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Zinc triflate catalyzed synthesis of thioethers

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Abstract: Zinc triflate-catalyzed arylation of thiols using various substituted benzylic alcohols has been developed for the synthesis of thioether (sulfide) derivatives. This procedure presents a greener approach for the synthesis of sulfides.

Keywords: Thioethers, Thiols, Aryl alcohol, Zinc triflate

Aryl sulfides are useful intermediates found in a number of natural products or compounds (e.g. proton pump inhibitors (PPIs) as shown in Figure 1) of medicinal significance.^[1]

There are many conventional route to these compounds involving the displacement reaction of an aryl/alkylthiolate with the appropriate alkyl halides.^[2] Other reported procedures are based on the construction of the aryl-sulfur bond, thus including nucleophilic aromatic substitution^[3] or treatment of aryllithium or Grignard reagents with sulfurated electrophiles.^[4]

In addition to their routine synthesis considering SN² substitution of alkylating agents with thiolate anions, a variety of other methods have been used for thioether preparation.^[5] Although

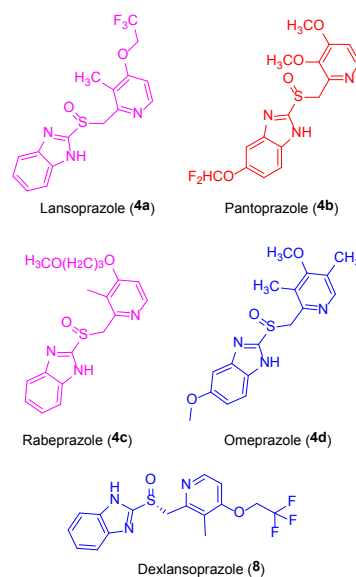
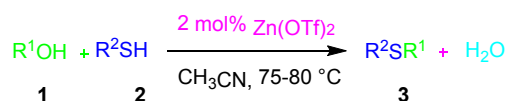


Figure 1. Chiral and achiral APIs

there are many methods still few synthetic difficulties that need to be addressed. For instance, high temperature, high stoichiometry of the base, or strong reducing agents are often required. Recently Guy *et.al* disclosed a method for the preparation of aryl alkyl sulfides by the reaction of arylboronic acids and alkanethiols in the presence of stoichiometric $\text{Cu}(\text{OAc})_2$ and pyridine in refluxing DMF.^[6]

Synthesis of sulfides (or thioethers) is most often achieved by the thiolate substitution of alkyl halides.^[7] The reaction conditions and yields depend on the solvent, the basic catalyst, and the acidity of thiols. In most of the cases harsh reaction conditions (refluxing for long periods) are required.^[8] In some cases improved yields can be obtained via phase transfer catalysis,^[9] palladium (0)^[10] or bis(diphenylstannyl) telluride^[11] or bis(diphenylphosphino)-methane complex of platinum(II),^[12] catalyzed or ligand transfer,^[13] or fluorodemetalation reactions.^[14]



Scheme 1. Zinc triflate catalyzed synthesis of thioethers (sulfides).

Proton pump inhibitors are a group of drugs [4(a-d) and 8] as shown in Figure 2 that elicit pronounced and long-lasting pharmacological effect by reducing the gastric acid production. These drugs are among the most widely marketed ones in the world due to their outstanding efficacy and safety.

We report herein the facile synthesis of thioethers **3** (a-r) by arylation of thiols **2** (a-e) with various substituted benzylic alcohols **1** (a-m) using zinc triflate as catalyst in the presence of acetonitrile solvent at 75-80 °C. In our initial screening experiments, diphenyl methanol **1d** and 2-(1-((benzhydrylthio)methyl)cyclopropyl) acetic acid **2e** were selected as substrates for optimization. Initial development was started with screening of solvents for synthesis of thioethers **3m**.

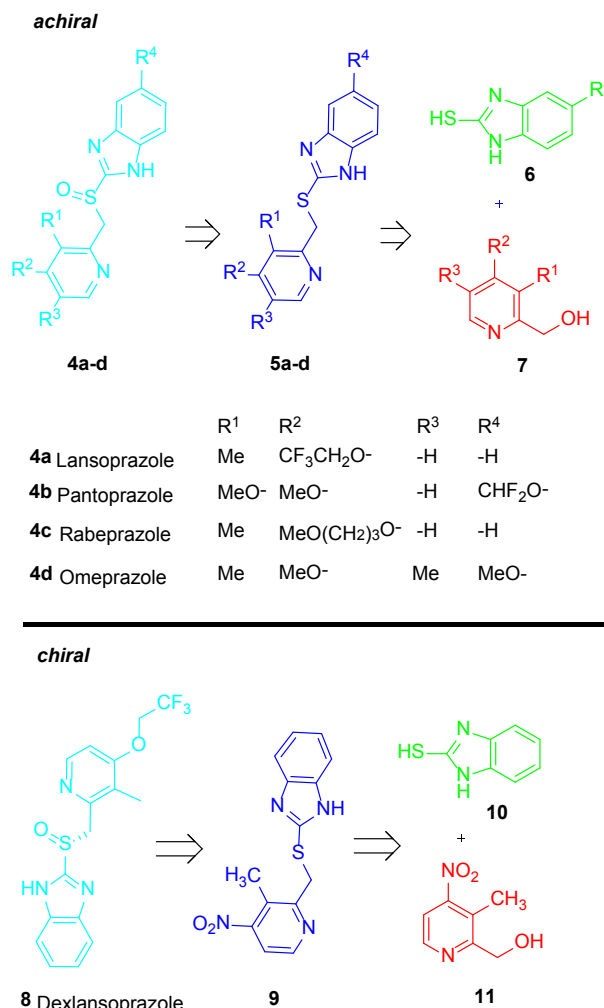
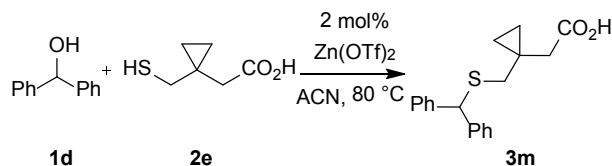


Figure 2. Retro synthetic analysis of Chiral and achiral APIs



Scheme 2. Screening of solvents for the synthesis of **3m**

Various solvents were screened in the synthesis of thioethers and the scope and limitations of the reaction were also studied. As this procedure involves the solution of diphenyl methanol **1d** and 2-(1-((benzhydrylthio)methyl)cyclopropyl) acetic acid **2e** in a solvent and stirred under nitrogen atmosphere at 75-80 °C

in the presence of a zinc triflate. We found that acetonitrile was the solvent of choice, whereas other toluene, dichloromethane and isopropyl alcohol, ethyl acetate, tetrahydrofuran and *N,N*-dimethyl formamide solvents performed poorly as shown in Table 1. With the optimized conditions, numerous benzylic alcohols and thiols were examined and this method is found to be quite general.

Table 1. Screening of solvents for synthesis of thioethers

S.No	Screening solvents	Temperature (°C)	Conversion %
1	Dichloromethane	38	84
2	Ethyl acetate	75	57
3	Acetonitrile	77	98
4	Tetrahydrofuran	65	--
5	Toulene	105	80
6	<i>N,N</i> -dimethyl formamide	90	65
7	Isopropyl alcohol	75	51t

Effect of number of equivalence of **1d** is also studied. Excess of (2.0 eq.) of **1d** in the reaction afforded biarylethers **12**, whereas in the same case with (2 eq.) of thiols, reaction did not proceed well to afford product **13**. In the case of protected alcohol **14**, the conversion for **3** was faster than the unprotected alcohol as shown in Figure 3.

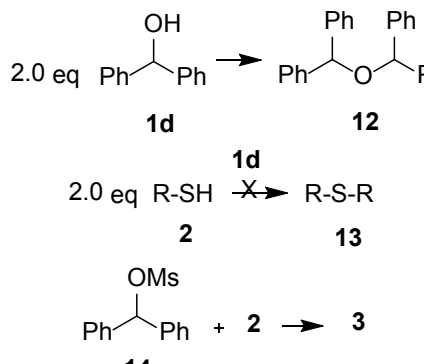


Figure 3. Impact of equivalents of alcohols and thiols on etherification

Table 2. Synthesis of thioethers using various alcohols

S. No	Alcohol (1a-m)	Thiol (2a-e)	Thioether (3a-r)	Time (h)	Yield ^a (%)
1	1a		3a	18	88
2	1b		3b	19	65
3	1c		3c	16	77
4	1d	2a	3d	24	58
5	1e		3e	22	62
6	1f		3f	18	64
7	1g		3g	20	62
8	1h	2b	3h	22	58
9	1i		3i	24	66
10	1j	2c	3j	20	60
11	1a	2d	3k	4	88
12	1d		3l	8	89
13	1d		3m	4	97
14	1a		3n	8	82
15	1i	2e	3o	9	92
16	1k		3p	10	88
17	1l		3q	26	44
18	1m		3r	25	35

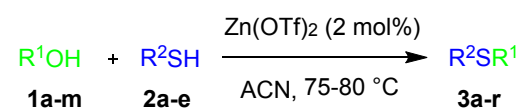
^a%; based on the isolated yields

It was observed that without catalyst, reaction did not get completed even in longer hours of reaction maintenance. In addition to this some impurities were found.

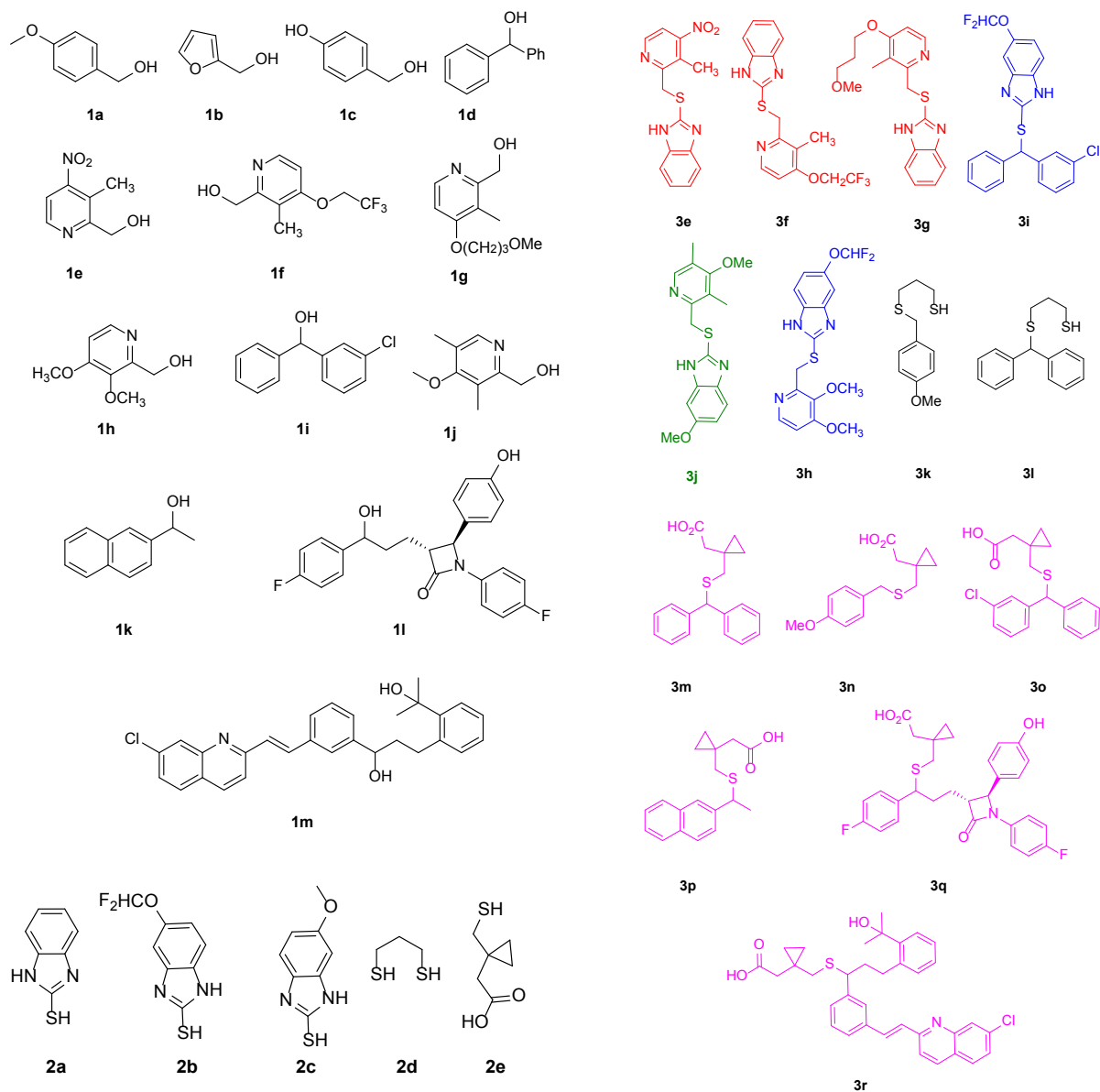
As demonstrated, various alcohols, substituted benzyl alcohols and primary or secondary aryl alcohols reacted with thiols in 4-9 h affording high yields (entry no. **11-15**). In some cases, longer reaction times were required particularly for macromolecules and electron withdrawing substituted alcohols. Interestingly, aliphatic primary alcohols were resistant to undergo these reactions reflecting that benzylic carbocation mechanistically plays important role as most of the substrates are benzylic in nature.

We exploited the potential of this methodology to synthesize key starting materials **5(a-d)** and **9** of active pharmaceutical like Lansoprazole **4a**, Pantoprazole **4b**, Rabeprazole **4c**, Omeprazole **4d** and Dexlansoprazole **8** (PPIs).

In addition to this, our method is found to be highly useful for the preparation of numerous alkyl and aryl thioethers.

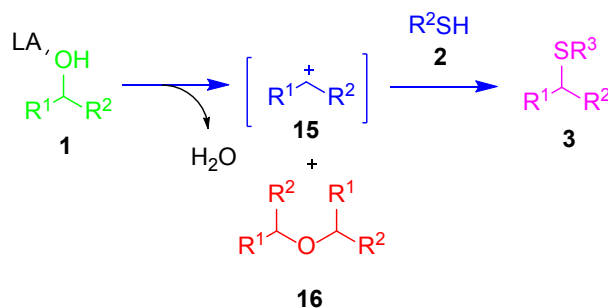


R¹=Benzylic R²=Aryl/alkyl



Scheme 3. Synthesis of thioethers using various benzylic alcohols

A plausible mechanism was envisaged (Scheme 4) based on the experimental observations. Mechanistically, removal of the water facilitates the formation of the benzylic stable carbocation^[15] **15** as a result of heterolytic cleavage in presence of Lewis acid $\text{Zn}(\text{OTf})_2$ affording thioethers **3** and by product **16** as shown in Scheme 4.



Scheme 4. Possible mechanism for the thioether synthesis

In conclusion, we have developed an efficient synthetic method for the synthesis of various thioethers via an arylation of thiols with alcohols in the presence of zinc triflate ($\text{Zn}(\text{OTf})_2$). This method has been applied on numerous substrates and active pharmaceutical intermediates like Pantoprazole, Lansoprazole, Rabeprazole Omeprazole and Dexlansoprazole.

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General Procedure for the Synthesis of thioethers (sulfides): Preparation of 2-(1-((benzhydrylthio) methyl) cyclopropyl) acetic acid (3m). To a stirred mixture of diphenyl methanol **1d** (1.0 g, 0.0054 mmol) in acetonitrile (10.0 mL) and 2-(1-((benzhydrylthio) methyl) cyclopropyl) acetic acid **2e** (0.82 g, 0.0056 mmol) was add $\text{Zn}(\text{OTf})_2$ (0.039 g, 0.0000108 mmol or 0.19 mol%) stir for 5-10 min at 25-35 °C. Raise the temperature to 75-80 °C, maintain the reaction at same temperature up to reaction completion (as per the time given in Table 2). After reaction completion total solvent was distilled off under reduced pressure. Thereafter, distillation reaction mass was extracted with ethyl acetate (2X10 mL). Combinde organic layers were washed with DM water (2X10 mL), dried over anhydrous Na_2SO_4 , filtered, and evaporated completely under vacuum to afford compound **3m** [2-(1-((benzhydrylthio) methyl)cyclopropyl)acetic acid] (1.64 g, 97.0%); ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.40 (m, 4H), 7.30-7.20 (m, 4H), 7.19-7.17 (m, 2H), 5.21 (s, 1H), 2.53-2.51 (s, 4H), 0.53-0.50 (t, 2H), 0.47-0.40 (t, 2H). ^{13}C NMR (400 MHz, CDCl_3): 178.5, 141.4, 128.6, 128.3, 127.2, 54.2, 40.2, 39.9, 16.5, 12.5; MS (+ve ES) 313 [M+H].