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The first example of the C-3 alkylation of indoles with cyclopropyl ketones promoted by $CeCl_3 \cdot 7H_2O$/LiI

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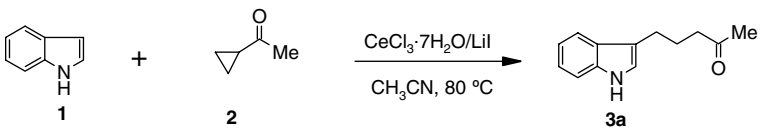
Abstract—Indoles undergo smooth alkylation with cyclopropyl ketones in the presence of the $CeCl_3 \cdot 7H_2O$/LiI reagent system in refluxing acetonitrile under neutral conditions to produce the corresponding C-3 substituted indole derivatives in good to high yields and with high selectivity. The use of $CeCl_3 \cdot 7H_2O$/LiI makes this method simple, convenient, and cost-effective.

The indole nucleus is an important structure in medicinal chemistry.[1] Substituted indoles have been referred to as *privileged structures* since they are capable of binding to many receptors with high affinity.[2] Therefore, the synthesis and selective functionalization of indoles have been the focus of active research.[3–5] 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.[6] In this context, lanthanide salts are examples of Lewis acids,[7] which are currently of significant research interest. In particular, cerium reagents are relatively non-toxic, readily available at low cost and are fairly stable to water. Owing to its unique properties, $CeCl_3$ has been extensively used for a variety of organic transformations.[8]

In continuation of our interest on the use of cerium(III) reagents for various organic transformations,[9] we report herein a novel method for the alkylation of indoles with activated cyclopropanes using the cerium(III) chloride heptahydrate/lithium iodide reagent system. Accordingly, treatment of indole (**1**) with cyclopropyl methyl ketone (**2**) in the presence of $CeCl_3 \cdot 7H_2O$/LiI afforded 5-(1*H*-indol-3-yl)pentan-2-one **3a** in 85% yield (Scheme 1).

The reaction proceeded smoothly in refluxing acetonitrile under neutral conditions. Encouraged by this result, we turned our attention to various indoles and cyclopropyl ketones. Interestingly, a variety of indole derivatives such as 5-cyano-, 5-nitro-, 5-methoxycarbonyl-, and 5-bromoindoles reacted readily with cyclopropyl methyl ketone to produce 3-alkyl indoles (Table 1, entries b–e). Other cyclopropyl ketones such as cyclopropyl phenyl ketone, cyclopropyl 4-fluorophenyl ketone, and cyclopropyl 4-methoxyphenyl ketone participated well in this reaction. The combination of cerium(III) chloride with LiI worked efficiently to furnish the corresponding three-substituted indoles in good to high yields (Table 1, entries a–l). In the absence of LiI, the products were obtained in low yields (30–45%). Interestingly, no chloro- or iodo-alkanes were formed arising from nucleophilic opening of the cyclopropane ring by chloride or iodide. Furthermore, TMSI was found to be equally effective for this conversion.



Scheme 1.

Keywords: Indoles; Cerium(III) compounds; Activated cyclopropanes; C-3 alkylation.
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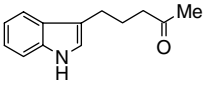
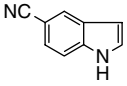
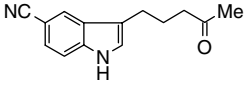
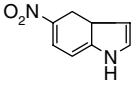
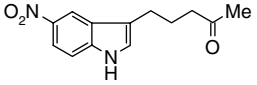
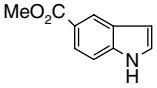
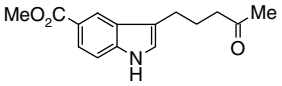
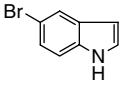
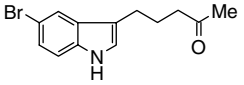
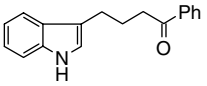
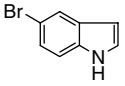
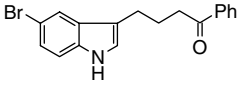
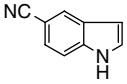
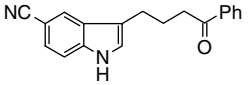
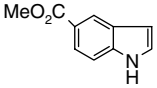
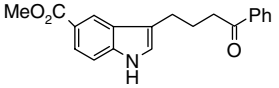
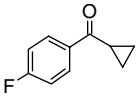
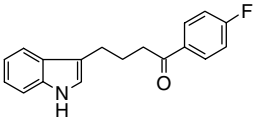
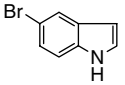
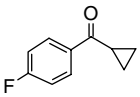
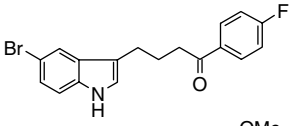
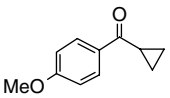
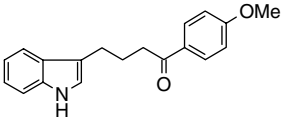
Among various metal iodides such as InI_3, GaI_3, AlI_3, and MgI_2, $CeCl_3{\cdot}7H_2O$/LiI was found to be superior in terms of conversion. For example, the reaction between indole and cyclopropyl phenyl ketone in the presence of $CeCl_3{\cdot}7H_2O$/LiI, TMSI, InI_3, GaI_3, AlI_3 and MgI_2 gave product **3f**, in 84%, 82%, 80%, 69%, 65%, and 62% yields, respectively. However, no reaction was observed in the absence of catalyst even after a long reaction time (12 h). The nature of the substituents on the aromatic ring showed some effect on this conversion with electron deficient groups such as cyano, nitro, and ester on the aromatic ring affording lower yields of products compared to simple indoles.

To examine the efficiency of this procedure, we carried out the reaction with other cerium salts such as cerium(III) triflate and ceric ammonium nitrate. Among these reagents, cerium(III) chloride was found to be

Table 1. $CeCl_3{\cdot}7H_2O$/LiI mediated C-3 alkylation of indoles with cyclopropyl ketones

Entry	Indole	Ketone	Product[a]	Reaction time (h)	Yield[b] (%)
a				6.0	85
b				6.0	80
c				7.0	73
d				5.5	79
e				6.0	82
f				5.0	84
g				8.0	78
h				5.5	75
i				6.0	80
j				6.0	85
k				7.0	79
l				6.5	86

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

the most effective whilst low conversions (10–15%) were obtained with CAN/LiI. As solvent, acetonitrile gave the best results. Furthermore, we examined the possibility of $CeCl_3{\cdot}7H_2O$ functioning catalytically or at least, in less than stoichiometric amounts, however, the best results were obtained with an equimolar ratio of $CeCl_3{\cdot}7H_2O$. There are many advantages in the use of cerium(III) chloride for this transformation, which avoids the use of strongly acidic conditions. The method does not require the use of expensive or corrosive reagents and no precautions need to be taken to exclude moisture from the reaction medium. The scope of the $CeCl_3{\cdot}7H_2O$/LiI promoted alkylation with respect to various indoles and cyclopropyl ketones is summarized in Table 1.[10]

In summary, we have developed a novel and efficient procedure for the C-3 alkylation of indoles with activated cyclopropanes using $CeCl_3{\cdot}7H_2O$/LiI under neutral conditions. The notable features of this procedure are mild reaction conditions, simplicity in operation, clean reaction profiles, good selectivity, and ready availability of reagents at low cost, which makes it a useful and attractive strategy for the synthesis of three-substituted indole derivatives.

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10. *General procedure*: A mixture of indole (1 mmol) and cyclopropyl ketone (1 mmol), $CeCl_3{\cdot}7H_2O$ (1.0 mmol) and LiI (1.5 mmol) in acetonitrile (5 mL) was stirred at reflux for a specified time as required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure corresponding 3-alkyl indole. The products were characterized by IR, NMR and HRMS spectroscopy and physical constants. Spectral data for selected products:
5-(1H-3-indolyl)-2-pentanone (entry a): Solid, mp 120–122 °C; IR (KBr): ν_{max} 3409, 3054, 2924, 2854, 1705, 1619, 1456, 1337, 1242, 1215, 1098, 1034, 1012, 925, 821, 743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.66 (s, 3H), 1.90–2.08 (m, 3H), 2.36–2.42 (m, 1H), 3.90–4.04 (m, 2H), 6.98 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.0–7.14 (m, 2H, Ar-H), 7.22 (d, $J = 7.6$ Hz, 1H, Ar-H), 7.62 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.96 (br s, 1H, NH); LC–MS: *m/z*: 202, ($M+1^+$) 184, 175, 149, 130, 102, 85, 74, 59; HRMS calcd for $C_{13}H_{16}NO$ ($M+H^+$): 202.1231, found: 202.1239.
Methyl-3-(4-oxo-4-phenylbutyl)-[1H]-5-indolecarboxylate (entry i): Solid, mp 139–141 °C; IR (KBr): ν_{max} 3283, 3061, 2924, 2951, 2915, 1865, 1704, 1617, 1577, 1439, 1243, 1113, 1029, 964, 856, 820, 752, 700, 667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.15 (m, 2H), 2.40–2.76 (m, 2H), 3.75 (s, 3H), 4.05–4.15 (m, 2H), 6.83 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.15–7.37 (m, 4H, Ar-H), 7.48 (dd, 2H $J = 2.1$ and 8.0 Hz, Ar-H), 7.69 (dd, $J = 2.2$ and 9.0 Hz, 1H, Ar-H), 8.35 (s, 1H), 8.46 (br s, 1H, NH); LC–MS: *m/z*: 322 (M+1), 301, 279, 258, 245, 229, 174, 157, 129, 74, 59; HRMS calcd for $C_{20}H_{20}NO_3$ ($M+H^+$): 322.1443; found, 322.1457.
4-(5-Bromo-[1H]-3-indolyl)-1-(4-fluorophenyl)-1-butanone (entry k): Solid, mp 115–117 °C; IR (KBr): ν_{max} 3423, 3289, 2924, 2879, 1676, 1600, 1505, 1415, 1336, 1223, 1156, 1036, 983, 929, 882, 832, 798, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.88–2.12 (m, 2H), 2.30–2.42 (m, 1H), 2.56–2.68 (m, 1H), 3.97–4.12 (m, 2H), 6.63 (d, $J = 3.0$ Hz, 1H, Ar-H), 6.90–6.98 (m, 3H, Ar-H), 7.13 (dd, $J = 2.2$ and 9.0 Hz, 1H, Ar-H), 7.34–7.42 (m, 2H),7.62 (s, 1H), 8.12 (br s, 1H, NH); LC–MS: *m/z*: 360, 362, ($^{79}Br+1/^{81}Br+1$), (M^+), 336, 314, 301, 279, 259, 245, 229, 214, 185, 174, 159, 148, 129, 113, 102, 81, 74, 59; HRMS calcd for $C_{18}H_{16}BrFNO$ ($M+H^+$): 360.0399; found, 360.0392.