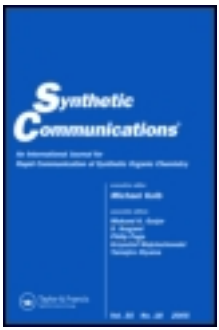

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A Versatile Procedure for the Preparation of Aryl Thiocyanates Using N-Thiocyanatosuccinimide (NTS)

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A VERSATILE PROCEDURE FOR THE PREPARATION OF ARYL THIOCYANATES USING N-THIOCYANATOSUCCINIMIDE (NTS).

F. Dean Toste, Vittorio De Stefano and Ian W.J. Still*

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ABSTRACT: A mild procedure for the thiocyanation of several types of arene substrate using N-thiocyanatosuccinimide (NTS) is described. The method appears generally applicable to benzenoid substrates with a wide range of substituents, as well as to heteroaromatic analogues such as indoles and thiophenes.

In connection with our ongoing program of synthesis we have recently been concerned with the development of viable procedures for the direct introduction of sulfur on an aromatic ring. Two general strategies have commonly been utilized for this purpose: sulfonation and thiocyanation. We felt that the latter would be more useful for our purposes but while several methods of electrophilic thiocyanation have been described the procedures are often limited in scope.[1] Another major drawback to these older procedures is their use of reagents which are either highly toxic or present serious disposal problems (or

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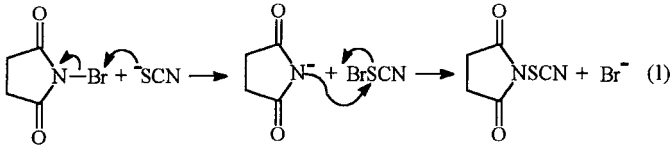
both). The rather unstable thiocyanogen, $(SCN)_2$, has often been used, generated usually *in situ* from copper or lead thiocyanates[2-4] or from molecular bromine and an alkali thiocyanate.[1a] Procedures involving the somewhat more reactive thiocyanogen chloride or iodide, XSCN, have also been described.[3, 5] These methods call for the use of the molecular halogen as coreagent, or call for other sources of Cl_2 such as $SbCl_5$ or $C_6H_5ICl_2$.

In our attempts to discover a milder, more convenient procedure we have investigated a number of different reaction conditions based upon the reaction of N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS) with alkali metal thiocyanates. We have found that NBS works best, in combination with sodium thiocyanate in methanol or acetic acid as solvent. While we have not directly identified the species responsible for carrying out the thiocyanation, we can rule out thiocyanogen since reactions carried out under conditions known to generate $(SCN)_2$ failed to yield any product. It seems likely that N-thiocyanatosuccinimide (NTS), generated by the following reactions, is the thiocyanating agent involved.



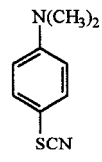
(1)

The results which we have obtained are collected in the Table. N-Protected (N-acetyl, N(Boc)) anilines were not thiocyanated under our conditions. Reactions with 3,4,5-trimethoxyacetophenone and 4-methoxyphenylacetonitrile

Table. Preparation of Aryl Thiocyanates

Substrate	temp/time/solvent (°C) (h)	Product	Isolated yield (%)
N,N-dimethylaniline	0/2/MeOH	**1**	99
thioanisole	25/4/HOAc	**2**	49[a]
N-(Boc)-3′,4′-dimethoxy-phenethylamine	25/4/HOAc	**3**	89[b]
N-(Boc)-3′-hydroxy-4′-methoxyphenethylamine	25/2/HOAc	**4**	81
2-methyl-5-nitroaniline	0/3/MeOH[c]	**5**	75
thiophene	25/4/HOAc	**6**	61
2-iodothiophene	25/4/HOAc	**7**	70
5-methoxy-2-methylindole	25/4/HOAc	**8** + **9**	59[d]

[a] After chromatography on silica:eluent $PhCH_3$:EtOAc = 4:1; R_f = 0.72.
[b] The 2′-disulfide corresponding to **3** was also formed (10%).
[c] Followed by additional 3 h at 25°C.
[d] The ratio of **8**:**9** was exactly 2:1, from the ^{1}H-NMR (400 MHz) spectrum of the mixture.



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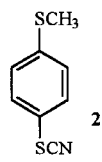

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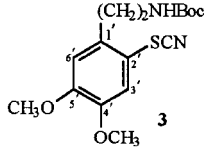

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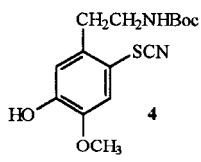

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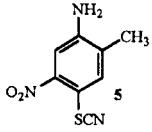

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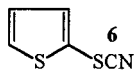

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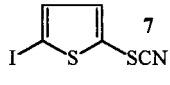

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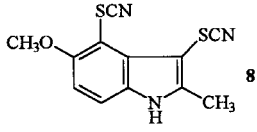

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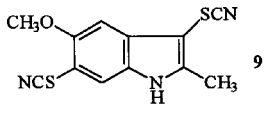

9

were also unsuccessful: while adverse steric effects cannot be ruled out in these cases, we think that the presence of enolizable α-protons may be responsible. Of the successful reactions listed in the Table the yields were generally good to very good and in one case superior to those obtained by existing procedures.[1a] In accordance with earlier work[4] there is a clearcut preference for substitution *para* to the most activating substituent. The reaction with 5-methoxy-2-methylindole is interesting in that not only were two products obtained but also in that this was the only case we encountered in which dithiocyanation was observed. In no case was there any evidence for the formation of isothiocyanates [6] (no IR band at $\sim 2060\ cm^{-1}$).

The results described herein have considerable potential for the efficient generation of aromatic thiocyanates. The synthetic versatility of the —SCN group is well documented and we plan to publish applications of this methodology to total synthesis shortly.

EXPERIMENTAL

Anhydrous conditions were found to be necessary to produce high yields of thiocyanated reaction products. Methanol was dried by refluxing (0.5 h) and distillation from magnesium turnings. NaSCN was maintained dry in an oven at 126°C. The NBS used was freshly recrystallized from hot water and dried over P_2O_5 for 48 h prior to use. All liquid substrates used were redistilled beforehand. The starting materials for compounds **3** and **4** were synthesized from 3,4-dimethoxyphenethylamine and 3-hydroxy-4-methoxybenzaldehyde respectively, by standard procedures.

IR spectra were run on a Nicolet 5DXB FTIR spectrometer and the mass spectra obtained under electron impact conditions at 70 eV. ^{1}H-NMR spectra were recorded at 60 MHz on a Varian EM360-L spectrometer: 100 MHz ^{13}C- and 400 MHz ^{1}H-NMR spectra were run on a Varian XL 400 in the case of compounds **8** and **9**. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Box 25, DK-2730 Herlev, Denmark.

REPRESENTATIVE PROCEDURES

A. N,N-Dimethyl-4-thiocyanatoaniline, **1**

A solution of NBS (2.20 g, 12.3 mmol) and NaSCN (1.33 g, 16.4 mmol) in dry methanol (20 mL) was stirred at 25°C for 15 min. N,N-Dimethylaniline (0.50 g, 4.1 mmol) was added and the resulting mixture stirred at 0°C for 2 h.[7] After removal of most of the methanol, water (25 mL) was added and the solution made alkaline with 20% NaOH aq. Suction filtration, followed by extraction of the filtrate with CH_2Cl_2 (3 x 25 mL), drying ($MgSO_4$) and evaporation afforded the crude product. Extraction with boiling heptane, hot filtration and cooling afforded **1** as yellow needles, mp 72-73°C, lit.[1a] mp 73-74 °C; IR (KBr): υ 3380, 2160, 1973, 765 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.45(d, J = 8.5 Hz, 2H, *H-3*, *H-5*), 6.70(d, J = 8.5 Hz, 2H, *H-2*, *H-6*), 3.03(s, 6H, $N(CH_3)_2$) ppm. Anal. Found: C, 60.51; H, 5.67; N, 15.53; S, 17.81. Calcd. for $C_9H_{10}N_2S$: C, 60.66; H, 5.65; N, 15.72; S, 17.99.

B. N-(Boc)-4′,5′-Dimethoxy-2′-thiocyanatophenethylamine, **3**

A solution of dry NaSCN (3.20 g, 39.5 mmol) and NBS (5.27 g, 29.7 mmol) in glacial acetic acid (50 mL) was stirred for 15 min at room

temperature. The N-(Boc)-3′,4′-dimethoxyphenethylamine (2.78 g, 9.88 mmol) was added to the orange solution and the mixture stirred 4 h at 25°C. After removal of the solvent under reduced pressure, dichloromethane (25 mL) was added to permit suction filtration of the orange solid formed. This solid was washed with CH_2Cl_2 (3 x 25 mL) and the washings combined, washed successively with 20% NaOH aq. (2 x 25 mL) and distilled water (25 mL), dried (Na_2SO_4), and concentrated to yield a yellow solid (3.22 g). Flash chromatography, eluting with toluene:ethyl acetate = 2:1, afforded the pure thiocyanate (2.99 g, 89%), R_f =0.38, as a beige solid, mp 95-96°C (hexane - CH_2Cl_2); IR (KBr): υ 3389, 2977, 2935, 2844, 2154, 1696, 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.03(s, 1H, *H-3′*), 6.73(s, 1H, *H-6′*), 4.75(br s, 1H, *NH*, exch. D_2O), 3.81(s, 6H, OCH_3), 3.31(td, J =13.2, 6.6 Hz, 2H, CH_2N), 2.92(t, J = 7.3 Hz, 2H, $ArCH_2$), 1.35(s, 9H, $OC(CH_3)_3$) ppm; ^{13}C-NMR($CDCl_3$): δ 155.58(*C=O*), 151.13(*C-5′*), 148.38(*C-4′*), 134.80(*C-1′*), 116.32(*C-6′*), 113.40(*C-3′*), 112.61(*C-2′*), 111.31(*SCN*), 79.18($OC(CH_3)_3$), 56.08, 55.92(OCH_3), 40.80(CH_2N), 34.29(ArCH_2), 28.23($OC(CH_3)_3$) ppm; EIMS: m/z(%) 338(4), M^+, 281(6), 225(7), 206(33), 164(24), 151(100), 107(13), 71(14), 57(39). Anal. Found: C, 56.36; H, 6.56; N, 8.09; S, 9.56. Calcd. for $C_{16}H_{22}N_2O_4S$: C, 56.77; H, 6.55; N, 8.28; S, 9.56.

A small amount of a fraction with R_f = 0.22 was also collected on chromatography. This compound[8] was shown to be the 2′-disulfide **10** (0.32 g, 10%), mp 143-145°C (hexane -CH_2Cl_2).

4-Methylsulfanyl-1-thiocyanatobenzene, **2**: thick yellow oil, after flash

chromatography ($PhCH_3$:EtOAc = 4:1, R_f = 0.72); IR(film); υ 3076, 3057, 2917, 2153, 1476, 1091, 739 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ7.44(collapsed dd, J $\approx$ 8.5 Hz, 4H, *Ar-H*), 2.58(s, 3H, SCH_3) ppm; EIMS: m/z(%) 181(100), M^+, 166(76), 155(13), 150(14), 149(14), 135(24), 122(20), 108(43), 77(13), 69(26), 57(12); HR-EIMS: found, 181.0013; calcd. for $C_8H_7NS_2$, 181.0020.

N-(Boc)-5′-Hydroxy-4′-methoxy-2′-thiocyanatophenethylamine, **4**: light yellow solid, after flash chromatography ($PhCH_3$:EtOAc = 1:1, R_f = 0.42), recrystallized from CH_2Cl_2:pet. ether, mp 119-120°C; IR(KBr): υ 3412, 3389, 2993, 2977, 2935, 2153, 1697, 1443, 1257 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.33(s, 1H, *H-6′*), 6.90(s, 1H, *H-3′*), 6.21(br s, 1H, *OH*, exch), 4.68(br s, 1H, *NH*, exch.), 3.93(s, 3H, OCH_3), 3.32(t, J = 5.5 Hz, 2H, CH_2N), 2.97(t, J = 5.5 Hz, 2H, $ArCH_2$), 1.48(s, 9H, $OC(CH_3)_3$) ppm; EIMS: m/z(%) 324(6), M^+, 294(11), 269(13), 268(43), 252(19), 208(26), 207(72), 195(58), 194(29), 180(44), 168(41), 167(26), 153(14), 59(24), 57(100); HR-EIMS: found, 324.1145; calcd. for $C_{15}H_{20}N_2O_4S$, 324.1144.

2-Methyl-5-nitro-4-thiocyanatoaniline, **5**: brick-red solid from hot CH_2Cl_2: ether (mp 184-186°C); IR(KBr): υ 3487, 3381, 2156, 1637, 1518, 1337 cm^{-1}; ^{1}H-NMR (d_6-DMSO): δ 7.57(s, 1H, *H-6*), 7.40(s, 1H, *H-3*), 5.96(br s, 2H, NH_2, exch.), 2.23(s, 3H, CH_3) ppm; EIMS: m/z(%) 209(100), M^+, 163(67), 148(13), 137(14), 136(31), 119(66), 104(11), 93(20), 92(22), 77(17); HR-EIMS: found, 209.0252; calcd. for $C_8H_7N_3O_2S$, 209.0259.

2-Thiocyanatothiophene, **6**: yellow oil, bp 134-136°C/12 mm;[9] IR(film): 3103, 2160, 1390, 1224, 852, 712 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 8.07(dd, J = 5.5,

1.5 Hz, 1H, *H-5*), 7.87(dd, J = 4.0, 1.5 Hz, 1H, *H-3*), 7.53(dd, J = 5.5, 4.0 Hz, 1H, *H-4*) ppm; EIMS: m/z(%) 141(100), M^+, 115(24), 114(24), 97(30), 96(19), 82(15), 71(68); HR-EIMS: found, 140.9704; calcd. for $C_5H_3NS_2$, 140.9707.

5-Iodo-2-thiocyanatothiophene, **7**: yellow, crystalline solid, mp 50-51°C (heptane); IR(KBr): υ 3167, 2160, 1392, 795 cm^{-1}; ^{1}H-NMR($CDCl_3$); δ7.25(d, J = 4.0 Hz, 1H, *H-3*), 7.10(d, J = 4.0 Hz, 1H, *H-4*) ppm; EIMS: m/z(%) 267(100), M^+, 140(93), 127(12), 114(41), 96(75), 82(43), 69(42), 57(24); HR-EIMS: found, 266.8665; calcd. for $C_5H_2INS_2$, 266.8673. Anal. Found: C, 22.52; H, 0.89; N, 5.14. Calcd. for $C_5H_2INS_2$: C, 22.49; H, 0.75; N, 5.24.

5-Methoxy-2-methyl-3,4-dithiocyanatoindole, **8**: major product isolated after flash chromatography ($PhCH_3$:EtOAc =1:1; R_f =0.28) as a colorless solid, mp 228-230°C (decomp.); IR(KBr): υ 3449, 2155, 1695, 1384 cm^{-1}; ^{1}H-NMR($CDCl_3$ + DMSO-d_6): δ 11.49(br s, 1H, *NH*), 7.14(dd, J = 8.8, 0.8 Hz, 1H, *H-7*), 6.57(d, J = 8.7 Hz, 1H, *H-6*), 3.62(s, 3H, OCH_3), 2.23(s, 3H, CH_3) ppm; ^{13}C-NMR($CDCl_3$ + DMSO-d_6): δ154.77(*C-5*), 146.35(*C-2*), 130.63(*C-7a*), 128.23(*C-3a*), 115.18(*C-7*), 111.79, 111.00(*SCN*), 107.11(*C-6*), 106.32(*C-4*), 97.29(*C-3*), 56.42(OCH_3), 11.51(CH_3) ppm; EIMS: m/z(%), 275(100), M^+, 260(19), 233(12), 232(12), 222(17), 217(27), 205(24), 173(11), 171(62); HR-EIMS: found, 275.0186; calcd. for $C_{12}H_9N_3OS_2$, 275.0187.

5-Methoxy-2-methyl-3,6-dithiocyanatoindole, **9**: minor isomer obtained on flash chromatography ($PhCH_3$:EtOAc = 1:1, R_f = 0.60) as a colorless solid, mp 184-185°C (decomp.): IR(KBr): υ 3380, 2160, 1672, 1395 cm^{-1};

^{1}H-NMR($CDCl_3$ + DMSO-d_6): δ 11.30(br s, 1H, *NH*), 7.24(d, J = 0.7 Hz, 1H, *H-7*), 6.74(s, 1H, *H-4*), 3.61(*OCH_3*), 2.19(s, 3H, *CH_3*) ppm; ^{13}C-NMR($CDCl_3$ + DMSO-d_6): δ151.14(*C-5*), 144.26(*C-2*), 130.04, 129.55(*C-3a, C-7a*), 113.28(*C-7*), 110.67, 110.57(*SCN*), 106.32(*C-6*), 98.65(*C-4*), 97.29(*C-3*), 55.85(*OCH_3*), 11.51(*CH_3*) ppm; EIMS: m/z(%), 275(100), M^+, 260(17), 249(14), 248(14), 233(19), 232(13), 217(19), 205(22), 171(60); HR-EIMS: found, 275.0176; calcd. for $C_{12}H_9N_3OS_2$, 275.0187.

ACKNOWLEDGEMENTS

We thank Mr. Kevin Bundscho for carrying out preliminary experiments. We are grateful to Glaxo Research & Development Ltd. and DuPont Agricultural Products for partial support of this research. One of us (F.D.T.) gratefully acknowledges the award of an Ontario Graduate Scholarship.

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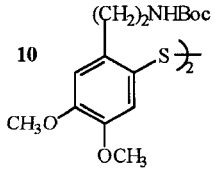
7. Treatment of N,N-dimethylaniline under otherwise identical conditions for 4 h at 25°C gave N,N-dimethyl-2,4-dithiocyanatoaniline, mp 75-76°C (from CH_2Cl_2:hexanes) in 95% yield. Spectral data (FTIR, ^{1}H-NMR, MS) were in accord with expectation; HR-EIMS: found, 235.0231; calcd. for $C_{10}H_9N_3S_2$, 235.0238.

8. Compound **10** had the expected spectral data and satisfactory elemental analysis (C,H, N, S; ±0.3%). It is also a useful synthetic intermediate, reacting very similarly to the thiocyanate **3** on treatment with reducing agents.

10



9. Kugelrohr (short-path) distillation: temperature is that of the oven.

(Received in the USA 13 October 1994)