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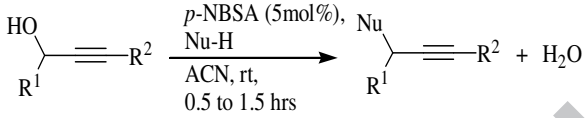

R^1 = aryl, alkyl, heterocycle
R^2 = aryl
Nu-H = nucleophile

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Nucleophilic substitution of propargyl alcohols with aliphatic alcohols, aliphatic amines and heterocycles catalyzed by 4-nitrobenzenesulfonic acid: A scalable and metal-free process

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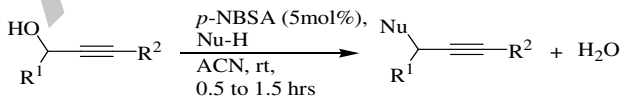
ABSTRACT

It is aimed to provide a cost effective *p*-NBSA catalyzed nucleophilic substitution of propargyl alcohols with alcohols, amines and heterocycles, without employing corrosive and costly metal catalysts, toxic solvents and column chromatography for purification. A systematic study of C-C, C-N and C-O bond formation and efficacy of the scalability have also been confirmed.

Bond forming reactions are most widely attempted transformations in organic synthesis. Formations of carbon-carbon and carbon-heteroatom bonds, in particular C-N and C-O, have received much focus as these linkages are constituent of numerous bioactive molecules,[1] pharmaceutical targets[2] and materials. These transformations often require transition metal catalysts[3] facing severe limitations as they are expensive and also generate toxic metal waste.[4] As a consequence, low cost and metal-free methods have received great interest in recent years.

Propargyl alcohol is an important moiety which has been routinely used as a scaffold for the synthesis of various heterocyclic compounds[5] of biological interest. Furthermore, it has been used as a potential source for carbon dioxide fixation[6] and also a valuable source for the synthesis of allene[7] derivatives. In particular, the hydroxyl group in the substituted propargyl alcohols can act as a good leaving group and can be displaced by various nucleophiles (Scheme 1).



R^1 = aryl, alkyl, heterocycle
R^2 = aryl
Nu-H = nucleophile

Scheme 1: Nucleophilic substitution of propargyl alcohols

Metal catalyzed[8] nucleophilic substitutions of hydroxyl group in substituted propargyl alcohols were previously reported, and in the recent years, metal chlorides ($FeCl_3$, $BiCl_3$, $InCl_3$ and $TiCl_4$) [9-10] have been used as catalysts. Yang *et al.* used titanocene dichloride for C-C bond formation.[11] $Sc(OTf)_3$ has been used for propargylation of indoles at 3-postion in dichloroethane (DCE)[12] solvent at 80°C and also in nitromethane[13] solvent at 60°C. The use of $Al(OTf)_3$[14] and $FeCl_3$[15] for such a C-C bond forming reaction is also reported. In contrast to C-O bond formation, C-N[16] bond forming reaction of a propargyl alcohol with an amine[17] is very limited. Almost all these reported synthetic methods have used either costly or corrosive catalysts or toxic solvents (DCE and nitro methane) at reflux temperature (40 to 80°C), proving a major drawback in commercial aspects. In general, the pharma industry prefers to avoid where possible the use of metal catalysts because of their costs and toxicity. Furthermore, in industrial scales, reactions under harsh conditions and the product purification through traditional column chromatography are not desired due to high cost associated with them. This urges an economically viable approach to synthesize propargyl derivatives whilst avoiding the undesirable elements that are corrosive metal catalysts and toxic solvents at reflux temperatures.

In this context, the target of this research is to achieve nucleophilic substitution of hydroxyl group in substituted propargyl alcohols with nucleophiles such as aliphatic alcohols, aliphatic amines and heterocycles by introducing a protic acid such as 4-nitrobenzenesulfonic acid (*p*-NBSA) a catalyst; this reagent is cheap and commercially available and also C-C, C-N and C-O bond forming reactions using catalytic protic acids at room temperature are not previously reported. An added advantage of this scalable process is easy purification without the aid of traditional column chromatography. Besides, this work does not include any costly or corrosive catalysts and toxic solvents.

In order to find out the effectiveness of protic acid catalysts, seven protic acids in acetonitrile (ACN), tetrahydrofuran (THF) and dichloromethane (DCM) solvents were screened. The details are listed in Table 1. Aliphatic sulfonic acid catalysts used in ACN led to charring of the reaction mass with below average yield (Table 1; Entries 3-4). With regard to aromatic sulfonic acids, the use of *p*-toluenesulfonic acid (*p*-TSA) with 1,3-diphenyl-prop-2-yn-1-ol (**1a**) offered inconsistent result while benzenesulfonic acid (BSA) resulted in a slight increase in yield (Table 1; Entry 5). The results also confirm that 5 mol% of 4-nitrobenzenesulfonic acid in ACN provided very good yields with the stated nucleophiles, methanol (Entry 7), allyl amine (Entry 10) and furan (Entry 11). The experimental condition in Table 1, entry 7 was adjudged the optimum reaction condition. The reactions involving C-C, C-N and C-O bond formations in Table 2 were performed under the optimum reaction condition.[18]

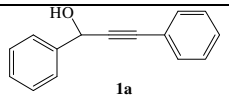
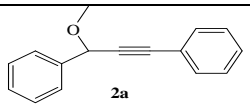
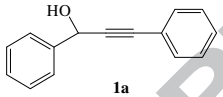
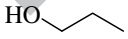
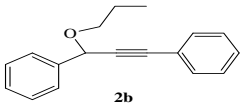
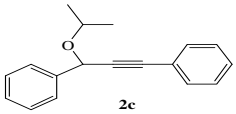
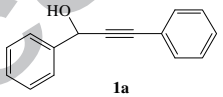
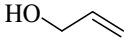
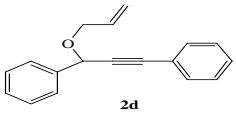
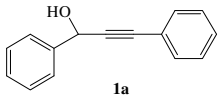
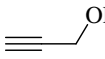
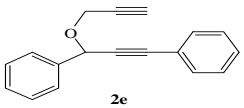
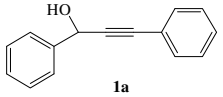
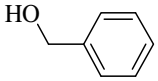
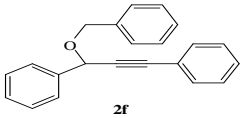
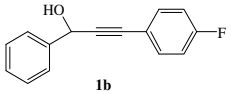
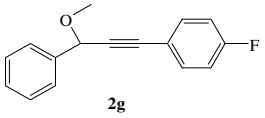
Table 1: Optimization of reaction conditions with **1a**

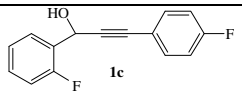
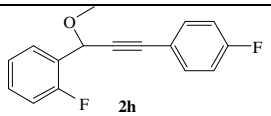
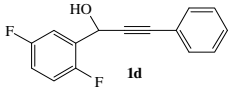
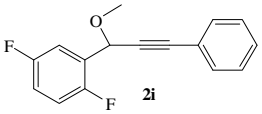
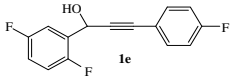
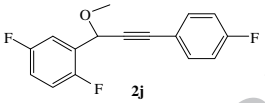
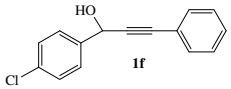
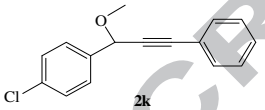
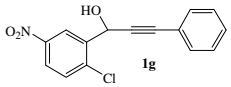
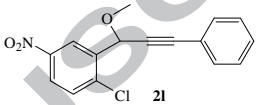
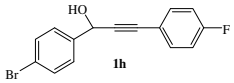
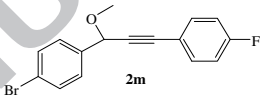
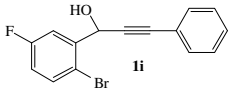
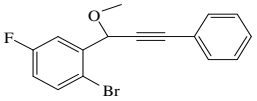
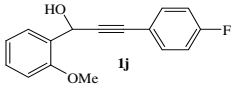
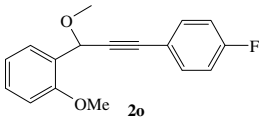
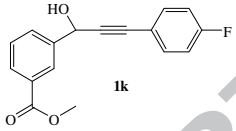
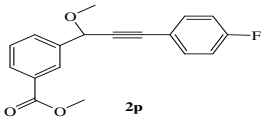
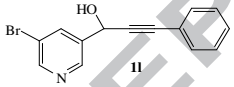
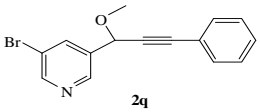
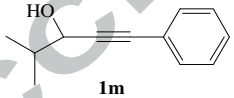
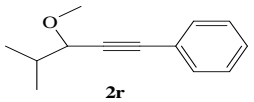
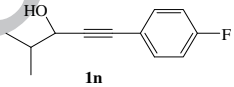
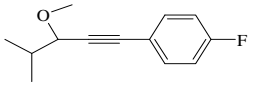
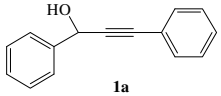
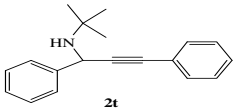
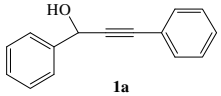
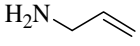
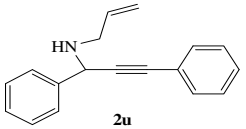
Entry	Solvent	Nu-H/ Eq.	Catalyst / mol %	Time	% yield
1	ACN	CH_3OH / 1.2	CH_3COOH / 10	2.0 h	0
2	ACN	CH_3OH / 1.2	CF_3COOH / 10	2.0 h	23
3	ACN	CH_3OH / 1.2	CH_3SO_3H / 10	0.5 h	35
4	ACN	CH_3OH / 1.2	CF_3SO_3H / 10	0.5 h	54
5	ACN	CH_3OH / 1.2	$C_6H_5SO_3H$ / 10	0.5 h	72
6	ACN	CH_3OH / 1.2	*p*-TSA / 10	0.5 h	52
7	ACN	CH_3OH / 1.2	*p*-NBSA / 5	0.5 h	89
8	THF	CH_3OH / 1.2	*p*-NBSA / 5	2.0 h	45
9	DCM	CH_3OH / 1.2	*p*-NBSA / 5	0.5 h	52
10	ACN	Allyl amine / 1.2	*p*-NBSA / 5	0.5 h	92
11	ACN	Furan / 1.2	*p*-NBSA / 5	0.5 h	93

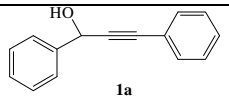
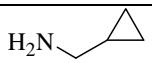
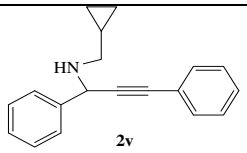
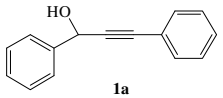
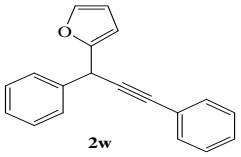
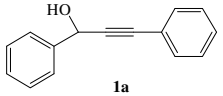
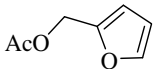
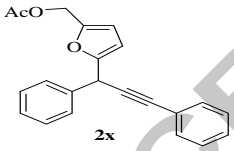
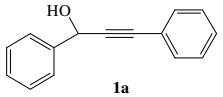
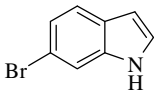
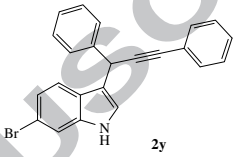
[a] Nu-H: nucleophile, Eq.: Equivalent. Reaction condition: room temperature (rt)

Considering the process involving carbon-oxygen bond formation (shown in Table 2), 1,3-diphenyl-prop-2-yn-1-ol (**1a**) was treated with both primary and secondary alcohols, which gave excellent yields of the corresponding products containing alkynic linkage (Table 2; Entries 1-3). Similar trials with allyl and propargyl alcohols also afforded 88% of **2d** and 85% of **2e** (Table 2; Entries 4-5), respectively, whereas benzyl alcohol yielded 79% of **2f** (Table 2; Entry 6).

Table 2: Nucleophilic substitution of propargyl alcohols with nucleophiles

Entry	Substrate	Nucleophile	Time	Product	% yield
1	 **1a**	CH_3OH	0.5 h	 **2a**	89
2	 **1a**		0.5 h	 **2b**	90
3	 **1a**		0.5 h	 **2c**	92
4	 **1a**		0.5 h	 **2d**	88
5	 **1a**		0.5 h	 **2e**	85
6	 **1a**		0.5 h	 **2f**	79
7	 **1b**	CH_3OH	0.5 h	 **2g**	82

Entry	Substrate	Nucleophile	Time	Product	% yield
8	 **1c**	CH_3OH	0.5 h	 **2h**	82
9	 **1d**	CH_3OH	0.5 h	 **2i**	83
10	 **1e**	CH_3OH	0.5 h	 **2j**	81
11	 **1f**	CH_3OH	0.5 h	 **2k**	85
12	 **1g**	CH_3OH	0.5 h	 **2l**	86
13	 **1h**	CH_3OH	0.5 h	 **2m**	80
14	 **1i**	CH_3OH	0.5 h	 **2n**	87
15	 **1j**	CH_3OH	0.5 h	 **2o**	89
16	 **1k**	CH_3OH	0.5 h	 **2p**	94
17	 **1l**	CH_3OH	1.5 h	 **2q**	84
18	 **1m**	CH_3OH	1.0 h	 **2r**	81
19	 **1n**	CH_3OH	1.0 h	 **2s**	84
20	 **1a**		0.5 h	 **2t**	81
21	 **1a**		0.5 h	 **2u**	92

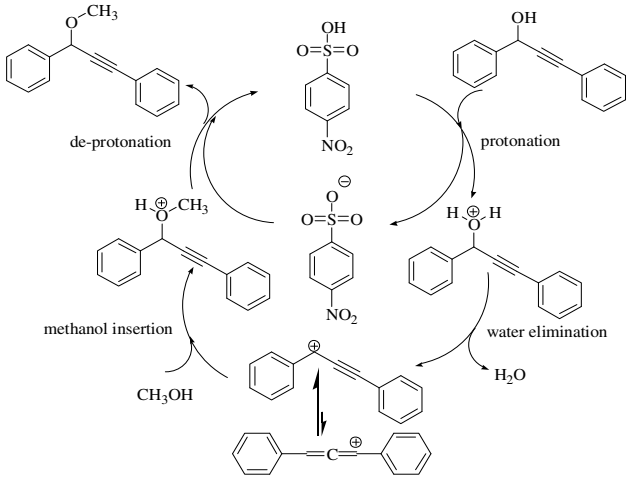
Entry	Substrate	Nucleophile	Time	Product	% yield
22	 **1a**		0.5 h	 **2v**	86
23	 **1a**		0.5 h	 **2w**	93
24	 **1a**		0.5 h	 **2x**	90
25	 **1a**		0.5 h	 **2y**	89

*Reaction condition: Substrate (1 mmol), Nu-H (1.2 mmol) and *p*-NBSA (5 mol %) in ACN at room temperature (rt).

Since yields in this category involving **1a** are exceptional, trials with thirteen substituted internal propargyl alcohols (**1b-1n**) were carried out. The reactions of methanol with propargyl alcohols, **1b** and **1c**, resulted in very good yields of the expected products (Table 2; Entries 7, 8). Methanol reacted separately with 1-(2,5-difluoro-phenyl)-3-phenyl-prop-2-yn-1-ol (**1d**) and 1-(2,5-difluoro-phenyl)-3-(4-fluoro-phenyl)-prop-2-yn-1-ol (**1e**) producing 83% of **2i** (Table 2; Entry 9) and 81% of **2j** (Table 2; Entry 10), respectively. **1f** and **1g**, carrying electron withdrawing (Cl, NO_2) groups, offered very good yields of **2k** (Table 2; Entry 11) and **2l** (Table 2; Entry 12), respectively. Also, both ortho (**1i**) and para (**1h**) substituted bromobenzene propargyl alcohols (Table 2; Entries 14, 13) afforded very good yields. The electron donating group carrying, **1j** (Table 2; Entry 15) gave 89% of **2o**. **1k,** obtained by esterification of 3-formyl-benzoic acid with methanol and subsequent treatment of the resulting ester with 4-fluorophenyl acetylene in presence of *n*-BuLi at < -70°C, was treated with methanol (Table 2; Entry 16) to get superior yield of **2p**. Furthermore, 1-(5-bromo-pyridin-3-yl)-3-phenyl-prop-2-yn-1-ol (**1l**) was successfully reacted with methanol to obtain very good yield of **2q** (Table 2; Entry 17). Thereafter, alkyl aryl substituted internal propargyl alcohols, i.e., 4-methyl-1-phenyl-pent-1-yn-3-ol (**1m**) and 1-(4-fluoro-phenyl)-4-methyl-pent-1-yn-3-ol (**1n**), were treated with methanol to obtain 81% of **2r** (Table 2; Entry 18) and 84% of **2s** (Table 2; Entry 19), respectively. These results clearly highlight that the proposed synthetic route is much productive regarding the C-O bond formation.

Three reactions were carried out with 1,3-diphenyl-prop-2-yn-1-ol (**1a**) as the substrate to explore the carbon-nitrogen[19] bond formation using both primary and secondary amines as nucleophiles. The first reaction with tert-butyl amine under optimum reaction condition produced 81% of the desired product (Table 2; Entry 20). The second reaction with allyl amine and third reaction with cyclopropyl-methyl amine yielded 92% of **2u** (Table 2; Entry 21) and 86% of **2v**, respectively (Table 2; Entry 22).

Finally, the carbon-carbon[20] bond formation was first tested with furan[21] as nucleophile. Although furan has two active centers i.e., 2- and 5-positions, its reaction with 1,3-diphenyl-prop-2-yn-1-ol (**1a**) resulted in selective monopropargylation (Table 2; Entry 23). The treatment of the 2-substituted furan, i.e., acetic acid furan-2-ylmethyl ester with **1a** afforded an excellent yield of acetic acid 5-(1,3-diphenyl-prop-2-ynyl)-furan-2-ylmethyl ester (**2x**) (Table 2; Entry 24). In addition, 6-bromoindole on treatment with **1a**, yielded 89% of 6-bromo-3-(1,3-diphenyl-prop-2-ynyl)-1H-indole (**2y**) (Table 2; Entry 25). As with C-O bond formation, the reactions involving C-N and C-C bond formation, through the suggested synthetic route, also offered exceptional yields.



Scheme 2: proposed reaction mechanism

In the feasible reaction mechanism proposed in Scheme 2, first, the hydroxyl group of 1,3-diphenyl-prop-2-yn-1-ol is protonated by *p*-NBSA. Subsequently water is eliminated to form secondary carbocation, which may be in equilibrium with allene carbocation (not observed). Afterwards, CH_3OH substituted into the secondary carbocation undergoes de-protonation to form propargyl ether. The eliminated proton is captured by sulfonium anion to form *p*-NBSA. Thus the reaction proceeds by S_N1 type mechanism. Use of a homochiral alcohol on the substrate would

give rise to an achiral ether following this S_N1 reaction mechanism.

The scalability of the substitution process was tested on gram scale in the cases of six moieties, **2d, 2e, 2o, 2u, 2x** and **2y** as presented in Table 3.

Table 3: Scalability of this process was tested in six compounds

Entry	Substrate / Quantity (g)	Product / Quantity (g)	Yield (%)
1	**1a** / 1.2	**2d** / 1.26	88
2	**1a** / 1.5	**2e** / 1.51	85
3	**1j** / 1.1	**2o** / 1.03	89
4	**1a** / 2.0	**2u** / 2.19	92
5	**1a** / 1.0	**2x** / 1.43	90
6	**1a** / 1.5	**2y** / 2.47	89

*Reaction condition: Substrate (1 mol), Nu-H (1.2 mol) and *p*-NBSA (5 mol %) in ACN (10 volume) at room temperature (rt).

In conclusion, we have found a metal-free economically viable and scalable new synthetic protocol for making a variety of compounds containing linkages C-C, C-N and C-O by catalytic 4-nitrobenzenesulfonic acid assisted nucleophilic substitution of substituted propargyl alcohols with aliphatic alcohols, aliphatic amines and heterocycles. Most importantly, this method does not employ any costly or corrosive metal catalysts and toxic solvents, and also avoids the traditional column chromatographic purification. The results confirm that the product yields are exceptional in all stated C-C, C-N and C-O bond forming reactions. Furthermore, this synthetic route makes it possible for widespread applications in synthetic chemistry, particularly in the formations of C-C, C-N and C-O bonds, as these linkages are constituent of numerous bioactive molecules, pharmaceutical targets and materials.

Supplementary data

The general synthetic procedure and the details of NMR and Mass spectra, associated with this article, are given in the supplementary data, available in the online version.

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18. Procedure for nucleophilic substitution of propargyl alcohols with nucleophiles

    A solution of substituted propargyl alcohol (1 mmol) and nucleophile (1.20 mmol) in acetonitrile (5 mL) was taken in round bottom flask (RBF) under nitrogen atmosphere and then *p*-NBSA (5 mol %) added at room temperature (rt). The reaction mixture was stirred at the same temperature and the progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was quenched by 10% of aq. $NaHCO_3$ solution, extracted with ethyl acetate, further the combined ethyl acetate layer was washed using brine solution. The ethyl acetate layer was dried over Na_2SO_4, filtered and then filtrate was treated with silica gel (2grams) for 30 minutes. Finally, the silica gel was filtered off and the filtrate was concentrated under vacuum to obtain the desired product.
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