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Solvent-free synthesis of β-hydroxysulfides on the surface of neutral alumina

Mohammad Soleiman-Beigi[a*], Mohammad Alikarami[b] and Hajar Jahedi[a]

[a]*Department of Chemistry, Ilam University, P. O. Box 69315-516, Ilam, Iran*
[b]*Department of Chemistry, Ilam Branch, Islamic Azad University, Ilam, Iran*

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Abstract: An improved procedure has been developed for the synthesis of β-hydroxy sulfides with thiolysis of epoxides on the surface of neutral alumina in the absence of solvent under environmentally benign conditions.

Keywords: β-Hydroxy sulfides, Solvent free, Epoxides, Neutral alumina.

Introduction

Solvent-free organic reactions have attracted considerable attention in recent years, since they offer a powerful tool for minimizing waste production and harmful organic solvent dispersal [1-4]. There are of course a great many reactions that can already be carried out on the absence of solvent. The examples reported on solvent-free reactions demonstrate that no-solvent reactions are generally faster, give higher selectivity and yields, and usually require easier work-up procedures and simpler equipment [5-8].

β-Hydroxysulfides are important class of organic compounds, which have been found to be useful in medicinal chemistry and organic synthesis [9-15]. Many methods have been reported for the synthesis of β-hydroxysulfides [16-18], but the easiest and most straightforward synthetic procedure for the preparation of β-hydroxysulfides is the thiolysis of 1–2 epoxides with thiols which it is generally performed in solution media [19-28]. However, many of these methods involve the use of toxic and expensive reagents, drastic reaction conditions, poor regioselectivity, extended reaction times, unsatisfactory yields and entail undesirable side reactions due to oxidation of thiols or rearrangement of oxiranes [29, 30].

Alumina serves as a catalyst support for many industrial catalysts, such as those used in hydrodesulfurization and some Ziegler-Natta polymerizations, also as a very inexpensive and easily available catalyst and catalyst support, has been widely used in organic reactions [31-33].

These issues interested us in using a procedure to contribute to the development of an environmentally and economically-responsible synthetic methodology, which could allow us to easily prepare the β-hydroxysulfides.

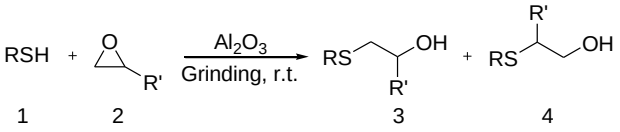
Results and discussion

Herein, we describe an efficient regioselective and chemoselective method for the ring opening of epoxides with thiols under mild solvent-free conditions at Alumina surface. It is found that for efficient thiolysis of 1,2-epoxides to the corresponding β-Hydroxysulfides (Scheme **1**), application of inorganic solid support is essential. Among several mineral supports examined, neutral alumina was found to give the best results. The optimum molar ratio of the thiols to the epoxides is found to be 1.2:1.0 in the presence of 2 g of neutral alumina at room temperature.

Therefore, various types of 1,2-epoxides and thiols were examined to the preparation of corresponding β-hydroxyslfide in the presence of neutral alumina under solvent free conditions. The process in its entirety involves a simple mixing of 1,2-epoxides and thiols on

*Corresponding author. Tel/fax: (+98) 8412227022
E-mail: SoleimanBeigi@yahoo.com

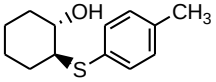
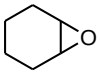
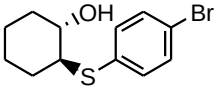
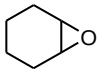
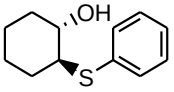
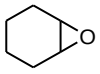
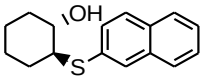
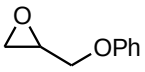
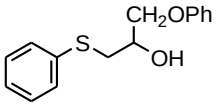
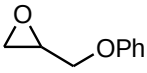
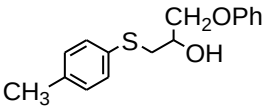
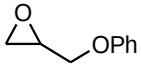
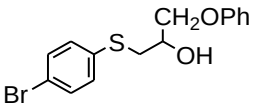
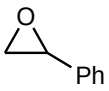
the surface of alumina (Scheme **1**). The mixture was then ground for the time specified in Table **1**.

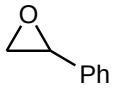
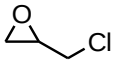
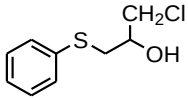
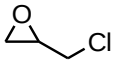
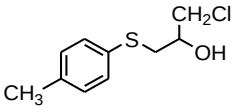
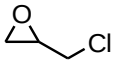
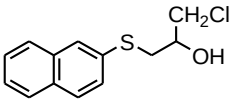
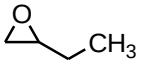
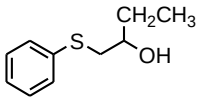
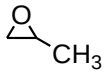
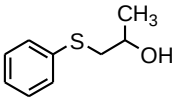
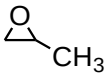
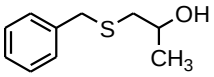


Scheme1: Thiolysis of epoxides on the surface of neutral alumina

As shown in Table **1**, the isolated yields of the reactions are good to excellent (73-94%) and the reaction times are short (20-60 min). Reaction with cycloalkene oxides led to stereoselective formation of the *trans*-2-hydroxysulfides (Table **1**, entries 1-4). Excellent regioselectivity was observed for unsymmetrical epoxides (Table **1**, entries 5-13). In case of styrene oxide, the hydroxyl sulfide from nucleophilic attack at the benzylic carbon of the epoxide was the major product (Table **1**, entries 8 and 9). Preferential nucleophilic attack by thiophenol took place at sterically less hindered position of the epoxide ring of unsymmetrical non-styrenoid alkene oxides (Table **1**, entries 5-7 and 10-15). Epichlorohydrin exemplified a case of chemo- and regioselective reaction with no detectable side product formation by direct displacement of the chlorine atom (Table **1**, entries 10-12). The ^{1}H NMR spectra of the crude products showed the formation of only **3** from 2-alkyl epoxides and the formation of **4** (along with a minor amount of **3**) from styrene oxide. The methodology was extended for an efficient synthesis of the β-hydroxy sulfides.

Table 1. Thiolysis of epoxides on the neutral alumina surface under solvent-free reaction conditions

Entry	R	Epoxide	Product	Time (min)	Yield (%)*
1	4-$CH_3C_6H_5$			20	89
2	4-BrC_6H_5			30	80
3	C_6H_5			30	90
4	2-naphtyl			40	73
5	C_6H_5			35	92
6	4-$CH_3C_6H_5$			30	94
7	4-BrC_6H_5			30	90
8	C_6H_5		**3/4**	25	16/75

9	4-BrC_6H_5		**3/4**	20	14/73
10	C_6H_5			45	80
11	4-$CH_3C_6H_5$			45	83
12	2-naphtyl			60	82
13	C_6H_5			45	87
14	C_6H_5			40	90
15	$C_6H_5CH_2$			55	85

*Isolated Yield

Conclusion

The present surface-mediated solid-phase procedure on the surface of neutral alumina provides an efficient methodology for the synthesis of a variety of β-hydroxy sulfides from easily accessible starting materials. The notable advantages of the present procedure include: (a) good yield, (b) reasonably rapid reactions (20-60 min), mild reactions conditions, (d) ease of set-up and work-up, (e) use of relatively non-toxic reagents and (f) general applicability accommodating a variety of substitution patterns. Alumina recovered after the reaction can be recycled after washing with methanol and activation with little variation of yield. Therefore, this thiolysis approach has set-out to minimize the use of offensive materials and maximized the use of renewable resources. For these reasons it can be considered as a relatively green procedure.

Experimental

Chemicals such as 1,2-epoxides, thiols and neutral alumina were purchased from the Fluka, Merck and Aldrich chemicals companies. All products are known compounds and are identified by comparison of their physical and spectral data with those of authentic samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

General procedure for the synthesis of β-hydroxy sulfides:

A mixture of thiols (1.2 mmol), epoxides (1.0 mmol) and neutral alumina (2 g) was ground at room temperature for the appropriate time (Table **1**). The progress of the reaction was monitored by TLC. After completion of the reaction, 20 ml dichloromethane was added to the mixture and the mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (silica gel, eluent, ethyl acetate: *n*-hexane (1: 4)). All the products are known compounds and were characterized by comparison of NMR spectral data and melting points with those reported in the literature [24, 20].

Selected spectral data for representative β-hydroxy sulfides:

*2-(Phenyl thio)-cyclohexanol (Table **1**, entry 3):*

IR (neat): ν_{max} 3434, 1582, 1477, 1067, 751, 694 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24-1.42 (m, 4H), 1.67-1.75 (m, 2H), 2.09-2.18 (m, 2H), 2.75-2.84 (m, 1H), 3.01 (br s, 1H), 3.34 (td, *J* = 9.9, 4.16 Hz, 1H), 7.28- 7.36 (m, 3H), 7.47-7.51 (m, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.3, 26.2, 32.7, 33.8, 59.5, 72.0, 127.8, 128.9, 132.6, 133.8 ppm.

*3-Chloro-1-phenyl thio-propan-2-ol (Table **1**, entry 10):*

(IR (neat): ν_{max} 3399, 1582, 1428, 1445, 1038, 739, 692 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.86 (brs, 1H), 3.09 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.19 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.64-3.72 (m, 2H), 3.93 (br m, 1H), 7.22-7.43 (m, 5H) ppm.^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.2, 48.0, 69.5, 126.9, 129.2, 130.1, 134.7 ppm.

*1-Phenyl thio-butan-2-ol (Table **1**, entry 13):*

IR (neat): ν_{max} 3410, 1584, 1471, 1021, 740, 690 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.53-1.64 (m, 2H), 2.64 (brs, 1H), 2.86 (dd, *J* = 13.6, 8.6 Hz, 1H), 3.18 (dd, *J* = 13.6, 3.5 Hz, 1H), 3.59-3.67 (m, 1H), 7.21-7.42 (m, 5H) ppm. ^{3}C-NMR (75 MHz, $CDCl_3$): δ 9.9, 28.9, 41.7, 70.6, 126.5, 129.1, 129.9, 135.4 ppm.

*1-Benzyl thio- propan-2-ol (Table **1**, entry 15):*

IR (neat): ν_{max} 3400, 1600, 1454 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.2 Hz, 3H), 2.40 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.47 (brs, 1H,), 2.61 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.75 (s, 2H), 3.80-3.86 (m, 1H), 7.23-7.34 (m, 5H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.0, 36.2, 40.7, 65.4, 127.2, 128.6, 128.9, 138.1 ppm.

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