Specific Synthesis of 1-Substituted Phenothiazines Using Carbon Dioxide Protection of the NH Group During Lithiation[1]

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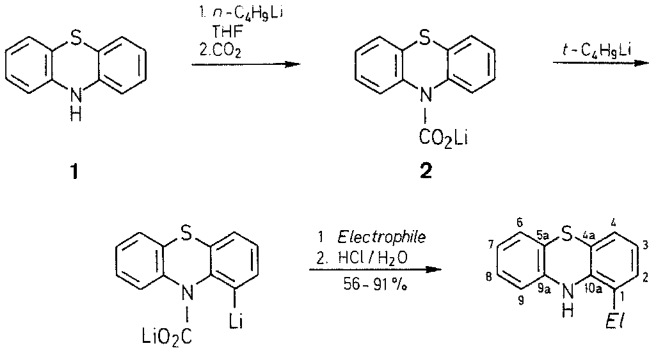
The lithiation of phenothiazine when protected as the lithium salt of its carbamate occurs exclusively at the C-1 carbon atom. Reaction of the lithiated species with a variety of electrophiles readily produced several new 1-substituted phenothiazines, as well as a number of known compounds in superior yield to existing methods.

The lithiation of heterocyclic compounds containing an NH group normally leads only to the *N*-lithio derivative, but when the nitrogen is protected by a blocking group *C*-lithiation can often occur. Thus the α-lithiation of pyrroles and indoles occurs readily when the amino hydrogen atom is replaced by species such as a β-trimethylsilylethoxymethyl,[2,3] methoxymethyl,[4] or arylsulfonyl group.[4] However, all of these protecting groups suffer from the drawback that either they are not readily introduced or they require strong conditions for their removal.

One solution to this problem came with the discovery that carbon dioxide can be used as a protecting group for indoles[5] and other nitrogen heterocycles,[6] with the carboxyl group being readily introduced and removed under relatively mild conditions in a simple one-pot procedure. We now report that the carbon dioxide protection method can also be used to mask the nitrogen atom of phenothiazine during the lithiation of that compound.

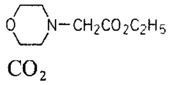
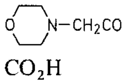
Phenothiazine actually undergoes *C*-lithiation even without a nitrogen protecting group,[7-13] but the advantage of the present method is that the lithiated species can now undergo electrophilic addition exclusively at the carbon center without any accompanying reaction at the nitrogen atom. Reaction of phenothiazine with two equivalents of *n*-butyllithium is reported[7-13] to give a di-lithio species where the site of *C*-lithiation is at C-1, and an identical site of lithiation was also observed in the present case.

Thus, treatment of phenothiazine **1** with one equivalent of *n*-butyllithium gave the mono-anion which was reacted with carbon dioxide to give the N-lithio carbamate **2**. Further treatment with *tert*-butyllithium gave a *C*-lithiated derivative which was shown to be the C-1 isomer **3** by reaction with a variety of electrophiles and subsequent hydrolysis to a number of previously known and unknown 1-substituted phenothiazine derivatives **4a–l** (Table 1). The more sterically hindered *tert*-butyllithium was employed in the lithiation step in order to prevent reaction at the carboxyl center. Loss of carbon dioxide occurred spontaneously on acidification with dilute hydrochloric acid at room temperature.



Even though excess lithiating agent was employed, no dilithiation was observed, and in all cases unreacted phenothiazine was recovered. Several of the reaction products were found to be light sensitive so all steps were performed as much as possible in

Table 1. 1-Substituted Phenothiazines **4** Prepared

Product	Electrophile	*El*	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
4a	D_2O	D	100[d]	186–188 (benzene)	187–189[13,e]
4b	CH_3I	CH_3	75	138–139 (benzene)	137.5–138.5[19]
4c	C_2H_5I	C_2H_5	68	126–127 (cyclohexane)	124–126[20]
4d	$C_6H_5CH_2Br$	$C_6H_5CH_2$	56	136–138 (cyclohexane)	$C_{19}H_{15}N$ (257.4)
4e	C_6H_5CHO	$C_6H_5CH(OH)$	91	oil	–[f]
4f	$C_6H_5COC_6H_5$	$(C_6H_5)_2C(OH)$	65	224–225[g] (EtOH)	213–213.5[8]
4g	$C_6H_5CO_2C_2H_5$	C_6H_5CO	80	90–91 (EtOH)	91[9]
4h[h]			61	104–105 (MeOH)	$C_{18}H_{18}N_2O_2S$[i] (326.4)
4i	CO_2	CO_2H	58	266–268 (MeOH)	265–267[21]
4j	i-$C_4H_9ONO_2$	NO_2	33	117–119 (EtOAc)	118–119[22]
4k	4-$CH_3C_6H_4SO_2F$	4-$CH_3C_6H_4SO_2$	70[j]	156–157 (MeOH)	$C_{19}H_{15}NO_2S_2$[k] (321.4)
4l	*N*-chlorosuccinimide	Cl	65	93–94 (MeOH)	92–93[12]
4l	CCl_3CCl_3	Cl	98	93–94 (MeOH)	92–93[12]

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.43, H ±0.11, N ±0.32.
[d] Material 90% deuterated as shown by ^{1}H-NMR spectroscopy.
[e] mp of 1,9-dideuteriophenothiazine.
[f] Product unstable; characterized by ^{1}H-NMR analysis.
[g] Satisfactory microanalysis obtained.
[h] The electrophile used to prepare **4h** was synthesized according to method of reference 16.
[i] Product previously known,[14] but not characterized. IR (Nujol): $\nu = 1640\ cm^{-1}$ (C=O).
[j] Use of 4-methylbenzenesulfonyl chloride gave a mixture of **4k** and **4l**, from which **4l** was isolated pure in 52% yield.
[k] IR (Nujol): $\nu = 1130, 1310\ cm^{-1}$ (SO_2).

the absence of light. The electrophiles chosen for this study, and the products obtained, are listed in Table 1. In the following cases our system gave superior yields to those given in the literature (see Table for references): **4b**, 75 vs 21 % (overall yield for three steps); **4g**, 80 vs 64 %; **4i**, 58 vs 53 %; **4l**, 98 vs 77 %. In the case of compound **4f** our yield (65 %) was slightly lower than that of the earlier method (70 %),[8] although the higher melting point obtained indicates a greater purity.

Compound **4h** has previously been prepared as an intermediate in the synthesis of the analogous alcohol,[14] but was not fully characterized. In that case it was obtained via a multi-step synthesis from 1,2-dioxo-1,2-dihydropyrrolo[3,2,1-*kl*]phenothiazine, which in turn was prepared from phenothiazine.[15] The advantage of the present method can be seen by the fact that the same compound can now be obtained in a simple one-pot procedure directly from phenothiazine and ethyl 2-morpholinoacetate.[16]

The site of lithiation and subsequent electrophilic addition was confirmed as being at C-1 (by comparison of the melting points of the previously known compounds with the literature values), and this is in agreement with the site of addition seen for treatment of *N*-acyl phenothiazines with lithium diisopropylamine.[17] No evidence for lithiation at any other site was observed. The fact that C-1 lithiation occurs exclusively indicates that the CO_2^--Li^+ unit is probably acting as a directing group by chelating with the lithiating agent. This is in sharp contrast to the situation seen with the lithiation of *N*-alkyl phenothiazines where the absence of any directing effect results in the formation of both C-1 and C-4 substituted products, with the latter usually predominating.[9,10,18]

The ^1H- and ^{13}C-NMR spectral data are shown in Tables 2 and 3, and are in consistent agreement with the site of substitution being at C-1. The ^{13}C-NMR assignments, which are based on those of reference 13, show that the addition of the substituent causes an upfield shift for the C-1a carbon resonance and downfield shifts for the C-6a, C-7, C-9 and C-9a resonances. These latter changes are fully consistent with a steric interaction between the substituent and NH groups which is being transmitted through the C-9a carbon to the *ortho* (C-6a and C-9) and *para* carbons (C-7). No such shift is observed with the analogous *meta* (C-6 and C-8) carbons. The chemical shifts of the carbon atoms in the substituted ring show the expected changes with the C-2 and C-4 resonances normally moving downfield and the C-3 upfield. Chemical shift assignments for the C-3 carbons were able to be obtained unequivocally from the uncoupled spectra due to the absence of long range (*meta*-hydrogen) coupling.

Table 2. ^1H-NMR Data of Compounds **4a**–**4l**[a]

Compound	δ, J (Hz)
4a	7.05 (m, 7H); 8.60 (s, 1H)
4b	2.20 (s, 3H); 7.35 (m, 7H); 7.45 (m, 1H)
4c	1.10 (t, 3H, J = 7 Hz); 2.60 (q, 2H, J = 7 Hz); 6.90 (m, 7H); 7.70 (s, 1H)
4d	3.95 (s, 2H); 5.85 (s, 1H); 6.05 (m, 1H); 6.85 (m, 6H); 7.30 (m, 5H)
4e	5.65 (s, 1H); 6.05 (s, 1H); 6.85 (m, 6H); 7.25 (m, 6H)
4f	5.85 (s, 1H); 6.25 (d, 1H, J = 8 Hz); 6.75 (m, 3H); 7.00 (m, 2H); 7.25 (m, 10H); 7.55 (s, 1H), 8.05 (s, 1H)
4g	6.65 (m, 2H); 6.95 (m, 4H); 7.25 (m, 1H); 7.55 (m, 5H); 10.18 (s, 1H)
4h	2.60 (t, 4H, J = 6 Hz); 3.75 (m, 6H); 6.80 (m, 6H); 7.55 (d, 1H, J = 8 Hz); 10.85 (s, 1H)
4i	6.75 (m, 7H); 7.60 (d, 1H, J = 8 Hz); 10.05 (s, 1H)
4j	6.85 (m, 6H); 7.85 (d, 1H, J = 8 Hz); 9.95 (s, 1H)
4k	2.40 (s, 3H); 6.65 (m, 1H); 6.85 (m, 3H); 7.05 (m, 2H); 7.30 (m, 2H); 7.55 (d, 1H); 7.80 (d, 2H); 8.65 (s, 1H)
4l	6.90 (m, 7H); 8.05 (s, 1H)

[a] Recorded at 200 MHz on a Varian XL 200 spectrometer in DMSO-d_6 (**4a–c, e, f, i, l**) and $CDCl_3$ (**4d, g, h, j, k**).

Table 3. ^{13}C-NMR Data of Compounds **4a**–**4m**[a] (DMSO-d_6)

Compound	Carbon Atom, δ											
	C-1	C-2	C-3[b]	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a
1	114.4	127.4	121.7	126.2	116.3	116.3	126.2	121.7	127.4	114.4	142.1	142.1
4a	114.1[c]	127.3	121.7	126.2	116.3	116.3	126.2	121.7	127.4	114.4	142.1	142.1
4b[d]	122.3	129.2	121.4	124.2	117.3	116.5	126.0	122.0	127.2	115.6	142.2	140.1
4c[e]	128.5	127.5	121.7	124.3	117.6	117.1	126.0	122.0	127.2	115.5	142.5	139.7
4d[f]	124.8	126.0	121.8	124.8	117.6	117.6	126.0	122.2	127.3	115.5	142.2	139.8
4f[g]	132.2	128.1	120.7	126.5*	119.5	118.3	126.2*	122.4	127.2	114.4	141.7#	141.5#
4g[h]	119.2*	130.8	120.3	132.1	119.1*	117.0	126.2	123.5	127.8	116.2	143.7	139.7
4h[i]	117.1*	129.8	120.4	131.3	118.4	116.7*	126.2	123.5	127.8	116.2	144.1	139.1
4i[j]	112.0	129.5	120.5	130.7	118.4	116.6	126.1	123.0	127.6	115.5	144.8	139.7
4j	133.1	124.4	120.8	132.2	120.8	117.0	126.0	124.0	127.8	117.4	138.8	137.9
4k[k]	123.8	128.0	122.1	132.3	121.0	117.2	126.4	124.0	127.8	116.6	144.9	139.2
4l	119.2	127.5	122.2	125.1	118.3	116.8	126.0	122.8	127.8	116.1	140.9	138.1
4m[l]	111.3	129.0	120.9	131.2	118.6	116.5	126.2	123.4	127.8	115.9	144.4	139.4

[a] Recorded at 50 MHz on a Varian XL 200 spectrometer. Assignments are based on those of reference 13 and a consideration of both steric and electronic aromatic substituent effects. Chemical shift values marked * or # may be interchangeable. Compound **4e** was too unstable for the accumulation of a good spectrum.

[b] Assigned unequivocally due to absence of long range (*meta*-hydrogen) coupling in undecoupled spectrum.

[c] Not seen in decoupled spectrum due to proximity of the C-9 resonance. Observed as a double triplet in the uncoupled spectrum.

[d] δ = 17.7 (CH_3).

[e] δ = 14.2 (CH_3); 23.3 (CH_2).

[f] δ = 35.6 (CH_2); 128.4 (C-3′, C-5′);[b] 128.7 (C-2′, C-6′); 129.1 (C-4′); 139.8 (C-1′).

[g] δ = 81.3 (COH); 127.3 (C-2′, C-6′); 127.4 (C-4′); 127.9 (C-3′, C-5′);[b] 145.7 (C-1′).

[h] δ = 128.3 (C-3′, C-5′);[b] 129.2 (C-2′, C-6′); 131.6 (C-4′); 197.8 (CO).

[i] δ = 53.1 (CH_2N); 64.7 (CH_2CO); 66.1 (CH_2O); 200.1 (CO).

[j] δ = 169.5 (CO_2H).

[k] δ = 20.9 (CH_3); 127.0, 130.2 (C-2′, 3′, 5′, 6′); 137.6, 140.1 (C-1′, C-4′).

[l] Methyl ester of **4i**: δ = 52.3 (CH_3); 167.6 (CO).

1-Substituted Phenothiazines 4; General Procedure:

To a solution of phenothiazine (0.5 g, 2.5 mmol) in dry THF (35 mL), under argon and reduced lighting conditions, is added a 2.5 M hexane solution of *n*-BuLi (1.2 mL, 3 mmol) at −75 °C. The mixture is stirred until a yellow precipitate is formed and is then allowed to warm to room temperature when a clear yellow solution is obtained. After 30 min the solution is cooled at −78 °C and gaseous CO_2 is bubbled through the mixture for 5 min. The colorless solution obtained is allowed to warm to room temperature and the solvent is evacuated under reduced pressure. The pale yellow solid residue is redissolved in cold dry THF (30 mL), cooled to −75 °C, and a 1.7 M pentane solution of *t*-BuLi (2.5 mL, 4.25 mmol) is added dropwise. The yellow-brown solution is then allowed to warm to −20 °C and maintained at this temperature for 90 min. It is then cooled to −78 °C, the electrophile (4.25 mmol) is added, and the solution is stirred for a further 90 min at −20 °C. The mixture is poured into water (50 mL), acidified with 1 N HCl, and extracted with EtOAc (3 × 50 mL). The combined organic extract is dried ($MgSO_4$), and the solvent is evaporated to give the crude product, which is purified by column chromatography on silica gel. The best solvents for chromatography are: hexane/EtOAc, 19:1 (**4b, 4c, 4f, 4g, 4j**); hexane/EtOAc, 50:1 (**4d**); benzene/CH_2Cl_2, 2:1 (**4k**); benzene/CH_2Cl_2 5:1 (**4e**); and hexane/benzene, 2:1 (**4l**).

The above general work-up procedure is modified for compounds **4h** and **4i**. In the first case the acidic solution is first neutralized with 1 N Na_2CO_3 solution before extraction with EtOAc and purification by chromatography (benzene/EtOAc, 1:10). In the second case the reaction solvent is removed under vacuum and the product is extracted into water with 0.1 N ammonia solution (100 mL). After filtration to remove unreacted phenothiazine the solution is acidified with 1 N HCl to give a precipitate, which is collected, dried, and recrystallized from MeOH.

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