Heteropoly Acid-catalyzed Direct Substitution of 2-Propynyl Alcohols with Sulfonamides

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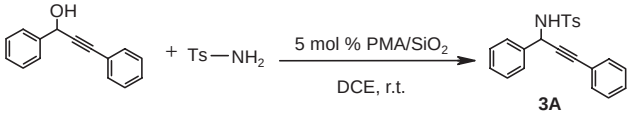
Direct substitution of the hydroxy group in 2-propynyl alcohols with sulfonamides has been achieved using 5 mol % of phosphomolybdic acid supported on silica gel (PMA/SiO_2) under mild reaction conditions to produce 2-propynyl amides in excellent yields and with high selectivity.

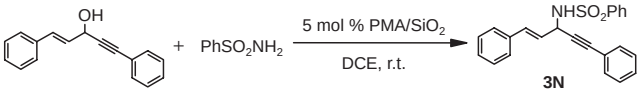
Aryl amines are found in a number of drug molecules such as cetirizine hydrochloride (histamine H_1-receptor), SNC80 (an opioid receptor agonist) and sertraline (anti-depressant).[1,2] The nucleophilic substitution of alcohols by amines is one of the direct and most important methods for carbon–nitrogen bond formation. However, the catalytic activation of alcohols is difficult due to the poor leaving ability of the hydroxy group. Consequently, hydroxy groups are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates, or related compounds.[3] However, such processes inevitably produce stoichiometric amounts of salt waste and also substitution with halides requires a stoichiometric amount of base which limits their use in large scale synthesis. Therefore, the development of catalytic methods for the synthesis of amines continues to be a challenging and active area of research.[4,5] However, little has been explored on nucleophilic substitution of 2-propynyl alcohols with amides.[6,7] In most cases, either a high reaction temperature or a promoter is required to enhance the leaving ability of the hydroxy group. Thus, the direct catalytic substitution of alcohols with amides using an efficient, cost-effective, and recyclable catalyst is highly desirable.

Recently, the use of heteropoly acids, HPAs, as environmentally friendly and economically viable solid acids, is increasing continuously owing to their ease of handling, high catalytic activities, and reactivities.[8] These compounds possess unique properties, such as well-defined structure, Brønsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc.[9] In view of green chemistry, the substitution of harmful liquid acids by reusable solid HPAs as catalysts in organic synthesis is the most promising application of these acids.[10] Among them, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is one of the less expensive and commercially available catalysts.[11]

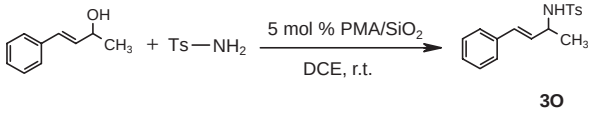
In continuation of our efforts to explore the synthetic utility of phosphomolybdic acid supported on silica gel ($PMA–SiO_2$),[12] we herein report a direct and efficient nucleophilic substitution of 2-propynyl alcohols with sulfonamides. Initially, we attempted the amidation of 1,3-diphenyl-2-propyn-1-ol (**1**) with $TsNH_2$ (**2**) in the presence of 5 mol % of PMA/SiO_2. The reaction went to completion at room temperature over 6.0 h to give the product, *N*-(1,3-diphenyl-2-propynyl)-4-methyl-1-benzenesulfonamide (**3A**) in 86% yield (Scheme 1).



Scheme 1.



Scheme 2.



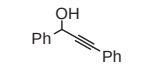
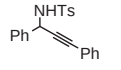
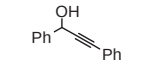
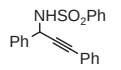
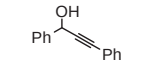
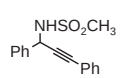
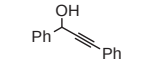
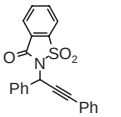
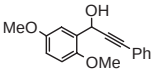
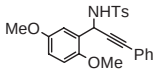
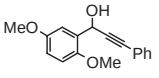
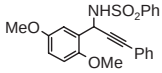
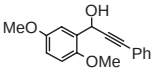
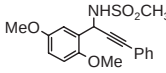
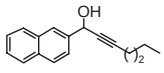
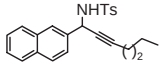
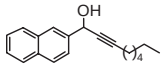
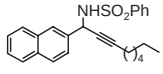
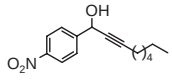
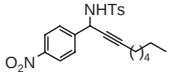
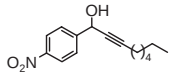
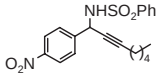
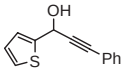
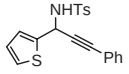
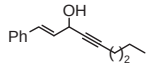
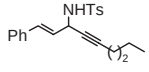
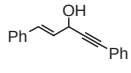
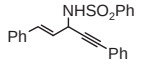
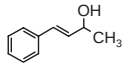
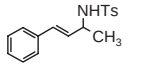
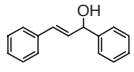
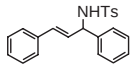
Scheme 3.

This remarkable catalytic activity of PMA/SiO_2 provided the incentive for further study of reactions with different 2-propynyl alcohols. Interestingly, various 2-propynyl alcohols such as 1-(2,5-dimethoxyphenyl)-3-phenyl-2-propyn-1-ol, 1-(2-naphthyl)-2-nonyn-1-ol, 1-(4-nitrophenyl)-2-nonyn-1-ol, and 3-phenyl-1-(2-thienyl)-2-propyn-1-ol reacted readily with sulfonamides to provide the corresponding propargylic amides in excellent yields (Entries **B**–**L**, Table 1). In addition, doubly activated (*E*)-1,5-diphenyl-1-penten-4-yn-3-ol underwent facile nucleophilic substitution with sulfonamides to furnish the respective 2-propynyl amide (Entries **M** and **N**, Scheme 2, Table 1).

The 2-propynyl alcohols reacted regioselectively at the 2-propynyl position. No allenic products were detected as a result of amide attack at the triple bond. Interestingly, allyl alcohols also reacted rapidly with $TsNH_2$ at room temperature to afford the corresponding allylic amides (Entries **O** and **P**, Scheme 3, Table 1).

In cases of allyl alcohols (Entries **M**–**P**, Table 1), no allylic rearrangement was observed which was confirmed by NMR spectrum of the crude product. Furthermore, secondary cyclic sulfonamide, saccharin also reacted easily with 2-propynyl alcohol (Entry **D**, Table 1). Other sulfonamides such as methanesulfonamide and benzenesulfonamide were also effective substrates for this conversion. However, carbamates and carboxamides were not so effective coupling partners for this reaction. In all cases, the reactions proceeded in excellent yields with high selectivity and were complete within 4.0–8.0 h. In the absence of PMA/SiO_2, no reaction was observed. This method is compatible with alkene, alkyne, ester, nitro, and ether functionalities. To know the effect of the solvent, the reaction was carried out in various solvents such as dichloroethane, acetonitrile, tetrahydrofuran, and ethanol. However, dichloroethane was the solvent of choice. The effects of various silica supported acid catalysts such as $HClO_4/SiO_2$, H_2SO_4/SiO_2, and $NaHSO_4/SiO_2$ were tested

Table 1. PMA/SiO_2-catalyzed amidation of 2-propynyl alcohols

Entry	2-propynyl alcohol	Sulfonamide	Product[a]	Time/h	Yield/%[b]
A		$TsNH_2$		6.0	86
B		$PhSO_2NH_2$		7.0	80
C		$CH_3SO_2NH_2$		8.0	78
D				8.0	70
E		$TsNH_2$		4.0	92
F		$PhSO_2NH_2$		4.5	90
G		$CH_3SO_2NH_2$		5.0	86
H		$TsNH_2$		5.5	83
I		$PhSO_2NH_2$		6.0	86
J		$TsNH_2$		7.5	76
K		$PhSO_2NH_2$		8.0	75
L		$TsNH_2$		4.0	72
M		$TsNH_2$		6.0	80
N		$PhSO_2NH_2$		5.0	83
O		$TsNH_2$		6.0	82
P		$TsNH_2$		4.0	88

[a]All products were characterized by ^1H, ^{13}C NMR, IR and mass spectrometry. [b]Yield refers to pure products after chromatography.

for this reaction. Of these catalysts, PMA/SiO_2 was found to give the best results in terms of conversion and reaction time. The use of supported catalyst under heterogeneous conditions facilitates ease of separation and recovery of the catalyst. The recovered catalyst was reused in further reactions without significant loss of activity. For instance, 1,3-diphenyl-2-propyn-1-ol and $TsNH_2$ gave the sulfonamide **3A** in 86, 84, and 82% yields over three cycles. The scope of this process is illustrated with respect to various 2-propynyl alcohols and sulfonamides and the results are presented in Table 1. The advantages of this method are the ready availability of alcohols, high atom efficiency, no salt formation and water as the only by-product.

In summary, we have described an efficient amidation of 2-propynyl alcohols with sulfonamides using PMA/SiO_2 as the novel catalytic system. In addition to its efficiency, simplicity, and mild reaction conditions, this method provides high yields of 2-propynyl amides in short reaction times with high selectivity. The use of inexpensive and recyclable PMA/SiO_2 catalytic system makes this process quite simple, more convenient, and cost-effective.

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