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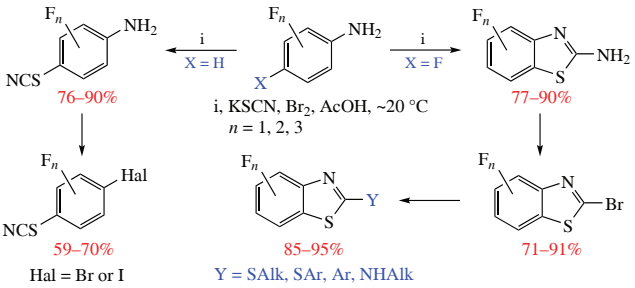
Novel fluorinated 4-thiocyanatoanilines and 2-aminobenzothiazoles: diazotization with post-transformations

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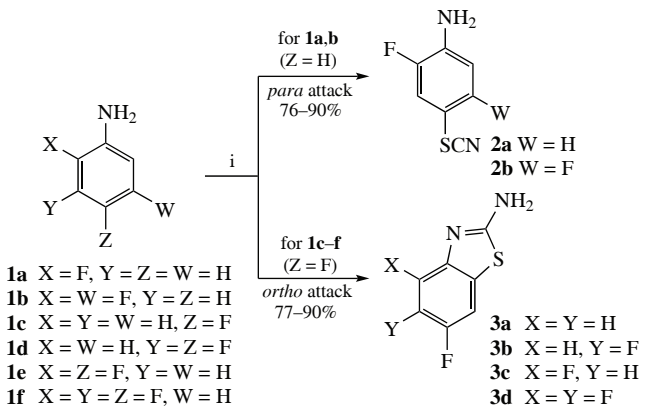
The reaction of fluorinated anilines with the KSCN/Br_2/AcOH reagent system at room temperature affords the corresponding 4-thiocyanatoanilines when the substrates contain *para*-positioned hydrogen atom; if this position is occupied by fluorine, the 'NCS$^+$' attack occurs at the *ortho* position thus leading to fluorinated 2-aminobenzothiazoles. The diazotization of these amino derivatives enables the facile synthesis of new bromine- and iodine-containing analogues. In such 2-bromo(polyfluoro)benzothiazoles, the bromine atom can be readily replaced by organylthio, aryl, or alkylamino groups.



Keywords: halogenated aryl thiocyanates, fluorinated benzothiazoles, diazotization, Suzuki cross-coupling, aromatic nucleophilic substitution, organofluorine compounds.

Organofluorine compounds exhibit special properties and improved biological activity compared to molecules of a similar structure without fluorine atoms.[1] Currently, about 20% of the commercial drugs are fluoropharmaceuticals.[2] Commercial fluorinated anilines play a noticeable role in organic fluorine chemistry serving as versatile building blocks for a wide range of significant chemicals, including biologically active heterocycles,[3,4] in particular, benzothiazoles.[5,6]

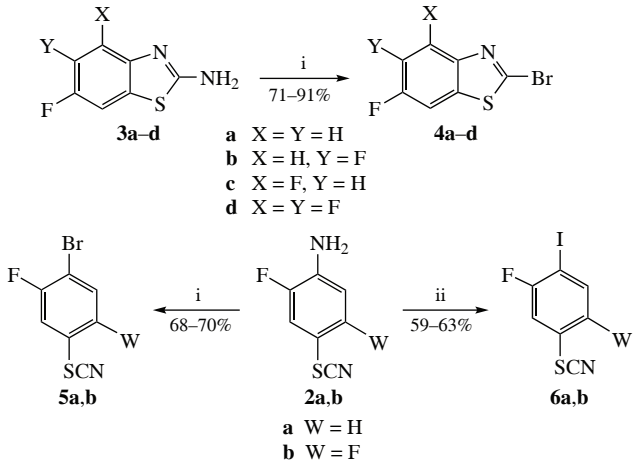
The purpose of this work was to study the reactivity of polyfluoroanilines **1a–f** in the KSCN/Br_2/AcOH reagent system to obtain practically important fluorinated compounds. In fact, the reaction products were either aryl thiocyanates **2a**,**b** or 2-aminobenzothiazoles **3a–d** (Scheme 1). The use of 2,4,5-trifluoroaniline proved ineffective: none of individual compounds was isolated from the reaction mass which was a complex mixture of initial reactant and unidentified substances (^{19}F NMR data).



Scheme 1 *Reagents and conditions*: i, KSCN, Br_2, AcOH (glacial), room temperature, 20 h, then ice and NH_3 (aq.).

It is noteworthy that the precursors of thiocyanates **2a**,**b** were anilines **1a**,**b** containing a hydrogen atom in the *para*-position, while 2-aminobenzothiazoles **3a–d** were formed from *para*-fluoro anilines **1c–f**. A number of test experiments were carried out to understand the mechanism of the transformations (see Scheme 1 as well as Scheme S1 of Online Supplementary Materials). Using **1e** as an example, it was found that the addition of excess KSCN to fluorinated anilines in AcOH at room temperature followed by stirring of the reaction mixture for 20 h does not lead to *N*-arylated thioureas (compound **1e** remained unchanged). This indicates that thiocyanic or isothiocyanic acids, into which KSCN should be transformed in AcOH, are not enough strong electrophiles to react with amino group of fluorinated anilines. On the other hand, it was found that careful addition of an equimolar amount of Br_2 to **1c** in AcOH leads to non-selective bromination of this substrate: after 20 h, the reaction mass was a multicomponent complex mixture (^{19}F NMR). From this observation, it can be supposed that the selective formation of **2** and **3** does not include the stage of electrophilic aromatic bromination of fluorinated anilines. Based on these experimental facts, it can be suggested that the active electrophile involved in the transformation of **1** into **2** and **3** can be *in situ* generated thiocyanogen $(SCN)_2$ arisen from the reaction of KSCN with Br_2 in AcOH (*cf.* ref. 7, see Scheme S1). Apparently, the precursor of the heterocyclic product **3** is 2-thiocyanatoaniline which would undergo the further heterocyclization.[7] So, the mechanism of the formation of 2-aminobenzothiazoles **3** from aniline in the KSCN/Br_2/AcOH system, widely used in laboratory practice,[8] differs from that of two-step procedure[9,10] consisting in the preparation of *N*-arylthiourea (formed by heating of aniline with KSCN in an acidic medium) and its subsequent cyclization by the action of bromine. In our case, the reaction begins with the attack of the electrophile $(SCN)_2$ on the carbon atom in the aromatic ring of

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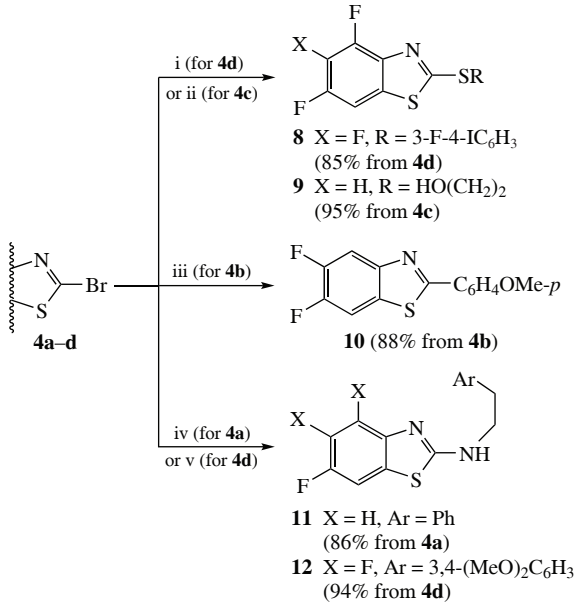
Scheme 2 *Reagents and conditions*: i, Bu^{t}ONO, $CuBr_2$, MeCN, Ar, room temperature, 20 h; ii, Bu^{t}ONO, I_2, MeCN, Ar, room temperature, 20 h.

aniline, while in the second case[9,10] the electrophile HSCN attacks the amino group.

Aryl thiocyanates are of interest in the preparation of sulfur-containing compounds;[7,11] accordingly, many methods of their synthesis have been developed.[12] For the direct introduction of the SCN-group into the aromatic ring, thiocyanatosaccharin with $FeCl_3$,[13] KSCN with NBS,[14] NH_4SCN with *o*-iodoxybenzoic acid,[15] electrogenerated thiocyanogen[16] and other reagents[17] were used. Herein, we found that the KSCN/Br_2/AcOH reagent system is a good contribution to the abovementioned pool applicable to 4-H-anilines with acceptor substituents.

To study the synthetic potential of amino derivatives **2** and **3**, we subjected them to diazotization with mild, easy-to-handle and environmentally friendly *tert*-butyl nitrite[18] in the presence of $CuBr_2$[19] or I_2[20] in MeCN at room temperature. As a result, new bromine- (**4**, **5**) and iodine-containing (**6**) (het)arenes were obtained (Scheme 2).

Fluorinated halo(het)arenes **4**–**6** were then subjected to reactions with nucleophiles (Scheme 3), the cross-coupling reactions being the formal versions of nucleophilic substitutions. 2-Bromobenzothiazole **4b** gave a Suzuki cross-coupling product **10** by reacting with 4-methoxyphenylboronic acid in 88% yield (reaction iii). However, an attempt to introduce aryl iodide **6a** into the Sonogashira cross-coupling with (ethynyl)triisopropylsilane ($Pr^i_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, room temperature, 72 h) was unsuccessful: the substrate **6a** unexpectedly underwent S-decyanation to afford thiophenol derivative **7** of formula 3-F-4-IC_6H_3SH (95% yield). No examples of similar transformations could be found in the literature, although it is known that aryl thiocyanates themselves can be obtained *via* the Au-catalyzed reactions of aryl iodides and AgSCN.[21] In any case, additional research is required to explain this experimental fact.



Scheme 3 *Reagents and conditions*: i, 3-F-4-IC_6H_3SH (**7**), DIPA, MeCN, 70 °C, 120 h; ii, $HO(CH_2)_2SH$, DIPA, MeCN, 50 °C, 18 h; iii, 4-$MeOC_6H_4B(OH)_2$, $PdCl_2(PPh_3)_2$, K_2CO_3, PhH, H_2O, 110 °C, 44 h; iv, $Ph(CH_2)_2NH_2$, DIPA, MeCN, 55 °C, 240 h; v, 3,4-$(MeO)_2C_6H_3(CH_2)_2NH_2$, DIPA, MeCN, 50 °C, 24 h.

The abovementioned thiophenol derivative **7** was successfully utilized as the S-nucleophile in the reaction with 2-bromo-4,5,6-trifluorobenzothiazole **4d** to produce sulfide **8** (see Scheme 3, reaction i). Analogous reaction of substrate **4c** with 2-mercaptoethanol (reaction ii) afforded sulfide **9**. The reaction of trifluoro bromide **4d** with primary amine (reaction v) carried out in the presence of DIPA in MeCN at 50 °C for 24 h led to secondary amine **12** in excellent yield. A decrease in the number of fluorine atoms in the benzene ring caused a serious decrease in electrophilicity of substrate **4a** as 240 h heating at 70 °C was required to achieve 86% yield of product **11** from phenethylamine (reaction iv). Unlike fluorinated 2-bromothiazoles **4**, bromoaryl thiocyanates **5** did not react with nucleophiles under similar reaction conditions remaining intact.

In conclusion, the study of the reactivity of fluorinated anilines in the KSCN/Br_2/AcOH system indicates that the substrate structure affects the type of product, namely, 4-H-anilines give rise to 4-thiocyanatoanilines while 2-aminobenzothiazoles are formed from 4-F-anilines. The halogen derivatives **4a–d** and **6a** (**7**) obtained via the diazotization of fluorinated 2-aminobenzothiazoles **3** and 4-thiocyanatoaniline **2a** were used in the synthesis of more complex benzothiazole objects **8**–**12** being of interest for biological study. The reactivity of 2-bromobenzothiazoles towards nucleophiles increases with an increase in the number of fluorine atoms in the benzene ring of the substrate due to the cumulative acceptor effect of these substituents.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8107.

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