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The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles†

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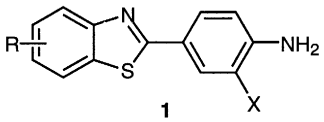
Abstract

The regiospecific synthesis of a range of antitumour 2-arylbenzothiazoles substituted in the benzothiazole ring is described. In this procedure a bromine atom situated *ortho* to the anilido nitrogen is used to direct a regiospecific cyclisation where, in the absence of bromine, a mixture of regioisomers is produced. The chemistry described is applicable to the synthesis of 2-arylbenzothiazoles bearing both electron-withdrawing (-NO_2) and electron-donating (-NH_2) substituents on the aryl ring. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: benzothiazoles; regiospecificity; antitumour compounds; cyclisation.

2-(4-Aminophenyl)benzothiazoles **1**, represent a novel class of potent and selective antitumour agents which exhibit nanomolar inhibitory activity against a range of human breast, ovarian, colon and renal cell lines in vitro.[1] These compounds are the subject of intense current interest in our laboratories due to their extremely interesting antitumour profile of activity and unique mechanism of action.

Recent studies directed to better understand the biological mechanism of action of the lead compound **1** (X=Me, R=H) have focused on the crucial role of oxidative metabolism mediated by the cytochrome P450 isoform CYP1A1, resulting in the formation of the 6-hydroxy metabolite (X=Me, R=6-OH).[2] In order to circumvent this undesirable hydroxylation, we required the synthesis of a range of mono- and di-fluorinated 2-(4-amino-3-methylphenyl)benzothiazoles **1** (X=Me, R=F) which might divert metabolism elsewhere in the molecule and lead to a new generation of more potent and efficacious antitumour agents.[3]



1
X = H,Me,Cl,Br,I
R = H,F

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† Part 9 of the series 'Antitumour benzothiazoles'.

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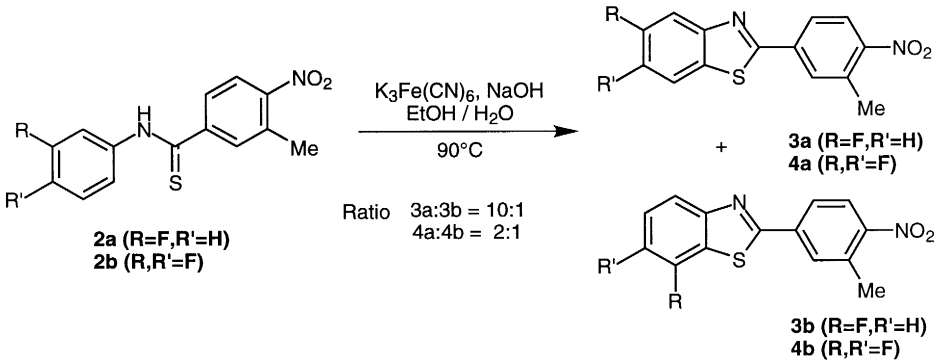
2-Arylbenzothiazoles are most commonly synthesised via one of two major routes. The most common direct method involves the condensation of an *ortho*-amino thiophenol with a substituted aromatic aldehyde, carboxylic acid, acyl chloride or nitrile.[4] This method, however, is often not appropriate for many substituted 2-arylbenzothiazoles due to the difficulties encountered in the synthesis of the readily oxidisable 2-amino thiophenols bearing substituent groups. Another method which we have used extensively in our laboratories is that based on the potassium ferricyanide (Jacobsen) radical cyclisation of thiobenzanilides.[5] In the case where cyclisation onto either carbon atom *ortho* to the anilido nitrogen produces only one product, the Jacobsen cyclisation is a highly effective strategy for benzothiazole synthesis (e.g. for the synthesis of 6-substituted benzothiazoles). In the case of the radical cyclisation of the 3-fluoro- or 3,4-difluoro-substituted thiobenzanilides **2a** or **2b**, however, a mixture of the regioisomeric fluorinated benzothiazole products **3a**/**3b** or **4a**/**4b** was produced, which proved difficult to separate by column chromatography (Scheme 1).



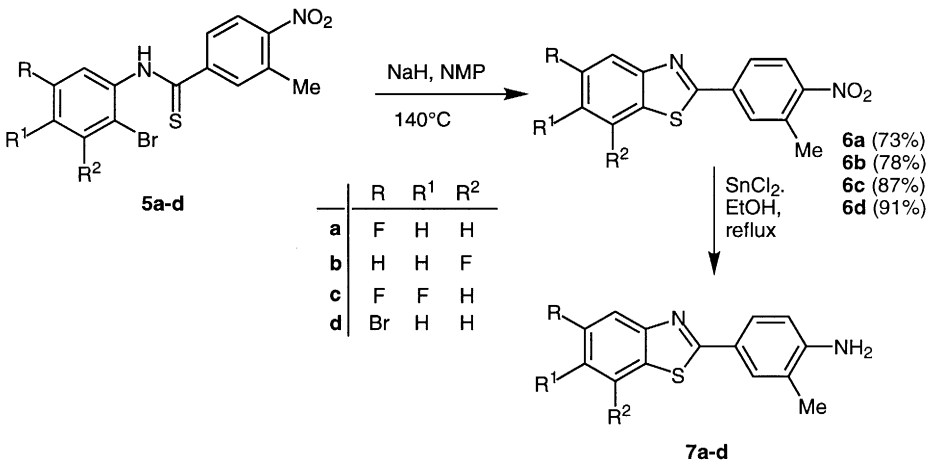
Scheme 1.

A similar mixture of regioisomeric products from the Jacobsen cyclisation has also been observed previously by Roe and Tucker for the synthesis of 5- and 7-fluoro-2-phenylbenzothiazoles.[6] A regiospecific synthesis of 2-arylbenzothiazoles unsubstituted in the phenyl ring was developed by the same authors through the use of a bromo substituent *ortho* to the anilido nitrogen and formation of a benzyne intermediate followed by intramolecular cyclisation. A similar strategy has been developed for the synthesis of a range of 7-substituted benzothiazoles via directed *ortho* metallation followed by benzyne formation and subsequent cyclisation.[7] These strategies, however, were found to be incompatible with the nitro functionality on the aryl ring and do not represent a general route to functionalised 2-arylbenzothiazoles.

In this paper we report the independent synthesis of 5-fluoro- and 7-fluoro-2-(4-amino-3-methyl)benzothiazole via a base-induced cyclisation/bromide displacement strategy. The methodology has been extended to the synthesis of the corresponding 5,6-difluoro and 5-bromo benzothiazoles, in all cases from readily available precursors.

The precursor *ortho*-bromothiobenzanildes **5a**–**d** are available from 2-bromo-5-fluoro aniline,[6] 2-bromo-3-fluoroaniline,[8] 2-bromo-4,5-difluoroaniline[9] and 2,5-dibromoaniline, respectively, via a well-established route involving amide-formation and thionation.[5] The key benzothiazole formation step is based on methodology reported by Spitulnik[10] for the synthesis of 2-methylbenzothiazoles and involves cyclisation of the thiobenzanilides using sodium hydride in NMP at 140°C in excellent yields, as shown below. A related base-induced cyclisation/chloride displacement has been reported for 2-arylbenzothiazoles bearing nitro functionality on the benzothiazole ring.[11,12] Reduction of the nitrophen-

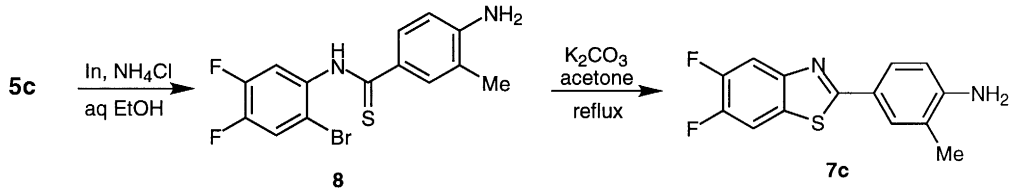
ylbenzothiazoles **6a**–**d** using tin(II) chloride in ethanol[5] gives the desired antitumour 2-(4-amino-3-methylphenyl)benzothiazoles **7a**–**d**[13] as single regioisomers in good yield (Scheme 2).



Scheme 2.

The methodology reported herein represents an attractive alternative to radical cyclisations as a strategy for benzothiazole formation. The Bu_3SnH/AIBN promoted cyclisation of aryl radicals onto thioamides to form simple 2-arylbenzothiazoles has previously been reported;[14] however under these conditions the (nitrophenyl)thioamides **5** underwent decomposition rather than benzothiazole formation.

An alternative strategy for regiospecific formation of **7** was designed which demonstrates that the regiospecific ring-forming methodology described herein can be extended to examples where the aryl substituent is an electron-donating ($-NH_2$) rather than an electron-withdrawing ($-NO_2$) group. Reduction of the (nitrophenyl)thioamide **5c** to the corresponding (aminophenyl)thioamide **8** was accomplished in 65% yield using the mild indium-mediated reduction conditions recently reported by Moody and Pitts.[15] Although yields for the reduction of other (nitrophenyl)thioamides **5** were at best moderate, this procedure represents an unusual example of the reduction of an aromatic nitro group in the presence of a thioamide. The facile cyclisation of **8** was then effected using milder basic conditions than for cyclisation of **6** (K_2CO_3 in refluxing acetone) to give benzothiazole product **7c** via an alternative route (Scheme 3).



Scheme 3.

In conclusion, the regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles has been accomplished. The methodology described herein is expected to be quite general for the synthesis of a wide range of substituted 2-arylbenzothiazoles, and work is currently underway to expand the scope of the key reaction.

Acknowledgements

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13. General cyclisation procedure: Sodium hydride (1.1 equiv.) was added slowly to a solution of thiobenzanilide in NMP (10 equiv.) with stirring at room temperature. The mixture was heated at 140°C for 2 h then allowed to cool and poured into excess water. The resulting white precipitate was collected by filtration and purified by flash column chromatography (chloroform) to give the required nitrophenylbenzothiazole. Reduction using tin(II) chloride (see Ref. 5) gave the desired substituted 2-(4-aminophenyl)benzothiazole. ^{1}H NMR data for product 2-(4-aminophenyl)benzothiazoles **7a**–**d**: **7a** (DMSO-d_6) 8.07 (1H, dd, *J* 5.5, 8.8 Hz, H-7), 7.75 (1H, dd, *J* 2.5, 10.0 Hz, H-4), 7.69 (1H, d, *J* 1.5 Hz, H-2′), 7.65 (1H, dd, *J* 1.5, 8.3 Hz, H-6′), 7.26 (1H, dt, *J* 2.5, 8.8 Hz, H-6), 6.70 (1H, d, *J* 8.3 Hz, H-5′), 5.77 (2H, brs, NH_2), 2.10 (3H, s, CH_3); **7b** (DMSO-d_6) 7.74 (3H, m, ArH), 7.51 (1H, td, *J* 5.8, 8.2 Hz, H-5), 7.26 (1H, m, ArH), 6.76 (1H, d, *J* 5.3 Hz, H-5′), 2.16 (3H, s, CH_3); **7c** (DMSO-d_6) 8.22 (1H, dd, *J* 8.0, 10.3 Hz, H-7), 7.98 (1H, dd, *J* 7.4, 11.4 Hz, H-4), 7.63 (2H, m, H-2′, H-6′), 6.71 (1H, d, *J* 8.3 Hz, H-5′), 2.15 (3H, s, CH_3); **7d** ($CDCl_3$) 8.13 (1H, d, *J* 2.0 Hz, H-4), 7.81 (1H, d, *J* 2.2 Hz, H-2′), 7.73 (1H, dd, *J* 2.2, 8.3 Hz, H-6′), 7.69 (1H, d, *J* 8.5 Hz, H-7), 7.42 (1H, dd, *J* 1.8, 8.5 Hz, H-6), 6.72 (1H, d, *J* 8.3 Hz, H-5′), 2.25 (3H, s, CH_3).
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