$InCl_3$-Catalyzed Alkylation of Aromatic and Heteroaromatic Compounds with Cyclic Allylic Acetates

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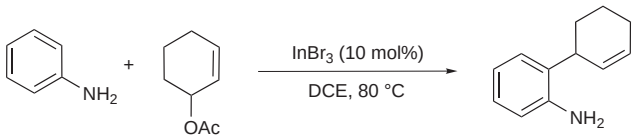
Abstract: Various aromatic and heteroaromatic compounds undergo smooth alkylation with cyclic allylic acetates in the presence of 10 mol% of indium trichloride under mild conditions to afford 3-substituted indoles, 2-substituted furan and pyrrole and cyclohexenyl-substituted arenes in good yields with high selectivity.

Keywords: indium(III) compounds, cyclic allylic acetates, alkylation, aromatics

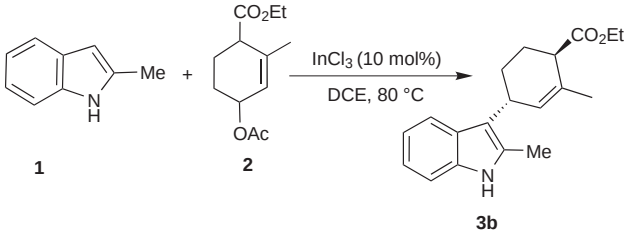
Lewis acid catalyzed carbon–carbon bond-forming reactions are of great importance in organic synthesis because of their high reactivity, selectivity and mild reaction conditions.[1] Indole and its derivatives are found abundantly in nature and are known to exhibit potent physiological properties.[2] Consequently, the synthesis and reactions of indole and its derivatives have attracted great importance in organic synthesis.[3–5] Allylic acetates are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo nucleophilic substitution reactions contributes largely to their synthetic value. However, there are no examples of the C-alkylation of indoles with cyclic allylic acetates. Recently, indium trichloride has evolved as mild and water-tolerant Lewis acid imparting high regio-, chemo- and diastereoselectivity in various organic transformations.[6] Compared to conventional Lewis acids, indium trichloride has advantages of water stability, recyclability and operational simplicity.[7] While studying the mechanism of the aminoglycosidation reactions of glycals with aryl amines, we observed that the reaction of cyclohexenyl acetate and aniline under the influence of indium tribromide (10 mol%) in dichloroethane at 80 °C afforded 2-(2-cyclohexenyl)aniline[8] (Scheme 1).



Scheme 1

To expand the scope of these reactions, we have studied the reaction of cyclic allylic acetates with other aromatic and heteroaromatic compounds. Now we wish to report our findings for the alkylation of aromatic and heteroaromatic compounds through S_N2-type substitution of cyclic allylic acetates using a catalytic amount of indium trichloride.

Accordingly, treatment of 2-methylindole (**1**) with 4-carbethoxy-3-methyl-2-cyclohexenyl acetate (**2**) in the presence of indium trichloride (10 mol%) in 1,2-dichloroethane afforded 3-(4-carbethoxy-3-methyl-2-cyclohexenyl)-1*H*-indole (**3b**) in 80% yield (Scheme 2).



Scheme 2

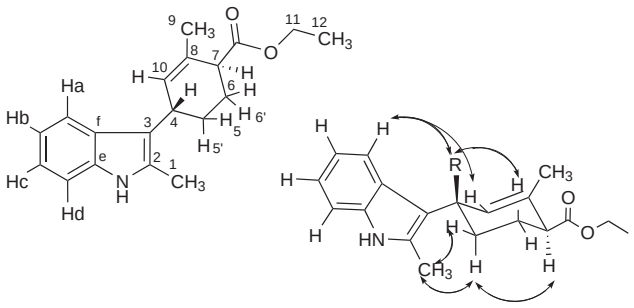


Figure 1 Characteristic NOE interactions for **3b**

The NMR studies were carried out for the structural characterization of compound **3b** making use of vicinal coupling and two-dimensional experiments like HSQC and NOESY. For compound **3b** the six-membered ring adopts a half-chair conformation. NOE cross peak between H7–H5′, H4–H6 and large coupling $J_{H4–H5'}$ = 10.0 Hz and $J_{H7–H6}$ = 10.3 Hz confirm the half-chair conformation (Figure 1). The presence of NOE cross peak between Ha–H4, Ha–H10, H1–H5, and H1–H5′ further supports

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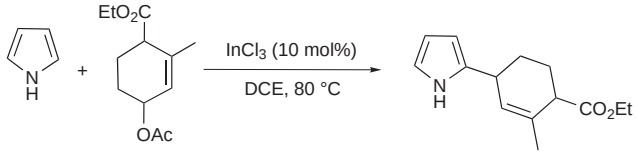
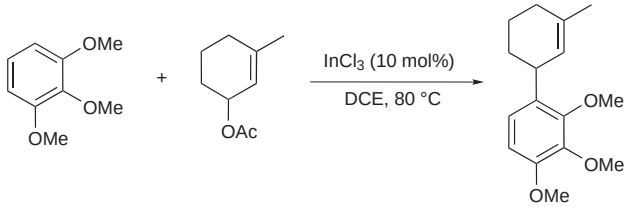
the assigned structure and that the stereochemistry is *trans*. Like entry **b** (Table 1), other reactions (entries **c**, **d**, **i**, **l**–**n**, Table 1) are highly stereoselective affording the corresponding products with *trans* stereochemistry. Similarly, substituted indoles such as 2-methyl- and 7-ethylindole derivatives reacted smoothly with cyclohexenyl acetates to give the corresponding 3-cyclohexenyl indoles in good yields (entries **a**–**c**, Table 1). Like indole, pyrrole and furan gave the respective 2-cyclohexenyl pyrrole and furan derivatives (entries **d** and **e**, Table 1, Scheme 3).

Similarly, electron-rich arenes underwent smooth alkylation with cyclohexenyl acetates under the same reaction conditions to give the respective cyclohexenyl-substituted arenes (entry **h**–**n**, Table 1, Scheme 4).



Scheme 3



Scheme 4

Table 1 $InCl_3$-Catalyzed Alkylation of Aromatic Compounds with Cyclic Allylic Acetates

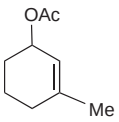
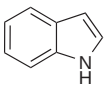
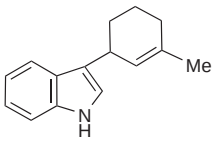
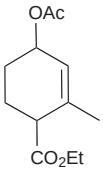
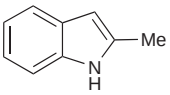
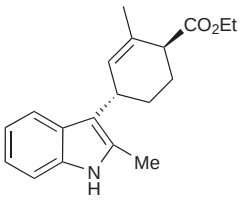
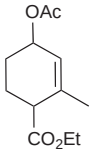
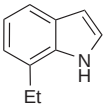
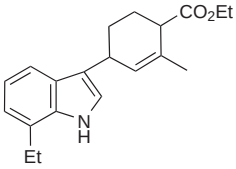
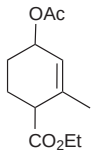
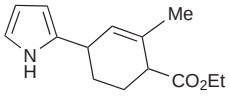
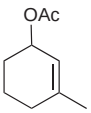
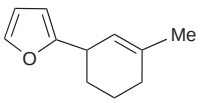
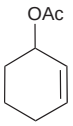
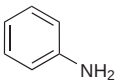
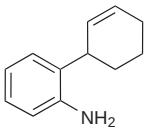
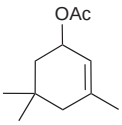
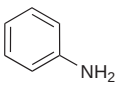
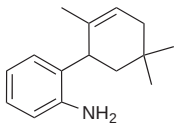
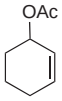
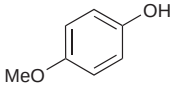
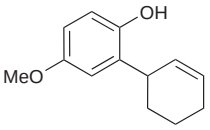
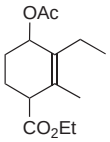
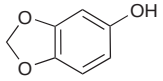
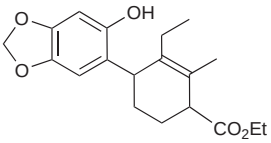
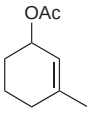
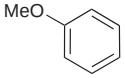
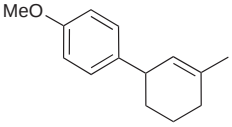
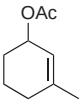
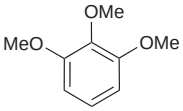
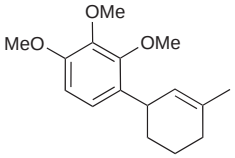
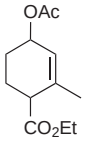
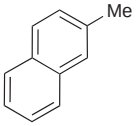
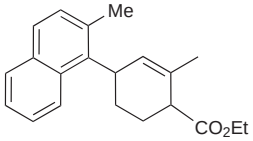
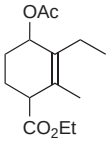
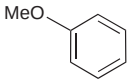
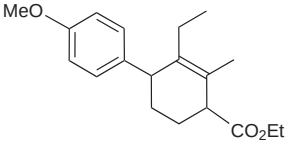
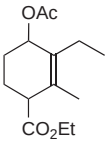
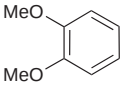
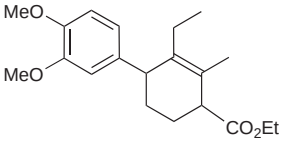
Entry	Allylic acetate	Nucleophile	Product **3**[a]	Time (h)	Yield (%)[b]
a				3.5	75
b				4.0	80
c				4.5	71
d				3.5	75
e				2.5	72
f				2.0	70
g				2.5	72

Table 1 $InCl_3$-Catalyzed Alkylation of Aromatic Compounds with Cyclic Allylic Acetates (continued)

Entry	Allylic acetate	Nucleophile	Product **3**[a]	Time (h)	Yield (%)[b]
h				1.0	82
i				1.5	75
j				1.5	81
k				1.0	87
l				2.5	79
m				2.5	80
n				2.0	83

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to products isolated after chromatography.

In all cases, the reactions proceeded efficiently with high selectivity and were complete within 0.5–4.5 hours. However, in the absence of the indium chloride, no reaction was observed between allylic acetates and aromatic compounds. No γ-substitution was observed in this case. The acetate group was simply replaced by the nucleophile in S_N2 manner. However, pyrrole underwent partial polymerization when metal triflates were used as catalysts. Pyrrole was also not compatible with conventional Lewis acids such as aluminum chloride or boron trifluoride etherate. This is because of the sensitivity of pyrrole to strong acidic conditions. Interestingly, this method is compatible with acid-sensitive substrates such as pyrrole and furan. Other functional groups such as olefins and esters are unaffected. The simple cyclohexyl acetates failed to undergo alkylation under similar reaction conditions. Furthermore, acyclic allylic acetates such as 3-phenyl-(*E*)-2-propenyl acetate and (*E*)-2-butenyl acetate did not undergo the expected S_N2 substitution with aromatic nucleophiles. This method was successful only with cyclic allylic acetates. As solvent, dichloroethane appears to give the best results. All the products were characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy. The scope and generality of this process was illustrated with respect to various indoles, pyrrole and arenes and the results are presented in Table 1.[9]

In conclusion, we have described a novel and efficient protocol for the alkylation of aromatic and heteroaromatic compounds through S_N2-type substitution of cyclic allylic acetates using indium trichloride as the catalyst. In addition to its efficiency, simplicity and mild reaction conditions, this method provides good yields of products with high selectivity, which makes it a useful and attractive process for the alkylation of aromatic compounds. It is an entirely new synthetic route for the functionalization of indoles, pyrrole, furan and electron-rich aromatic systems.

References and Notes

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(9) **General Procedure**: A mixture of cyclic allylic acetate (1 mmol), arene or indole (2 mmol) and/or pyrrole or furan (4 mmol) and $InCl_3$ (10 mol%) in 1,2-dichloroethane (10 mL) was stirred at reflux temperature for the time required to complete the reaction (Table 1). After complete conversion as indicated by TLC, the reaction mixture was diluted with water and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 1:9) to afford the corresponding cyclohexenyl-substituted aromatic or heteroaromatic compound in pure form.

Spectral Data for Selected Products:

Entry **a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.80 (br s, 1 H, NH), 7.65 (d, *J* = 8.0 Hz, 1 H), 6.85–7.40 (m, 4 H), 5.60 (br s, 1 H), 3.65 (br s, 1 H), 2.05 (m, 4 H), 1.75 (s, 3 H), 1.65 (m, 2 H). IR (KBr): 3416, 2920, 2857, 1697, 1453, 1338, 1087, 743 cm^{-1}. EIMS: *m*/*z* (%) = 211 (100) [M$^+$], 196 (70), 168 (53), 130 (31), 117 (30), 77 (15), 41 (18). HRMS (LSIMS): *m*/*z* [M$^+$] calcd for $C_{15}H_{17}N$: 211.1361; found: 211.1359.

Entry **b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (br s, 1 H, NH), 7.47 (d, *J* = 7.1 Hz, 1 H, Ha), 7.25 (d, *J* = 7.1 Hz, 1 H, Hd), 7.05 (t, *J* = 7.1 Hz, 1 H, Hc), 7.01 (t, *J* = 7.1 Hz, 1 H, Hb), 5.74 (q, *J* = 2.2 Hz, 1 H, H-10), 4.20 (q, *J* = 7.2 Hz, 2 H, H-11), 3.70 (dddd, $J_{H4–H10}$ = 2.2 Hz, $J_{H4–H5}$ = 5.6 Hz, $J_{H4–H5'}$ = 10.0 Hz, $J_{H4–H7}$ = 2.0 Hz, 1 H, H-4), 3.24 (dddd, $J_{H4–H7}$ = 2.0 Hz, $J_{H6–H7}$ = 5.6 Hz, $J_{H6'–H7}$ = 10.3 Hz, $J_{H9–H7}$ = 1.1 Hz, 1 H, H-7), 2.36 (s, 3 H, H-1), 2.13 (m, 1 H, H-6), 1.95–1.98 (m, 2 H, H5, H6′), 1.76–1.78 (m, 4 H, H5′, H-9), 1.29 (t, *J* = 7.2 Hz, 3 H, H-12). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5 (Ce), 130.1 (C-10), 129.4 (C-2), 126.9 (C=O), 126.9 (Cf), 124.0 (C-8), 120.6 (Cc), 118.8 (Ca), 118.8 (Cb), 115.0 (C-3), 110.2 (Cd), 60.2 (C-11), 46.7 (C-7), 33.2 (C-4), 27.9 (C-5), 26.8 (C-6), 21.5 (C-9), 14.2 (C-12), 11.6 (C-1). IR (KBr): 3390, 2924, 2364, 1721, 1458, 1167, 745 cm^{-1}. EIMS: *m*/*z* (%) = 297 (77) [M$^+$], 282 (35), 207 (27), 182 (47), 167 (18), 147 (100), 97 (15), 84 (73), 43 (65).

Entry **l**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.75 (d, *J* = 8.0 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 5.30 (br s, 1 H), 3.85 (s, 9 H), 3.60 (br s, 1 H), 1.95 (m, 3 H), 1.75 (s, 3 H), 1.65 (m, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, ^{1}H-decoupled): δ = 151.5, 142.2, 135.0, 132.9, 126.1, 124.7, 122.6, 107.1, 61.1, 60.6, 56.0, 34.7, 31.1, 29.9, 23.9, 21.5. IR (KBr): 3452, 2928, 1601, 1492, 1462, 1280, 1097, 1022, 717 cm^{-1}. EIMS: *m*/*z* (%) = 262 (100) [M$^+$], 247 (43), 219 (20), 203 (17), 167 (10), 95 (16), 84 (24), 49 (43). HRMS (LSIMS): *m*/*z* [M$^+$] calcd for $C_{16}H_{22}O_3$: 262.1569; found: 262.1565.