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Thiocyanation of alkylanilines. A simple and efficient synthesis of thiosulfonates containing 2-aminobenzothiazole

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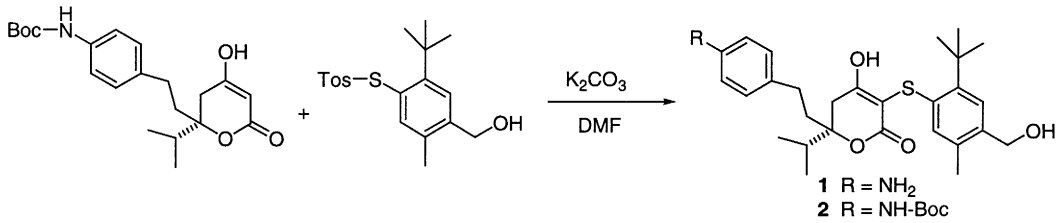
Abstract

Thiocyanation of anilines was used to introduce a thiol functionality and to construct the aminothiazole ring, all in a single step. A systematic study of thiocyanation of alkyl anilines was investigated to understand the regiochemistry of the reaction. X-Ray crystal structures of two 2-aminobenzothiazoles were determined to assign the structures without any ambiguity. The intermediates obtained were further expanded to thiosulfonates containing 2-aminobenzothiazoles, which are extremely valuable intermediates to synthesize HIV protease inhibitors. © 2000 Elsevier Science Ltd. All rights reserved.

Recently we described a non-peptide (**1**, PD 178390) as a lead inhibitor of Human Immunodeficiency Virus-1 protease possessing a 3-SPh(2-*tert*-butyl-4-hydroxymethyl-5-methyl) moiety.[1] The synthesis of **1** involves the reaction of an appropriately substituted 5,6-dihydropyran-2-one with the corresponding thiosulfonate (Eq. (1)).[2] We have been interested in replacing the 3-SPh(2-*tert*-butyl-4-hydroxymethyl-5-methyl) moiety with 3-*S*-2-alkyl-benzoheterocycle to study the resulting structure–activity relationships. Though thiosulfonates have been used extensively in the literature,[3,4] thiosulfonates containing 2-aminobenzothiazoles are not yet known. Herein we describe a simple and efficient synthesis of such thiosulfonates.



(1)

Anilines (**3**–**9**) were chosen as the starting materials for the synthesis of these thiosulfonates. It is known that aromatic hydrocarbons having strong electron-donating groups such as -OH or NH_2 groups

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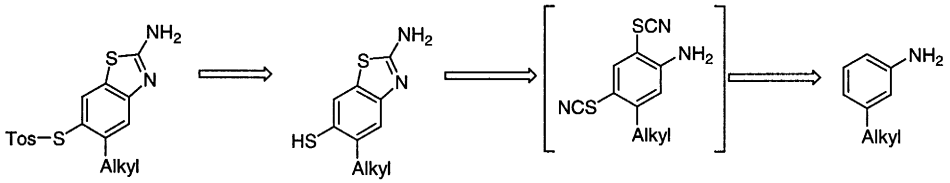
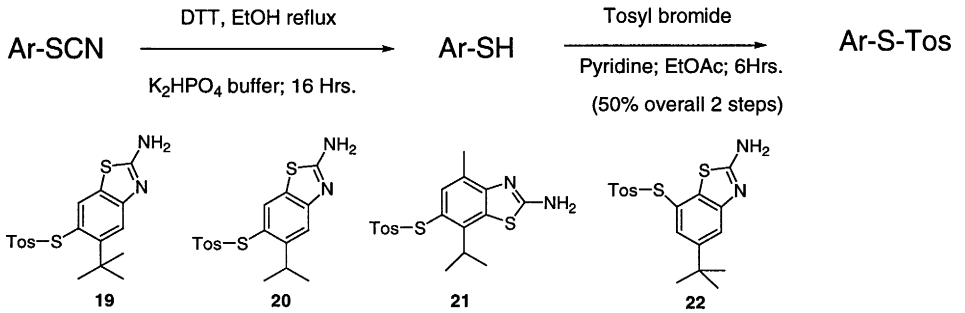
react with thiocyanogen (formed in situ from KSCN and Br_2) to yield aryl thiocyanates resulting in *ortho* and/or *para* thiocyanato products.[5–10] The thiocyanate functionality was chosen due to the fact that it could be useful as a masked thiol group and also due to the reactivity of the thiocyanate group with an amine functionality to form an aminothiazole ring. Thus, thiocyanation of anilines resulted in the introduction of the thiol functionality and formation of the aminothiazole ring in a single step. Finally, thiocyanate functionality could be converted to thiol as shown in Scheme 1.



Scheme 1.

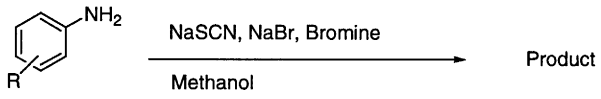
Initially, thiocyanation of alkyl-substituted anilines was studied in order to understand the regioselectivity of the reaction, and the results are shown in Table 1. *meta-tert*-Butyl[11] and *iso*-propyl anilines (**3** and **4**) yielded products **10** and **11**, respectively, in excellent yields. No other regioisomers were obtained. However, *m*-toluidine (**5**) gave a mixture of two regioisomers (**12** and **13**) in the ratio of 1:4, resulting from the thiocyanation of both the *ortho* positions with the respect to the amine group. The structures and the ratio of the regioisomers were confirmed by 1D-NOE, INEPT and APT experiments. From these results, it appears that thiocyanation on the other *ortho*-position with respect to the amino group was prevented in the case of *m-tert*-butyl and *iso*-propylanilines due to the bulkiness of the alkyl groups. This was further confirmed by the lack of dithiocyanation and/or aminothiazole ring formation when 5-*tert*-butyl-2-methylaniline (**6**) was exposed to similar reaction conditions.[12] Thus compound **6** yielded **14** as the only product. However, when 5-*iso*-propyl-2-methylaniline (**7**) was subjected to thiocyanation reaction conditions, **15** was formed along with the monothiocyanation product, **16**, in a smaller amount. Interestingly, when *p-tert*-butylaniline (**8**) and *p*-toluidine (**9**), were subjected to thiocyanation reaction conditions; **17** and **18**, respectively, were isolated resulting from only *ortho*-thiocyanation at both the *ortho* positions of the amine group. The structures of **17** and **18** were confirmed by 1D-NOE, INEPT and APT experiments. Final conformation of the structures **10** and **15** were obtained by X-ray crystal structure determination (Fig. 1).

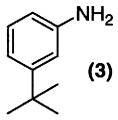
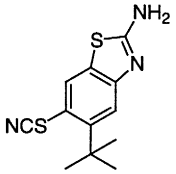
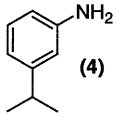
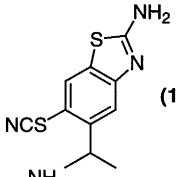
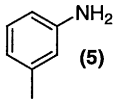
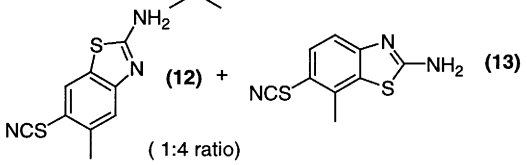
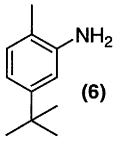
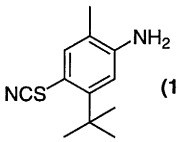
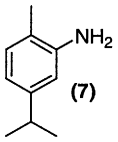
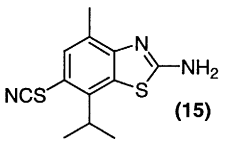
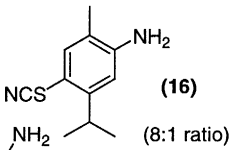
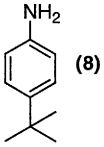
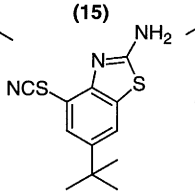
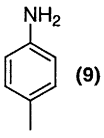
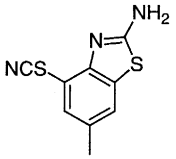
Thiocyanates (**10**, **11**, **15**, **17**) were converted into the corresponding thiosulfonates in two steps (Eq. (2)): (a) transformation of the thiocyanate functionality to thiol by treating with dithiothreitol (DTT); (b) conversion of thiol to the corresponding thiosulfonate by treatment with tosyl bromide[13] in the presence of a weak base like pyridine. In step (b), although the amine functionality of the aminobenzothiazole was not protected, no sulfonamides arising from the amine were noticed.



(2)

Table 1



Aniline	Product(s)	% Isolated Yield
 (3)	 (10)	75%
 (4)	 (11)	78%
 (5)	 (12) + (13) (1:4 ratio)	80%
 (6)	 (14)	72%
 (7)	 (15)  (16) (8:1 ratio)	72%
 (8)	 (17)	65%
 (9)	 (18)	75%

The heterocyclic thiosulfonates (**19**, **20**, **21**, **22**) prepared were coupled successfully with various 6,6-disubstituted-5,6-dihydro-pyran-2-ones in the presence of potassium carbonate in DMF as described in Eq. (1). HIV protease and anti-HIV activities and their pharmacokinetic data of 5,6-dihydropyran-2-ones containing 3-position aminobenzothiazoles will be published in due course.

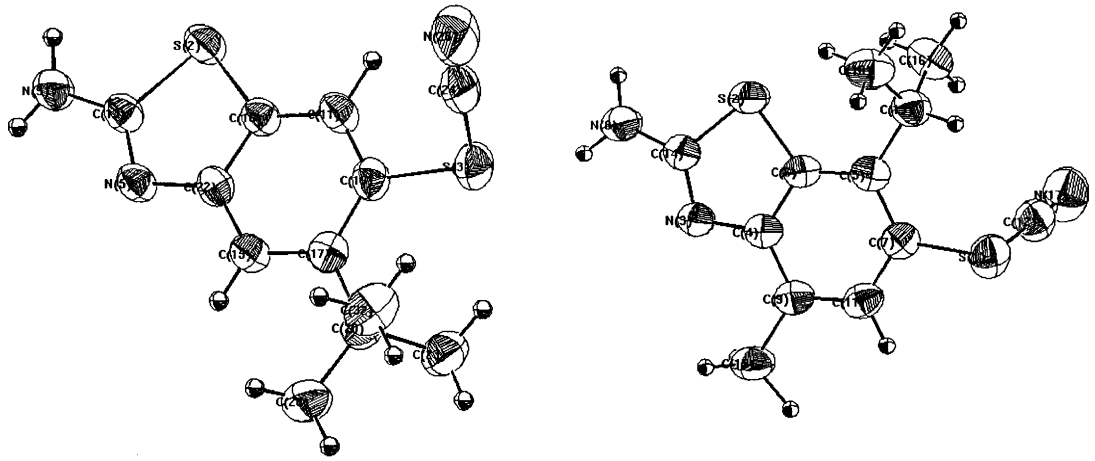


Fig. 1. X-Ray structures of **10** and **15**

Acknowledgements

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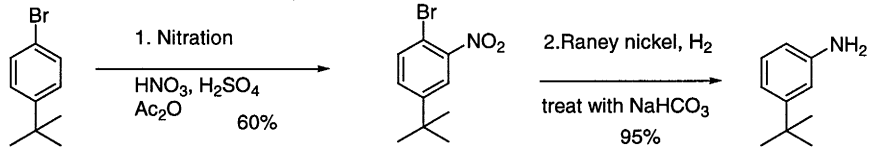

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