Tetrahedron Letters 53 (2012) 1048–1050

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$Al(OTf)_3$: an efficient recyclable catalyst for direct nucleophilic substitution of the hydroxy group of propargylic alcohols with carbon- and heteroatom-centered nucleophiles to construct C–C, C–O, C–N and C–S bonds

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ARTICLE INFO

Article history:
Received 14 September 2011
Revised 6 December 2011
Accepted 16 December 2011
Available online 23 December 2011

Keywords:
Aluminum triflate
Propargylic alcohols
Nucleophiles
Regioselectivity

ABSTRACT

A general and highly efficient $Al(OTf)_3$-catalyzed methodology has been developed for the direct nucleophilic substitution of the hydroxy group in propargylic alcohols with a variety of carbon- and heteroatom-centered nucleophiles such as alcohols, aromatic compounds, amides, and thiols, leading to the construction of C–C, C–O, C–N and C–S bonds.

The substitution of the hydroxy group of an alcohol by a nucleophile is an important process in organic chemistry for the construction of C–C or carbon–heteroatom bonds.[1] Substitution of the hydroxy group of propargylic alcohols by nucleophiles, in particular, gives access to functionalized alkynes which can be readily converted into a variety of other functional groups.[2] As a result of the wide synthetic applicability associated with the alkyne functional group, the propargylic alcohol substitution reaction has played a major role in organic synthesis. In this regard, the most useful methodologies are based on transition metal,[3] Lewis[4] and Brønsted acid[5] catalyzed/mediated substitution reactions. Many of these and other methods[6] are, however, hampered by the cost and availability of the catalysts, excessive catalyst loading and/or limited nucleophile applicability. While a few catalyst systems ($FeCl_3$ in CH_3CN, $MoCl_5$ in CH_2Cl_2, and phosphomolybdic acid on silica) have been reported for propargylic alcohol substitution reactions in good yields,[7] none of these methods allow for C–C bond formation. In view of the synthetic importance of these propargylic synthons, the development of a general and convenient method for their synthesis is desired.

Metal triflates have received wide attention for their role as Lewis acids in a number of reactions.[8] Examples such as $Bi(OTf)_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$ in ionic liquids have been used successfully for the propargylation of arenes and the synthesis of propargylic ethers.[9] Ytterbium triflate catalyzed propargylations of carbon- and heteroatom-centered nucleophiles with propargylic alcohols were reported by Huang et al.,[10] whereas Noji et al.[11] disclosed novel lanthanoid, scandium, and hafnium triflate catalyzed direct substitutions of benzyl alcohols with nucleophiles. All of these, however, contain expensive metal ions. On the other hand, aluminum triflate [$Al(OTf)_3$], which has been utilized in various organic transformations,[12] not only contains a readily available cheap metal ion, but is also reusable and therefore represents a desirable catalyst from an environmental point of view. To the best of our knowledge, $Al(OTf)_3$-catalyzed direct nucleophilic substitution of propargylic hydroxy groups by nucleophiles has not been reported to date. In this Letter, we disclose our results on the $Al(OTf)_3$-catalyzed direct substitution of propargylic hydroxy groups with various aromatic and heteroatomic nucleophiles to afford the corresponding products in excellent yields (Table 1). Furthermore, water is the only side product from the reaction.

At first we investigated the $Al(OTf)_3$-catalyzed coupling reaction of diphenylpropargyl alcohol (**1a**) with benzyl alcohol (**2a**) as the nucleophile (Table 1, entry 1). We were pleased to find that 0.5 mol % of $Al(OTf)_3$ in acetonitrile at 60 °C produced the corresponding propargylic ether **3aa** in excellent yield.[13] Increased amounts of catalyst failed to improve the yield, while decreasing the amount of catalyst had a negative impact on the yield, so a catalyst concentration of 0.5 mol % was optimal. Extending the reaction to alcohols such as methanol (**2b**) and ethanol (**2c**) also led to excellent yields of ethers **3ab** and **3ac** (Table 1, entries 2 and 3). In all the cases, the reaction proceeded smoothly without taking any precautions to exclude moisture or air from the reaction mixture.

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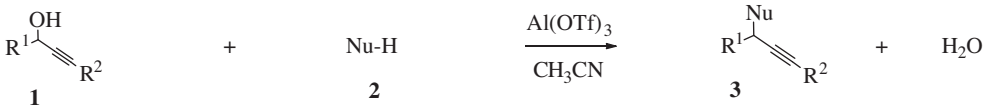
doi:10.1016/j.tetlet.2011.12.060

Table 1
Substitution of the hydroxy group in propargylic alcohols with various nucleophiles[a]



1a $R^1 = R^2 = Ph$
1b $R^1 = Ph$, $R^2 = nC_4H_9$
1c $R^1 = p\text{-}MeOC_6H_4$, $R^2 = Ph$
1d $R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$

2a $PhCH_2OH$
2b MeOH
2c EtOH
2d PhOH
2e PhOMe
2f thiophene
2g pyrrole
2h $PhCONH_2$
2i $PhSO_2NH_2$
2j $p\text{-}MeC_6H_4SO_2NH_2$
2k $p\text{-}NO_2C_6H_4NH_2$
2l PhSH
2m $PhCH_2SH$

Entry	Alcohol	NuH	Time (min)	Product[b]	Yield (%)
1	**1a**	**2a**	60	**3aa**[4a]	92
2	**1a**	**2b**	60	**3ab**[4a]	92[c]
3	**1a**	**2c**	80	**3ac**[4a]	90[c]
4	**1a**	**2d**	120	**3ad**[9]	92
5	**1a**	**2e**	120	**3ae**[4c]	92
6	**1a**	**2f**	40	**3af**[3i]	90[d]
7	**1a**	**2g**	30	**3ag**[9]	92[d]
8	**1a**	**2h**	100	**3ah**[4c]	85
9	**1a**	**2i**	390	**3ai**[5a]	89
10	**1a**	**2j**	180	**3aj**[3n]	95
11	**1a**	**2k**	180	**3ak**[9]	85[e]
12	**1a**	**2l**	150	**3al**[3d]	90
13	**1a**	**2m**	60	**3am**[6b]	93
14	**1b**	**2a**	260	**3ba**[6a]	90
15	**1b**	**2j**	220	**3bj**[3k]	89
16	**1c**	**2e**	30	**3ce**[6c]	93
17	**1c**	**2j**	120	**3cj**[6d]	94
18	**1d**	**2e**	150	**3de**[3n]	90
19	**1d**	**2j**	240	**3dj**	94

[a] Substrates in equimolar amounts, $Al(OTf)_3$ (0.5 mol %), CH_3CN, 60 °C unless specified differently.
[b] References to full analytical data for known compounds.
[c] 2.5 equiv of alcohol was required to achieve maximum conversion.
[d] Substrates in equimolar amounts, $Al(OTf)_3$ (0.5 mol %), CH_3CN, room temperature.
[e] Substrates in equimolar amounts, $Al(OTf)_3$ (2.5 mol %), CH_3CN, 80 °C.

When phenol (**2d**), anisole (**2e**), thiophene (**2f**), and pyrrole (**2g**) were used as nucleophiles, the corresponding C-substituted products were obtained in excellent yields (Table 1, entries 4–7). While a reaction temperature of 60 °C was required for acceptable rates in the case of anisole (**2e**) and phenol (**2d**), reactions with the more nucleophilic reagents, thiophene (**2f**) and pyrrole (**2g**), could be run at room temperature. For all these nucleophiles (**2d**–**2g**), substitution involved regioselective attack by the aromatic carbon with the highest electron density, that is, C-4 for phenol and anisole and C-2 for thiophene and pyrrole.

Subsequent extension of the reaction to include amides such as benzamide (**2h**), benzenesulfonamide (**2i**) and *p*-tolyl-sulfonamide (**2j**) led to the formation of C–N bonds with the corresponding products being obtained in excellent yields using the optimized reaction conditions (Table 1, entries 8–10). Surprisingly, the reaction of aniline with alkynol (**1a**) was unsuccessful. However, aromatic amines having electron-withdrawing substituents, such as 4-nitroaniline (**2k**), could be reacted with the alkynol in the presence of a slight excess of the catalyst (2.5 mol %) to give the secondary propargylic amine (**3ak**) in high yield (Table 1, entry 11). Finally, the reactions of thiophenol (**2l**) and benzyl mercaptan (**2m**) with propargylic alcohol (**1a**) gave the corresponding thioethers **3al** and **3am** in excellent yields through the application of the previously optimized reaction conditions (Table 1, entries 12 and 13).

Electron-donating substituents at the *para* position of an aromatic ring located at the propargylic position were found to enhance the reactivity, thus increasing the rate of the reaction (Table 1, entries 16 and 17 vs 5 and 10, respectively), while electron-withdrawing substituents in the same position slowed down the substitution process (Table 1, entries 18 and 19 vs 5 and 10, respectively). When the terminal aromatic ring of the alkyne was replaced by an aliphatic group as in **1b**, excellent product yields could still be obtained at acceptable rates (Table 1, entries 14 and 15).

Since the reusability of catalysts is an important factor from both an economical and environmental point of view, this topic has attracted wide attention in recent years. To check this aspect of the $Al(OTf)_3$ catalyst, it was recovered after completion of some of the reactions (TLC) by adding a mixture of ethyl acetate and water (1:1, v/v; 10 mL) to the reaction mixture and stirring for five minutes. The water layer was subsequently concentrated in vacuo at an elevated temperature[14] and the catalyst reused. The recovered catalyst could be successfully recycled 3 times in this way with only minimal loss of efficiency (Table 2).

In summary, $Al(OTf)_3$ was found to be an effective and recyclable Lewis acid catalyst in an improved, general and efficient method for the direct substitution of the hydroxy group of propargylic

Table 2
Reusability of the $Al(OTf)_3$ catalyst

Entry	Product	1st Cycle	2nd Cycle	3rd Cycle
1	**3ae**	92	92	90
2	**3ak**	85	85	84

alcohols with carbon- and heteroatom-centered nucleophiles such as alcohols, aromatic compounds, amides, amines, and thiols, leading to the construction of C–C, C–O, C–N and C–S bonds. The corresponding propargylic products were obtained in high yields with complete regioselectivity.

Acknowledgment

Financial support by SASOL is gratefully acknowledged.

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13. $Al(OTf)_3$ (0.5 mol %) was added to the propargyl alcohol (1 mmol) and the nucleophile (1 mmol, 1 equiv) in CH_3CN (2.5 mL) and the mixture heated to 60 °C for the time indicated in Table 1. After completion of the reaction (TLC), the solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel (EtOAc:hexane 5:95, v/v) to afford the pure product. The physical data of known compounds were identical to those published (see references in Table 1).
{[(1-Phenyl-2-heptyn-1-yl)oxy]methyl}-benzene **3ba**[6a]: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59–7.49 (m, 2H), 7.47–7.29 (m, 8H), 5.24 (s, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 2.37–2.31 (m, 2H), 1.61–1.55 (m, 2H), 1.50–1.45 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 138.1, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 88.9, 77.8, 70.8, 69.8, 30.8, 22.1, 18.7, 13.7.
N-[1-(4-Chlorophenyl)-3-phenyl-2-propyn-1-yl]-4-methylbenzene-sulfonamide **3dj**: White solid; mp 199–200 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.5 Hz, 3H), 7.29–7.23 (m, 4H), 7.13(d, J = 7.3 Hz, 2H), 5.53 (d, J = 9.2 Hz, 1H), 5.06 (d, J = 9.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.78, 137.13, 135.95, 134.43, 131.57, 129.64, 128.84, 128.78, 128.19, 127.52, 121.68, 87.02, 84.88, 49.22, 21.45; HRMS (ES+) m/z calcd for $C_{22}H_{18}NO_2NaSCl$ $[M+23]^+$ 418.0644, found 418.0641.
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