_6H_5$.[6(a)] (b) Isolated yield. (c) The indole was added to a mixture of 10 equiv. of $POCl_3$ in DMF and the reaction was heated at 75 °C.[6(b)] (d) 100 °C. (e) 2.7 equiv. of $POCl_3$ was used and the reaction was performed at rt. (f) Reactions were performed with 1.25 equiv. of dried *m*-CPBA and 1 equiv. of PTSA in CH_2Cl_2 at 10 °C, followed by quenching with Me_2S and hydrolysis with EtOH. (g) The reaction of lithium isopropylamide with the ethyl 3-formylindole-2-carboxylate gave the starting 3-formylindole-2-isopropylamide in 88% yield.[4]

References

1. (a) Unangst, P. C.; Connor, D. T.; Stabler, S. R.; Weikert, R. J.; Carethers, M. E.; Kennedy, J. A.; Thueson, D. O.; Chestnut, J. C.; Adolphson, R. L.; Conroy, M. C. *J. Med. Chem.* **1989**, *32*, 1360–1366. (b) Boschelli, D. H.; Kramer, J. B.; Khatana, S. S.; Sorenson, R. J.; Connor, D. T.; Ferin, M. A.; Wright, C. D.; Lesch, M. E.; Imre,

K.; Okonkwo, G. C.; Schrier, D. J.; Conroy, M. C.; Ferguson, E.; Woelle, J.; Saxena, U. *J. Med. Chem.* **1995**, *38*, 4597–4614.

2. For illustrative examples, see: (a) Gray, N. M.; Dappen, M. S.; Cheng, B. K.; Cordi, A. A.; Biesterfeldt, J. P.; Hood, W. F.; Monahan, J. B. *J. Med. Chem.* **1991**, *34*, 1283–1292. (b) Unangst, P. C.; Connor, D. T.; Stabler, S. R.; Weikert, R. J. *J. Heterocyclic Chem.* **1987**, *24*, 811–815.
3. Sukari, M. A.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2219–2223.
4. Unangst, P. C.; Connor, D. T.; Miller, S. R. *J. Heterocyclic Chem.* **1996**, *33*, 1627–1630.
5. Bourlot, A. S.; Desarbre, E.; Mérour, J.-Y. *Synthesis* **1994**, 411–416.
6. For illustrative examples, see: (a) Troschütz, R.; Hoffmann, A. *J. Heterocyclic Chem.* **1997**, *34*, 1431–1440. (b) Murakami, Y.; Watanabe, T.; Yokoyama, Y.; Naomachi, J.; Iwase, H.; Watanabe, N.; Morihata, M.; Okuyama, N.; Kamakura, H.; Takahashi, T.; Atoda, H.; Tojo, T.; Morita, K.; Ishii, H. *Chem. Pharm. Bull.* **1993**, *41*, 1910–1919.
7. (a) All new compounds gave satisfactory ^{1}H, ^{13}C NMR and MS data. (b) Spectral data for diethyl 3-hydroxyindole-2,5-dicarboxylate (Table 1, entry 5). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.44 (br s, 1H), 8.42 (br s, 2H), 7.93 (dd, 1H), 7.45 (d, 1H), 4.41 (q, 2H), 4.34 (q, 2H), 1.37 (m, 6H) ppm. ^{13}C NMR (500 MHz, acetone-d_6) δ 167.0, 163.4, 146.8, 138.0, 127.6, 123.3, 122.4, 118.4, 113.0, 110.7, 61.2, 61.1, 14.7, 14.6 ppm. MS m/z $(M+H)^+$ calcd 278.1029, observed 278.1030.
8. Ethyl 4- and 6-bromoindole-2-carboxylate were prepared from starting azidocinnamates according to Ref. 6b.
9. Diethyl indole-2,5-dicarboxylate: Chen, C.-y.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676–2677.
10. Chatterjee, A.; Biswas, G. K.; Kundu, A. B. *J. Indian Chem. Soc.* **1969**, *46*, 429–433.