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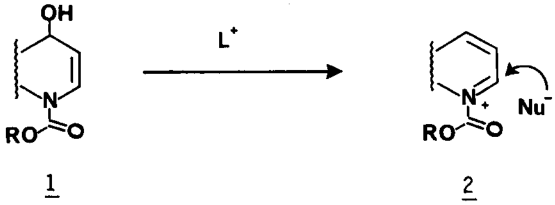
SYNTHESIS OF 3-SUBSTITUTED INDOLES VIA N-ACYLINDOLIUM IONS

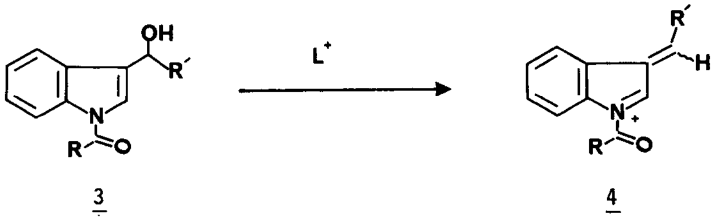
Daniel L. Comins* and Eric D. Stroud

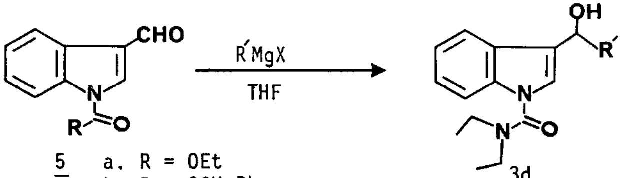
Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322 0300

Summary: 3-Substituted N-(N'N'-diethylcarbamyl)indoles are prepared from indole-3-carboxaldehyde in good overall yield via N-acylindolium ion intermediates.

In recent years there has been considerable interest in N-acyliminium ion reactions as applied to organic synthesis.[1] These reactions have been shown in several cases to occur with high regio- and stereocontrol. Recently, Kozikowski[2] and we[3] have shown that γ-hydroxy enecarbamates (i.e., 1) are valuable N-acyliminium ion precursors. Attack by nucleophiles generally occurs at the 2-position of the 3,4-unsaturated iminium ion 2. It occurred to us that if the ene portion of a γ-hydroxy enecarbamate was the 2,3-double bond of an N-acylindole ring (e.g., in 3), then treatment with a Lewis acid would give a potentially very useful N-acylindolium ion (4). Although indolium ions have been postulated as reactive intermediates in synthetically useful reactions,[4] virtually nothing has been done with N-acylindolium ions.[5] For preparation of the N-acylindolium ion precursors 3, we explored the reaction of Grignard reagents with N-acylindole-3-carboxaldehydes 5. Initial attempts to prepare the desired indolecarbinols from indolecarboxaldehydes 5a-c were not very successful. The yields were low for many Grignard reagents, apparently due to 1,4-addition

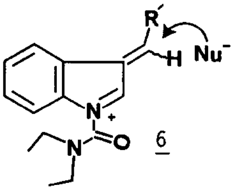






5 a. R = OEt
b. R = OCH_2Ph
c. R = NMe_2
d. R = NEt_2

3d



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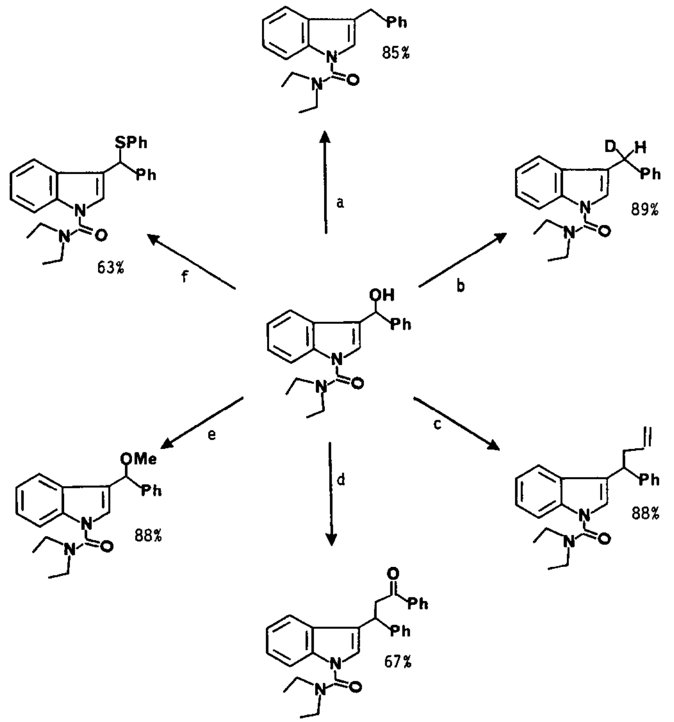
and attack at the N-acyl carbonyl. The reactions of Grignard reagents with indolecarboxaldehyde 5d were successful, however, and clean indolecarbinols 3d were obtained in high yield (85-95%). The crude indolecarbinols were reduced with triethylsilane and stannic chloride to give 3-alkylindoles 7 in good overall yields from indolecarboxaldehyde 5d as shown in Table I. The reaction undoubtedly proceeds via a 1,4-reduction of N-acylindolium ion 6.

Nucleophiles other than hydride also attack in a 1,4- manner as is shown in Scheme I.



Scheme I

a) Et_3SiH, $SnCl_4$; b) Et_3SiD, $SnCl_4$; c) allyltrimethylsilane, $SnCl_4$; d) silyl enol ether of acetophenone, TMSOTf; e) MeOH, pyridinium p-toluenesulfonate, RT; f) thiophenol, TMSOTf, CH_2Cl_2, -78°C

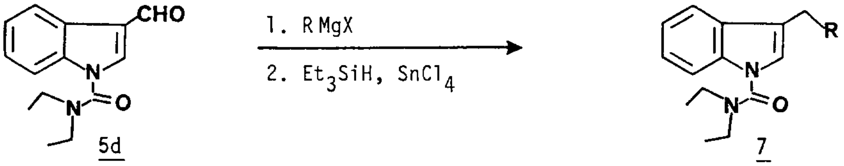
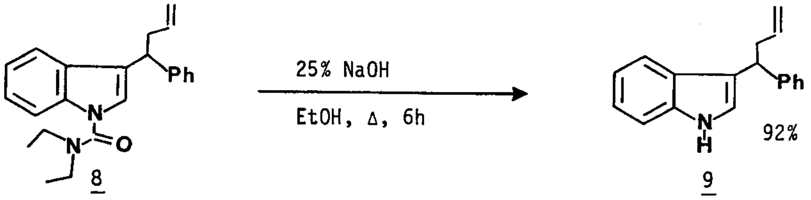


Table I. Synthesis of 3-Alkylindoles 7 from Indolecarboxaldehyde 5d

RMgX[a]	reduction conditions	overall yield[b] of 7, %
methylmagnesium chloride	1.2 Et_3SiH, 1.2 $SnCl_4$ CH_2Cl_2, -78°C, 20 min	79
n-propylmagnesium chloride	1.2 Et_3SiH, 1.2 $SnCl_4$ CH_2Cl_2, -78°C, 20 min	87
allylmagnesium chloride	1.2 Et_3SiH, 1.2 $SnCl_4$ CH_2Cl_2, -78°C, 20 min	69
n-butylmagnesium chloride	1.2 Et_3SiH, 1.2 $SnCl_4$ CH_2Cl_2, -78°C, 20 min	63
n-hexylmagnesium bromide	1.2 Et_3SiH, 1.2 $SnCl_4$ CH_2Cl_2, -78°C, 20 min	89
phenylmagnesium chloride	1.2 Et_3SiH, 1.2 $SnCl_4$ CH_2Cl_2, -78°C, 20 min	82

[a] Reactions were performed on a 2 mmol scale in tetrahydrofuran (-23°C, 20 min). The crude product was used directly in the next step. [b] Yields are for isolated, pure material obtained from radial preparative layer chromatography (silica gel, ethyl acetate-hexanes). All products gave the expected IR and NMR spectra and elemental analysis.

The N,N-diethylcarbamyl group can be readily removed from the indole ring with sodium hydroxide. For example, N-acylindole 8 gave the 3-substituted indole 9 in high yield as shown below.



The preparation of 9 demonstrates a new and efficient synthesis of 3-substituted indoles from commercially available indole-3-carboxaldehyde.[6] The scope of this synthesis and the application of N-acylindolium ions as intermediates for the synthesis of pyridocarbazole alkaloids[7] are under study.

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References and Notes.

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5. For a recent paper describing some reactions of N-acylindoles, see: S. F. Vice,C. R. Copeland, S. P. Forsey, and G. I. Dmitrienko, Tetrahedron Lett., 26, 5253 (1985).

6. Indole-3-carboxaldehyde was purchased from Aldrich Chemical Co. and converted to indolecarboxaldehyde 5d with sodium hydride and diethylcarbamyl chloride in THF (85% yield).

7. For a recent review on pyridocarbazole alkaloids, see: G. W. Gribble and M. G. Saulnier, Heterocycles, 23, 1277 (1985).

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