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Catalyst-Free Facile Synthesis of 2-Substituted Benzothiazoles

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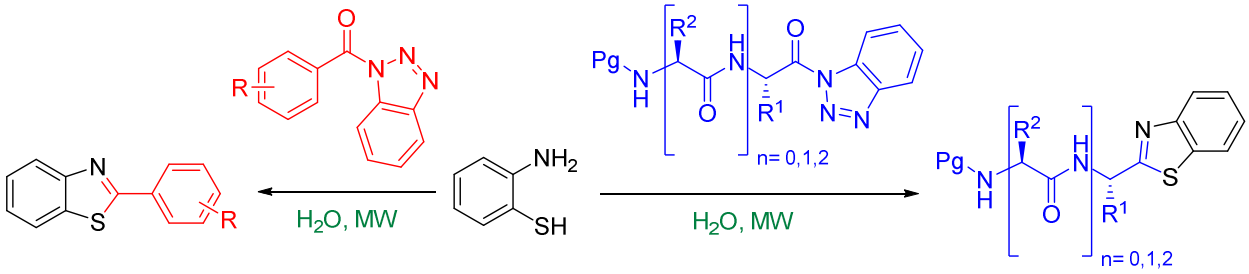

A protocol for the synthesis of 2-aryl/peptidyl benzothiazoles is reported from aryl and peptidyl benzotriazolides and 2-aminothiophenol in high yields in a one-pot reaction with in water under microwave irradiation.

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Communication

Catalyst-Free Facile Synthesis of 2-Substituted Benzothiazoles

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2-Substituted benzothiazoles are synthesized in excellent yields by using a benzotriazole methodology, with conditions being efficient, green, economical, and suitable for broad applications in medicinal chemistry and synthesis of specialty chemicals.

Introduction

2-Substituted azoles such as benzoxazoles, benzimidazoles, benzothiazoles have attracted much attention because of their importance as pharmaceuticals, bioactive compounds, and imaging agents. Benzothiazoles in particular have been studied intensively because of their antitumor,[1] anti-inflammatory,[2] antimicrobial,[3] antitrypanosomal,[4] anticonvulsant,[5] and antituberculosis activity.[6] Benzothiazole moieties are also found in fluorescent pH indicators,[7] an iminocoumarin-based zinc sensor,[8] bioluminogenic substrate,[9] cleavage agents for soluble oligomers [1] of amyloid β-peptides and ligands for catalytic reactions.[11]

Because of this importance, many synthetic methods have been developed, based on (a) condensation of 2-aminothiophenol with carbonyl compounds such as aldehydes,[12–14] carboxylic acids,[15–17] acid chlorides,[18] or esters;[19] (b) conversion of 2-halo amides into the corresponding thioamides using P_4S_{10}, or Lawesson's reagent, but generally not feasible for substrates containing ketone, ester, and amide moieties;[20] (c) cyclization of thioformanilides with the aid of transition-metal catalysts,[21] under S_NAr,[22] or radical conditions,[23] and cyclization of an arylthioamide using potassium ferricyanide (Jacobson's method).[24] Copper catalysis of reactions between iodo amides and sodium sulfide[25] or iodo amines and aldehydes[26] have been reported by Ma *et al.* and Deng *et al.* respectively, both synthetic methods affording respectable yields of 2-substituted benzothiazole.

These methods still suffer from disadvantages such as harsh reaction conditions, use of metal catalysts and additional reagents, use of air sensitive and toxic substances, cumbersome work-up procedures and the generation of acidic and metallic wastes.

Recent efforts to overcome these drawbacks have included (i) use of a palladium catalyzed thiol cross-coupling reaction of 2-haloanilides and 2-ethylhexyl 3-mercapto propionate[27] and (ii) a one-pot synthesis of benzothiazoles with sodium hydrosulfide as the source of sulfur.[28] These methods however use expensive catalysts (Pd) and reagents (aryl iodide) and require long reaction times and high temperatures.

Benzotriazole chemistry has been practiced extensively in our group and has often been found to be superior to conventional routes[29]. In this communication we report a novel synthetic route to 2-substituted benzothiazoles through N-acylated benzotriazoles using no catalyst, auxiliary reagent or solvent. The reaction gives quantitative yields and runs smoothly either under microwave or conventional heating. The best results are achieved when water is used as a reaction medium with microwave irradiation as a source of heat. To the best of our knowledge, this is the first catalyst- and auxiliary-free and environmentally benign synthesis of 2-substituted benzothiazoles affording near quantitative yields under mild reaction conditions.

Results and discussion

2-Aminothiophenol 1 and benzoyl benzotriazolide 2a couple in quantitative yield without any catalyst or solvent if a substantial excess (10 equiv.) of 2-aminothiophenol is used. In fact, the reaction occurs in liquid 2-aminothiophenol, which serves both as a solvent and a reagent for the solid benzotriazolide. Optimization of reaction conditions (Table 1) revealed best results under microwave heating at 70 oC for 1 h; conventional heating was less efficient.

Although, excess of one reagent is not desirable, stoichiometric amounts of **1** and **2a–e** do not afford a good reaction medium, because solid benzotriazoles **2a–e** dominates on a volume-by-volume basis. We therefore ran the reactions of 2-aminothiophenol and benzotriazoles **2a–e** in water under microwave irradiation, as shown in Scheme 1. Excellent yields were obtained for all five aryl derivatives of N-acyl benzotriazole, with melting points of the 2-arylbenzothiazoles **3a–e** being in a good agreement with the literature (see Table 2). Equimolar reactions in water gave yields comparable to those carried out with an excess of 2-aminothiophenol, but the mechanism is different: since neither reagents nor products are soluble in water; the reaction is heterogeneous, and therefore controlled by diffusion. Hexane was also tested as a reaction medium in which both reagents are insoluble; giving almost equally good results, but non-

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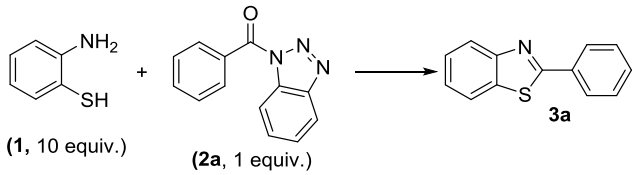
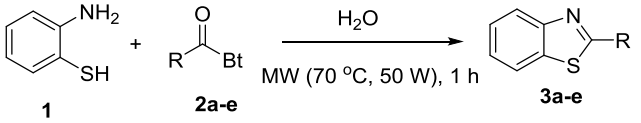
flammable water is preferred.

Table 1 Optimization of reaction condition



Entry	Reaction temp. (°C)	Reaction time	Yield (%)[a]
1	20 (Room temp.)	12 h	0
2	50 (Conv.)	6 h	58
3	100 (Conv.)	3 h	82
4	50 (MW)	3 h	80
5	70 (MW)	1 h	95

[a]Isolated yield



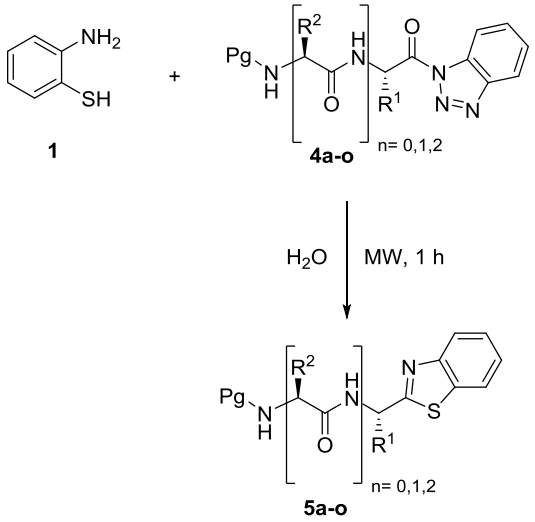
Scheme 1 Synthesis of 2-substituted benzothiazole **3a–e**

Table 2 Preparation of 2-arylbenzothiazole **3a–e**

Entry	R	Yield (%)	Mp (°C)	Lit. Mp (°C)
1	C_6H_5	95	99–100	97–99[27]
2	4-CH_3-C_6H_4	92	88–89	86–88[27]
3	4-OCH_3-C_6H_4	90	115–116	114–116[27]
4	2-thiophenyl	95	91–93	92–94[27]
5	1-napthyl	91	oil	oil[13]

For comparison, 2-phenyl benzothiazole was synthesized by the reaction of 2-aminothiophenol with benzoyl chloride, used in 1:1 stoichiometric amounts. The reactions were run solvent-free under both microwave and normal heating conditions: 70 °C for 1 h. The first reaction step (amine acylation) occurred quickly and almost violently, but the second step (cyclo condensation) required either MW or conventional heating. The yield of 2-phenylbenzothiazole was 89% under microwave and 85% under conventional heating, but the product from the latter contained the N-acylated intermediate. Thus benzotriazole is preferred, since it is a mild and easy to control acylating agent. The benzotriazole route is also greener, since BtH can be easily recycled.

Benzothiazoles with peptidic functions at position 2 afford promising therapeutic or bioimaging agents with good bioavailability. Thus we extended this "suspension-in-water" methodology to the synthesis of 2-peptidylbenzothiazoles **5a–o** by coupling 2-aminothiophenol with peptidylbenzotriazolides **4a–o** (Scheme 2 and Table 3). Good to excellent yields were obtained under 50 W microwave heating at 70 °C in water for 1 h.



Scheme 2 Synthesis of 2-peptidyl benzothiazole **5a–o**

To elucidate the mechanism and range of applicability, **5f** (Cbz-Ala-Bt) was selected for coupling with 2-aminothiophenol in five organic solvents, tap and distilled water, and also under solvent-free conditions. The yields and purity are shown in Table S4. Tap and distilled water gave essentially identical results, and hexane performed almost as well, whereas the other solvents gave inferior results to water and hexane. A solvent-free reaction in an excess of 2-aminothiophenol also gave very high yield and purity. This somewhat surprising reactivity can be rationalized if one takes into account the solubility characteristics of the reagents and products. Water and hexane do not dissolve 2-aminothiophenol, Cbz-Ala-Bt, or the resultant benzothiazole. Toluene is a solvent for 2-aminothiophenol and the product but not for Cbz-Ala-Bt, while EtOH, THF, and DMF freely dissolve both the reagents and products. In the latter reaction media, the reactions are homogenous and kinetically controlled, as the N-acylation of 2-aminothiophenol occurs quickly and irreversibly. The next step, cyclo condensation needs more heating to generate the thermodynamic product, but, as the product is soluble, it exists in equilibrium with the reagents and therefore is produced in smaller yields with similar reaction times. By contrast, the reactions in water and hexane are more likely to be diffusion controlled, because the reagents are sparingly soluble, and the products are virtually insoluble in these solvents. The first step (N-acylation) occurs quickly even at low concentrations of the reagents, while the second step (cyclization) is a unimolecular reaction whose products precipitate and thus drive the reaction to completion. When solubilization was induced by adding 5 mol % of a phase-transfer catalyst (Aliquat 336), the yields were expectedly smaller thus confirming the proposed reaction mechanism. The physical conditions are also important: the uniformly penetrating microwave irradiation plus vigorous stirring greatly improve the heat and mass transfer, which results in significantly higher yields and purity.

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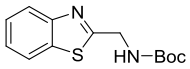
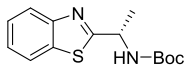
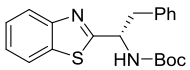
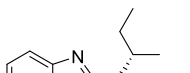
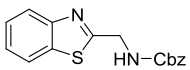
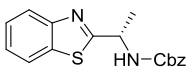
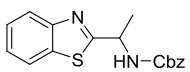
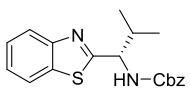
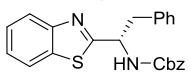
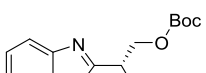
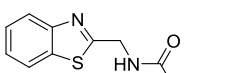
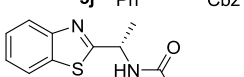
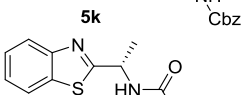
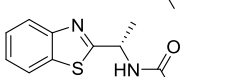
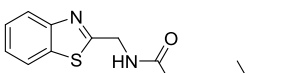
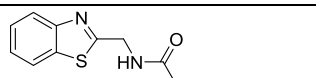
Table 3 Preparation of 2-peptidyl benzothiazole **5a–o**

Entry	Product **5**	Yield (%)	mp (°C)
1	 **5a**	84	68–70
2	 **5b**	82	70–72
3	 **5c**	83	99–101
4	 **5d**	80	130–132
5	 **5e**	82	123–125
6	 **5f**	78	92–94
7	 **5f+5f'**	73	88–90
8	 **5g**	78	220–222
9	 **5h**	70	180–182
10	 **5i**	88	oil
11	 **5j**	76	149–151
12	 **5k**	78	117–116
13	 **5l**	70	179–181
14	 **5m**	89	184–186
15	 **5n**	75	110–112
16	 **5o**	88	163–165

Conclusions

In conclusion, we report a novel, facile and green conditions for synthesis of 2-substituted benzothiazoles without the use of catalysts, synthetic auxiliaries, or even solvent. The heterogeneous reaction run in water produces, without loss of chirality, almost quantitative yields of 2-aryl benzothiazoles and 2-peptidyl benzothiazoles, promising candidates for therapeutic or bioimaging agents. The reaction conditions were optimized at 70 °C in for one hour under microwave irradiation. The uniform heating by MW plus vigorous stirring improve the heat and mass transfer of the diffusion controlled reaction thus explaining the observed high yields and providing a plausible mechanism for the reaction. Given the high yield, "greenness", and possibility of scaling-up the reaction has a considerable potential for adoption by the pharma and fine chemicals industries.

Experimental Section

In a typical procedure, a mixture of 2-aminothiophenol (0.1 g, 0.085 mL, 0.80 mmol) and N-protected aminoacylbenzotriazole or N-protected peptidylbenzotriazole (0.80 mmol) was subjected to microwave irradiation (50 W, 70 °C) in water (3 mL) for 1 h. After completion of the reaction, aqueous $NaCO_3$ solution was added and the mixture was extracted with ethyl acetate followed by washing with 4 N HCl. When the supernatant water retained the product in a colloidal form, the product was isolated by extraction with ethyl acetate. The organic phase was dried over $MgSO_4$ and then evaporated to obtain the desired product. Benzotriazole could be recovered from the aqueous layer by pH controlled acidification.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental details, ^{1}H NMR, ^{13}C NMR, CNH/HRMS and HPLC of all new compounds]. See DOI: 10.1039/b000000x/

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