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A novel and highly selective conversion of alcohols, thiols, and silyl ethers to azides using the triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone(DDQ)/*n*-Bu_4NN_3 system

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Abstract—Alcohols, thiols, and silyl ethers are converted into alkyl azides in good to excellent yields by treatment with PPh_3/DDQ/*n*-Bu_4NN_3 in CH_2Cl_2 at room temperature. The method is highly selective for 1° alcohols in the presence of 2° and 3° ones, and also thiols and silyl ethers.

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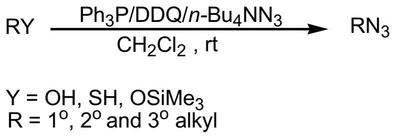
Azides[1] are important functional groups in organic synthesis for many purposes and have been extensively used for the introduction of amino groups and construction of heterocycles.[2] Aliphatic azides are usually prepared by nucleophilic substitution of the corresponding halides or sulfonates by azide ion.[3,4] 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[5–7] are widely applied. These methods utilize reagents such as hydrazoic acid, diphenylphosphoryl azide, the bispyridine complex of zinc azide or the tetrabromocyclohexadienone/Ph_3P system as the azide source/nucleophilic component. The use of NaN_3 in the presence of excess BF_3–Et_2O[8] 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[9] and the use of bis(*p*-nitrophenyl) phosphorazidate[10] 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.

In continuation of our recent work on the use of TPP/DDQ/nucleophile, for the preparation of alkyl halides, and nitriles,[11] we report the successful preparation of primary, secondary, tertiary, and cycloalkyl azides from alcohols, thiols, and trimethylsilyl ethers under mild reaction conditions using the TPP/DDQ/*n*-Bu_4NN_3 system in high to excellent yields (Scheme 1).

The use of diethyl azodicarboxylate (DEAD) in Mitsunobu reactions as an expensive reagent, which easily explodes on heating and the use of HN_3 as the source of nucleophile are the two main problems for utilizing this method for the conversion of alcohols to alkyl azides.

In order to reduce the problems encountered in this conversion and to provide a safer and simpler method, we decided to use *n*-Bu_4NN_3 as the source of the azide ion instead of HN_3 and studied the possibility of replacing diethyl azodicarboxylate (DEAD) with other electron-deficient reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), 2,3,5,6-tetrachlorobenzoquinone (*p*-chloranile), tetraphenylcyclopentadienone (tetracyclone), tetracyanoethylene (TCNE), diethyl acetylenedicarboxylate (DEACD), and



Scheme 1.

Keywords: Triphenylphosphine (TPP); 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ); Azide; Alcohol; Thiol; Trimethylsilylether.

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Table 1. The conversion of benzyl alcohol to benzyl azide using n-Bu_4NN_3 in the presence of Ph_3P and different reagents in dichloromethane at room temperature

Entry	Mixed reagent	Time	Conversion[a] (%)
1	Ph_3P/DEAD	24 h	10
2	Ph_3P/DDQ	Immediately	100
3	Ph_3P/*p*-chloranile	24 h	90
4	Ph_3P/tetracyclone	24 h	0
5	Ph_3P/TCNE	24 h	0
6	Ph_3P/DEACD	24 h	0
7	Ph_3P/PTAD	24 h	0

[a] GC yield using internal standard.

phenyl-1,2,4-triazoline-3,5-dione (PTAD) in conjunction with Ph_3P (TPP). In a set of experiments, we studied the conversions of benzyl alcohol to benzyl azide with n-Bu_4NN_3 in the presence of Ph_3P and the above-mentioned reagents. The results of this study are shown in Table 1. According to the results obtained, Ph_3P/DDQ was found to be the most suitable and efficient reagent system for this conversion. The use of the other reagent systems (Table 1, entries 1, 3–7) was not successful.

The optimized stoichiometric ratios of ROH/Ph_3P/DDQ/n-Bu_4NN_3 for the conversion of benzyl alcohol to benzyl azide were found to be 1/1.5/2/2 and the reaction was performed in CH_2Cl_2 at room temperature. The amount of DDQ should be higher than Ph_3P otherwise the Ph_3P can convert the alkyl azide to an iminophosphorane, which reduces the yield of the reaction.

We then applied the optimized conditions to the conversion of different alcohols into the corresponding alkyl azides. The results obtained are shown in Table 2. These show the general applicability of the method for the conversion of primary, secondary, and tertiary alcohols to alkyl azides.

Table 2. Conversion of alcohols, thiols, and silyl ethers into alkyl azides

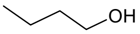
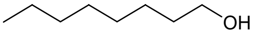
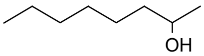
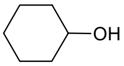
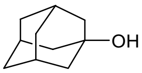
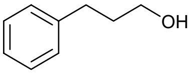
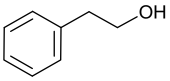
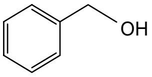
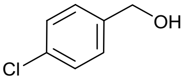
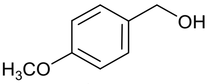
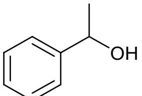
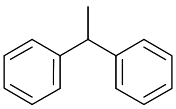
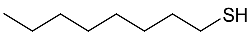
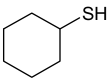
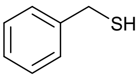
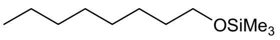
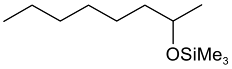
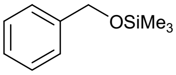
Entry	ROH	Time	Conversion[a] (%)	Isolated yield (%)
1		3 h	100	—
2		2 h	80	75
3		10 h	80	78
4		20 h	90	88
5		24 h[b]	70	65
6		2 h	100	95
7		5 min	100	95
8		Immediately	100	96
9		40 min	100	97
10		Immediately	100	94
11		10 min	100	90
12		24 h	70	68
13		24 h	90	85
14		24 h	90	84
15		5 h	100	95

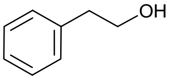
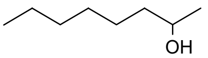
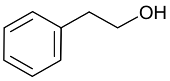
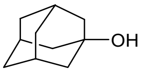
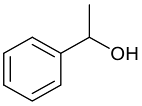
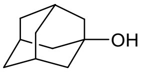
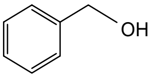
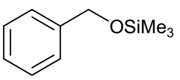
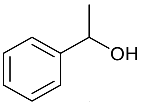
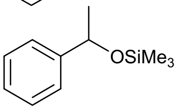
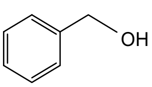
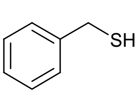
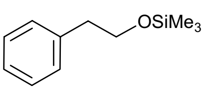
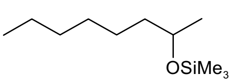
Table 2 (*continued*)

Entry	ROH	Time	Conversion[a] (%)	Isolated yield (%)
16		5 h	100	93
17		10 h	80	73
18		5 min	100	92

[a] GC yield using internal standard.

[b] Reflux conditions.

Table 3. Selective reactions of different binary mixtures with Ph_3P/DDQ/n-Bu_4NN_3[a]

Entry	Binary mixture	Time (min)	Conversion[b] (%)
1		10	100
			5
2		5	100
			0
3		15	100
			0
4		Immediately	100
			0
5		10	100
			0
6		5	100
			3
7		15	100
			5

[a] The stoichiometry of the binary mixture/Ph_3P/DDQ/n-Bu4NN$_3$ was 1/1/1.5/2/2.

[b] GC yield using internal standard.

We also applied this method successfully for the conversion of thiols and silyl ethers into the corresponding azides (Table 2, entries 13–18).

This method was found to be highly selective for primary alcohols. In a binary mixture of 2-phenylethanol and 2-octanol, the primary alcohol was completely converted into its azide, while only a 5% conversion was observed for the secondary alcohol (Table 3, entry 1). Excellent selectivity was also observed for the conversion of 1° and 2° alcohols in the presence of a 3° alcohol (Table 3, entries 2 and 3). Similarly, this method showed excellent selectivity for the conversion of 1° and 2° alcohols into the corresponding azides in the presence of trimethylsilyl ethers (Table 3, entries 4 and 5). High selectivity for the conversion of alcohols in the presence of thiols was also achieved with this method (Table 3, entry 6). This method is also selective for the conversion of 1° silyl ethers into the corresponding alkyl azides in the presence of a 2° silyl ether (Table 3, entry 7).

In conclusion, replacement of DEAD with DDQ as a safe and easily available reagent and HN_3 with n-Bu_4NN_3 in combination with Ph_3P provides a simple, novel, and general method for the conversion of alcohols, thiols, and trimethylsilylethers into the corresponding azides. In addition, this method shows excellent selectivity for alcohols in the presence of trimethylsilyl ethers and thiols as well as between structurally different alcohols.

Typical procedure for the conversion of benzyl alcohol to benzyl azide in dichloromethane: To a flask containing a stirred mixture of Ph_3P (1.5 mmol, 0.393 g) and DDQ (2 mmol, 0.454 g) in dry dichloromethane (5–7 mL), was added tetra-*n*-butylammonium azide (2 mmol, 0.568 g) at room temperature. Benzyl alcohol (1 mmol, 0.1 mL) was then added to the reaction mixture. GC analysis showed the immediate completion of the reaction. The solvent was evaporated under reduced pressure. Column chromatography of the crude residue on silica gel using *n*-hexane as an eluent gave benzyl azide in 96% yield (bp 73 °C, 11 mmHg. Lit.[12] 108 ° C, 23 mmHg).

Acknowledgements

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