A New and Convenient Method of Generating Alkyl Isocyanates from Alcohols, Thiols, and Trimethylsilyl Ethers Using a 2,4,6-Trichloro[1,3,5] Triazine/n-Bu$_4$NOCN

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Alkyl isocyanates 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$_4$NOCN in acetonitrile. This method is highly selective for conversion of 1° alcohols to alkyl isocyanates in the presence of 2° and 3° alcohols, thiols, and trimethylsilyl ethers.

Key Words: 2,4,6-Trichloro[1,3,5] triazine (TT), alcohol, thiol, trimethylsilyl ether, alkyl isocyanate.

Introduction

Isocyanates are useful compounds capable of participating in a variety of reactions, including nucleophilic addition reactions with alcohols and amines, to produce carbamates and ureas, cycloaddition reactions to generate heterocycles, and polymerization reactions to produce commodities, such as polyurethanes.[1−3] The high yields and lack of by-products associated with isocyanate chemistry have led to its widespread application in the pharmaceutical, agrochemical, and polymer industries. Typically, aliphatic and aromatic isocyanates are generated from amines reacting with phosgene[4−6] or phosgene equivalents, such as diphosgene (trichloromethyl chloroformate)[7,8] or triphosgene [bis(trichloromethyl) carbonate],[9−10] or via thermal dissociation of carbamic acid derivatives using chloroformates,[11−13] diphenylcarbonate,[14] or N,N'-carbonyldiimidazole.[15] Aryl isocyanates can also be generated from non-amine precursors via the rearrangement of acyl azides (Curtius rearrangement)[16−18] and hydroxamic acids (Lossen rearrangement).[19−20]

In this research, the use of a novel and inexpensive reagent for efficient generation of alkyl isocyanates from alcohols, thiols, and trimethylsilyl ethers is reported.

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$$RX \xrightarrow[\text{CH}_3\text{CN, reflux}]{\text{TT}/n\text{-Bu}_4\text{NOCN}} RNCO$$
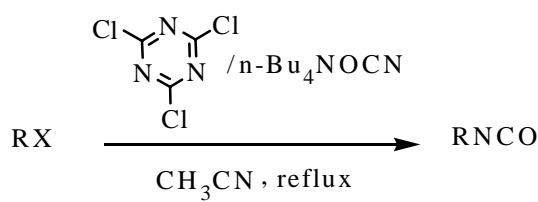
$X = OH, SH, OSiMe_3$

R = 1 °, 2 °, and 3 ° alkyl

Scheme 1

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 Brucker Avance DPX 250 MHz spectrometer. The products were purified by column chromatography and purity determination of the products was accomplished with GLC on a Shimadzu model GC 10-A gas chromatograph using n-octane as the internal standard or by thin layer chromatography on silica gel polygram on SIL G/UV 254 plates.

Typical Procedure for the Conversion of Benzyl Alcohol to Benzyl Isocyanate

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$_4$NOCN (0.568 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 2.5 h. The solvent was evaporated under reduced pressure. Column chromatography of the crude product on silica-gel using n-hexane as eluent gave benzyl isocyanates in 98% yield.

Results and Discussion

Recently, we reported the application of $Ph_3P/DDQ/$ R$_4$NX (X = Cl, Br, I, CN, N$_3$, ONO, OCN) and TT/R$_4$NX (X = CN, ONO) systems for conversion of alcohols, thiols, selenols, trimethylsilyl ethers, and tetrahydropyranyl ethers into their corresponding alkyl halides, cyanides, azides, nitrites, and isocyanates.[21−29] In a continuation of these studies, we now report that 1°, 2°, and 3° alcohols, thiols, and trimethylsilyl ethers can be efficiently and smoothly converted into their corresponding alkyl isocyanates in good to excellent yields using TT/n-Bu$_4$NOCN under neutral and mild reaction conditions (Scheme 1).

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,[30−34] alcohols, and aldehydes,[35−36] as well as alkyl chlorides[37] and acyl azides.[38]

In order to optimize the reaction conditions, at first the effect of different molar ratios of ROH/TT/n-Bu$_4$NOCN, solvent, and temperature for conversion of $PhCH_2OH$ to $PhCH_2NCO$ were examined. Employing the ratio of 1:2:2 in refluxing CH_3CN gave the best result and produced $PhCH_2NCO$ after 2.5 h in 98%

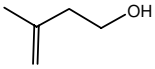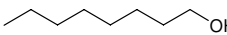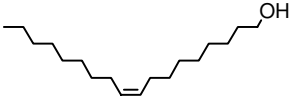**Table 1.** Conversion of alcohols, thiols, and trimethylsilyl ethers into alkyl isocyanates in dry acetonitrile.
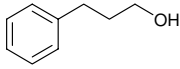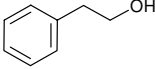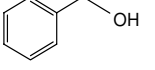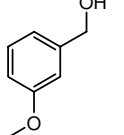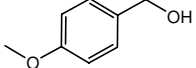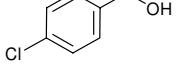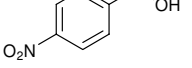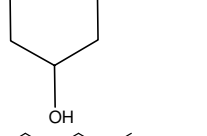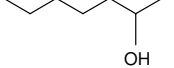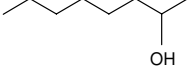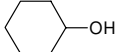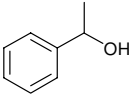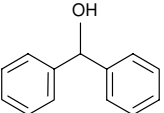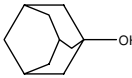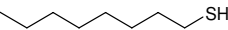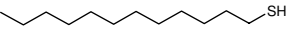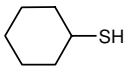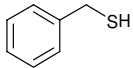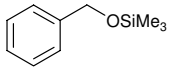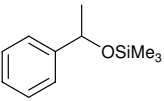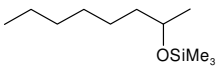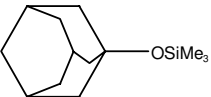
Entry	ROH	Time(h)	Conversion %[a]	Isolated Yield %
1		3	100	98
2		3.5	100	92
3		3	100	94
4		5	100	90
5		5.5	100	93
6		2.5	100	98
7		1.5	100	98
8		1	100	98
9		3	100	97
10		6.5	100	92
11		10	100	98
12		10.5	100	96
13		11	100	95
14		12	100	99

Table 1. Continued.

Entry	ROH	Time(h)	Conversion % [a]	Isolated Yield %
15		8	100	90
16		27	100	94
17		21	100	97
18		25	100	95
19		28	100	97
20		30	100	97
21		31	100	96
22		28	100	94
23		5	100	98
24		10	100	90
25		16	100	95
26		35	100	92

[a] GC yield using internal standard

Table 2. Selective reaction of different binary mixtures with TT/n-Bu₄NOCN.
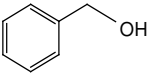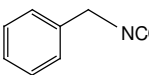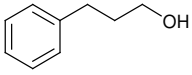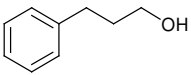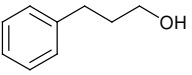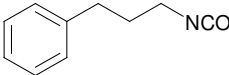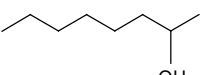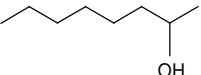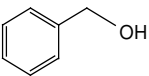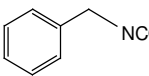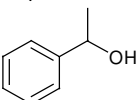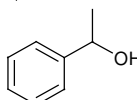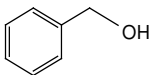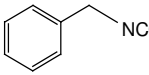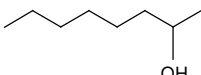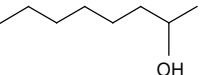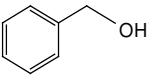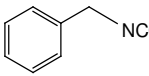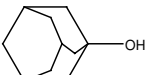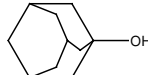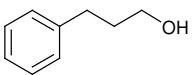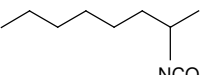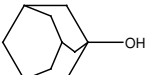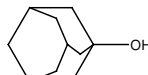
Entry	Binary Mixture	Products	Time (h)	Yield %[a]
1			3.5	100
				96
2			5.5	100
				93
3			4.5	100
				95
4			4	100
				98
5			6.5	100
				97
6			10.5	100
				98

Table 2. Continued.
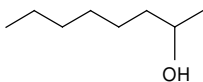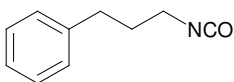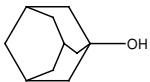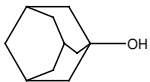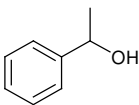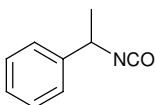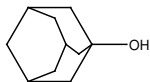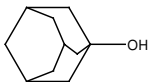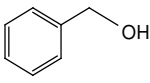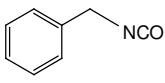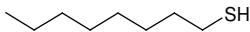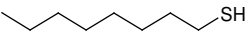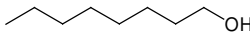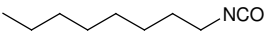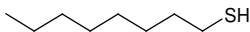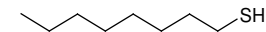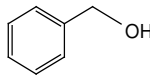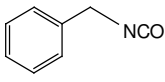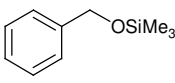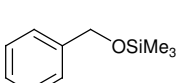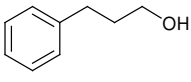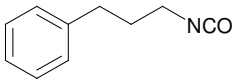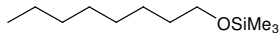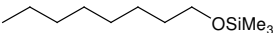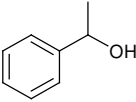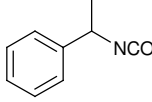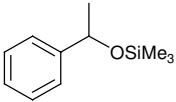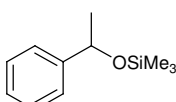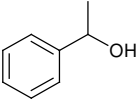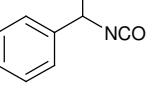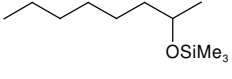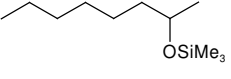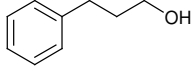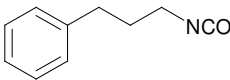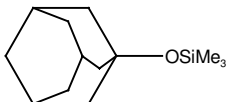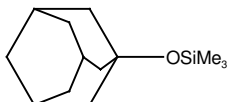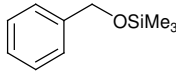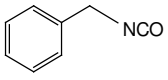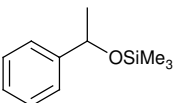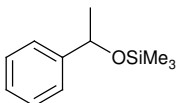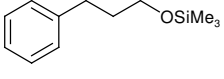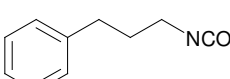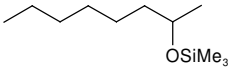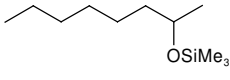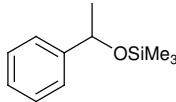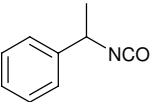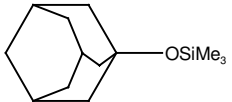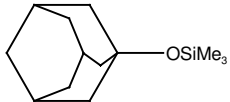
Entry	Binary Mixture	Products	Time (h)	Yield %[a]
7	(2-heptanol, OH)	(3-phenylpropyl NCO)	25	100
	(1-adamantanol, OH)	(1-adamantanol, OH)		97
8	(1-phenylethanol, OH)	(1-phenylethyl NCO)	11	100
	(2-adamantanol, OH)	(2-adamantanol, OH)		97
9	(benzyl alcohol, OH)	(benzyl NCO)	5	100
	(octanethiol, SH)	(octanethiol, SH)		95
10	(octanol, OH)	(octyl NCO)	5.5	100
	(octanethiol, SH)	(octanethiol, SH)		98
11	(benzyl alcohol, OH)	(benzyl NCO)	6	100
	(benzyl OSiMe$_3$)	(benzyl OSiMe$_3$)		97
12	(3-phenylpropanol, OH)	(3-phenylpropyl NCO)	7	100
	(octyl OSiMe$_3$)	(octyl OSiMe$_3$)		92

Table 2. Continued.

Entry	Binary Mixture	Products	Time (h)	Yield %[a]
13			13	100
				94
14			9.5	100
				97
15			8	100
				96
16			7	100
				95
17			10.5	100
				96
18			12	100
				97

[a]GC yield using internal standard.

isolated yield. We then applied our optimized conditions for the conversion of structurally different alcohols into their corresponding alkyl isocyanates. The results are shown in Table 1, which show that this method is very suitable for the conversion of primary, secondary, tertiary, and benzylic alcohols. We also applied this method for the conversion of thiols and trimethylsilyl ethers to their corresponding alkyl isocyanates (Table 1, entries 18-25).

A ^{13}C-NMR signal at 127 ppm is assigned to the quaternary carbon of N=C=O, as well as a strong and sharp absorption band at 2280-2230 cm^{-1} and a weak absorption band at 1450-1380 cm^{-1}due to the isocyanate group.

As is demonstrated in Table 1, the use of TT/n-Bu$_4$NOCN is very suitable for conversion of primary, secondary, and benzylic alcohols. We also used this method for the conversion of thiols to their corresponding alkyl isocyanates (Table 1, entries 18-21). When we applied our method to trimethylsilyl ethers, the reactions furnished their corresponding alkyl isocyanates in high yields (Table 1, entries 22-25).

This method is highly selective for alcohols. In a binary mixture of 3-phenyl-1-propanol and 2-octanol, the primary alcohol was completely converted to its isocyanate, while the secondary alcohol remained intact (Table 2, entry 2). Excellent selectivity was also observed for the conversion of 1° alcohol in the presence of a 3° alcohol and 2° alcohol in the presence of a 3° alcohol (Table 2, entries 5-8). The high selectivity for the conversion of alcohols in the presence of thiols was also demonstrated (Table 2, entries 9 and 10). Similarly, this method showed excellent selectivity for conversion of 1°, 2°, and 3° alcohols to their corresponding isocyanates in the presence of trimethylsilyl ethers (Table2, entries 11-15). Moreover, 1° silyl ether was converted to its isocyanates in the presence of 2° and 3° silyl ether (Table 2, entry 16-18).

In conclusion, the present investigation demonstrated that the use of TT/n-Bu$_4$NOCN offers a simple, novel, and convenient method for conversion of a wide variety of alcohols, thiols, and trimethylsilyl ethers to their corresponding alkyl isocyanates. The method shows excellent selectivity, not only between different alcohols, but also between alcohols, thiols, and trimethylsilyl ethers. Availability, safety, ease of handling the reagents, high yields, and mildness of the reaction conditions make this method novel for direct conversion of alcohols, thiols, and trimethylsilyl ethers to isocyanates.

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