J. Mater. Environ. Sci. 6 (5) (2015) 1451-1456
ISSN: 2028-2508
CODEN: JMESCN

Alkylation of Thiols in Green Mediums

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Received 15 Dec 2014, Revised 27 Mar 2015, Accepted 27 Mar 2015
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Abstract
Sulfides are very valuable and important compounds in the various fields especially in the synthesis of biological and pharmaceutical active materials. The alkylation of thiols is the most common strategy for the synthesis of thioethers. In recent years, a series of protocols was reported for the synthesis of thioethers via the S-alkylation of thiols in green mediums. In this paper, we focused on the reports presented from 2008 to 2014.

Key words: Sulfides, Alkylation, Thiols, Biological, Pharmaceutical.

1. Introduction
Organosulfur chemistry is one of the most important and valuable branches of in organic synthesis. Compounds containing C-S bond in particular sulfides have a long and rich history as excellent intermediates in organic chemistry [1-4]. In organic synthesis; sulfides are generally used for the synthesis of sulfoxides**,** sulfones, sulfonamides, sulfonyl chlorides and olefins [5-11]. Thioethers are very efficient and valuable compounds in various areas such as medicine, pharmaceutical, bio-chemistry, agriculture, industry, heterocyclic chemistry and biological processes [12-20]. In the field of agriculture, it can be indicated to Chlorbenside that widely applied as pesticide [21].

In the field of medicine, organosulfur compounds extensively used for treatment of various diseases such as cancer, leprosy, alzheimer's, Parkinson and tuberculosis [22-26]. Furthermore, alkyl aryl sulfides play a significant role in the synthesis of natural products and also are important and supplement reagents in the synthesis of the most of antibiotics and medicinal active compounds [27-32]. In the field of industry, sulfides play an impressive and crucial role in most of industry processes especially in food supplement, organic solvents, fragrance and cosmetic materials production [33-35].

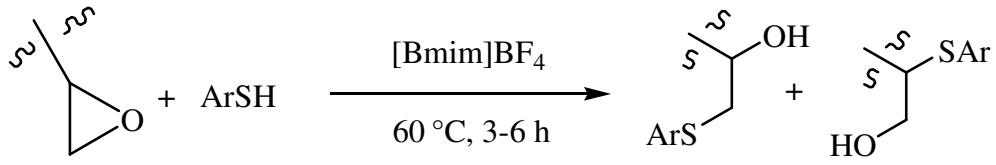
Every day chemistry science researcher especially organic chemists are looking for finding novel and convenient reagents in order to prepare various organic compounds. Since thioethers play a key and valuable role in various areas in particular medicine and industry processes, therefore designing new and available catalytic systems for the preparation of these compounds is one of the most important priorities among organic chemistry researches. For this purpose, in recent years, a number of procedures have been described for the synthesis of thioethers.

2. The alkylation of thiols in green mediums
The thiols (RSH) and alkyl halides (RX) are useful, available and valuable reagents that are widely used in the various fields in particular chemistry laboratory and industry processes. Some characters of thiols and alkyl halides such as being cheep and available have caused that organic chemists to use these compounds for the synthesis of sulfides in large scale.

Alkylation of thiols is the most common technique for the synthesis of thioethers and usually is carried out via the treatment of thios with alkyl halides in the presence of strong bases under reflux condition [36-38]. In

the past decades, a large number of methods have been presented for the synthesis of sulfides via the alkylation of thiols with the use of various reagents and catalysts such as tetraethylammonium hydrogen carbonate [39], microwave irradiation [40], hydrotalcite clays [41], phase transfer catalyst [42], Kf/Al2O3 [43], N-bromosuccinimide (NBS) [44] ionic liquids [45], CsF–Celite [46-47] and solvent free-conditions [48]. The use of hazardous and toxic reagents in chemistry laboratories and the chemical industry have led to increasing public concerns due to thier threat to human life and environmental. But, the chemical industry plays a vital role in the all aspect of human life in particular in food supplements, cosmetic materials, medicinal and natural products production. For this purpose, green chemistry opens up a new chapter in the all aspect of chemistry science especially in organic synthesis. The use of greener and safer chemical materials to carry out chemical and organic processes has turned into the most important topic among chemists. In recent years, the performance of organic processes and reactions in green mediums has received particular attention among organic researchers. In this paper, we wish to focus on a number of strategies that has recently been reported for the alkylation of thiols in green mediums and also we wish to study results and advantages of these strategies.

The β-hydroxy sulfides are key and valuable compounds in pharmaceutical industry and medicine [49-50]. For this purpose, in the year 2008, an interesting and favorable strategy was developed for the synthesis of unsymmetrical thioethers by Yang and his colleagues [51]. In this technique, β-hydroxy sulfides derivatives were synthesized in very high yields and suitable times (3-6 h) at 60 ^{0}C in the presence of [Bmim]BF_4. [Bmim]BF_4 (.3 g, 1.4 mmol) was applied as recyclable ionic liquid in which was acted both as promoter and medium of reaction in order to prepare β-hydroxy thioethers via the regioselective ring-opening reactions of 1,2-epoxides (1.2 mmol) with aromatic thiols (1 mmol) (Scheme 1). The use of economical and environmentally benign conditions, excellent yield of products (81-100%), operation simplicity, high regio and chemoselectivity demonstrated high efficiency of this protocol for the synthesis of β-hydroxy sulfides.

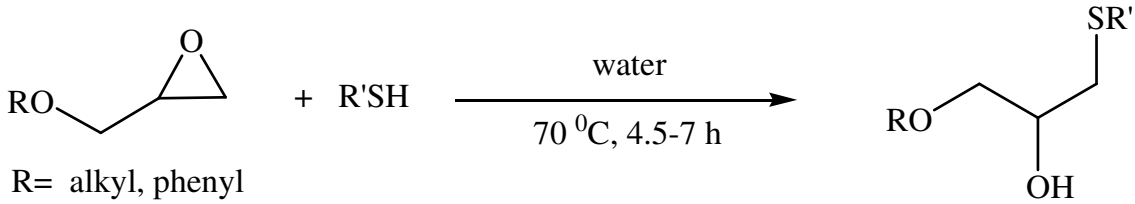


Ar= phenyl, naphthyl

100%

Scheme 1

In the year 2008, Misra and co-workers reported an efficient, economical and environmentally friendly protocol for the synthesis of a diverse range of β-hydroxy sulfides under catalyst-free conditions. [52]. in this methodology, mild and regioselective ring-opening reactions of 1,2-epoxides with various aliphatic and aromatic thiols in water lead to the synthesis of β-hydroxy sulfides in good to excellent yields. The reactions were performed at 70 ^{0}C (Scheme 2).



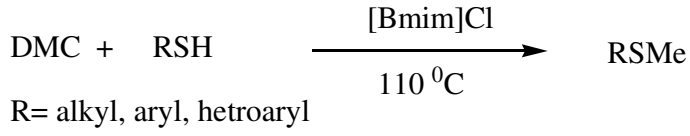
R= alkyl, phenyl

R'= alkyl, phenyl, naphthyl

95%

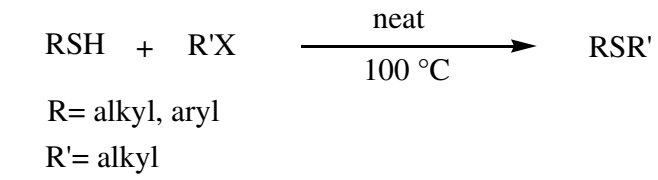
Scheme 2

Under mild conditions, high-yielding and effecient alkylation of aromatic and aliphatic thiols with dimethyl carbonate (DMC) in order to synthesize alkyl aryl and dialkyl sulfides was also observed in the presence of 1-butyl-3-methylimidazolium chloride [Bmim]Cl as [53]. The S-methylation reactions were performed at 110 ^{0}C (Scheme 3). It is noteworthy that a diverse range of sulfides were achieved in good to excellent yields and suitable times. The use of nono-toxic and availble reagent, high yields of products and the use of effecint and recycable ionic liquid as the promoter and catalyst demonstrated the high effecincy of this methodolgy for the synthesis of alkyl aryl and dialkyl sulfides.



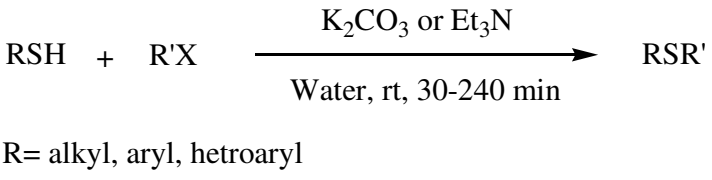
Scheme 3

Furthermore, Movassagh and Soleiman-beigi introduced an effective, mild and simple protocol in order to prepare alkyl aryl and dialkyl sulfides via the alkylation of thiols under solvent-free conditions [54]. Symmetrical and unsymmetrical thioethers were obtained from reaction of various aliphatic and aromatic thiols (1.1 mmol) with a wide range of alkyl halides (1 mmol) at 100 ^{0}C without use of any solvent and catalyst under neat conditions (Scheme 4). Some important advantages of this methodology were diverse range of products, high yields, neat conditions, use of cheep and available reagents as well as being valuable both from economical and environmental points of view. The conversion of tertiary alkyl halides (adamantly and t-butyl) to corresponding sulfides was one of most important features of this system.



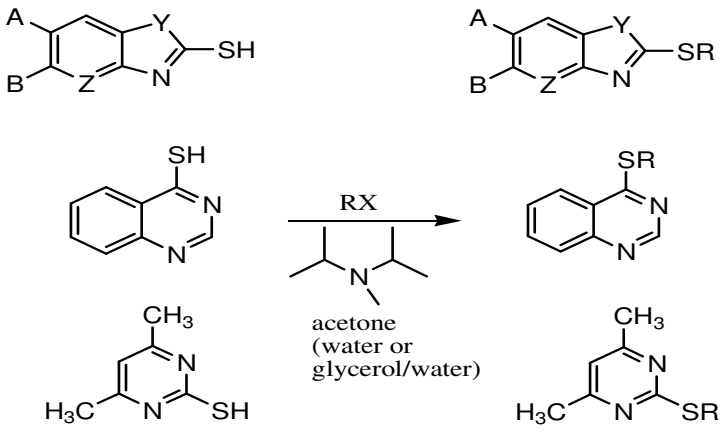
Scheme 4

To generate symmetrical and unsymmetrical sulfides, a simple, practical, green and friendly environmentally system was designed for the alkylation of aliphatic, aromatic and hetroaromatic thiols with different alkyl halides [55]. A wide range sulfides were generated from treatment of thiols (3 mmol) with various alkyl halides (3 mmol) using potassium carbonate (K_2CO_3) or triethyl amine (Et_3N) in the presence of water (Scheme 5). In this strategy, cesium carbonate and triethyl amine were used as base as well as water was applied as reaction medium. The reactions were accomplished at room temperature and relatively short times. The variety, purity and excellent yields of the products, appropriate reaction times, simple isolation, operational simplicity, mild reaction conditions and environmentally friendly were most valuable aspects of this strategy which were worth mentioning.



Scheme 5

In recent years, ultrasound irradiation is transformed into one of the most common and valuable issues in chemistry science in particular organic synthesis and among organic researchers [56-57]. In continuation of the issue of the synthesis of sulfides via the alkylation of thiols, Deligeorgiev research group presented an efficient and valuable protocol with the use of ultrasound irradiation technique in the presence of acetone, water or glycerol/water (Scheme 6) [58]. A wide range of products, mild condition, high yields and high purity of products, high selectivity, high reactivity, mild conditions and short reaction times demonstrated the high potential of this technique for the synthesis of sulfides.



A, B = H, F, Cl, NH_2, NO_2, CH_3

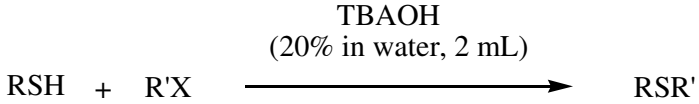
R = CH_3, C_2H_5, C_3H_7, C_4H_9, $CH_2C_6H_5$, $CH_2CH{=}CH_2$, C_2H_4CN, $CH_2CH_2CH_2N(CH_3)_2$

X = Br, I Y = O, S, N Z = CH or N

97%

Scheme 6

Finally, in the year 2014, a valuable and interesting method was introduced in which it demonstrated the alkylation processes of thiols successfully had been carried out under neat conditions [59]. In this method, aqueous tetra-n-butyl ammonium hydroxide solution was presented as versatile and excellent basic catalyst for the synthesis of symmetrical and unsymmetrical thioethers via the alkylation of aliphatic and aromatic thiols with various alkyl halides. The aqueous tetra-n-butyl ammonium hydroxide solution (TBAOH) was applied as strong base, reaction medium and phase-transfer catalyst (Scheme 6). In this system, corresponding sulfides were obtained from reaction of aliphatic and aromatic thiols (1 mmol) with various alkyl halides (1.5 mmol) in the presence of aqueous tetra-n-butyl ammonium hydroxide solution (2 mL) without use of organic solvent and phase transfer catalyst (Scheme 7).



R= alkyl, aryl

R'= alky, benzyl

92%

Scheme 7

The transformation of secondary alkyl halides to corresponding sulfides in high yields (80-88%) was one of important advantages of this methodology. Also, variety and purity of products, good to excellent yields, mild and neat conditions, simple isolation, high reactivity, short reaction times and avoiding the use of hazardous solvents showed the high efficiency of aqueous tetra-n-butyl ammonium hydroxide solution (TBAOH) for the synthesis of alkyl aryl and dialkyl sulfides.

Conclusion

Due to great importance of these compounds in the various areas, in recent years, a series of protocols was reported for the synthesis of thioethers via the alkylation of thiols. The discussions summarized in this paper clearly indicates that the S-alkylation of thiols promoted by various catalytic systems has been and continues to be of great attention. The use of hazardous and toxic reagents in chemistry laboratories and the chemical industry have led to increasing public concerns due to thier threat to human life and environmental. But, the chemical industry plays a vital role in the all aspect of human life. The use of greener and safer chemical materials to carry out chemical and organic processes has become the most of important topic among chemists. Therefore, many studies for finding new and efficient catalytic systems have been carried out from 2008 to 2014. In this paper, we investigated recent achievements in the synthesis of sulfides via the alkylation of thiols in green mediums and also focused on important benefits and drawbacks of these catalytic systems. We think that a large number of protocols will be found in the future for the synthesis of sulfides via the alkylation of thiols. With these recent highlighted examples we hope to increase the attention of organic researchers to find new, simple, practical, efficient and environmentally friendly systems for the alkylation of thiols in future years.

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