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Iodine-catalyzed C- and O-nucleophilic substitution reactions of aryl-propargyl methanols

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Abstract—Aryl propargylic methanols undergo C- and O-nucleophilic substitution reactions in the presence of a catalytic amount of iodine in short reaction times with good yields.

During recent years, the mild Lewis acid nature of molecular iodine with its high tolerance to air and moisture has been well exploited and received considerable attention as an inexpensive, non-toxic and readily available reagent/versatile catalyst for several organic transformations under mild conditions affording the products in excellent yields with high stereoselectivity.[1] Our group has disclosed iodine as an efficient reagent/catalyst for several organic transformations such as allylation of aza aromatics, allylation of cyclic allylic acetates,[2] cleavage of cyclic and acyclic ethers,[3] thiocyanation of aromatics and heteroaromatics,[4] synthesis of sugar acetylenes, allyl glycosides, glycosyl cyanides and glycosyl azides,[5] coupling of alkynylsilanes with acid chlorides,[6] 1,2-addition of trimethylsilyl cyanide to ketones[7] and [4+2] cycloaddition reactions of *O*-quinomethanes.[8] In continuation of our investigations on the catalytic properties of iodine as a cheap and ecofriendly reagent, herein, we disclose the C- and O-nucleophilic substitution reactions of aryl propargyl methanols.

Very recently, propargylic substitution reactions of activated and unactivated propargyl alcohols, propargyl acetates and propargyl esters with C-nucleophiles and heteroatom centred nucleophilies such as alcohols, thiols and amines have been well studied.[9] These reactions are generally achieved by activation of the acetylene moiety by cobalt complexation, the Nicholas reaction,[10] or by using metal complexes of rhenium,[11] ruthenium[12] or gold.[13] However, these reactions suffer from a high cost barrier. Recently, $FeCl_3$, $BiCl_3$[14] and the heterogenous catalyst montmorillonite clay[15] have been used for these reactions but which involve either high concentrations of the catalyst, multiple step reactions or heating conditions. Thus, an inexpensive reagent system with good selectivity for this transformation is highly desirable.

To our knowledge, there are no reports of iodine-catalyzed C- and O-nucleophilic substitution reactions of aryl propargylic methanols. In continuation of our studies with molecular iodine mediated reactions,[16] we reasoned that iodine might be used to effect the nucleophilic substitution reactions of aryl propargyl methanols. As a preliminary study, we treated 1,3-diphenyl propargyl alcohol with allyl alcohol in the presence of iodine (10 mol %) at room temperature in acetonitrile. Within 45 min complete consumption of the starting material was observed resulting in a multispot mixture. However, by running the reaction at lower temperature from −10 to room temperature, a single spot was observed. After work-up, the product was isolated and characterized as the *O*-allyl substituted product in good yield.

To determine the effectiveness of the catalyst, reactions were run with different concentrations of iodine (1 mol %, 5 mol %, 10 mol % and 20 mol %). The reaction progressed well at all concentrations, 5 mol % of iodine was found to be the best in terms of yields and duration. We next investigated the scope and generality of the reaction with other nucleophiles and found that

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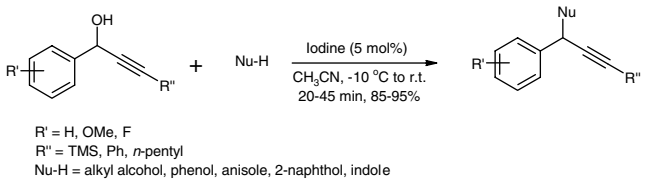
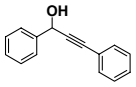
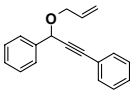
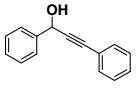
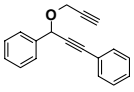
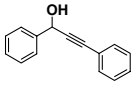
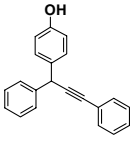
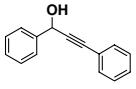
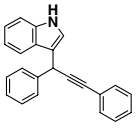
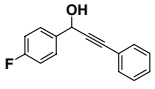
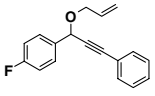
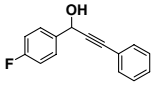
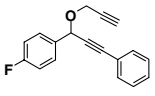
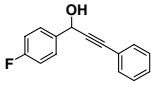
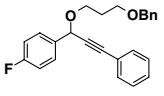
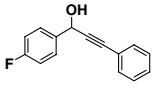
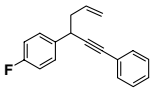
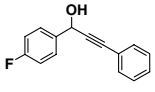
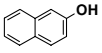
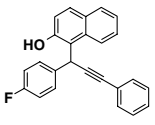
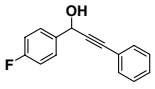
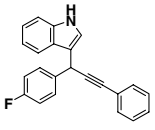
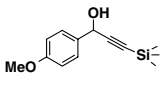
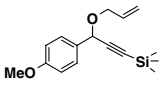


Scheme 1.

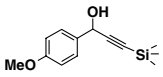
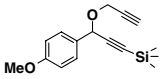
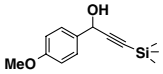
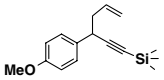
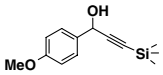
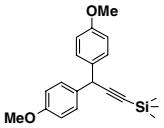
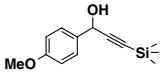
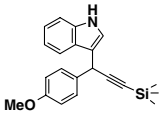
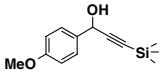
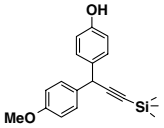
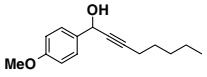
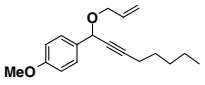
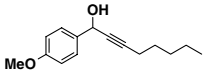
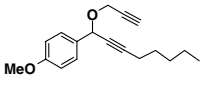
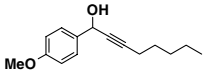
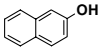
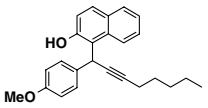
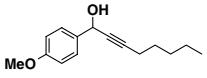
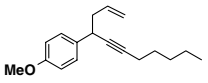
the reaction worked well and produced the expected products (see Scheme 1). It is assumed that the reaction proceeds by direct displacement of the hydroxy group with nucleophiles in an S_N2 fashion. Substitution reactions with benzene thiol, cyclopentylamine and benzylamine were studied but we observed only the recovery of starting materials. Interestingly, when phenol (entry 3), β-napthol (entries 9 and 19), anisole (entry 14) and

Table 1. Iodine-catalyzed C- and O-nucleophilic substitution reactions of aryl propargyl methanols

Entry	Alcohol a	Nucleophile b	Product[a] c	Time (min)	Yield[b] (%)
1				45	90
2				45	92
3				30	90
4				30	92
5				40	88
6				40	90
7				50	85
8				30	85
9				40	90
10				40	92
11				30	90

(*continued on next page*)

Table 1 (*continued*)

Entry	Alcohol a	Nucleophile b	Product[a] c	Time (min)	Yield[b] (%)
12				30	93
13				20	90
14				25	92
15				20	95
16				20	95
17				30	92
18				30	95
19				30	90
20				40	87

[a] All the products are characterized by IR, ^{1}H NMR and mass spectroscopy.
[b] Isolated and unoptimized yields.

indole (entries 4, 10 and 15) were treated with aryl propargyl methanols under the present reaction conditions, the corresponding C-nucleophilic substituted products were obtained in good yields (see Table 1). In all cases, substitution occurred at the carbon with greater electron density. During the course of our studies, Liu et al.[17] reported the iodine-catalyzed allylation and propargylation of indoles with allylic and propargylic acetates. By utilizing our procedure, product **4c** was obtained within 30 min.[18] This procedure also worked well with allyltrimethyl silane to give the C-nucleophilic substituted products (entries 8, 13 and 20). To further evaluate the nature of the substituents on this reaction, several propargyl alcohols with different aryl substituents were subjected to the present protocol.[19] Substrates with electron donating groups on the aromatic ring underwent the reaction much faster than unsubstituted aryl propargyl methanols.

In conclusion, we have demonstrated that elemental iodine acts as an excellent catalyst in mediating the C- and O-nucleophilic substitution reactions of aryl propargyl methanols. The use of an inexpensive reagent under mild reaction conditions, and with short reaction times and good yields makes this an attractive addition to existing procedures.

Acknowledgements

Three of us (D.C.B.), (P.S.) and (S.S.M.) thank CSIR, New Delhi, for financial assistance.

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16. For our other contributions with iodine see: (a) Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Krishna, A. D. *Tetrahedron Lett.* **2007**, *48*, 5243–5246; (b) Yadav, J. S.; Reddy, B. V. S.; Narayana Kumar, G. G. K. S.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205–2208; (c) Yadav, J. S.; Balanarsaiah, E.; Raghavendra, S.; Satyanarayana, M. *Tetrahedron Lett.* **2006**, *47*, 4921–4924; (d) Yadav, J. S.; Satyanarayana, M.; Raghavendra, S.; Balanarsaiah, E. *Tetrahedron Lett.* **2005**, *46*, 8745–8748.
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18. The same product was obtained in 3 h utilizing the acetate derivative of 1,3-diphenylpropargyl methanol in 69% yield by Liu et al.[17] The significant feature of our protocol is the direct use of aryl propargylic alcohol as the substrate.
19. *General experimental procedure*: To a solution of aryl propargyl methanol (1 mmol) and nucleophile (1.2 mmol) in acetonitrile (4 mL) was added iodine (5 mol %) at −10 °C and the mixture was stirred until completion of the reaction by allowing the reaction mixture to warm to room temperature. Work-up gave the crude product, which was purified by silica gel column chromatography (ethyl acetate/hexane as the eluents). Spectroscopic data for representative examples: **1c**: IR (neat): ν_{max} 2926, 2856, 1601, 1450, 1273, 1064, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.04–4.19 (m, 2H), 5.12–5.33 (m, 3H), 5.82–5.95 (m, 1H), 7.21–7.31 (m, 6H), 7.37–7.40, (m, 2H), 7.46–7.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 69.1, 71.0, 86.8, 87.5, 117.6, 122.5, 127.4, 128.1, 128.3, 129.4, 130.0, 131.6, 134.2, 138.6. LSMS: *m/z*: 271 (M^++23). HRMS for $C_{18}H_{16}ONa$: Calcd 271.1111; found, 271.1098. Compound **8c**: Yellowish liquid. IR (neat): ν_{max} 3447, 3074, 2926, 1600, 1508, 1226, 756, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.55 (t, $J = 7.0$ Hz, 2H), 3.86 (t, $J = 7.0$ Hz, 1H), 5.02–5.13 (m, 2H), 5.74–5.98 (m, 1H), 6.92–7.08 (m, 2H), 7.20–7.50 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.6, 46.2, 86.2, 89.04, 114.8, 115.2, 115.6, 123.3, 128.3, 128.5, 128.5, 131.7, 131.8, 131.9, 134.3, 134.6, 160.7, 164.0. ESIMS: 251 [M^++H]. HRMS for $C_{18}H_{16}F$ (M^++H): Calcd 251.1236; found, 251.1235. Compound **15c**: Yellow sticky liquid. IR (KBr): ν_{max} 3415, 3056, 2958, 2836, 2369, 2169, 1610, 1508, 1458, 1250, 1176, 1031, 844, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 9H), 3.68 (s, 3H), 5.07 (s, 1H), 6.71 (d, $J = 8.3$ Hz, 2H), 6.90–6.94 (m, 2H), 7.03 (t, $J = 8.3$ Hz, 1H), 7.15–7.24 (m, 3H), 7.37 (d, $J = 7.5$ Hz, 1H), 7.77 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.08, 35.0, 55.1, 87.0, 107.4, 111.1, 113.7, 116.6, 119.2, 119.5, 121.9, 122.4, 125.8, 128.7, 133.2, 136.6, 158.2.

ESIMS: 333 [M^+]. HRMS for $C_{21}H_{22}NOSi$: Calcd 332.1476; found, 332.1470. Compound **16c**: Pale yellow sticky liquid. IR (neat): ν_{max} 3415, 2957, 2927, 2855, 2376, 2169, 1608, 1508, 1459, 1248, 1174, 1034, 842, 761, 573 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 3.69 (s, 3H), 4.66 (br s, 1H, OH), 4.77 (s, 1H), 6.62 (d, $J = 8.3$ Hz, 2H), 6.71 (d, $J = 9.0$, 2H), 7.07 (d, $J = 8.3$ Hz, 2H),7.12 (d, $J = 8.3$ Hz,2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.0, 42.4, 55.2, 88.6, 107.2, 113.9, 115.3, 128.7, 128.9, 134.0, 134.2, 154.3, 158.4. ESIMS: 311 [M^++H]. HRMS for $C_{19}H_{23}O_2Si$ (M^++H): Calcd 311.1475; found, 311.1467.