Pergamon

Tetrahedron Letters, Vol. 38, No. 45, pp. 7813-7814, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10090-9

A Convenient Method of Protecting Oxindoles[∞]

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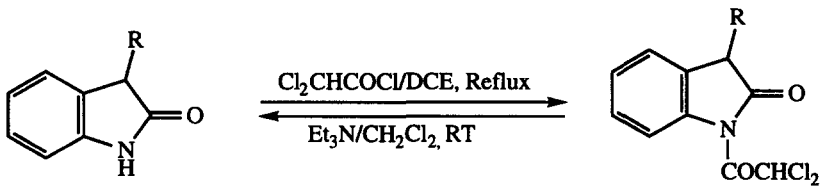
Abstract : The nitrogens of oxindoles and indole were protected by dichloroacetyl group in refluxing DCE. The deprotection of these protected oxindoles and indole has been carried out under basic condition using triethylamine. © 1997 Elsevier Science Ltd.

The widespread occurrence of indoles in both plant and animal metabolites has provided the primary stimulus in the search for novel and more effective drugs based on this ring system. To our knowledge, there has been no viable synthetic route available for 2-fluoro derivatives of bioindoles. The benzene substituted fluoroindoles were prepared from fluorobenzene derivatives by indole ring syntheses.[1] The synthetic routes available for other 2-haloindoles[2] could not be applied to the synthesis of 2-fluoroindoles. It was our interest to synthesize 2-fluoroindoles from N-protected oxindole derivatives. An ideal protecting group, for such a purpose, should 1) be able to tie-up the lone pair, on the lactamyl nitrogen, more effectively and 2) be readily removable under mild condition after the desired fluorination. To our surprise, we found that protection of oxindoles has not been well documented in the literature. The known N-phenylsufonyloxindole[3] is not easily accessible and the readily accessible N-acetyl or N-benzoyloxindole requires more than a mild condition for deprotection.

Herein, we report a simple and efficient method of protecting oxindoles. The trifluoroacetyl group first appeared to be a good choice for the purpose. But, treatment of oxindole with trifluoroacetic anhydride and DIEA yielded only 3-trifluoroacetyloxindole. All our attempts to synthesize N-trifluoroacetyloxindole were in vain. Then our attention was drawn towards the dichloroacetyl group. Although the dichloroacetyl derivatives have been widely studied for their biological activity,[4,5] the potentiality of dichloroacetyl as a protecting group for oxindoles has not previously been explored. The usual method[5] of dicholoroacetylation of amines did not work for oxindoles. After some experimentation, we found that oxindole **1a** or 3-methyloxindole **1b** could be treated[6] with dichloroacetyl chloride in refluxing DCE to yield N-dichloroacetyloxindole[7] **2a** or N-dichloroacetyl-3-methyloxindole[8] **2b** in 88% and 78% yields, respectively.



1

a) R=H; b) R=Me

2

a) R=H; b) R=Me

[∞] Dedicated to the late Dr. Louis A. Cohen on his 71st birth anniversary.

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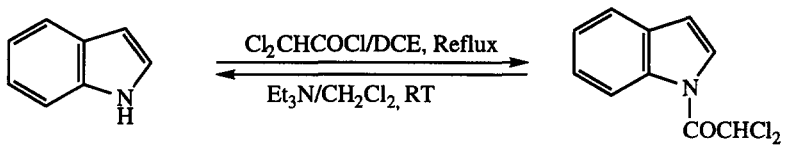
Similarly, treatment of indole **3** with dichloroacetyl chloride in refluxing DCE yielded N-dichloroacetyl-indole[9] **4** in 88% yield.



3 **4**

Deprotection of N-dichloroacetyloxindoles **2a, b** or N-dichloroacetylindole **4** was carried[10] out under mild non-nucleophilic basic condition using Et_3N in CH_2Cl_2 at room temperature. This simple method of protection of oxindoles opens up new avenues for the synthesis of 2-fluoro derivatives of bioindoles. We believe this simple approach could also be extended to protection of other amides. Our further work on protection of oxindoles will be reported in due course.

Acknowledgments: WGR thanks the National Institutes of Health for a visiting fellowship.

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6. A typical procedure: To a solution of **1a, b** or **3** (2 mmol) in DCE was added dichloroacetyl chloride (2 mmol). The solution was refluxed for 2-4h. Then the solvent was removed and the residue was crystallized from appropriate solvents.
7. **2a** : Mp. 117 °C (benzene/hexane); IR ($CHCl_3$) 1762, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s, 2H), 7.25 - 7.47 (m, 4H), 8.22 (d, 1H, J = 9.3 Hz); Anal. calcd. for $C_{10}H_7NO_2Cl_2$: C, 49.21; H, 2.89; N, 5.74. Found: C, 49.42; H, 3.00; N, 5.63.
8. **2b** : Mp. 91 °C (benzene/hexane); IR ($CHCl_3$) 1766, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (d, 3H, J = 9 Hz), 3.75 (q, 1H, J = 9 Hz), 7.27 - 7.49 (m, 4H), 8.23 (d, 1H, 9 Hz); Anal. calcd. for $C_{11}H_9NO_2Cl_2$: C, 51.19; H, 3.51; N, 5.43. Found: C, 51.28; H, 3.56; N, 5.41.
9. **4** : Mp. 122 °C (benzene/hexane); IR ($CHCl_3$) 1725, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.51 (s, 1H), 6.67 (d, 1H, J = 3.85 Hz), 7.25 - 7.37 (m, 2H), 7.51 (d, 1H, J = 7.7 Hz), 7.59 (d, 1H, J = 3.85 Hz), 8.36 (d, 1H, J = 7.7 Hz); Anal. cacld. for $C_{10}H_7NOCl_2$:C, 52.66; H, 3.09; N, 6.14. Found: C, 52.61; H, 3.14; N, 6.12.
10. A typical procedure for deprotection : To a solution of dichloroacetyl derivative **2a, b** or **4** (1 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (1.4 ml, 10 mmol) and the solution was stirred at room temperature for 2h. Then the solution was shaken with water (3x20 ml), dried (Na_2SO_4) and concentrated. The concentrated solution was applied to a preparative TLC plate and eluted with appropriate solvents. Yields : 85 - 92%

(*Received in USA* 23 *June* 1997; *accepted* 3 *September* 1997)