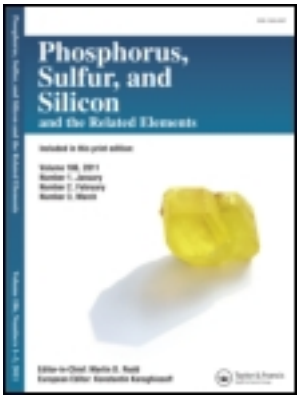

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Remarkably Fast and Mild Solvent-Free Conversion of Epoxides into Thiocyanohydrins Using Mukaiyama Reagent

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REMARKABLY FAST AND MILD SOLVENT-FREE CONVERSION OF EPOXIDES INTO THIOCYANOHYDRINS USING MUKAIYAMA REAGENT

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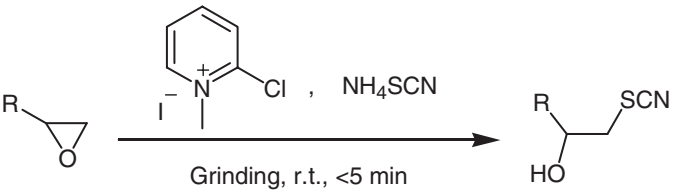
GRAPHICAL ABSTRACT



Abstract *A mild and operationally simple method for the synthesis of thiocyanohydrins is described. Mukaiyama reagent is used as an effective reagent for the solvent-free conversion of epoxides into their corresponding thiocyanohydrins. The reactions were completed in <5 min to give thiocyanohydrins with perfect regioselectivity and isolated yields.*

Keywords Mukaiyama reagent; 2-chloro-1-methylpyridinium iodide; ring opening; epoxide; thiocyanohydrin; solvent-free

INTRODUCTION

N-Alkyl-2-halopyridinium salts have gained a lot of interest in organic synthesis as they can be used as an acid-activating agent.[1] In particular, 2-chloro-1-methylpyridinium iodide (CMPI) (Mukaiyama reagent) has been used to convert carboxylic acids into esters,[2] amides,[3] lactones,[4] lactams,[5] and ketenes,[6] as well as thioureas into carbodiimides[7] and quinazolin-4-one into 3-alkylquinazolin-4-ones.[8] The modified Mukaiyama reagent such as polymer-supported[9,10] and fluorous Mukaiyama reagent[11] was also used for the dehydration of thioureas, guanylation of primary amines,[9] and for synthesis of esters and amides.[10,11]

Although there are many methods reported for activating carboxylic acid with Mukaiyama reagent, the activation of epoxide with this reagent is rarely found in the literature. The use of benzoxazolium salt was reported for the conversion of epoxides into *vic*-symmetrical dichloride.[12]

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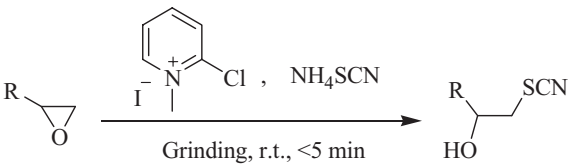
Ring-opening of epoxides with thiocyanate ion is a synthetically useful method for the preparation of thiocyanohydrins. There are many methods reported in the literature for this preparation and the most general one has been the conversion of epoxides to thiocyanohydrins with different types of reagents and catalysts such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[13] $Ph_3P(SCN)_2$,[14] isothiocyanatotrimethylsilane,[15] phenol-containing macrocyclic diamides,[16] tetraphenylporphyrins (TPP),[17] 2-phenyl-2-(2-pyridyl)imidazolidine,[18] metalloporphyrins,[19] poly(ethylene glycol)-bound sulfonic acid (PEG-SO_3H),[20] boron sulfonic acid [$B(HSO_4)_3$],[21] dowex,[22] silica sulfuric acid,[23] gallium trichloride,[24] thioxanthenone-fused azacrown ethers,[25] schiff-base metal (II) complexes,[26] multisite phase-transfer catalyst (MPTC),[27] $Al(HSO_4)_3$/silica gel,[28] and Zeolite molecular sieve 4 Å,[29] and using high quantities of NH_4SCN in the absence of any catalysis.[30] Though the reported methods are useful for preparation of thiocyanohydrin from epoxide, however, some of these protocols suffer from disadvantages such as long reaction times, use of volatile organic solvents and expensive reagents, low regioselectivity, and high reaction conditions. Thus, the development and introduction of convenient which use green and mild reaction conditions are practically concerned and still in demand.

RESULTS AND DISCUSSION

Recently, we reported a new application of Mukaiyama reagent for the conversion of alcohols into alkyl thiocyanates both under solvent and solvent-free conditions.[31] In conjunction with this research, and in continuation of our previous work on the synthesis of thiocyanate compounds,[32] we would like to report the successful use of Mukaiyama reagent (CMPI) and NH_4SCN for the conversion of epoxides into corresponding thiocyanohydrins under solvent-free condition (Scheme 1).



Scheme 1 Conversion of epoxide into thiocyanohydrin using CMPI/NH_4SCN.

In order to obtain the optimum conditions, several reactions were carried out on oxiranylmethyl phenyl ether as a model substrate by varying the amount of CMPI and

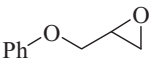
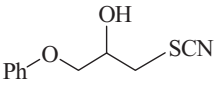
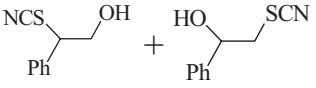
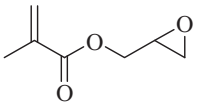
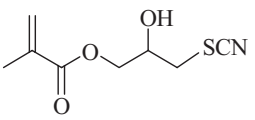
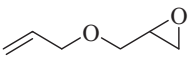
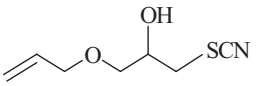
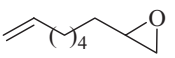
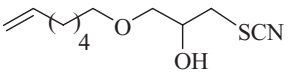
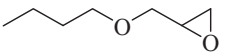
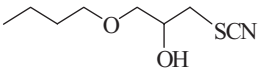
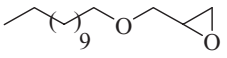
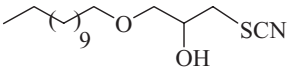
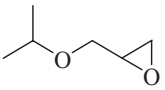
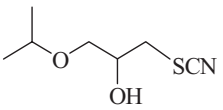
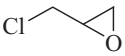
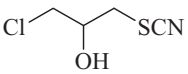
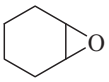
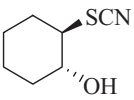
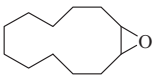
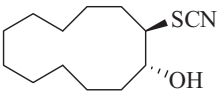
Table 1 Reaction of 1 mmol of oxiranylmethyl phenyl ether with CMPI and NH_4SCN under solvent-free condition

Entry	Molar ratio of CMPI/NH_4SCN	T (°C)	Time (min)	Yield (%)[a]
1	2:2	60	<5	98
2	2:2	r.t.	<5	96
3	1.5:1.5	r.t.	<5	95
4	1:1	r.t.	<5	97
5	0.5:1	r.t.	60	48
6	0.5:1	60	60	54

[a]Isolated yield; r.t. = room temperature.

NH_4SCN under solvent-free condition. Based on our previous finding for the conversion of alcohols into alkyl thiocyanates,[31] initial experiments were done with 2:2 molar ratio of CMPI/NH_4SCN. Subsequently, experiments using lower molar ratio of CMPI/NH_4SCN gave complete conversion of epoxide into corresponding thiocyanohydrin (Table 1, entry 4). Therefore, this molar ratio was selected as optimal condition and applied for other epoxides.

Table 2 Conversion of epoxides into thiocyanohydrines with CMPI and NH_4SCN under solvent-free condition at room temperature

Entry	Substrate	Product	Yield (%)[a]	Ref.[c]
1			90	20[a]
2			88 (96:4)[b]	25
3			86	20[b]
4			98	20[b]
5			80	20[b]
6			90	20[a]
7			78	20[b]
8			75	18
9			80	16
10			90	20[b]
11			70	21

[a]Isolated yield. [b]The ratio of isomers was determined by ^1H NMR spectroscopy. [c]All the products are known compounds and are identified by comparison of their physical and spectral data with literature.

Table 3 Comparison of thiocyanation of 1 eq. of styrene oxide using different methods

Entry	Reagent	NH_4SCN(eq)	Solvent	Condition	Time (min)	α attack[a]	β attack[b]	Yield (%)
1	DDQ[13]	—	CH_3CN	Reflux	50	89	11	91
2	TPP[17]	1	CH_3CN	Reflux	20	—	—	96
3	$Co^{II}T$(p-OH P)P [19]	1	CH_3CN	Reflux	25	17	83	96
4	PEG-SO_3H[20a]	3	Water	r.t.	60	96	4	83
5	$B(HSO_4)_3$[21]	1.5	Solvent-free	r.t.	4	92	8	91
6	MPTC[27]	2	H_2O	Reflux	15	95	5	88
7	$Al(HSO_4)_3$–Silicagel[28]	2	Solvent-free	r.t.	5	—	—	96
8	Zeolite molecular sieve 4 Å[29]	2	Solvent-free	r.t.	5	100	0	98
9	Catalyst-free[30]	2.4	CH_3CN	Reflux	75	70	30	80
10	NTS[32c]	1.5	CH_3CN	r.t.	15	90	10	95
11	CMPI	1	Solvent-free	r.t.	<5	96	4	88

[a]Attack of nucleophile on the more substituted carbon of epoxide. [b]Attack of nucleophile on the less substituted carbon of epoxide; r.t. = room temperature.

The product can be easily purified by washing with water successively to remove the byproducts *N*-methyl-2-pyridinone and other impurities.

Ring opening of other epoxides with the present method was also examined and the results summarized in Table 2. Styrene oxide underwent cleavage by this reagent in a regioselective manner with preferential attack at the benzylic carbon of styrene oxide (Table 2, entry 2). In the case of cyclic oxides, the reaction worked well and gave exclusively the corresponding trans-thiocyanohydrin (Table 2, entries 10, 11). The relative stereochemistry was determined based on the coupling constants of the peaks at δ 3.16 (m, $J = 15.4$ Hz, 1 H, CHSCN) and δ 3.34 ppm (m, $J = 15$ Hz, 1 H, CHOH) in their ^{1}H NMR spectra of 2-hydroxycyclohexylthiocyanate. This method is also compatible with functionalities such as ester groups, carbon–carbon double bond, and halogen. This reaction is highly selective for the formation of thiocyanohydrin as the only product in excellent yields keeping the intact other functionalities (Table 2, entries 3–5, 9).

The full comparison of previously reported method and present procedure is shown in Table 3. The present thiocyanolysis of epoxide have some priority over previously reported method with respect to the amount of NH_4SCN, reaction time and temperature, requirement of solvent, and regioselectivity of the product.

CONCLUSIONS

In summary, the present investigation has demonstrated that the use of Mukaiyama reagent with ammonium thiocyanate offers a simple, novel, and convenient method for the selective conversion of epoxides to their corresponding thiocyanohydrins under solvent-free condition. The experimental simplicity, mild reaction condition, reduced reaction times, inexpensive reagent, and high yields of the products with excellent regioselectivities, which make it potentially useful for the industrial applications.

EXPERIMENTAL

Products were characterized by comparison of their spectroscopic data (^{1}H and ^{13}C NMR, IR) with those reported in the literature. All yields refer to isolated products. The FT-IR spectra of neat samples between NaCl disks were obtained on a BOMEM 450 instrument. The high-field NMR spectra were obtained on a Bruker 400 MHz Avance ultrashield instrument. ^{1}H and ^{13}C chemical shifts are quoted relative to solvent resonance(s) as internal standard.

Typical procedure for the solvent-free preparation of 2-hydroxy-3-phenoxypropyl thiocyanate from oxiranylmethyl phenyl ether using CMPI/NH_4SCN: The preparation of 2-hydroxy-3-phenoxypropyl thiocyanate was carried out by grinding CMPI (0.255 g, 1 mmol) and NH_4SCN (0.076 g, 1 mmol) in a mortar for 1 min. Next, oxiranylmethyl phenyl ether (0.16 mL, 1 mmol) was added to the mixture and grinding was continued for an additional 2 min. After completion of the reaction, H_2O (5 mL) was added and the organic layer extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent and chromatography on a short silica gel column using *n*-hexane/EtOAc (5/2) as eluent gave 2-hydroxy-3-phenoxypropyl thiocyanate (0.188 g, 90%).

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