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Article

A Novel and Highly Selective Conversion of Alcohols, Thiols, and Silyl Ethers to Azides using the 2,4,6-Trichloro[1,3,5]triazine/n-Bu$_4$NN$_3$ System

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Alquil azidas são preparadas em bons a excelentes rendimentos, pelo tratamento de álcoois, tióis e trimetilsilil éteres com 2,4,6-tricloro[1,3,5]triazina/n-Bu$_4$NN$_3$ em acetonitrila. Este método é altamente seletivo para conversão de álcoois primários a alquil azidas na presença de álcoois secundários e terciários, tióis e trimetilsilil éteres.

Alkyl azides are prepared in good to excellent yields by treatment of alcohols, thiols and trimethylsilyl ethers with 2,4,6-trichloro[1,3,5]triazine/n-Bu$_4$NN$_3$ in acetonitrile. This method is highly selective for conversion of primary alcohols to alkyl azides in the presence of secondary and tertiary alcohols, thiols and trimethysilyl ethers.

Keywords: 2,4,6-trichloro[1,3,5] triazine (TT), alcohol, thiol, trimethylsilyl ether, alkyl azide

Introduction

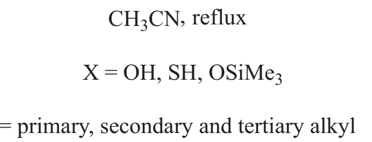
Azides[1] are important functional groups in organic synthesis for many purposes and have been extensively used for the introduction of amino groups and construction of heterocycles.[2-4] Aliphatic azides are usually prepared by nucleophilic substitution of the corresponding halides or sulfonates by azide ion.[5-8] Due to the advantageous and attractive strategy of the direct synthesis of azides from alcohols, some limited methods have been developed. Along this line, methods based on Mitsunobu conditions[7-11] are widely applied. These methods utilize reagents such as hydrazoic acid, diphenylphosphoryl azide, the bispyridine complex of zinc azide or the tetrabromocyclohexadienone/Ph$_3$P system as the azide source/nucleophilic component. The use of NaN$_3$ in the presence of excess BF$_3$–Et$_2$O[12] at 80-90 °C was reported to be effective for the conversion of allylic and benzylic alcohols to azides. The conversion of activated alcohols to azides by the use of diphenyl phosphorazidate (DPPA) and DBU[13] and the use of bis(p-nitrophenyl) phosphorazidate[14] have also been reported. The latter method cannot be applied for cyclic alcohols, for example, cyclohexanol does not react with this reagent even after 24 h reflux in toluene.

Recently, we have reported the application of Ph$_3$P/DDQ/R$_4$NX (X=Cl, Br, I, CN, N$_3$, ONO, OCN) and 2,4,6-trichloro[1,3,5]triazine (TT)/R$_4$NX (X= CN, ONO, OCN) systems for conversion of alcohols, thiols, selenols, trimethlsilyl ethers and tetrahydropyranyl ethers into their corresponding alkyl halides, cyanides, azides, nitrites and isocyanates.[15-25]

In this article, the use of a novel and cheap reagent for efficient generation of alkyl azides from alcohols, thiols and trimethylsilyl ethers is reported.

Results and Discussion

In continuation of our studies, we now report that primary, secondary and tertiary alcohols, thiols and trimethylsilyl ethers can be efficiently and smoothly converted into their corresponding alkyl azides in good to excellent yields using TT/n-Bu$_4$NN$_3$ under neutral and quite mild reaction conditions (Scheme 1).



X = OH, SH, OSiMe$_3$

R= primary, secondary and tertiary alkyl

Scheme 1.

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2,4,6-Trichloro[1,3,5] triazine (TT) is a commercially available, inexpensive reagent that has found increasing application in organic synthesis. This reagent and its derivatives have been used for the activation of carboxyl groups in the preparation of esters, amides, peptides,[26-30] alcohols, aldehydes,[31,32] as well as alkyl chlorides[33] and acyl azides.[34]

In order to optimize the reaction conditions, at first the effect of different molar ratios of ROH/TT/*n*-Bu_4NN_3, solvent and temperature for conversion of $PhCH_2OH$ to $PhCH_2N_3$ were examined. Employing the ratio of 1/2/2 in refluxing CH_3CN gave the best result and produced $PhCH_2N_3$ after 3h in 98% isolated yield. We then applied

Table 1. Conversion of alcohols, thiols and trimethlsily ethers into azides in dry acetonitrile

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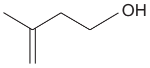
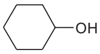
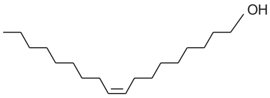
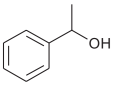
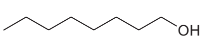
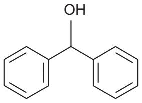
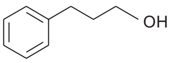
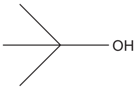
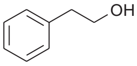
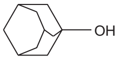
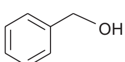
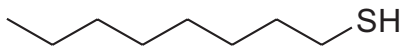
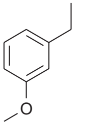
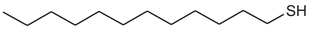
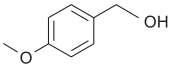
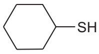
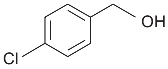
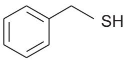
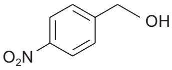
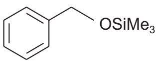
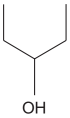
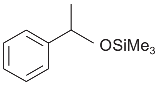
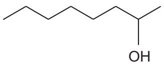
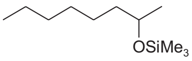
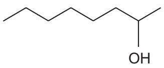
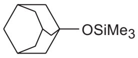
1		3.5	98	14		13	95
2		6.5	97	15		7.5	97
3		7	95	16		26	94
4		6	93	17		22	93
5		8	97	18*		24	95
6		3	98	19		20	95
7		2.5	96	20		21	96
8		1.5	94	21		22	94
9		3.5	95	22		20	93
10		9	93	23		4	98
11		11	98	24		8	94
12		10	95	25		11	97
13		10.5	97	26		27.5	95

*mp of 1-adamantyl azide 81.5 °C (Lit.[35] 82-83 °C).

Table 2. Selective reaction of different binary mixtures with TT/nBu$_4$NN$_3$

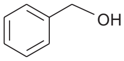
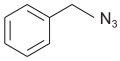
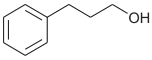
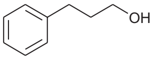
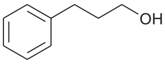
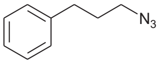
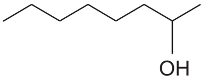
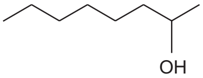
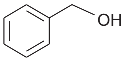
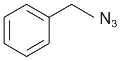
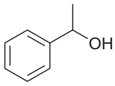
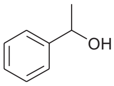
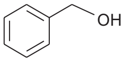
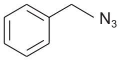
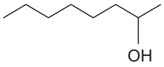
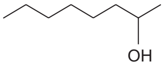
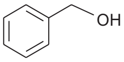
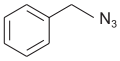
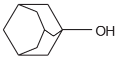
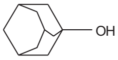
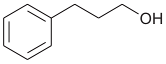
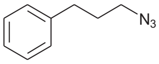
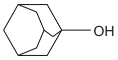
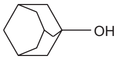
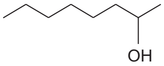
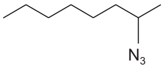
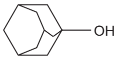
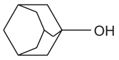
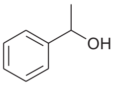
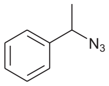
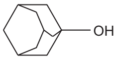
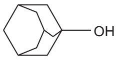
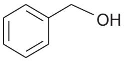
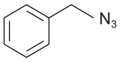
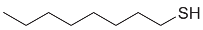
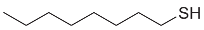
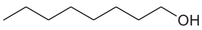
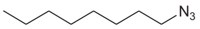
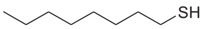
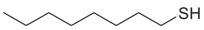
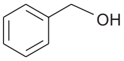
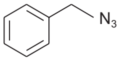
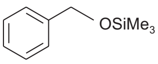
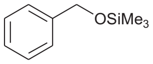
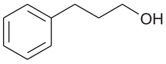
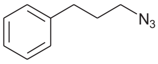
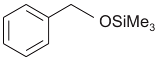
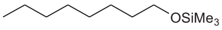
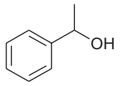
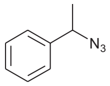
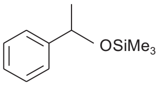
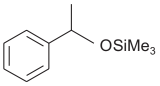
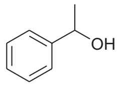
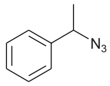
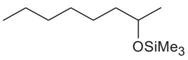
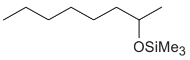
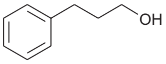
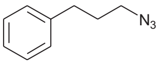
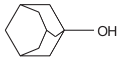
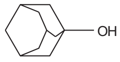
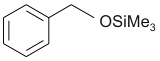
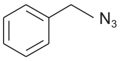
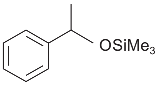
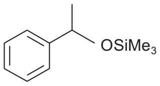
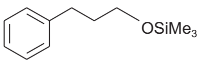
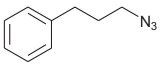
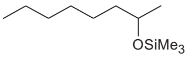
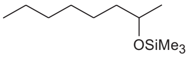
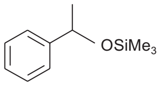
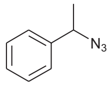
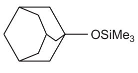
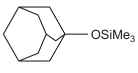
Entry	Binary mixture	Products	time/h	Yield / %
1			3.5	97
				98
2			7	96
				98
3			7.5	95
				96
4			4.5	97
				98
5			8	95
				96
6			10.5	96
				97
7			13.5	98
				99
8			9	97
				98
9			4	96
				97
10			8	96
				97
11			4.5	97
				98
12			8	95
				96

Table 2. Selective reaction of different binary mixtures with TT/*n*Bu_4NN_3

Entry	Binary mixture	Products	time/h	Yield / %
13			10.5	96
				97
14			30	98
				99
15			7	96
				97
16			6.5	97
				98
17			24	96
				97
18			13.5	97
				98

our optimized conditions for the conversion of structurally different alcohols into their corresponding alkyl azides with 100% conversion (substrate consumption) which determined by GC. The results are shown in Table 1. IR spectra of the isolated products showed a strong absorption band at 2160-2120 cm^{-1} due to the asymmetric stretching of azide group which occurs as doublet.

As is demonstrated in Table 1, the use of TT/*n*-Bu_4NN_3 is very suitable for method for the conversion of thiols to their corresponding alkyl azides (Table 1, entries 19-22). When we applied our method to trimethylsilyl ethers, the reactions furnished their corresponding alkyl azides in high yields (Table 1, entries 23-26).

This method was found to be highly selective for alcohols. In a binary mixture of 3-phenyl-1-propanol and 2-octanol, the primary alcohol was completely converted to its corresponding azide, while the secondary alcohol remained intact (Table 2, entry 2). Excellent selectivity was also observed for the conversion of primary in the presence of a tertiary alcohols, and secondary alcohols in the presence of tertiary alcohols (Table 2, entries 5-8). The high selectivity for the conversion of alcohols in the presence of thiols was also demonstrated (Table 2, entry 9, 10). Similarly, this method showed excellent selectivity for conversion of primary, secondary and tertiary alcohols to their corresponding azides in the presence of trimethylsilyl ethers (Table 2, entries 11-15). Also, a primary silyl ether was converted to its azides in the presence of secondary and tertiary silyl ether (Table 2, entry 16-18).

Conclusions

In conclusion, the present investigation has demonstrated that the use of TT/*n*-Bu_4NN_3 offers a simple, novel, and convenient method for conversion of wide variety of alcohols, thiols and trimethylsilyl ethers to their corresponding alkyl azides. The method shows excellent selectivity not only among different alcohols but also between alcohols, thiols, and trimethylsilyl ethers. Availability, safety, ease in handling of the reagents, high yields, and mildness of the reaction conditions make this method very attractive for direct conversion of alcohols, thiols, and trimetylsilyl ethers into azides.

Experimental

Chemicals were obtained from Merck and Fluka chemical companies. FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument. The products were purified by column chromatography and the purity determination of the products were accomplished by GC on a Shimadzu model GC 10-A instrument using *n*-octane as internal standard or by thin layer chromatography on silica gel polygram on SIL G/UV 254 plates. All products were identified by their comparison with authentic samples.

Typical procedure for conversion of alcohols to azides

To a flask containing 2,4,6-trichloro[1,3,5] triazine (0.369 g, 2 mmol) in dry CH_3CN (3-5 mL), was added n-Bu_4NN_3 (0.576 g, 2 mmol) under stirring. Benzyl alcohol (0.108 g, 1 mmol,) was added and the mixture was refluxed. GC analysis showed that the reaction was completed after 3 h. The solvent was evaporated under reduced pressure. Column chromatography of the crude product on silica-gel using *n*-hexane as eluent gave benzyl azide in 98% yield (bp 73°C, 11 mmHg, Lit.[36] 108 ° C, 23 mmHg).

Acknowledgments

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