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Metallation reactions XXVII.[☆] Metallation of (methylthio)anilines

M.G. Cabiddu, S. Cabiddu *, E. Cadoni, R. Cannas, S. De Montis, C. Fattuoni, S. Melis

Dipartimento di Scienze Chimiche, Complesso Universitario di Monserrato, SS 554 Bivio per Sestu, I-09042 Monserrato (CA), Italy

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Dedicated to Emeritus Professor Antonio Maccioni

Abstract

The metallation reactions of (methylthio)anilines with organolithium reagents and with the butyllithium–potassium *tert*-butoxide superbasic mixture are here described. The results show that the *para* isomer when treated with butyllithium gave a mixture of products with no selectivity. Using *tert*-butyllithium or superbases we obtained the substitution of the thiomethyl hydrogen. Moreover, superbase allowed to prepare the disubstituted product with the new groups in the thiomethyl and in *ortho* to this group. On the other side, both *ortho* and *meta* isomers were lithiated at the thiomethyl carbon by butyllithium and the other reagents. Starting from the unalkylated amine we prepared through three successive one-pot monometallations *N*,*N*-disubstituted amines with equal or different groups and bearing an alkylthio chain as long as wanted. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Metallation; Organolithium; Superbases; Thioethers; (Alkylthio)aminobenzenes

1. Introduction

In the last years the research on heteroatom promoted metallation has been developed to improve the synthesis of polysubstituted aromatics and heterocycles [2–9]. In our recent works we examined the behaviour of the thioether group as *ortho* directing group in metallation reactions and its competition with methoxy and trifluoromethyl group and fluorine atom [10–12]. Other works in literature examined the competition between the *N*,*N*-dimethylamino group and the alkoxy and trifluoromethyl group and fluorine atom when both linked at the same aromatic ring. The results show a stronger directing power of these last three functions [10,13].

On the other hand, there are only few reports on the competition between the amino and the thioether as directing groups in metallation reactions. In fact, there is a unique work by Gilman and Webb published in 1949 [14] describing the monometallation of *N*,*N*-dimethyl-4-(methylthio)aniline that gave, after treatment with carbon dioxide, an arylthioacetic acid in 22.4% yield and the starting compound in 52.1% yield.

In this work we examined the regiochemistry of the metallation of (methylthio)anilines using organolithium compounds and superbases.

2. Results and discussion

The starting compounds were reacted with different metallating reagents: butyllithium, *tert*-butyllithium, superbasic mixture obtained by mixing butyllithium and potassium *tert*-butoxide (LICKOR), in various working conditions. All metallated compounds were quenched with iodomethane and analysed by GC/MS.

The metallation reaction was first performed on the *N*,*N*-dimethyl-4-(methylthio)aniline (**1a**) (Scheme 1) using butyllithium and hexane as solvent at reflux. We

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* Corresponding author. Tel.: +39-070-6754387; fax: +39-070-6754388.

E-mail address: scabiddu@unica.it (S. Cabiddu).

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Table 1
Metallation of 1-dimethylamino-4-(methylthio)benzene (**1a**) [a]

RM (equivalents)	TMEDA (equivalents)	Solvent	T (°C)	t (min)	Starting material (%)	**2** (%)	**3** (%)	**4** (%)	**5** (%)	**6** (%)	**7** (%)	**8** (%)
BuLi (1)		Hexane	Reflux	60	100							
BuLi (1)	1	Hexane	20→40	60	67	15	12	6				
BuLi (2)	2	Hexane	20→40	60	13	27	12	9	24	12	3	
BuLi (1+1) [b]	2	Hexane	20→55	60	18	22	11	18	18	13		
BuLi (2+2) [b]	4	Hexane	20→55	60	10	27	8	12	30	13		
BuLi (4) [c]	4	Hexane	0→45	120	10	14	9	11	21	13	10	
t-BuLi (1)		THF	0→20	120	63		37					
t-BuLi (2)		THF	0→20	120	46		54					
LICKOR (1)		Hexane	−40→20	60	56		44					
LICKOR (2)		Hexane	−40→20	60	13		18	13	6	50		
LICKOR (3)		Hexane	−40→20	60	4		16		6	62		12

[a] The metallation products were quenched with iodomethane; the yields were determined by GC analyses; LICKOR = equimolar mixture of butyllithium and potassium *tert*-butoxide.

[b] The organolithium compound was injected in two subsequent times (the second after 15 min).

[c] The substrate was poured onto the organolithium compound.

recovered only the starting compound (Table 1). The second step was to introduce the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in equimolar amount as butyllithium. After quenching with iomethane the GC/MS analysis revealed three monometallation products **2**, **3** and **4** in the yield of 15, 12 and 6% derived by metallation in *ortho* to the dimethylamino group, in *alpha* at the thiomethyl group and in *ortho* to the sulphur atom, respectively. Using two moles of the same reagent, unreacted starting material was lowered (13%) and we obtained three monometallated products **2**, **3**, and **4** (in the yield of 27, 12 and 9%) and three bimetallated **5** (24%), **6** (12%) and **7** (3%)**:** **5** arises from metallation in *alpha* at the thiomethyl group and in *ortho* to the amino group; **6** from lithiation in *alpha* and *ortho* to the thiomethyl group; **7** from substitution in *ortho* to both dimethylamino and thiomethyl groups. When the reaction was performed using two molar equivalents of butyllithium, injecting one mole and after 15 min the second mole, we obtained five products (**2**, **3**, **4**, **5** and **6**) in the ratio of 27:13:22:22:16. The remaining starting material was 18%. We obtained analogous results injecting 2 moles and after 15 min another 2 moles.

At this point we changed the metallation procedure treating the organolithium dropwise with the substrate: we obtained products mixtures as before.

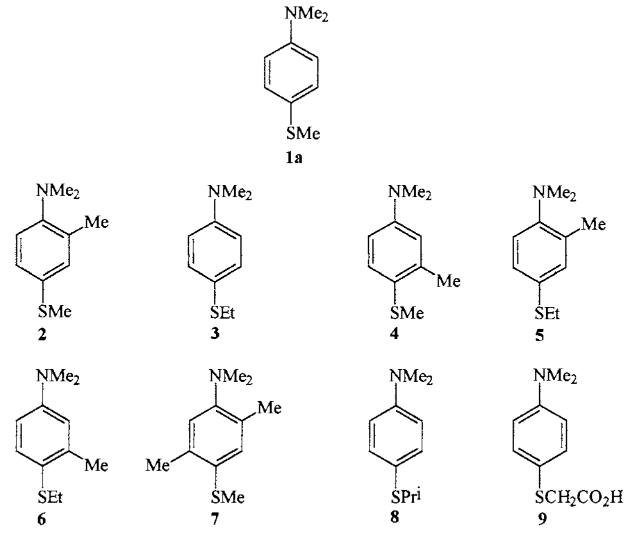
To improve selectivity we tested the more basic *tert*-butyllithium and we obtained only the monometallated product **3**: using one molar equivalent of *tert*-butyllithium we obtained 37% of **3**, while with two molar equivalents of the same reagent we found 54% of **3**. Analogous results were obtained using LICKOR as metallating reagent (see Table 1).

The *ortho* isomer **1b** gave analogous results (Scheme 2): using one molar equivalent of butyllithium and TMEDA we obtained only the monometallated product **10**, derived from lithiation at the thiomethyl carbon, in good yield (82%) (Table 2). Using two molar equivalents of butyllithium and TMEDA we obtained a mixture of three mono- **10** (54%), **11** (14%) and **12** (1%) and two bimetallated products **13** (4%) and **14** (2%). With 1 molar equivalent of *tert*-butyllithium we obtained only **10** (44%). Better results derived from the use of 1 or 2 molecular equivalents of LICKOR that gave only the monometallated **10** with good yield (81 and 89%, respectively). Increasing this organometallic (3 molar equivalents) to improve yield of monometallated **10**, we obtained a mixture of **10** (50%) and three bimetallated products **13** (4%), **14** (23%) and **15** (16%).

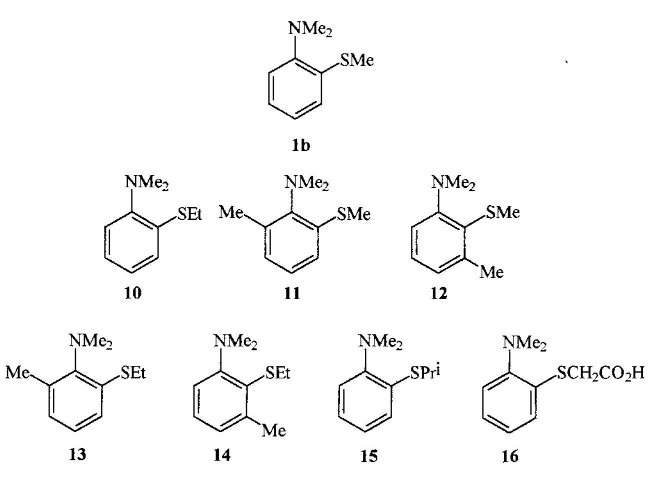
The metallation of the *meta* isomer **1c** using one molar equivalent of butyllithium, *tert*-butyllithium or superbasic reagent gave only the product **17**, derived by substitution in the *alpha* position of the thiomethyl group (Scheme 3), with yields of 67, 46 and 34%, respectively. Using four molar equivalents of butyllithium, injected in two subsequent times, we revealed four mono- **17** (37%), **18** (5%), **19** (3%), and **20** (5%) and three bimetallated products **21** (13%), **22** (9%) and **23** (10%) (Table 3). When **1c** was poured onto the same amount of reagent (four equivalents) we obtained three products: **17** (66%), **21** (7%) and **22** (8%). Analogously, to compounds **1a** and **1b**, even **1c** gave an α,α′-dilithiated product **24** (11%), when treated with three molar equivalents of superbase, beside **17** (65%) and **23** (12%).

In conclusion, these reactions can be used to functionalise the thiomethyl carbon, as proved by the attainment of carboxylic acids **9**, **16**, **25**. Starting from **1a** and LICKOR it is possible to prepare *ortho*,*alpha*-SMe-disubstituted products as proved by attainment of **6**.

Using the unsubstituted amine **26** as starting compound, it is possible to obtain *N*,*N*-disubstituted alkylthioamines with equal or different groups on N and S, through three subsequent one-pot metallations. This is proved by the attainment of 2-(butylthio)-*N*-ethyl-*N*-methylaniline (**29**) starting from 2-(methyltio)aniline (**26**) through a metallation/quenching with iodomethane, followed by a second metallation/quenching with iodoethane, and a third metallation/quenching with iodopropane (Scheme 4). This procedure allowed to prepare even compounds **10** and **30**. Moreover, a monometallation/electrophilic quenching followed by a bimetallation/electrophilic quenching allowed to introduce two equal and one different groups as showed by the formation of **31** and **32** (Scheme 4).



Scheme 1.



Scheme 2.

The results obtained on the *para* isomer **1a** show that the regioselectivity of the metallation is dependant on the structure of the substrate and of the organometallic (the lithiating power of butyllithium depending on the coordinating attitude of the substituents on the aromatic ring) and on the solvent [2]: when butyllithium–TMEDA–hexane is used the dimethylamino group is a better directing group than methylthio. In fact (see Table 1), the ratio *ortho*-NMe$_2$/*ortho*-SMe is between 51/21 and 40/31 for entries 2–5. These results can be explained by the complexation of butyllithium–TMEDA preferentially on nitrogen. These data allow to add new information to the study on the hierarchy of directing groups in metallation: since it was shown that the alkoxy is a stronger directing group than alkylthio and the dimethylamino [2,11], we can write this series for the directing power:

$$\mathrm{OMe} > \mathrm{NMe_2} > \mathrm{SMe}$$

On the other side, the metallation with one molar equivalent of more basic reagents as *tert*-butyllithium or superbases have place exclusively at the more acidic thiomethyl carbon. With more equivalents of superbase the ratio *ortho*-NMe$_2$/*ortho*-SMe is 6/63 and 6/62 for **1a** (see Table 1, entries 10 and 11), 4/23 for **1b** (see Table 2 entry 6), 0/12 for **1c** (see Table 3, entry 6). These results can be explained assuming that the determining factor is the acidity of hydrogens in the substrate [5,7,15].

The *ortho* isomer **1b**, on the contrary, was lithiated at the thiomethyl carbon even with one molar equivalent of butyllithium with good yield and selectivity. These results can be accounted for by the stabilization of the thiomethyl carbanion by the adjacent amino group (Fig. 1). Such an intermediate cannot be formed in **1a**.

The formation of products **8**, **15**, **24**, bearing the isopropylthio function, can be explained by a further attack of LICKOR on derivatives **3**, **10**, **17**, respectively [10].

The identification of all the products was performed by interpretation of the mass and NMR spectra or by comparison with authentic samples.

The product **2** was distinguished from its isomer **4** by their different retention times, **4** was prepared other way (see Section 3). Moreover, the mass spectrum of **4** shows the peaks at 121 and 122 more abundant than for **2**. The peak 122 is due to the loss of methyl and CS:

Table 2
Metallation of 1-dimethylamino-2-(methylthio)benzene (**1b**) [a]

RM (equivalents)	TMEDA (equivalents)	Solvent	*T* (°C)	*t* (min)	Starting material (%)	**10** (%)	**11** (%)	**12** (%)	**13** (%)	**14** (%)	**15** (%)
BuLi (1)	1	Hexane	20 → 40	45	18	82					
BuLi (1+1) [b]	2	Hexane	20 → 55	60	25	54	14	1	4	2	
t-BuLi (1)		THF	0 → 20	180	56	44					
LICKOR (1)		Hexane	−40 → −20	60	11	89					
LICKOR (2)		Hexane	−40 → −20	60	19	81					
LICKOR (3)		Hexane	−40 → −20	60	7	50			4	23	16

[a] The metallation products were quenched with iodomethane; the yields were determined by GC analyses; LICKOR = equimolar mixture of butyllithium and potassium *tert*-butoxide.

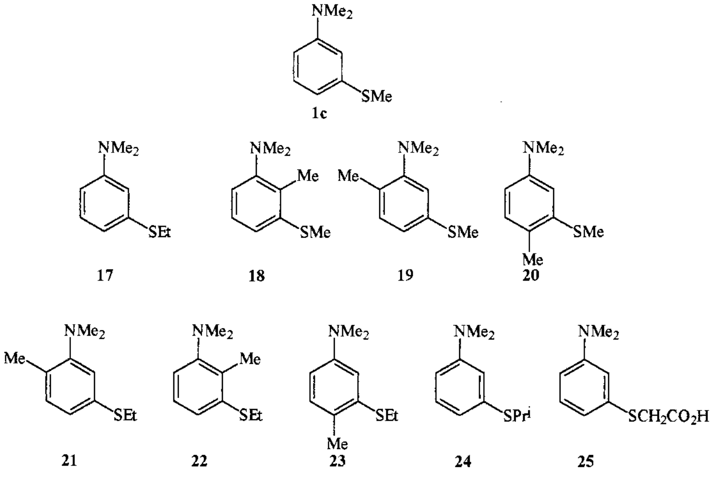
[b] The organolithium compound was injected in two subsequent times (the second after 15 min).

Table 3
Metallation of 1-dimethylamino-3-(methylthio)benzene (**1c**) [a]

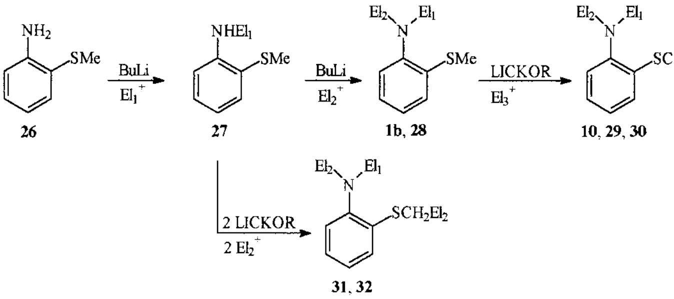
RM (equivalents)	TMEDA (equivalents)	Solvent	*T* (°C)	*t* (min)	Starting material (%)	**17** (%)	**18** (%)	**19** (%)	**20** (%)	**21** (%)	**22** (%)	**23** (%)	**24** (%)
BuLi (1)	1	Hexane	Reflux	150	33	67							
BuLi (4)	4	Hexane	0 → 30	120	19	66				7	8		
BuLi (2+2) [b]	4	Hexane	30	120	18	37	5	3	5	13	9	10	
t-BuLi (1)		THF	0 → 20	120	54	46							
LICKOR (1)		Hexane	−45	60	66	34							
LICKOR (3)		Hexane	−45	60	12	65						12	11

[a] The metallation products were quenched with iodomethane; the yields were determined by GC analyses; LICKOR = equimolar mixture of butyllithium and potassium *tert*-butoxide.

[b] The organolithium compound was injected in two subsequent times (the second after 15 min).



Scheme 3.



Scheme 4. **27**, $El_1 = Me$; **1b**, $El_1 = El_2 = Me$; **10**, $El_1 = El_2 = El_3 = Me$; **28**, $El_1 = Me$, $El_2 = Et$; **29**, $El_1 = Me$, $El_2 = Et$, $El_3 = Pr$; **30**, $El_1 = El_2 = Me$, $El_3 = Et$; **31**, $El_1 = Me$, $El_2 = Pr$; **32**, $El_1 = Me$, $El_2 = allyl$.

this fragmentation is favoured by a methyl group in *ortho* to the SR. The Scheme 5 shows that the structure derived from **4** is stabilized by the inductive effect of the *ortho* methyl (structure **4A**).

Thus, **4A** is more stable than **2A** and the CS bond in **4** has a greater double bond character and it is easier the elimination of CS [16,17]. Analogously we identified **5** and **6**: **6** was prepared other way and its MS spectrum shows the peak 122 due to the loss of ethyl and CS; this fragmentation is absent in **5**.

The structure of **7** was determined by its molecular ion ($m/e = 195$) and by the very abundant peak at $m/e = 180$ ($M^+ - CH_3$). The first datum indicates that **7** is a bisubstituted derivative, the second shows the presence of methylthio group: so the reaction leaded to substitution of two annular hydrogens by two methyl groups. We can easily exclude that these two methyls are both in *ortho* to the amino or to the thiomethyl group, because these substituents are not able to coordinate more than one metal atom at time (the first lithiation diminishing the effectiveness of these groups) [21]. It is also reasonable to exclude the possibility of two methyls in *ortho* one each other: this product should derive by a dicarbanion bearing two negative charges on neibouring carbons (this can not assure the minimization of charge repulsion between the two lithiums). The consequence is that these two groups are in *para* one each other, as already stated for other substrates [2,18,19,21,22].

For what concerns the products derived from the *ortho* isomer **1b**, compounds **11** and **12** were distinguished assuming these considerations: the peak at 180 ($M^+ - H$) is shown by **12** but not by **11**. The loss of a hydrogen atom is difficult (see methyl(methylthio)benzenes [23]) and can be observed only when other concurrent fragmentations are impossible (see *N*,*N*-dimethyltoluidines [20]). These compounds have a very high ($M^+ - H$) peak but in the *ortho* isomer it has a lower abundance than in the *meta*. **12** has a *meta* arrangement for the methyl and the amino group. Both compounds show the peak 148 due to the loss of SH: in **11** it has an abundance of 41.6, in **12** of 24.9. This fragmentation is favoured when the methyl group is in *meta* to the methylthio (compare to 2-methyl- and 3-methyl(methylthio)benzene [17]), while decreases in the *ortho* isomer, and even disappears in the 2,6-dimethyl(methylthio)benzene.

14 was distinguished from its isomer **13** because in **14** the loss of ethyl is greater than the loss of ethylene: this happens when the alkylthio group has a methyl in the *ortho* position (compare MS spectra of (ethylthio)methylbenzenes [23] and [12]). The product **15** was identified by the presence of the peak 153 due to the loss of an isopropyl group from the SR. If the isopropyl group would be bonded to the N we should observe a high peak due to the loss of methyl.

For what concerns the products derived from isomer **1c** we identified the compound **17** by the peaks 153 and 152 revealing the ethylthio moiety. It is noteworthy the abundance of the peak 148 ($M^+ - SH$) that is present in all compounds containing the ethylthio group. This fragmentation is favoured by the alkylated amino group in *meta* to the SC_2H_5 [17]. Compound **18** was distinguished from **19** and **20** by the higher intensity of the peak 166 ($M^+ - CH_3$): this is due to the greater steric hindrance; moreover it is useful the comparison with the MS spectra of 2-methyl(methylthio)benzene and *N*,*N*,2-trimethylaniline which show a peak ($M^+ - CH_3$) greater than their isomers. Compound **19** was distinguished from **20** by the greater intensity of the peak 150 ($M^+ - CH_3$–CH_4) whose relative intensity were 22.1 and 9.6, respectively: this can be explained by a primary loss of methyl from the methylthio group followed by elimination of CH_4 between $N(CH_3)_2$ and the methyl in *ortho* to this group [23].

The peak 120, due to the loss of methyl and CH_2S, is more abundant in **19** than in **20**: this fragmentation leads for **19** to an ion stabilized by inductive effect by the *ortho* methyl, while a such stabilization is impossible for **20**.

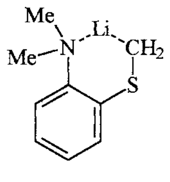
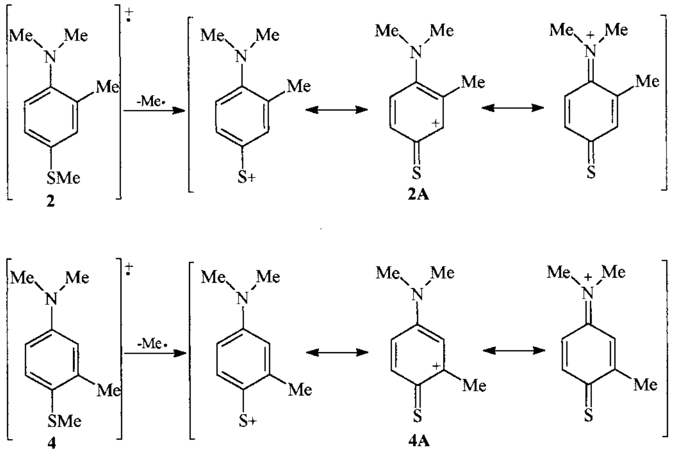


Fig. 1.



Scheme 5.

Compounds **22** and **23** bear a methyl in *ortho* to the ethylthio group because the fragment 166 ($M^+ - C_2H_5$) is more abundant than 167 ($M^+ - C_2H_4$) [12,20]. In the compound **21** the peak 167 is more abundant than 166. We assigned to the compound **22** the structure with the methyl in *ortho* to the amino group by the occurrence of the peak 180 ($M^+ - CH_3$) that is absent in **23** (Scheme 6): this in analogy with the MS spectra of *N*,*N*-dimethyltoluidines that show a greater loss of methyl for the *ortho* isomer.

3. Experimental

3.1. General

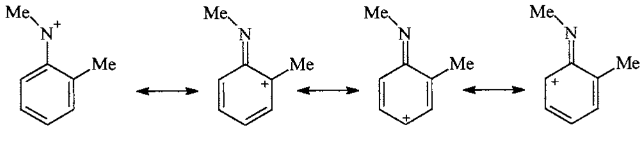
^{1}H-NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a Perkin–Elmer 1310 grating spectrophotometer. The GC-MS analyses were performed with a Hewlett Packard 5989A GC-MS system with HP 5890 GC fitted with a capillary column (50 m × 0.2 mm) packed with DH 50.2 Petrocol (0.50 m film thickness). All flash chromatography was on silica G60 (Merck) columns. Microanalyses were carried out with a Carlo Erba 1106 elemental analyser. Melting points were obtained on a Kofler hot stage microscope and are uncorrected.

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane and *tert*-butyllithium in pentane were obtained from Aldrich Chemical Company and were analysed by the Gilman double titration method before use [21]. 1-(Methylthio)-2-(methylthio) and 3-(methylthio)aniline were purchased (Aldrich).

3.2. Starting materials

3.2.1. N,N-Dimethyl-4-(methylthio)aniline (*1a*)

A solution of 4-(methylthio)aniline (72 mmol) in dry tetrahydrofuran (100 ml) was blanketed with dry argon and then treated dropwise at −10°C with a 1.2 M solution of butyllithium in hexane (79 mmol). When the addition was complete the mixture was stirred for ca. 30′ at 20°C, cooled at −10°C and then treated with iodomethane (79 mmol). The resulting solution was successively treated dropwise with a 1.2 M solution of butyllithium in hexane (79 mmol) and with iodomethane (79 mmol). The mixture was then kept 12 h at the same temperature with stirring, then poured into water (250 ml) and the pH adjusted to 5–6 by addition of 5% hydrochloric acid. The organic layer was separated, the aqueous layer extracted with diethyl



Scheme 6.

ether, and the combined organic solutions were dried (Na_2SO_4) and concentrated. Yield 78%. Pale yellow oil; b.p. 80–82°C/0.3 mmHg; ^{1}H-NMR ($CDCl_3$): δ 2.30 (s, 3H, SCH_3), 2.83 (s, 6H, NCH_3), 6.56 (d, 2H, H-2 and H-6), 7.16 (d, 2H, H-3 and, H-5). ^{13}C-NMR ($CDCl_3$): δ 17.51, 41.83, 116.57, 130.15,140.43, 150.07. EI-MS: $m/e = 167$ (M^+, 67.2), 152 ($M^+ - CH_3$, 100.0), 136 ($M^+ - CH_3$–CH_4, 14.7), 108 ($C_6H_4S^+$, 10.1), 77 ($C_6H_5^+$, 6.5), 65 ($C_5H_5^+$, 6.8). This compound was also identified by comparison with an authentic sample [22].

3.2.2. *N,N-Dimethyl-2-(methylthio)aniline* (***1b***)

Obtained as above described starting from 2-(methylthio)aniline. Yield 82%. Pale yellow oil; b.p. 91–93°C/0.3 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 2.20 (s, 3H, SCH_3), 2.52 (s, 6H, NCH_3), 6.87 (m, 4H, Ar–H); ^{13}C-NMR ($CDCl_3$) δ: 17.54, 42.03, 112.61, 114.56, 122.02, 123.98, 131.03, 141.55. EI-MS: $m/e = 167$ (100%, M^+), 166 (8.6%, $M^+ - H$), 152 (51.7%, $M^+ - CH_3$), 151 (20.7%, $M^+ - CH_4$), 150 (32.7%, $M^+ - CH_4$–H), 137 (37.9%, $M^+ - C_2H_6$), 136 (31.0%, $M^+ - C_2H_6$–H), 134 (24.1%, $M^+ - SH$), 118 (20.0%, $M^+ - CH_3$–H_2S), 109 (19%, $C_6H_5S^+$), 91 (20.7%, $C_7H_7^+$), 77 (13.7%, $C_6H_5^+$), 65 (10.6%, $C_5H_5^+$). This compound was also identified by comparison with an authentic sample [23].

3.2.3. *N,N-Dimethyl-3-(methylthio)aniline* (***1c***)

Obtained as above described starting from 3-(methylthio)aniline. Yield 76%. Pale yellow oil; b.p. 86–88°C/0.3 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 2.36 (s, 3H, SCH_3), 2.82 (s, 6H, NCH_3), 6.65 (m, 4H, Ar–H); ^{13}C-NMR ($CDCl_3$) δ: 16.05, 41.81, 114. 54, 119.20, 126.01, 140.02, 141.74, 151.04. EI-MS: $m/e = 167$ (100%, M^+), 166 (68.8%, $M^+ - H$), 151 (21.3%, $M^+ - H$–CH_3), 134 (26.2%, $M^+ - SH$), 108 (13.1%, $C_6H_4S^+$), 91 (6.5%, $C_7H_7^+$), 77 (6.9%, $C_6H_5^+$), 65 (7.1%, $C_5H_5^+$). This compound was also identified by comparison with an authentic sample [24].

3.3. *Authentic samples*

N,N-Dimethyl-2-(ethylthio)aniline (**10**) was prepared by a published method [23].

3.3.1. *4-(Methylthio)-N,N,3-trimethylaniline* (***4***)

This product was prepared starting from 3-methyl-4-(methylthio)aniline [25] following the method used to prepare **1a**. The crude product was purified by flash-chromatography with light petroleum as eluent. Yield 79%. Pale yellow oil; b.p. 115–117/1.5 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 2.03 (s, 3H, Ar–CH_3), 2, 51 (s, 3H SCH_3), 2.97 (s, 6H, NCH_3), 6.35 (m, 2H, H-3 and H-5), 7.70 (m, 1H, H-6);^{13}C-NMR ($CDCl_3$) δ: 15.95, 21.5, 39.91, 114.09, 115.08, 130.01, 130.63, 142.02, 148.03. EI-MS: $m/e = 181$ (93.5%, M^+), 166 (100%, $M^+ - CH_3$), 151 (11.3%, $M^+ - CH_3$–CH_3), 150 (16.7%, $M^+ - CH_3$–CH_4), 122 (19.3%, $M^+ - CH_3$–CS), 121 (22.2%, $M^+ - CH_3$–CS–H), 120 (11.6%, $M^+ - CH_3$–CS–2H), 91 (12.9%, $C_7H_7^+$), 65 (4.8%, $C_5H_5^+$), 45 (5.9%, CHS^+). This compound was also identified by comparison with an authentic sample [25].

3.3.2. *4-(Ethylthio)-N,N,3-trimethylaniline* (***6***)

A suspension of 4-nitro-2-methylaniline (33 mmol), water (60 ml) and concentrated hydrochloric acid (80 ml) was diazotized at 0–5°C with an aqueous solution of sodium nitrite (36 mmol). The resulting mixture was added on a solution of potassium ethyl xanthogenate (69 mmol) in ethanol (30 ml) keeping the reaction at 70–80°C. When the addition was complete the mixture was stirred for ca.1 h at the same temperature. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic solutions were concentrated. The residue was refluxed 6 h with a solution of potassium hydroxide (118 mmol) in ethanol (20 ml) and then treated with diethylsulphate (33 mmol). When the addition was complete, the mixture was refluxed for ca. 1 h, cooled and poured into water (200 ml). The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic solutions were dried (Na_2SO_4) and concentrated. The crude 1-(ethylthio)-2-methyl-4-nitrobenzene (25 mmol) was reduced, according to the literature method [26], to 3-methyl-4-(ethylthio)aniline using iron (141 mmol), hydrochloric acid (2 ml) and water (6 ml). The crude product was then methylated following the method used to prepare **1a**. The resulting **6** was purified by flash-chromatography with light petroleum as eluent. The overall yield was 41%. Pale yellow viscous oil; b.p. 131–133/2 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 3H, SCH_2CH_3), 2.10 (s, 3H, ArCH_3), 2.65, (q, 2H, SCH_2CH$_3$), 2.93 (s, 6H, NCH_3), 6.29 (m, 2H, H-2 and H-6), 7.81 (m, 1H, H-5); ^{13}C-NMR ($CDCl_3$) δ: 13.99, 20.85, 28.02, 39.53, 114.85, 115.61, 129.41, 130.03, 141.98, 147.93. EI-MS: $m/e =$ 195 (67.7%, M^+), 166 (100%, $M^+ - C_2H_5$), 151 (10.1%, $M^+ - C_2H_5$–CH_3), 150 (13.6%, $M^+ - C_2H_5$–CH_4), 134 (4.8%, $M^+ - SC_2H_5$), 122 (16.1%, $M^+ - C_2H_5$–CS), 121 (17.7%, $M^+ - C_2H_5$–CS–H), 120 (9.7%, $M^+ - C_2H_5$–CS–2H), 91 (7.0%, $C_7H_7^+$), 77 (6.4%, $C_6H_5^+$), 45 (9.6%, CHS^+). Elemental analysis. Found: C, 67.55; H, 8.69; N, 7.11; S, 16.25. $C_{11}H_{17}NS$ (195.3). Calc.: C, 67.65; H, 8.78; N, 7.18; S, 16.39%.

3.4. Metallation of **1a**

3.4.1. Method A

A 1.2 M solution of butyllithium in hexane (20 mmol) was gradually added under argon at 20°C to a vigorously stirred solution of **1a** (18 mmol) and hexane (15 ml). The resulting mixture was then warmed to reflux for 1 h. After cooling to room temperature iodomethane (20 mmol) was added. The mixture was then kept 12 h with stirring at the same temperature, then poured into water (100 ml) and the pH was adjusted to 5–6 by addition of 5% hydrochloric acid. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the combined organic solutions were dried (Na_2SO_4) and analysed. The GC/MS analyses (see Table 1) exhibited only the starting material.

3.4.2. Method B

A 1.2 M solution of butyllithium in hexane (20 mmol) was gradually added under argon at 20°C to a vigorously stirred solution of **1a** (18 mmol), anhydrous TMEDA (20 mmol) and hexane (15 ml). The resulting mixture was then warmed to 40°C and kept at this temperature for 1 h. After cooling to room temperature iodomethane (20 mmol) was added. The mixture was then worked up in the same manner above described. The GC/MS analyses (see Table 1) exhibited three products **2**, **3** and **4** in the ratio of 45:37:18. The starting material remaining was 67%.

2. EI-MS: *m*/*e* = 181 (91.9%, M^+), 180 (16.4%, $M^+ - H$), 166 (100%, $M^+ - CH_3$), 151 (12.9%, $M^+ - CH_3{-}CH_3$), 150 (22.6%, $M^+ - CH_3{-}CH_4$), 118 (6.4%, $M^+ - SCH_3{-}CH_4$), 91 (8.4%, $C_7H_7^+$), 77 (6.7%, $C_6H_5^+$), 65 (6.4%, $C_5H_5^+$), 45 (10.1%, CHS^+).

3. EI-MS: *m*/*e* = 181 (54.8%, M^+), 166 (2.4%, $M^+ - CH_3$), 153 (5.2%, $M^+ - C_2H_4$), 152 (100%, $M^+ - C_2H_5$), 136 (9.7%, $M^+ - C_2H_5{-}CH_4$), 109 (4.8%, $M^+ - C_2H_5{-}CH_2{=}N{-}CH_3$), 108 (6.4%, $M^+ - C_2H_5{-}CS$), 91 (2.3%, $C_7H_7^+$), 77 (3.1%, $C_6H_5^+$), 65 (3.8%, $C_5H_5^+$), 45 (2.5%, CHS^+).

4. EI-MS: *m*/*e* = 181 (93.5%, M^+), 166 (100%, $M^+ - CH_3$), 151 (11.3%, $M^+ - CH_3{-}CH_3$), 150 (16.7%, $M^+ - CH_3{-}CH_4$), 122 (19.3%, $M^+ - CH_3{-}CS$), 121 (22.2%, $M^+ - CH_3{-}CS{-}H$), 120 (11.6%, $M^+ - CH_3{-}CS{-}2H$), 91 (12.9%, $C_7H_7^+$), 65 (4.8%, $C_5H_5^+$), 45 (5.9%, CHS^+).

If the reaction was performed using two molar equivalents of butyllithium, the GC/MS (see Table 1) exhibited six products (**2**, **3**, **4**, **5**, **6** and **7**) in the ratio of 31:14:10:28:14:3. The remaining starting material was 13%.

If the reaction was performed using two molar equivalents of butyllithium, injecting 1 mole and after 15 min the 2nd mole, the GC/MS (see Table 1) exhibited five products (**2**, **3**, **4**, **5** and **6**) in the ratio of 27:13:22:22:16. The remaining starting material was 18%.

When the reaction was performed with four molar equivalents of organolithium, injected in two times, the GC/MS (see Table 1) exhibited five products (**2**, **3**, **4**, **5** and **6**) in the ratio of 30:9:13:34:14. The remaining starting material was 10%.

When the reaction was performed at 0°C pouring **1a** onto four equivalents of butyllithium, the GC/MS (see Table 1) exhibited six products (**2**, **3**, **4**, **5**, **6** and **7**) in the ratio of 18:11:14:27:17:13. The remaining starting material was 22%.

5. EI-MS: *m*/*e* = 195 (61.2%, M^+), 194 (4.8%, $M^+ - H$), 180 (6.4%, $M^+ - CH_3$), 166 (100%, $M^+ - C_2H_5$), 151 (7.1%, $M^+ - C_2H_5{-}CH_3$), 150 (12.6%, $M^+ - C_2H_5{-}CH_4$), 118 (4.2%, $M^+ - SC_2H_5{-}CH_4$), 77 (6.4%, $C_6H_5^+$), 65 (4.1%, $C_7H_7^+$), 45 (7.7%, CHS^+).

6. EI-MS: *m*/*e* = 195 (67.7%, M^+), 166 (100%, $M^+ - C_2H_5$), 151 (10.1%, $M^+ - C_2H_5{-}CH_3$), 150 (13.6%, $M^+ - C_2H_5{-}CH_4$), 134 (4.8%, $M^+ - SC_2H_5$), 122 (16.1%, $M^+ - C_2H_5{-}CS$), 121 (17.7%, $M^+ - C_2H_5{-}CS{-}H$), 120 (9.7%, $M^+ - C_2H_5{-}CS{-}2H$), 91 (7.0%, $C_7H_7^+$), 77 (6.4%, $C_6H_5^+$), 45 (9.6%, CHS^+).

7. EI-MS: *m*/*e* = 195 (93.5%, M^+), 194 (9.5%, $M^+ - H$), 180 (100%, $M^+ - CH_3$), 165 (22.6%, $M^+ - CH_3{-}CH_3$), 164 (16.1%, $M^+ - CH_3{-}CH_4$), 135 (9.3%, $M^+ - CH_3{-}CHS$), 121 (9.7%, $M^+ - CH_3{-}CS{-}CH_3$), 91 (11.3%, $C_7H_7^+$), 77 (8.4%, $C_6H_5^+$), 65 (6.7%, $C_5H_5^+$), 45 (7.1%, CHS^+).

3.4.3. Method C

To a vigorously stirred solution of **1a** (18 mmol) and anhydrous tetrahydrofuran (30 ml) cooled to 0°C, a 1.5 M solution of *tert*-butyllithium in pentane (22 mmol) was gradually added under argon. When the addition was complete the mixture was stirred for ca. 2 h at room temperature and then treated with iodomethane (22 mmol) at 0°C. The resulting solution was then worked up in the same manner above described. The GC/MS analyses (see Table 1) exhibited only the product **3** in 37% yield. The remaining starting material was 63%.

If the reaction was performed with 2 molar equivalents of organolithium we obtained **3** in 54% yield. The remaining starting material was 46%.

From the reaction mixture 4-(ethylthio)-*N*,*N*-dimethylaniline (**3**) was isolated by distillation. Yield 51%; b.p. 139–141/4 mmHg. This product was identified by comparison with an authentic sample.

3.4.4. Method D

A 1.2 M solution of butyllithium in hexane (7.2 mmol), was cooled to −40°C under argon and a solution of **1a** (6 mmol) in hexane (5 ml) was added. Finely powdered potassium *tert*-butoxide (7.2 mmol) was added. The mixture was kept for 1 h at −20°C, then an excess of iodomethane (8.4 mmol) was slowly added, the cooling bath removed and the reaction completed by stirring overnight at room temperature.

The resulting solution was then worked up in the same manner above described. The GC/MS analyses (see Table 1) exhibited only the product **3** (44%). The remaining starting material was 56%.

When 2 molar equivalents of superbase were used, the reaction mixture exhibited four products (**3**, **4**, **5** and **6**) in the ratio 21:15:7:57. The remaining starting material was 13%.

When 3 molar equivalents of superbase were used, the reaction mixture exhibited four products (**3, 5**, **6** and **8**) in the ratio of 17:6:65:12. The remaining starting material was 4%.

8. EI-MS: $m/e = 195$ (79%, M^+), 153 (55.5%, $M^+ - C_3H_6$), 152 (100%, $M^+ - C_3H_7$), 136 (12.2%, $M^+ - C_3H_7{-}CH_4$), 120 (15.9%, $M^+ - SC_3H_7$), 109 (4.5%, $C_6H_5S^+$), 108 (6%, $C_6H_4S^+$), 77 (1.8%, $C_6H_5^+$), 65 (5.4%, $C_5H_5^+$), 43 (5.7%, $C_3H_7^+$), 42 (8.6%, $C_3H_6^+$).

From the reaction mixture the major component, 4–(ethylthio)-*N*,*N*,3-trimethylaniline (**6**), was isolated by distillation. Yield 57%; b.p. 143–144°C/4 mmHg. This product was identified by comparison with an authentic sample.

3.4.5. Reaction of monometallated **1a** with carbon dioxide: [4-(dimethylamino)phenylthio]acetic acid (**9**)

The mixture derived by metallation of **1a**, obtained as described above (Method C, Section 3.4.3) was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous sodium bicarbonate and then with diethyl ether. The alkali layer was separated, washed with diethyl ether, and then acidified with cold concentrated hydrochloric acid, extracted with chloroform, dried (Na_2SO_4) and concentrated. The crude product was crystallized from benzene. Yield 58%; m.p. 84–86°C [13]; IR (CCl_4): 3160 (OH), 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.88 (s, 6H, NC*H*$_3$), 3.45 (s, 2H, SC*H*$_2$), 6.35 (d, 2H, Ar–*H*), 6.61 (d, 2H, Ar–*H*), 9.20 (s, 1H, O*H*); ^{13}C-NMR ($CDCl_3$) δ: 32.57, 42.35, 118.18, 129.06, 140.04, 1502.27, 171.08. EI-MS: $m/e = 211$ (9.5%, M^+), 196 (2.3%, $M^+ - CH_3$), 169 (24.9%, $M^+ - C_2H_4N$), 152 (31.8%, $M^+ - CH_2CO_2H$), 108 (8.1%, $C_5H_4N(CH_3)_2^+$), 106 (9.1%, $C_6H_5NCH_3^+$), 83 (24.1%, $C_4H_3S^+$), 71 (31.8%, $C_3H_3S^+$), 59 (100%, $C_2H_3O_2^+$), 58 (47.7%, $C_2H_2O_2^+$), 57 (48.1%, $C_2HO_2^+$).

3.5. Metallation of **1b**

3.5.1. Method A

Using one molar equivalent of 1.2 M solution of butyllithium in hexane, we obtained a 18% of **1b** and a 82% of the monometallated product **10**. When we used two molar equivalents of the same reagent injecting 1 mole and then the 2nd after 15 s, we obtained three monosubstituted products **10**, **11** and **12** and two disubstituted **13** and **14** in the ratio of 72:19:1:5:3. The remaining starting material was 25%.

10. EI-MS: $m/e = 181$ (M^+, 100.0), 166 (42%, $M^+ - CH_3$), 165 (15.5%, $M^+ - CH_4$), 164 (24.5%, $M^+ - CH_4{-}H$), 151 (49%, $M^+ - C_2H_6$), 150 (50.2%, $M^+ - CH_3{-}CH_4$), 148 (41.6%, $M^+ - SH$), 134 (9.8%, $M^+ - SCH_3$), 132 (11.2%, $M^+ - CH_3{-}H_2S$), 118 (8.7%, $M^+ - SCH_3{-}CH_4$), 105 (10.8%, $C_7H_7N^+$), 91 (16%, $C_7H_7^+$), 77 (11.7%, $C_6H_5^+$), 65 (11%, $C_5H_5^+$).

11. EI-MS: $m/e = 181$ (100%, M^+), 166 (4.4%, $M^+ - CH_4$), 153 (37.3%, $M^+ - C_2H_4$), 152 (33.3%, $M^+ - C_2H_5$), 150 (25.3%, $M^+ - C_2H_6{-}H$), 148 (38.8%, $M^+ - SH$), 137 (49.9%, $M^+ - C_2H_4{-}CH_4$), 136 (50%, $M^+ - C_2H_5{-}CH_4$), 120 (25.1%, $M^+ - SC_2H_5$), 109 (22.5%, $C_6H_5S^+$), 91 (18.1%, $C_7H_7^+$), 77 (13.7%, $C_6H_5^+$), 65 (15.5%, $C_5H_5^+$).

12. EI-MS: $m/e = 181$ (100%, M^+), 180 (14.6%, $M^+ - H$), 166 (33.3%, $M^+ - CH_3$), 165 (26.2%, $M^+ - CH_4$), 164 (29.9%, $M^+ - CH_4{-}H$), 151 (44.8%, $M^+ - CH_3{-}CH_3$), 150 (56.3%, $M^+ - CH_3{-}CH_4$), 148 (24.9%, $M^+ - SH$), 132 (15.8%, $M^+ - CH_3{-}H_2S$), 118 (11.7%, $M^+ - SCH_3{-}CH_4$), 104 (9.6%, $C_7H_6N^+$), 91 (14.6%, $C_7H_7^+$), 77 (13.5%, $C_6H_5^+$), 65 (13%, $C_5H_5^+$).

13. EI-MS: $m/e = 195$ (100%, M^+), 180 (3.6%, $M^+ - CH_3$), 167 (61.4%, $M^+ - C_2H_4$), 166 (32.6%, $M^+ - C_2H_5$), 164 (26.3%, $M^+ - C_2H_6{-}H$), 162 (42.9%, $M^+ - SH$), 151 (83.1%, $M^+ - C_2H_4{-}CH_4$), 150 (85.7%, $M^+ - C_2H_4{-}CH_4{-}H$), 134 (35.7%, $M^+ - SC_2H_5$), 120 (31.9%, $C_8H_{10}N^+$), 105 (13.1%, $C_7H_7N^+$), 91 (22.1%, $C_7H_7^+$), 77 (18.9%, $C_6H_5^+$), 65 (14.4%, $C_5H_5^+$).

14. EI-MS: $m/e = 195$ (100%, M^+), 194 (1.1%, $M^+ - H$), 180 (9.9%, $M^+ - CH_3$), 167 (15.6%, $M^+ - C_2H_4$), 166 (31.8%, $M^+ - C_2H_5$), 165 (21.9%, $M^+ - C_2H_6$), 164 (35.8%, $M^+ - C_2H_6{-}H$), 162 (51.2%, $M^+ - SH$), 151 (68%, $M^+ - C_2H_4{-}CH_4$), 150 (72.8%, $M^+ - C_2H_4{-}CH_4{-}H$), 134 (13.3%, $M^+ - SC_2H_5$), 132 (17%, $M^+ - CH_3{-}H_2S$), 120 (18.8%, $C_8H_{10}N^+$), 104 (44.1%, $C_7H_6N^+$), 91 (16.4%, $C_7H_7^+$), 77 (18.6%, $C_6H_5^+$), 65 (17.2%, $C_5H_5^+$).

3.5.2. Method B

Using one molar equivalent of 1.5 M solution of *tert*-butyllithium in pentane, the reaction mixture showed only the product **10** (44%). The remaining starting material was 56%.

3.5.3. Method C

Using 1 molar equivalent of superbase we obtained only the product **10** (81%). The remaining starting material was 19%.

When we used two molar equivalents of the same reagent we obtained **10** in 89% yield. The remaining starting material was 11%. From the reaction mixture this product was isolated by distillation. Yield 78%; b.p. 112–114°C/1 mmHg. This product was identified by comparison with an authentic sample.

The reaction with three molar equivalents of superbase leaded to a 50% of **10** and a mixture of three bisubstituted products **13**, **14** and **15** in the ratio of 9:54:37. The remaining starting material was 7%.

14. EI-MS: *m*/*e* = 195 (100%, M^+), 162 (17.1%, $M^+ - SH$), 153 (76.1%, $M^+ - C_3H_6$), 152 (46.5%, $M^+ - C_3H_7$), 138 (38.3%, $M^+ - C_3H_6\text{–}CH_3$), 137 (69.1%, $M^+ - C_3H_6\text{–}CH_4$), 136 (60.9%, $M^+ - C_3H_7\text{–}CH_4$), 120 (46.1%, $M^+ - SC_3H_7$), 109 (25%, $C_6H_5S^+$), 91 (16.7%, $C_7H_7^+$), 77 (14.5%, $C_6H_5^+$), 65 (16.3%, $C_5H_5^+$), 44 (36.8%, $C_3H_8^+$), 42 (20.9%, $C_3H_6^+$).

3.5.4. Reaction of monometallated **1b** *with carbon dioxide: [2-(dimethylamino)phenylthio]acetic acid* **(16)**

The monometallated mixture of **1b**, obtained as described above (Method C, Section 3.5.3) by reaction with 2 molar equivalents of superbase was poured onto ca. 100 g of crushed solid carbon dioxide and worked up in the same manner above described. Yield 87%. Viscous yellow oil; IR (neat): 3160 (OH), 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.90 (s, 6H, NC*H*$_3$), 3.63 (s, 2H, S C*H*$_2$), 7.40 (m, 4H, Ar–*H*), 10.26 (s, 1H, O*H*); ^{13}C-NMR ($CDCl_3$) δ: 36.29, 43.05, 11.03, 119,61, 126.04, 129.83, 141.33, 174.05. EI-MS: *m*/*e* = 211 (90.9%, M^+), 193 (52.3%, $M^+ - H_2O$), 178 (6.1%, $M^+ - H_2O\text{–}CH_3$), 167 (7.3%, $M^+ - CO_2$), 166 (7.4%, $M^+ - CO_2H$), 152 (50.9%, $M^+ - CH_2CO_2H$), 151 (30.7%, $M^+ - CH_3CO_2H$), 150 (80.1%, $M^+ - CH_3CO_2H\text{–}H$), 137 (99.8%, $M^+ - CO_2\text{–}CH_3\text{–}CH_3$), 136 (100%, $M^+ - CO_2\text{–}C_2H_6\text{–}H$), 132 (50.3%, $M^+ - CO_2H\text{–}H_2S$), 121 (26.7%, $M^+ - SCHCO_2H$), 120 (29.7%, $M^+ - SCH_2CO_2H$), 118 (24.3%, $M^+ - SCH_2CO_2H\text{–}2H$), 109 (40.5%, $C_6H_5S^+$), 104 (14.8%, $C_7H_6N^+$), 91 (28.4%, $C_7H_7^+$), 77 (27.2%, $C_6H_5^+$), 65 (23.3%, $C_2H_5^+$). Elemental analysis. Found: C, 56.78; H, 6.14; N, 6.59; S, 15.05. $C_{10}H_{13}NO_2S$ (211.3). Calc.: C, 56.85; H, 6.20; N, 6.63; S, 15.17%.

3.6. Metallation of **1c**

3.6.1. Method A

The reaction of **1c** with one molar equivalent of 1.2 M solution of butyllithium in hexane at reflux temperature leaded to the monometallated product 17 in a 67% yield beside a 33% of starting compound **1c**. From the reaction mixture this product was isolated by distillation. Yield 56%. Pale yellow oil; b.p. 107–108°C/1 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 1.19 (t, 3H, SCH$_2$C*H*$_3$), 2.68 (q, 2H, SC*H*$_2$CH$_3$), 2.97 (s, 6H, NC*H*$_3$), 6.55 (m, 2H, Ar–*H*), 6.95 (m, 2H, Ar–*H*); ^{13}C-NMR ($CDCl_3$) δ: 14.65, 28.33, 40.81, 116.10, 118.35, 131.63, 138.99, 150.01. EI-MS: *m*/*e* = 181 (100%, M^+), 180 (25.8%, $M^+ - H$), 153 (70.9%, $M^+ - C_2H_4$), 152 (54.8%, $M^+ - C_2H_5$), 151 (16.1%, $M^+ - C_2H_5\text{–}H$), 148 (29%, $M^+ - SH$), 120 (12.9%, $M^+ - SC_2H_5$), 109 (16.1%, $C_6H_5S^+$), 108 (19.3%, $C_6H_4S^+$), 91 (6.1%, $C_7H_7^+$), 77 (9.5%, $C_6H_5^+$), 65 (10.1%, $C_5H_5^+$). Elemental analysis. Found: C, 66.17; H, 8.28; N, 7.65; S, 17.51. $C_{10}H_{15}NS$ (181.3). Calc.: C, 66.25; H, 8.34; N, 7.73; S, 17.69%.

Using four molar equivalents of the same reagent we obtained a 66% of 17 and two bisubstituted products **21** and **22** in the ratio of 47:53. The remaining starting material was 19%.

When 4 equivalents were injected in the reaction flask in two times (2 equivalents + 2 equivalents) we revealed four monosubstituted products **17**, **18**, **19** and **20** and three bisubstituted **21**, **22** and **23** in the ratio of 45:6:4:6:16:11:12. The remaining starting material was 18%.

18. EI-MS: *m*/*e* = 181 (100%, M^+), 166 (87.8%, $M^+ - CH_3$), 151 (16%, $M^+ - CH_3\text{–}CH_3$), 150 (21.1%, $M^+ - CH_3\text{–}CH_4$), 132 (5.2%, $M^+ - CH_3\text{–}H_2S$), 121 (7.1%, $M^+ - CH_3\text{–}CS\text{–}H$), 118 (9.5%, $M^+ - SCH_3\text{–}CH_4$), 117 (9.3%, $M^+ - SCH_3\text{–}CH_4\text{–}H$), 91 (11.8%, $C_7H_7^+$), 77 (9%, $C_6H_5^+$), 65 (5.4%, $C_5H_5^+$).

19. EI-MS: *m*/*e* = 181 (100%, M^+), 166 (42.7%, $M^+ - CH_3$), 153 (10.5%, $M^+ - C_2H_4$), 150 (22.1%, $M^+ - CH_3\text{–}CH_4$), 148 (16%, $M^+ - SH$), 132 (9.5%, $M^+ - CH_3\text{–}H_2S$), 122 (16.4%, $M^+ - CH_3\text{–}CS$), 120 (22.7%, $M^+ - CH_3\text{–}CH_2S$), 118 (12.9%, $M^+ - SCH_3\text{–}CH_4$), 117 (15.7%, $C_8H_7N^+$), 104 (9.9%, $C_7H_6N^+$), 91 (12.3%, $C_7H_7^+$), 77 (12.1%, $C_6H_5^+$), 65 (8.5%, $C_5H_5^+$).

20. EI-MS: *m*/*e* = 181 (100%, M^+), 166 (36.9%, $M^+ - CH_3$), 165 (13.2%, $M^+ - CH_4$), 153 (13.8%, $M^+ - C_2H_4$), 152 (16.4%, $M^+ - C_2H_4\text{–}H$), 150 (9.6%, $M^+ - CH_3\text{–}CH_4$), 148 (14.7%, $M^+ - SH$), 134 (17.1%, $M^+ - SCH_3$), 122 (9.8%, $M^+ - CH_3\text{–}CS$), 120 (4.7%, $M^+ - CH_3\text{–}CH_2S$), 118 (9.7%, $M^+ - CH_3\text{–}CH_4$), 109 (4.1%, $C_6H_4S^+$), 91 (12%, $C_7H_7^+$), 77 (8.9%, $C_6H_5^+$), 65 (7.6%, $C_5H_5^+$).

21. EI-MS: *m*/*e* = 195 (100%, M^+), 180 (79.9%, $M^+ - CH_3$), 167 (14.2%, $M^+ - C_2H_4$), 166 (11.6%, $M^+ - C_2H_5$), 165 (11.6%, $M^+ - C_2H_6$), 164 (12.6%, $M^+ - C_2H_6\text{–}H$), 162 (6.6%, $M^+ - SH$), 152 (16.9%, $M^+ - C_2H_4\text{–}CH_3$), 151 (18.5%, $M^+ - C_2H_4\text{–}CH_4$), 136 (7.9%, $M^+ - CH_3\text{–}CS$), 123 (7.8%, $M^+ - C_2H_4\text{–}CS$), 91 (7.8%, $C_7H_7^+$), 77 (10.4%, $C_6H_5^+$), 65 (4.8%, $C_5H_5^+$).

22. EI-MS: *m*/*e* = 195 (100%, M^+), 180 (15%, $M^+ - CH_3$), 167 (11.3%, $M^+ - C_2H_4$), 166 (25.5%, $M^+ - C_2H_5$), 162 (37.6%, $M^+ - SH$), 152 (9.6%, $M^+ - C_2H_4\text{–}CH_3$), 151 (9.3%, $M^+ - C_2H_4\text{–}CH_4$), 150 (11.4%, $M^+ - C_2H_4\text{–}CH_4\text{–}H$), 135 (21.9%, $M^+ - CH_3\text{–}CHS$), 134 (24.2%, $M^+ - SC_2H_5$), 118 (17%, $M^+ - SC_2H_5\text{–}CH_4$), 117 (15.5%, $M^+ - SC_2H_5\text{–}CH_4\text{–}H$), 104 (4.3%, $C_7H_6N^+$), 91 (10.8%, $C_7H_7^+$), 77 (12.2%, $C_6H_5^+$), 65 (6.7%, $C_5H_5^+$).

23. EI-MS: *m*/*e* = 195 (100%, M^+), 167 (33.7%, $M^+ - C_2H_4$), 166 (72.4%, $M^+ - C_2H_5$), 162 (16%, $M^+ - SH$), 150 (11.5%, $M^+ - C_2H_4\text{–}CH_4\text{–}H$), 134 (26.8%, $M^+ - SC_2H_5$), 122 (16.1%, $M^+ - C_2H_5\text{–}CS$), 121 (9.2%, $M^+ - C_2H_5\text{–}CHS$), 106 (4.4%, $C_7H_8N^+$), 91 (9.9%, $C_7H_7^+$), 77 (8.9%, $C_6H_5^+$), 65 (5.9%, $C_5H_5^+$).

3.6.2. Method B

Using 1 molar equivalent of 1.5 M solution of *tert*-butyllithium in pentane, we obtained only the product **17** (46%) The remaining starting material was 54%.

3.6.3. Method C

Using one molar equivalent of superbase we obtained only the product **17** (34%). The remaining starting material was a 66%.

When we used 3 molar equivalents of superbase we revealed a 65% of **17** and two bisubstituted products **23** and **24** in the ratio of 52:48. The remaining starting material was a 12%.

24. EI-MS: $m/e = 195$ (71.4%, M^+), 162 (17.6%, $M^+ - SH$), 153 (89.9%, $M^+ - C_3H_6$), 152 (100%, $M^+ - C_3H_7$,), 136 (6.7%, $M^+ - C_3H_7–CH_4$), 120 (8.2%, $M^+ - SC_3H_7$), 109 (12.5%, $C_6H_5S^+$), 108 (13.2%, $C_6H_4S^+$), 91 (4.7%, $C_7H_7^+$), 77 (6.7%, $C_6H_5^+$), 65 (9.3%, $C_5H_5^+$), 43 (10%, $C_3H_7^+$), 42 (16.6%, $C_3H_6^+$).

3.6.4. Reaction of monometallated **1c** with carbon dioxide: [3-(dimethylamino)phenylthio]acetic acid (**25**)

The monometallated mixture of **1c**, obtained as described above (Method C, Section 3.6.3) by reaction with 3 molar equivalents of superbase was poured onto ca. 100 g of crushed solid carbon dioxide and worked up in the same manner above described. Yield 71%. Viscous yellow oil; IR (neat): 3400 (OH), 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ: 2.90 (s, 6H, NC*H*$_3$), 3.65 (s, 2H, SC*H*$_2$), 7.00 (m, 4H, Ar–*H*), 7.90 (s, 1H, O*H*); ^{13}C-NMR ($CDCl_3$) δ: 33.75, 43.18, 114.08, 116.89, 120.16, 130.97, 141.33, 152.07, 174.21. EI–MS: $m/e =$ 211 (100%, M^+), 210 (35.6%, $M^+ - H$), 193 (12.1%, $M^+ - H_2O$), 178 (72.5%, $M^+ - H_2O–CH_3$), 167 (6.8%, $M^+ - CO_2$), 166 (16.3%, $M^+ - CO_2H$), 152 (32.7%, $M^+ - CH_2CO_2H$), 151 (37.1%, $M^+ - CH_3CO_2H$), 150 (25.4%, $M^+ - CH_3CO_2H–H$), 137 (31%, $M^+ - CO_2–CH_3–CH_3$), 136 (29.3%, $M^+ - CO_2–C_2H_6–H$), 132 (11.6%, $M^+ - CO_2H–H_2S$), 121 (15.5%, $M^+ -$ $SCHCO_2H$), 120 (15.7%, M^+–SCH_2CO_2H), 109 (20.3%, $C_6H_5S^+$), 108 (20%, $C_6H_4S^+$), 104 (7.2%, $C_7H_6N^+$), 91 (12.4%, $C_7H_7^+$), 77 (15.8%, $C_6H_5^+$), 65 (14.2%, $C_6H_5^+$). Elemental analysis. Found: C, 56.71; H, 6.16; N, 6.54; S, 15.01. $C_{10}H_{13}NO_2S$ (211.3). Calc.: C, 56.85; H, 6.20; N, 6.63; S, 15.17%.

3.6.5. 2-(Butylthio)-N-ethyl-N-methylaniline (**29**)

A solution of **26** (14 mmol) in dry hexane (20 ml) was blanketed with argon and then treated dropwise at − 10°C with 1.2 M solution of butyllithium in hexane (15 mmol). When the addition was complete the mixture was stirred for ca. 30 min at 20°C, cooled at − 10°C and then treated with iodomethane (15 mmol). The resulting solution was successively treated dropwise with 1.2 M solution of butyllithium in hexane (15 mmol) and with iodoethane (15 mmol). The mixture was kept for ca. 30 min at 20°C and treated successively dropwise at − 40°C with 1.2 M solution of butyllithium in hexane (15 mmol). Finely powdered potassium *tert*-butoxide (15 mmol) was added. The mixture was kept for 1 h at − 20°C, then an excess of bromopropane was slowly added, the cooling bath removed and the reaction completed by stirring overnight at room temperature and worked up in the same manner above described. Yield 57%. Pale yellow oil; b.p. 132–135°C/10 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, 3H, SCH$_2$CH$_2$CH$_2$C*H*$_3$ or NCH$_2$C*H*$_3$), 0.94 (t, 3H, SCH$_2$CH$_2$CH$_2$C*H*$_3$ or NCH$_2$C*H*$_3$), 1.50 (m, 2H, SCH$_2$C*H*$_2$CH$_2$), 1.69 (m, 2H, SCH$_2$C*H*$_2$), 2.74 (s, 3H, NC*H*$_3$), 2.88 (q, 2H, SC*H*$_2$), 2.98 (q, 2H, NC*H*$_2$), 7.05 (m, 4H, Ar–*H*); ^{13}C-NMR ($CDCl_3$) δ: 12.15 13.75, 22.53, 29.98, 32.99, 40.16, 43. 22, 112.37, 115.13, 122.05 123.98, 130.17, 141.63. EI-MS: $m/e = 223$ (39.1%, M^+), 208 (100%, $M^+ - CH_3$), 167 (8.3%, $M^+ - C_4H_8$), 152 (41.5%, $M^+ - CH_3–C_4H_8$), 151 (75.4%, $M^+ - CH_3–C_4H_8–H$), 150 (69.7%, $M^+ - CH_3–C_4H_8–2H$), 137 (18.8%, $C_7H_7NS^+$), 136 (20.5%, $C_7H_6NS^+$), 77 (13.4%, $C_6H_5^+$). Elemental analysis. Found: C, 69.81; H, 9.41; N, 6.20; S, 14.22. $C_{13}H_{21}NS$ (223.4). Calcd.: C, 69.90; H, 9.48; N, 6.27; S, 14.35%.

3.6.6. N,N-Dimethyl-2-(ethylthio)aniline (**10**)

Obtained as above described using iodomethane as first, second and third electrophile. Yield 67%. Pale yellow oil; b.p. 100–101°C/1.5 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 1.34 (t, 3H, SCH$_2$C*H*$_3$), 2.73 (s, 6H, NC*H*$_3$), 2.89 (q, 2H, SC*H*$_2$CH$_3$), 7.08 (m, 4H, Ar-*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.97, 28.77, 41.88, 110.94, 113.31, 122.03, 124.99, 132.01, 139. 94. EI-MS: $m/e = 181$ (M^+, 100.0), 166 (42%, $M^+ - CH_3$), 165 (15.5%, $M^+ - CH_4$), 164 (24.5%, $M^+ - CH_4–H$), 151 (49%, $M^+ - C_2H_6$), 150 (50.2%, $M^+ - CH_3–CH_4$), 148 (41.6%, $M^+ - SH$), 134 (9.8%, $M^+ - SCH_3$), 132 (11.2%, $M^+ - CH_3–H_2S$), 118 (8.7%, $M^+ - SCH_3–CH_4$), 105 (10.8%, $C_7H_7N^+$), 91 (16%, $C_7H_7^+$), 77 (11.7%, $C_6H_5^+$), 65 (11%, $C_5H_5^+$). This compound was also identified by comparison with an authentic sample [23].

3.6.7. N,N-Dimethyl-2-(propylthio)aniline (**30**)

Obtained as above described using iodomethane as first and second and iodoethane as third electrophile. Yield 60%. Pale yellow oil; b.p. 115–116°C/5 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 1.05 (t, 3H, SCH$_2$C*H*$_3$), 1.61(m, 2H, SCH$_2$C*H*$_2$CH$_3$), 1.72 (q, 2H, SC*H*$_2$CH$_2$CH$_3$), 2.74 (s, 6H, NC*H*$_3$), 7.05 (m, 4H, Ar–*H*); ^{13}C-NMR ($CDCl_3$) δ: 14.08, 23.17, 39.53, 41.68, 112.88, 115.77, 122.67, 124.07, 132.01, 141.07. EI-MS: $m/e = 195$ (74.2%, M^+), 180 (3.2%, $M^+ - CH_3$), 162 (16.1%, $M^+ - SH$), 153 (100%, $M^+ - C_3H_6$), 152 (35.5%, $M^+ - C_3H_7$), 151 (22.5%, $M^+ - C_3H_6–2H$), 150 (35.5%, $M^+ - C_3H_7–2H$), 138 (32.3%, $M^+ - C_3H_6–CH_3$), 137 (48.4%, $M^+ - C_3H_6–CH_4$), 136 (51.6%, $M^+ - C_3H_6$–

2H–CH_3), 120 (32.4%, $M^+ - SC_3H_7$), 109 (22.6%, $C_6H_5S^+$), 77 (12.9%, $C_6H_5^+$). Elemental analysis. Found: C, 67.69; H, 8.72; N, 7.12; S, 16.31. $C_{11}H_{17}NS$ (195.3). Calc.: C, 67.64; H, 8.77; N, 7.17; S, 16.42%.

3.6.8. 2-(Butylthio)-N-methyl-N-propyl-aniline (***31***)

A solution of **26** (14 mmol) in dry hexane (20 ml) was blanketed with argon and then treated dropwise at −10°C with 1.2 M solution of butyllithium in hexane (15 mmol). When the addition was complete the mixture was stirred for ca. 30 min at 20°C, cooled at −10°C and then treated with iodomethane (15 mmol). The mixture was kept for ca. 30 min at 20°C and treated successively dropwise at −40°C with 1.2 M solution of butyllithium in hexane (30 mmol). Finely powdered potassium *tert*-butoxide (30 mmol) was added. The mixture was kept for 1 h at −20°C, then an excess of bromopropane was slowly added, the cooling bath removed and the reaction completed by stirring overnight at room temperature and worked up in the same manner above described. Yield 65%. Pale yellow oil; b.p. 145–146°C/3 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, 3H, $NCH_2CH_2CH_3$ or $SCH_2CH_2CH_2CH_3$), 0.94 (t, 3H, $NCH_2CH_2CH_3$ or $SCH_2CH_2CH_2CH_3$), 1.53 (m, 4H, $SCH_2CH_2CH_2$ and NCH_2CH_2), 1.69 (m, 2H, SCH_2CH_2), 2.70 (s, 3H, NCH_3), 2.87 (t, 2H, SCH_2CH_2), 2.90 (t, 2H, NCH_2CH_2), 7.09 (m, 4H, Ar–*H*); ^{13}C-NMR ($CDCl_3$) δ: 12.57, 13.69, 21.73, 22.09, 29.97, 41.43, 55.78, 110.65, 114.77, 121.13, 123.83, 130.61, 142.17. EI-MS: $m/e = 237$ (37%, M^+), 208 (100%, $M^+ - C_2H_5$), 181 (7.4%, $M^+ - C_4H_8$), 152 (44.4%, $M^+ - C_2H_5{-}C_4H_8$), 151 (74.1%, $M^+ - C_2H_5{-}C_4H_8{-}H$), 150 (70.4%, $M^+ - C_2H_5{-}C_4H_8{-}2H$), 137 (16.7%, $C_7H_7NS^+$), 136 (18.5%, $C_7H_6NS^+$), 77 (11.1%, $C_6H_5^+$). Elemental analysis. Found: C, 70.71; H, 9.70; N, 5.84; S, 13.38. $C_{14}H_{23}NS$ (237.4). Calc.: C, 70.83; H, 9.77; N, 5.90; S, 13.50%.

3.6.9. N-Allyl-2-[(3-butenyl)thio]-N-methylaniline (***32***)

Obtained as described previously (Section 3.6.8) using iodomethane as the first and allyl bromide as the second electrophile. Yield 42%. Pale yellow oil; b.p. 135–136°C/1.5 mmHg; ^{1}H-NMR ($CDCl_3$) δ: 2.44 (m, 2H, SCH_2CH_2), 2.70 (s, 3H, NCH_3), 2.96 (t, 2H, SCH_2CH_2), 3.56 (d, 2H, NCH_2CH), 5.07 (m, 4H, $CH=CH_2$), 5.91 (m, 2H, $CH=CH_2$), 7.07 (m, 3H, Ar–*H*), 7.18 (m, 1H, Ar–*H*); ^{13}C-NMR ($CDCl_3$) δ: 34.35, 3507, 41.25, 47.98, 112.71, 114.99, 117.63, 121.08, 122.03, 125.02, 125.74, 132.01, 139.02, 140.07. EI-MS: $m/e = 233$ (16.1%, M^+), 204 (7.1%, $M^+ - CH_3$), 179 (29%, $M^+ - C_4H_6$), 178 (48.4%, $M^+ - C_4H_7$), 163 (32.3%, $M^+ - C_4H_6{-}CH_4$), 150 (100%, $M^+ - C_4H_7{-}C_2H_4$), 146 (22.7%, $M^+ - SC_4H_7$), 144 (37.1%, $C_{10}H_{10}N^+$), 138 (35.8%, $C_7H_8NS^+$), 136 (64.5%, $C_7H_6NS^+$), 130 (19.4%, $C_9H_6N^+$), 109 (30.7%, $C_6H_5S^+$), 94 (25.8%, $C_6H_8N^+$), 77 (20.1%, $C_6H_5^+$). Elemental analysis. Found: C, 71.96; H, 8.27; N, 6.06; S, 13.60. $C_{14}H_{19}NS$ (233.4). Calc.: C, 72.05; H, 8.21; N, 6.00; S, 13.74%.

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