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# Melamine Sulfonic Acid: A Recoverable Catalyst for the Ecofriendly Synthesis of Thiocyanohydrins Under Solvent-Free Conditions

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# MELAMINE SULFONIC ACID: A RECOVERABLE CATALYST FOR THE ECOFRIENDLY SYNTHESIS OF THIOCYANOHYDRINS UNDER SOLVENT-FREE CONDITIONS

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***Melamine sulfonic acid as a novel and efficient solid acid catalyst has been synthesized and used in the ring opening of epoxides under solvent-free conditions. This catalyst afforded the corresponding thiocyanohydrins with good regioselectivity and very short reaction times. The catalyst can be easily separated and reused several times without appreciable loss of activity. The availability and recoverability of the catalyst with easy operation and workup make this method attractive for organic synthesis.***

***Keywords***: Melamine sulfonic acid; ring opening of epoxide; solid acid catalyst; thiocyanohydrin

Industrial chemists are widely adopting the concept of "green chemistry" to meet the key scientific challenges of protecting human health and the environment while simultaneously achieving commercial profitability.[1] To realize this goal, in recent years, significant articles have appeared reporting efficient solvent-free reactions by grinding.[2] This technique has many advantages such as reduced pollution, low cost, process simplicity, and easy workup. In addition, because of environmental acceptability, recently more attention has been paid to the application of inorganic acidic salts in organic synthesis.[3] Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal. Also, wastes and by-products can be minimized or avoided by using solid acids in developing cleaner synthetic routes.

The development of versatile and efficient methods for the synthesis of β-hydroxy thiocyanates has still been an active area of research, because β-hydroxy thiocyanates are important intermediates in agricultural biological and pharmaceutical chemistry.[4] As a suitable route to thiiranes, the reaction of epoxides with thiocyanate anion has been widely studied. It has been proved that this reaction is achieved thorough the β-hydroxy thiocyanate as an intermediate.[5] For this synthesis, it has been reported that the presence of some hydroquinone[6] or

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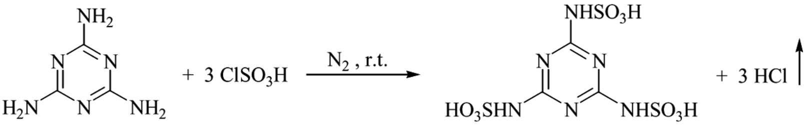


**Scheme 1.** Preparation of MSA.

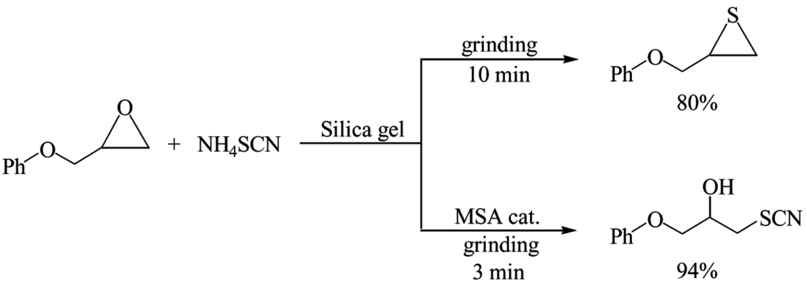
2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[4] is required to stabilize the produced β-hydroxy thiocyanate and to inhibit its conversion to thiirane. Although a few useful reagents have been reported for the ring opening of epoxides to the thiocyanohydrins,[7–11] some of these methods are not always fully satisfactory and suffer from disadvantages such as relative poor yields, long reaction times, use of toxic solvents or catalysts, high cost of reagents, poor regioselectivity, difficulty in workup, or harsh reaction conditions. Therefore, it seems that there is still a need for the development of novel methods that proceed under mild and economically appropriate conditions.

In continuation of our research on using water as a reaction medium[12–14] and our interest in developing a true catalyst using inexpensive and nonpolluting reagents,[14–17] here we report the regioselective ring opening of epoxides with thiocyanate anion in the presence of melamine sulfonic acid (MSA) as catalyst at room temperature under solvent-free conditions.

As described in Scheme 1, MSA, a novel and efficient solid acid, was easily prepared by addition of chlorosulfonic acid to melamine under an $N_2$ atmosphere at room temperature. The reaction is very easy and clean, because the evolved HCl gas can be removed from the reaction vessel immediately. This solid acid is not soluble in water or common polar or nonpolar organic solvents.

To ascertain the possible catalytic property of this solid acid, the reaction of 2, 3-epoxypropyl phenyl ether (1 mmol) with $NH_4SCN$ (1.5 mmol) in the presence of a catalytic amount of melamine sulfonic acid was studied under solvent-free conditions. This reaction was completed after 3 min and the corresponding thiocyanohydrin was obtained, whereas in the absence of catalyst, this reaction was completed after 10 min and corresponding thiirane was obtained as the only product (Scheme 2).

The results of the ring opening of 2,3-epoxypropyl phenyl ether in the presence of MSA using various solvents are summarized in Table 1. The results clearly show that although this reaction proceeded in refluxing acetonitrile, the best result was



**Scheme 2.** Ring opening of 2,3-epoxypropyl phenyl ether with and without catalyst.

**Table 1.** Solvent optimization in the ring opening of 2,3-epoxypropyl phenyl ether (1 mmol) by $NH_4SCN$ (1.5 mmol) in the presence of MSA (0.3 mmol)

| No. | Solvent/condition | Time (h) | Result |
|---|---|---|---|
| 1 | $CH_2Cl_2$/rt | 6 | No reaction |
| 2 | $CH_2Cl_2$/reflux | 6 | Thiocyanohydrin (60%) |
| 3 | $H_2O$/rt | 6 | Thiocyanohydrin (40%) |
| 4 | $H_2O$/reflux | 1 | Thiocyanohydrin + thiirane |
| 5 | $CH_3CN$/rt | 6 | Thiocyanohydrin (45%) |
| 6 | $CH_3CN$/reflux | 3 | Thiocyanohydrin (85%) |
| 7 | PEG/rt | 6 | Thiocyanohydrin + thiirane |
| 8 | —/silica gel (0.5 g) | 3 min | Thiocyanohydrin (94%) |

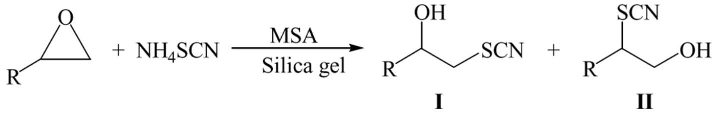
obtained under solvent-free conditions. Although the MSA can be stabilized the produced β-hydroxy thiocyanate under solvent-free conditions and without using silica gel, the presence of silica gel (0.5 g) for facile grinding of reaction media is necessary.

To show the general applicability of this method, we extended it to a variety of epoxides (Scheme 3, Table 2), and in all cases very clean reactions were observed. The structure of all the products were settled from their analytical and spectral (IR, $^1$H NMR, and $^{13}$C NMR) data and by direct comparison with authentic samples.[14]

The regioselectivity of the ring opening of epoxides is thoroughly dependent on the mechanism of the reaction and particularly on steric and electronic factors. According to $^1$H and $^{13}$C NMR spectra, unlike those obtained from epoxides carrying electron-withdrawing groups [which gave the regioisomer (I) based on steric effect], styrene oxide and 1,2-butene oxide gave regioisomer (II) according to more important electronic effect. Furthermore, cycloalkyl epoxides were reacted smoothly in an $S_N2$ fashion with $NH_4SCN$ in the presence of a catalytic amount of MSA to afford the corresponding β-hydroxy thiocyanates in excellent isolated yields. The stereochemistries of the ring-opening products were found to be *trans* from the coupling constants of the ring protons in $^1$H NMR spectrums (Scheme 4).

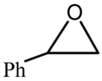
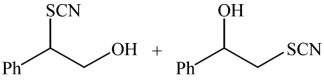
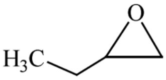
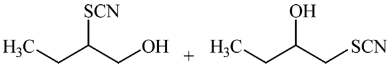
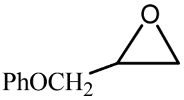
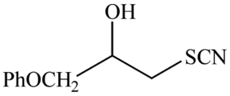
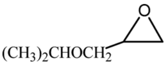
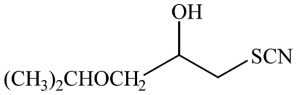
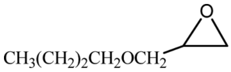
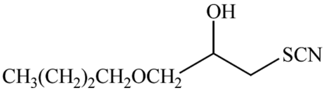
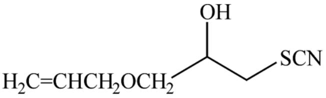
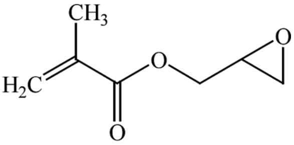
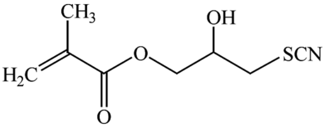
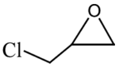
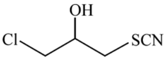
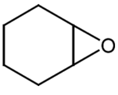
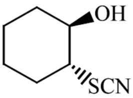
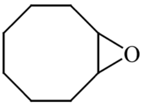
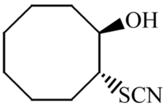
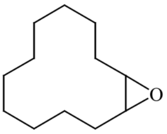
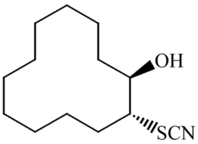
By comparison, the obtained results for the conversion of 2,3-epoxypropyl phenyl ether to the corresponding thiocyanohydrin in the presence of acidic catalysts are given in Table 3. As shown in Table 3, MSA has greater efficiency and shorter reaction time than other catalysts.

In conclusion, we have found that MSA can be easily prepared from inexpensive and nontoxic materials and can serve as an excellent catalyst in the conversion of a variety of epoxides carrying activated and deactivated groups into their corresponding β-hydroxy thiocyanates under solvent-free conditions. The advantages of the present protocol, such as environmental friendliness, short reaction times, simplicity in operation, the low cost of catalyst, high regioselectivity and stereoselectivity,



**Scheme 3.** Ring opening of epoxides to the thiocyanohydrins.

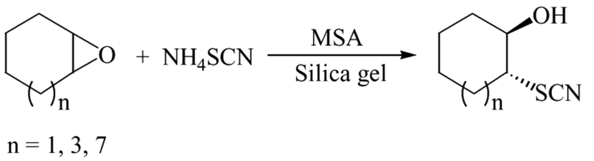
**Table 2.** MSA-catalyzed regioselective thiocyanation of epoxides

| No. | Substrate | Product(s)[a] | Time (min) | Yields (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 2 | 88 (89:11)[c] |
| 2 |  |  | 3 | 85 (94:6)[c] |
| 3 |  |  | 3 | 94 |
| 4 |  |  | 3 | 85 |
| 5 |  |  | 3 | 90 |
| 6 |  |  | 3 | 88 |
| 7 |  |  | 2 | 95 |
| 8 |  |  | 3 | 85 |
| 9 |  |  | 2 | 90 |
| 10 |  |  | 10 | 86 |
| 11 |  |  | 4 | 84 |

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples.

[b] Isolated yields.

[c] According to gas chromatographic (GC) analysis.



**Scheme 4.** Stereoselectivity in ring opening of cycloalkyl epoxides.

**Table 3.** Comparison of catalytic ability of acidic catalysts in the thiocyanation of 2,3-epoxypropyl phenyl ether under solvent-free condition

| No. | Catalyst | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | MSA | 3 | 94 |
| 2 | SSA | 10 | 88[15] |
| 3 | Dowex | 8 | 85[16] |
| 4 | PEG-$SO_3H$ | 5 | — |
| 5 | $B(HSO_4)_3$ | 4 | 92[17] |
| 6 | $Mg(HSO_4)_2$ | 10 | 85 |
| 7 | $Zn(HSO_4)_2$ | 10 | 89 |
| 8 | $Al(HSO_4)_3$ | 5 | 91 |

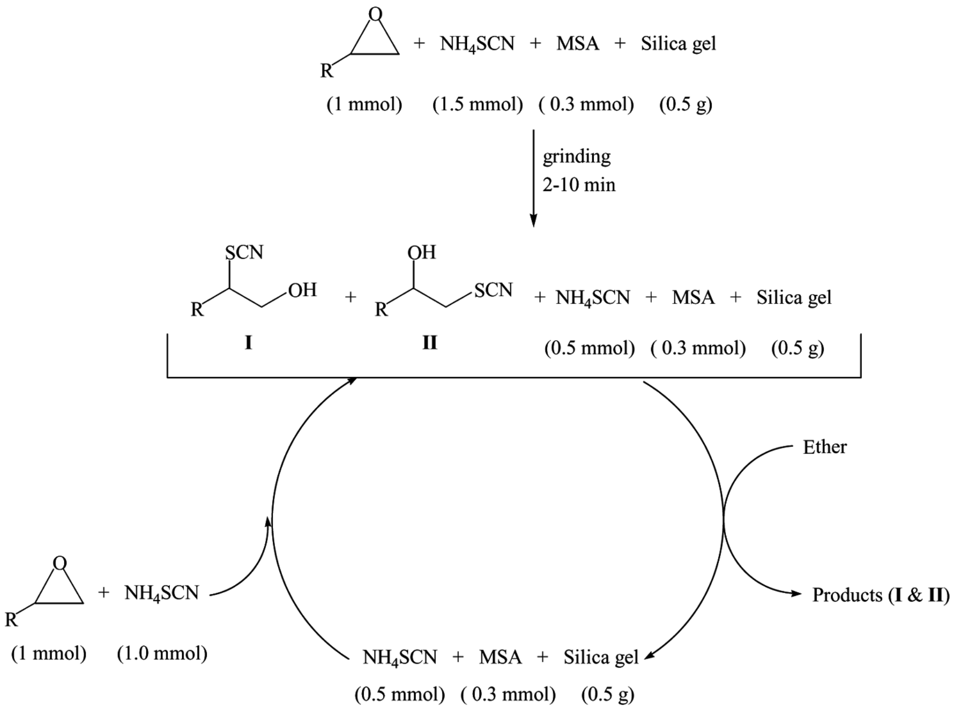
and excellent yields of products, make this new catalytic process as an attractive alternative to current methodologies.

We recently reported the synthesis of thiocyanohydrins in the presence of poly(ethylene glycol) (PEG)-$SO_3H$ as an acidic phase-transfer catalyst.[17] Unfortunately, the use of recycled PEG-$SO_3H$ resulted in a substantial loss of its activity as the yield of products dropped to a low value. The most ideal synthetic methodology could be defined as a system wherein 100% atom economy is preserved, the catalyst is recycled, and excess of reagent remains throughout in the medium and does not lose activity for several runs. In this procedure, ring opening of epoxides with $NH_4SCN$ in the presence of catalyst furnished the corresponding thiocyanohydrins in excellent yields. The catalyst, the additional ammonium thiocyanate (0.5 mmol), and silica gel were conveniently separated from the reaction mixture by simple filtration. The mixture was reused three consecutive times with only a slight variation in the yields of the corresponding products. Table 4 demonstrates the usability of the catalyst after three runs in thiocyanation of 2,3-epoxypropyl phenyl ether. The facile nucleophilic ring opening of epoxides with ammonium thiocyanate in the atom economical method is described in Scheme 5.

**Table 4.** Reusability of the catalyst[a]

| Experiment | Cycle | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | 1 | 3 | 94 |
| 2 | 2 | 3 | 93 |
| 3 | 3 | 3 | 90 |

[a] All reactions carried out under similar conditions.



**Scheme 5.** Facile nucleophilic ring opening of epoxides in the atom economical method.

## EXPERIMENTAL

### Preparation of MSA

A 50-mL suction flask was equipped with a constant pressure-dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Melamine (1.26 g, 10 mmol) was charged in the flask, and chlorosulfonic acid (3.5 g, ca. 2 mL, 30 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise over a period of 30 min at room temperature. HCl gas was evolved immediately. After completion of the addition, the mixture was shaken for 2 h, while the residual HCl was eliminated by suction. Then the mixture was washed with excess $CH_2Cl_2$ to remove the unreacted chlorosulfonic acid. Finally, a white solid powder was obtained (3.3 g, 90%).

The IR spectrum of MSA showed the broad O–H absorption in the region between 2600 and 3600 $cm^{-1}$, strong S=O absorptions between 1150 and 1200 $cm^{-1}$, strong S–O absorption at 650 $cm^{-1}$, and medium C=N absorption at 1620 $cm^{-1}$. This solid acid leads to a decrease in the pH from 7 to 2 and decomposed at 350 °C.

### Typical Procedure for the Preparation of β-Hydroxy Thiocyanates in the Presence of MSA Under Solvent-Free Conditions

A mortar was charged with epoxide (1 mmol), $NH_4SCN$ (1.5 mmol), MSA (0.3 mmol), and silica gel (0.5 g). The mixture was ground with a pestle for the time specified in Table 2. On completion of the reaction, the reaction mixture was poured into ether (10 mL) and filtered to remove the solids. The solid residue was washed with ether ($2 \times 5$ mL). The organic layer was dried over anhydrous $Na_2SO_4$, and solvent evaporated under reduced pressure to give the corresponding β-hydroxy thiocyanates in excellent isolated yields. For styrene oxide and 1,2-butene oxide, further purification was achieved by preparative thin-layer chromatography (TLC) or by silica-gel column chromatography.

### Representative Examples of Spectra Data of Thiocyanohydrin

**3-Phenoxy-2-hydroxypropyl thiocyanate (3).** IR (neat): $= 2156\,\mathrm{cm}^{-1}$; $^1$H NMR ($CDCl_3$): $\delta = 3.13$–$3.31$ (2H, d), 3.78 (1H, s), 4.01–4.05 (2H, d), 4.29 (1H, m), 6.95 (2H, m), 7.02 (1H, m), 7.22–7.34 (2H, m); $^{13}$C NMR ($CDCl_3$): $\delta = 37.39$, 68.06, 69.51, 112.99, 114.64, 121.32, 129.88, 158.49.

**3-Allyloxy-2-hydroxypropyl thiocyanate (6).** IR (neat): $= 2155\,\mathrm{cm}^{-1}$; $^1$H NMR ($CDCl_3$): $\delta = 3.04$–$3.24$ (3H, m), 3.53 (2H, d), 4.01–4.08 (3H, m), 5.19–5.29 (2H, m), 5.87 (1H, m); $^{13}$C NMR ($CDCl_3$): $\delta = 37.35$, 69.17, 71.09, 71.59, 113.07, 117.46, 133.66.

**2-Hydroxy-3-thiocyanatopropyl methacrylate (7).** IR (neat): $= 2157\,\mathrm{cm}^{-1}$; $^1$H NMR ($CDCl_3$): $\delta = 1.85$ (3H, m), 3.01–3.18 (2H, d), 3.40 (1H, m), 4.12 (1H, s), 4.13–4.17 (2H, m), 5.56 (1H, m), 6.07 (1H, m); $^{13}$C NMR ($CDCl_3$): $\delta = 18.40$, 37.34, 66.14, 68.07, 112.80, 126.56, 135.23, 167.06.

**3-Chloro-2-hydroxypropyl thiocyanate (8).** IR (neat): $= 2157\,\mathrm{cm}^{-1}$; $^1$H NMR ($CDCl_3$): $\delta = 1.27$ (2H, d), 3.10–3.28 (2H, m), 3.64–3.84 (1H, m), 4.20 (1H, s); $^{13}$C NMR ($CDCl_3$): $\delta = 37.31$, 47.11, 69.88, 112.01.

**2-Hydroxycyclohexyl thiocyanate (9).** IR (neat): $= 2151\,\mathrm{cm}^{-1}$; $^1$H NMR ($CDCl_3$): $\delta = 1.21$–$1.28$ (4H, m), 1.69 (2H, m), 1.98 (2H, m), 3.13–3.16 (2H, m), 3.34 (2H, m); $^{13}$C NMR ($CDCl_3$): $\delta = 23.14$, 25.20, 30.04, 31.42, 51.51, 79.12, 110.60.

## ACKNOWLEDGMENT

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