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Preparation of thiocyanates and isothiocyanates from alcohols, thiols, trimethylsilyl-, and tetrahydropyranyl ethers using triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)/*n*-Bu_4NSCN system

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Abstract—A combination of triphenylphosphine (PPh_3) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) provides a safe and easily available mixed reagent system for the conversion of 1° and 2° alcohols, thiols, trimethylsilyl-, and tetrahydropyranyl ethers to their corresponding thiocyanates and the 3° ones to isothiocyanates in good to high yields.

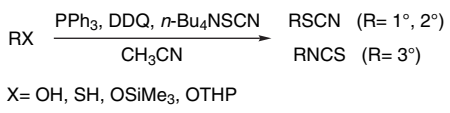
1. Introduction

The Mitsunobu reaction has been widely used for the displacement of alcohols by different nucleophiles.[1–3] In this reaction, in which a mixture of triphenylphosphine, diethyl azodicarboxylate (DEAD), and a nucleophile is used, the phosphine and the azodicarboxylate accepts the oxygen and the hydrogen atoms, respectively, to give triphenylphosphine oxide and a hydrazine derivative with the consequent replacement of the hydroxyl group by the nucleophile. Among these transformations, the conversion of a hydroxyl group to a thiocyanate functionality is widely used for the preparation of heterocycles.[4,5] Recently, we reported a new application for the Mitsunobu reaction and studied the reaction of alcohols, thiols, carboxylic acids, trimethylsilyl ethers, and carboxylates with PPh_3/DEAD/NH_4SCN.[6]

Prior to this work, we also reported on the use of in situ generated $PPh_3(SCN)_2$ for the conversion of alcohols,[7b] thiols,[8] and also trimethylsilyl ethers[9] to alkyl thiocyanates. Apart from the above mentioned methods, the use of $KSCN{\cdot}CuBr_2$,[10] solid-supported potassium thiocyanate,[11] and thiocyanate ion[12] preferably in the presence of phase-transfer agents[13–16] are widely used for the preparation of thiocyanates from alkyl halides.

2. Results and discussion

Recently we reported the use of DDQ as a suitable replacement for DEAD for the preparation of alkyl halides, nitriles, and azides from alcohols.[17] Very recently, the use of DDQ for the preparation of isocyanides from alcohols and thiols was also reported.[18] To reduce the problems encountered in thiocyanation reactions using the Mitsunobu reagent system[6] or $PPh_3(SCN)_2$,[7–9] e.g., DEAD is expensive, is not easily available, and may explode on heating and the poisonous $PPh_3(SCN)_2$ should be prepared freshly before use, we now report that the combination of PPh_3 and DDQ in the presence of *n*-Bu_4NSCN, which are readily available solid reagents, offers a simple and safe method for the conversion of primary and secondary alcohols as well as thiols, trimethylsilyl-, and tetrahydropyranyl ethers into their corresponding thiocyanates and tertiary systems into their isothiocyanates in good to high yields (Scheme 1).



Scheme 1.

We first carried out a comparative study on the possibility of using different electron-deficient reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), 2,3,5,6-tetrachlorobenzoquinone (*p*-chloranil), tetracyanoethylene (TCNE), tetraphenylcyclopentadienone (tetracyclone), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) as well as diethyl acetylenedicarboxylate (DEACD) in conjunction with PPh_3

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and *n*-Bu_4NSCN for the conversion of benzyl alcohol to benzyl thiocyanate as a model reaction. The results obtained from this study (Table 1) show that the combination of PPh_3/DDQ/*n*-Bu_4NSCN and PPh_3/*p*-chloranil/*n*-Bu_4NSCN provides the most suitable reagent systems for this transformation and benzyl thiocyanate was formed in quantitative yield. Of these two reagent systems, the use of DDQ provides a much shorter reaction time (almost immediately) compared to using *p*-chloranil (8 h). The combination of PPh_3/DEAD/*n*-Bu_4NSCN produced only 20% of benzyl thiocyanate after 24 h and other reagent systems none. As we reported already,[6] this reaction occurs using the combination of DEAD, PPh_3, and NH_4SCN. However, apart from the problems encountered using DEAD, ammonia is also produced in the reaction, which could be harmful to some base-sensitive functional groups.

Table 1. Conversion of benzyl alcohol to benzyl thiocyanate using *n*-Bu_4NSCN in the presence of Ph_3P and different reagents in acetonitrile at room temperature

Entry	Reagent[a]	Time (h)	Conversion %[b]
1	DDQ	<1 min	100
2	*p*-Chloranil	8	100
3	DEAD	24	20
4	DEACD	24	0
5	TCNE	24	0
6	Tetracyclone	24	0
7	PTAD	24	0

[a] The stoichiometric ratio of PPh_3/DDQ/*n*-Bu_4NSCN/ROH is 2:2:2:1.
[b] GC yield using an internal standard.

We also used NH_4SCN instead of *n*-Bu_4NSCN but the reaction did not finished after 24 h and benzyl thiocyanate was formed only in 30% yield.

The order of addition of reagents is also very important. The mixture of PPh_3 and DDQ is first prepared in acetonitrile and *n*-Bu_4NSCN is added to this mixture followed by the addition of alcohol.

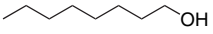
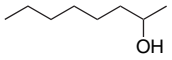
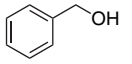
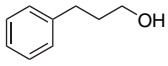
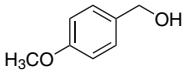
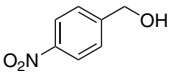
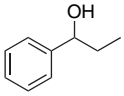
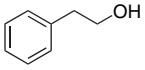
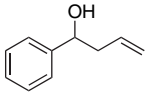
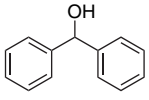
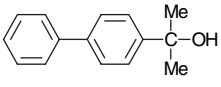
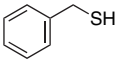
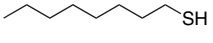
Using this method, primary alcohols are converted to their corresponding alkyl thiocyanates without the formation of any isothiocyanates, but secondary alcohols give also some minor amounts of isothiocyanates as a side-product. In the case of a tertiary alcohol, the isothiocyanate is formed as the major product together with small amounts of eliminated product.

^{13}C resonance of the –SCN and –NCS groups at ~111 and ~145 ppm, respectively, are very characteristic for thiocyanate and isothiocyanate functionalities.[7b,9,19] The formation of isothiocyanates does not occur through the isomerization of the corresponding thiocyanates since, when we heated the crude reaction mixture obtained from the reaction of 1-phenylpropanol at 25 °C to 60–70 °C, no change in the distribution of the isomeric products (RSCN, RNCS) was observed. Thus, their formation is due to the ambident nature of the NCS^- nucleophile and this is in agreement with the reported data in the literature.[20,21] Lowering the reaction temperature from 25 to 0 °C had also no significant effect on this distribution.

We then applied this method for the conversion of thiols to their corresponding thiocyanates. The results are shown in Table 2. In these reactions, thiocyanates were obtained in high yield without the formation of any disulfides through the dimerization of thiols.

Trimethylsilyl- and tetrahydropyranyl ethers are popular forms of protected hydroxyl groups, which are practical precursors for the preparation of many other compounds and their controlled transformation to other functional groups has been considered as an interesting goal in organic synthesis.[22,23]

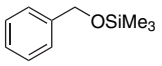
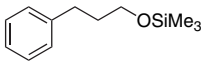
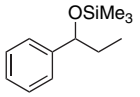
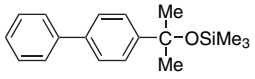
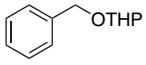
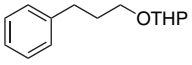
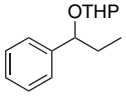
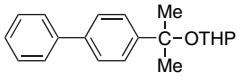
Table 2. Conversion of alcohols and thiols to alkyl thiocyanates or isothiocyanates

Entry	RX	RSCN/RNCS[a]	Time	Isolated yield % (ref)
1		100/0	5 min	90 (19a)
2		74/26	15 min	88[b] (20)
3		100/0	<1 min	95 (7b)
4		100/0	<1 min	92 (7b)
5		100/0	<1 min	92 (7b)
6		100/0	<1 min	90 (19)
7		61/39	<1 min	94[b] (7b)
8		100/0	<1 min	90 (7b)
9		60/10	<1 min	55[b,c] (19)
10		82/18	75 min	92[b] (7b)
11		0/80	20 h	68[c,d] (19)
12		100/0	45 min	90 (7b)
13		100/0	1 h	87 (19a)
14		80/20	90 min	90[b] (7b)

[a] GC and NMR yield using an internal standard.
[b] Mixture of thiocyanate and isothiocyanate was obtained.
[c] Eliminated product (15–20%) was also produced.
[d] This reaction was performed under reflux.

Trimethylsilyl- and tetrahydropyranyl ethers reacted efficiently with the same mixed reagent system and produced the corresponding thiocyanates or isothiocyanates in high yields. The results are shown in Table 3.

Table 3. Conversion of silyl- and THP-ethers to thiocyanates or isothiocyanates in acetonitrile[a]

Entry	RX	RSCN/RNCS[b]	Time	Isolated yield %
1		100/0	<1 min	91
2		100/0	<1 min	93
3		78/22	10 min	90
4		0/80	24 h	72[c,d]
5		100/0	13 h	92
6		100/0	15 h	88
7		77/23	20 h	90
8		0/85	40 h	78[c]

[a] The reactions of silyl ethers were performed at room temperature and THP-ethers under reflux conditions.
[b] GC and NMR yield using an internal standard.
[c] Eliminated products are also produced.
[d] Reflux condition.

Similar to the reaction of alcohols and thiols, primary silyl- and tetrahydropyranyl ethers produced exclusively the corresponding thiocyanates. In the case of secondary alcohols and thiols, thiocyanates were also formed as the major products together with minor amounts of the corresponding isothiocyanates, however, tertiary systems produced only isothiocyanates and small amounts of the eliminated product.

In conclusion, the use of DDQ instead of DEAD in conjunction with PPh_3 and *n*-Bu_4NSCN as safe, available, and easy handling reagents offers a simple, novel, and convenient method for the conversion of wide varieties of alcohols, thiols, trimethylsilyl-, and tetrahydropyranyl ethers to their corresponding thiocyanates or isothiocyanates.

3. Experimental

All the solvents and reagents were purchased from Fluka or Merck chemical Companies. The products were purified by column or prep. TLC techniques and identified by comparison of their spectral data with those of known compounds.[7b,9,19] FTIR spectra were recorded on a Shimadzu DR-8001 spectrometer. NMR spectra were recorded on a Brucker Avance DPX 250 MHz instrument. Mass spectra were recorded on a Shimadzu GC–MS-QP 1000PX.

3.1. Typical procedure for the conversion of benzyl alcohol to benzyl thiocyanate

A mixture of DDQ (2.0 mmol, 0.454 g) and PPh_3 (2.0 mmol, 0.524 g) in dry CH_3CN (5 ml), was stirred at room temperature for 5 min. Then, *n*-Bu_4NSCN (2.0 mmol, 0.6 g) was added and while the reaction mixture was stirring, benzyl alcohol (1.0 mmol, 0.108 g) was added. GC analysis showed the immediate completion of the reaction. The solvent was evaporated. Column chromatography of the crude mixture on silica-gel using *n*-hexane–ethyl acetate (3:1) as eluent gave benzyl thiocyanate as pale yellow crystals, 0.134 g, 95% yield (mp 40 °C, lit.[19a] mp 39–40 °C). IR (–SCN): 2155 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 7.3 (5H, s), 4.1 (2H, s); ^{13}C NMR ($CDCl_3$): δ (ppm) 134.8, 132.6, 129.6, 129.4, 112.2, 38.7.

3.2. Typical procedure for the conversion of trimethyl-(1-phenyl-propoxy)-silane to (1-thiocyanato-propyl)-benzene

To a flask containing a stirring mixture of DDQ (2.0 mmol, 0.454 g) and PPh_3 (2.0 mmol, 0.524 g) in dry CH_3CN (5 ml), was added *n*-Bu_4NSCN (2.0 mmol, 0.6 g) at room temperature. Then, trimethyl-(1-phenyl-propoxy)-silane (1 mmol, 0.2 g) was added to the mixture. The progress of the reaction was followed by GC. After completion of the reaction, solvent was evaporated. Column chromatography of the crude mixture on silica-gel using *n*-hexane–ethyl acetate (3:1) as eluent gave (1-thiocyanato-propyl)-benzene (Table 3, entry 3) as the main product with 75% yield. IR (–SCN): 2160 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 0.96 (3H, t), 2.1 (2H, m), 4.6 (1H, t), 7.2–7.4 (5H, m); ^{13}C NMR ($CDCl_3$): δ (ppm) 137.1, 127.8, 127.7, 124.7, 111.9, 54.2, 31.3, 11.1.

3.3. Typical procedure for the conversion of 2-(1-biphenyl-4-yl-ethoxy)-tetrahydro-pyran to 4-(1-isothiocyanato-1-methyl-ethyl)-biphenyl

To a refluxing solution of PPh_3 (2 mmol, 0.524 g), DDQ (2 mmol, 0.454 g), and *n*-Bu_4NSCN (2 mmol, 0.6 g) in dry CH_3CN (5 ml) was added 2-(1-biphenyl-4-yl-ethoxy)-tetrahydro-pyran (1 mmol, 0.296 g). After 40 h, the solvent was evaporated. Column chromatography on silica-gel using *n*-hexane–ethyl acetate (3:1) as eluent gave 4-(1-isothiocyanato-1-methyl-ethyl)-biphenyl (Table 3, entry 8) in 78% yield.

IR (–NCS): 2085 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.8 (6H, s), 7.1 (2H, d), 7.5 (5H, m), 8.3 (2H, d); ^{13}C NMR ($CDCl_3$): δ (ppm) 158.9, 145.9, 138.1, 132.2, 130.8, 129.7, 128.2, 124.9, 120.8, 56.0, 19.9.

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