SYNTHESIS AND REACTION OF 7-BROMO-2-(TRIFLUOROMETHYL)-10-METHYLPHENOTHIAZINE WITH NITRILES AND AMINES UNDER ARYNE-FORMING CONDITIONS

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Abstract - The titled compound (**3**) was prepared by treating commercially available 3-(trifluoromethyl)phenothiazine successively with sodium hydride, methyl iodide, and N-bromosuccinimide, and its structure was ascertained by X-ray analysis. The reaction of **3** with certain aliphatic nitriles and LDA gave typical 7- and 6-addition products *via* aryne (**4**) in ratios of *ca.* 85:15, **5**:**6**, respectively. However, treatment of **3** with certain primary and secondary amines and the corresponding lithiated amide afforded a single 7-aminated product (**7**) in good yields in each case. The reaction of **3** with various phenylacetonitriles and LDA gave mixtures containing an 7-addition product (**10**) and a 6-arylmethyl-7-cyano rearranged nitrile (**11**) in similar ratio of 85:15, respectively. The structure of **11** was assigned on the basis of the greater tendency for the requisite adduct (**12**), obtained from anion addition to the less favored 4-position of **4**, to participate in the TARA pathway than that for the adduct (**13**), formed from anion addition to the more favored 3-position. The greater regioselectivity of amine additions to **4** as compared to those of nitrile anion additions is explained on the basis of the relative reactivities of the amine and nitrile anion nucleophiles.

INTRODUCTION

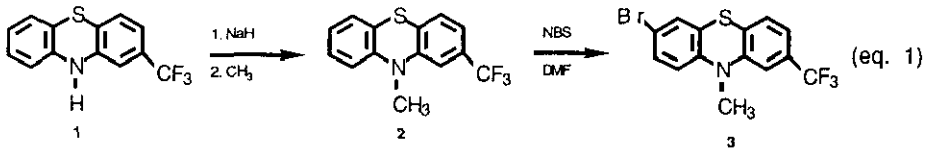
We[2] showed previously that 1,2-didehydro-10-methylphenothiazine, generated by the reaction of 2-chloro-10-methylphenothiazine and LDA in THF, reacted with pre-formed α–lithiated arylacetonitriles to give rearranged 2-(arylmethyl)-1-cyano-10-methylphenothiazines, after proton quench, presumably *via* the tandem-addition rearrangement aryne (TARA) mechanism.[3] In contrast, treatment of that aryne with anions of aliphatic nitriles supplied 2-(α-alkylcyanomethyl)-10-methylphenothiazines, most likely by the usual aryne mechanism.[4] When these aryne-nitrile reactions were conducted in liquid ammonia using sodium amide as aryne-generating base, 1,2-didehydro-10-methylphenothiazine underwent exclusive amination by the ammonia solvent yielding 2-amino-10-methylphenothiazine; none of the desired nitrile addition products was obtained.[5] By taking advantage of the propensity of 1,2-didehydro-10-methylphenothiazine to react with amines, we were able to prepare several 2-(N-

alkylamino)- and 2-(N,N-dialkylamino)-10-aminophenothiazines by carrying out sodium amide-mediated reactions of 2-chloro-10-methylphenothiazine in various primary and secondary amine solvents.[5] The high degree of regiocontrol exerted by the 10-nitrogen atom on additions to the 1,2-didehydrophenothiazines (i.e. exclusive 2-addition), which has precedent in the aniline system,[4] has also been observed by other workers.[6] In contrast, the chemistry of 3,4-didehydrophenothiazines has been little studied. In the only study of arynes of that type, Jones [6a] found that 3-chloro- and 4-chloro-10-methylphenothiazine, when treated with N-methyl piperazine and sodium amide, gave 10-methyl-3-N-methylpiperazylphenothiazine in yields of 81% and 38%, respectively. These findings showed that 3,4-didehydro-10-methylphenothiazine was formed exclusively and underwent nucleophilic addition regioselectively to the 3-position, suggesting that the generation of and orientation to that 3,4-hetaryne was governed by the 5-sulfur atom. The other secondary amines in Jones' study[6] reacted with 3,4-didehydro-10-methylphenothiazine to give tertiary aminophenothiazines in poor yields (< 5%), thus preventing a more detailed assessment of the chemistry of that hetaryne.

In order to obtain more insight into 3,4-hetaryne chemistry, we studied the reaction of 7-bromo- 2-(trifluoromethyl)-10-methylphenothiazine (**3**) with alkyl and aryl nitriles as well as primary and secondary amines under LDA-THF aryne-forming conditions, and report the results herein. The aryne precursor (**3**) was chosen since it can be prepared from readily available materials, and the nitriles and amine derivatives of (trifluoromethyl)-phenothiazine products obtained from these reactions may prove interesting from a pharmacological point of view.[7]

RESULTS AND DISCUSSION

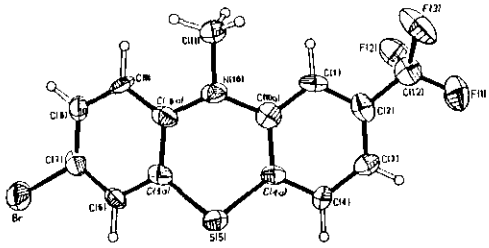
The titled bromoarene (**3**) was prepared by treating commercially available 2-(trifluoromethyl)phenothiazine (**1**) successively with sodium hydride and methyl iodide, and brominating the 10-methyl derivative (**2**) so formed



(eq. 1)

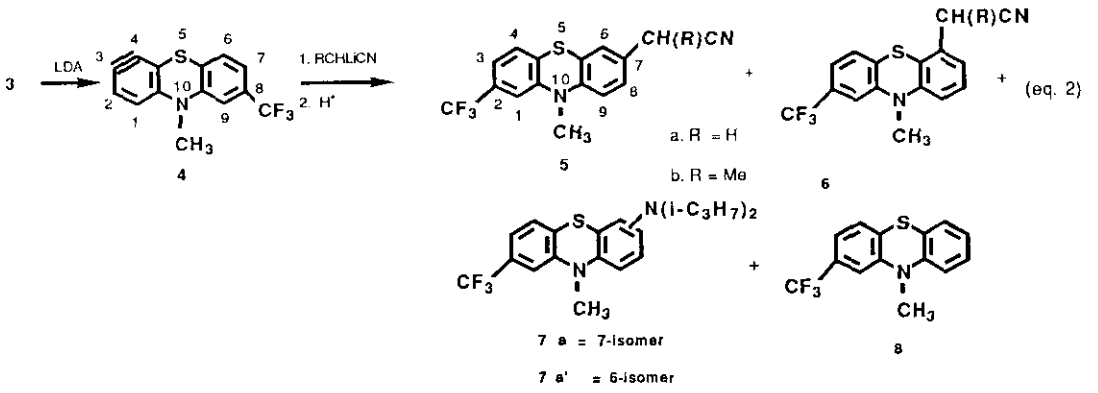
with N-bromosuccinimide in dimethylformamide (eq. 1). X-Ray single crystal analysis of **3** confirmed that the bromination occurred at the 7-position; the similarly structured 2-chloro-10-methylphenothiazine was found previously to undergo nitration at the 7-position.[8] The identification and location of the atoms in **3** are shown in the ORTEP[9] drawing (see figure) and the bond lengths, bond angles, and torsion angles are listed in Tables 1-3, respectively. As shown, the phenothiazine ring is folded with the central ring in a boat conformation, and the 10-N-methyl group is located in the *quasi* equatorial or synperiplanar position with respect to the central ring of **3**. The folding angle of **3** is 150(4)° which is slightly greater than that of 10-methylphenothiazine (143.7°).[10] With titled compound (**3**) on hand, it was first made to react with ethanenitrile and LDA in THF, and was found to give a 85:15 mixture of 7-(cyanomethyl) (**5a**)- (42.5%) and 6-(cyanomethyl) (**6a**) (8%) derivatives of-2-(trifluoromethyl)-10-methylphenothiazine (eq. 2), presumable *via* aryne (**4**). Similarly, the reaction of **3** with propanenitrile and LDA supplied a 84:16 mixture of 7-(α-cyanoethyl)-(**5b**) (42%) and 6-(α-cyanoethyl)-2-(trifluoromethyl)-10-methylphenothiazine (**6b**) (9%). Rearranged nitriles could be detected in none of

these reactions. The major products (**5a**) and (**5b**) were obtained in pure state by flash chromatography; no



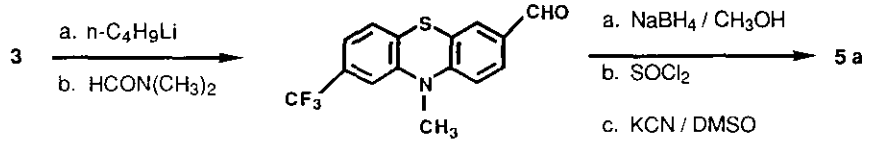
Figure

attempt was made to isolate the other products. Replacing the LDA with the sterically demanding bases, lithium *tetra-methylpiperidide* or *lithium cyclohexylisopropylamine*, did not improve significantly the nitrile yields. Additionally, a 85:15 mixture of 7- and 6-N,N-diisopropylamino-2-(trifluoromethyl)-10-methylphenothiazine (**7a** and **7a'**, respectively) in overall yields ranging from 20-25% and the debrominated product, 2-(trifluoromethyl)-10-methylphenothiazine (**8**) (10%) were produced. The isomer product distributions were determined by integra-



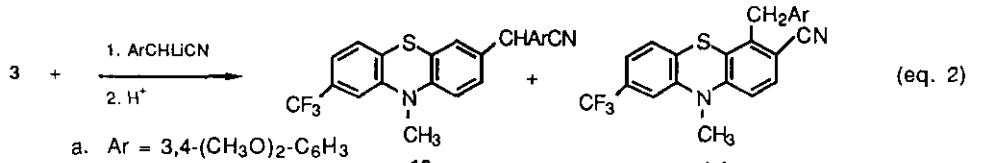
tion of the -CH(R)CN (δ = 3.60-3.85 ppm) nmr signal of the nitrile isomers.

The ^{1}H nmr, ir and mass spectra of the various products shown in eq. 2 were consistent with proposed structures. The structure of **5a** was further confirmed by an unambiguous synthesis (see Scheme 1) in which **3** was treated successively with n-butyllithium and dimethylformamide to the aldehyde (**9**), which was then converted to **5a** in a straightforward manner.



Scheme 1

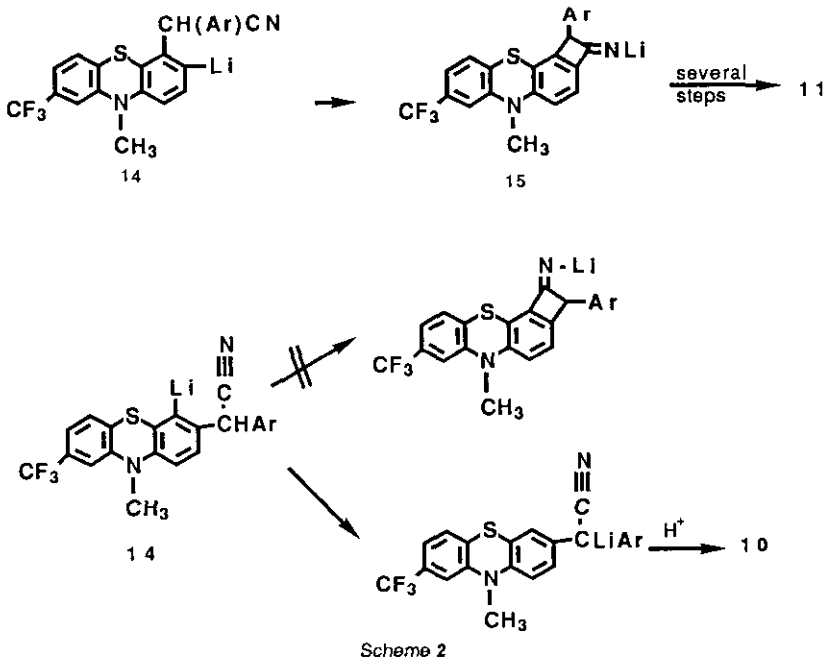
The 85:15 product distribution of products (**5**) and(**6**), respectively, shows that it is 5-sulfur that controls the generation of and addition to aryne (**4**), presumably since 10-nitrogen is located at a more remote site from the "triple bond". That nitrile addition to (**4**) occurs less regioselectively to the 3,4-didehydrophenothiazine **4** than to 1,2-didehydrophenothiazines[5,6] could reflect the weaker orienting ability (i.e.lower electronegativity) of the 5-sulfur in additions to (**4**) as compared the stronger orienting ability of the 10-nitrogen in additions to the latter aryne. It is also conceivable that reduced regioselectivity in additions to 3,4-didehydrophenothiazines is due to the smaller steric effect of S atom in **4** as compared to that of N-methyl group in 1,2-didehydrophenothiazine.
The reaction of **3** and LDAwith the arylacetonitriles, 3-methoxyphenylacetonitrile and 3,4-dimethoxyphenyl-acetonitrile, unlike that of 2-chloro-10-methylphenothiazine which gave only rearranged nitrile products, afforded inseparable mixtures containing an aryne 3-addition product (**10**) and a 6-arylmethyl-7-cyano rearranged nitrile (**11**) in similar ratios of 85:15, respectively, and in yields in the range of 40-50% . The yields and product isomer distributions of these products were estimated by integration of the ^{1}H nmr signals of the -CH(Ar)CN (δ = 5.00-5.05 ppm) and -CH_2Ar (δ = 4.30-4.35 ppm) signals of **10** and **11**, respectively.



(eq. 2)

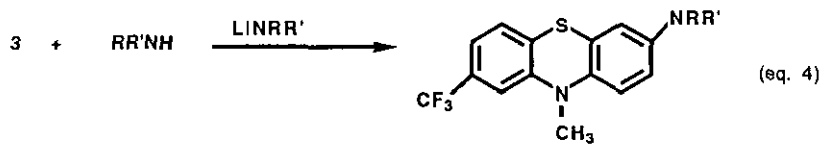
a. Ar = 3,4-$(CH_3O)_2$-C_6H_3
b. Ar = 4-(CH_3O)-C_6H_4
c. Ar = 3,4,5-$(CH_3O)_3$-C_6H_2
d. Ar = 3-CF_3-C_6H_4

The structure of **11** was assigned on the basis of the greater tendency of the requisite adduct (**12**), obtained from anion addition to the less favored 4-position of **4**, to participate in the TARA pathway than adduct (**14**) formed from anion addition to the more favored 3-position (see Scheme 2). We suggested previously that arynes possessing electron-releasing groups tend to proceed *via* the former pathway, while those possessing electron-attracting groups preferentially proceed along the latter.[11] Recently, we showed that of the two isomeric adducts formed by the addition of nitrile anions to 2,6-dimethoxy-3-pyridyne, only the one in which the two methoxy groups enhanced the negative charge of the cyclization site (the 3-lithiated carbon in that case) proceeded along the TARA pathway to rearranged products.[12] Using these arguments, the former of the two adducts (**12**) and (**14**) shown in Scheme 2, would be more likely to cyclize to the cyclobutanimine ring (**13**) (the key step in the TARA mechanism) due to a) the greater negative charge at the cyclization site in **12** brought about by the resonance effect of the lone pair of electrons on 10-nitrogen atom, which is *para* to the lithiated carbon, and b) the location of the electronegative 5-sulfur atom at a remote site. Similar resonance interactions are not possible in **14** since there the 10-nitrogen atom is situated *meta* to the cyclization site. The absence of 10-nitrogen resonance and the location of the electronegative 5-sulfur adjacent to the lithiated carbon in **14** combine to decrease electron density at the cyclization site to such an extent that adduct (**14**) is unable to participate in the TARA pathway. It is unlikely that the CF_3 group can affect the electron density at the cyclization site, since substituent effects are not normally transmitted from one benzo ring to the other in phenothiazines due to the non-planarity of the central ring.[13]
The titled compound (**3**) was then treated with various primary and secondary amines using the corresponding lithium amide to see if synthetic advantage could be taken from the high propensity of LDA to react with the aryne



Scheme 2

(4). As shown in eq. 4, good yields (82-89%) of the 7-products (**7a-d**) were obtained, and as a bonus, these



(eq. 4)

7

a) R = R' = Iso-C_3H_7; 83%
b) R = R' = C_2H_5; 83%
c) R = R' = sec-C_4H_9; 82%
d) R = H, R' = t-C_4H_9; 89%

products were free from any 6-isomeric amines. Bunnett[14] and we[15] showed that the addition of neutral nucleophiles to unsymmetrical aryne occurred more regioselectively than addition of charged nucleophiles. Thus the regioselectivity observed in these amination reactions indicates that it is the free amine, and not the amide base, which adds predominantly to the aryne, which is consistent with previous observations in other arynic systems.[16]

EXPERIMENTAL

All reagents were purchased from Aldrich Chemical Company. The amines were dried over calcium hydride and distilled prior to use; n-butyllithium was used as received. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Ir spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on an IBM-Bruker WP 200-SY spectrometer and chemical shifts were related to tetramethylsilane as an internal standard. High resolution mass spectral analyses were performed

by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8211164).

Preparation of Titled Bromoarene (3). To a stirred solution containing 9.3 g (0.035 mol) of 2-(trifluoromethyl)phenothiazine (**1**) in THF (50 ml) was added 1 g of sodium hydride (97% dry), and the resulting mixture was stirred for an additional 2 h. Then methyl iodide (4.5 ml) was added, and the mixture was stirred overnight during which time the solution changed in color from red to gray. A few ml of ethanol was then added to quench any unreacted sodium hydride, the THF was removed in vacuo (rotatory evaporator), and the residue dissolved in methylene chloride (75 ml). The resulting solution was washed with water, dried (Na_2SO_4), and evaporated to yield a brown residue. Kugelrohr distillation of the brown residue afforded 2-(trifluoromethyl)-10-methylphenothiazine (**2**) (9.0 g, 91%) as a thick oil, which solidified upon standing, mp 60-63 °C. N-Bromosuccinimide (5.0 g, 0.028 mol) was then added to a solution containing 7.5 g (0.027 mol) of **2** in 50 ml of DMF, and the mixture was stirred for 1h at room temperature. At that time, water (75 ml) was added, and the milky suspension was extracted with methylene chloride (2 X 100 ml). The combined methylene chloride extracts were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to yield a thick oil, which was distilled in a Kugelrohr apparatus to yield 8.3 g (81%) of titled compound (**3**): colorless crystals; mp 103-105 °C (hexane / EtOAc); ^{1}H nmr ($CDCl_3$) δ 3.34 (s, 3 H), 6.63 (d, J = 8.6 Hz, 1 H), 6.95 (s, 1H), 7.17-7.28 (m, 4 H). HRms. Calcd for $C_{14}H_9NBrF_3S$: 359.2520. Found 359.2490.

General Procedure for the Reaction of 3 with Various Acetonitriles Under Aryne-Forming Conditions. In a flame-dried flask flushed with nitrogen, LDA (30 mmol) was prepared by adding diisopropylamine (30 mmol) to a solution of n-butyllithium (30 mmol, 2.5 M in hexane) in THF (50 ml) at -78 ° C. After stirring for 10 min, the appropriate nitrile (10 mmol) in THF (50 ml) was added dropwise over 20 min and the stirring was continued at -78° C. After warming to -40 °C, **3** (10 mmol) in THF (50ml) was added dropwise at -40 °C, and the resulting solution was allowed to warm to room temperature slowly over a period of 2 h. The resulting dark reddish solution was then quenched with absolute ethanol, the THF was evaporated under reduced pressure, and the remaining residue was extracted with methylene chloride (2 X 50 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to provide an oil which was purified by flash column chromatography (silica gel) using a mixture of hexane / acetone (19:1) as the eluent. The characterization of those products which could be obtained in pure state are given below.

7-(Cyanomethyl)-2-(trifluoromethyl)-10-methylphenothiazine (5a): Colorless crystals (hexane); mp 148-150 °C; ^{1}H nmr ($CDCl_3$) δ 3.37 (s, 3 H), 3.66 (s, 2 H), 6.80 (dd, J = 8.3 Hz, 1 H), 6.97 (s, 1 H), 7.07-7.20 (m, 4 H); ir ($CHCl_3$) ν_{max} 2240 (CN), 1595, 1470, 1405 cm^{-1}. Anal. Calcd for $C_{16}H_{11}N_2F_3S$: C, 59.99; H, 3.46; N 8.75. Found: C, 59.82; H, 3.61; N, 8.87.

7-(α-Methylcyanomethyl)-2-(trifluoromethyl)-10-methylphenothiazine (5b): Colorless solid (hexane), mp 97-100 °C; ^{1}H nmr ($CDCl_3$) δ 1.63 (d, J = 7.2 Hz, 3 H), 3.41 (s, 3 H), 3.83 (q, J = 7.2 Hz, 1 H) 6.82 (d, J = 8.3 Hz, 1 H), 6.98 (s, 1 H), 7.12-7.20 (m, 4 H); ir ($CHCl_3$) ν_{max} 2245 (CN), 1605, 1465 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_2F_3S$: C, 61.07 ; H, 3.92; N, 8.38. Found: C, 61.13 ; H, 3.95 ; N, 8.52.

General Procedure for the Reaction of 3 with Lithium Amides in Amine Solvents. The primary or secondary amine (50ml) was added to a 250 ml round-bottom flask equipped with balloon filled with dry nitrogen and cooled to -50 °C. The n-butyllithium (30 mmol, 12 ml of 2.5 M solution in THF) was added dropwise. After the solution was stirred for 10 min, **3** (30 mmol) in THF (40 ml) was added and the resulting

solution was allowed to warm to room temperature during which time the solution developed a deep red color. After stirring overnight, the reaction mixture was quenched with 2 ml of ethanol, and worked up in the same manner as that described for the reaction of **3** with nitriles.

2-(Trifluoromethyl)-7-N,N-diisopropylamino-10-methylphenothiazine (7a): Colorless thick oil; ^{1}H nmr ($CDCl_3$) δ 1.10 (d, J = 6.6 Hz, 12 H), 3.37 (s, 3 H), 3.52 (septet, J = 6.5 Hz, 1 H), 6.74-7.28 (m, 6 H); ir ($CHCl_3$) ν_{max} 1595, 1470, 1405 cm^{-1}. Anal. Calcd for $C_{20}H_{23}N_2F_3S$: C, 63.13; H, 6.09; N 8.43. Found: C, 63.30; H, 6.13; N, 8.54.

2-(Trifluoromethyl)-7-N,N-diethylamino-10-methylphenothiazine (7b): Colorless needles (hexane); mp 105-107 °C; ^{1}H nmr ($CDCl_3$) δ 1.10 (t, J = 7.5 Hz, 6 H), (q, J = 7.5 Hz, 1 H), 6.74-7.28 (m, 6 H); ir ($CHCl_3$) ν_{max} 1602, 1508, 1474, 1420, 1335, 1219 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_2F_3S$: C, 61.34; H, 5.43; N, 8.43. Found: C, 61.50; H, 5.40; N, 8.57.

2-(Trifluoromethyl)-7-N,N-di-*Sec*-butylamino-10-methylphenothiazine (7c): Colorless thick oil; ^{1}H nmr ($CDCl_3$) δ 0.84–1.53 (m, 16 H), 2.65 (m, 2 H), 3.31 (s, 3 H), 6.72-7.32 (m, 6 H); ir ($CHCl_3$) ν_{max} 1604, 1505, 1472, 1433, 1416, 1334, 1216 cm^{-1}. Anal. Calcd for $C_{22}H_{27}N_2F_3S$: C, 64.68 H, 6.66; N, 6.86. Found: C, 64.80; H, 6.57; N, 6.71.

2-(Trifluoromethyl)-7-N-*t*-butylamino-10-methylphenothiazine (7d): Colorless needles (hexane); mp 131-133 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 3.35 (s, 3 H), 6.67 (m, 2 H), 6.93 (s, 1 H), 7.18 (m, 3 H); ir ($CHCl_3$) ν_{max} 1602, 1522, 1475, 1419, 1212 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_2F_3S$: C, 61.34; H, 5.43; N, 8.43. Found: C, 61.25; H, 5.50; N, 8.60.

Preparation of Authentic Sample of 5a : To a solution containing 7.2 g (20 mmol) of **3** in THF (60 ml) was added 8 ml of a 2.5 M solution of n-butyllithium dropwise at -78 °C. After the solution was stirred at that temperature for 30 min, it was quenched with N,N-dimethylformamide (4 ml), the solution was allowed to warm to room temperature, where it was stirred for 2 h. The solution was then washed with saturated aqueous ammonium chloride solution, the solvent was removed under vacuo (rotary evaporator), and the residue was extracted with methylene chloride (2 X 25 ml). The combined extracts were washed with water (3 X 25 ml), dried (Na_2SO_4), and the solvent was removed under vacuo to give the aldehyde (**9**) (6.1 g, 98 %) as a yellow solid, mp 111-113 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ3.47 (s, 3 H), 6.90 (d, J = 8.5 Hz, 1 H), 7.01 (s, 1 H), 7.22 (m, 2 H), 7.61 (s, 1 H), 7.72 (d, J = 8.0 Hz, 1 H), 8.78 (s, 1 H).

Sodium borohydride (450 mg, 118 mmol) was then added to a solution containing 3.1 g (10 mmol) of **9** in ethanol (25 ml), and the resulting mixture was stirred at room temperature for 1 h. After the solvent was evaporated at reduced pressure, methylene chloride (25 ml) and water (25 ml) were added. The aqueous layer was further acidified by the dropwise addition of conc HCl. The organic layer was separated, and washed with water, dried (Na_2SO_4), and the solvent was removed in vacuo to give the alcohol in nearly quantitative yield. The alcohol, without any further purification, was dissolved in benzene (40 ml) to which thionyl chloride (10 ml, 890 mmol) was added dropwise at 0 °C, and the resulting mixture was stirred at room temperature overnight. The benzene and excess thionyl chloride were removed under vacuum (rotatory evporator) and the remaining crude chloromethyl product was dissolved in dimethyl sulfoxide (20 ml). Potassium cyanide (1 g, 15 mmol)) was then added and the resulting mixture was stirred at room temperature for 24 h. At that time, water (50 ml) and ether (100 ml) were added, and the resulting mixture was stirred for a few minutes. The ether layer was separated, and the remaining aqueous layer was extracted with an additional portion of ether (50

ml). NOTE: Extraction should be done carefully in exhaust hood since aqueous solution still contains some KCN. The combined ether extracts were washed with cold water (4 X 50 ml), dried (Na_2SO_4), and evaporated to give 2.2 g (69%) of **5a** as white crystals (hexane / EtOAc); mp 148-150 °C; the spectral properties of this product was identical as that obtained from the reaction of **3** with acetonitrile and LDA.

Crystal Data and Data Collection and Processing. Colorless cubic shaped crystal (0.5 x 0.4 x 0.3 mm) was mounted on Nicolet R3m/V diffractometer unit cell parameters by least-squares fit of 25 reflections in the range 15<2q<23°. **a** = 17.673(3), **b** = 16.971(5), **c** = 7.607(2)Å, b = 111.83(2). Space group Cc (hkl, h+k odd; h0l, l odd) was confirmed by satisfactory refinement. Graphite monochromated MoKa radiation (l = 0.71073Å), 2q/q scan mode, scan speed 3.0-15.0 deg min^{-1}, 2179 measured reflection 2075 independent reflections in the range 3<20<50°, hkl range h -21-->19, k 0-->20, l 0-->9, 1693 observed reflections with F>6s(F). Three standard reflections measured after every 100 reflections showed crystal and electronic stability. Lorentz-polarization, absorption correction based on psi-scans, and no extinction correction were applied.

Structure Analysis and Refinement. Direct methods. Full-matrix least-squares refinements with all non hydrogen atoms anisotropic. Hydrogen atom in calculated positions and riding model with fixed isotropic parameters. Find R = 0.034 and wR = 0.048, w = $[s^2(F)] + 0.0022\ F^2]^{-1}$, Sw(|Fol-1|Fcl)2 minimized. SHELXTL-Plus 88[17] on microvax II was used. Final positional parameters and thermal parameters and their estimated standard deviations are available upon request.

Table 1. Bond Lengths (Å)

Br-C(3)	1.882 (11)	S(5)-C(4A)	1.804 (10)
S(5)-C(5A)	1.748 (10)	F(1)-C(12)	1.294 (14)
F(2)-C(12)	1.351 (15)	F(3)-C(12)	1.325 (14)
N(10)-C(9A)	1.421 (14)	N(10)-C(10A)	1.422 (15)
N(10)-C(11)	1.464 (12)	C(1)-C(2)	1.333 (16)
C(1)-C(10A)	1.416 (15)	C(2)-C(3)	1.366 (15)
C(3)-C(4)	1.416 (15)	C(4)-C(4A)	1.348 (15)
C(4A)-C(10A)	1.401 (14)	C(5A)-C(6)	1.392 (15)
C(5A)-C(9A)	1.417 (15)	C(6)-C(7)	1.372 (15)
C(7)-C(8)	1.389 (16)	C(8)-C(9)	1.400 (16)
C(8)-C(12)	1.484 (17)	C(9)-C(9A)	1.361 (15)

Table 2. Bond Angles (°)

C(4A)-S(5)-C(5A)	97.6(5)	C(9A)-N(10)-C(10A)	118.7(8)
C(9A)-N(10)-C(11)	116.2(8)	C(10A)-N(10)-C(11)	118.3(8)
C(2)-C(1)-C(10A)	120.9(10)	C(1)-C(2)-C(3)	121.6(10)
Br-C(3)-C(2)	122.9(8)	Br-C(3)-C(4)	117.4(8)
C(2)-C(3)-C(4)	119.7(10)	C(3)-C(4)-C(4A)	118.3(9)
S(5)-C(4A)-C(4)	119.5(7)	S(5)-C(4A)-C(10A)	117.7(8)
C(4)-C(4A)-C(10A)	122.8(10)	S(5)-C(5A)-C(6)	120.1(8)
S(5)-C(5A)-C(9A)	120.1(8)	C(6)-C(5A)-C(9A)	119.7(9)
C(5A)-C(6)-C(7)	120.7(10)	C(6)-C(7)-C(8)	119.3(10)

Table 2, con't.

C(7)-C(8)-C(9)	120.4(10)	C(7)-C(8)-C(12)	121.1(11)
C(9)-C(8)-C(12)	118.3(10)	C(8)-C(9)-C(9A)	120.5(10)
N(10)-C(9A)-C(5A)	117.8(9)	N(10)-C(9A)-C(9)	123.0(10)
C(5A)-C(9A)-C(9)	119.2(10)	N(10)-C(10A)-C(1)	123.4(9)
N(10)-C(10A)-C(4A)	119.9(9)	C(1)-C(10A)-C(4A)	116.6(10)
F(1)-C(12)-F(2)	104.1(10)	F(1)-C(12)-F(3)	105.6(10)
F(2)-C(12)-F(3)	104.1(10)	F(1)-C(12)-C(8)	116.0(11)
F(2)-C(12)-C(8)	111.8(10)	F(3)-C(12)-C(8)	114.1(11)

Table 3. Torsion Angles(°)

C(5a)-S(5)-C(4a)-C(4)	144.9(0.9)	C(5a)-S(5)-C(4a)-C(10a)	-38.5(0.9)
C(4a)-S(5)-C(5a)-C(6)	-143.7(0.8)	C(4a)-S(5)-C(5a)-C(9a)	40.7(0.9)
C(10a)-N(10)-C(9aA)-C(5a)	-41(1)	C(10a)-N(10)-C(9a)-C(9)	136.1(1.1)
C(11)-N(10)-C(9a)-C(5a)	168.6(0.9)	C(11)-N(10)-C(9a)-C(9)	-14.7(1.4)
C(9a)-N(10)-C(10a)-C(1)	-136(1)	C(9a)-N(10)-C(10a)-C(4a)	42.5(1.3)
C(11)-N(10)-C(10a)-C(1)	14.6(1.4)	C(11)-N(10)-C(10a)-C(4a)	-167(1)
C(10a)-C(1)-C(2)-C(3)	-4.5(1.7)	C(2)-C(1)-C(10a)-N(10)	-178.2(1.0)
C(2)-C(1)-C(10a)-C(4a)	3.6(1.6)	C(1)-C(2)-C(3)-Br	-178.4(0.9)
C(1)-C(2)-C(3)-C(4)	3.7(1.7)	Br-C(3)-C(4)-C(4a)	179.9(0.8)
C(2)-C(3)-C(4)-C(4a)	-2.0(1.6)	C(3)-C(4)-C(4a)-S(5)	177.8(0.8)
C(3)-C(4)-C(4a)-C(10a)	1.3(1.6)	S(5)-C(4a)-C(10a)-N(10)	3.2(1.3)
S(5)-C(4a)-C(10a)-C(1)	-178.5(0.8)	C(4)-C(4a)-C(10a)-N(10)	179.7(1.0)
C(4)-C(4a)-C(10a)-C(1)	2.0(1.5)	S(5)-C(5a)-C(6)-C(7)	-175.6(0.8)
C(9a)-C(5a)-C(6)-C(7)	0.0(1.5)	S(5)-C(5a)-C(9a)-N(10)	7.0(1.3)
S(5)-C(5a)-C(9a)-C(9)	176.2(0.8)	C(6)-C(5a)-C(9a)-N(10)	177.4(0.9)
C(6)-C(5a)-C(9a)-C(9)	0.6(1.5)	C(5a)-C(6)-C(7)-C(8)	1.3(1.6)
C(6)-C(7)-C(8)-C(9)	-3.3(1.6)	C(6)-C(7)-C(8)-C(12)	-177.7(1.1)
C(7)-C(8)-C(9)-C(9a)	3.9(1.7)	C(12)-C(8)-C(9)-C(9a)	178.5(1.0)
C(7)-C(8)-C(12)-F(1)	-22.1(1.6)	C(7)-C(8)-C(12)-F(2)	97.0(1.2)
C(7)-C(8)-C(12)-F(3)	-145.2(1.1)	C(9)-C(8)-C(12)-F(1)	163.3(1.0)
C(9)-C(8)-C(12)-F(2)	77.5(1.3)	C(9)-C(8)-C(12)-F(3)	40.2(1.5)
C(8)-C(9)-C(9a)-N(10)	-179.2(1.0)	C(8)-C(9)-C(9a)-C(5a)	-2.6(1.6)

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REFERENCES

1 a) Summer Undergraduate Scholar from Harvard University; b) Welch Undergraduate Fellow; c) Summer Undergraduate Scholar from Rice University; d) Summer Undergraduate Student.

2 E. R. Biehl, S. P. Khanapure, U. Siriwardane, and M. Tschantz, *Heterocycles*, **1989**, *29*, 485.

3. a) A. I. Meyers and P. D. Pansegrau, *Tetrahedron Lett.*, **1984**, *25*, 2941. b) S. P. Khanapure, L. Crenshaw, R. T. Reddy, and E. R. Biehl, *J. Org. Chem.*, **1988**, *53*, 4915.

4. J. D. Roberts, D. A. Semenow, H. E. Simmons, and L. A. Carlsmith, *J. Am. Chem. Soc.*, **1956**, *76*, 601.

5 E. R. Biehl, V. Patrizi, S. Lapis, and P. C. Reeves, *J. Heterocycl. Chem.*, **1974**, *11*, 965.

6. D. H. Jones, *J. Chem. Soc. (C)*, **1971**, 132. b) A. Hallberg, P. Dunbar, N. M. Hintermeister, A. Svensson, and A. R. Martin, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 969.

7. J. P. Rieu, A. Boucherle, H. Cousse, and G. Mouzin, *Tetrahedron* , **1986**, *42*, 4095.

8. M. V. Jovanovic, P. de Meester, E. R. Biehl, and S. S. C. Chu, *J. Heterocycl. Chem.*, **1986**, *23* 801.

9. C. K. Johnson, ORTEP (1965), Report ORNL-3794, Oak Ridge National Laboratory, Tennessee.

10. S. S.C. Chu and D. Van der Helm, *Acta Cryst.*, **B30**, **1974**, 2489.

11. See E. R. Biehl and S. P. Khanapure, *Acc. Chem. Res.*, **1989**, *22*, 275 and references therein.

12. S. P. Khanapure and E. R. Biehl, *Heterocycles*, **1990**, *31*, 505.

13. M. V. Jovanovic and E. R. Biehl, *Org. Mag. Reson.*, **1984**, *22*, 491.

14. J. F. Bunnett, D. A. R. Happar, C. Pyun, and H. Takayama, *J. Am. Chem. Soc.*, **1966**, *88*, 5250.

15. E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **1969**, *34*, 3595.

16 See, for example: E. R. Biehl, S. M. Smith, and P. C. Reeves, *J. Org. Chem.*, **1971**, *36*, 1841; E. R. Biehl, S. M. Smith, R. Patrizi, and P. C. Reeves, *J. Org. Chem.*, **1972**, *37*, 137; E. R. Biehl and R. Levine, *J. Org. Chem.*, **1975**, *40*, 2416.

17. G. M. Sheldrick, SHELX 76, Programs for Crystal Structure Determination, University of Cambridge, England, 1976.

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