http://dx.doi.org/10.5012/bkcs.2013.34.9.2819

# A Convenient Method for Synthesis of Benzo[*d*]thiazoles in Water and Solvent Free Condition

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*Received February 27, 2013, Accepted June 15, 2013*

**Key Words :** Benzothiazoles, Water, Solvent free, Condensation reaction

Benzo[*d*]thiazoles and their derivatives are of great interest during the last decades, because bicyclic aromatic rings containing benzo[*d*]thiazole derivatives have a wide range of biological properties[1] and developed as new drugs for several diseases such as tumors, diabetes, Parkinson's diseases, tuberculosis, inflammatory diseases, epilepsy, viral infections, insomnia, and atherosclerosis.[2] Due to the high profile of biological application of benzo[*d*]thiazole structures, there are numerous methods have been reported for the synthesis of benzo[*d*]thiazoles. Benzo[*d*]thiazoles and their derivatives are most commonly synthesized by one of the following methods; the condensation of 2-aminothiophenol with substituted carboxylic acids, aldehydes, acyl chlorides, and esters.[3] And also many reactions for synthesis of benzo[*d*]thiazoles by cyclocondensation of 2-aminothiophenol and aldehydes were proceeded under the presence of catalyst such as (pmlm)Br,[4] $I_2$,[5] $ZrOCl_2 \cdot 8H_2O$,[6] TMSCl,[7] $H_2O$,[8] PCC,[9] CAN,[10] and hypervalent iodine(III).[11] One of the other route is intramolecular cyclization of *N*-(2-halophenyl)benzo[*d*]thioamides.[12] Recently one of the new method was reported for the formation thiazole ring from the reaction between *o*-aminohalo moiety and isothiocyanates.[13] However, most of the existing methods suffer from certain shortcomings such as poor yield, use of strong oxidants, demand of catalysts, long reaction times and general toxic solvents etc. Thus the development of novel and efficient routes for rapid access to such benzo[*d*]thiazoles under environmentally friendly methods is of high demand.

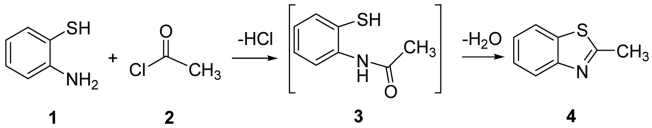
So far, to the best of our knowledge, there have been no reports on the synthetic routes to synthesize benzo[*d*]thiazoles under environmentally friendly methods. Therefore we decide to research the synthetic routes to synthesis of benzo[*d*]thiazoles under solvent free and in water condition.

In this report, a convenient route to facile access of benzo[*d*]thiazoles by solvent free and in water condition has been described. We initiated our investigations by examining 2-aminobenzenethiol **1** and acetyl chloride **2** (Scheme 1) as model reaction. The reaction was initially carried out under various solvent to give low yields than moderate. So, we added small amount of water as reaction catalyst and also the reaction proceeded only in water and the results were summarized in Table 1. According to results of the Table 1, a small amount of water accelerate reaction rate and gave more yield. This because one equivalent of HCl generate during the reaction process and water help the act of HCl as a catalyst of cyclocondensation between thiol and amide functional group of reaction intermediate **3**. During the separation of the product **4** from crude reaction mixtures, the reaction intermediate **3** was separated in THF, $CH_2Cl_2$, $CH_3CN$ and THF with water as solvent.

The investigation of the optimized condition from the reaction of 2-aminobenzenethiol **1** and acetyl chloride **2** revealed that more yields were obtained when more water was existed in the solvent. And also the reaction rate is fast.

Based on in preliminary studies in Table 1, we realized that water is the best solvent in an aspect of yields and reaction time for the synthesis of benzo[*d*]thiazoles. Inspired by these attractive features of water as a solvent, we synthesized various benzo[*d*]thiazoles from the reaction of 2-aminobenzenethiol and acyl derivatives in water and the results were summarized in Table 2.

Encouraged by the results of the synthesis of benzo[*d*]-



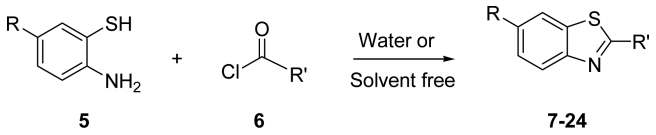

1 2 3 4

**Scheme 1.** Synthesis of 2-methylbenzo[*d*]thiazole in various solvent.

**Table 1.** Evaluation of Different Solvent Systems in Optimization of 2-methylbenzo[*d*]thiazoles[a]

| Entry | Solvent[a] | water[b] | Temp. (°C) | Time (h) | Yield[c] |
|---|---|---|---|---|---|
| 1 | THF | No | 20 | 32 | 40 |
| 2 | | | 35 | 25 | 40 |
| 3 | | | reflux | 20 | 40 |
| 4 | THF | 10 | 20, 30, reflux | 8, 15, 20 | 50, 52, 60 |
| 5 | | 20 | 20, 35, reflux | 8, 14, 17 | 50, 55, 60 |
| 6 | | 30 | 20, 35, reflux | 8, 8.5, 10 | 50, 60, 65 |
| 7 | | Water | 20 | 6 | 80 |
| 8 | | | 35 | 3 | 86 |
| 9 | | | Reflux | 2 | 75 |

[a]$CH_2Cl_2$ and $CH_3CN$ were investigated as solvent and the results were similar with THF. All solvents controlled with 10 mL volume. [b]At each water mol ratio, reaction carried in three different temp. [c]Isolated yield is corresponded with temperature and time.

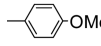
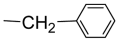
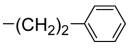
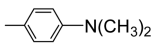
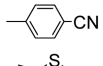
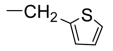



5 6 7-24

**Scheme 2.** Environmentally friendly synthesis of benzothiazoles.

thiazoles in water solvent, we tried to get same products without solvents for pursue under environmentally friendly condition. For reasons of economy and pollution, solvent free reaction conditions are of great interest in order to follow request in recent chemistry which called as a green chemistry. So, we carried out the synthesis of benzo[*d*]-thiazoles under solvent free condition. The results were summarized in Table 2 with together the results of in water condition. The reaction of alkyl and aryl substituted acyl chlorides and 2-aminobenzenethiol afforded the corresponding benzo[*d*]thiazoles in excellent yields. Most of the case, desired benzo[*d*]thiazoles were obtained with good yield in solvent free condition than water used as solvent. In the case of R is alkyl in the acyl chlorides, the reaction rate was late than aryl (entry 1-7, Table 2). The reaction rate of the alkylated acyl chlorides (entry 1-7, Table 2) was comparatively late than arylated acyl chlorides (entry 8-18, Table 2)

**Table 2.** Synthesis of benzenzo[*d*]thiazoles under environmentally friendlly condition

| Entries | R | R' | Products | Time (h) | | Yield (%) | |
|---|---|---|---|---|---|---|---|
| | | | | W[a] | SA[b] | W | SA |
| 1 | H | -$CH_3$ | 7 | 5 | 4 | 86 | 91 |
| 2 | H | -$CH_2CH_3$ | 8 | 6 | 4 | 84 | 88 |
| 3 | H | -$(CH_2)_5CH_3$ | 9 | 3 | 2 | 76 | 90 |
| 4 | H | -$(CH_2)_7CH_3$ | 10 | 3.5 | 2 | 83 | 88 |
| 5 | H | -$(CH_2)_{11}CH_3$ | 11 | 3 | 2 | 84 | 85 |
| 6 | H | -$CH_2OCH_3$ | 12 | 5 | 45 | 82 | 90 |
| 7 | H |  | 13 | 3 | 1 | 86 | 88 |
| 8 | H |  | 14 | 3 | 1 | 90 | 92 |
| 9 | H |  | 15 | 2.5 | 2 | 85 | 90 |
| 10 | H |  | 16 | 3.5 | 3 | 84 | 88 |
| 11 | H |  | 17 | 3 | 2 | 87 | 88 |
| 12 | $CH_3$ |  | 18 | 1.5 | 1 | 86 | 88 |
| 13 | $CH_3$ |  | 19 | 2 | 0.5 | 90 | 95 |
| 14 | H |  | 20 | 1.5 | 1 | 90 | 95 |
| 15 | H |  | 21 | 1.5 | 1 | 91 | 95 |
| 16 | H |  | 22 | 2.5 | 1.5 | 91 | 94 |
| 17 | H |  | 23 | 3 | 2 | 85 | 85 |
| 18 | H |  | 24 | 2 | 1 | 86 | 87 |

[a]water used as solvent. [b]solvent free

in both of solvent free and water condition. In the case of the reaction between electron withdrawing group substituted aryl acyl halides (entry 13-15) with 2-aminobenzenethiol gave more good yields than the other aryl chlorides (entry 8-12) and heteroaromatics (entry 16-18). During the reaction is under proceeding in water, we checked the reaction product by HPLC and column chromatography. And realized all of the reactions were proceed *via* corresponding thio amide as reaction intermediate such as **3**.

Finally, we tried to synthesis of biologically active compound thioflavin derivative, *N,N*-dimethyl-4-(6-methylbenzo[*d*]-thiazole-2-yl)aniline (entry 12)[14] by using the investigated both methods. The reaction of 4-methyl-2-mercaptoaniline with 4-(dimethylamino)benzoyl chloride gave corresponding benzo[*d*]thiazole **18** in good yield (88 %) with one step.

In conclusion, a convenient and environmentally friendly method for the synthesis of benzo[*d*]thiazoles was developed. All of the reactants were well converted to desired product. The generality of this method could be able to synthesis of variable corresponding benzo[*d*]tiazole derivatives.

## Experimental

General procedure for the synthesis of benzo[*d*]thiazoles: A mixture of 2-aminobenzenethiol (0.2 g, 1.6 mmol) and corresponding acyl chlorides was stirred at ambient temperature or 35 °C with stirring under water (10 mL) or solvent free condition for 1-7 h. After stirring 30 min the whole reaction mixture melts, in the case of the water as solvent turned to a homogeneous liquid and in solvent free reaction forms a paste. The progress of the reaction was monitored by thin layer chromatography and complete transformation was observed in a short period of 1-7 h. The reaction mixture was then poured into methylene chloride (30 mL), and separated only organic layer. The organic layer washed with water (2 × 20 mL), dried over $MgSO_4$ and evaporation of organic layer gave crude product. The crude product was purified by column chromatography gave pure liquid or solid product.

**Acknowledgments.** Soon Byung Yoon and Eun Jeong Chun are equally contributed to this work. This work was supported by the Brain Korean Program 21 (BK 21) and Lee is thankful to the NRF (Grant No. 2010-0023775) for the financial support.

**Supporting Information.** The IR, NMR ($^1$H and $^{13}$C) and Mass data for characterization of the products (**7-24**) were supported.

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