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NBS-Catalyzed Hydroamination and Hydroalkoxylation of Activated Styrenes

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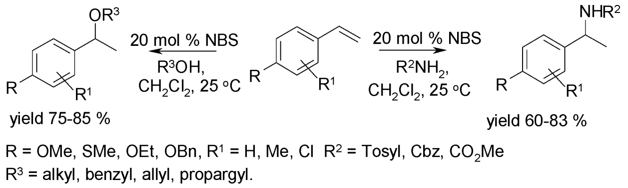
ABSTRACT



***N*-Bromosuccinimide efficiently catalyzes the hydroamination and hydroalkoxylation of activated styrenes using tosylamides, carbamates, and alcohols as the nucleophiles to afford amino and ether derivatives, respectively. Both the processes give good to excellent yields of the products with 100% regioselectivity (Markovnikov fashion).**

The catalytic addition of organic amines and their derivatives to alkenes or alkynes (hydroamination) to produce nitrogen-containing organic molecules is of great importance for synthetic chemists in basic research as well as for the chemical industry.[1] While a variety of protocols exist for the functionalization of alkynes,[2] relatively few reports describe the hydroamination of alkenes.[3] Hydroaminations are generally catalyzed by transition metals (d- and f-block),[4] alkali metals,[5] and Bronsted and Lewis acids.[6] However, many of these catalysts are difficult to synthesize, expensive, sensitive to air and moisture, or highly toxic. Further, hydroamination of alkenes with weaker nucleophiles such as sulfonamides and carbamates as amine sources has been carried out generally under intramolecular fashion only.[6a,7] Recently, we have reported a high-yielding preparative procedure for the aminobromination of a variety of olefins to give vicinal haloamine derivatives **2** by using Cu, Mn, or V catalysts with stoichiometric *p*-toluenesulfonamide ($TsNH_2$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources, respectively.[8]

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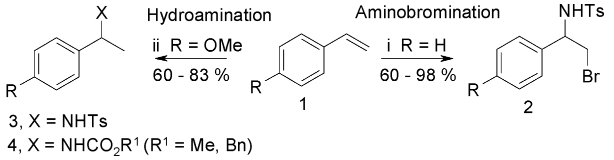
While screening various olefinic substrates for the aminobromination process, we found that 4-methoxystyrene took a different course and furnished the unexpected hydroaminated product **3** in a Markovnikov fashion instead of the bromoaminated product **2**. In continuation of this work, we present herein NBS-catalyzed intermolecular hydroamination of activated styrenes using sulfonamides and carbamates as mild nucleophiles to produce hydroaminated products **3** and **4**, respectively (Scheme 1).

Scheme 1 [a]



[a] Conditions: (i) $TsNH_2$ (2 mmol), NBS (2.2 mmol), CuI/$MnSO_4$/V_2O_5 (5 mol %), CH_2Cl_2, 25 °C. (ii) $TsNH_2$ or $NHCO_2R^1$, NBS (20 mol %), CH_2Cl_2, 25 °C.

When 4-methoxystyrene was treated with either $TsNH_2$ or benzyl carbamate (1.0 equiv) in the presence of a catalytic amount of NBS (20 mol %) at 25 °C in CH_2Cl_2, the corresponding hydroaminated product **3** or **4** was obtained in good yields with excellent regioselectivity (Markovnikov fashion). Encouraged by this result, a systematic study was undertaken to screen various bromine-based catalytic systems for the hydroamination process. The data presented in Table 1 show the effect of the catalyst and solvent on the efficiency of the hydroamination process. Although pyridinium bromide perbromide and *N*-bromoacetamide have displayed comparable activity, the activity of NBS is found to be superior, as it provides excellent yields of the hydroaminated product. Lowering the NBS concentration below 20 mol % led to a decline in the yield (entry 1).

Table 1. Effect of Catalyst on Hydroamination of 4-Methoxystyrene with $TsNH_2$ at 25 °C[a]

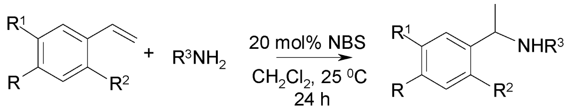
entry	catalyst (mol %)	solvent	yield of **3**[b] (%)
1	*N*-bromosuccinimide (10)	CH_2Cl_2	60
2	*N*-bromosuccinimide (20)	CH_2Cl_2	82
3	*N*-bromosuccinimide (20)	CH_3CN	68
4	*N*-bromosuccinimide (20)	THF	18
5	*N*-bromoacetamide (20)	CH_2Cl_2	65
6	*N*-chlorosuccinimide (20)	CH_2Cl_2	25
7	pyridinium bromide perbromide (20)	CH_2Cl_2	70
8	zinc bromide (20)	CH_2Cl_2	0

[a] General Procedure: To a mixture of 4-methoxystyrene (2 mmol) and *p*-toluenesulfonamide (2 mmol) in 4 mL of solvent was added catalyst (20 mol %) at 25 °C. After stirring for 24 h, the reaction mixture was concentrated and purified using silica gel (ethyl acetate/petroleum ether). [b] Isolated yield after column chromatographic purification.

The NBS-catalyzed hydroamination reactions were generally conducted at ambient temperatures in methylene chloride, as other solvents were found to be less effective. An increase in temperature (50 °C), for enhancing the rate, had a deleterious effect on the yield and selectivity of the process. Other catalysts such as $ZnBr_2$, I_2, etc. have failed to give the hydroaminated products. In the absence of NBS, no product formation was observed even after 78 h of stirring.

We have applied the optimized procedure of NBS-catalyzed hydroamination to a variety of electron-rich styrenes to determine the scope of the hydroamination process, and the results are presented in Table 2. As can be seen, both sulfonamides and carbamates were successfully employed as the amine sources to produce the corresponding amino derivatives in high yields.

Table 2. NBS-Catalyzed Hydroamination of Activated Styrenes Using Sulfonamides and Carbamates[a]



entry	R	R1	R2	R^3NH_2	yield (%)[b]
1	OMe	H	H	$TsNH_2$	82
2	OMe	H	H	$CbzNH_2$	80
3	OMe	H	H	$MeOCONH_2$	74
4	OEt	H	H	$TsNH_2$	75
5	OEt	H	H	$CbzNH_2$	60
6	OBn	H	H	$TsNH_2$	78
7	SMe	H	H	$TsNH_2$	83
8	SMe	H	H	$MeOCONH_2$	80
9[c]	OMe	H	Me	$TsNH_2$	60
10	OMe	Cl	H	$TsNH_2$	78
11	OMe	Cl	H	$MeOCONH_2$	80
12	O^{i}Pr	H	H	$TsNH_2$	66
13	OCp[d]	H	H	$TsNH_2$	62

[a] All reactions were performed at 25 °C for 24 h unless otherwise mentioned. [b] Isolated yield after column chromatographic purification. [c] Reaction was performed for 48 h. [d] Cp = cyclopentyl.

However, the reaction of 2-methyl-4-methoxystyrene with $TsNH_2$ proceeded slowly (48 h), yielding 60% of the hydroaminated product (entry 9). Surprisingly, the methodology fails in the case of aliphatic olefins, electron-deficient styrenes, as well as with more nucleophilic amines.

We further extended the scope of this methodology by subjecting a variety of alcohols as nucleophiles for the hydroalkoxylation of electron-rich styrenes (Table 3).

Remarkably, even allyl and propargyl alcohols readily underwent hydroalkoxylation with activated styrenes using 20 mol % NBS, under ambient conditions, to produce the corresponding ethers in high yields (entries 6 and 7). However, in the case of aliphatic and less activated styrenes, the bromoalkoxylated products were obtained as expected under stoichiometric NBS conditions.[9] Generally, olefin hydroalkoxylation is catalyzed by Bronsted acids as well as transition metal complexes.[10]

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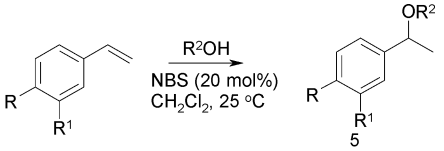
Table 3. NBS-Catalyzed Hydroalkoxylation of Activated Styrenes Using Alcohols as Nucleophiles[a]



entry	R	R1	R2	yield of **5** (%)[b]
1	OMe	H	benzyl	81
2	OMe	H	methyl	84
3	SMe	H	benzyl	85
4	SMe	H	methyl	86
5	OMe	Cl	benzyl	83
6	OMe	H	allyl	85
7	OMe	H	propargyl	76
8	OMe	H	1-phenethyl[c]	70

[a] General Procedure: To a mixture of 4-methoxystyrene (2 mmol) and alcohol (2 mmol) in CH_2Cl_2 (4 mL) was added NBS (20 mol %) at 25 °C. After stirring for 36 h, the reaction mixture was concentrated and purified using silica gel (5% ethyl acetate/petroleum ether). [b] Isolated yield after column chromatographic purification. [c] Dr = 1:1.

The proposed mechanistic pathway for the NBS-catalyzed hydroamination process is shown in Figure 1 and is based on the following observations. The species TsNHBr was isolated (as characterized by ^{1}H and ^{13}C NMR and MS) when $TsNH_2$ was reacted with NBS (in equimolar proportions).[8] Subsequently, the interaction between TsNHBr and 4-methoxystyrene leads to the protonation of a styrenic double bond in Markovnikov fashion [as evidenced by the in situ UV studies, which showed a λ_{max} at 590 nm typical of benzylic carbocation species[11] and by in situ ^{1}H NMR studies, which showed a doublet at δ 1.39 (J = 6.6 Hz) for the methyl group].[12] Finally, the regeneration of the species TsNHBr takes place by the reaction of intermediate A with $TsNH_2$, thereby giving the hydroaminated product. Further, involvement of radical species in the reaction was ruled out, as the reaction proceeded smoothly in the presence of TEMPO. The mechanism for the hydroalkoxylation is not yet clearly understood.

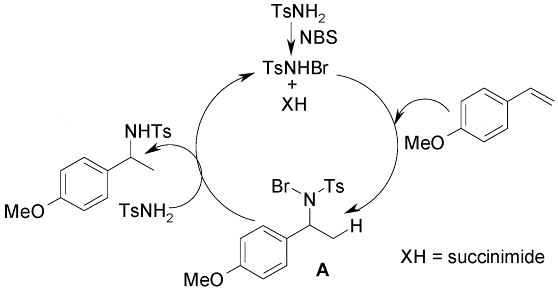


Figure 1. Proposed mechanism for the hydroamination of activated styrenes catalyzed by NBS.

In conclusion, we have developed, for the first time, a new, practical, and “metal-free” procedure for the hydroamination and hydroalkoxylation of activated styrenes catalyzed by NBS under ambient conditions using sulfonamides, carbamates, and alcohols as nucleophiles. Further work to expand this catalytic process to an asymmetric version is under investigation.

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Supporting Information Available: Spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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