METALATION OF 2-TRIFLUOROMETHYLPHENOTHIAZINE: SYNTHESIS AND REACTIONS OF TRIMETHYLSILYL DERIVATIVES

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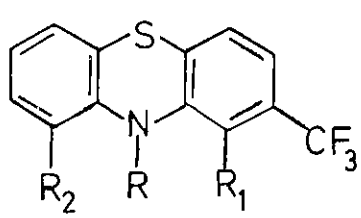
Abstract - Dimetalation of 2-trifluoromethylphenothiazine followed by reaction with electrophiles such as carbon dioxide, DMF, hexachloroethane and 1,2-dibromoethane gives 1-substituted 2-trifluoromethylphenothiazines with only traces of the 9-substituted products being formed. Reaction of 1,10-dilithio-2-trifluoromethylphenothiazine with an excess of trimethylysilyl chloride gave a mixture of 2-trifluoromethyl-10-trimethylsilylphenothiazine and 2-trifluoromethyl-1,10-di(trimethylsilyl)phenothiazine. The 10-trimethylsilyl- and 2-trifluoromethyl-1,10-di(trimethylsilyl)phenothiazines were prepared from 10-lithio- and 1-lithio-2-trifluoromethylphenothiazine, respectively. The basis for the unusual stability of 1,10-dilithio-2-trifluoromethylphenothiazine is discussed.

As a part of a project directed toward the synthesis of compounds related to the phenothiazine tranquilizers with conformational restriction in the side chain we sought to regioselectively functionalize the 1- and/or 10-positions of the phenothiazine ring system while retaining an electronegative substituent in the 2-position. We chose to utilize metalation chemistry with 2-trifluoromethylphenothiazine (1_a) as a substrate, since 2-chlorophenothiazine readily forms dehydrophenothiazines under metalation conditions.[1,2] Indeed, 1_a had previously been successfully metalated using n-butyllithium in ether (5-10° C for 6 h) and reacted with solid carbon dioxide[3] to give predominantly 1-carboxyl-2-trifluoromethylphenothiazine (1_b) and a trace of the 9-carboxy



1(a) R=R_1=R_2=H
(b) R=R_2=H; R_1=CO_2H
(c) R=R_1=H; R_2=CO_2H
(d) R=R_1=Li; R_2=H
(e) R=R_2=Li; R_1=H
(f) R=R_2=H; R_1=CHO
(g) R=R_2=H; R_1=Cl
(h) R=R_2=H; R_1=Br
(i) R=R_2=H; R_1=CH_3
(j) R=$SiMe_3$; R_1=R_2=H
(k) R=R_1=$SiMe_3$; R_2=H
(l) R=R_2=H; R_1=$SiMe_3$
(m) R=Li; R_1=$SiMe_3$; R_2=H

derivative ($\mathbf{1}_c$). We found that it was possible with tetramethylethylenediamine (TMEDA) in ether to successfully carry out the reaction at room temperature and for a shorter time. The use of n-butyllithium at room temperature failed to give characteristic products and, in fact, destroyed the starting material $\mathbf{1}_a$. The presumed 1,10-dilithio intermediate $\mathbf{1}_d$ was similarly reacted, in turn, with N,N-dimethylformamide, hexachloroethane and 1,2-dibromethane to obtain, respectively, 1-formyl-2-trifluoromethylphenothiazine ($\mathbf{1}_f$), 1-chloro-2-trifluoromethylphenothiazine ($\mathbf{1}_g$) and 1-bromo-2-trifluoromethylphenothiazine[4] ($\mathbf{1}_h$). Although traces of 9-substituted derivatives were probably formed (i.e., via $\mathbf{1}_e$) in these reactions,[3] as indicated by tlc, they were not isolated. The yields obtained in these reactions (37-45%) are generally somewhat lower than those obtained from the reactions of 1,10-dilithiophenothiazine with various electrophiles,[5-8] but nonetheless illustrate the general utility of the method.

The reaction of $\mathbf{1}_d$ with an excess of trimethylsilyl chloride gave a mixture (41% yield) of $\mathbf{1}_j$ and $\mathbf{1}_k$ in a ratio of 1:7 based on integration of the trimethylsilyl peaks in the ^{1}H-nmr spectrum. This result led us to believe that the trimethylsilyl group could be used to block the 1-position and, assuming that the N-trimethylsilyl group of $\mathbf{1}_k$ could be removed to give $\mathbf{1}_l$, the nitrogen atom in the latter could then be utilized to direct metalation[5-8] into the 9-position. Reaction of the corresponding 9,10-dilithio-2-trifluoromethyl-1-trimethylsilylphenothiazine with electrophiles followed by removal of the trimethylsilyl group should then give 9-substituted phenothiazines. To our surprise, $\mathbf{1}_k$ failed to undergo N-desilylation under conditions normally used for the removal of N-trialkylsilyl groups[9] (refluxing in dilute hydrochloric, sulfuric or trifluoroacetic acids). Trifluoroacetic acid and potassium fluoride removed both trimethysilyl groups from $\mathbf{1}_k$. On the other hand, the mono-trimethylsilyl derivative $\mathbf{1}_j$, prepared by reacting $\mathbf{1}_a$ with one equivalent of methyllithium and then one equivalent of trimethylsilyl chloride, was readily cleaved in dilute acid.

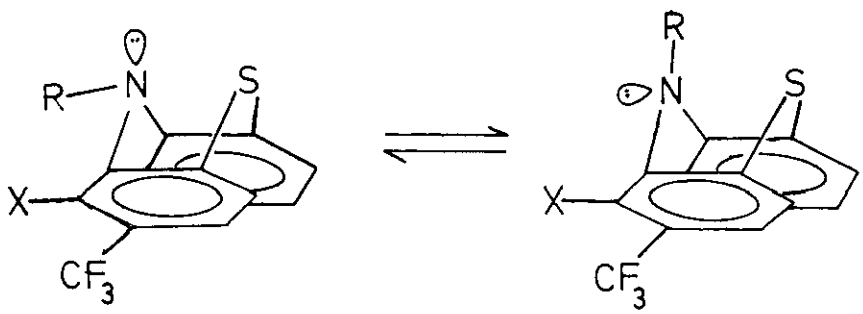
The desired 1-trimethylsilyl derivative $\mathbf{1}_l$ was finally prepared from $\mathbf{1}_h$ (46% yield) by halogen-metal exchange in ether at -78°C followed by reaction with trimethylsilyl chloride[10] at reflux. Only a small amount of $\mathbf{1}_k$ was obtained suggesting that halogen metal exchange of $\mathbf{1}_h$ is more facile than its deprotonation under the reaction conditions. Unfortunately, attempts to dimetalate $\mathbf{1}_l$ and react it with electrophiles (e.g., DMF) gave $\mathbf{1}_k$ and $\mathbf{1}_a$ as the only isolable products. Apparently, intermolecular C→N migration of the trimethylsilyl group from $\mathbf{1}_l$ to the N-lithiated derivative $\mathbf{1}_m$ must have occurred. Metalation of $\mathbf{1}_l$ followed by reaction with trimethylsilyl chloride, also gave $\mathbf{1}_k$. No 9-trimethylsilyl substituted products were formed, even when large excess of metalating and silylating reagents were employed, indicating that $\mathbf{1}_l$ probably does not readily undergo dimetalation.

The remarkable stability of $\mathbf{1}_k$ to cleavage of the silicon-nitrogen bond and the apparent failure of $\mathbf{1}_l$ to undergo dimetalation can both be explained on the basis of conformational effects. The phenothiazine ring system is believed to exist as an equilibrium of butterfly-like conformations shown in figure 1 where the 1,4-

thiazine ring is a flattened boat. Two extremes can be defined based on the configuration of the nitrogen atom:[11,12] a nearly planar conformation in which the nitrogen is trigonal (sp^2); and a tetragonal folded one in which the nitrogen is tetrahedral (sp^3). In the tetragonal folded conformation two distinct configurations for the nitrogen substitutent are possible: **intra**[11] (or **synperiplanar**)[13] and **extra**[11] (or **synclinal**).[13] These conformations become equivalent when the nitrogen is trigonal. Crystallographic studies support the nearly planar conformation for both 10-unsubstituted[14-16] and 10-substituted phenothiazines in the ground state.[17-19] However, the **p** character of the nitrogen atom appears to increase with the size of the 10-substituent.[17-19] A preference for the **synclinal** conformation has been invoked[11,20] to explain the apparently paradoxical reduction in reactivity toward electrophilic reagents and increase in oxidation potential brought about by the introduction of a 10-substituent in phenothiazines. It will be noted that delocalization of the nitrogen lone pair into the aromatic ring is disfavored in the **synclinal** compared with the **synperiplanar** conformation.

Figure 1

Tetragonal Folded Conformations



synperiplanar **synclinal**

1_k R = X = $SiMe_3$

1_l R = Li; X = $SiMe_3$

Molecular models of 1_k reveal the presence of severe steric interactions between the trimethylsilyl groups when the nitrogen atom is trigonal (i.e., the nearly planar conformation) or when the N-trimethylsilyl group is held in the **synperiplanar** tetragonal conformation. On the other hand, steric interaction between the trimethylsilyl groups is minimal in the **synclinal** tetragonal conformation. Attack on the silicon atom by water is severely restricted by hindrance from the phenothiazine ring system in this conformation, this explaining the stability of 1_k to hydrolytic cleavage. Similarly, in the 10-lithio derivative 1_m, the **p** orbital associated with the anion is sterically forced into the **extra** conformation by the bulky 1-trimethylsilyl group. The coordinated lithium atom is, therefore, not appropriately oriented to direct a second metalation by alkyllithium[3,5-8] into

the 9-position, thereby explaining the failure of 1_m to undergo an additional electrophilic substitution under metalation conditions.

EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. NMR spectra were recorded on a Jeol FX90Q spectrometer and on a Bruker WM-250 spectrometer (250 mHZ) using tetramethylsilane as an internal standard. The high resolution mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer.

1-Carboxy-2-trifluoromethylphenothiazine (1_b). A mixture of 10.75 ml (16 mmol) of methyllithium (0.67N) and 2.4 ml (16 mmol) of TMEDA in dry ether was stirred for 20 min. 2-Trifluoromethylphenothianzine 1.04g (4 mmoles), dissolved in dry ether was added dropwise and the mixture was stirred for 3 h at room temperature. An excess of solid carbon dioxide was added to the solution, and when the gas evolution had stopped water was added. The organic phase was extracted with 2N sodium hydroxide and the combined water phases were acidified with concentrated hydrochloric acid. The formed yellow precipitation was dissolved in ether and extracted with water. Evaporation of the ether phase yielded 522 mg (42%) of 1_b as thin yellow needles, mp 197-199°C (lit.[3] 199-200°C); m.s.: m/e 311; ir: C=O 1650 cm-1, nmr (DMSO-d_6): δ 14.0 (s, 1H, CO_2H), 8.38 (s, 1H, NH), 7.36 - 6.85 (m, 6H, arom); at 250 MHZ an AB quartet for H-3, H-4 (J = 8.2 HZ) was apparent.

1-Formyl-2-trifluoromethylphenothiazine (1_f). The same metalation procedure as above was followed; thus 0.58 g (8 mmol) of dimethylformamide in 5 ml of ether was added at room temperature. After stirring for 2 h, water and 5% HCl were added. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. The red residue was chromatographed (silica gel, hexane) to give 520 mg (44%) of 1_f as a red-orange solid, mp 140-142°C; ir: CHO 1660 cm^{-1}; nmr ($CDCl_3$): δ 11.1 (s, 1H, NH), 10.2 (s, 1H, CHO), 7.1-6.5 (m, 6H, arom). Anal. molecular weight calcd. for $C_{14}H_8F_3NOS$: 295.0279. Found (high resolution mass spectrum): 295.0281.

1-Chloro-2-trifluoromethylphenothiazine (1_h). Using the same metallation procedure as above, 2.2 g (10 mmoles) of hexachloroethane was added at room temperature. After stirring for 1 h, water was added. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. Chromathography (silica gel, hexane/ethyl acetate, 9/1) yielded 0.55g (4.5%) of 1_g as a light tan solid, mp 170-172°C; nmr ($CDCl_3$) δ 7.3 - 6.5 (m, 7H, arom). Anal. molecular weight calcd. for $C_{13}H_7ClF_3NS$: 300.9940. Found (high resolution mass spectrum): 300.9935.

1-Bromo-2-trifluoromethylphenothiazine (1_h). To a solution of 4.16 g (16 mmol) of 1_a in dry ether under nitrogen at 0°C was added 30 ml of n-butyllithium (1.65N in hexane) and the solution was stirred for 6 h at 0°C. 1,2-Dibromoethane (9 ml, 72 mmol) was then slowly added with stirring, maintaining the temperature at

0-5°C. After allowing the reaction to warm to 25°C over a period of 2 h, water and 5% HCl were added. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. The yellow oily residue was chromatographed (silica, hexanes) to give 2.05 g (37%) of 1_j as pale yellow flakes, mp 152-154°C; ir: NH 3370 cm^{-1}; nmr ($CDCl_3$): δ 7.3-6.3 (m, 7H, arom). Anal. molecular weight calcd. for $C_{13}H_7BrF_3NS$: 344.9435. Found (high resolution mass spectrum): 344.9444.

1-Methyl-2-trifluoromethylphenothiazine (1_j). A mixture of 21.5 ml (32 mmol) of methyllithium (0.67N) and 4.8 ml (32 mmol) of TMEDA were stirred for 20 min. 2-Trifluoromethylphenothiazine (1_a, 2.08 g, 8 mmol) dissolved in dry ether was added dropwise and the solution stirred for 2 h at 25°C. 1,2-Dibromoethane (1.2 ml, 10 mmol) was added and the solution stirred for an additional hour. Water was then added and the ether layer separated, washed with water, dried ($MgSO_4$) and evaporated. The brown oily residue was chromatographed (silica, hexanes) to give 400 mg (14.5%) of 1_j as a yellow crystalline solid, mp 174-117°C, nmr ($CDCl_3$): δ 7.4-6.8 (m, 6H, arom), 6.2 (bs, 1H, NH), 2.52 (s, 3H, CH_3). Anal. molecular weight calcd. for $C_{14}H_{10}F_3NS$: 281.0477. Found (high resolution mass spectrum): 281.0486.

10-Trimethylsilyl-2-trifluoromethylphenothiazine (1_j). A mixture of 2.68 ml (4 mmol) of methyllithium (0.67 N) and 0.6 ml (4 mmoles) of TMEDA in dry ether was stirred for 20 min at room temperature. 2-Trifluoromethylphenothiazine, 1.04 g (4 mmol), dissolved in dry ether was added dropwise and the mixture was stirred 2 h. A solution of 0.5 ml (4 mmol) of trimethylsilyl chloride in dry ether was then added and the mixture was stirred for 1 h. It was hydrolyzed with 5% $NaHCO_3$. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography (silica, hexanes) gave 0.42 g (31%) of the title compound [the compound desilylates if left more than a few minutes on the column] as a pale yellow solid, mp 67-69 °C, nmr ($CDCl_3$): δ 7.3-6.7 (7H, m, arom), 0.31 (9H, s, N-Si(CH_3)$_3$). Anal. molecular weight calcd. for $C_{16}H_{16}F_3NSSi$: 339.0725. Found (high resolution mass spectrum): 339.0712.

1,10-Di-trimethylsilyl-2-trifluoromethylphenothiazine (1_k). Method A. A mixture of 21.5 ml (32 mmol) of methyllithium and 4.8 ml (32 mmol) of TMEDA in dry ether was stirred for 20 min. 2-Trifluoromethylphenothiazine 2.08 g (8 mmol), dissolved in dry ether was added dropwise and the mixture was stirred for 2 h at room temperature. The solution was then transferred to a flask containing 5.0 ml (40 mmol) of trimethylsilyl chloride in 50 ml of dry ether. After stirring for 1 h the solution was hydrolyzed with $NaHCO_3$. The organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated. The resulting solid was refluxed in 5N HCl for 0.5 h. Separation of the organic phase, washing, drying (Na_2SO_4), evaporation and chromatography (silica, hexanes) yielded 0.97 g (36%) of 1_k as a pale tan rhombic crystals mp 63-65°C; nmr ($CDCl_3$): δ 7.4-7.0 (m, 6H, arom), 0.42 (d, 9H, N-Si (CH_3)$_3$), 0.05 (s, 9H, C-Si($CHCH_3$)$_3$). Anal. molecular weight calcd. for $C_{19}H_{24}F_3NSSi_2$: 411.1120. Found (high resolution mass spectrum):

411.1128. Method B: To a solution of 50 mg (0.15 mmol) of 1-trimethysilyl-2-trifluorophenothiazine (1_j) in 15 ml of dry ether was added 0.5 ml (0.75 mmol) of methyllithium at room temperature. After stirring for 2 h 0.6 ml (4.8 mmol) of trimethylsilyl chloride was added. The solution was stirred for an additional 2 h and hydrolyzed with 5% $NaHCO_3$. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. Chromatography on prep-tlc (silica, hexanes) yielded 29 mg (48%) of 1_k as a colorless oil.

1-Trimethylsilyl-2-trifluoromethylphenothiazine (1_l). A mixture of 1.0 g (2.86 mmol) of 1-bromo-2-trifluoromethylphenothiazine (1_h) and 0.75 ml (5.86 mmol) of trimethylsilyl chloride in dry ether was cooled to -78°C and transferred to a solution of n-butyllithium (2.0 ml, 3.21 mmol) in ether at -78°C. The mixture was stirred for 4 h at -78°C and then refluxed for 1 h. The solution was hydrolyzed with 5% $NaHCO_3$. The organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated. Chromatography (silica, hexanes) yielded 0.45 g (46%) of the title compound 1_l, mp 171-174°C; nmr ($CDCl_3$): δ 7.5-6.8 (6H, m, arom), 0.21 (9H, s, C-Si(CH_3)$_3$). Anal. molecular weight calcd. for $C_{16}H_{16}F_3NSSi$: 339.0725. Found (high resolution mass spectrum): 339.0712.

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