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A catalytic approach for the synthesis of allylic azides from aryl vinyl carbinols

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ABSTRACT

A metal-free and catalytic approach for the preparation of allylic azides starting from aryl vinyl carbinols is described herein.

Azides have been the valuable intermediates in synthetic organic chemistry.[1] Being stable and can be easily reduced to corresponding amines that find applications in therapeutic agents, amino acids, natural product synthesis and material science,[2] they have attained a significant importance. Recently, with the advent of click chemistry, the azides have attained more prominence towards their synthesis for triazole formation.[3]

The ready availability of the allylic alcohols makes them the first preferred substrates for the preparation of allylic azides. Though several methods[4–6] are available for azidation reactions (direct and non-direct approaches) involving nucleophilic displacement of hydroxy group (either directly or through pre-activation as the corresponding ester, or triflate or conversion to halide), many of them utilize either metal catalysts (expensive) or employ heating conditions and thus a new procedure for the preparation of allylic azide is always welcome to the existing literature.

Our own interest in exploration of acid catalysis for transformations involving C–C bond or C–X bond formation reactions such as nucleophilic substitution reactions on benzyl and aryl propargyl alcohols[7] has initiated us to investigate a similar substitution reaction with aryl vinyl substrates. We were delighted to observe that these substrates easily undergo nucleophilic addition type of reaction to get the allylic azides (terminal azides) rather than the expected nucleophilic substitution reaction (–OH displaced with $-N_3$). The present manuscript describes our results in identifying a facile approach for the preparation of allylic azides (Scheme 1).

Initially, it was envisaged to explore the nucleophilic substitution reaction at benzylic and allylic site with the azide moiety. In addition, if a substitution is present at the ortho position on aryl moiety for example –OH group, it might also undergo an addition type of reaction onto olefin with simultaneous internal migration of the double bond resulting in cleavage of azido moiety to get the chromene (see Scheme 2).

Thus, we began with salicylaldehyde to get the substrate for our investigations. Salicylaldehyde was subjected to Grignard reaction (in situ generated vinyl magnesium bromide) to yield the diol **1a** for our current investigation. The diol **1a** was subjected to nucleophilic substitution reaction with $TMSN_3$ (1 equiv) in the presence of Lewis acid $BF_3{\cdot}OEt_2$ (0.1 equiv) to undergo azido substitution at benzylic and allylic position or may further react to produce expected chromene. After 2 h of reaction duration, we observed the formation of two new spots with low polarity compared to the starting material present in minor amounts. After characterizing the major product, we were indeed surprised to note that the product obtained was the allylic azide **1b**[8] (see Scheme 3) rather than the expected secondary azido substituted product **1b′** or chromene (see Scheme 2). Simultaneously, the minor product was characterized to be the di-trimethylsilyl protected compound **1c**.

This result has prompted us to further explore this methodology. From the literature survey, it was found that $TMSN_3$ itself acts as the protective group reagent and aids in the masking of free hydroxyl groups to the corresponding trimethylsilylether.[9] As silylation was known in THF, we tried a similar reaction in THF and found that TMS protected compound was obtained and there was no significant change in the reaction rate or in terms of yield. We further investigated the effect of concentration for the Lewis acid $BF_3{\cdot}OEt_2$ and it was found that 20 mol % of $BF_3{\cdot}OEt_2$ was essential for optimum yields. And when the concentration was increased to 50 mol %, there was no significant improvement in the yield and thus we opted to proceed further with 20 mol % of the Lewis acid.

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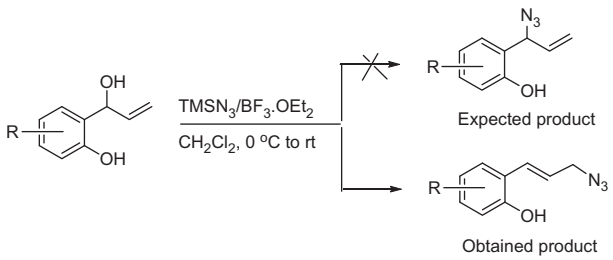
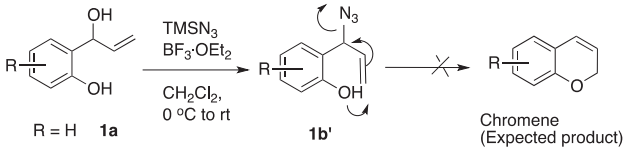
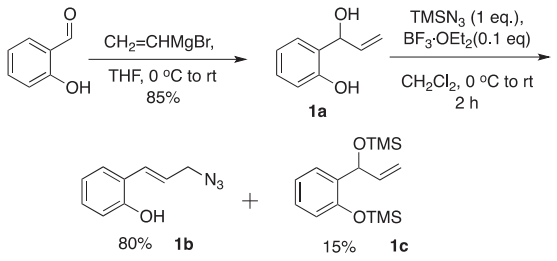


Scheme 1. Synthesis of allyl azides from aryl vinyl carbinols.



Scheme 2. Attempted nucleophilic substitution reaction towards chromene formation.



Scheme 3. Synthesis of allylic azide and disilylated product.

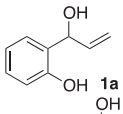
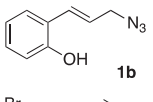
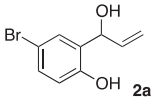
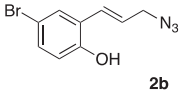
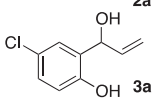
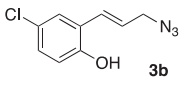
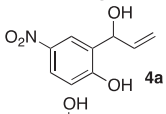
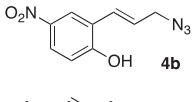
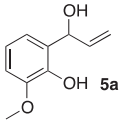
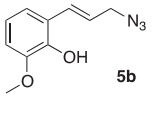
As we have earlier explored I_2[7d,e] and $NbCl_5$[7f] as mild Lewis acids for nucleophilic substitution reactions, the diol was also treated with $TMSN_3$ in the presence of these Lewis acids (20 mol %). It was observed that the reaction ended up with multi spots leading to decomposition of the starting material when I_2 was used as Lewis acid. Interestingly, positive results were obtained with $NbCl_5$ wherein the reaction was much faster compared to that of reaction with $BF_3{\cdot}OEt_2$. However, the reaction was not complete even after a prolonged duration of the reaction and minor amount of starting material was always left over resulting in overall reduced yield. In the case of reaction with $BF_3{\cdot}OEt_2$ as Lewis acid, complete consumption of starting material occurred within 2 h. As the reaction was best yielding with $BF_3{\cdot}OEt_2$, we proceeded further with the same Lewis acid for further investigations.

Though, chromene was not formed in our preliminary studies with **1a**, we proceeded further to check the possibility with various other substrates as given in Table 1. Aryl vinyl carbinols such as bromo substituted, nitro substituted and methoxy-substituted aryl containing diols (synthesized through Grignard reaction from the correspondingly derived salicylaldehydes) were treated with $TMSN_3$ (1.0 equiv) and $BF_3{\cdot}OEt_2$ (20 mol %) (see Table 1). Interestingly in all the cases, corresponding terminal allylic azides were formed in a range of 65–90% yield with complete consumption of the starting material. In no case we could observe the formation of chromene. It was also observed that when electron donating group like methoxy (entry 5 and 6) was present on the aromatic system, the reaction progressed in longer durations and when electron withdrawing group like nitro moiety (entry 8) was present in the ring system, the reaction was completed within 45 min at room temperature.[10]

Since the substrates having unsubstituted olefin have responded well to provide only allylic azides, we now turned our attention to investigate the substrates with substituted olefins. It was observed that the substrates with substituted olefin also react in the present conditions and provide corresponding allylic azides in good yields (entry 7, 8 and 11). Even the substrate with an *ortho* substituted amine gave the corresponding allylic azide (entry 10).[11]

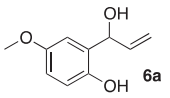
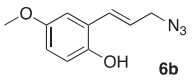
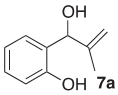
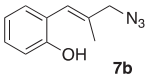
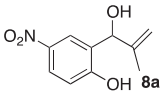
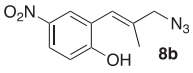
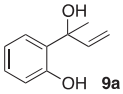
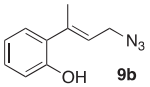
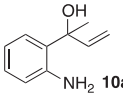
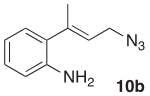
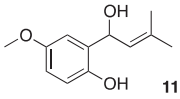
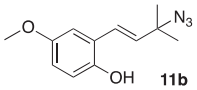
Mechanistically, we envisaged that the benzylic alcohol gets activated as the corresponding trimethyl silyl ether and undergoes nucleophilic addition (azide addition) onto the olefin with simultaneous elimination of the trimethyl silyloxy moiety through double bond migration. This postulate was confirmed by a controlled experiment wherein, the diol was treated with $TMSN_3$ in DCM at 0 °C in the absence of Lewis acid to give a mixture of TMS protected products **1c** and **1d** (characterized after their isolation) and no azido product was observed in this reaction. (Scheme 4). However,

Table 1
Synthesis of allylic azides from aryl vinyl methanol

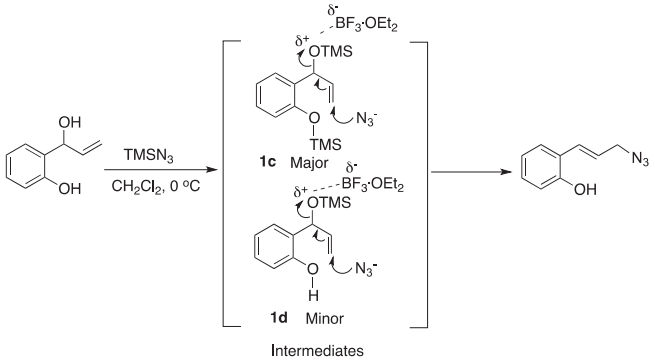
Entry no	Substrate	Product	Reaction time	Azide yield[a]in (%)	Disilylated product[a] in (%)
1	 1a	 1b	90	80	8
2	 2a	 2b	90	82	10
3	 3a	 3b	90	80	10
4	 4a	 4b	45	90	<5
5	 5a	 5b	120	75	15

(*continued on next page*)

Table 1 (*continued*)

Entry no	Substrate	Product	Reaction time	Azide yield[a] in (%)	Disilylated product[a] in (%)
6	 **6a**	 **6b**	120	70	14
7	 **7a**	 **7b**	90	80	12
8	 **8a**	 **8b**	45	90	<5
9	 **9a**	 **9b**	90	85 *E*/*Z* (1:1:5)[b]	10
10	 **10a**	 **10b**	90	80 *E*/*Z* (4:1)[c]	8
11	 **11a**	 **11b**	120	65	15

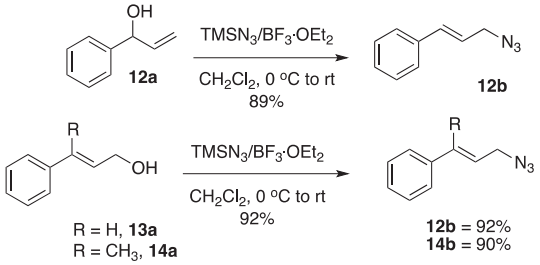
[a] Isolated yields.
[b] Percentage based on LCMS analysis.
[c] Percentage based on ^{1}H NMR analysis



Scheme 4. Plausible mechanism for allylic azide formation.

after the addition of $BF_3{\cdot}OEt_2$ to these intermediates, the corresponding allylic azide was formed as the only product. Thus, the reaction was presumed to undergo a straight forward nucleophilic addition (azide addition) onto the olefin displacing the –OTMS moiety to get the allylic azide.

As we ended up with allylic azides and no chromene was formed, we now investigated aryl vinyl methanol without hydroxyl substitution on aryl moiety. Towards this, we experimented with phenyl vinyl carbinol **12a** and found that azidation occurs with the azide moiety at the terminal end rather than the expected substitution at benzylic and allylic site to give **12b** (Scheme 5). As we were ending up with terminal azides in all the above cases, we attempted similar reaction conditions on terminal allylic alcohols for direct azidation reaction. Thus, when *trans*-cinnamyl alcohol **13a** was subjected to our reaction conditions, we were gratified to note that the reaction ended up with cinnamyl azide **13b** (see Scheme 5). Even α-methyl cinnamyl alcohol **14a** yielded the corresponding terminal cinnamyl azide **14b**. Thus the present strategy becomes an example for direct catalytic azidation reaction for cinnamyl alcohols. Though cinnamyl alcohols responded well, crotyl alcohol and benzyl alcohol did not respond to our present reaction



Scheme 5. Azidation reactions.

conditions and ended up with recovery of starting material even after heating the reaction mixture for 2 h at reflux temperature.

In conclusion, a facile method for synthesis of allylic azides has been developed starting from aryl vinyl methanol. Simple catalytic reaction condition with easy work-up procedure and involvement of no expensive metal catalyst make this method more attractive. Application of this method for the synthesis of biologically potent natural products is of current interest in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR data of new compounds are available as supplementary material) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.094.

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8. The amine derivative obtained from this product was utilized as tether group in the synthesis of new class of macrocyclic antagonists. see Marsault, E.; Hoveyda, H. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vezina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; Benakli, K.; Beauchemin, S.; Deziel, R.; Peeters, T.; Fraser, G. L. *J. Med. Chem.* **2006**, *49*, 7190–7197.

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10. *General procedure for preparation of allylic azide*: To the solution of diol (0.84 mmol) in anhydrous CH_2Cl_2 (15 mL) was added $TMSN_3$ (1.26 mmol), followed by $BF_3{\cdot}Et_2O$ (20 mol %) at 0 °C. The reaction mixture was stirred at room temperature for complete consumption of the starting material (see Table 1). The reaction mixture was diluted with aq sat. $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by silica gel column chromatography with ethylacetate/hexane (1:9) as an eluent to furnish the allylic azide.

11. LCMS analysis was carried out using Agilent technologies 1100 series HPLC which is hyphenated with LCMSD ion trap mass spectrometer. HPLC conditions include Discovery C8 column of length 250 × 4.6 mm, 5 microns with mobile phase 75% CH_3CN in water (0.1% formic acid) with PDA detector at 268 nm. Mass conditions include positive ion polarity with ESI ion source, dry gas temperature at 300 °C and nebulizer press 30 psi with dry gas (nitrogen) flow rate of 8.0 L/min.