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RESEARCH ARTICLE

Highly selective conversion of 1° and 2° tetrahydropyranyl ethers to thiocyanates and 3° ones to isothiocyanates using triphenylphosphine/diethyl azodicarboxylate/NH_4SCN

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An efficient and selective method is described for the conversion of 1° and 2° tetrahydropyranyl (THP) ethers to their corresponding thiocyanates and 3° ones to isothiocyanates using a triphenylphosphine/diethyl azodicarboxylate (DEAD)/NH_4SCN reagent system. This system is highly selective for thiocyanation of 1° THP-ethers in the presence of 2° and 3° ones and also 2° THP-ethers in the presence of a 3° analog. With this selective method, alcohols and trimethylsilyl ethers react, while THP-ethers remained intact in the presence of alcohols and trimethylsilyl ethers.

Keywords: Triphenylphosphine (PPh_3); Diethyl azodicarboxylate (DEAD); Thiocyanation; Tetrahydropyranyl ether

1. Introduction

Tetrahydropyranylation is one of the most practical and important ways of protecting hydroxyl groups of alcohols and phenols especially, in the synthesis of multi-functional organic molecules. Tetrahydropyranyl ethers (THP ethers) show remarkable stability towards many reagents and their synthetic transformation to other functional groups is an important step in organic synthesis [1]. A literature search reveals that only a few reports are available for direct conversion of THP ethers to functional groups other than the hydroxyl group. The examples are, conversion to bromides [2, 3], to sulfides [4], to acetates [5] and into esters [6].

2. Results and discussion

Recently, we have reported on the application of triphenylphosphine/diethyl azodicarboxylate (DEAD)/NH_4SCN as a useful thiocyanating system for conversion of alcohols, thiols, carboxylic acids, trimethylsilyl ethers and trimethylsilyl carboxylates into their corresponding

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Figure 1. Conversion of THP-ethers to thiocyanates or isothiocyanates.

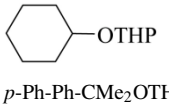
thiocyanates or isothiocyanates [7]. In this method which is an advancement of the Mitsunobu reaction [8, 9], we used NH_4SCN as a source of thiocyanate ion instead of $(SCN)_2$ [10–12] for thiocyanation reactions. In development of new synthetic applications for tetrahydropyranyl ethers, we wish to report the efficient conversion of primary and secondary tetrahydropyranyl ethers to their corresponding thiocyanate derivatives and tertiary THP ethers into isothiocyanates using the $PPh_3/DEAD/NH_4SCN$ reagent system (figure 1).

Optimization of the reaction conditions showed that for a mixture of benzyl tetrahydropyranyl ether/PPh_3/DEAD/NH_4SCN, the stoichiometric ratio of 1/2/2/2.5 and refluxing acetonitrile are the most suitable conditions for conversion of benzyl tetrahydropyranyl ether to benzyl thiocyanate.

Using this method, benzyl and 4-substituted benzyl tetrahydropyranyl ethers with electron withdrawing or donating groups (table 1, entries 1–4) were transformed to their thiocyanates in excellent yields without the formation of any isothiocyanates as by-products. Previous reports indicate that the preparation of benzyl thiocyanate from its alcohol is a difficult task due to the formation of a substantial amount of benzyl isothiocyanate [13]. With this reagent system, a selection of primary and secondary alkyl tetrahydropyranyl ethers were also converted to their corresponding thiocyanates in excellent selectivity and yields (table 1, entries 5–9). The formation of isothiocyanate only arose from the reaction of a tertiary benzylic tetrahydropyranyl ether with this method shown in table 1, entry 10.

On the basis of Mitsunobu reaction [8], a mechanism was suggested for this transformation (figure 2). The formation of ammonia in the first step of this reaction was observed after addition of ammonium thiocyanate to a solution of triphenyl phosphine and diethyl azodicarboxylate in refluxing acetonitrile. Since inversion has been reported for the conversion of secondary alcohols into alkyl halides by Mitsunobu reaction [8d], a inversion of configuration is proposed in the mechanism.

Table 1. Conversion of THP-ethers to thiocyanates or isothiocyanates.

Entry	ROTHP	Time (h)	Yield (%)[a]	RSCN/RNCS[b]	Ref.[c]
1	$C_6H_5CH_2OTHP$	12	98	100/0	14(a)
2	4-$NO_2C_6H_5CH_2OTHP$	28	95	100/0	10(a)
3	4-$ClC_6H_5CH_2OTHP$	24	95	100/0	14(c)
4	4-$MeOC_6H_5CH_2OTHP$	20	96	100/0	10(b)
5	$CH_3(CH_2)_6CH_2OTHP$	7	100	100/0	14(d)
6	$CH_3(CH_2)_5CH(CH_3)OTHP$	18	75	96/4	14(c)
7	$C_6H_5CH(CH_3)OTHP$	28	82	95/5	11
8	$C_6H_5CH_2CH_2OTHP$	9	90	100/0	10(a)
9		30	90c	96/4	14(a)
10	*p*-Ph-Ph-CMe_2OTHP	30	65	0/100	15, 16

[a]Isolated yield.
[b]GC yield using internal standard.
[c]All the products are known compounds and were identified by comparison of their physical and spectral data with those of known compounds.

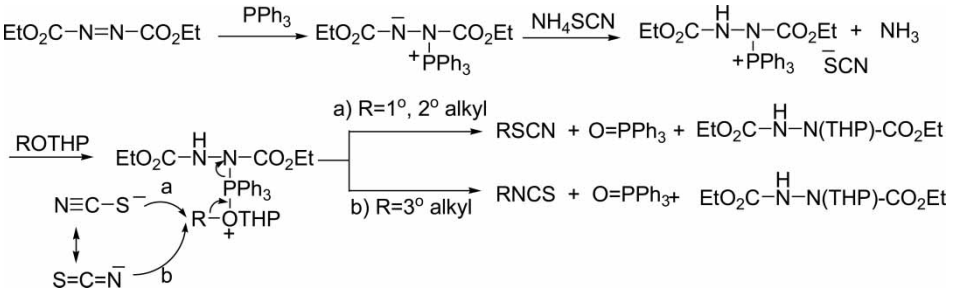


Figure 2. Suggested mechanism for reaction of THP-ethers with PPh_3/DEAD/NH_4SCN.

In order to investigate the selectivity of this method, we studied the thiocyanation reaction between different classes of THP ethers, alcohols and THP ethers and also silyl ethers and THP ethers in binary mixtures. Good to high selectivity was observed for the conversion of a 1° THP ether in the presence of 2°, and 3° ones, and a 2° THP ether in the presence of a 3° one (table 2, entries 1–3).

We also observed that in the presence of reacting alcohols, tetrahydropyranyl ethers remain intact. For example, primary, secondary, and also tertiary alcohols are converted to their corresponding thiocyanates or isothiocyanates with excellent selectivity in the presence of their THP ethers (table 2, entries 4–7). Similarly, this method showed excellent selectivity for the conversion of 1° and 2° trimethylsilyl ethers to their corresponding thiocyanates and 3°

Table 2. Selective reaction of different binary mixtures with PPh_3/DEAD/NH_4SCN.

Entry	Binary mixture	Time (h)	Yield (%)[a]
1	$C_6H_5CH_2OTHP$ $CH_3(CH_2)_5CH(CH_3)OTHP$	15	90 0
2	$CH_3(CH_2)_6CH_2OTHP$ *p*-Ph-Ph-CMe_2OTHP	30	85 0
3	$CH_3(CH_2)_5CH(CH_3)OTHP$ *p*-Ph-Ph-CMe_2OTHP	35	75 0
4	$C_6H_5CH_2OH$ $C_6H_5CH_2OTHP$	7	100 0
5	$CH_3(CH_2)_6CH_2OH$ $CH_3(CH_2)_6CH_2OTHP$	24	90 0
6	$CH_3(CH_2)_5CH(CH_3)OH$ $CH_3(CH_2)_5CH(CH_3)OTHP$	35	75 0
7	*p*-Ph-Ph-CMe_2OH *p*-Ph-Ph-CMe_2OTHP	48	60 0
8	$C_6H_5CH_2OSiMe_3$ $C_6H_5CH_2OTHP$	27	90 0
9	$CH_3(CH_2)_6CH_2OSiMe_3$ $CH_3(CH_2)_6CH_2OTHP$	25	100 0
10	$CH_3(CH_2)_5CH(CH_3)OSiMe_3$ $CH_3(CH_2)_5CH(CH_3)OTHP$	72	80 0
11	*p*-Ph-Ph-CMe_2OSiMe_3 *p*-Ph-Ph-CMe_2OTHP	72	74 0

[a]GC and NMR yield using internal standard.

trimethylsilyl ethers to isothiocyanate in the presence of their tetrahydropyranyl ethers (table 2, entries 8–11).

In conclusion, the high selectivity for conversion of 1° and 2° tetrahydropyranyl ethers to their corresponding thiocyanates and 3° ones to isothiocyanates and selectivity between themselves are strong points favouring this method. In addition, the chemical resistance of THP ethers towards thiocyanation in the presence of alcohols and trimethylsilyl ethers can also be considered as another advantage for this method which will find value in synthetic applications.

3. Experimental

The products were purified by column chromatography and the purity determinations of the products were accomplished by GLC on a Shimadzu model GC-10A instrument or by TLC on silica-gel PolyGram SIL G/UV 254 plates. FT-IR spectra were recorded on a Shimadzu DR-8001 spectrometer. NMR spectra were recorded on a Brucker Avance DPX 250 MHz instrument.

Typical procedure for the conversion of benzyl tetrahydropyranyl ether to benzyl thiocyanate

To a flask containing a stirring mixture of PPh_3 (0.524 g, 2 mmol) and DEAD (0.348 g, 2 mmol) in reflux acetonitrile, was added ammonium thiocyanate (0.19 g, 2.5 mmol). Benzyl tetrahydropyranyl ether (0.192 ml, 1 mmol) was then added to this mixture. GC analysis showed the completion of the reaction after 12 h. The solvent was evaporated under reduced pressure. Column chromatography of the crude mixture on silica-gel using *n*-hexane as eluent gave benzyl thiocyanate in 0.146 g, 98% yield (m.p. 40 °C, Lit. [14a] m.p. 39–40 °C); IR (CCl_4): 2155 cm^{-1}(-SCN), ^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.

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