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Solid phase synthesis of benzothiazolyl compounds

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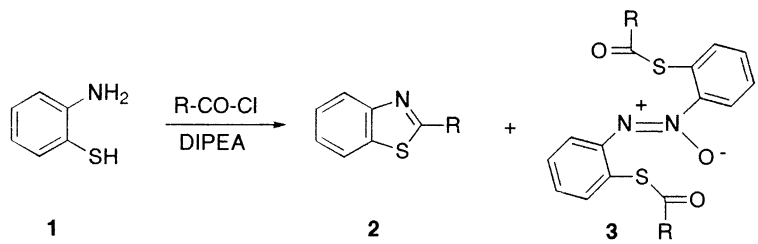
Abstract—2-Aminobenzenethiol, bound through its thiol function to the 2-chlorotrityl (Clt)-, trityl (Trt)-, 4-methyltrityl (Mtt)- and 4-methoxytrityl (Mmt)-resins, was acylated at the amino-function by aliphatic and aromatic acids. The obtained 2-*N*-acyl-aminobenzenethiols were cleaved from the resin by treatment with trifluoroacetic acid solutions in dichloromethane. The 2-*N*-acyl-aminobenzenethiols released from the resin were cyclised to the corresponding 2-substituted benzothiazoles, by standing in a solution of dithiothreitol in DMF or methanol for 1–3 h at room temperature. © 2001 Elsevier Science Ltd. All rights reserved.

The benzothiazolyl-moiety is a structural element of compounds with potent and selective antitumour activity,[1–3] of wide spectrum Ca^{2+} channel antagonists[4] and of inhibitors of several enzymes such as monoamine oxidase (MAO),[5–8] lipoxygenase,[9] acetylcholinesterase,[10] thrombin,[11] of collagenase and neutral proteases,[12] of aldose reductase,[13,14] of H^+–K^+ ATPase[15] and of carbonic anhydrase.[16]

Benzothiazoles are synthesised in solution by the condensation of *ortho*-amino thiophenols with carboxylic acid derivatives,[17] the radical cyclisation of thioacylbenzanilides[18,19] or the base induced cyclisation of the corresponding *ortho*-haloanilides.[18–20] These methods are performed under conditions not appropriate for solid phase synthesis (SPS) and give in several cases complex product mixtures. A SPS of benzothiazolyl compounds carried out under mild conditions would therefore simplify the discovery of new pharmacologically interesting structures, by applying combinatorial methods. We studied this possibility using 2-aminobenzenethiol **1** (Scheme 1) as the model starting material.

For comparison to SPS, we reacted **1** with an equimolar amount of benzoyl- and acetyl chloride and diisopropylethylamine (DIPEA) in dimethylformamide (DMF). HPLC-analysis (Fig. 1a) of the reaction mixtures showed, besides the expected benzothiazole **2** and minor byproducts, the formation of the azoxybenzene derivative **3**, as the main reaction product. Both were identified by ES-MS (Fig. 1b: **2b**, $m/z = 212.02$ $[M+H]^+$; Fig. 1c: **3b**, $m/z = 471.28$ $[M+H]^+$).

To suppress these side reactions, the thiol function of **1** should be protected. Groups of the trityl-type, which are removed by mild acidolysis are suitable thiol protecting groups, as shown in the case of the protection of cysteine during peptide synthesis.[21] The corresponding, commercially available, trityl-type resins **4**[22–24] (Scheme 2) are, in addition, suitable solid supports for thiols.[25]



1 2 3

2, **3**; R = CH_3 (**a**), C_6H_5 (**b**)

Scheme 1.

Keywords: benzothiazoles; benzothiazole equivalent; solid phase synthesis; trityl resin.

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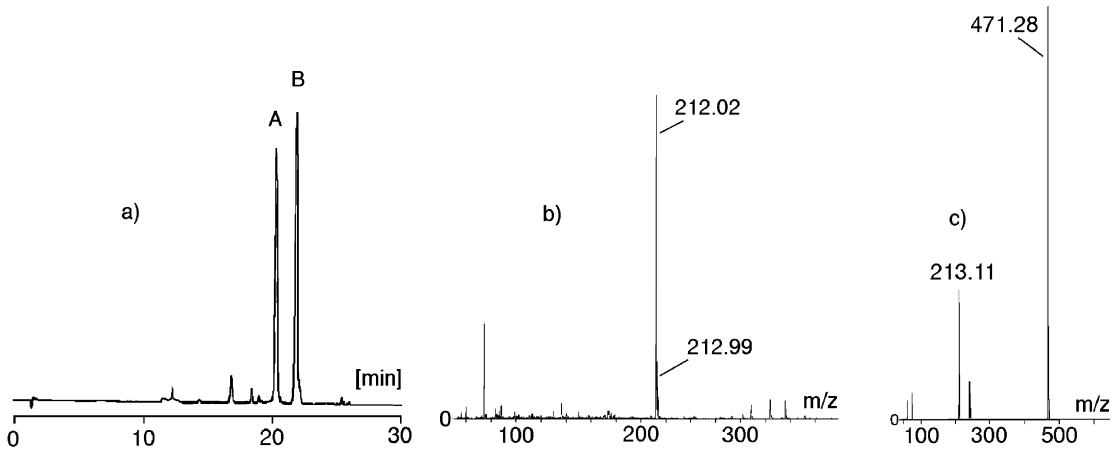
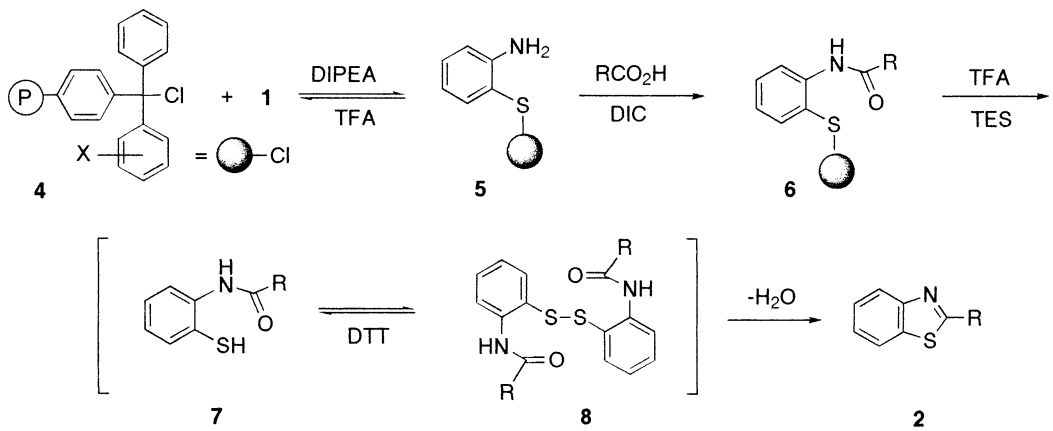


Figure 1. (a) Analytical HPLC of the crude mixture obtained after the reaction of benzoyl chloride with **1** in DMF; Column: Lichrospher RP-8, 5 μm; 4×250 mm; gradient: from 20 to 100% acetonitrile in water within 30 min; flow rate 1 ml/min; detection at 265 nm; (b) ES-MS of the component A; (c) ES-MS of the component B.



4, 5, 6; X = 2-Cl (**a**), H (**b**), 4-CH_3 (**c**), 4-CH_3O (**d**).- **2, 6-8**; R = CH_3 (**a**), C_6H_5 (**b**), C_2H_5 (**c**), C_6H_{13} (**d**), $C_{15}H_{31}$ (**e**), 2-Cl-C_6H_4 (**f**), 4-Cl-C_6H_4 (**g**), 2,4-$Cl_2C_6H_3$ (**h**), 4-CH_3O-C_6H_4 (**i**), 4-NO_2-C_6H_4 (**j**)

Scheme 2.

To achieve the SPS of 2-benzothiazolyl compounds and to suppress simultaneously the above side reactions taking place in solution, we tested the resins **4** for the attachment of **1** on solid phase. In fact, treatment of the resin-chlorides with an equimolar amount of the thiol **1** and 0.7 equivalents of diisopropylethylamine (DIPEA) in dichloromethane (DCM) for 0.5–4 h at rt, led to the corresponding resins **5**. Under these conditions, attachment of **1** through its amine function onto the resin is not possible. The remaining unreacted trityl chloride was converted to the corresponding trityl-methyl ether, by washing the resin with a mixture of DCM/methanol/DIPEA (85:10:5). The loading of the resins obtained was determined by sulfur analysis. We observed highest attachment rates in the case of **4d.** That affords the resin **5d**, within 30 min with a loading of 0.7–0.8 mmol **1**/g. In contrast, **4a** gave at the same time resins with a loading of 0.3–0.4 mmol/g.

The acid stability of the thioether bond in **1** to the various resins was tested by treating **5** with trifluoroacetic acid (TFA) solutions in DCM. The cleavage is reversible and triethylsilane (TES) was added for scavenging the trityl-cations formed on the resin during cleavage. As expected, the acid sensitivity increases considerably from **5a** to **5d**. Thus, a 3×5 min treatment of the resins with 65, 50, 15 and 1.1% TFA, respectively in DCM/TES (95:5), led to 88, 90, 95 and 100% cleavage of **1** from the corresponding resin, while in the absence of TES the cleavage yield dropped to 27, 48, 64 and 100%.

Resins **5** were then acylated with a threefold molar excess of acyl- or aroyl chloride and DIPEA in DMF for 3–4 h at rt. The acylation of **5** was also performed using the acid anhydrides. Complete acylation (Scheme 2) in addition was achieved using several aliphatic and

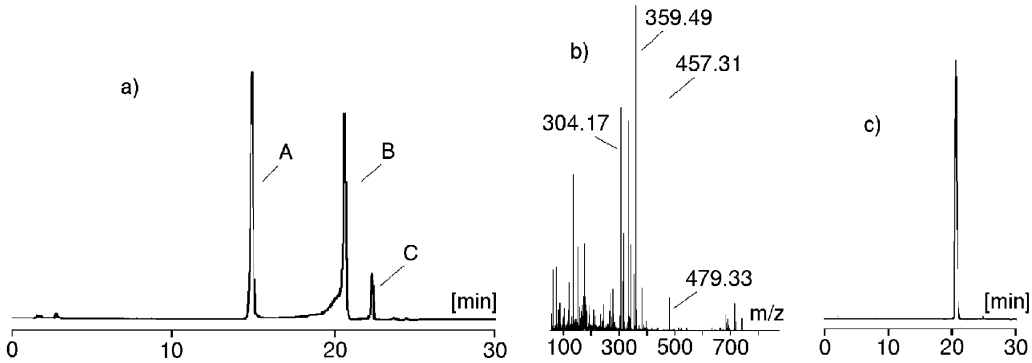


Figure 2. (a) Analytical HPLC of the solution obtained during the cleavage of **7b** from the 4-methoxy-trityl resin, by treatment with 1.1% TFA (conditions as in Fig. 1); (b) ES-MS of component C; (c) HPLC-analysis of crude **7b** after treatment with DTT.

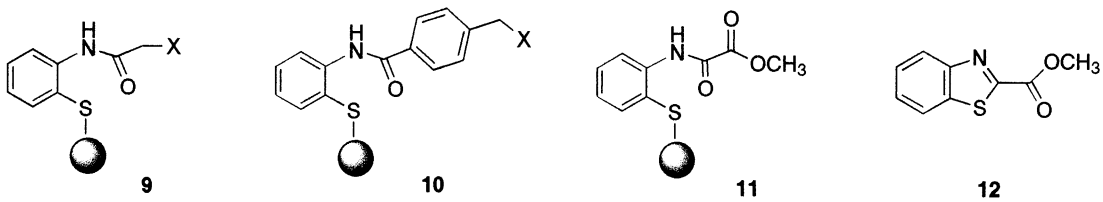


Figure 3.

aromatic acids activated in situ with diisopropylcarbodiimide (DIC). 1-Hydroxybenzotriazole, frequently used as an additive in peptide synthesis, led to slower and in most cases incomplete acylations in this case. The products **6** obtained were then treated with the appropriate TFA solutions (see above) in order to cleave the benzenethiols **7a–j** from the various resins.

A sample of the mixtures obtained was concentrated under a stream of nitrogen, and analysed by HPLC (Fig. 2a shows the HPLC analysis of the mixture obtained during the cleavage of **7b** from the 4-methoxytrityl resin by treatment with 1.1% TFA). The individual components A–C were collected and subjected to ES-MS analysis, after standing for 3 h at rt. Surprisingly both components A and B showed identical molecular masses, which corresponds to the benzothiazolyl compound **2b** and C corresponds (Fig. 2b: **8b**, $m/z=457.3$ $[M+H]^+$) to the oxidised dimer **8b**. Azoxybenzene derivatives as **3b** were not detected. We concluded that component A corresponds to the acyl-derivative **7b**. This cyclises spontaneously to the corresponding benzothiazole by standing in the acetonitrile/water mixture used for their HPLC-elution. To reduce the disulfide **8b**, dithiothreitol (DTT) was added to the solution. Indeed, we observed that **8b** was converted to **7b** and **2b** and the latter was the only product (Fig. 2c: **2b**) of the reaction after standing for 2–3 h at rt. In all cases tested, the acylation of **5** with various acids proceeded very similarly to that of the benzoylation reaction. These observations led to the development of an improved protocol[26] for the SPS, in 80–90% yield, of several 2-alkyl- and aryl-benzothiazoles **2** in 90–97% purity. The ring closure reaction from **7** to **2** is

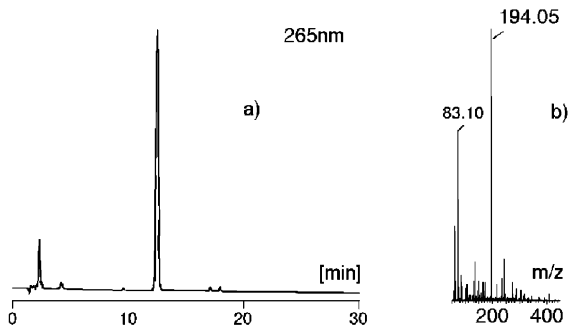


Figure 4. (a) Analytical HPLC (conditions as in Fig. 1); (b) ES-MS of crude **12**.

so much favoured, that even the haloalkyl- and carboxy-derivatives **9–11** (Fig. 3), which can be considered as precursors of various benzothiazolyl compounds, gave the corresponding benzothiazoles in 90–95% purity (Fig. 4a shows the HPLC-analysis of the reaction mixture and Fig. 4b the ES-MS-analysis of the main product obtained after the conversion of **11** to the methylester of 2-benzothiazolylcarboxylic acid **12**).

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26. General procedure for the solid phase synthesis of 2-substituted benzothiazoles: 1 g resin-bound benzenethiol **5** with a loading of 0.74 mmol **1**/g was suspended in 5–6 ml DMF. Then, 2.1 mmol of the carboxylic acid and 2.2 mmol DIC were added and the mixture was shaken for 3 h at rt. The completion of the acylation reaction was checked by cleaving the product from a sample of resin and analysing by HPLC. In cases of uncompleted acylation, a second acylation was performed with the same quantities. Then, the resin was filtered and washed with 5×10 ml DMF and 5×10 ml DCM. The resin still remaining on the filter was then treated (2 min each) with 7×6 ml of 1.1% TFA in DCM/TES (95:5). The filtrates of the seven treatments were concentrated in vacuum to an oily residue and dissolved in 6–10 ml of DMF/methanol (9:1) which contained 0.1–0.2 mmol DTT. After 3 h of standing at rt, the mixture was extracted with diethylether or ethyl acetate, washed with water, dried and concentrated in vacuum. Ether or *n*-hexane were then added and the solid product **2** was filtered, washed with a mixture of ether/hexane and dried. Yield: 80–90% **2b** with purity, determined by HPLC at 220–300 nm, varying from 90–97%.