1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane Bis(tetrafluoroborate) as Novel and Versatile Reagent for the Rapid Thiocyanation of Indoles, Azaindole, and Carbazole

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Selectfluor™ is found to catalyze efficiently the electrophilic thiocyanation of indoles and pyrrole with ammonium thiocyanate under mild and neutral conditions to produce the corresponding 3-indolyl and 2-pyrrolyl thiocyanates, respectively, in excellent yields with high selectivity. This method is effective even with azaindole and carbazole while many of reported procedures failed to produce thiocyanates from azaindole.

The electrophilic thiocyanation of aromatics and heteroaromatics is one of the most important carbon–heteroatom bond-forming reactions in organic synthesis.[1] Aryl and heteroaryl thiocyanates are useful intermediates in the synthesis of sulfur-containing heterocycles.[2] They are useful intermediates for drugs and pharmaceuticals.[2b] They can be easily transformed into various sulfur-containing functional groups.[3] The thiocyanate functionality is useful as a masked sulfanyl group. Therefore, the direct thiocyanation of aromatic systems is of prime importance. As a result, several methods have been developed for the thiocyanation of arenes using a variety of reagents under certain conditions.[4] However, a few reagents such as *N*-halosuccinimides, ceric ammonium nitrate, acidic K10 clay, iodine/methanol, and oxone have been applied for the thiocyanation of indoles.[5,6] However, these methodologies suffer from drawbacks such as the use of strong oxidizing agents, toxicity of metal thiocyanates, low yields of products in some cases, less availability or hard preparation of precursors and the formation of mixtures of products as a result of bisthiocyanation especially in case of pyrroles. In addition, many of these methods fail to induce electrophilic thiocyanation on azaindole. In view of the versatility of thiocyanate group in the field of drugs and pharmaceuticals, the development of simple, convenient, and highly efficient approaches are desirable. Selectfluor™ [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] has recently been introduced commercially as a user-friendly electrophilic fluorinating reagent (Figure 1).[7]

It is a commercially available, stable, nonvolatile, nonhygroscopic, and easy to handle solid and is more widely used for site-selective fluorination of a variety of carbonyl compounds. Besides its fluorinating ability, it is also recognized as a convenient mediator of several "fluorine free" functionalization of organic compounds.[8] These kinds of reactions are based on the fact that F-TEDA-BF_4 has considerable oxidative power, one of the strongest in the family of N–F reagents. But investigations taking advantage of this property are still scarce.[9] Furthermore, there have been no examples on the use of Selectfluor™ for the electrophilic thiocyanation of indoles.

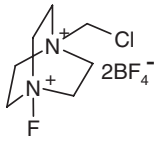
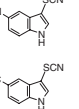


Figure 1.

In this article, we report a simple, convenient, and efficient protocol for the thiocyanation of N-heterocycles using Selectfluor™ in acetonitrile. Initially, we attempted the electrophilic thiocyanation of indole (**1**) with 1 equiv of ammonium thiocyanate (**2**) using a stoichiometric amount of Selectfluor™.

Table 1. Thiocyanation of N-heterocycles with ammonium thiocyanate using Selectfluor™

Entry	Substrate	Product[a]	Time/min	Yield%[b]
a			10	95
b			10	92
c			12	94
d			10	93
e			10	92
f			10	93
g			9.0	96
h			15	89
i			12	94
j			15	85
k			15	88
l			10	92
m			10	98
n			15	82
o			20	78

[a]All products were characterized by ^{1}H NMR, IR, and mass spectrometry. [b]Yield refers to pure products after chromatography.

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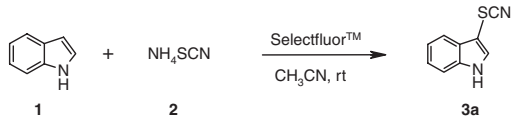
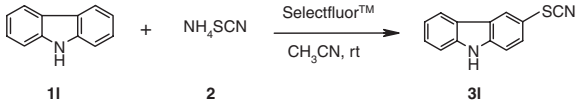
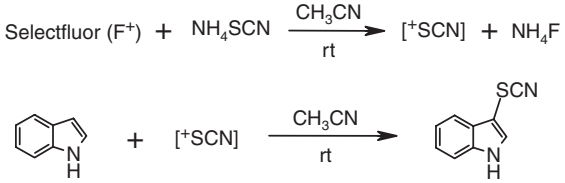


Scheme 1.



Scheme 2.



Scheme 3.

The reaction went to completion within 10 min. at room temperature and the product, 3-thiocyanatoindole (**3a**), was obtained in 95% yield (Entry a, Table 1 and Scheme 1).

Encouraged by this result, we turned our attention to various indoles. Interestingly, several substituted indoles such as 2-methyl-, 7-ethyl-, 5-nitro-, 5-cyano-, 5-bromo-, 5-methoxy-, and 2-phenylindoles reacted rapidly with ammonium thiocyanate to afford the corresponding 3-thiocyanatoindole derivatives (Entries b–h, Table 1). In addition, N-protected indoles such as *N*-benzyl- and *N*-ethyl derivatives also participated effectively in this reaction (Entries i and j, Table 1). It is noteworthy to mention that less reactive 7-azaindole also gave the corresponding 3-thiocyanato-7-azaindole in 88% yield (Entry k, Table 1) while most of the reported procedures failed to induce an electrophilic thiocyanation on azaindole.[5,6] Furthermore, 9*H*-carbazole also reacted well under similar conditions to give 3-thiocyanato-9*H*-carbazole (Entry l, Table 1, Scheme 2).

In case of carbazole, monothiocyanation took place at the 3-position of benzene ring. Like indoles, pyrrole was also easily transformed into the monothiocyanatopyrrole. In case of pyrrole, the substitution took place at 2-position to produce 2-thiocyanatopyrrole (Entry m, Table 1). No bisthiocyanation was observed in case of pyrrole. Furthermore, *N*-alkylanilines also underwent smooth thiocyanation under these reaction conditions (Entries n and o, Table 1).[12]

In all cases, the reactions proceeded rapidly at room temperature with high regioselectivity. As solvent, acetonitrile appeared to give the best results. No fluorination of indole was observed under the reaction conditions. The products were characterized by ^{1}H NMR, IR, and mass spectrometry and also by comparison with authentic samples.[5,6] The scope and generality of this process is illustrated with respect to various N-heterocycles and the results are presented in Table 1. The redox potentials of indole and Selectfluor™ are -1.050 and -0.296 V, respectively.[10] Mechanistically, the reaction may proceed via the electrophilic substitution of indole by in situ generated thiocyanogen ($^+$SCN) from Selectfluor™ and ammonium thiocyanate (Scheme 3).[11]

In conclusion, Selectfluor™ has proved to be an effective reagent for the electrophilic thiocyanation of N-heterocycles under extremely mild and neutral conditions. In addition to its simplicity and efficiency, this method produces monothiocyanated products in excellent yields in short reaction times. This method provides the direct access to a wide range of potentially valuable biologically well-defined heteroaryl thiocyanates. This method can be used for the thiocyanation of even deactivated indoles in an efficient manner.

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12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/.

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