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Regioselective acylations at the 2 and 6 position of *N*-acetylindole

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Abstract—Regioselective acylations under Friedel–Crafts conditions at C6 and C2 positions of *N*-acetylindole are described.

Indoles with substitutions at the 2 or 6 positions are powerful intermediates for the synthesis of a great range of indolic alkaloids. Among these are marines and members of the of Aspidosperma (1), Ervatamine (2), Fumitremorgin (3) and Teleocidine (4) families (Fig. 1).

Due to the biological importance of those alkaloids, their synthesis has been extensively studied. However, the direct introduction of substituents at the C6 or C2 positions has been a problem. In the majority of the synthetic routes, these substituents are introduced early into the heterocyclic system, through the preparation of the indole skeleton by a Fischer-type process.

Direct acylations at the 6 position. The eletrophilic substitutions at the 6 position are usually performed on systems with an electron withdrawing group at the 1 or 3 positions. 3-Acylindoles are nitrated by HNO_3 and result in mixtures of C4 and C6 3-acylnitroindoles, while a mixture of C5 and C6 3-acylnitroindoles is formed with H_2SO_4/HNO_3.[1] On the other hand, when the nitrating agent is $NO_2BF_4/SnCl_4$, C5 or C6 nitro-3-acetylindoles are obtained selectively, depending on the temperature.[2] In the case of acylations, Hino[3] described the formation of mixtures of C5, C6 and C7 3-diacylated products when the substrate was a 3-acetylindole. Apparently, no pattern of regioselectivity exists in these cases.

For 1-acylindole, a single case of substitution in a regioselective fashion was described by Nakatsuka[4] in which 1,6-diacylated indoles were obtained under Friedel–Crafts conditions by using activated acid chlorides. In spite of Nakatsuka's suggestion that the 6 position of 1-acylindoles is the most reactive position in the benzene portion of the indole molecule, theoretical studies carried out by us[5] indicated the most reactive positions should be on C3 and C4, in disagreement with Nakatsuka. A hypothesis that could account for the preferential attack at the 6 position would be the formation of an $AlCl_3$–carbonyl complex, as shown in

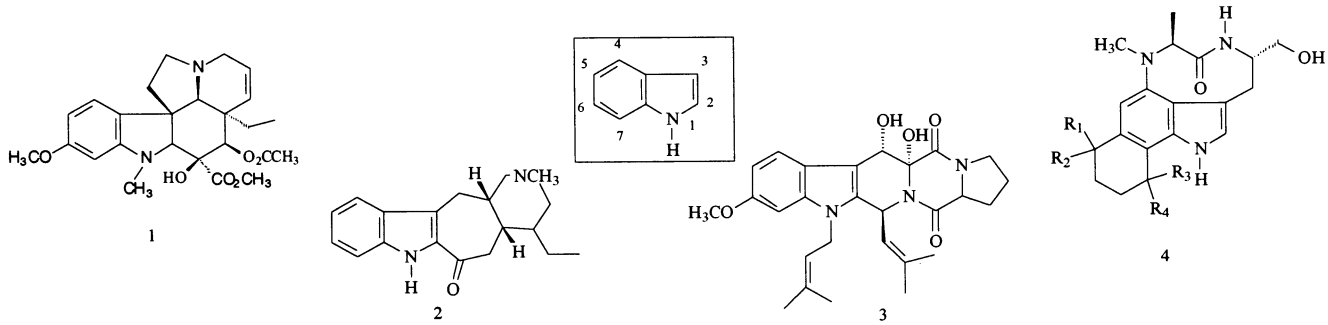

Figure 1.

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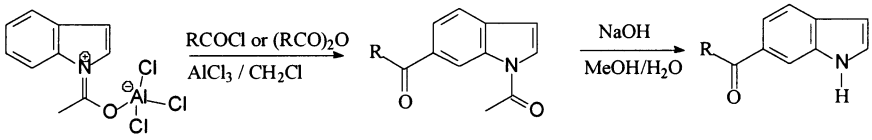
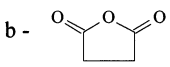
Table 1. Friedel–Crafts acylation of *N*-acetylindole–$AlCl_3$ complex



5a - e **6a - e**

Entry	Acylating agent	(R)	**5** (%)	**6** (%)
1	a-$(CH_3CO)_2O$	CH_3	90	96
2	b- 	$CH_2CH_2CO_2H$	75	92
3	c-$(ClCH_2CO)_2O$	CH_2Cl	71	92
4	d-CH_3COCl	CH_3	65	95
5	e-$ClCH_2COCl$	CH_2Cl	80	96

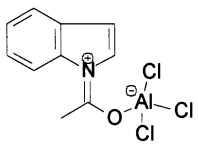


Figure 2.

Fig. 2. This intermediate would be a '*meta*' director group towards the benzene ring, favoring substitution at C4 and C6 and, not at C3, and, at the same time, it should deactivate the heterocyclic ring towards electrophilic substitution.

In order to test this hypothesis, we added 1-acetylindole to a stirred suspension of $AlCl_3$ in dichloromethane followed by the acylating agent. Surprisingly, these reaction conditions worked fairly well; giving, as the only product, the 1,6 diacylated compounds in good yields for both acid chlorides and anhydrides as acylating reagents (Table 1). However, when the reaction was carried out without the previous formation of the $AlCl_3$–N-acetylindole complex, 1,3-diacetylindole was isolated in 90% by using acetic anhydride as acylating agent and in 55% yield for the acetylchloride case. The latter conditions also led to the production of 1,6-diacetylindole in 23%. However, it seems that the regioselectivity does not depend on the nature of the acylating agent when the complex is used as the substrate, in contrast to what was suggested by Nakatsuka, who observed such dependence.

Acylations at the 2 position. 2-Acylindoles are usually made by the Fischer indole synthesis,[1] lithiation of the indolic ring followed by acylation,[6] or by electrophilic substitution of 3-alkylindoles as reported by Jackson.[7] Surprisingly, during the acylations of *N*-acetylindole by using acid dichlorides, the only products observed were the 1,2-diacylindoles **7** and **8**† (Scheme 1). These results, though unexpected, are of great significance since there are no reports in the literature about the formation of 2-acylindoles unsubstituted at the 3-position under Friedel–Crafts conditions.

It is particularly intriguing that while the succinic anhydride gives only substitution at the 6 position with succinyl chloride the reaction site is the 2 position. The mechanism that operates in these acylations with dichlorides is not clear. A rearrangement of a 3-acyl compound that could have been formed initially was discharged since no other compound was detected by TLC during the reaction time. A possible explanation could be an '*ortho*' effect involving the *N*-acyl group (Scheme 1), which is unlikely in the case of the anhydrides.

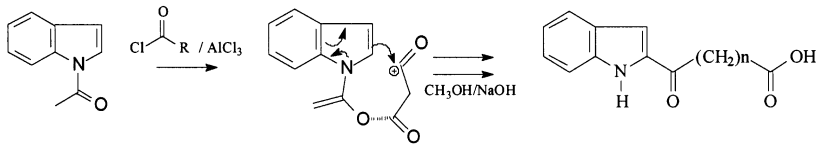
In summary, regioselective acylations at the 6 position with acid chlorides as well as anhydrides were accomplished in good yields. An inedited direct acylation at the 2 position of *N*-acylindoles by using acid dichlorides was discovered. This represents an advance in indole chemistry and the synthesis of indole alkaloids by using this methodology is in progress.

Typical experimental procedures for the acylations of *N*-acetylindole are described below.

6-Acylation: $AlCl_3$ (2.67 g, 20 mmol) was added to a stirred solution of 1-acetylindole (800 mg, 5 mmol) in CH_2Cl_2 (30 mL), resulting in a red solution. After 15 minutes, a solution of the acylating agent (20 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The reaction was stirred at room temperature until no starting material could be detected by TLC. The mixture was poured into cold water and extracted with ethyl acetate. The organic extracts were dried with Na_2SO_4 and the solvent removed in vacuo. The crude product was chromatographed on silica, to yield a pure compound.

2-Acylation: $AlCl_3$ (2.67 g, 20 mmol) was added to a stirred solution of the acylating agent (20 mmol) in

† **7**. 2D ^1H NMR (DMSO-d_6): δ 11.7 (s, broad, NH); 7.0–7.4 (m, 5H); 4.2 (s, CH_2). IR (KBr): 3300, 1780, 1658 cm^{-1} **8**. 2D ^1H NMR (DMSO-d_6): δ 11.4 (s, broad, NH); 7.1–7.9 (m, 5H); 3,3 (t, $J=7.5$, CH_3). 2.65 (t, $J=7.5$, CH_3), 3323, 1714, 1649 cm^{-1}.



R = CH_2COCl **7 - 87%** **n = 1**
R = CH_2CH_2COCl **8 - 80%** **n = 2**

Scheme 1.

CH_2Cl_2 (30 mL). A solution of 1-acetylindole (800 mg, 5 mmol), in 10 mL of CH_2Cl_2, was then added dropwise. The reaction was stirred at room temperature until no starting material could be detected by TLC. The mixture was poured into cold water and extracted with ethyl acetate. The organic extracts were dried with Na_2SO_4 and the solvent removed in vacuo. The crude product was chromatographed on silica, to yield a pure compound.

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