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About the reaction of aryl fluorides with sodium sulfide: investigation into the selectivity of substitution of fluorobenzonitriles to yield mercaptobenzonitriles via S_NAr displacement of fluorine

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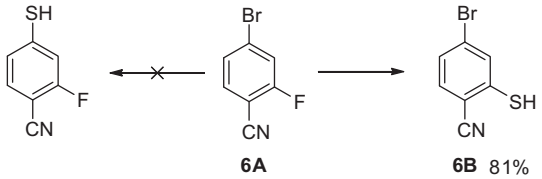
ABSTRACT

In this report we describe a simple synthesis of mercaptobenzonitriles from the reaction of fluorobenzonitriles with Na_2S in DMF at room temperature and following direct treatment with Zn/HCl. Significantly, 2- and 4-fluorobenzonitriles substituted with chlorine or bromine, but not iodine, undergo selective substitution of fluorine at room temperature to yield synthetically useful halo-substituted mercaptobenzonitriles.

Aryl thiols are an important class of compounds as intermediates in the synthesis of biologically active natural products and pharmaceutical drugs. Unfortunately, because of their tendency to oxidize relatively few aryl thiols are available commercially. As a result, they are generally synthesized and used as required. Despite recent advances in transition metal catalyzed methods for their synthesis,[1] aryl thiols are still commonly prepared using classical methods such as Newman–Kwart and Schonberg rearrangement,[2] Grignard reaction with sulfur,[3] and reduction of aryl sulfonyl chlorides[4] or aryl disulfides.[5] These reactions typically require harsh conditions and suffer from a limited scope of substrate. As a result, the development of efficient methods for the synthesis of aryl thiols is always welcome.

In the course of our drug discovery efforts we required a series of mercaptobenzonitriles as intermediates in the synthesis of thioethers. A convenient synthesis of a limited number of 4-mercaptobenzonitriles from 4-bromo- and chlorobenzonitriles in a single step with Na_2S has been reported.[6] This reaction requires heating the bromide or chloride in NMP at high temperatures. Using a modification of this procedure we obtained 4-mercaptobenzonitrile in 51% yield by heating a mixture of 4-bromobenzonitrile and Na_2S in DMF at 130 °C for 3.5 h and following reduction with Zn/HCl. However, when we attempted to prepare 2-fluoro-4-mercaptobenzonitrile by reacting 4-bromo-2-fluorobenzonitrile (**6A**) with Na_2S, we obtained 4-bromo-2-mercaptobenzonitrile (**6B**) cleanly and in 81% yield at room temperature, with no evidence of the desired product (Scheme 1). This result, including the mild conditions required, led us to investigate S_NAr displacement of aromatic fluorides with Na_2S as a method to yield substituted mercaptobenzonitriles.

Although there is much precedent in the use of aryl fluorides possessing strong electron withdrawing groups in the *o*- or *p*-positions to prepare aryl sulfides,[7] their use in synthesizing aryl thiols is much less common.[8] In one instance 4-mercaptobenzonitrile was reportedly obtained as a minor component along with disulfide and sulfide sideproducts following the reaction of 4-fluorobenzonitrile with K_2S (1.1 equiv) at 50–55 °C in DMF for 21 h.[8d] However, it was not isolated but used directly in the further synthesis of methyl 4-mercaptobenzoate. That there are only a few reports describing such a synthesis of aryl thiols is understandable in light of the fact that S_NAr substitution of aromatic fluorides typically requires two



6A **6B** 81%

Scheme 1. Reagents and condition: Na_2S, DMF, rt, 1 h.

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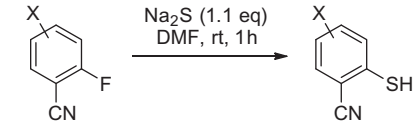
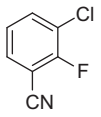
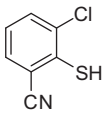
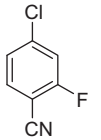
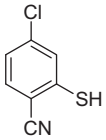
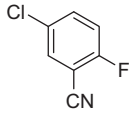
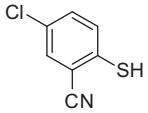
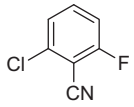
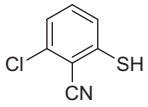
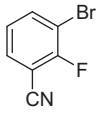
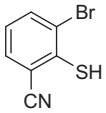
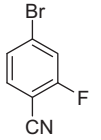
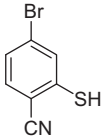
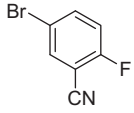
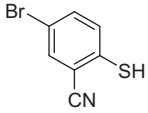
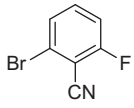
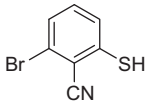
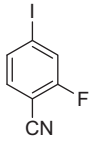
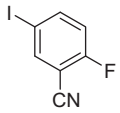
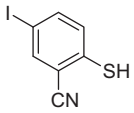
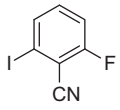
Table 1
Reaction of halo-substituted 2-fluorobenzonitriles with Na_2S



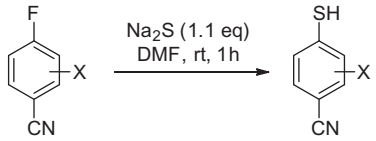
X= Cl, Br, I

Entry	Aryl fluoride **A**	Product **B**	Yield (%)
1			86
2			69
3			84
4			86
5			88
6			81
7			72
8			77
9		Mixture[a]	n.a.
10			86
11		Mixture[a]	n.a.

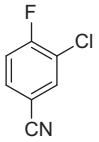
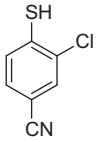
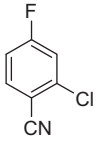
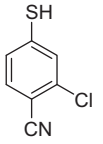
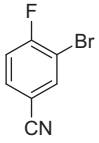
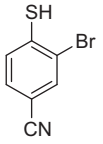
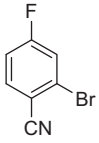
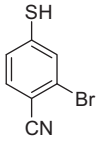
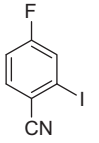
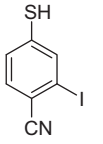
n.a. not applicable.
[a] Incomplete after 1 h and results in a complex mixture after 24 h.

electron-withdrawing groups, which limit the scope of this reaction. However, in this report we show that synthetically useful halo-substituted mercaptobenzonitriles can be conveniently synthesized from fluorobenzonitriles through selective substitution of fluorine with Na_2S in good to excellent yields at room temperature.

Table 2
Reaction of halo-substituted 4-fluorobenzonitriles with Na_2S



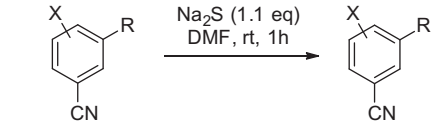
X= Cl, Br, I

Entry	Aryl fluoride **A**	Product **B**	Yield (%)
12			68
13			78
14			86
15			77
16			66[a]

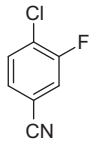
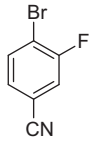
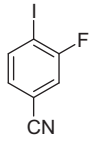
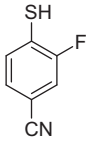
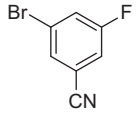
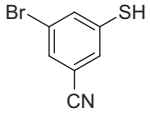
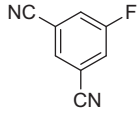
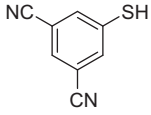
[a] Minor quantities of 4-fluro-2-mercaptobenzonitrile were formed.

The cyano group is a strong electron withdrawing group and it is well known that such groups activate the 2- and 4-positions to nucleophilic substitution. Indeed, we found that the reaction of chloro- and bromo-substituted 2- and 4-fluorobenzonitriles with Na_2S occurs with exclusive substitution of fluorine at room temperature and is complete in less than 1 h to yield the corresponding mercaptobenzonitrile in good to excellent yields (Tables 1 and 2; entries **1–8** and **12–15**).[9] Exclusive substitution of fluorine was observed irrespective of the position of the chlorine or bromine. However, in the case of iodo-substituted 2- and 4-fluorobenzonitriles exclusive substitution of fluorine occurred only in the case of **10A**, whereby the iodine is located *meta* to the cyano group, to give **10B** in 86% yield. When the iodine was also in an activated position (i.e. *ortho* or *para* to the cyano group) it could be substituted as well and in the case of **9A** and **11A** resulted in a complex mixture including both substitution products. It is of significance that in contrast to all other 2- and 4-fluorobenzonitriles reacted, reaction with **9A** and **11A** was not complete after 1 h. It is likely that a combination of factors are responsible for the sluggishness of these two substrates to react as well as the mixture of substitution products obtained. These include the decreased activating effect of iodine compared to chlorine or bromine, its placement *meta* to fluorine,

Table 3
Reaction of substituted 3-fluorobenzonitriles with Na_2S

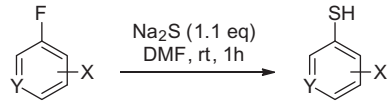


X= Cl, Br, I, CN

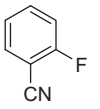
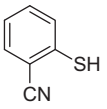
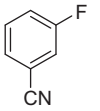
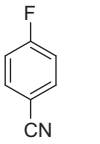
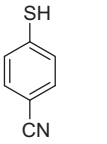
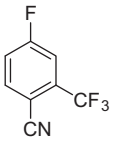
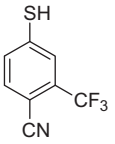
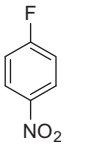
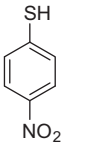
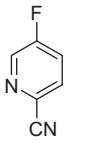
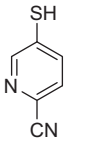
Entry	Aryl fluoride **A**	Product **B**	Yield (%)
17		Mixture[a]	n.a.
18		Mixture[a]	n.a.
19			58[b]
20			52[c]
21			70

n.a. not applicable.
[a] Incomplete after 1 h and results in a complex mixture after 24 h.
[b] 48 h.
[c] 24 h.

Table 4
Reaction of arylfluorides with Na_2S



Y= C, N
X= CN, CF_3, NO_2

Entry	Aryl fluoride **A**	Product **B**	Yield (%)
22			70[a]
23		No reaction[b]	
24			46[c]
25			85
26			75
27			76

[a] 24 h.
[b] 48 h.
[c] 36 h.

and the leaving ability of iodine. Iodo **16A** yielded the fluoro-substituted compound **16B** as the major product, however, a minor amount of 4-fluoro-2-mercaptobenzonitrile was detectable by ESI-MS. Based on the results in Tables 1 and 2, the procedure described here likely represents the best general method for the synthesis of chloro- or bromo-substituted 2- or 4-mercaptobenzonitriles.

In the case of halo-substituted 3-fluorobenzonitriles we found that reactions generally do not occur as readily and that each of the 4-substituted halogens can compete with fluorine (Table 3; entries **17–19**). Reactions with chloro **17A** and bromo **18A** were incomplete after 1 h at room temperature and after 24 h a complex mixture was obtained that included both substitution products. Interestingly, we found that iodo **19A** results in exclusive substitution of iodine to yield **19B** in 58% yield after 48 h at room temperature (Table 3). In this case it appears that selective substitution of iodine occurs as a result of a combination of factors including its leaving ability and activation by two electron withdrawing groups. When bromine was *meta*-substituted as in **20A** selective substitution of fluorine was observed and **20B** was isolated in 52% yield, though the reaction was still sluggish and required 24 h. Installation of an additional *meta*-substituted cyano group as in **21A** restores reactivity and enables for convenient substitution of fluorine to yield **21B** in 70% yield after 1 h.

In order to probe the reactivity and examine the scope of S_NAr displacement of aryl fluorides with Na_2S as a method to produce mercaptobenzonitriles, we examined the reaction of unsubstituted fluorobenzonitriles (**22A–24A**, Table 4). Reactions with 2- and 4-fluorobenzonitrile were not complete even after 24 and 36 h, respectively, however, in both cases substantial amounts of product were obtained. Heating either **22A** or **24A** at 50 °C for 3 h resulted in complete consumption of starting material, however, yield was not improved in either case as it is likely that competing side reactions occur. Reaction with 3-fluorobenzonitrile at room temperature does not occur appreciably, even after 48 h at room temperature. As expected, the addition of an electron withdrawing trifluoromethyl group in **25A** enables substitution of the fluorine to give **25B** in 85% yield after 1 h at room temperature. The presence of a stronger electron withdrawing group in 4-fluoro-nitrobenzene **(26A)** enables for this reaction to occur readily at room temperature to give **26B** in 75% yield after 1 h. Finally, pyridine derivative **27A** also reacts readily to give heterocyclic thiol **27B** in 76% yield after 1 h.

In conclusion, we show that fluorobenzonitriles substituted with electron withdrawing groups can undergo S_NAr displacement of fluorine with Na_2S at room temperature to yield the corresponding mercaptobenzonitrile in good to excellent yields following

treatment with Zn/HCl. One of the most significant results derived from these studies is that 2- and 4-fluorobenzonitriles substituted with chlorine or bromine undergo exclusive substitution of fluorine to yield the corresponding thiol in good to excellent yields. Reactions with iodo-substituted fluorobenzonitriles or with 3-fluorobenzonitriles are less predictable. The procedure described here enables for the preparation of mercaptobenzonitriles in good to excellent yields from appropriately substituted fluorobenzonitriles in sufficient purity to be useful as important intermediates in synthesis. It is hoped that the foregoing discussion provides a rational framework for the synthesis of mercaptobenzonitriles and other aryl thiols from S_NAr reactions with aryl fluorides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03. 032.

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9. *General procedure*: Into an oven-dried flask equipped with a magnetic stir bar was added aryl fluoride (1.00 g, 1.0 equiv), Na_2S (1.1 equiv), and DMF (5 mL) under argon. The reaction mixture was stirred at room temperature for 1 h. Then 1 M NaOH (50 mL) was added and washed with CH_2Cl_2 (2×25 mL). The aqueous layer was acidified to pH ~1–2 with 6 N HCl and extracted with CH_2Cl_2 (2×50 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a crude residue. To the residue was added 10% HCl (40 mL) and cooled with an ice-water bath. Then zinc dust (4 g) was added and the mixture was stirred for 1 h. Then EtOAc (100 mL) was added and the mixture was stirred for an additional 30 min. The organic layer was separated and washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated to provide the desired product with satisfactory purity.