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Novel Synthesis of 2-Arylbenzothiazoles Mediated by Ceric Ammonium Nitrate (CAN)

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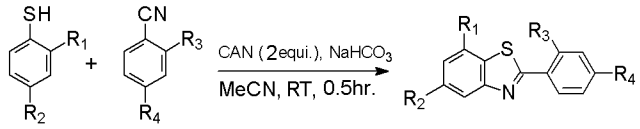
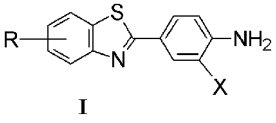
ABSTRACT



Cyclization of the intermediate radical formed after initial oxidative coupling between thiophenols and aromatic nitriles leads to the synthesis of a wide range of 2-arylbenzothiazoles.

The benzothiazole nucleus is of particular interest especially within the realm of medicinal chemistry. Many useful therapeutic agents contain the benzothiazole moiety. For example, 2-(4-aminophenyl)benzothiazoles (**I**) represent a novel class of potent and selective antitumor agents.[1]



I

X= H, Me, Cl, Br, I
R=H, F

2-Arylbenzothiazoles are most commonly synthesized via one of the two major routes. The most commonly used direct method involves the condensation of ortho amino thiophenols with substituted aldehydes, carboxylic acids, acyl chlorides, and nitriles.[2] This method, however, suffers from limitations such as the difficulties encountered in the synthesis of readily oxidizable 2-aminothiophenols bearing substituent groups. Another route is based on the potassium ferricyanide (Jacobson's method) cyclization of thiobenzanilides.[3]

Roe and Tucker reported the synthesis of 2-arylbenzothiazoles through the use of a bromo substituent ortho to the anilido nitrogen and formation of a benzyne intermediate followed by intramolecular cyclization.[4] A similar strategy, for the synthesis of a range of 7-substituted benzothiazoles via directed metalation followed by benzyne formation and subsequent cyclization, has also been reported.[5] These strategies, however, were found to be incompatible with nitro functionality on the aryl ring and do not represent a general route to 2-arylbenzothiazoles. On the basis of the strategy of Spitulnik[6] for the synthesis of 2-methylbenzothiazoles, recently the regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted-2-arylbenzothiazoles via base-induced cyclization/bromide displacement strategy has been reported.

All the above routes to 2-arylbenzothiazoles except the very first one need the precursor thiobenzanilides, whose synthesis involves a multistep transformation.[7] Therefore, a new alternative route for the synthesis of 2-arylbenzothiazoles needs to be explored. It was reasoned that ceric ammonium

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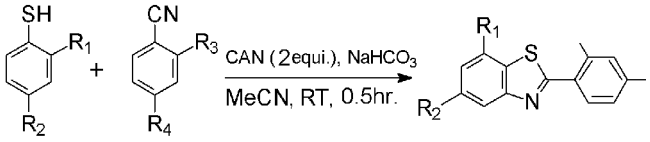
nitrate (CAN), an excellent one-electron oxidant,[8] can be employed for radical generation and subsequent cyclization. Accordingly, the thiophenols were treated with aromatic nitriles in the presence of ceric ammonium nitrate, and as envisaged the reactions proceed smoothly to afford the corresponding 2-arylbenzothiazoles in excellent yield[9] (Scheme 1).

Scheme 1



The results are summarized in Table 1. As shown in the table, the synthesis of 2-arylbenzothiazoles bearing substituents in both the benzothiazolyl and aryl rings is accomplished in excellent yield. It is further seen that 2-arylbenzothiazole bearing nitro functionality on the aryl ring (entry 1e) is obtained in good yield by this method. This contrasts, however, with the Bu_3SnH/AIBN-promoted[10] cyclization of aryl radical onto thioamides for the synthesis of arylbenzothiazoles, where under these conditions thioamides containing a nitro functionality on the aryl ring underwent decomposition rather than benzothiazole formation.

Table 1. CAN-Mediated Synthesis of 2-Arylbenzothiazoles

	R_1	R_2	R_3	R_4	yield[a] (%)
1a	H	H	H	H	95
1b	H	H	H	CH_3O	95
1c	H	CH_3	H	CH_3	90
1d	H	CH_3	CH_3O	CH_3O	89
1e	CH_3	H	H	NO_2	85
1f	F	H	Cl	H	87
1g	Cl	Cl	H	Cl	87
1h	H	CF_3	H	Br	78
1i	H	CF_3	I	H	80
1j	Br	H	H	CN	96

[a] Yield refers to the pure isolated product.

The usefulness of this methodology lies in the fact that the reactions are carried out rapidly under extremely mild conditions to give the product 2-arylbenzothiazoles (entries 1a−j) in excellent yield. Moreover, the method is compatible with many substituents such as halogen, alkoxy, cyano, nitro, etc. in the substrate. Unfortunately, the presence of an amino substituent in the substrate leads to the quinone type product via ready oxidation under reaction conditions rather than benzothiazole formation. In conclusion, the methodology reported herein is expected to be a quite general route for the synthesis of a wide range of 2-arylbenzothiazoles.

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Supporting Information Available: Experimental procedure, ^{1}HNMR spectral data, and elemental microanalysis. This material is available free of charge via Internet at http://pubs.acs.org.

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(9) **Experimental:** All chemicals were of analytical grade. Solvents were distilled before use. The products were characterized by their physical constants and spectral analysis. **Preparation of 7-methyl-2-(4-nitrophenyl)-benzothiazole:** *O*-thiocresol (0.248 g, 2 mmol), 4-nitrobenzonitrile (0.296 g, 2 mmol), and $NaHCO_3$ (0.5 g) were dissolved in 20 mL of anhydrous acetonitrile. Ceric ammonium nitrate (CAN) (2.192 g, 2 equiv) was added to the above solution at room temperature under stirring. After 0.5 h (attention: the yellow color of ceric ammonium nitrate disappeared) at room temperature the mixture was filtered, washed with water, and extracted with chloroform (3 × 10 mL). After drying over anhydrous Na_2SO_4, solvent was evaporated under reduced pressure to give the product. The product was purified by column chromatography (petroleum ether:ethyl acetate 9:1). ^{1}H NMR ($CDCl_3$): 2.53, (s, 3H), 7.10 (d, 1H), 7.34 (t, 1H), 7.83 (d, 1H), 7.20 (d, 2H), 8.27 (d,2 H). Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.22; H, 3.76; N,10.38. Found: C, 62.19; H,3.56; N, 10.37.

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