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Sc(OTf)$_3$-catalyzed alkylation of indoles with propargyl alcohols: an expeditious synthesis of 3-substituted indoles

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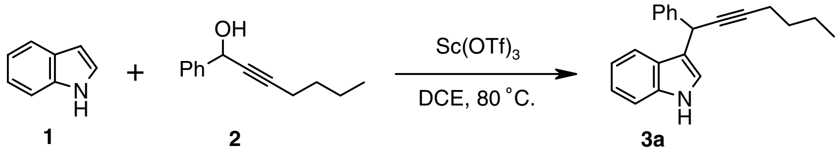
Abstract—Indoles undergo smooth alkylation with propargylic alcohols in the presence of 10 mol % of scandium triflate under mild conditions to produce 3-propargylated indoles in excellent yields with high selectivity.

Indole and its derivatives are found abundantly in Nature and are known to exhibit potent physiological properties.[1] Consequently, the synthesis and reactions of indole and its derivatives have attracted great attention in organic synthesis.[2–4] Propargylic alcohols 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.[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] Of these, lanthanide triflates are unique Lewis acids that are currently of great research interest. They are highly oxophilic and form strong but labile bonds with oxygen donor ligands. This feature has often allowed sub-stoichiometric amounts of the lanthanide Lewis acid to be used to promote a variety of reactions. Indeed, such Lewis acids are found to be effective in promoting many organic transformations.[7] In continuation of our interest in the catalytic applications of lanthanide triflates as water-tolerant and recyclable Lewis acids,[8] we herein, report for the first time, an efficient alkylation of indoles with propargylic alcohols using a catalytic amount of scandium triflate. Initially, we attempted the alkylation of indole (**1**) with 1-phenylhept-2-yn-1-ol (**2**) in dichloroethane in the presence of 10 mol % of Sc(OTf)$_3$. The reaction went to completion within 25 min and the product **3a** was obtained in 90% yield (Scheme 1).

Encouraged by this result, we turned our attention to various indoles and propargyl alcohols. Interestingly, substituted indoles such as 5-bromo-, 5-nitro-, 2-methyl- and 5-methoxycarbonyl reacted well with 1-phenylhept-2-yn-1-ol to give the corresponding 3-propargylated indoles in excellent yields (Table 1, entries b–e). Other propargylic alcohols such as 1,3-diphenyl-2-propyn-1-ol reacted efficiently with indole, 5-bromoindole, 5-nitroindole, 2-methylindole and 5-methoxycarbonyl



Scheme 1.

Keywords: Scandium(III) triflate; Propargyl alcohols; Indoles; Alkylation.

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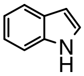
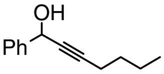
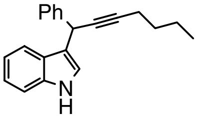
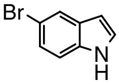
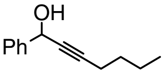
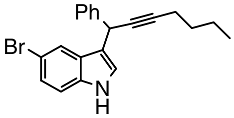
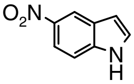
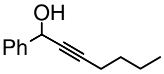
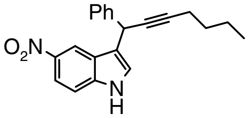
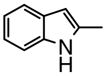
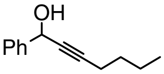
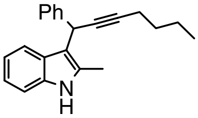
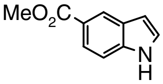
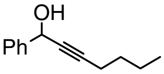
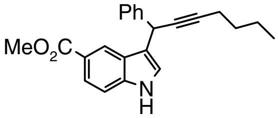
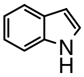
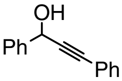
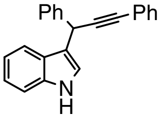
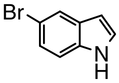
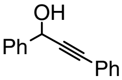
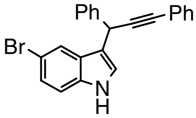
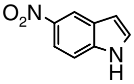
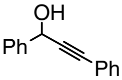
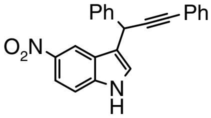
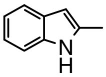
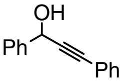
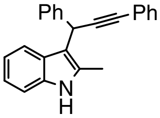
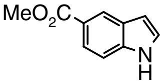
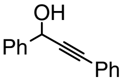
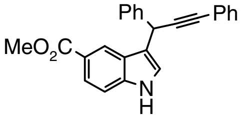
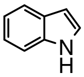
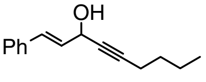
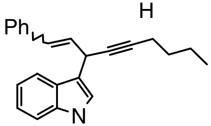
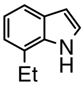
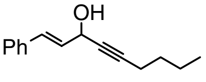
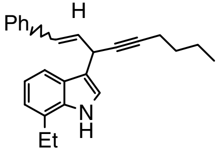
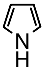
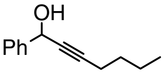
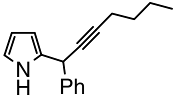
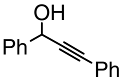
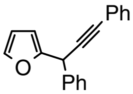
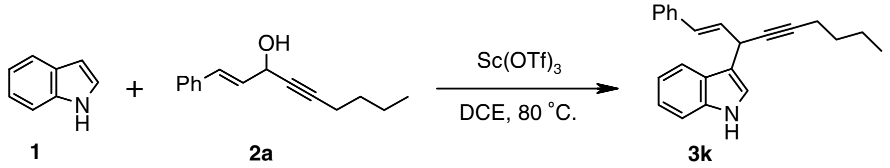
Table 1. Scandium triflate catalyzed alkylation of heteroaromatic systems with propargyl alcohols

Entry	Substrate	Propargyl alcohol	Product[a]	Time (min)	Yield[b] (%)
a				25	90
b				30	92
c				50	83
d				30	85
e				35	86
f				25	91
g				30	93
h				45	85
i				30	89
j				35	87
k				20	90[c]
l				25	89[c]
m				30	86
n				35	85

[a] All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy.

[b] Isolated and unoptimized yield.

[c] *E*/*Z* ratio 9:1.



Scheme 2.

indole to furnish the respective 3-substituted indoles (Table 1, entries f–j). Furthermore, 1-phenyl-(*E*)-1-nonen-4-yn-3-ol also participated well in this reaction (Scheme 2, Table 1, entries k and l).

Like indole, pyrrole and furan gave the respective 2-propargylated pyrrole and furan derivatives. Interestingly, electron-deficient indoles such as 5-nitroindole and methyl 1*H*-indole-5-carboxylate also underwent smooth alkylation with propargylic alcohols under the reaction conditions to give the respective propargylated indoles (Table 1, entries c, e, h and j). In all cases, the reactions proceeded efficiently with high selectivity and were completed within 20–50 min. However, in the absence of scandium triflate, no reaction was observed. No addition or rearranged products were observed in this reaction. The hydroxyl group was simply replaced by the indole in an S_N2' manner. It is noteworthy to mention that highly acid sensitive pyrrole and furan gave the desired propargylated derivatives without the formation of any side products arising from polymerization.

Simple propargylic and homopropargylic alcohols failed to undergo alkylation under similar reaction conditions. Furthermore, propargylic alcohols derived from aliphatic aldehydes such as 1-cyclohexylhept-2-yn-1-ol did not undergo the expected S_N2' substitution with heteroaromatic systems. This method was successful only with propargylic alcohols derived from aromatic and α,β-unsaturated aldehydes. As solvent, dichloroethane appeared to give the best results. All the products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. Among various metal triflates such as $Bi(OTf)_3$, $In(OTf)_3$, $Sm(OTf)_3$ and $Yb(OTf)_3$, $Sc(OTf)_3$ was found to give the best results in terms of conversion. The scope and generality of this process was illustrated with respect to various heteroaromatic systems and the results are presented in Table 1.[9]

In summary, we have described an efficient alkylation of indoles with propargylic alcohols using scandium triflate as a novel catalyst. In addition to its efficiency, simplicity and mild reaction conditions, this method provides high yields of propargylated indoles in a short reaction time with high selectivity.

Acknowledgement

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9. *Experimental procedure*: A mixture of indole (1 mmol), 1-phenylhept-2-yn-1-ol (1.0 mmol), scandium triflate (0.1 mmol %) in dichloroethane (5 mL) was stirred at 80 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water 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, 2:8) to afford pure 3-propargylated indoles. Compound **3c**: 5-nitro-3-(1-phenyl-2-heptynyl)-1*H*-indole: Solid, mp 169–171 °C, IR (KBr): ν 3439, 3309, 2957, 2925, 2854, 2362, 1625, 1515, 1456, 1324, 1209, 1083, 730, 697 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, 3H, $J = 7.3$ Hz), 1.34–1.62 (m, 4H), 2.26 (dt, 2H, $J = 2.2$, 6.6 Hz), 5.20 (s, 1H), 7.16–7.33 (m, 4H), 7.38–7.48 (m, 3H), 7.95 (dd, 1H, $J = 2.2$, 8.8 Hz), 8.46 (d, 1H, $J = 2.2$ Hz), 11.2 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.5, 18.5, 22.0, 30.9, 34.7, 79.7, 84.3, 111.0, 117.1, 117.8,

120.6, 125.2, 125.5, 126.9, 127.6, 128.5, 139.6, 141.0, 141.6 ppm. LCMS: *m*/*z* (%): (M+H$^+$) 333. HRMS calcd for $C_{21}H_{21}N_2O_2$ (M+H$^+$): 333.1603. Found: 333.1609. Compound **3f**: 3-(1,3-diphenyl-2-propynyl)-1*H*-indole: Liquid, IR (KBr): *v* 3418, 3061, 2923, 2853, 2360, 2196, 1696, 1595, 1451, 1285, 1214, 882, 795, 755, 697 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 5.33 (s, 1H), 6.99 (d, 1H, $J = 1.7$ Hz), 7.11 (d, 1H, $J = 8.4$ Hz), 7.18–7.33 (m, 6H), 7.39–7.47 (m, 6H), 7.69 (d, 1H, $J = 1.7$ Hz), 7.89 (br s, 1H). ^{13}C NMR (CDCl$_3$, 50 MHz): δ 35.4, 83.2, 90.5, 111.1, 116.7, 119.5, 122.1, 122.5, 123.6, 126.0, 126.7, 127.7, 127.8, 128.1, 128.4, 131.6, 136.6, 141.2 ppm. LCMS: *m*/*z* (%): (M+H$^+$) 308. HRMS calcd for $C_{23}H_{18}N$ (M+H$^+$): 308.1439. Found: 308.1446. Compound **3m**: 2-(1-phenyl-2-heptynyl)-1*H*-pyrrole: Liquid, IR (KBr): *v* 3429, 2957, 2926, 2855, 1490, 1455, 1026, 717 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.93 (t, 3H, $J = 7.1$ Hz), 1.38–1.60 (m, 4H), 2.27 (dt, 2H, $J = 2.4$, 6.9 Hz), 4.97 (m, 1H), 5.87 (m, 1H), 6.04 (dd, 1H, $J = 2.8$, 3.2 Hz), 6.60 (m, 1H), 7.16–7.34 (m, 5H), 8.00 (br s, 1H). ^{13}C NMR (CDCl$_3$, 50 MHz): δ 13.2, 18.2, 21.7, 30.6, 36.3, 78.6, 84.1, 105.6, 108.2, 116.5,126.6, 127.2, 128.2, 131.0, 140.5 ppm. LCMS: *m*/*z* (%): (M+H$^+$) 238. HRMS calcd for $C_{17}H_{20}N$ (M+H$^+$): 238.1595. Found: 238.1601.