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An Effective Procedure for the Acylation of Azaindoles at C-3

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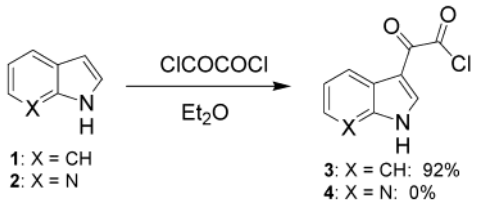
Abstract: Conditions for attachment of acetyl chloride, benzoyl chloride, and chloromethyl oxalate to the 3-position of 4-, 5-, 6-, or 7-azaindoles were explored. Best results were achieved with an excess of $AlCl_3$ in CH_2Cl_2 followed by the addition of an acyl chloride at room temperature.

3-Acylated azaindoles have been reported to possess a range of biological activities including the potential for the treatment of inflammation, asthma, anxiety, depression, sleeping disorders, Alzheimer's disease, migraine, and pain.[1] In an ongoing medicinal chemistry project, we directed our efforts toward developing practical methodology for acylating at the 3-position of 4-, 5-, 6-, and 7-azaindoles.

The acylation of indole (**1**) at C-3 is a well documented process that takes advantage of the electron-rich nature of this position, which can be viewed as possessing enamine-like character.[2] However, we have observed that when one carbon atom of the benzene ring of indole is replaced by a nitrogen atom, acylation at the 3-position is considerably more difficult. For example, the reaction of 7-azaindole (**2**) with oxalyl chloride in Et_2O was unproductive while indole (**1**), under the same conditions, provided the corresponding 3-acylated indole **3** in excellent yield (Scheme 1).[3]

The inertness of the 3-position of azaindole when compared to that of indole is presumably the result of the electron-deficient nature of the pyridine moiety, which reduces the overall nucleophilicity of the heterocyclic system. This would be further exacerbated by the potential of oxalyl chloride, which is typically used in excess, to acylate the pyridine nitrogen atom. As a consequence, documented examples of the direct functionalization of the 3-position of azaindoles are restricted to halogenation,[4] Mannich reactions,[5] carbonylation,[6] and

SCHEME 1



condensation with an aldehyde.[7] A few examples of acylation, conducted under forcing conditions, have been described.[5,8] Moreover, with the exception of bromination, a reliable, common procedure for derivatization of C-3 of azaindoles has not emerged, and conditions have generally been optimized for individual azaindole substrates.

Reported strategies for the direct C-3 acylation of azaindoles have relied upon either enhancing the nucleophilicity of the azaindole or activation of the electrophile. As an example of the former approach, Shadrina and co-workers heated 7-azaindole with a Grignard reagent and dimethyl oxalate to form an α-keto ester in 64% yield.[8b] Sycheva and colleagues were able to prepare a 7-azaindole derivative in 74% yield[8c] in $ClCH_2CH_2Cl$ at reflux by activating the electrophile, acetyl chloride, with an excess of $AlCl_3$. Galvez and Viladoms introduced the acetyl moiety at C-3 of 7-azaindole using $AlCl_3$ and Ac_2O in CS_2,[8d] while Kato et al. accomplished a similar transformation using $AlCl_3$ and an acid chloride in CS_2 at room temperature.[8e] However, all of these reactions involved the use of elevated temperature and/or the unpleasant solvent CS_2 and, in each case, reports were restricted to a single heterocyclic example. Consequently, a survey of the scope and limitations of this reaction has not been undertaken.

In pursuit of a Friedel−Crafts-type approach that relies upon activation of the electrophile, a convenient temperature, preferably ambient, and a replacement for noxious CS_2 as the solvent were specifically sought. Careful screening of solvents revealed that CH_2Cl_2 was the most acceptable substitute in terms of operative simplicity and product yield. Thus, treatment of 7-azaindole (**2**) with 3−5 equiv of $AlCl_3$ in CH_2Cl_2 at room temperature followed by the addition of methyl oxalyl chloride afforded the desired product **5** in 76% yield (Scheme 2). It was found that a minimum of 3 equiv of $AlCl_3$ is required to achieve good results, but the use of additional $AlCl_3$ did not improve the yield further. The requirement for greater than stoichiometric quantities of $AlCl_3$ could be interpreted by the formation of a

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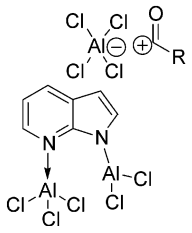
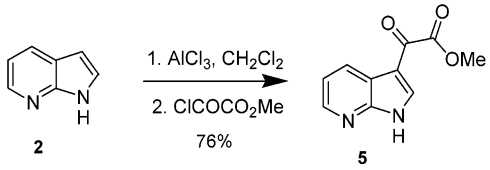


FIGURE 1.

SCHEME 2



complex between the azaindole and $AlCl_3$. Presumably, the first equivalent of $AlCl_3$ is consumed in coordinating to the pyridine nitrogen atom, a complex in which the pK_a of the pyrrole NH will be lowered. Reaction with the second equivalent of $AlCl_3$ may lead to deprotonation and the formation of the aluminum salt depicted in Figure 1 as the reactive species. The third equivalent of $AlCl_3$ forms an "ate complex" with the acyl chloride, the active intermediate during Friedel–Crafts reactions.

Encouraged by this result, these conditions were examined with isomeric azaindoles that, in turn, were prepared either according to literature procedures[9] or by application of a Bartoli-type process.[10] Reaction with a variety of acid chlorides under similar conditions proceeded smoothly in all cases at room temperature to produce products in moderate to high yield, as summarized in Table 1.

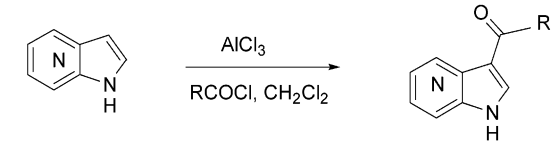
In general, 5- and 7-azaindoles provided C-3 acylated products in higher yields than 4- and 6-azaindoles, a trend that appears to be consistent with the electron-withdrawing effect of the pyridine-like nitrogen atom on the pyrrole moiety. In the 4- and 6-azaindole ring systems, the olefin element of the pyrrole moiety is more directly conjugated with the pyridine-like nitrogen atoms, an electronic effect that will reduce its overall nucleophilicity.

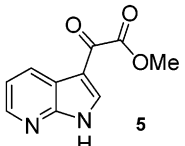
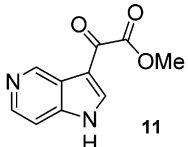
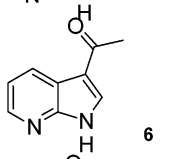
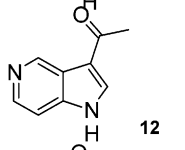
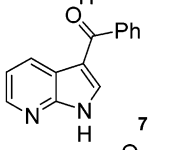
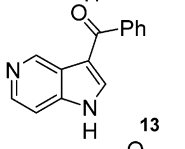
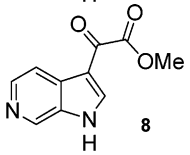
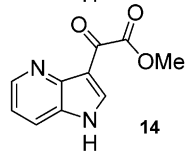
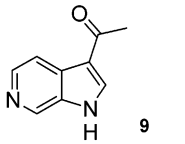
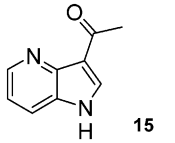
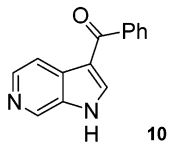
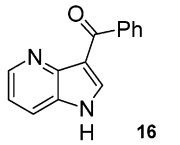
In summary, we have reported general conditions for the C-3 functionalization of 4-, 5-, 6-, and 7-azaindoles with acid chlorides. This method is attractive due to the simplicity of the operational procedure, the mildness of the conditions, and the applicability to all of the isomeric azaindoles.

Experimental Section

General Methods. Aluminum chloride, 7-azaindole, acetyl chloride, benzoyl chloride, and methyl oxalyl chloride (Table 1) are commercially available and were used as received. 4-, 5-, and 6-azaindole were prepared according to documented procedures.[9,10] ^{1}H and ^{13}C NMR spectra were obtained at 500 MHz with samples dissolved in CD_3OD, $CDCl_3$, or DMSO-d_6.

TABLE 1. Acylation of Azaindoles at C-3



Product	Isolated Yield	Product	Isolated Yield
 **5**	76%	 **11**	70%
 **6**	93%	 **12**	94%
 **7**	92%	 **13**	92%
 **8**	42%	 **14**	42%
 **9**	63%	 **15**	70%
 **10**	68%	 **16**	35%

Acylation of Azaindole: Preparation of Methyl (5-Azaindol-3-yl)oxoacetate, Compound 11. 5-Azaindole (0.5 g, 4.2 mmol) was added to a stirred suspension of $AlCl_3$ (2.8 g, 21.0 mmol) in CH_2Cl_2 (100 mL). After the mixture was stirred at room temperature for 1 h, methyl oxalyl chloride (2.5 g, 21.0 mmol) was added dropwise and the resulting mixture stirred for 8 h. MeOH (20 mL) was added cautiously to quench the reaction, the solvents were removed under vacuum, and the residual solid was purified by silica gel chromatography using a mixture of EtOAc and MeOH (10:1) as eluent to afford the acylated product (0.60 g, 70%).

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Supporting Information Available: ^{1}H and ^{13}C spectra and HRMS data of compounds **5**–**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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