DIRECTED SYNTHESIS OF 1-SUBSTITUTED PHENOXAZINES[1]

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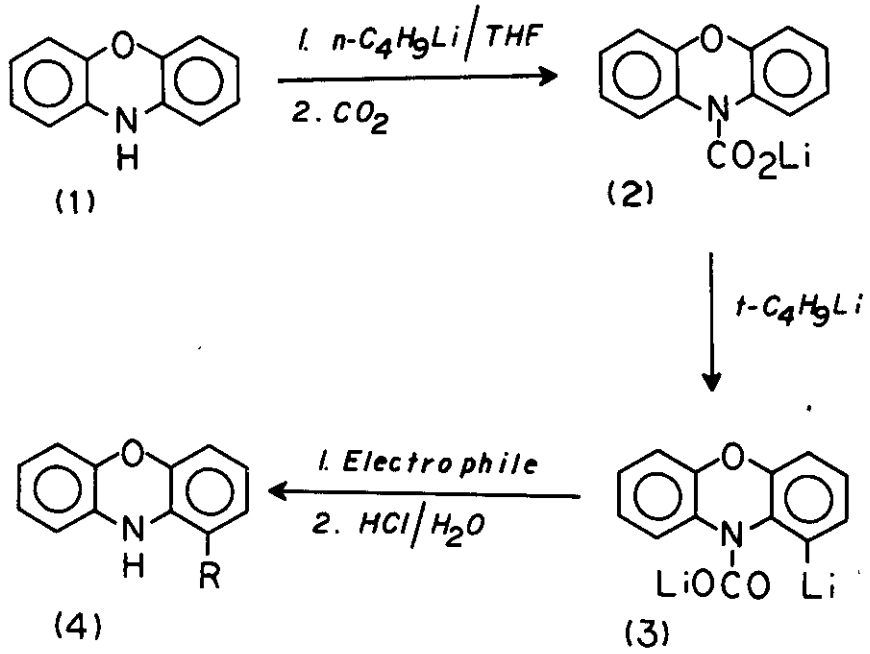
Abstract - Phenoxazine protected as its N-lithiocarbamate undergoes lithiation exclusively at the C-1 carbon atom. Reaction of the lithiated species with a variety of electrophiles readily produces several new 1-substituted phenoxazines, as well as two known compounds in superior yield to those of existing methods.

Although several synthetic routes to phenoxazines have been reported,[2-5] the yields are frequently mediocre, and the methods are often not generally applicable for the preparation of a wide variety of derivatives. An example of such a method is the direct lithiation of phenoxazine, which occurs in much lower yield than that of the analogous phenothiazine. Thus, Gilman and Moore[5] obtained only a 5% (purified) yield of the 1-carboxylic acid after sequential treatment of phenoxazine 1 with n-butyllithium and carbon dioxide, compared with a 52% yield of the phenothiazine-1-carboxylic acid obtained under the same conditions.[6] The original workers assigned the structure of their product as the 4-acid,[5] but later workers showed by unequivocal synthesis that it was actually the 1-acid **4a**.[7]

We have recently shown[8] that improved yields can be obtained in the lithiation of phenothiazine if the N-H group is first protected by conversion to the N-lithiocarbamate; we have now extended this work to phenoxazine and wish to report that not only is the lithiation of phenoxazine much improved over the earlier method, but that the yields of 1-substituted phenoxazines obtained are now fully comparable with those achieved from phenothiazine under the similar conditions.

The procedure that we followed now for the lithiation of phenoxazine and previously[8] for phenothiazine, is simillar to that first developed for indole.[9] It involves initial treatment of the N-H heterocycle with n-butyllithium to form the N-lithio anion, addition of carbon dioxide gas gives the N-lithio carbamate (cf. 2), which is then further lithiated with tert-butyllithium. Addition of an electrophile followed by acidic workup leads finally to the desired product.



(1) (2) (3) (4)

(for designation of R
see Table 1)

In the case of phenoxazine, C-lithiation occurred exclusively at the C-1 carbon to give 3 and no evidence of any dilithiation was seen. Addition of a range of electrophiles gave the products listed in Table 1. Several of the reaction products were found to be light sensitive, so all steps were performed as much as possible in the absence of light. In all cases, except in the deuteration to give **4b**, some unreacted phenoxazine was recovered. The 65% yield

achieved for the synthesis of phenoxazine-1-carboxylic acid **4a** is not only much greater than the 5% yield obtained from direct lithiation,[5] but it is also significantly greater than the alternative four step[7] procedure which gave a 44% overall yield. In the case of phenoxazine-1-aldehyde **4g** our system gave superior yield (75%) than that of the earlier method (65%)in a multi-step synthesis.[12] When benzaldehyde was used as the electrophile, instead of the expected α-hydroxybenzyl derivative (**4**, R = C_6H_5-CHOH), the analogous aryl ketone **4d** was obtained; monitoring by TLC showed that the α-hydroxybenzyl derivative was in fact initially formed, but that it underwent rapid aerial oxidation on replacement of the argon atmosphere of the lithiation reaction by air on work-up.

Table 1. 1-Substituted phenoxazines (4) Prepared.

Cpd	Electrophile	R	Yield[a] [%]	mp[°C]	recryst.	lit. mp [°C]	lit. ref.
4a	CO_2	-CO_2H	65	247-249	methanol	247-248	7
4b	D_2O	-D	100[b]	156-158	benzene	c	
4c	C_4H_9I	-C_4H_9	70	oil		d	
4d	PhCHO	-COPh	50	134-135	ethanol		
4e	Ph_2C=O	-C(OH)Ph_2	68[A]	182-184	ethanol	d	
4f	$PhCO_2C_2H_5$	-COPh	78	134-135	ethanol	e	
4g	$(CH_3)_2NCHO$	-CHO	75	111-112	ethanol	106-110°C	12
4h	Cl_3C-CCl_3	-Cl	85	84-85	methanol	f	

[a] Yield of isolated pure product.

[b] Material 80% deuterated by ^{1}H- and ^{13}C-nmr spectroscopy.

[c] Phenoxazine: lit.[10] mp 149-153°C.

[d] Product unstable; characterized by ^{1}H- and ^{13}C-nmr analysis.

[e] Found C,78.90; H,4.01; N,4.72. $C_{19}H_{13}NO_2$ requires C, 79.43; H, 4.56; N, 4.78.

[f] Found C, 66.09; H, 3.44; N, 6.27. $C_{12}H_8ClNO$ requires C, 66.22; H, 3.70; N, 6.43.

Table 2. ^{1}H-Nmr Data of Compounds 4a-4h (d^{6}-DMSO)

Cpd	δ[ppm]
4a	6.57-6.83 (m, 6 H), 7.34 (dd, 1 H), 8.96 (s, 1 H, N-H)
4b	6.40-6.80 (m, 7 H), 8.15 (s 1 H, N-H)
4c	0.92 (t, 3 H), 1.46 (m, 4 H), 2.44 (t, 2 H), 6.40-6.80 (m, 7 H), 7.41 (s, 1 H, N-H)
4e	5.95 (d, 1 H), 6.25 (d, 1 H), 6.40-6.70 (m, 5 H), 7.15-7.40 (m, 11 H)
4f	6.50-6.90 (m, 7 H), 7.45-7.68 (m, 5 H), 9.08 (s, 1 H, N-H)
4g	6.50-6.85 (m, 6 H), 7.18 (d, 1 H), 9.08 (s, 1 H, N-H), 9.78 (s, 1 H)
4h	6.57-6.60 (m, 4 H), 6.65-6.90 (m, 3 H), 7.90 (s, 1 H, N-H)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope, and are uncorrected. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a Varian XL200 (FT mode) spectrometer. Elemental analyses were performed under the supervision of Dr. R.W. King of this Department. Phenoxazine (Mp 155-156°C) lit.[10] Mp 149-153°C was prepared in 25% yield from 2-aminophenol by the procedure of Gilman and Moore,[10] and recrystallized from benzene prior to use.

1-Substituted Phenoxazines (4); General Procedure:

To a solution of phenoxazine (0.5 g, 2.73 mmol) in dry tetrahydrofuran (30 ml), under argon was added n-butyllithium (2.5 M in hexane, 1.2 ml, 3 mmol) at -75°C. The mixture was stirred until a vivid yellow precipitate formed (ca. 10 min) and was then allowed to warm to room temperature. After 20 min the yellow solution was again cooled to -78°C and carbon dioxide gas was bubbled in for 10 min. The colorless solution which was obtained was then allowed to warm to room temperature where the solvent was evacuated under reduced presure. The solid residue was redissolved in cold dry tetrahydrofuran (30 ml), cooled to -75°C, and tert-butyllithium (1.7 M in pentane, 2.00 ml, 3.4 mmol) was added dropwise. The orange-brown solution was then allowed to warm to -15°C and maintained there for 90 min. It was then cooled to -78°C, the electrophile (3.4 mmol) was added, and after 2h at that temperature, the solution was gradually warmed to room-temperature over a period of 12 h. The reaction mixture was poured into ethyl acetate (3x50 ml). The combined organic extracts were dried over magnesium sulfate, and the solvent was evaporated to give the crude product which was purified by column chromatography on silica gel. The best solvents for chromatography were: hexane-ethyl acetate 10:1 for (**4g**), 20:1 for (**4f**, **4h**), and 100:3 for (**4e**) and pure hexane for (**4c**).

The ^{1}H 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 11, show that the addition of the substituent causes an upfield shift for the C-10a carbon resonance and downfield shifts for the C-5a, C-7, C-9 and C-9a. 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 obtained unequivocally from the uncoupled spectra due to the absence of long rangAe (meta-hydrogen) coupling. Similar chemical shifts were observed[8] for 1-phenothiazine derivatives.

Table 3. ^{13}C-Nmr Data of Phenoxazine Carbons (d^6-DMSO)

Com-	Carbon Atom δ [ppm]											
pound	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a
1[a]	113.1	123.7	120.1	114.9	142.7	142.7	114.9	120.1	123.7	113.1	132.3	132.3
4a[b]	111.3	125.2	118.9[c]	118.6	142.6	143.5	114.9	121.8	124.0	114.6	135.6	129.9
4b	112.8[d]	123.7	120.2[c]	114.9	142.7	142.7	114.9	120.2	123.8	113.2	132.3	132.2
4c[e]	126.1	124.2	119.7[c]	112.8	142.7	142.7	114.5	120.3	123.4	114.0	132.4	129.6
4e[f]	127.5	124.4	118.8[c]	114.6	143.8	142.4	114.9	120.8	123.8	113.5	131.4	130.4
4f[g]	118.5	127.3	118.6[c]	118.6	143.7	143.0	114.9	122.1	124.0	115.0	135.1	129.0
4g[h]	118.4	128.6	119.4[c]	119.2	143.1	143.0	115.1	122.5	124.0	115.1	134.5	129.2
4h	116.6	123.9	120.2[c]	113.7	142.4	143.7	114.8	121.2	124.0	114.7	131.0	129.6

[a] Literature assignments.[11]

[b] δ 168.7 (CO_2H).

[c] Unequivocally assigned due to absence of $^{3}J_{CH}$ coupling component.

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

[e] δ 13.8, 21.8, 29.0 and 31.0 (n-But).

[f] δ 81.6 (COH), 127.1 (C-4′), 127.4 (C-2′ and C-6′), 127.7 (C-3′ and C-5′)[c] and 145.6 (c-1′).

[g] δ 128.3 (C-3′ and C-5′)[c], 128.9 (C-2′ and C-6′), 131.5 (C-4′), 138.5 (C-1′) and 196.8(CO).

[h] δ 193.6 (CO)

An exception to the above procedure occurred with phenoxazine-1-carboxylic acid where the solvent was removed under vacuum and the product extracted into water with dilute NH_4OH. After filtration to remove unreacted phenoxazine the solution was acidified with 1 N HCl to give the acid which was collected, dried and recrystallized from methanol.

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