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Efficient One-Step Synthesis of Benzazoles in Aqueous Media

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Benzazoles (benzoxazoles, benzothiazoles, and benzimidazoles) were efficiently prepared by the aquatic reaction of the corresponding thioamidinium salts and 2-aminophenol, 2-aminothiophenol, and 1,2-diaminobenzene, respectively. The thioamidinium salt was successfully applied as an alternative to a carboxylic acid derivative to react smoothly with an amino precursor and in the presence of catalytic amounts of hexadecyltrimethylammonium bromide salt to produce benzazoles in good to excellent yields.

Introduction

Benzazoles are very important compounds due to their presence in natural products,[1] and their use in medicinal chemistry[2–5] (Figure 1) and industry.[6–7]

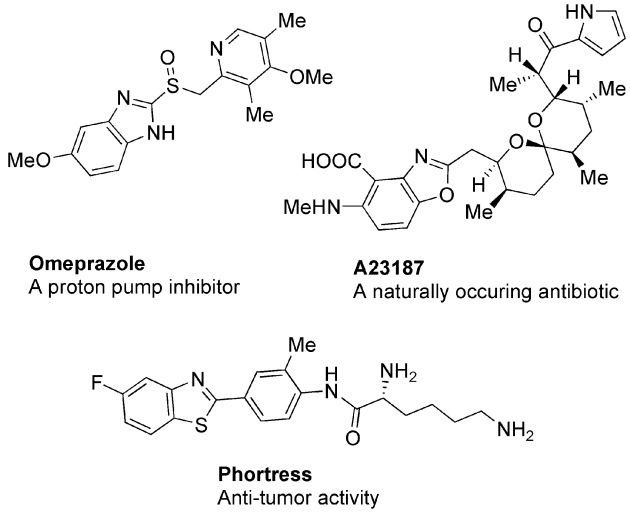

Figure 1. Representative examples of benzazoles in medicinal chemistry.

The standard approach to the synthesis of benzazole derivatives is cyclocondensation reaction of the corresponding 2-aminophenol, 2-aminothiophenol, or 1,2-diaminobenzene with carboxylic acids or derivatives and under somewhat severe reaction conditions.[8] Benzothiazoles can be also synthesized directly by the reaction of 2-aminothiophenol with an aromatic aldehyde under various reaction conditions.[9] They are also prepared by means of oxidative cyclization of thiobenzanilides with a large number of oxidizing agents.[10] Recently, a one-step preparation of benzoxazole[11] and benzimidazole[12] derivatives by direct oxidation of the respective benzanilides and amidines with air and/or oxygen and in the presence of catalytic amounts of copper salts or complexes has been reported. More recently, transition-metal-catalyzed hydrogen transfer reaction of alcohols has been utilized for the synthesis of benzazoles in moderate to very good yields.[13] However, use of expensive catalysts and rather harsh reaction conditions (refluxing in toluene) accompanied with long reaction times (8–24 h) are some disadvantages of this method.

Undoubtedly, thioamides are very important building blocks in the synthesis of heterocyclic compounds and especially sulfur heterocycles.[14] To increase the reactivity of thioamides toward nuleophilic reactions and to block the sulfur atom in the heterocyclization process, *S*-alkylation is often employed. The resulting *S*-alkylthioamidinium salts have gained wide applications in the synthesis of five-membered heterocycles.[15] On the other hand, both the nitrogen and sulfur atoms of the thioamide moiety in a thioamidinium salt undergo substitution in the reaction with dinucleophilic compounds (such as 1,2-diaminobenzene, 2-aminophenol, and 2-aminothiophenol) leading to the corresponding benzo-fused azoles (benzazoles). The only reported procedure for the synthesis of benzazoles from thioamidinium salts is restricted to 2-arylbenzoxazole and benzothiazoles.[16] However, the use of reflux conditions in an environmentally unfriendly and noxious solvent (pyr-

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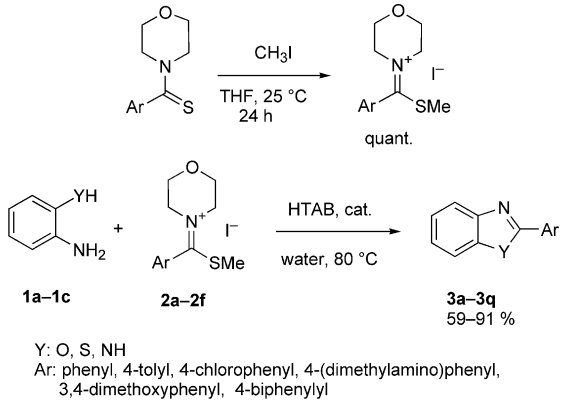
idine), the preparation of the thioamidinium salts under drastic multi-step reaction conditions, and the rather narrow aryl group scope (only examples with indol-3-yl and pyrrol-2-yl substituents were reported) are other major drawbacks.

Results and Discussion

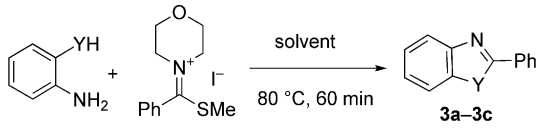
Recently, we reported that benzothiazoles could be formed by oxidative cyclization of thiobenzanilide derivatives.[17] We were eager to synthesize all three kinds of benzazoles by a unique and environmentally benign method due to their considerable applications in medicinal and industrial chemistry. Herein we disclose a novel one-step and eco-friendly procedure for the synthesis of the three different types of benzazoles (benzoxazole, benzothiazole, and benzimidazole derivatives) by reaction of the corresponding 2-amino precursors with a suitable *S*-methylthioamidinium salt in water and in the presence of a catalytic amount of hexadecyltrimethylammonium bromide (HTAB) (Scheme 1).



Scheme 1. Convenient synthesis of benzazoles in water.

Starting thioamides in this study were readily obtained by the Willgerodt–Kindler reaction of the corresponding benzaldehydes and quantitatively transformed to the desired *S*-methylthioamidinium salts by the action of methyl iodide in THF and at ordinary temperatures. We started our study with examining the reaction of the *S*-methylthioamidinium salt **2a** as a test substrate with 2-aminophenol, 2-aminothiophenol, and *o*-phenylenediamine, to produce 2-phenyl-substituted benzoxazole (**3a**), benzothiazole (**3b**), and benzimidazole (**3c**), respectively. At the outset of our study, DMF was used as reaction medium. Therefore, the starting phenyl *S*-methylthioamidinium salt and equimolar amounts of one of the 2-amino precursors were dissolved in small quantities of DMF, and the reaction mixture was heated at 80 °C to produce the corresponding benzazoles in rather good yields. Besides DMF, other solvents were also examined, and the results indicate a significant increase of the yields in polar solvents (Table 1). These outcomes are in accordance with the ionic nature of the thioamidinium salts and the low solubility of such substrates in less polar solvents. It is also noteworthy that the reaction course in less polar solvents takes place sluggishly and produces some tarry materials.

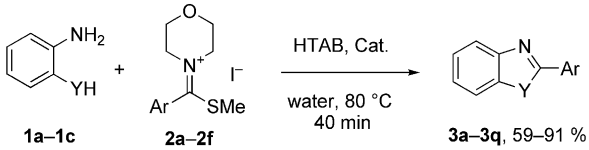
Table 1. Solvent screening in the synthesis of the benzazoles.



Entry	Solvent	Y	Compound	Yield (%)
1	DMF	O	**3a**	78
	EtOH	O	**3a**	70
	THF	O	**3a**	51
	$CHCl_3$	O	**3a**	25
2	DMF	S	**3b**	81
	EtOH	S	**3b**	73
	THF	S	**3b**	54
	$CHCl_3$	S	**3b**	31
3	DMF	NH	**3c**	72
	EtOH	NH	**3c**	63
	THF	NH	**3c**	37
	$CHCl_3$	NH	**3c**	17

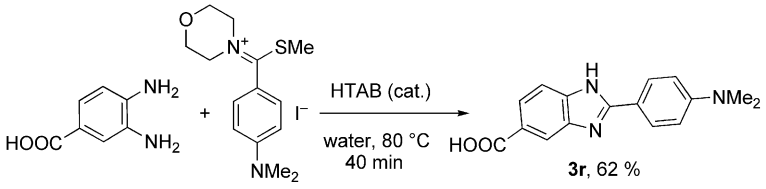
According to these results, we were intrigued to investigate the reaction in aqueous media. Surprisingly, it was found that the reaction course could also be successfully performed in water and in the presence of hexadecyltrimethylammonium bromide (HTAB) to afford benzazoles in good to excellent yields and in shorter time (40 min). This approach would remove the requirement for the use of organic solvents as reaction media and consequently, the reaction course is quite eco-friendly. After optimizing the condi-

Table 2. Efficient synthesis of benzazoles in water.



Entry	1	Y	2	Ar	Product[a]	Ref.	Yield (%)[b]
1	**a**	O	**a**	Ph	**3a**	[18]	85
2	**b**	S	**a**	Ph	**3b**	[18]	89
3	**c**	NH	**a**	Ph	**3c**	[18]	75
4	**a**	O	**b**	4-tolyl	**3d**	[13]	86
5	**b**	S	**b**	4-tolyl	**3e**	[18]	88
6	**c**	NH	**b**	4-tolyl	**3f**	[18]	70
7	**a**	O	**c**	$4\text{-}ClC_6H_4$	**3g**	[18]	62
8	**b**	S	**c**	$4\text{-}ClC_6H_4$	**3h**	[18]	69
9	**c**	NH	**c**	$4\text{-}ClC_6H_4$	**3i**	[18]	59
10	**a**	O	**d**	$4\text{-}Me_2NC_6H_4$	**3j**	[18]	88
11	**b**	S	**d**	$4\text{-}Me_2NC_6H_4$	**3k**	[18]	91
12	**c**	NH	**d**	$4\text{-}Me_2NC_6H_4$	**3l**	[18]	76
13	**a**	O	**e**	$3,4\text{-}(MeO)_2C_6H_3$	**3m**	[18]	77
14	**b**	S	**e**	$3,4\text{-}(MeO)_2C_6H_3$	**3n**	–	81
15	**c**	NH	**e**	$3,4\text{-}(MeO)_2C_6H_3$	**3o**	[18]	71
16	**a**	O	**f**	4-biphenylyl	**3p**	[18]	69
17	**b**	S	**f**	4-biphenylyl	**3q**	[18]	73

[a] All products were characterized by melting points, IR and ^1H NMR spectroscopy, and their spectroscopic data were similar to those reported in the literature. [b] All yields refer to pure isolated products.



Scheme 2. Synthesis of a functionalized benzimidazole.

tions, we next examined the generality of these conditions to other substrates by using several thioamidinium salts and 2-amino precursors. The results are summarized in Table 2. A variety of substituted phenyl groups were tolerated on the thioamidinium salts, and reactions occurred with different 2-amino precursors to lead to 2-aryl-substituted benzazoles.

It is also worthwhile to note that the 2-amino precursor should be dissolved in water prior to addition of the thioamidinium salt to the reaction mixture. Otherwise, significant decrease in the yield of the product is observed. Our investigations revealed that partial hydrolysis occurred in this case. In addition, thioamidinium salts bearing electron-withdrawing groups (Entries 7, 8, 9) had more tendencies to hydrolysis when the reaction was run in water. Interestingly, the presence of a carboxylic acid moiety on the 2-amino precursor does not affect the efficiency of the reaction. Hence, the reaction of 3,4-diaminobenzoic acid with the *S*-methylthioamidinium iodide **2d** led to the formation of corresponding benzimidazole (**3r**, Scheme 2) in rather good yield (62%).

Conclusions

We have developed an efficient and simple method for the preparation of three different types of 2-aryl-substituted benzazoles. High product yield, the ease of product separation, safe and eco-friendly reaction medium, and low cost of the reagents are the salient features of this method. These advantages promote the method as a promising alternative to the synthesis of 2-aryl-substituted benzoxazoles, benzothiazoles, and benzimidazoles, which are extremely important compounds in medicinal and industrial chemistry.

Experimental Section

General Procedure for the Preparation of Benzazoles in Aqueous Media: In a round-bottomed flask the 2-amino precursor (2-aminophenol, 2-aminthiophenol, or *o*-phenylenediamine; 1 mmol) and hexadecyltrimethylammonium bromide (HTAB; 0.1 mmol, 36 mg) were dissolved in water (5 mL) with vigorous stirring and heated to 80 °C. Thereafter, the thioamidinium salt (1.2 mmol) was added portionwise to the reaction mixture during 2 min, and stirring was continued for 40 min. The reaction mixture was then cooled, and the precipitated compound was filtered and washed with water (2 × 5 mL). The resulting crude product was then recrystallized from a suitable solvent (EtOH) to obtain pure benzoxazole, benzothiazole, or benzimidazole, respectively.

Supporting Information (see footnote on the first page of this article): Complete experimental procedures, ^{1}H NMR spectroscopic data (including their copies), and elemental microanalysis for some compounds.

Acknowledgments

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