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A Direct Access to 3-(2-Oxoalkyl)indoles via Aluminum Chloride Induced C−C Bond Formation†

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Abstract: 3-Methylindole is acylated regioselectively at the methyl group when treated with a variety of acyl chlorides in 1,2-dichloroethane in the presence of $AlCl_3$, affording a mild and direct method for the synthesis of 3-(2-oxoalkyl)-indoles. The product formation in this one-pot reaction largely depends on the conditions of the reaction employed. The methodology does not require protection−deprotection steps and is amenable for the scale-up synthesis of these indole derivatives.

Indoles are known to play an important role in biology and are a frequently found motif in natural products.[1] 3-Alkyl-substituted indoles are of considerable interest as NK-1 antagonists for the treatment of pain, asthma, arthritis, and migraine[2] and as serotonin (5-HT) reuptake inhibitors for the treatment of depression.[3] They are also useful intermediates for the synthesis of nonsteroidal antiinflammatory drugs (NSAIDs) such as Etodolac, Pemedolac, etc.,[4a,b] and a number of optically pure α-methyltryptamines as well as other indole derivatives (Figure 1) of pharmacological significance have been synthesized from 3-(2-oxomethyl)indoles (commonly known as indole-2-propanone or 3-indolylacetone).[4c−d]

The interesting pharmacological and chemical properties of indole have inspired organic and medicinal chemists to design and synthesize a variety of indoles.[5] Among the classical methods for the synthesis of indole ring, the Fischer indole synthesis, the Batcho−Limgruber synthesis (from *o*-nitrotoluenes and dimethylformamide acetals), the Gassman synthesis (from *N*-haloanilines), the reductive cyclization of *o*-nitrobenzyl ketones, and the

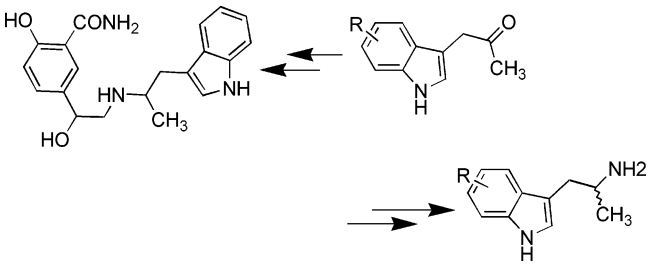

FIGURE 1. Synthesis of indole derivatives of biological significance.

Madelung cyclization of *N*-acyl-*o*-toluidines are used very often. While a number of methods are available for the synthesis of 3-alkyl-substituted indoles,[6,7] only a few are known for the synthesis of 3-(2-oxoalkyl)indoles. These includes (a) the alkylation of indole with α-diazocarbonyl compounds[8a,b] or nitroethane (followed by the treatment with either $NaOMe/TiCl_3$ or Fe/HOAc),[4c,8c] (b) the ring opening of epoxides by indole in the presence of lanthanide cations[6d] or organometallic reagents [followed by oxidation in the presence of $Al(OPr\text{-}i)_3$ or Swern's reagent],[7,8d,e] (c) the Lewis acid mediated reaction of 3-(trimethylsilyl)indoles with Michael acceptors,[8f] (d) a two-step method involving the reaction of 3-indolylacetic acid with acetic anhydride in the presence of AcONa followed by the subsequent hydrolysis of the resulting 1-acetyl-3-indolylacetone,[8g] and (e) other methods.[8h,i] However, many of these methods suffer from several drawbacks (e.g., the use of either unstable diazo compounds or moisture-sensitive organometallic reagents or expensive catalysts) and are only useful for the synthesis of specific indole derivatives. Moreover, some of them involve multistep synthesis and are not suitable for the preparation of these compounds in large quantity.

As part of our ongoing drug discovery program we required a variety of 3-(2-oxoalkyl)indoles as intermediates

† DRL publication no. 420.

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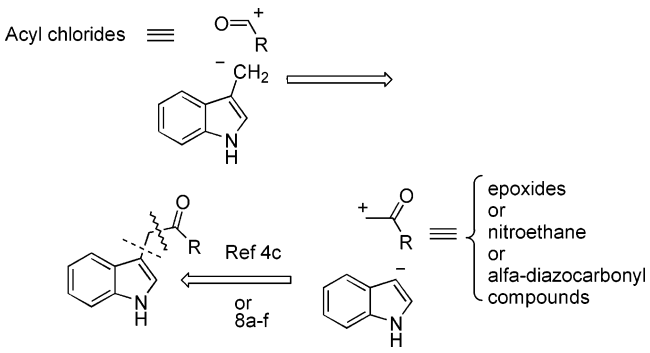
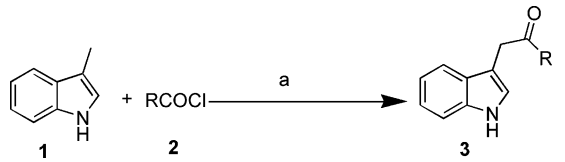


FIGURE 2. Synthetic strategy for the preparation of 3-(2-oxoalkyl)indoles.

SCHEME 1[a]

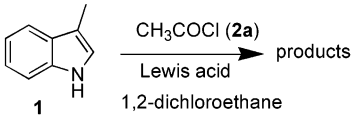


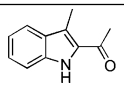
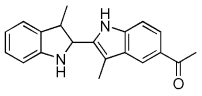
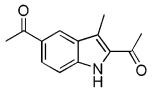
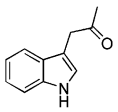
[a] Reagents and conditions: (a) $AlCl_3$, 1,2-dichloroethane, 25 °C, 24−48 h.

toward the synthesis of various heterocyclic structures[9] to generate a library of molecules for biological testing. We therefore needed a simple procedure for the synthesis of 3-(2-oxoalkyl)indoles. Since the existing routes to obtain this class of compounds were unattractive we therefore decided to develop an alternative method for their synthesis. Our synthetic strategy, which involved a different disconnection approach than that associated with the other methods,[4c,8a−f] is shown in Figure 2.

Recently, we have reported $AlCl_3$-induced heteroarylation[10] of arenes and heteroarenes as a convenient tool for C−C bond formation. More recently, we have found that $AlCl_3$-induced acylation could be utilized as a novel route to 3-(2-oxoalkyl)indoles **3** by reacting 3-methylindole **1** with acyl chloride **2** under the Friedel−Crafts reaction condition (Scheme 1). To the best of our knowledge, this is the first example of $AlCl_3$-mediated C−C bond formation via activation of C−H bond at the position α to the aromatic ring. Because of their importance in the disconnection strategies for the synthesis of complex organic molecules[11] C−H activation processes are the focus of recent research. In this article we report our novel reaction that may ultimately lead to the facile synthesis of various drugs based on the indole scaffold.

TABLE 1. Effect of Lewis Acids on the C−C Bond Formation Reaction of 3-Methylindole with Acetyl Chloride[a]



Entry	Lewis acid catalyst	Temp.(°C); Time (h)	Product[b]; Yield (%)[c]
1	$ZnCl_2$	25; 36	 **4**; 40%
2	$ZnCl_2$	55; 1.5	**4**; 65%
3[d]	$FeCl_3$	25; 15	 **5**; 15% +  **6**; 10%
4	$TiCl_4$	25; 24	Mixture of products
5	$SnCl_4$	25; 45 min.	**4**; 45% + **5**; 12%
6[e]	$AlCl_3$	25; 15	Inseparable mixture
7[d]	$AlCl_3$	25; 6	**4**; 76%
8	$AlCl_3$	25; 48	 **3a**; 58% + **6**; 10%
9	$AlCl_3$	55; 6	**6**; 30%

[a] Reaction conditions: **1** (1.0 equiv), **2a** (1.12 equiv), Lewis acid (3.0 equiv) in 1,2-dichloroethane under nitrogen atmosphere. [b] Identified by ^1H NMR, ^{13}C NMR, IR, and MS. [c] Isolated yields. [d] 1.2 equiv of catalyst used. [e] The reaction was carried out in the absence of solvent.

In the beginning of our study, it was rationalized that the methyl group of the 3-methyl indole (**1**) could be activated perhaps through the complexation of the adjacent double bond of the indole moiety with a Lewis acid. Accordingly, we studied the acetylation of **1** in the presence of a variety of Lewis acids under the varying reaction conditions. We initially preferred to examine the use of Lewis acids other than $AlCl_3$ as the latter is known to acylate the aromatic ring well. We observed that the reaction of 3-methylindole **1** with acetyl chloride **2a** yielded various products including the acylation of the indole ring depending on the condition of the reaction employed. The results of this study are summarized in Table 1. While unsubstituted indole is known to give 3-acetyl indole when treated with acetyl chloride under

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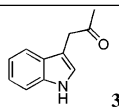
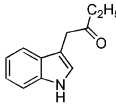
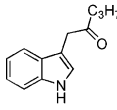
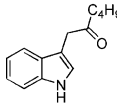
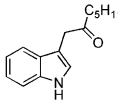
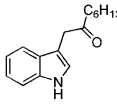
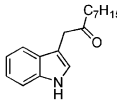
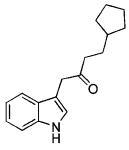
the Friedel−Crafts reaction conditions,[1,12] 3-methylindole however, yielded the corresponding 2-acetyl derivative **4**[13a] as a sole or major product when $ZnCl_2$ or $SnCl_4$ was used as catalysts (entries 1 ,2, and 5, Table 1). $FeCl_3$ yielded dimeric product **5**[13b,c] and diacetylated product **6** (entry 3, Table 1) in low yields. The use of $TiCl_4$ led to the formation of a mixture of unidentified products (entry 4, Table 1). These results clearly indicated that the π-electron of the indole ring failed to interact with the Lewis acids under the conditions employed in the reaction. We therefore opted for the use of a relatively stronger Lewis acid, i.e., $AlCl_3$ for our study. The use of 1.2 equiv of $AlCl_3$ yielded **4** in good yield when the reaction was carried out for 6 h (entry 7, Table 1). Encouragingly, the expected formation of 3-(2-oxomethyl)indole **3a**[13d] was observed as a major product in addition to the diacetylated product **6** with a 6:1 ratio when the reaction was carried out for a longer time (48 h) in the presence of 3.0 equiv of $AlCl_3$ (entry 8, Table 1). The diacetylated product **6**, however, was isolated as the only product when the reaction was carried out at higher temperature, i.e., at 55 °C (entry 8, Table 1). Compound **3a** was isolated as a light brown solid and its molecular structure was determined and characterized by IR, MS, and ^{1}H and ^{13}C NMR.[14] The methylene group of **3a** appeared at δ 3.82 and 40.7 in ^{1}H and ^{13}C NMR spectr,a respectively, and an absorption at 1709 cm^{-1} in the IR spectra indicated the presence of an aliphatic C=O group.

We were delighted to discover the formation of 3-(2-oxomethyl)indole (**3a**) and, therefore, decided to test the reaction condition with other acyl chlorides. Using the optimized procedure for the synthesis of **3a** as described above (entry 8, Table 1), a number of 3-(2-oxoalkyl)indoles **3** were synthesized and the results are shown in Table 2.

The reaction was carried out using 1.0 equiv of 3-methylindole (**1**), 1.12 equiv of acyl chloride (**2**), and 3.0 equiv of fused $AlCl_3$ (see the Experimental Section) in dry 1,2-dichloroethane with vigorous stirring at 25 °C for 24−48 h. It is noteworthy that the best yield of product was noted when $AlCl_3$ was fused before use. In a typical procedure, the reaction was carried out as follows: to a solution of compound **1** in dry 1,2-dichloroethane was added fused $AlCl_3$ at 0 °C. The mixture was warmed to 25 °C with vigorous stirring and the stirring continued for 30 min at the same temperature. After the mixture was cooled to 0 °C, acyl chloride was added slowly and dropwise. The mixture was then stirred at 25 °C according to the time indicated in Table 1. A variety of acyl chlorides were used successfully in this $AlCl_3$-mediated C−C bond-forming reaction, and the yields of the isolated products (**3**) after purifying by column chromatography were found to be moderate (entries 1−8, Table 1). The reason for observing the moderate yields of products was due to the formation of unidentified polar impurities.

We have described a direct synthesis of 3-(2-oxoalkyl)-indoles via $AlCl_3$-mediated regioselective acylation of 3-methylindole without NH protection. It is noteworthy that the successful Friedel−Crafts acylation of indole is an indirect method[15] as the method involves N-protection, acylation, and N-deprotection processes to overcome the concurrent formation of 1-acyl derivatives and to limit polymerization. Moreover, Friedel−Crafts acylation of

TABLE 2. : $AlCl_3$-Mediated Synthesis of 3-(2-Oxoalkyl)indoles via Activation of C−H Bond

Entry	Substrate **2** R =	Time (h)	Product[a]	Yield (%)[b]
1.	CH_3	48	 **3a**	58
2.	CH_2CH_3	48	 **3b**	54
3.	$CH_2CH_2CH_3$	48	 **3c**	36
4.	$CH_2CH_2CH_2CH_3$	24	 **3d**	66
5.	$CH_2CH_2CH_2CH_2CH_3$	24	 **3e**	69
6.	$CH_2CH_2CH_2CH_2CH_2CH_3$	24	 **3f**	50
7.	$CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	24	 **3g**	72
8.		24	 **3h**	56

[a] Identified by ^{1}H NMR, ^{13}C NMR, IR, and MS. [b] Isolated yields.

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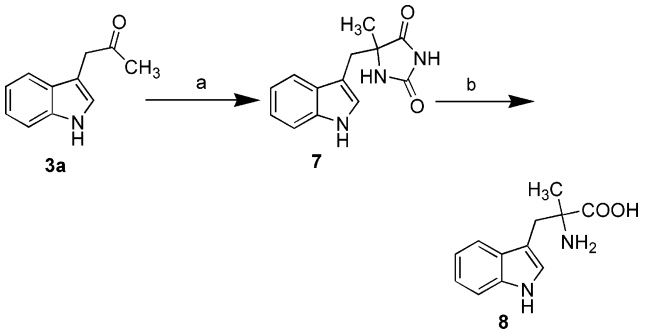
(13) (a) Jones, C. F.; Taylor, D. A.; Bowyer, D. P. *Tetrahedron* **1974**, *30*, 957−961. (b) Banerji, J.; Saha, M.; Kanrar, S.; Mukherjee, P. *Indian J. Chem. Sect. B* **1995**, *34*, 1095−1097. The dimeric product **5** was formed due to the reaction of 5-acetyl-3-methylindole (generated in the reaction mixture by acetylation of 3-methylindole) with the unreacted 3-methylindole in the presence of acid. For a detailed discussion on the mechanism of acid-catalyzed dimerization of 3-methylindole, see: (c) Hinman, R. L.; Shull, E. R. *J. Org. Chem.* **1961**, *26*, 2339−2342. (d) The methyl group of the starting material, i.e., 3-methylindole (**1**), and of the other products **4**−**6** appeared in the region of δ 2.3−2.6 in their ^{1}H NMR spectra, which was found to be missing in the case of **3a**.

(14) Spectral and analytical data for **3a**: mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, D_2O exchangeable, NH), 7.54 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 6.2 Hz, 1H), 7.23 (t, J = 6.2 Hz, 1H), 7.19 (t, J = 6.9 Hz, 2H), 3.82 (s, 2H, CH_2), 2.16 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.6 (C=O), 136.1, 127.1, 123.2, 122.1, 119.6, 118.5, 111.2, 108.5, 40.7 (CH_2), 28.8 (CH_3); IR (KBr, cm^{-1}) 3327.1, 1709.7 (C=O), 755.3; *m/z* (DIP CI method) 174 (100, M + 1); HPLC 99%, HICHROM RPB (250 × 4.6 mm), 0.01 M KH_2PO_4: CH_3CN (70:30), 1.0 mL/min, 220 nm, retention time 19.6 min., VU (MeOH, nm), 280, 220. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.37; H, 6.25; N, 8.23.

SCHEME 2[a]

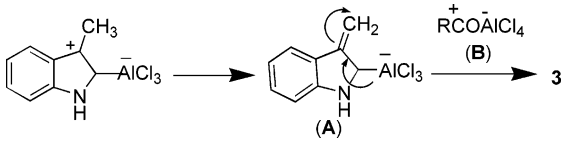


[a] Reagents and conditions: (a) KCN, $(NH_4)_2CO_3$, 80% ethanol, 60 °C, 24 h.

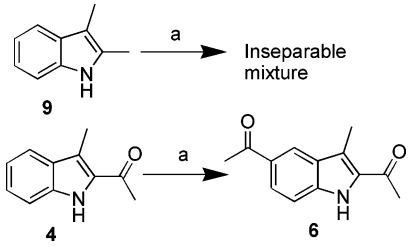
N-protected 3-methylindole yielded 2-acylated product.[15b] To demonstrate the merit of this novel methodology, synthesis of 3-indolylacetone, i.e., 1-(1*H*-3-indolyl)-2-propanone (**3a**) was carried out in a bigger scale. Thus, 12 g of 3-methylindole yielded ~9 g of **3a** (60% yield) successfully in a single step when treated with acetyl chloride in the presence of $AlCl_3$ at 25 °C. Due to the milder nature of the reaction condition, the present methodology has advantages over the alkali mediated two step synthesis of **3a** at elevated temperature (i.e., at 135−140 °C) as reported earlier.[8g] Compound **3a** could be utilized for the synthesis of compounds of potential biological interest.[16] For example, α-methyltryptophane **8** (an indole derivative having bacteriostatic and bactericidal properties) was conveniently prepared from **3a** by a two-step process (Scheme 2) comprising the reaction of **3a** with potassium cyanide in the presence of ammonium carbonate in aqueous ethanol at 60 °C for 24 h to produce **7** [5-methyl-5-skatylhydantoin (5-indol-3-ylmethyl-5-methylimidazolidine-2,4-dione)] followed by subsequent hydrolysis in the presence of sodium hydroxide at 100 °C for 22 h.[16b] Compound **3a** was also converted to the 3-(2-isopropylhydrazino-2-methyl)ethylindole possessing pharmacological activity (central nervous system stimulant) when treated with isopropylhydrazine under a hydrogen atmosphere in the presence of acetic acid and platinum oxide.[8d]

A plausible mechanism for this unprecedented $AlCl_3$-mediated C−C bond formation via activation of C−H bond at the sp^3 carbon is shown in Scheme 3. Initial complexation[17] of $AlCl_3$ with 3-methylindole (**1**) activates the methyl group at the C-3 position of the indole ring, which eventually interacts with the complex **B** [generated from acyl chloride (**2**) and $AlCl_3$ in situ] to give the product **3**. It is evident that the initial complexation with $AlCl_3$ via C-2 of the indole ring to generate **A** is crucial

SCHEME 3



SCHEME 4[a]



[a] Reagents and conditions: (a) CH_3COCl, $AlCl_3$, 1,2-dichloroethane, 25 °C, 48 h.

for the subsequent acylation at the sp^3 carbon. To gain further evidence on the role of the C-2 position of the indole ring, acetylation of 2-substituted 3-methylindole, e.g., 2,3-dimethylindole and 2-acetyl-3-methylindole (**4**), was carried out (Scheme 4) under the same reaction conditions as described earlier (entry 8, Table 1). Isolation of an inseparable mixture of unidentified products in the first case and diactyl derivative (**6**) in the second case indicated that a substituent at the C-2 position did not favor the acylation at the sp^3 carbon at the C-3 position. Crowding at the C-2 position perhaps prevented the formation of complex **A** in both the cases. Deficiency of π-electron density in the five-membered ring of **4** could be the other reason for forcing the compound **4** to undergoes normal Friedel−Crafts acylation to afford **6**.

In conclusion, a novel and easy method has been developed for the synthesis of 3-(2-oxoalkyl)indoles using commercially available starting materials. The method does not require troublesome protection−deprotection steps for the successful acylation and appears to be more straightforward in comparison to other methods. The methodology was used for the scale-up synthesis of 3-indolylacetone, a key precursor for the synthesis of compounds of potential biological interest. Although the acylation at sp^2 carbon (Friedel−Crafts acylation) is a well-known and widely used process, acylation at the sp^3 carbon is not known in the literature. We expect that the methodology and the chemistry described here would be a new addition to the indole chemistry and would find wide usage in both organic and medicinal chemistry.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Complexation of indole with a variety of Lewis acids has been reported previously; see: Schmitz-Dumount, O.; Motzkus, E. *Chem. Ber.* **1929**, *62*, 2, 466−468. See also ref 12b.