Iodine-Catalyzed Nucleophilic Substitution Reactions of Benzylic Alcohols

Pabbaraja Srihari,* Dinesh C. Bhunia, Pamu Sreedhar, Jhillu S. Yadav
Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax +91(40)27160512; E-mail: srihari@iict.res.in

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Abstract: Molecular iodine efficiently catalyzes the direct nucleophilic substitution of the hydroxy group of benzylic alcohols with carbon and oxygen nucleophiles.

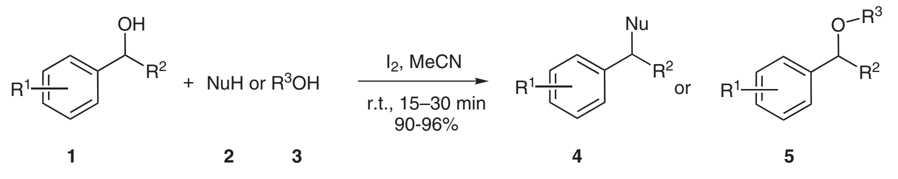
Key words: nucleophilic substitution, benzyl alcohols, carbocation, Lewis acid

The displacement of hydroxy groups in alcohols by nucleophiles is a direct method for C–C bond-formation reaction. This reaction has gained importance due to readily available starting materials and also the environmentally benign byproduct (water) formed during the reaction. The direct nucleophilic substitution reactions of alcohols are generally attained by employing stoichiometric amounts of Lewis acids[1] or by using excess of sulfuric acid or phosphoric acid.[2] Since the hydroxy group is not a good leaving group, very often it has to be derivatized as acetate or halide for substitution with different nucleophiles.[3] Recently, there have been many precedents for the direct nucleophilic substitution reactions of benzyl alcohols, remarkable are the reactions catalyzed by *p*-toluenesulfonic acid monohydrate, polymer-bound *p*-toluenesulfonic acid,[4] metal salts such as Bi, La, Sc, or Hf salts,[5] or Fe[3a] or Au[6] catalysis including the more recent $InCl_3$.[7] However, these reactions are generally performed at elevated temperatures or require more than catalytic amount of the catalyst. Therefore, the development of new methods for direct substitution of hydroxy group is a challenging goal to organic chemists.

During the last decade molecular iodine has been well explored as a versatile catalyst for several organic transformations such as synthesis of bis(indolyl)methanes,[8] thioketalization of carbonyl compounds,[9] Michael addition,[10] protection/deprotection,[11] and multicomponent reactions.[12] Our group has been on a long-term project where iodine is being investigated as catalyst for several organic reactions.[13] In continuation towards these studies, we have recently demonstrated that iodine could be used efficiently for nucleophilic substitution reactions of aryl propargyl alcohols with C- and O-nucleophiles.[14] In this context, we disclose the nucleophilic substitution reactions of substituted benzyl alcohols (**1**) with O- (**2**) and C- (**3**) nucleophiles in the presence of catalytic amount of iodine (see Scheme 1).

Initially, as a preliminary example, diphenyl carbinol was treated with propargyl alcohol in the presence of 5 mol% of iodine at room temperature. Within 20 minutes, the starting material was completely consumed to produce a single product that was isolated and characterized as the propargylated diphenyl carbinol. Encouraged by this result, we proceeded further, investigating the scope and generality of this reaction. Thus, various other nucleophiles such as allyl alcohol **2b** (entry 2), 3-benzyloxypropan-1-ol (**2c**, entry 3), propargyl alcohol (**2a**, entries 1 and 4) were treated with benzylic alcohols and found to produce the corresponding O-nucleophilic substituted products in good yields (see Table 1).

When naphth-2-ol (**3a**, entries 6, 9, and 12), *p*-cresol (**3d**, entry 11), and resorcinol (**3c**, entries 8 and 15) were treated, the products obtained were only the C-nucleophilic products rather the O-nucleophilic products, also in the resulting products substitution was present only on electron-rich carbon site resulting in a single regioisomer as evidenced from spectral data.[15] For example, the regioisomer formed from the reaction of **1a** with **3a** was assumed to be product **5a**, inline with literature precedent having a melt-



R^1 = H, OH, OMe
R^2 = Ph, Me

NuH = naphth-2-ol, indole, resorcinol, anisole, *p*-cresol
R^3 = allyl, propargyl, 3-benzyloxypropyl

Scheme 1

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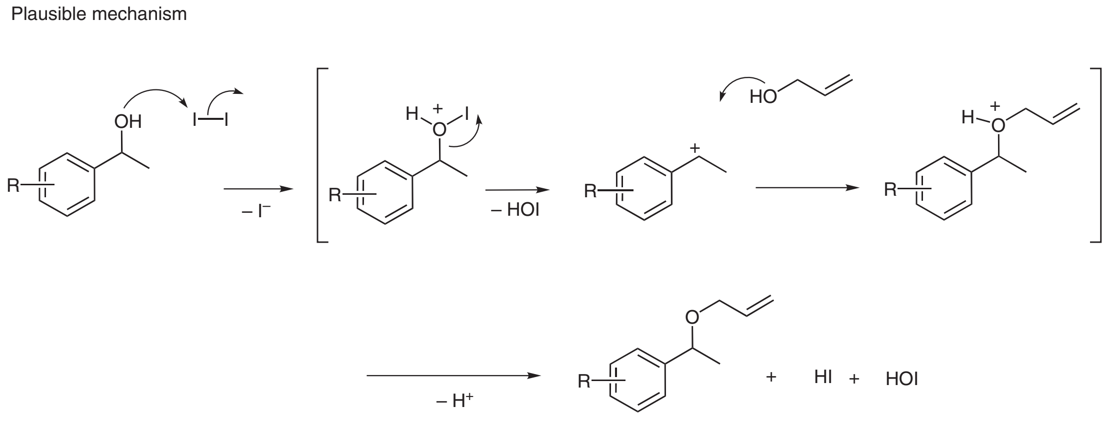
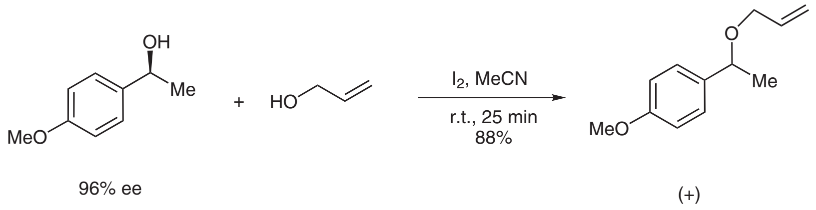


Scheme 2



Scheme 3

ing point of 110 °C in agreement with the known product.[16a] Similarly, anisole (**3e**, entry 14) responded well to give the C-nucleophilic product.[16b] The data clearly reveals that the diaryl carbinols react faster than aryl alkyl carbinols (see Table 1). This may be attributed towards the formation of a more stable carbocation intermediate, which would facilitate the reaction towards the product. A plausible mechanism is shown in Scheme 2.

The resulting HI may facilitate the generation of a carbocation from the activated aryl alcohols. And since the carbocation is involved in the process, the reaction may proceed through S_N1 mechanism. Benzyl alcohol, α-phenyl ethyl alcohol, and α-phenyl ethyl alcohols with electron-withdrawing groups (entries 5 and 16) did not respond to this protocol, but α-phenyl ethyl alcohols bearing electron-releasing groups responded well under the present protocol to give the corresponding products in good yields.

When a reaction of chiral 1-(4-methoxyphenyl)ethanol[17] with allyl alcohol was studied, racemic product was obtained (see Scheme 3). This example clearly reveals that S_N1 type of mechanism is involved in this reaction. During the course of these studies, we needed product **5a** for one of our academic programs in larger amounts (≥ 2 g). For this, a two-gram reaction was run and we noticed that within one hour complete consumption of the starting material occurred and resulted in 94% of the required product. Thus this protocol was also found to be amenable for large-scale synthesis.

Table 1 Iodine-Catalyzed Nucleophilic Substitution Reactions of Aryl Alcohols

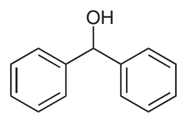
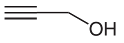
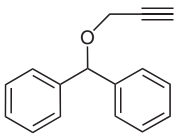
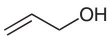
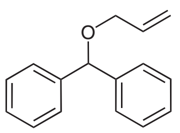
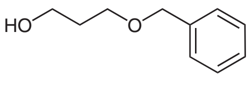
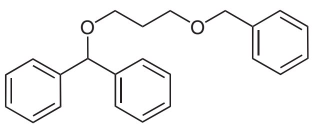
Entry	Aryl carbinol		Nucleophile		Product[a]		Time (min)	Yield (%)[b]
1	**1a**		**2a**		**4a**		15	95
2	**1a**		**2b**		**4b**		20	92
3	**1a**		**2c**		**4c**		20	92

Table 1 Iodine-Catalyzed Nucleophilic Substitution Reactions of Aryl Alcohols (continued)

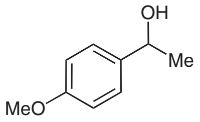
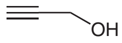
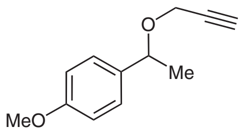
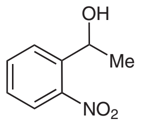
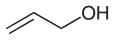
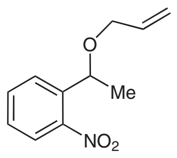
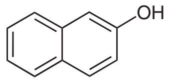
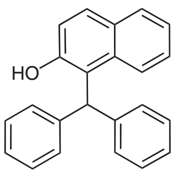
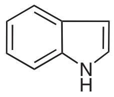
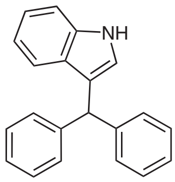
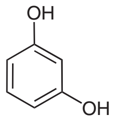
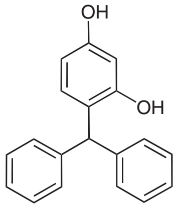
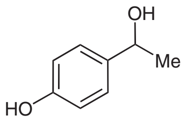
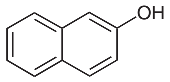
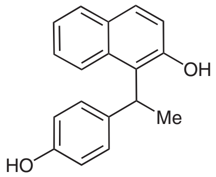
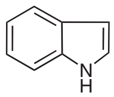
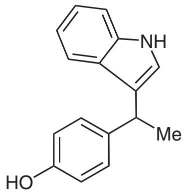
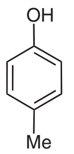
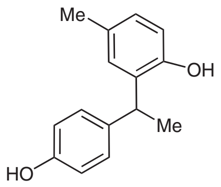
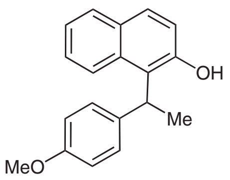
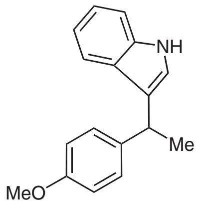
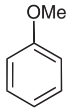
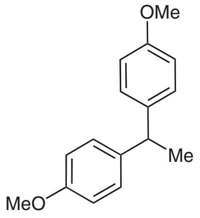
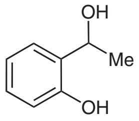
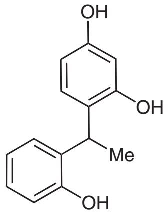
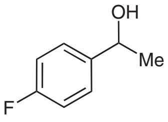
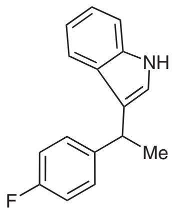
Entry	Aryl carbinol	Nucleophile	Product[a]	Time (min)	Yield (%)[b]
4	**1b** 	**2a** 	**4d** 	15	92
5	**1c** 	**2b** 	**4e** 	no reaction	
6	**1a**	**3a** 	**5a** 	20	96
7	**1a**	**3b** 	**5b** 	15	90
8	**1a**	**3c** 	**5c** 	25	93
9	**1d** 	**3a** 	**5d** 	20	95
10	**1d**	**3b** 	**5e** 	15	96
11	**1d**	**3d** 	**5f** 	30	90
12	**1b**	**3a**	**5g** 	15	95

Table 1 Iodine-Catalyzed Nucleophilic Substitution Reactions of Aryl Alcohols (continued)

Entry	Aryl carbinol		Nucleophile		Product[a]		Time (min)	Yield (%)[b]
13	**1b**		**3b**		**5h**		10	92
14	**1b**		**3e**		**5i**		20	90
15	**1e**		**3c**		**5j**		30	90
16	**1f**		**3b**		**5k**		no reaction	

[a] Products were characterized by MS, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

[b] Isolated yields after column chromatography.

In conclusion, an efficient benzylic substitution reaction with different nucleophiles has been demonstrated using elemental iodine. Reactions at ambient temperature with shorter reaction times and operationally simple procedures involving readily available inexpensive iodine make this procedure a very attractive and valid contribution to the existing procedures. Application of the present protocol for other nucleophilic substitution reactions are currently in progress and will be published in due course.

Acknowledgment

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(15) **General Experimental Procedure**

To a solution of the benzylic alcohol (1 mmol) and nucleophile (1.2 mmol) in MeCN (3 mL) was added I_2 (5 mol%) and the mixture was stirred at 0 °C to r.t. After completion of the reaction (monitored by TLC), the reaction mixture was washed with sat. aq $Na_2S_2O_3$ solution and extracted with EtOAc. The organic layer was separated and washed with brine, dried over anhyd Na_2SO_4, and the solvent was evaporated under vacuum. The resulting crude product was purified by silica gel column chromatography (EtOAc–hexane as the eluents).

Spectroscopic Data of Representative Examples

Compound **4c**: yellow liquid. IR (neat): 3061, 3029, 2924, 2859, 1952, 1601, 1493, 1452, 1094, 1028, 739, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (p, *J* = 6.1 Hz, 2 H), 3.53 (t, *J* = 6.1 Hz, 2 H), 3.58 (t, *J* = 6.2 Hz, 2 H), 4.44 (s, 2 H), 5.26 (s, 1 H), 7.13–7.30 (m, 15 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 138.1, 127.8, 127.1, 127.0, 126.8, 126.7, 126.5, 83.2, 72.5, 66.9, 65.5, 29.8. MS (EI): *m/z* = 355 [M^+ + Na]. HRMS: *m/z* calcd for $C_{23}H_{24}O_2Na$: 355.1673; found: 355.1683.

Compound **5a**: solid; mp 110–112 °C.[16a] IR (KBr): 3491, 3057, 2924, 1616, 1593, 1490, 1387, 1200, 1135, 812, 740, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, 1 H, *J* = 8.7 Hz), 7.76 (dd, 1 H, *J* = 7.8 Hz), 7.72 (d, 1 H, *J* = 8.7 Hz), 7.20–7.42 (m, 12 H), 7.06 (d, 1 H, *J* = 8.7 Hz), 6.41 (s, 1 H), 5.27–5.40 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.9, 141.8, 133.5, 129.8, 129.7, 129.3, 129.2, 128.9, 127.3, 126.9, 123.3, 123.0, 120.3, 119.9, 48.6. MS (EI): *m/z* = 310 [M^+]. Anal. Calcd (%) for $C_{23}H_{18}O$: C, 89.03; H, 5.80. Found: C, 89.4; H, 5.64.

Compound **5e**: white solid; mp 86–88 °C. IR (KBr): 3444, 2964, 3024, 2964, 2855, 2372, 1876, 1599, 1509, 1444, 1331, 1254, 1090, 823, 743 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO): δ = 1.62 (d, *J* = 7.0 Hz, 3 H), 4.20 (q, *J* = 7.0 Hz, 1 H), 6.62 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 2 H), 6.83 (dt, *J* = 1.1, 8.9 Hz, 2 H), 6.93–7.06 (m, 2 H), 7.21–7.30 (m, 1 H), 8.57 (br s, 1 H, NH), 10.13 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 136.4, 135.5, 126.7, 125.4, 119.7, 119.3, 117.9, 116.9, 113.8, 113.7, 110.0, 34.6, 21.4. MS (EI): *m/z* = 238 [M^+ + H]. HRMS: *m/z* calcd for $C_{16}H_{16}NO$: 238.1231; found: 238.1239.

(16) Only a single product was obtained in all these cases. For regioselectivity purpose, the analytical data of the products **5a** and **5i** were compared with the data obtained from the earlier literature and was found to be in accordance, see: (a) Mustafa, A.; Mansour, A. K. *J. Org. Chem.* **1960**, *25*, 2223. (b) Clennan, E. L.; Pan, G.-I. *Org. Lett.* **2003**, *5*, 4979.

(17) Optically active *p*-methoxy α-phenyl ethanol was obtained from the corresponding ketone following the standard reduction procedure using CBS catalyst; ee was calculated using chiral HPLC.