Synthesis of 3,7-Disubstituted 10-Methylphenothiazines

Søren Ebdrup
Novo Nordisk A/S, Novo Nordisk Park, D9, DK-2760 Måløv, Denmark
Fax +45(44)434742; E-mail: sebd@novo.dk.

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Abstract: Lithiation at the C-3 and C-7 positions of *N*-methylphenothiazine (**1**) can be achieved by halogen metal exchange reaction starting from 3,7-dibromo-10-methylphenothiazine **(2)**. Reaction of the lithiated species with carbon, sulfur and silicon electrophiles results in new 3,7-disubstituted 10-methylphenothiazines **4a–g**. The described procedure gives high yield and an easy excess to important enzyme mediators.

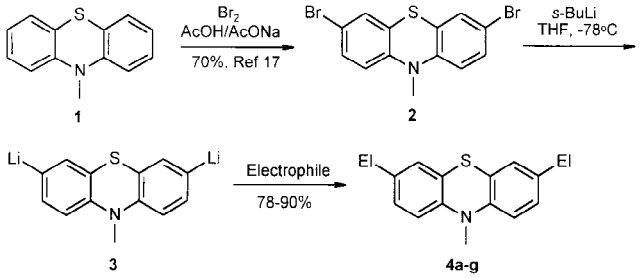
Key words: 10-methylphenothiazine, dilithiation, 3,7-disubstituted 10-methylphenothiazines

10-Substituted phenothiazine derivatives can be used to reversibly mediate the reaction of different oxidative enzymes like peroxidases[1,2] and laccases[3] by radical formation. The concept is well suited for important industrial applications such as, *e.g.* dye transfer inhibition during wash, denim bleaching, waste water purification and as glucose sensors.[1–4] The radicals are capable of forming oligomers (waste reaction) by carbon–carbon bond formation (*ortho* and *para* positions are reactive).[5]

N-H and *N*-alkylphenothiazines can be metalated at different positions. A C-1 anion of phenothiazine can be generated by in situ protection of the N-10 position followed by deprotonation with *t*-BuLi.[6] Reaction of phenothiazine with 2 equivalents of BuLi gives access to a C-1 and N-10 doubly lithiated species.[7–9] 10-Alkylphenothiazines can be lithiated at C-4 with BuLi[8,10] or preferably with *s*-BuLi/TMEDA.[11] Metalation at C-3 can be accomplished under Grignard conditions from 3-iodo-10-ethylphenothiazine[10] or from 3-bromo-10-ethylphenothiazine[12] both in moderate yield. Different substituted phenothiazine derivatives can also be formed from substituted diphenylamines by cyclization with sulfur,[13,14] or from phenothiazine by electrophilic aromatic substitution.[14,15]

The aim of this work was to investigate the possibilities of introducing different substituents into both the C-3 and C-7 position of 10-alkylphenothiazine in one step (3,7-dibromo-10-methylphenothiazine **2** used as an example) by a double bromine-lithium exchange reaction.

Phenothiazine was alkylated to give 10-methylphenothiazine **(1)**[10,16] which was brominated with bromine to give 3,7-dibromo-10-methylphenothiazine **(2)**.[17] Halogen-metal exchange in **2** and subsequent reaction with methyl iodide was investigated under different conditions (Scheme, Table 1). As can be seen from Table 1 the yield of 3,7,10-trimethylphenothiazine **(4b)** is in the same range when BuLi (89%), *s*-BuLi (92%) or *t*-BuLi (92%) was used for experiments performed at room temperature in diethyl ether (Entries 1–3). By comparing Entries 4 and 5 it can be concluded that changing the solvent to THF and reducing the temperature to –78 °C increases the yield of **4b** to 97–98% (BuLi and *s*-BuLi). In all experiments, formation of byproducts was observed. GC/MS of a representative crude reaction mixture indicated that the main by-products were 3,10-dimethylphenothiazine **(5)** and 10-methyl-phenothiazine **(1)**. No byproducts formed as a result of a rearrangement of the C-3 lithium anion to the more stable C-4 anion[8,10,11] were detected.



El: **4a:** D, **4b:** Me, **4c:** SMe, **4d:** CHO, **4e:** CO_2H, **4f:** CHOHBu^t, **4g:** $SiMe_3$

Scheme

Table 1. Optimization of the Conditions for the BuLi/Br Exchange Reaction of **2** and Subsequent Reaction with Methyl Iodide

Entry	Base	Temp (°C)	Products (%)[a]		
			4b	**1**	**5**
1	BuLi	20	89	11	1
2	*s*-BuLi	20	92	5	4
3	*t*-BuLi	20	92	3	5
4	BuLi	–78	97	2	0.2
5	*s*-BuLi	–78	98	2	0.3

[a] Product distribution based on GC data.

Based on the results in Table 1 it can be concluded that the optimal reaction condition is to apply 4 equivalents of *s*-BuLi in THF at –78 °C followed by addition of an electrophile after 0.5 hour. The resulting different 3,7-disubstituted 10-methylphenothiazines can be prepared in high yields (78–90%) by this procedure (Scheme and Table 2). The same procedure can also be applied for the syntheses of other C-3 and -7 disubstituted 10-alkylphenothiazines.[5]

The site of substitution was confirmed to be C-3 and C-7 based on recorded spectroscopic data, literature data[11,18] and comparisons with the assignment of **4g**. Unambiguous signals were assigned via a 2D heterocorrelated HSQC, a long-range HMBC (optimized for 7 Hz) and a NOE spectra (details in experimental part). The coupling constants measured for the ^{1}H NMR spectra (Table 3) demonstrate a symmetric *meta* or *para* substitution pattern. The ^{13}C NMR data (Table 4) show the absence of protonated carbon atoms at about δ =122 and the appear-

Table 2. Preparation of 3,7-Disubstituted Phenothiazines **4a–g**

Product[a]	Electrophile	El	Yield (%)	mp (°C)[b]
4a[c]	D_2O	D	88	94–95
4b	MeI	Me	89	77–77.5[d]
4c	Me_2S_2	SMe	85	125–125.5
4d	DMF	CHO	88	196.5–197[e]
4e	CO_2	CO_2H	90	310 (dec)
4f	*t*-BuCHO	$CH(OH)Bu^t$	85	153.5–154
4g	Me_3SiCl	$SiMe_3$	78	128.5–129

[a] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.20, N ± 0.30, S ± 0.20. Compounds **4e** and **4f** contained 0.25 and 0.5 equiv of occluded H_2O.
[b] Uncorrected; recrystallized from EtOH. Compounds **4a–c**, **f**, **g** are colorless to light yellow crystals, **4d**, **e** are yellow crystals.
[c] Material 97% deuterated as shown by ^1H NMR analysis.
[d] Lit.[19] mp 81 °C.
[e] Lit.[20] mp 202–203 °C, Lit.[21] mp 204 °C.

ance of nonprotonated carbons at δ = 122–136 (C-3 and C-7). The melting point of 3,7,10-trimethylphenothiazine **(4b)** corresponded to that reported[19] for **4b** synthesized by Friedel–Crafts formylation of the not readily available **5** followed by Wolf–Kishner reduction. The melting point of 10-methylphenothiazine-3,7-dicarboxaldehyde **(4d)** was in agreement with that reported[20] for **4d** synthesized in 3.5% yield by Vilsmeier formylation of **1** and in a 86% yield by a two step procedure[21] via a bisimidazoline derivative from **1**. Compounds **4b** and **4d** have not yet been characterized in the literature.

All reactions involving air-sensitive reagents were performed under N_2 or Ar using syringe-septum cap techniques. The glassware was flame dried prior to use. $MgSO_4$ was used for drying the organic solvents and the solvents were evaporated under reduced pressure. Melting points are uncorrected. The ^1H NMR spectra were recorded on a 400 MHz instrument using TMS as internal standard. The ^{13}C NMR spectra were recorded at 100 MHz using $CDCl_3$ (76.90 ppm) or DMSO-d_6 (39.60 ppm) as internal standards. Coupling constants (*J*) are given in Hz. Flash chromatography[22] was performed using silica gel Merck 60 size 40–63 μm. THF was dried by distillation from sodium/benzophenone ketyl. Phenothiazine was obtained from Hoechst. Trimethylacetaldehyde was distilled prior to use.

Compound **1** was prepared with a slight modification of the published procedure:[10,16] A mixture of phenothiazine (18 g, 90 mmol), MeOH (8 mL) and MeI (7 mL, 110 mmol) was heated in a glass screw cap vessel[23] for 18 h at 105°C. Standard workup gave **1** (32.6 g, 79%), mp 99–100°C (EtOAc/EtOH); (Lit.[16] mp 102–104 °C). 3,7-Dibromo-10-methylphenothiazine (**2**) was prepared with slight modification of the published method[17] by changing the solvent sytem to AcOH/AcONa; mp 146–147 °C (EtOAc/EtOH) (Lit.[24] mp 151–152 °C). BuLi, *s*-BuLi and *t*-BuLi were titrated[25] prior to use.

Bromine-Lithium Exchange Reaction of 3,7-Dibromo-10-methylphenothiazine (2):

Compound **2** (1.0 g, 2.7 mmol) was dissolved in Et_2O (100 mL) or THF (20 mL) under an atmosphere of N_2. The base BuLi, *s*-BuLi or *t*-BuLi (11 mmol, 1.4 M solution in hexane, 1.3 M solution in cyclohexane and 1.5 M solution in pentane, respectively) was added slowly at r.t. or at –78°C and the mixture was stirred for 30 min. The electrophile was added slowly and the mixture stirred for 4 h or for 1 h at –78 °C followed by warming to r.t. and stirring for 4 h. After evaporation of the solvent, CH_2Cl_2 (30 mL) and H_2O (25 mL) were added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried and evaporated to dryness to give the crude product. The composition of the crude mixtures were analyzed by GC (Table 1).

3,7-Disubstituted 10-Methylphenothiazines 4a–g; General Procedure:

Compound **2** (1.0 g, 2.7 mmol) was dissolved in anhyd THF (20 mL) under an atmosphere of N_2. *s*-BuLi (7.7 mL of a 1.4 M solution in hexane, 11 mmol) was added slowly at –78 °C and the mixture (suspension) stirred for 30 min, followed by addition of an electrophile (12 mmol) and stirring for 1 h. The mixture was allowed to warm to r.t. followed by stirring for an additional 4 h. The mixture was poured into satd NH_4Cl solution (30 mL), the phases were separated and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic phases were dried and evaporated to give the crude product. Purification was performed by flash chromatography for **4a, 4f** and **4g** using the following eluents: EtOAc/heptane (1:8) (**4a**); EtOAc/heptane (1:6 → 1:4) (**4f**); heptane → EtOAc/heptane (1:4) (**4g**). Compounds **4b** and **4c** were recrystallized from EtOH and **4d** and **4e** were suspended in EtOH and filtered. *Spectroscopic data for* **4g**: Long range HMBC, optimized for 6 Hz: C-10a with *N*CH_3, H-2 and H-4; C-2 with H-4; C-3 with $Si(CH_3)_3$, and H-2; C-4 with H-2 and C-4a with H-1. NOE: *N*CH_3 with H-1 and H-1 with H-2.

The above general procedure was modified for three of the compounds. For **4d** the reaction mixture was warmed to 0 °C, poured into HCl (4.5% w/v; 170 mL) and stirred for an additional 30 min (suspension of yellow crystals). The Et_2O phase was separated and the aqueous phase extracted with CH_2Cl_2 (5 x 75 mL). The organic phase was dried and evaporated to give the crude product. For **4f** the reaction mixture was allowed to warm to r.t. and poured into HCl (5% w/v; 50 mL) instead of satd NH_4Cl solution. For **4e** the lithiated intermediate **3** was poured into solid CO_2 (40 g) in Et_2O (40 mL). When the CO_2 had evaporated, aq NaOH (8% w/v; 100 mL) was added and the two phases separated. The aqueous phase was washed with CH_2Cl_2 (3 × 50 mL), acidified with HCl (37% w/v) and the precipitated crude product was filtered. The aqueous phase was extracted with CH_2Cl_2

Table 3. ^1H NMR Data of Compounds **4a–g**[a,b]

Product	δ, *J* (Hz)			
	1-H, 9-H	2-H, 8-H	4-H, 6-H	NCH_3
4a	6.80 (d, 2H, *J* = 8.0)	7.15 (m, 2H, *J* = 8.0)	7.14 (m, 2H)	3.34 (s, 3H)
4b	6.67 (d, 2H, *J* = 8.5)	6.94 (dd, 2H, *J* = 2.0, 8.5)	6.95 (m, 2H)	3.31 (s, 3H)
4c	6.70 (d, 2H, *J* = 8.5)	7.10 (dd, 2H, *J* = 8.0, 2.0)	7.08 (d, 2H, *J* = 2.5)	3.31 (s, 3H)
4d	6.92 (d, 2H, *J* = 8.5)	7.68 (dd, 2H, *J* = 8.5, 2.0)	7.60 (d, 2H, *J* = 2.0)	3.49 (s, 3H)
4e	7.06 (d, 2H, *J* = 8.5)	7.79 (d, 2H, *J* = 8.5)	7.63 (s, 2H)	3.41 (s, 3H)
4f	6.74 (d, 2H, *J* = 8.5)	7.07–7.10 (m, 4H)		3.35 (s, 3H)
4g	6.79 (d, 2H, *J* = 8.0)	7.28 (dd, 2H, *J* = 8.0, 0.5)	7.25 (d, 2H, *J* = 1.0)	3.36 (s, 3H)

[a] Recorded in $CDCl_3$ except for **4e** which was recorded in DMSO-d_6. Assignment based on HSQC, HMBC and NOE spectra recorded for **4f**,[11,18] and the observed coupling constants.
[b] Additional peaks not listed in Table 3 are as follows. **4b**: 2.23 (s, 6H, ArCH_3); **4c**: 2.42 (s, 6H, SCH_3); **4d**: 9.83 (s, 2H, CHO); **4e**: 12.81 (br s, 1H, CO_2H); **4f:** 0.90 [s, 18H, $C(CH_3)_3$], 1.82 (br s, 2H, C*H*OH), 4.29 (s, 2H, ArCH); **4g**: 0.22 [s, 18H, $Si(CH_3)_3$].

Table 4. ^{13}C NMR Data of Compounds **1**, **2**, and **4a–g**[a,b]

Product	δ						
	C-1, C-9	C-2, C-8	C-3, C-7	C-4, C-6	C-4a, C-5a	C-9a, C-10a	NCH_3
1	113.9	127.0	122.3	127.3	123.2	145.7	35.1
2	115.2	129.3	124.7	130.2	114.8	144.4	35.3
4a	113.9	126.9*	122.0[c]	127.2*	123.2	145.7	35.1
4b	113.5	127.5*	131.6	127.7*	123.1	143.5	35.0
4c	114.2	126.7	131.2	127.5	123.7	143.7	35.2
4d	114.5	128.0	132.0	130.4	123.4	149.3	36.2
4e	114.9	127.7	121.5	129.8	125.5	148.1	35.9
4f	112.9	126.1*	136.4	126.6*	122.4	144.7	35.6
4g	113.5	132.5	133.6	131.9	122.7	146.1	35.0

[a] Recorded in $CDCl_3$ except for **4e** which was recorded in DMSO-d_6. Assignment based on HSQC, HMBC and NOE spectra recorded for **4f**.[11,18] Chemical shift values marked * may be interchangeable.

[b] Additional peaks not listed in Table 4 are as follows. **4b**: 20.2 (Ar*C*H_3); **4c**: 17.4 (SCH_3); **4d**: 189.8 (CHO); **4e**: 166.5 (CO_2H); **4f**: 25.8 [C(*C*$H_3)_3$], 35.2 [*C*$(CH_3)_3$], 81.6 (CHOH); **4g**: –1.2 [Si$(CH_3)_3$].

[c] (t, J = 98.5 Hz)

(3×50 mL), the crystals and the organic phases were combined and evaporated. The main characteristics of the synthesized compounds are presented in Tables 2–4.

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