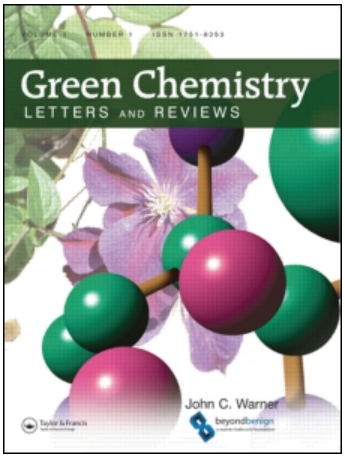

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RESEARCH LETTER

An efficient green protocol for the synthesis of 2-aryl substituted benzothiazoles

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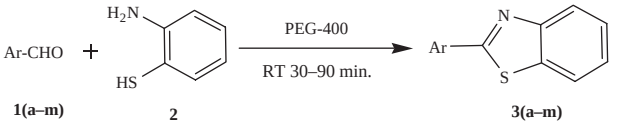
Cyclocondensation of 2-aminothiophenol and various aryl/heteryl aldehydes was carried in polyethylene glycol-400 as a catalyst and reaction medium at room temperature to obtain 2-aryl substituted benzothiazoles with excellent yields.



Keywords: cyclocondensation; 2-aminothiophenol; aldehyde; polyethylene glycol-400; 2-arylbenzothiazoles

Introduction

2-Arylbenzothiazoles are highly important fused heterocyclic units in the realm of organic and medicinal chemistry and possess diverse biological and pharmacological properties, including, anti-tumor, anti-consultant, anti-viral, and anti-cancer (*1–4*). Furthermore, benzothiazoles have emerged as β-amyloid, anti-parasitics anti-tuberculosis, and chemiluminescent agents, and also as photosensitizers (*5–11*). Owing to the wide range of pharmacological and biological activities, the synthesis of 2-aryl substituted benzothiazoles has become an important target in recent time.

In the twenty-first century, the development of environmentally benign chemical processes has been gaining considerable importance both in academic and industrial research (*12,13*). The use of volatile, toxic, and hazardous organic solvents has been replaced by alternatives, such as water (*14–16*), ionic liquids (*17–20*), and polyethylene glycols (PEGs) (*21–25*). The use of solvent-free techniques (*26*) and biocatalysts (*27*) in organic syntheses is gaining tremendous importance due to their nonflammability and easy recyclability.

In organic synthesis, PEGs play an important role and display some noticeable properties, such as, nontoxicity, thermal stability, eco-friendliness, easy recyclability/reusability, bio-degradability, and the ability to act as phase transfer catalysts (*28*). PEGs are relatively inexpensive catalysts. Therefore, many organic transformations have been carried out for obtaining benzimidazoles (*29*), β-amino sulfides (*30*), β-keto sulfones (*31*), 3-amino-1*H*-pyrazoles (*32*), and amino functionalized 2,4,6-triaryl pyridines (*33*) using PEGs as a media. There are reports on the use of PEGs for Michael addition (*34*) and Heck reactions (*35*).

In the literature, various methods have been reported for the synthesis of 2-arylbenzothiazoles involving the condensation of 2-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, or esters (*36*). Various catalysts, such as I_2 (*37*), TMSCl (*38*), H_2O (*39*), H_2O_2/Fe $(NO_3)_3$ (*40*), and Dowex 50W (*41*) have been employed to carry out the cyclocondensation of 2-aminothiophenols and aldehydes for obtaining high yields of benzothiazoles. There have been reports that the thiobenzanilides and potassium ferricyanide (Jacobson's method) (*42*), when condensed, give benzothiazoles. In other approaches, microwave accelerated reactions of aromatic aldehydes with 2-aminothiophenols have been carried out in the presence of ionic liquids (*43*) or silica gel (*44*). Unfortunately, most of these methods have suffered from one or more limitations, such as stringent reaction conditions, tedious work-up in obtaining pure products, requirement of high boiling solvents, and presence of side reactions.

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In quest to provide convenient synthetic protocols for obtaining benzothiazoles, recently, several modifications for carrying the cyclocondensation of aryl aldehydes and 2-aminothiophenols have been reported. Okimoto et al (*45*) have carried the cyclocondensation of the imines generated from aldehydes and amines using electro oxidative cyclization. The cyclocondensation of aryl aldehydes and 2-aminothiophenol have been performed by Itoh et al. (*46*) using scandium triflate and obtained better yields of the benzothiazoles. Al-Qalaf et al. (*47*) have reported the cyclization of 2-aminothiophenols and aldehydes using ceric ammonium nitrate as an oxidant in methanol and obtained moderate yields of the benzothiazoles.

It has been noticed that the above methods can be carried out at room temperature, but each has some disadvantage. The reported electro oxidative cyclization requires two steps and is relatively troublesome. The cyclization is carried out in the presence of ceric ammonium nitrate to give moderate yields of benzothiazoles due to ceric ammonium nitrate possibly oxidizing 2-aminothiophenol to the respective disulfides. The reagent/catalyst employed in the ring closure of the condensation, such as scandium triflate is relatively costly. The above observations/limitations of the reported methods have prompted us to undertake the work related to the development of an efficient method for the condensation. Recently, we have made an attempt to synthesize benzothiazoles using whole cell enzyme, i.e. baker's yeast, as an enzymatic catalyst under mild reaction condition (*48*).

Considering the significance of PEGs and in continuation of our interest toward the development of environmentally benign, rapid, synthetic routes for bioactive heterocycles (*49*), we have made an attempt to carry out the cyclocondensation of aryl aldehydes and 2-aminothiophenol in PEG-400 for obtaining the desired 2-arylbenzothiazoles efficiently and conveniently.

Results and discussion

In our endeavourer to develop new synthetic route (*50*), we report a simple and efficient methodology for the cyclocondensation of 2-aminothiophenol with various aldehydes in the presence of PEG-400 as reaction medium.

To optimize the reaction conditions, the cyclocondensation of 2-aminothiophenol and 4-methoxy benzaldehyde was chosen as a reference reaction. Attempts were made to run the cyclocondensation at room temperature by varying concentrations of aqueous solutions of PEG-400. It was also observed that the condensations do not run in water at room temperature and after prolong heating, yields of the benzothiazoles are relatively lower. However, it was found that there was an increase in yield with an increase in concentration of aqueous PEG-400. In another attempt, when the condensation was carried out in neat PEG-400 at room temperature, the reaction was found to be completed within 30 min and gave 90% yield.

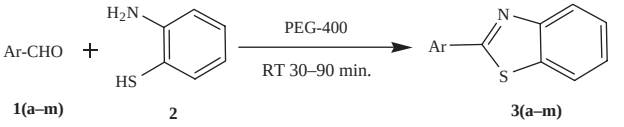
To generalize our methodology, we have synthesized 2-arylbenzothiazoles by the cyclocondensation of 2-aminothiophenol with various aldehydes in the PEG-400 as reaction medium to afford excellent yields (Scheme 1, Table 1). It is noticed that PEG-400 was easily recyclable/reusable without loss of activity. The results of cyclocondensations of 2-aminothiophenol and 4-methoxy benzaldehyde carried out using reused/recycled PEG-400 are incorporated in Table 2. The several aromatic aldehydes bearing either electron donating or withdrawing groups were smoothly employed to prepare the corresponding benzothiazole derivatives with 90–93% yields. In a similar fashion, the other heteroaromatic aldehydes, such as pyridine-2-carboxyaldehyde and furfuraldehyde have also been condensed with 2-aminothiophenol to afford the corresponding benzothiazoles with 87–89% yields.

In this course, PEG-400 might be enhancing electrophilic behavior of carbonyl carbon of the aldehydes by forming intermolecular hydrogen bonding between carbonyl oxygen and that with terminal hydroxyl groups of PEG-400, expediting the intermediate formation of the imines. The addition of a mercapto group (SH) of 2-aminothiophenol to the in situ formed imino has been found to be accelerated because of increased nucleophilicity of mercapto group (SH) of 2-aminothiophenol probably due to hydrogen bonding of mercapto group (SH) with those ethereal oxygens of PEG-400. Finally, the oxygen present in the air might be acting as an oxidant which facilitates aromatization of the *in situ* generated cyclic product benzothiazolines through dehydrogenation resulting in the benzothiazoles.

Experimental

General procedure for 2-arylbenzothiazoles

A mixture of the 2-aminothiophenol (8 mmole) and aldehydes (8 mmole) was dissolved in PEG-400



Scheme 1. One-pot synthetic route for 2-arylbenzothiazoles.

Table 1. Physical parameters of the 2-arylbenzothiazoles **3(a–m)**.

Entry	Ar	Product	Time (min) at room temperature	Yield[a,b] (%)	MP (°C) (ref.)
1	4-$OCH_3 \cdot C_6H_4$	**3a**	30	90	119–120 (*44*)
2	C_6H_5	**3b**	35	91	113–114 (*44*)
3	4-$N(CH_3)_2 \cdot C_6H_4$	**3c**	45	90	159–160 (*41*)
4	4-$CH_3C_6H_4$	**3d**	40	91	86–87 (*44*)
5	2-$OH \cdot C_6H_4$	**3e**	35	90	129–130 (*38*)
6	4-ClC_6H_4	**3f**	50	93	117–118 (*44*)
7	4-BrC_6H_4	**3g**	50	93	131–132 (*44*)
8	4-FC_6H_4	**3h**	50	93	101–102 (*37*)
9	4-$NO_2C_6H_4$	**3i**	40	92	229–230 (*42*)
10	2-Pyridyl	**3j**	90	87	127–129 (*38*)
11	2-Furyl	**3k**	85	89	102–103 (*37*)
12	$-CH=CH \cdot C_6H_5$	**3l**	120	30	110–111 (*39*)
13	$-CH=CH \cdot C_6H_5$[c]	**3m**	4h[c]	60	110–111 (*39*)

[a]The products were characterized by comparison of their spectroscopic and physical data with those reported in literature.
[b]Isolated yield.
[c]Carried at 110°C.

(10 ml) and the solution was stirred at room temperature. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mass was poured in ice water and then extracted with diethyl ether. The ethereal extract was evaporated under rotary vacuum and the crude product obtained was purified by crystallization. PEG-400 was recovered from the aqueous layer by removing water under reduced pressure.

Conclusion

We have demonstrated here that PEG-400 offers a safer medium and an efficient catalyst for the cyclocondensation of 2-aminothiophenol with aldehydes to afford the corresponding 2-arylbenzothiazoles with excellent yields. The notable advantages of this method are easy work up, no side products/clean reaction, reduced reaction time, and easy recyclablity of the solvent. Hence, this protocol would be a good addition as a convenient and an efficient method to the methods available for the synthesis of benzothiazoles.

Table 2. Results of cyclocondensations of 2-aminothiophenol and 4-methoxy benzaldehyde carried using reused/recycled polyethylene glycol-400.

Entry	PEG-400	Yields[a] (%)
1	Fresh	90
2	Run 1	90
3	Run 2	87
4	Run 3	80

[a]Isolated yields.

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