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$InBr_3$ as a versatile and highly efficient catalyst for the synthesis of 3-allyl- and 3-benzylindoles

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Abstract—Indoles undergo smooth alkylation with allylic and benzylic alcohols in the presence of 10 mol % of $InBr_3$ under mild conditions to produce 3-allyl- and 3-benzyl indoles, respectively, in excellent yields and with high selectivity. This is the first example of the alkylation of indoles with benzylic alcohols using $InBr_3$ as an acid catalyst.

The indole scaffold is one of the most relevant structures 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 over the years.[3–5] Nucleophilic substitution of the hydroxy group in alcohols with nucleophiles generally requires preactivation of the alcohols because of the poor leaving ability of the hydroxyl group.[6] Consequently, hydroxyl groups are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates or related compounds.[7] However, such processes inevitably produce stoichiometric amounts of salt waste and also substitution with halides requires a stoichiometric amount of base, which limits their use in large scale synthesis. In most cases, either a high reaction temperature is required or a promoter is added to enhance the leaving ability of the hydroxyl group. Therefore, the direct catalytic substitution of alcohols with indoles using an efficient, water-tolerant and recyclable catalyst is highly desirable.

Recently, indium tribromide has received increasing attention as a water-tolerant green Lewis acid catalyst for organic synthesis demonstrating highly chemo-, regio- and stereoselective results.[8] Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts. Furthermore, there have been no reports on the alkylation of indoles with benzylic alcohols.

In continuation of our interest on the catalytic use of indium tribromide,[9] herein, we report a novel and efficient alkylation of indoles with benzylic and allylic alcohols. Initially, we attempted the alkylation of indole (**1**) with 1,3-diphenyl-prop-2-en-1-ol (**2**) in the presence of 10 mol % of $InBr_3$. The reaction went to completion at room temperature within 30 min to give product **3a** in 91% yield (Scheme 1).

Encouraged by this result, we turned our attention to various indoles. Interestingly, 5-bromo- and 5-cyano-substituted indoles reacted well with 1,3-diphenyl-prop-2-en-1-ol to give the corresponding 3-allylated indoles in excellent yields (Table 1, entries b and c). Furthermore, cyclohex-2-enol also reacted smoothly with indole at room temperature to produce 3-(cyclohex-2-enyl)-1*H*-indole (Table 1, entry d). In addition, (*E*)-4-phenylbut-3-en-2-ol also participated well in this reaction (Table 1, entries e and f). Likewise the benzylic alcohol, tetrahydronaphthalen-1-ol reacted rapidly with indole to give 3-(1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-indole in 92% yield (Table 1, entry g, Scheme 2).

Keywords: Indium reagents; Benzylic/allylic alcohols; Indoles; Benzylation; Allylation.
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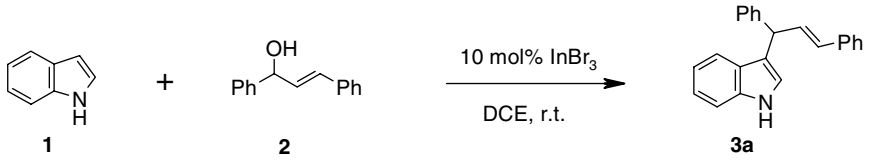


Scheme 1.

Table 1. $InBr_3$-catalyzed alkylation of indole derivatives with allylic and benzylic alcohols

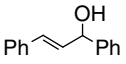
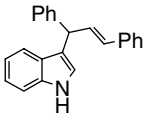
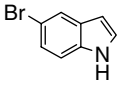
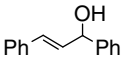
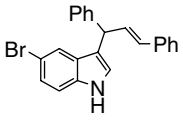
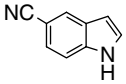
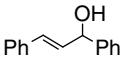
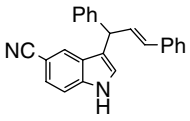
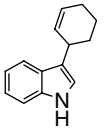
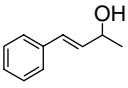
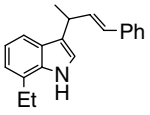
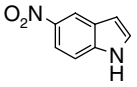
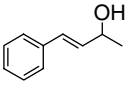
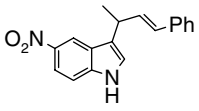
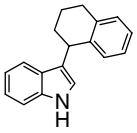
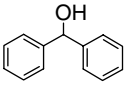
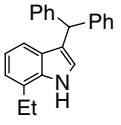
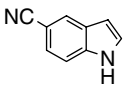
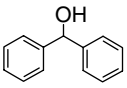
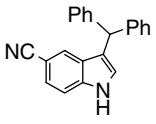
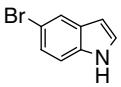
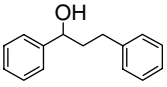
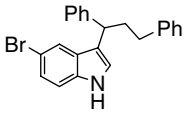
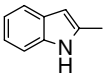
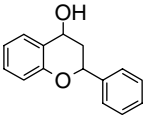
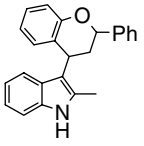
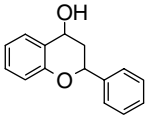
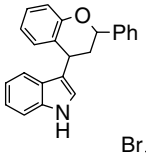
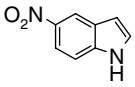
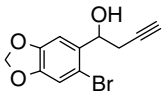
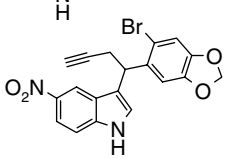
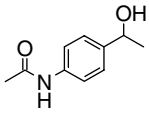
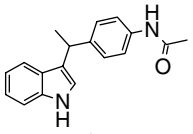
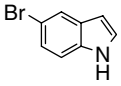
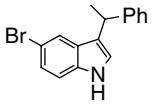
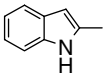
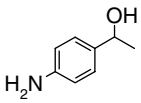
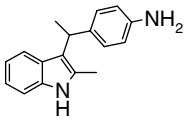
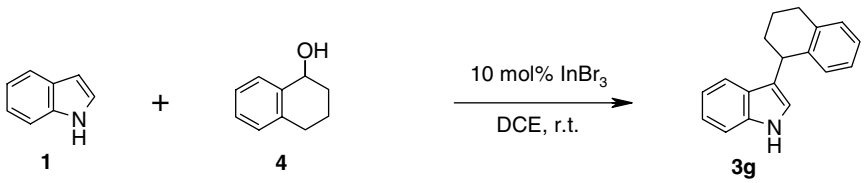
Entry	Indole	Alcohol	Product[a]	Time (min)	Yield[b] (%)
a				30	91
b				35	93
c				35	85
d				45	88
e				30	91
f				35	88
g				50	92
h				35	87
i				30	90
j				55	92
k				50	87

Table 1 (*continued*)

Entry	Indole	Alcohol	Product[a]	Time (min)	Yield[b] (%)
l				35	89
m				50	86
n				45	84
o				45	86
p				50	84

[a] All products were characterized by ^{1}H ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2.

Interestingly, various benzylic alcohols such as diphenylmethanol, 1,3-diphenylpropan-1-ol, 2-phenylchroman-4-ol, 1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)but-3-yn-1-ol and 2-phenylethanol derivatives reacted efficiently with various indoles to furnish the respective 3-substituted indoles (Table 1, entries h–p). Electron-deficient indoles such as 5-nitroindole and 5-cyanoindole also underwent smooth alkylation with allylic and benzylic alcohols under similar reaction conditions to give the corresponding 3-substituted indoles (Table 1, entries c, f, i and m). In all cases, the reactions proceeded efficiently with high selectivity and were complete within 30–55 min. In the absence of $InBr_3$, no reaction was observed. No addition or rearranged products were observed in the cases of allylic and homopropargylic alcohols (Table 1, entries e, f and m). The OH group was simply replaced by the indole in an S_N2' manner. This method is compatible with alkene, ether, amine, amide, halide, nitro-, cyano- and alkyne functional groups. Primary benzylic alcohols failed to react with indoles under similar reaction conditions. This method was successful with secondary benzylic and allylic alcohols. As solvent, dichloroethane gave the best results. All the products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. Amongst various catalysts such as InF_3, $InCl_3$, $In(ClO_4)_3$ and $In(OTf)_3$ tested, $InBr_3$ was found to give the best results in terms of conversion. Alternatively, 10 mol % of scandium triflate was also equally effective for this conversion. The scope and generality of this process was illustrated with respect to various indoles and allylic as well as benzylic alcohols and the results are presented in Table 1.[10]

In summary, $InBr_3$ has proved to be an effective catalyst for the alkylation of indoles with benzylic and allylic alcohols in high yields and short reaction times with high selectivity, making it a useful and attractive process.

Acknowledgement

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References and notes

1. (a) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996, p 7; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49; (c) Ninomiya, I. *J. Nat. Prod.* **1992**, *55*, 541–564.
2. (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207; (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515; (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930; (d) Tois, J.; Franzen, R.; Koskinen, A. *Tetrahedron* **2003**, *59*, 5395–5405.
3. (a) Cacchi, S.; Fabrici, G. *Chem. Rev.* **2005**, *105*, 2873–2920; (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222; (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
4. (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556; (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173; (c) Jensen, K. B.; Thorhange, J.; Hazel, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160–163.
5. (a) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114; (b) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594–4597.
6. (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 2921–2944; (b) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865–9868; (c) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2005**, *46*, 639–641.
7. (a) Westermaier, M.; Mayr, H. *Org. Lett.* **2006**, *8*, 4791–4794; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199–3202; (c) De la Herrán, G.; Segura, A.; Csáky, A. G. *Org. Lett.* **2007**, *9*, 961–964.
8. (a) Zhang, Z.-H. *Synlett* **2005**, 711–712; (b) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2005**, *46*, 6407–6409; (c) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126–7129; (d) Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375–3377; (e) Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, 948–950.
9. (a) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V.; Raj, K. S.; Prasad, A. R.; Kumar, S. K.; Kunwar, A. C.; Jayaprakash, P. J.; Jagannath, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5198–5201; (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M. *Synlett* **2001**, 1781–1783; (c) Yadav, J. S.; Reddy, B. V. S.; Baishya, G. *Synlett* **2003**, 396–398; (d) Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 6055–6058; (e) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Synthesis* **2004**, 106–110; (f) Yadav, J. S.; Reddy, B. V. S.; Gakul, B. *Green Chem.* **2003**, *5*, 264–266; (g) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Parimala, G. *Synthesis* **2003**, 2390–2394.
10. *Experimental procedure*: A mixture of indole (1.0 mmol), 1,3-diphenyl-prop-2-en-1-ol (1.0 mmol), and $InBr_3$ (10 mol %) in dichloroethane (5 mL) was stirred at room temperature 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 (2×15 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 pure 3-substituted indole. The spectroscopic data of the products were identical with the data reported in the literature 11.
    Spectral data for selected products:
    Compound **3d**: 3-(2-cyclohexenyl)-1*H*-indole: IR (KBr): ν 3415, 2927, 2856, 1455, 1419, 1339, 1222, 1090, 742 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.57–1.87 (m, 3H), 1.97–2.13 (m, 3H), 3.69 (m, 1H), 5.82 (m, 2H), 6.86 (d, 1H, $J = 2.3$ Hz), 6.99–7.15 (m, 2H), 7.25 (d, 1H, $J = 7.7$ Hz), 7.58 (d, 1H, $J = 7.7$ Hz), 7.74 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1, 30.1, 32.8, 50.7, 109.5, 111.1, 119.0, 119.4, 120.8, 121.3, 121.8, 127.5, 130.3, 136.5. MS: *m*/*z* (%): (M^++Na) 220. HRMS calcd for $C_{14}H_{15}NNa$: 220.1102. Found: 220.1110.
    Compound **3e**: 7-ethyl-3-[(*E*)-1-methyl-3-phenyl-2-propenyl]-1*H*-indole: IR (KBr): ν 3420, 2962, 2924, 1453, 1417, 1338, 1094, 965, 743, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, 3H, $J = 7.3$ Hz), 1.55 (d, 3H, $J = 6.6$ Hz), 2.83 (q, 2H, $J = 7.3$ Hz), 3.90 (m, 1H), 6.44 (m, 2H), 6.90–7.02 (m, 3H), 7.07–7.32 (m, 5H), 7.45 (dd, 1H, $J = 2.2$, 6.6 Hz), 7.79 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6, 29.6, 34.1, 45.9, 111.0, 119.1, 119.5, 120.2, 120.3, 121.8, 126.1, 126.8, 128.1, 128.2, 128.4, 135.3, 136.4, 137.7; MS: *m*/*z* (%): (M^++Na) 298. HRMS calcd for $C_{20}H_{21}NNa$: 298.1571. Found: 298.1578.
    Compound **3p**: 4-[1-(2-methyl-1*H*-3-indolyl)ethyl]aniline: IR (KBr): ν 3401, 2966, 1618, 1513, 1459, 1271, 828, 745 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.69 (d, 3H, $J = 7.5$ Hz), 2.27 (s, 3H), 3.06 (br s, 2H), 4.27 (q, 1H, $J = 7.5$ Hz), 6.49 (d, 2H, $J = 8.3$ Hz), 6.86–7.05 (m, 4H), 7.13 (d, 1H, $J = 7.5$ Hz), 7.31 (d, 1H,$J = 8.3$ Hz), 7.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.9, 20.6, 34.4, 110.1, 115.1, 118.6, 119.2, 120.3, 124.5, 128.0, 129.3, 130.3, 135.1, 136.5, 143.3; MS: *m*/*z* (%): (M^++Na) 273. HRMS calcd for $C_{17}H_{18}N_2Na$: 273.1367. Found: 273.1373.
11. (a) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y. Ch.; Wang, D.; Chen, Y. J. *Tetrahedron Lett.* **2007**, *48*, 3963–3967; (b) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793–796.