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Amberlite IR-120H as an efficient and versatile solid phase catalyst for nucleophilic substitution of propargylic alcohols

Satheesh Gujarathi, Howard P. Hendrickson, Guangrong Zheng *

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

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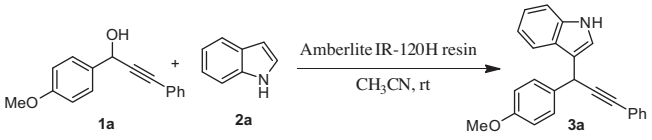
ABSTRACT

A highly efficient Amberlite IR-120H resin mediated nucleophilic substitution of the hydroxyl group of propargylic alcohols with a wide range of nucleophiles is reported. The reactions were achieved under very mild conditions in excellent yields.

A challenging yet important goal in organic synthesis is to maximize synthetic efficiency in transforming starting materials to the target molecules. Readily available starting materials and reagents, high yield, high selectivity, mild reaction conditions, and high atom economy are characteristics of an efficient synthetic method. Propargylic substitution reactions of activated or unactivated propargylic alcohols or propargylic esters with *C*-nucleophiles and heteroatom centered nucleophiles have recently been extensively explored. These reactions are generally achieved through activation of the acetylene moiety by forming cobalt complexes (Nicholas reaction)[1] or through the catalysis of rhenium,[2] ruthenium,[3] or gold[4] metal complexes. However, these reactions suffer from the high cost of reagents and catalysts. Alternative catalysts, including $FeCl_3$,[5] $BiCl_3$,[6] [bmim]PF_6/$Bi(NO_3)_3$,[7] PMA-silica gel,[8] I_2,[9] $InCl_3$,[10a] $InBr_3$,[10b] $Sc(OTf)_3$,[11] $Yb(OTf)_3$,[12] $Al(OTf)_3$,[13] $CeCl_3$,[14] Pd-Sn,[15] and PTSA,[16] have been introduced for these reactions; however, many of them involve either large amount of catalyst or limited to selective nucleophiles. Thus, highly efficient, inexpensive reaction systems with good selectivity for these transformations are still highly desirable.

Heterogeneous catalysis has played a central role in various organic transformations. Among heterogeneous catalysts, ion-exchange resins are widely used owing to their low cost, reusability, wide range of acid/base strength, ease of handling, environmental compatibility, and low toxicity. Moreover, they can be easily recovered from reaction mixtures by filtration and can be reused after activation or even without activation, making the process economically viable. Herein, we report a simple and straightforward method using Amberlite IR-120H ion-exchange resin as a catalyst for the nucleophilic substitution of propargylic alcohols with various nucleophiles in excellent yields under very mild reactions conditions.

Using 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (**1a**) and indole (**2a**) as model reactants, it was observed that the reaction proceeded smoothly in CH_3CN at room temperature in the presence of Amberlite IR-120H resin (Scheme 1). Amberlite IR-120H



Scheme 1. Substitution of the OH group in propargylic alcohol with indole.

Table 1
Optimization of the reaction conditions[a]

Entry	Amberlite IR-120H (mg/mmol)	Time[b] (min)	Yield[c] (%)
1	50	120	45
2	150	60	70
3	300	30	93

[a] All reactions were carried out with **1a** (1 mmol), and **2a** (1.2 mmol) in CH_3CN at rt.
[b] Reaction time before filtration; both 1 and 2 were incomplete.
[c] Isolated yield.

* Corresponding author. Tel.: +1 501 526 6787; fax: +1 501 526 5945.
E-mail address: gzheng@uams.edu (G. Zheng).

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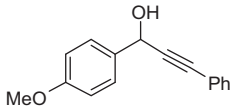
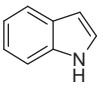
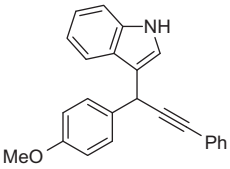
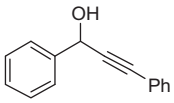
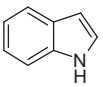
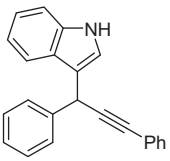
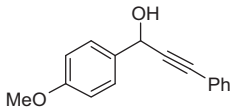
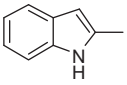
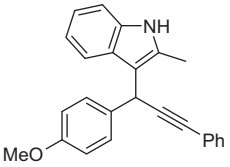
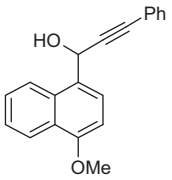
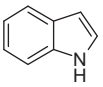
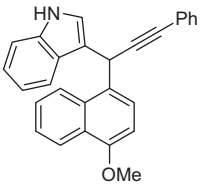
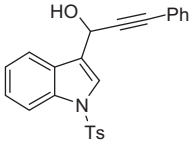
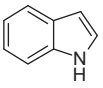
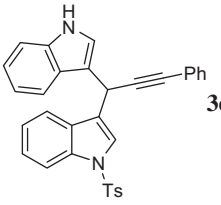
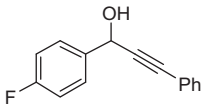
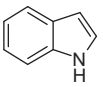
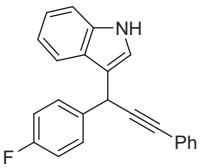
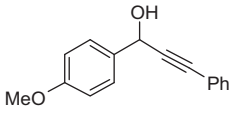
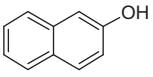
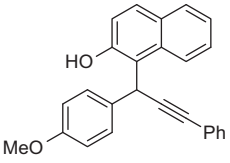
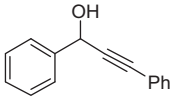
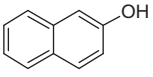
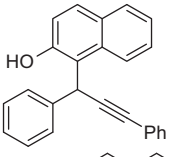
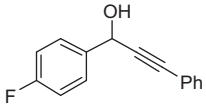
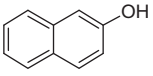
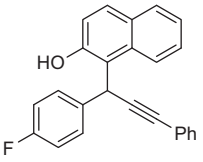
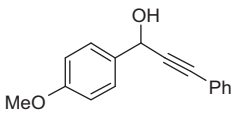
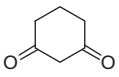
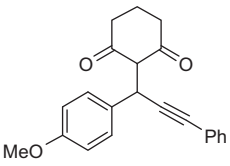
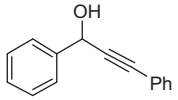
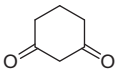
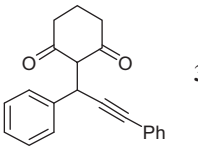
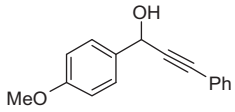
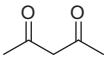
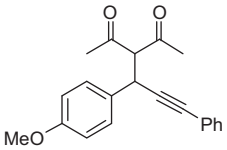
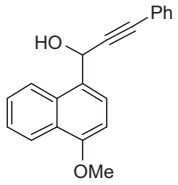
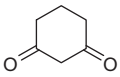
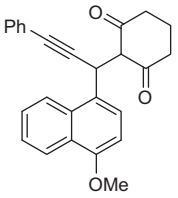
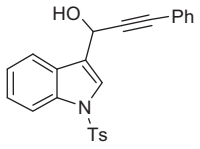
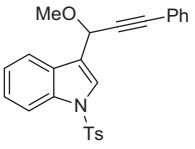
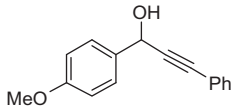
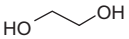
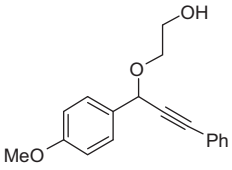
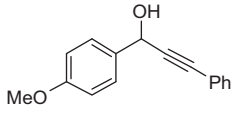
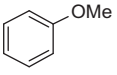
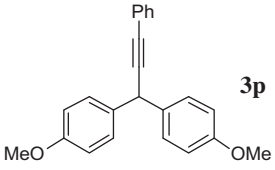
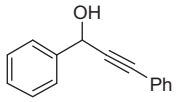
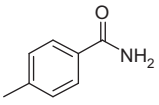
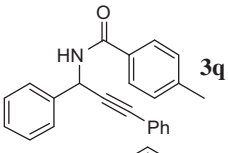
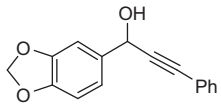
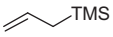
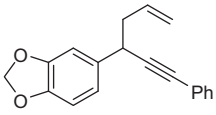
Table 2
Amberlite IR-120H resin promoted substitution of the hydroxyl group in propargylic alcohols with various nucleophiles[a]

Entry	Alcohol	Nucleophile	Product[b]	Time (min)[c]	Temperature (°C)	Yield (%)[d]
a			 **3a**	30	rt	93
b			 **3b**	30	60	87
c			 **3c**	30	rt	90
d			 **3d**	120	rt	87
e			 **3e**	90	rt	87
f			 **3f**	180	60	83
g			 **3g**	60	rt	93
h			 **3h**	90	60	90
i			 **3i**	180	60	90
j			 **3j**	120	rt	90

(*continued on next page*)

Table 2 (*continued*)

Entry	Alcohol	Nucleophile	Product[b]	Time (min)[c]	Temperature (°C)	Yield (%)[d]
k			 **3k**	120	60	87
l			 **3l**	150	rt	86
m			 **3m**	180	rt	90
n		MeOH	 **3n**	180	rt	90
o			 **3o**	180	rt	83
p			 **3p**	180	rt	87
q			 **3q**	180	60	90
r			 **3r**	180	60	87

[a] All reactions were carried out with alcohol/nucleophile in a molar ration of 1:1.2 in CH_3CN in the presence of 300 mg/mmol of Amberlite IR-120H.
[b] Products were characterized by ^1H NMR, ^{13}C NMR, and MS.
[c] Time required for complete consumption of propargylic alcohol (monitored by TLC and GC–MS).
[d] Isolated yield.

is a gel type, strongly acidic, cation exchange resin of the sulfonated polystyrene type. It has excellent physical, chemical, and thermal stability and has been used for various organic transformations.[17] The rate of the reaction is correlated with the amount of resin used. Various quantities of Amberlite IR-120H per mmol of **1a** (mg/mmol) were tested in the reaction (examples listed in Table 1); with 300 mg/mmol of resin, the reaction completed within 30 min at room temperature to give 3-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-1*H*-indole **3a** in 93% yield (Table 1, entry 3).

While the rate of reaction seemed slightly increased (suggested by TLC analysis) when increasing the amount of resin, the yield was decreased, possibly due to decomposition of **3a** and/or higher absorption of **3a** on the resin. On the other hand, no reaction was observed when Amberlite IR-120H was replaced by Amberlite CG-50 or Amberlite IRC-50, likely due to the decreased acidity of these resins.

The scope of the application of this reaction system was then investigated. Initially, a variety of propargylic alcohols were treated with indole (Table 2, entries b and d–f) or 2-methyl indole (Table 2, entry c).[18] When the *p*-MeO (entries a and c) on the phenyl ring at the benzylic position of the propargylic alcohol was removed (entry b) or replaced by an electron-withdrawing group (fluoro, entry f), elevated temperature (60 °C) was needed for completion of the reactions. Regardless of the reaction temperature, all reactions were in excellent yields (Table 2, entries b–f). A variety

of nucleophiles, including 2-naphthol, 1,3-cyclohexanedione, acetylacetone, methanol, ethylene glycol, anisole, amide, and allyltrimethylsilane, were then tested under these reaction conditions. Similarly, electron-donating *p*-MeO group on the phenyl ring at the benzylic position of the propargylic alcohol was found to have beneficial effects on reactivity compared to H atom and electron-withdrawing F atom on the same position (Table 2, entry g vs entries h and i; entry j vs entry k). Complete regioselectivity was observed with nucleophiles containing more than one electron-rich carbon (2-naphthol, 1,3-cyclohexanedione, acetylacetone, and anisole). In all cases, *C*-substitution was on the carbon with the highest electron density, that is, C-1 for 2-naphthol, C-2 for 1,3-cyclohexanedione and acetylacetone, and C-4 for anisole.

In summary, we have developed a novel, efficient, and general method for the direct nucleophilic substitution of the hydroxyl group of propargylic alcohols with various nucleophiles using Amberlite IR-120H resin as a catalyst. The method features short reaction times, mild reaction conditions, simplicity in operation, zero aqueous waste generation, complete regioselectivity, and a clean reaction profile. Moreover, the resin is inexpensive, stable, noncorrosive, easy to handle, and potentially reusable.

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18. *General experimental procedure:* to a stirred mixture of arylpropargy alcohol **1** (1 mmol) and nucleophile (1.2 mmol) was added Amberlite IR-120H resin (0.3 g) in acetonitrile (5 mL). The mixture was stirred at rt –60 °C (Table 1) for an appropriate time. When the reaction was complete (GC and TLC analyses), the mixture was filtered and evaporated to dryness in vacuo to yield the crude product, which was purified by silicagel column chromatography (EtOAc-hexane).
Spectral data for selected products: 3-(1-(4-methoxynaphthalen-1-yl)-3-phenylprop-2-ynyl)-1*H*-indole (**3d**): solid; mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (bt, 1H), 8.19 (bt, 1H), 7.97 (s, 1H), 7.64 (dd, J = 8.0, 16.0 Hz, 2H), 7.41–7.49 (m, 4H), 7.36 (d, J = 8.0 Hz, 1H), 7.26 (br s, 3H), 7.19 (t, J = 8.0 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.08 (s, 1H), 4.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 136.7, 131.7, 128.2, 128.1, 127.7, 126.5, 126.4, 126.1, 124.9, 124.0, 123.3, 122.6, 122.2, 119.8, 119.6, 116.6, 111.2, 103.3, 90.7, 55.5, 32.2 ppm; HRMS (ESI): m/z calcd for $C_{28}H_{20}NO$ [M−H] 386.1545; found 386.1563. 3-(1-(1*H*-indol-3-yl)-3-phenylprop-2-ynyl)-1-tosyl-1*H*-indole (**3e**): solid; mp: 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (br s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.49 (br s, 1H), 7.39–7.45 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.24–7.31 (m, 4H), 7.14–7.20 (m, 5H), 7.04 (t, J = 8.0 Hz, 1H), 5.59 (s, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 136.7, 135.7, 135.1, 131.7, 129.8, 129.7, 128.2, 128.0, 126.8, 125.9, 124.7, 124.3, 123.3, 123.1, 122.7, 122.3, 120.4, 119.5, 119.4, 114.2, 113.8, 111.4, 88.8, 82.7, 27.0, 21.5 ppm; HRMS (ESI): m/z calcd for $C_{32}H_{23}N_2O_2S$ [M−H] 499.1480; found 499.1496. 1-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)naphthalen-2-ol (**3g**): solid; mp: 62–64 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.21–7.45 (m, 9H), 7.13 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 7.3 Hz, 2H), 6.52 (s, 1H), 6.21 (s, 1H), 3.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 152.2, 132.3, 131.8, 131.5, 129.7, 129.6, 128.8, 128.4, 128.3, 128.2, 126.8, 123.3, 123.0, 122.6, 119.1, 117.7, 114.0, 88.7, 85.7, 55.2, 32.9 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{19}O_2$ [M−H] 363.1385; found 363.1381. 2-(1-(4-methoxynaphthalen-1-yl)-3-phenylprop-2-ynyl)cyclohexane-1,3-dione (**3m**): solid; mp: 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.0 Hz, 1H,), 8.05 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.38–7.59 (m, 5H), 7.24–7.33 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 3.99 (s, 3H), 2.39–2.60 (m, 4H), 1.84–2.12 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 174.2, 155.5, 131.8, 131.7, 128.4, 128.3, 127.1, 126.7, 126.5, 125.5, 123.8, 123.8, 122.6, 122.6, 115.3, 102.8, 88.5, 88.4, 55.5, 36.5, 29.5, 27.9, 20.4 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{21}O_3$ [M−H] 381.1490; found 381.1492. *N*-(1,3-diphenylprop-2-ynyl)-4-methylbenzamide (**3q**): solid; mp: 146–148 °C; ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.23–7.48 (m, 8H), 7.21 (d, J = 7.6 Hz, 2H), 6.73 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 142.4, 139.2, 131.9, 131.0, 129.3, 128.8, 128.6, 128.4, 128.2, 127.2, 122.5, 87.1, 85.0, 45.6, 21.5 ppm; HRMS (ESI): m/z calcd for $C_{23}H_{18}NO$ [M−H] 324.1389; found 324.1372.