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Acylation of Indole under Friedel–Crafts Conditions—An Improved Method To Obtain 3-Acylindoles Regioselectively

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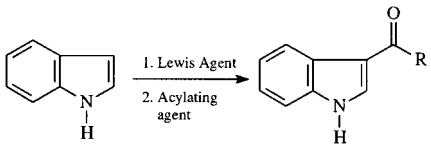
ABSTRACT



The reaction of unsubstituted indole with different acylating agents such as acid chlorides, anhydrides, nitriles, and amino acid derivatives in the presence of Lewis acid is reported.

The synthesis of 3-acylindoles has been the subject of considerable interest not only because they are used as synthetic intermediates in alkaloid synthesis but also because they have biological activities.[1] Three major synthetic methods have been employed to prepare this class of compounds using indole as the starting material: (1) acylation of indole Grignard reagents,[2−4] (2) acylation of N-protected indoles,[5] and (3) the Vilsmeier−Haack reaction.[2] There are also other methods based on acyl cation equivalents such as nitrilium salts[6] and dialkyl carbenium ions.[7,8] Another method, using *N*-(α-haloacyl)pyridinium salts, gives predominantly 3-acylindoles under controlled conditions, but it seems to be restricted to some very reactive α-haloacyl halides.[9] Each of these methodologies has merits and shortcomings that limit their scope and yield.

Although the 3-position is the most reactive site for electrophilic attack,[2] low yields encountered are usually attributed to the competitive formation of 1-acylated and/or 1,3-diacylated products due to the ambident character of the indole system. Other side reactions, often observed in acidic conditions, are the self-polymerization of indole and the less common formation of di-indolylmethanes.[10]

The use of N-protecting groups is generally the chosen strategy to overcome the concurrent formation of 1-acyl derivatives and to limit polymerization, which has not been observed when the indole system is deactivated by the presence of electron-withdrawing groups on the ring. Nevertheless, troublesome protection−deprotection steps are necessary in such situations.[11,12] Additionally, the Vilsmeier−Haack reaction, involving amides and $POCl_3$, is not always effective,[3,13,14] providing only moderate yields and requiring the preparation of the amide if it is not commercially available.

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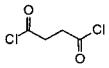
Table 1. Effectiveness of Different Lewis Acids in Obtaining 3-Acylindole

entry	acylating agent[b] (AA)	lewis acid (LA)	ratio indole/AA/LA	reaction time/h[a]	product (R)	yields %
1		$AlCl_3$	1/1/2	10	CH_3	78
2		$TiCl_4$	1/1/2	10	CH_3	50
3		$SnCl_4$	1/1/2	4	CH_3	42
4	CH_3CN	$SnCl_4$	1/10/1.2	4	CH_3	96
5		$AlCl_3$	1/1/1.2	6	CH_3	71
6		$SnCl_4$	1/1/1.2	2	CH_3	95
7		$SnCl_4$	1/1/1.2	10	CH_2CH_3	80
8		$SnCl_4$	1/1/1.2	10	CH_2NHCH_2Ph	40
9		$SnCl_4$	1/1/4	10	CH_2CH_2COOH	72
10		$SnCl_4$	1/1/1.2	8	CH_2Cl	80
11		$SnCl_4$	1/1/1.2	8	CH_2Br	70
12		$SnCl_4$	1/1/1.2	8	CH_2Br	50

[a] Refers to the period of time after the complete addition of nitromethane. [b] The acylating agent was slowly added to the reaction mixture at 0 °C.

Herein we describe a Friedel−Crafts-type acylation of unsubstituted indole, through a very easy method that gives 3-acylindoles regioselectively and in high yields without laborious workups.[15] Trying to find out what happens with indoles under the Friedel−Crafts conditions, we came across several reports about different problems faced during these reactions. In the presence of a Lewis acid such as $SnCl_4$, DeGraw[8] reported that the reaction of indole with acid chlorides produced mostly red tars, whose composition was not investigated. According to our experience, the tarry mixtures sometimes obtained when unsubstituted indole reacts under Friedel−Crafts conditions are mainly composed of indole trimers and monoacylated indole trimers, plus a minor quantity of 3-acylated indole. The polymerization processes are almost absent when the indole ring is substituted by electron-withdrawing groups. For instance, 5-cyanoindole reacts with different acid chlorides and $SnCl_4$, affording 5-cyano-3-acylindoles in yields ranging from 38% to 70%.[8] Also, the Friedel−Crafts reaction of ethyl indole-2-carboxylate with acyl chlorides or anhydrides generally produces a mixture of three monoacylated products, 3-, 5-, and 7-acylindole-2-carboxylate.[9] In addition, *N*-(phenylsulfonyl)indole reacts with acid chlorides and anhydrides in the presence of $AlCl_3$, giving 3-acyl-1-(phenylsulfonyl)indoles in 81−99% yields.[5] No polymerization products were reported in any of these cases.

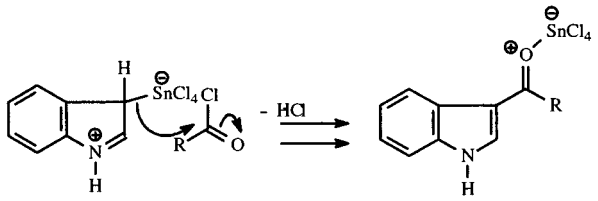
During our attempts to obtain 3-acylated indoles under Friedel−Crafts conditions, we noticed that whenever we added the Lewis acid to the reaction mixture containing indole and the acylating agent, a strong color change occurred. By changing the addition order, as soon as we added $AlCl_3$, $SnCl_4$, or $TiCl_4$ to a solution of only indole in CH_2Cl_2 at 0 °C, orange, blue, or dark violet precipitates were formed, respectively. The subsequent addition of the acylating agent to these suspensions, followed by CH_3NO_2 as cosolvent, produced only 3-acylindoles, without the undesirable presence of indole oligomers or the other products previously observed, *N*-acyl and 1,3-diacylindoles. It is noteworthy that without CH_3NO_2 the acylation process was slow (24−48 h) and the starting material was always recovered. However, addition of CH_3NO_2 increased the solubility of the solid indole−Lewis acid complexes in the reaction media, shortening the reaction time and raising the yields up to 96%. This indicates a strong solvent effect. Preliminary studies on the effectiveness of different Lewis acids in the acetylation of indole by using acetyl chloride or acetonitrile as acylating agents showed that the best yields were obtained in the presence of $SnCl_4$ (Table 1). The wide scope of this methodology is demonstrated by the preparation of several 3-acylindoles, using a variety of acylating agents such as acid chlorides, anhydrides, nitriles, and even an amino acid derivative (Table 1).

The high regioselectivity observed and the unusual absence of indole dimers and trimers under such acidic conditions prompted us to try to elucidate the nature and, ultimately, the structure of the colored compounds formed during the first step of the reaction. According to the work of Schmitz-Dumont and Motzkus[16] published in 1929, indole forms addition compounds with $SnCl_4$, $TiCl_4$, and $AlBr_3$ with the following stoichiometry: $SnCl_4 \cdot 2C_8H_7N$, $TiCl_4 \cdot 2C_8H_7N$, and $AlBr_3 \cdot C_8H_7N$.

Our complexes with $SnCl_4$ and $TiCl_4$ have the same physical aspect as those reported by the German group;[10] however, as a result of their relatively low stability in the air and reduced solubility in most aprotic organic solvents, attempts to obtain by purification any of the compounds (powders) in a crystalline form have failed. The structures of those complexes are under investigation. Even without these data, some questions are pertinent: why does not the trimerization process occur and why is the process highly regioselective? Even though our interests are strictly synthetic, these intriguing observations deserve some comments.

The most reactive site for electrophilic attack is the 3-position, so it is probable that the Lewis acid complexes at that point forming an intermediate that should be very polar and insoluble in organic solvents (Scheme 1). This intermediate would collapse in a nucleophilic attack toward the acyl chloride. The formation of this kind of complex would interfere in the trimerization process, avoiding any

Scheme 1. Acylation of the Complex Indole−$SnCl_4$



action of indole as a nucleophile. A simple methodology under acidic conditions for the synthesis of 3-acylindoles from unsubstituted indole is presented. The method works well for different acylating agents, as can be inferred from the high yields obtained in most of the cases.

No indole polymerization byproducts were detected in any of the reactions performed. This ready access to 3-acylindoles is specially important in view of the few useful synthetic strategies reported to date for the preparation of this class of compounds.[17]

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(17) **3-Acetylindole. General Procedure.** To a stirring solution of indole (1.17 g, 10 mmol) in CH_2Cl_2 (20 mL) under argon at 0 °C was added $SnCl_4$ (1.44 mL, 12 mmol) was added in a single portion via syringe. After the ice bath was removed, the mixture was stirred at room temperature for 30 min, and then acetic anhydride (10 mmol) was added in small portions to the suspension, followed by nitromethane (15 mL). The mixture was stirred for 2 h at room temperature. After being quenched with ice and water (30 mL), the mixture was filtered to remove inorganic precipitates, and the organic material was extracted with ethyl acetate (50 mL). The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to give the product as a crystalline solid.