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An Expedient and Highly Selective Conversion of Alcohols to Azides using a $NaN_3/BF_3.Et_2O$ System

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Abstract : Alkyl azides were prepared in good yields by treatment of allylic and benzylic alcohols with a molar equivalent of NaN_3 in the presence of $BF_3.Et_2O$ in dioxane.

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Key words : Alcohols, Azides, $BF_3.Et_2O$, Dioxane.

Alkyl azides are versatile substrates in organic synthesis.[1] They serve as precursors for nitrene and amino compounds and are good 1,3-dipoles. While aromatic azides can be obtained relatively easily by a variety of methods, aliphatic azides are mainly prepared by substitution of alkyl halides, diazo transfer to aliphatic amines or HN_3 addition to olefins.[2] Although, the direct synthesis of azides from the corresponding alcohols is a highly advantageous and attractive strategy, the known methods for accessing alkyl azides from alcohols are mainly limited to tertiary alcohols.[3] Application of Mitsunobu conditions[4] for the conversion of alcohols to azides mainly utilizes hydrazoic acid, diphenylphosphoryl azide, the bispyridine complex of zinc azide or the tetrabromocyclohexadienone-PPh_3 system as the azide source/nucleophilic component. The direct conversion of

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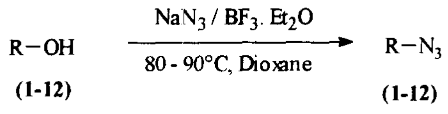
allylic and benzylic alcohols into azides, employing Lewis acids, is a significant improvement for the synthetic entry of these compounds.[5] However, reported methods utilize a large excess of HN_3, whose generation, storage and handling is relatively cumbersome when compared to alkali metal azides such as NaN_3. During the course of our study on the application of various reagents involving Lewis acids and inorganic azides for the direct one-pot conversion of alcohols to azides, we found that the NaN_3-$BF_3.Et_2O$ system was effective for this transformation and this communication deals with the scope and limitations of this newly developed azidation method.

Scheme



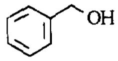
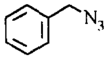
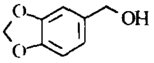
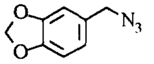
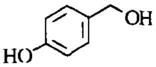
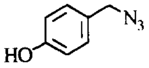
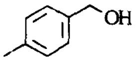
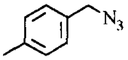
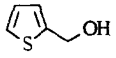
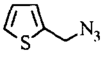
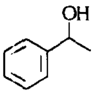
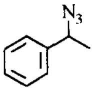
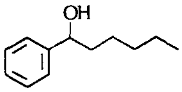
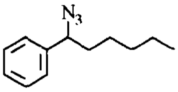
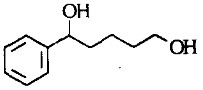
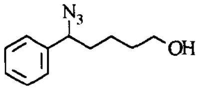
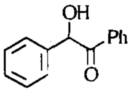
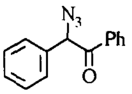
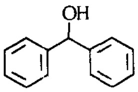
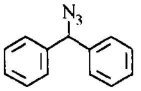
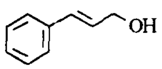
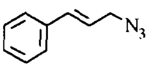
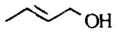
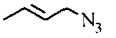
$$\underset{\textbf{(1-12)}}{R{-}OH} \xrightarrow[80-90°C,\ Dioxane]{NaN_3 / BF_3.Et_2O} \underset{\textbf{(1-12)}}{R{-}N_3}$$

R = benzylic and allylic

A variety of benzylic and allylic alcohols were converted into the corresponding azides when treated with a molar equivalent of NaN_3 in presence of $BF_3.Et_2O$. Optimum conditions for the reaction have been explored and the reaction was found to proceed smoothly to completion at a temperature of 80-90°C within 3-5 hrs. Among the various solvents studied, 1,4-dioxane was found to be the solvent of choice. The products were isolated by aqueous workup followed by solvent extraction and purified by flash chromatography if necessary to afford pure alkyl azides.

This reaction is found to be highly selective as only allylic and benzylic alcohols are converted to azides in high yields (80-92%), whereas saturated aliphatic alcohols did not yield azides even after prolonged heating in dioxane. The remarkable selectivity of this reaction allowed only allylic and benzylic hydroxyls to be azidated without affecting other OH groups present in the molecule (eg. 8). Furthermore a

Table : Conversion of alcohols to azides

Entry	Substrate	Product^a	Reaction time (h.)	Yield (%)^b
1.			4	85
2.			4	86
3.			4	84
4.			4	86
5.			3	92
6.			3	90
7.			3	86
8.			4	84
9.			5	82
10.			5	80
11.			3	86
12.			3	88
13.		No Reaction	8	--

a : All products are identified by the ^{1}H NMR and IR spectra. All reactions are carried out at a temperature of 80-90°C in dioxane

secondary OH group at an allylic or benzylic position could easily be substituted by an azide group in high yields using this technique. As the reaction proceeds with gradual consumption of $BF_3.Et_2O$ by the byproduct NaOH, a molar equivalent of $BF_3.Et_2O$ is essential in order to achieve complete conversion of the alcohol.

In conclusion the highly selective, simple, direct, and high yielding azidation of allylic and benzylic alcohols using $NaN_3/BF_3.Et_2O$ system in dioxane, presented in this paper, serves as useful synthetic entry to valuable alkyl azides.

Conversion of benzylic and allylic alcohols into azides - General Procedure :

The alcohol (50mmol) was dissolved in dry 1,4-dioxane (25ml) to which $BF_3.Et_2O$ (75mmol) and NaN_3 (50mmol) were added and the resulting mixture was stirred at a temperature of 80-90° under an N_2 atmosphere. After the complete consumption of the starting alcohol, as indicated by TLC, the reaction mixture was poured into ice-cold water and extracted with dichloromethane (2 x 20ml). The combined organic layer was washed with brine (2 x 10ml), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The product was purified wherever necessary, by column chromatography on SiO_2 using a gradient mixture of ethyl acetate / hexane to afford pure alkyl azide (for yields and conditions, see table).

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