Tetrahedron Vol. 46, No. 3, pp. 861-884, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

METALATION REACTIONS. XIV. REGIOSPECIFIC PREPARATION OF POLYSUBSTITUTED BENZENES VIA MONO- OR DI-LITHIATION REACTIONS OF AROMATIC THIOETHERS#

Salvatore Cabiddu*, Claudia Fattuoni, Costantino Floris, Gioanna Gelli
Stefana Melis and Francesca Sotgiu
Istituto di Chimica Organica, Università, Via Ospedale, 72, I-09124 Cagliari, Italy

(*Received in UK* 12 *October* 1989)

Abstract - The preparation of polyfunctionalized aromatic thioethers either by one-step dilithiation or by two successive one-flask monometalation reactions is described. By acting on **1** two equal or different electrophiles one on the thiomethyl group and one in the ortho-position with respect to it are introduced; by acting on **11** and on **35** the substitution involves the thiomethyl carbon atom and that in the ortho-position with respect to the alkoxy group. In the case of the homologous isopropylthio (**23**) the substitution involves the two aryl carbon atoms in the ortho-position to both functions. In the case of the p-disubstituted isomers (**49**, **59**) analogous behaviour to ortho isomers in one-step metalation reaction is observed, while the two hydrogen atoms in the ortho-positions to the methoxy group are substituted when two successive monometalations are employed. The metalation of **40** results low selective. The behaviour of **79** and **93** is analogous to **1**, while **72**, **88** and **96** undergo only one-step monometalation reactions.

The use of organolithium compounds as versatile intermediates in organic synthesis has attracted widespread attention in recent years.[1-7]

We have previously shown that direct dimetalation yields stable dilithiated intermediates which could be used for the introduction of two identical electrophiles as well as for the synthesis of heterocyclic compounds when the two lithiated sites are in ortho to each other.[8-12]

In this paper we report in more detail regarding the dimetalation reactions of variously substituted aromatic thioethers.

RESULTS AND DISCUSSION

Monometalation reactions were performed by treating one equivalent of thioether with 1.2 equivalents of the n-butyllithium N,N,N',N'-tetramethyl-1,2-ethanediamime (TMEDA) complex. Dimetalation reactions were carried out

For preliminary comunication see ref. 9.

with 2.2 or more equivalents of the n-butyllithium-TMEDA complex with one equivalent of thioether. The lithiation intermediates were never isolated but were detected by reaction with electrophiles. The products were identified by their analytical and spectral data and, where possible, by comparison with authentic samples; where necessary, analysis of their desulphuration products obtained by treatment with Raney nickel was carried out.

The behaviour of thioethers upon lithiation depends upon their structure as described below.

i) **(Methylthio)benzene (1).** Monometalation of **1** followed by reaction with an electrophile yields the substitution product of a thiomethyl hydrogen.[13] Dimetalation yields **2** (Scheme 1) where the two lithium atoms are bound to the thiomethyl carbon atom and to the ortho ring carbon atom, respectively. Thus, by using an excess of electrophile, it is possible to introduce two identical electrophilic groups simultaneously into the substrate.[9]

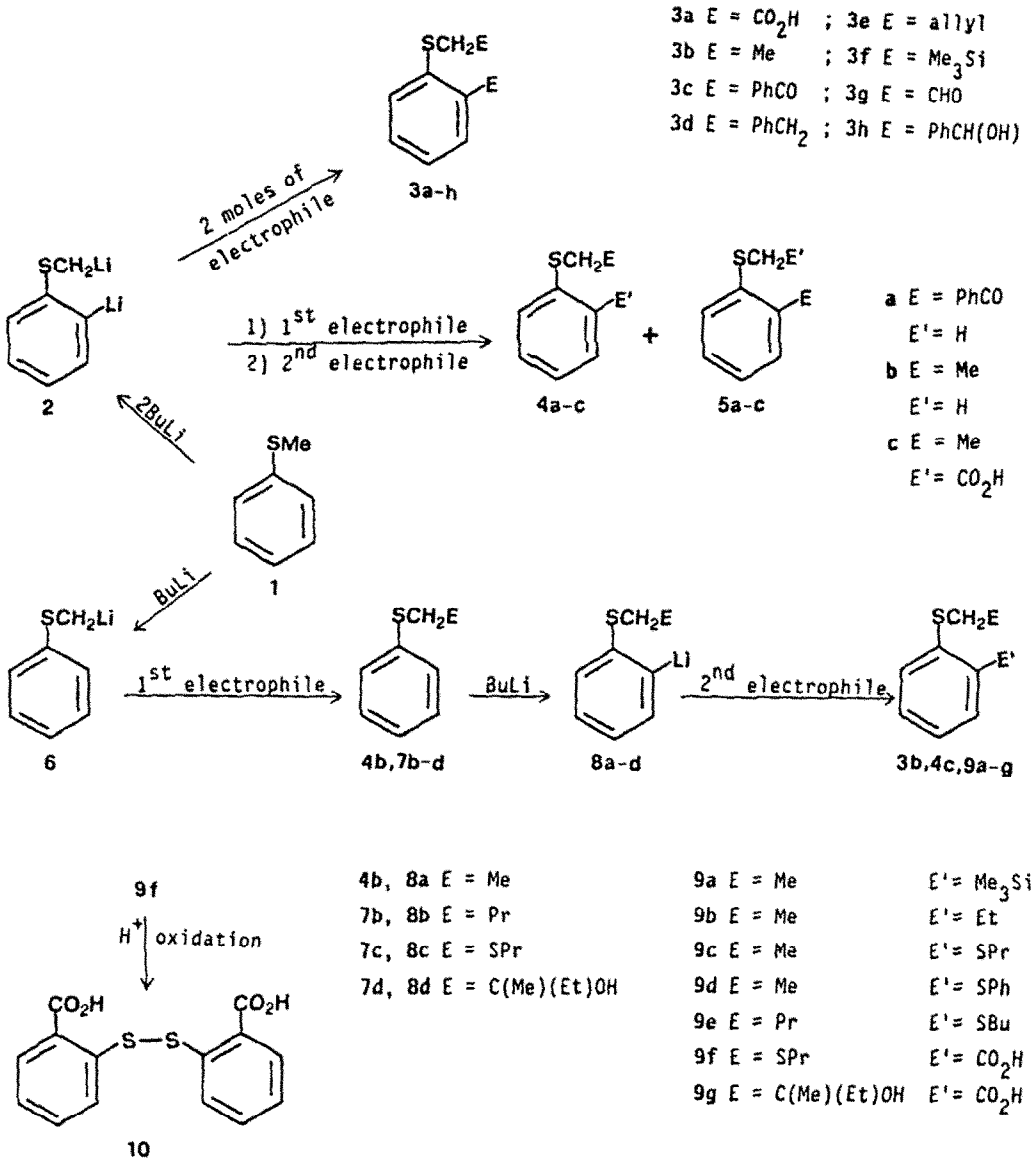
Reaction of **2** with only one equivalent of benzoyl chloride at -80°C, followed by quenching with methanol, yields 1-phenyl-2-(phenylthio)ethanone (**4a**)[10] and 1-benzoyl-2-(methylthio)benzene (**5a**) in a 70:30 ratio (GLC). Similarly, reaction of **2** with an equivalent of methyl iodide, followed by quenching with methanol, yields a mixture of (ethylthio)benzene (**4b**) and 1-methyl-2-(methylthio)benzene (**5b**) in a 60:40 ratio (GLC). The last reaction, when quenching was performed with dry ice, gives a 60:40 mixture of 2-(ethylthio)benzoic acid (**4c**) and [(2-methylphenyl)thio]acetic acid (**5c**).

Two successive "one flask" monometalations allow the introduction into the substrate of two different electrophiles at the thiomethyl carbon and at the ortho ring carbon atom (Scheme 1). Thus, starting from commercial **1** and alkyl halides, one can conveniently obtain 2-alkyl substituted 1-(alkylthio)-benzenes (e.g. **3b**, **9b**). Similarly, from **1**, alkyl halides and disulphides, one can prepare 1,2-bis(alkylthio)- and 1-(alkylthio)-2-(arylthio)-benzenes (e.g. **9c-e**). This procedure appears to be much simpler than the traditional methods.[14-16]

Starting from **1**, alkyl halides, and carbon dioxide or chlorosilanes 2-(alkylthio)benzoic acids (e.g. **4c**) and 2-(trialkylsilyl)-1-(alkylthio)benzenes (e.g. **9a**) were obtained in good yields. Reaction of lithiated **1** with dipropyldisulphide and carbon dioxide gives **9f** when the hydrolysis is performed with ammonium acetate or **10** when a strong acid is used. From **1**, ketones and carbon dioxide derivatives as **9g** can also been obtained.

ii) **2-(Methylthio)- (11) and 2-(Isopropylthio)-1-methoxybenzene (23).** It is known that the coordination ability of oxygen directs the monolithiation of **23** in ortho to the methoxy group,[8,17] while it assists the lithiation of the thiomethyl group in **11**.[17] In a preliminary paper we showed that direct dimetalation substitutes the ortho positions of the two substituents in **23** and

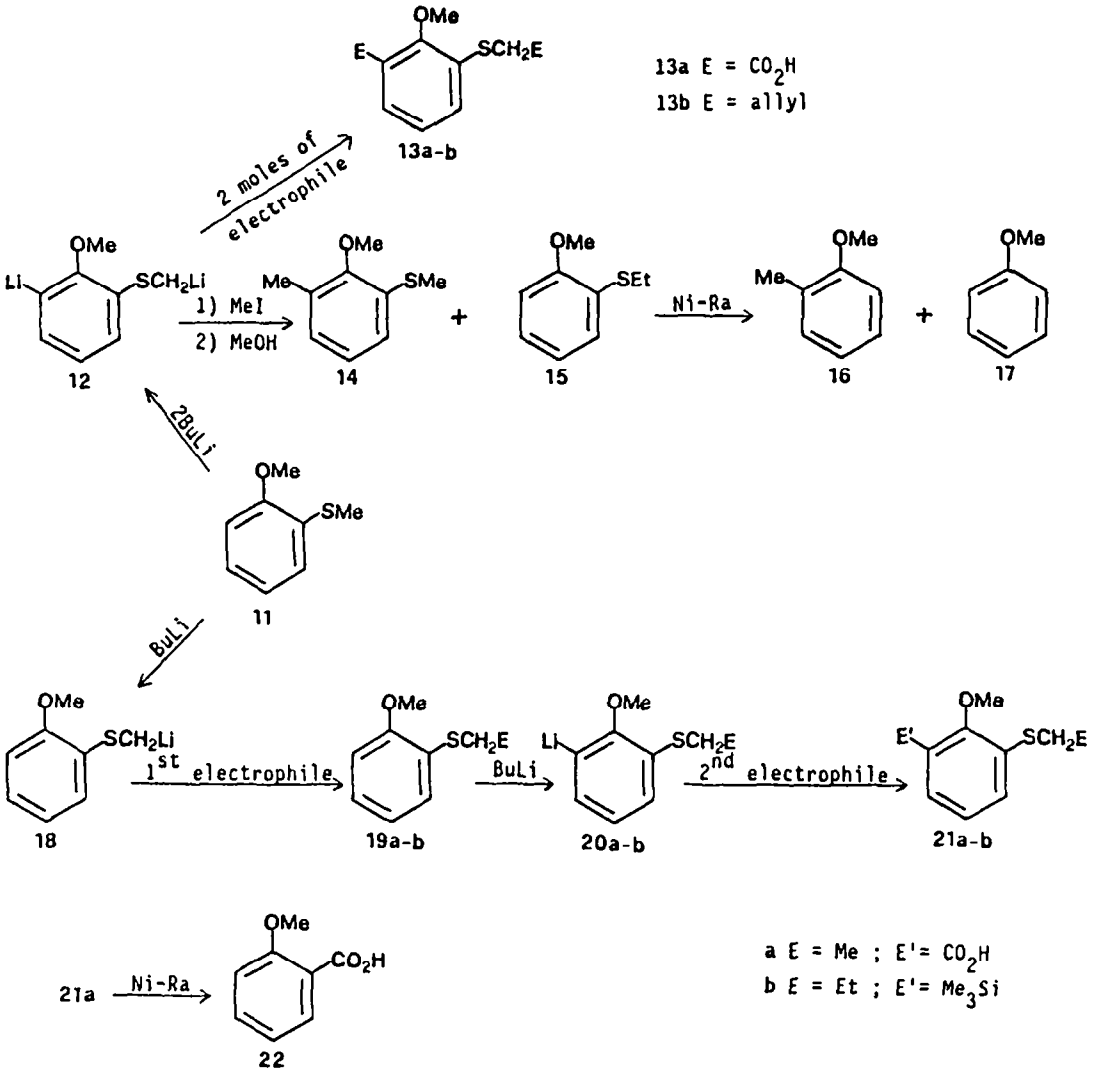
Scheme 1



the ortho position of the alkoxy substituent and of the thiomethyl carbon of 11.[9] Thus, it is possible to functionalize the molecule with two identical functional groups (Schemes 2 and 3).

Attempts to functionalize regioselectively the dianions with different electrophiles always resulted in a mixture of isomers. Thus, when 12 is

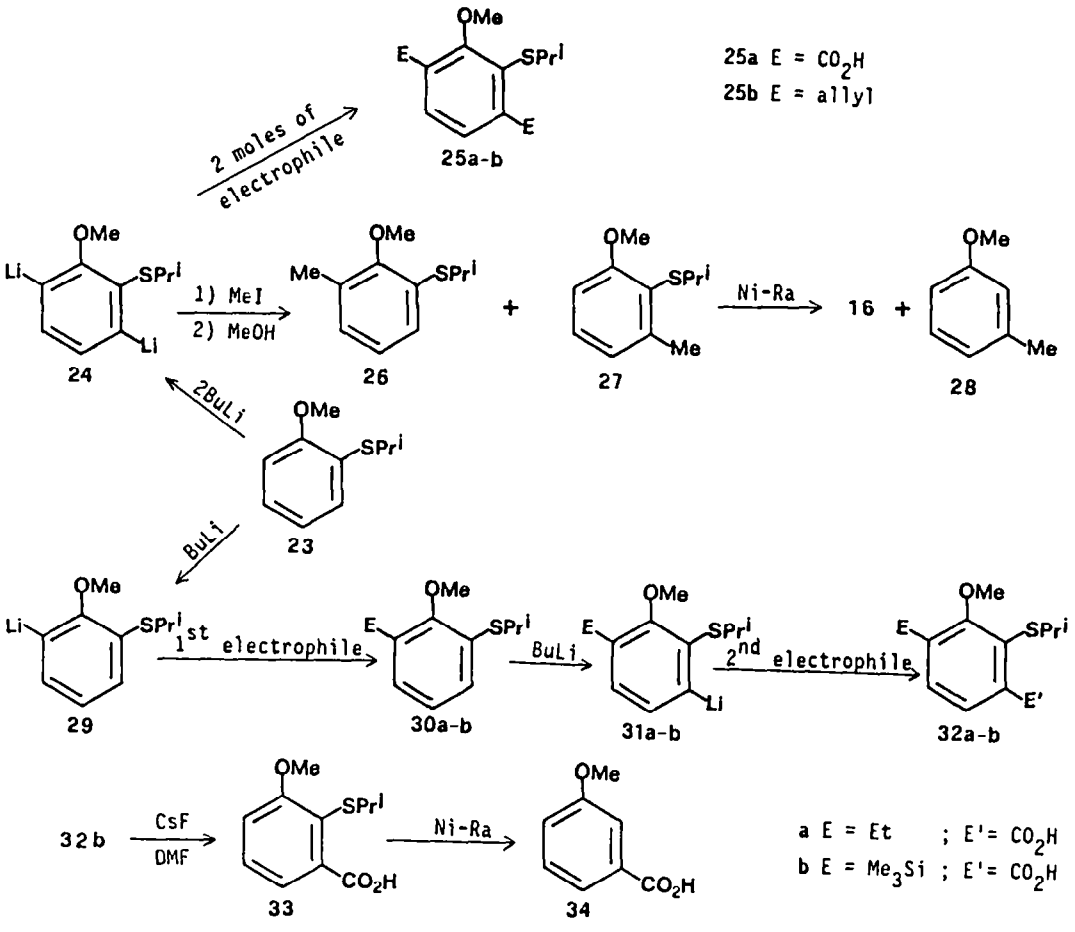
Scheme 2



treated first with one equivalent of methyl iodide and later with one equivalent of methanol a mixture of **14** and **15** (ca. 40:60) is obtained. The products were identified through GLC comparison of their desulphuration products **16** and **17** with authentic samples. Similarly, **26** and **27** were obtained in about equimolar amounts from **24**, methyl iodide, and methanol.

The regioselective functionalization of **11** and **23** can be obtained via two successive "one-flask" monometalations. This is shown (Schemes 2 and 3) by

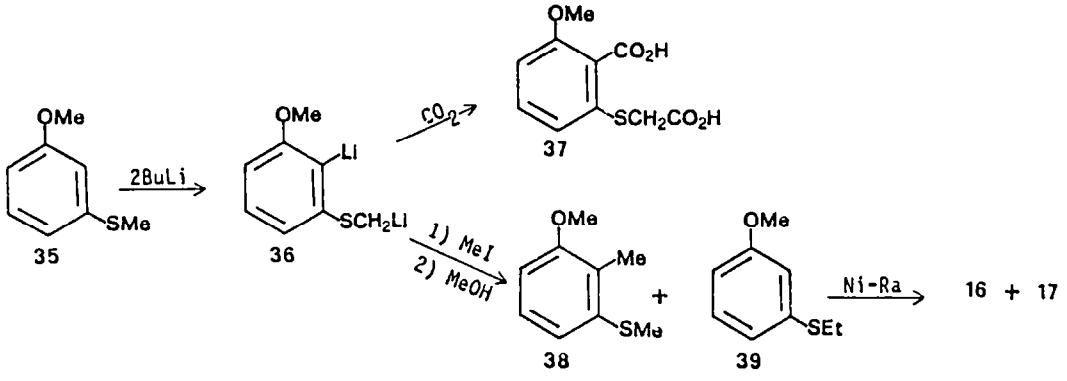
Scheme 3



the preparation of **21a-b** starting from **11** and of **32a-b** starting from **23**. The structure of these compounds was established by assuming the normal regioselectivity for the ortho-lithiation and by analysis of their desulphuration products. The ^1H NMR spectra of the acids **21a**, **32a** and **32b** were in accord with the expected structures. In **21a** the OCH_3 signal lies at δ 3.90 with respect to that at δ 3.65 for the starting product **11**, thus indicating that the carboxylic group is in ortho to the methoxy group.[18] In **32a** and **32b** the CH signal of the isopropyl group lies at about δ 3.50-3.55 with respect to the value of δ 3.30 of the starting product **23**. This indicates that the carboxylic group is in ortho to the thioisopropyl group.[18]

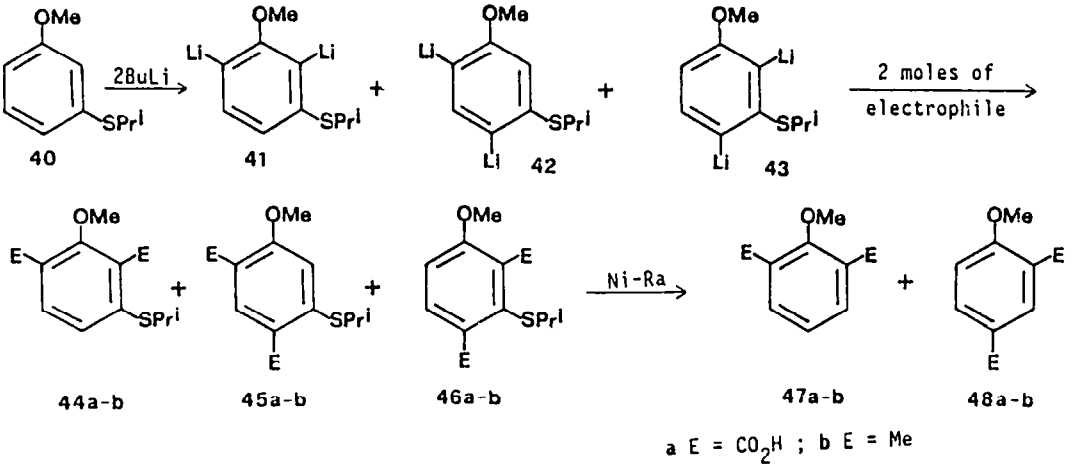
iii) **3-(Methylthio)- (35) and 3-(Isopropylthio)-1-methoxybenzene (40).** Monometalation of these substrates yields mainly substitution products in the ortho position to both substituents, and minor amounts of substitution at the other ortho positions.[19] Dimetalation of **35** yields almost exclusively the dianion **36**, where the second lithium atom substitutes a thiomethyl hydrogen as shown by the formation, after treatment with carbon dioxide, of the dicarboxylic acid **37** (Scheme 4).

Scheme 4



Dimetalation of **40** is less selective. Three isomeric dianions (**41**, **42**, **43**) were obtained which, after treatment with two equivalents of electrophiles, yield **44a-b**, **45a-b**, and **46a-b**, in a 80:13:7 ratio respectively. Evidence for the three acids (**44a**, **45a**, **46a**) was obtained by their transformation in the

Scheme 5



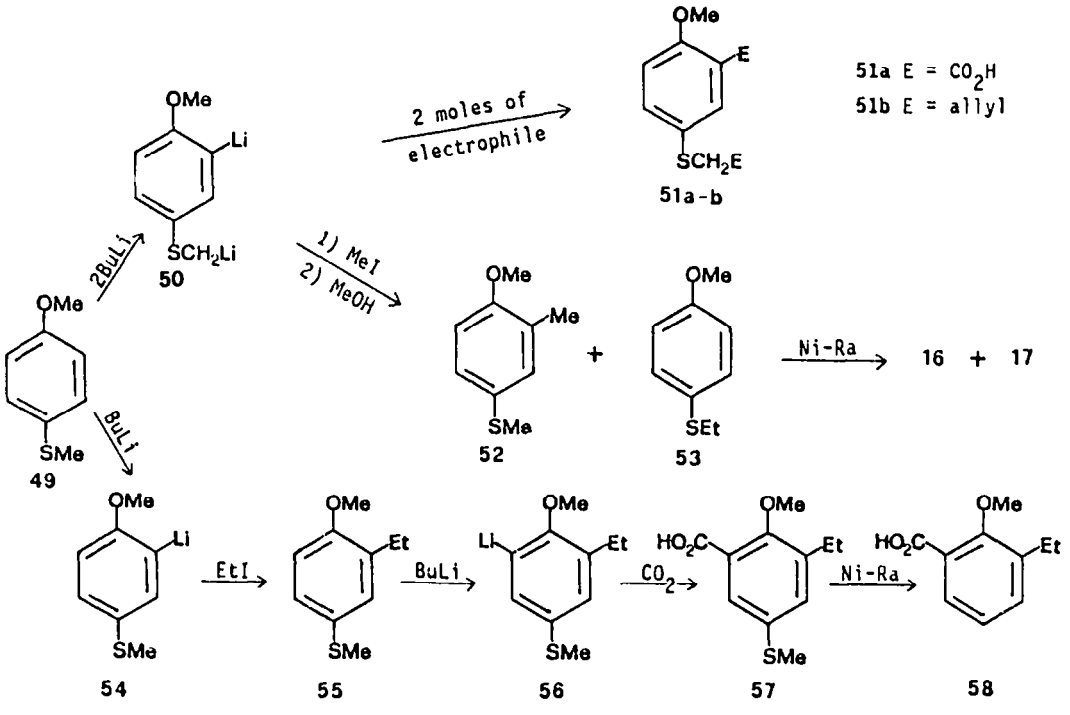
corresponding methyl esters with diazomethane. GC/MS analysis has shown three peaks with the same molecular ion M^+ at m/z 298. Desulphuration yields the isomeric esters in the 80:20 ratio (GLC) (Scheme 5). They were identified by comparison with authentic samples.

A similar procedure was used to characterize the mixture of **44b**, **45b**, **46b**: GC/MS analysis showed three peaks with the same molecular ion M^+ at m/z 210 and desulphuration yielded the two products **47b** and **48b** in the ratio 80:20 (GLC).

The reaction of the dianion **36** with one equivalent of electrophile showed low selectivity. Equimolar amounts of **36** and methyl iodide yielded **38** and **39** in the ratio 65:35. We expect the same behaviour from **40**.

iv) **4-(Methylthio)- (49) and 4-(Isopropylthio)-1-methoxybenzene (59).** It has already been shown that the ortho directing ability of oxygen predominates in the monometalation of these two products.[8] Direct dimetalation of the two substrates follows two different dilithiation patterns. Both substrates are

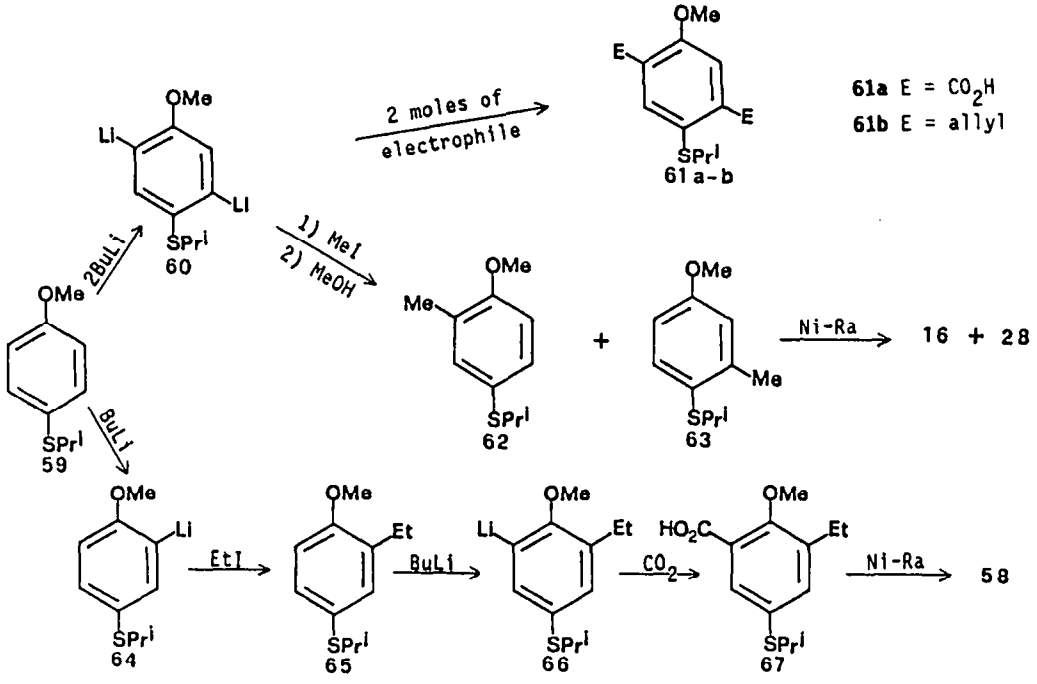
Scheme 6



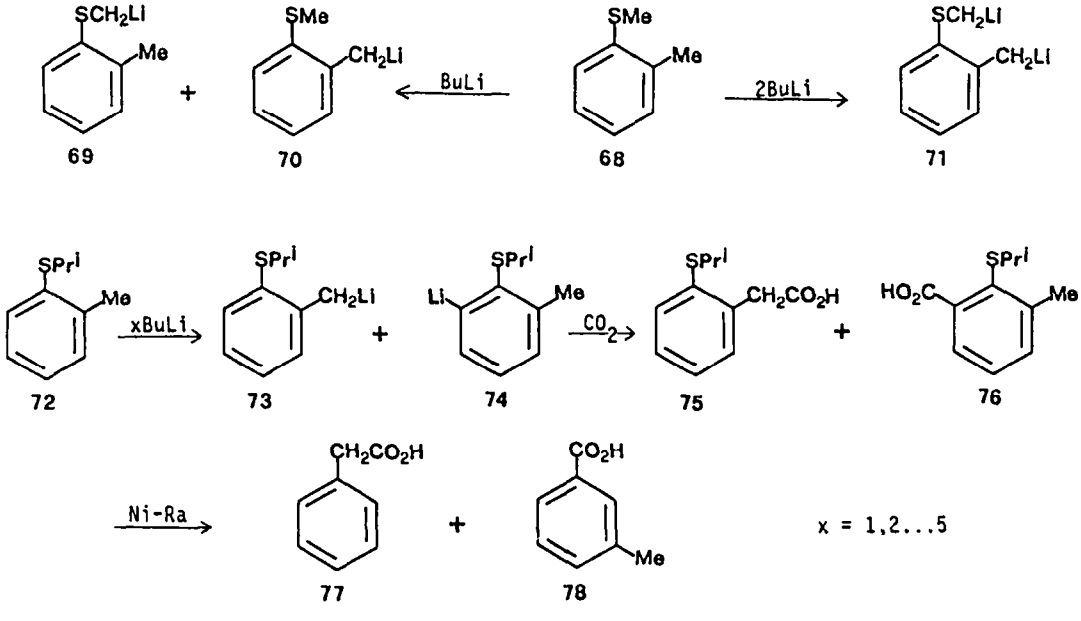
lithiated at the ortho position of the methoxy group; however, the methylthio derivative is lithiated at the methylthio carbon atom (**50**), while the isopropylthio derivative is lithiated at the ortho position of the isopropylthio group (**60**) (Schemes 6-7).[9]

The two dianions cannot be functionalized regioselectively upon treatment

Scheme 7



Scheme 8



with one equivalent of electrophile. In both cases isomeric mixtures were obtained. Successive additions of one equivalent of methyl iodide and of one equivalent of methanol to **50** and to **60** yielded **52** and **53** (molar ratio 60:40), and **62** and **63** (molar ratio 45:55), respectively. All isomers were identified by GC/MS analysis and through their desulphuration products. Isomers **52** and **53** display the same molecular ion M^+ at m/z 168 and yield **16** and **17** upon desulphuration; **62** and **63** have the same M^+ at m/z 196 and yield **16** and **28**.

Regioselective bifunctionalization was obtained with two successive monometalations.In this case, however, the two electrophiles enter both at the ortho positions relative to the methoxy group, as shown by the formation of **57** from **49** and of **67** from **59**. The ortho position of the carboxylic group is shown by the ^1H NMR spectrum, which shows the signal of the methoxy group at δ 3.95-4.00. This value is 0.30-0.35 ppm lower than that of the corresponding starting materials. Moreover, desulphuration yields in both cases **58**.

v) **2-(Methylthio)- (68) and 2-(Isopropylthio)-1-methylbenzene (72).** Monometalation of **68** is not selective: it yields a mixture of substitution products either at the methyl or at the thiomethyl carbon.[20] Dimetalation yields exclusively the substitution product of the methyl and thiomethyl hydrogens (Scheme 8).[12]

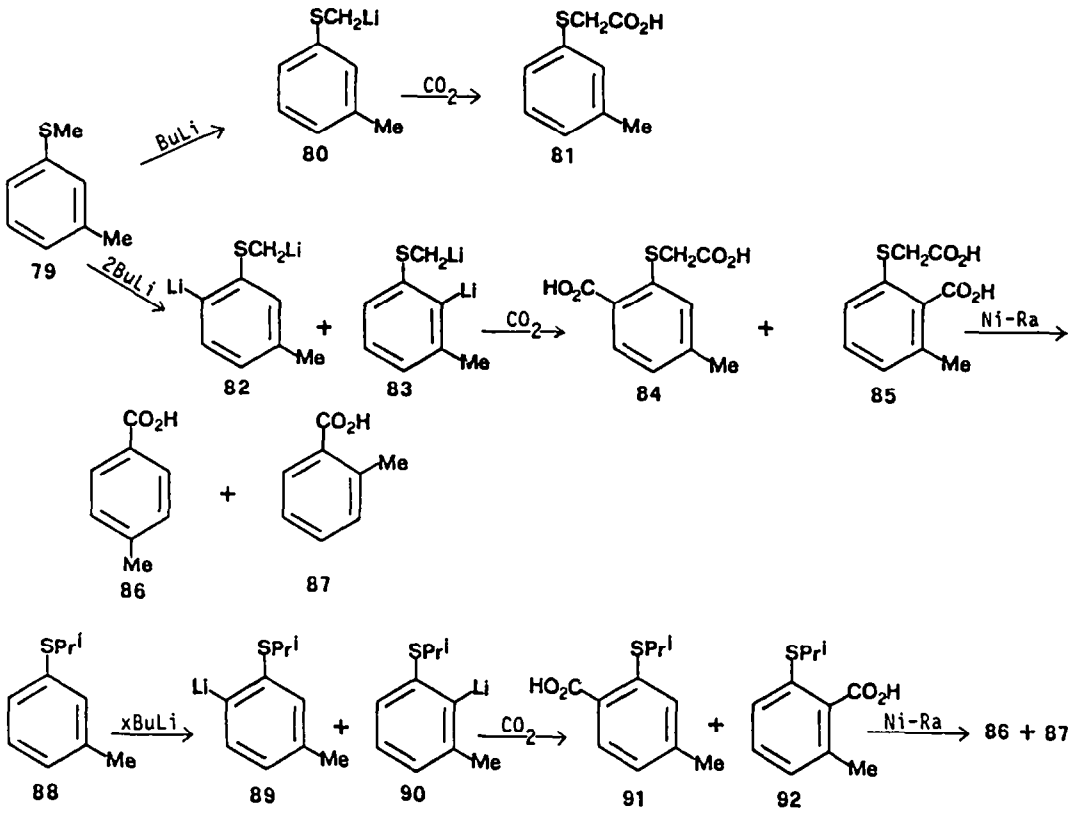
Metalation of **72** yields a mixture of monolithiated products independently of the number of organolithium reagent equivalents (Scheme 8). The lithium cation substitutes a hydrogen group, as shown by the formation of the corresponding acids **75** and **76** upon treatment with carbon dioxide.[20] Lithiation of one of the two positions prevents further metalation.

vi) **3-(Methylthio)- (79) and 3-(Isopropylthio)-1-methylbenzene (88).** Monolithiation of **79** substitutes selectively the thiomethyl hydrogen (**80**) and, after carbonation, it yields the acid **81** (Scheme 9). Dilithiation of **79** is not totally selective: it yields the products **84** and **85** in the ratio 85:15 (GLC). The latter were identified by ^1H NMR analysis of the mixture (the two signals were at δ 3.70 and δ 3.80 chemical shifts characteristic of SCH_2 and were in the ratio 85:15) and by GLC comparison of the desulphuration products (**86** and **87**) with authentic samples.

One, two or more equivalents of organolithium reagent react with **88** yielding the monolithiated product **89** with traces of **90** (Scheme 9). The intermediates were identified through their corresponding acids (after carbonation) and their corresponding desulphuration products.

vii) **4-(Methylthio)- (93) and 4-(Isopropylthio)-1-methylbenzene (96).** Monometalation of **93** yields exclusively the substitution product of the thiomethyl hydrogen. In dimetalation the second lithium atom enters ortho to the thiomethyl function[9] (Scheme 10). On the contrary, lithiation of **96** yields exclusively **97**, the ortho lithiated intermediate, independently of the number of equivalents of organolithium reagent (Scheme 10). As expected, the lithium

Scheme 9

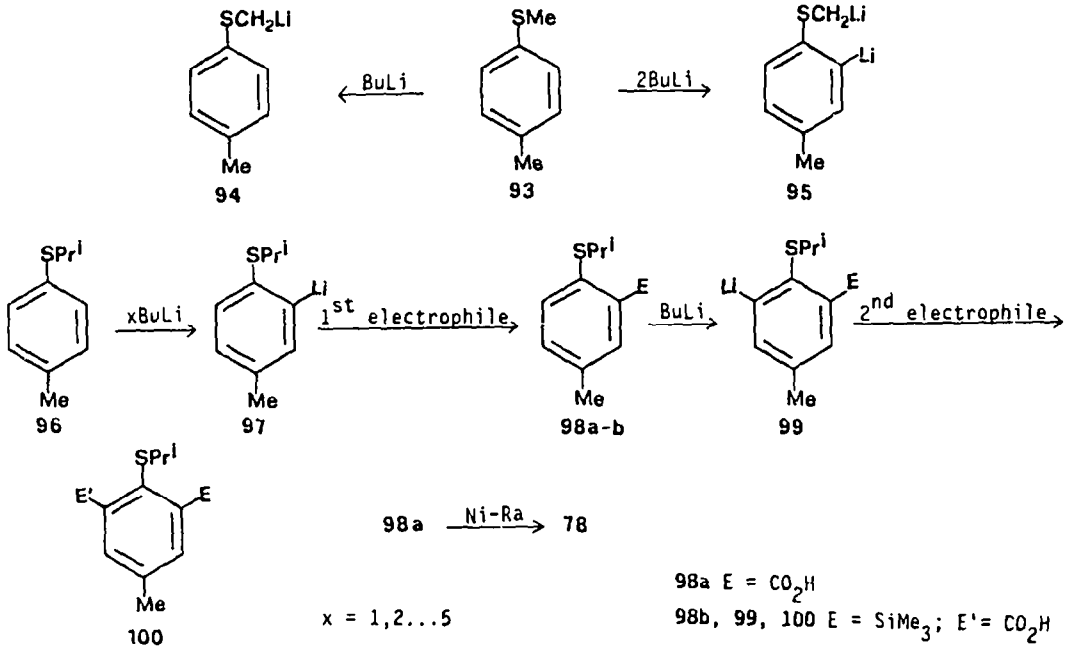


atom enters ortho to the thioethereal group, as shown by the identification, after carbonation, of the acid **98a**.

Disubstitution of **96** can be performed in a one-flask, two-step procedure, as shown by the preparation of **100**.

The above results emphasize the synthetic potential of dilithiation in the preparation of polyfunctionalized aromatic derivatives either in a single or in two successive "one-flask" monolithiation steps. In particular, from compounds **1**, **11**, and **23** one can obtain the dilithio compounds **2**, **12**, **24** in good yields allowing the regioselective introduction of two identical functional groups in the molecule. On the other hand, these intermediates do not allow the regioselective introduction of two different functional groups, since a mixture of isomers is always formed; this is probably due to the similar reactivity of the two carbanionic centres towards electrophiles, the thio-

Scheme 10



methylenic carbanion being slightly more reactive than the ring carbanion. This obstacle can be overcome by two successive monometalations which allow the introduction in the molecule of different functional groups, one in each step.

Similarly, direct dimetalation of compounds **35**, **49**, **59** yields the dilithio derivatives **36**, **50**, and **60**. Two identical functional groups can be introduced upon treatment with electrophiles: the first enters in ortho to the methoxy group of each compound, while the second functionalizes the thiomethyl carbon of **35** and **49** and the carbon in ortho to thioisopropyl group of **59**. The dilithio intermediates do not permit the regioselective introduction of two different electrophiles and a mixture of isomers is obtained. On the other hand, two successive monometalations allow the introduction of two different electrophiles, even though the sites of reaction are not the same as in direct dimetalation. The two-step procedure functionalizes the two positions in ortho to the methoxy group.

These results agree with previous data which indicated that the oxygen has a high directing power:[17] in direct dimetalation, because of coordination of the lithium cation with the oxygen atom, the first molecule of organolithium reagent reacts with the ring carbon atom in ortho to the alkoxy group. The oxygen atom at this point is no longer available for coordination so that the second organolithium molecule of reagent reacts either with the

thiomethyl carbon, or, for higher alkylthio homologues, with the ring carbon ortho to the sulphur atom. When the reaction is performed in two successive steps, the first step allows the introduction of the first electrophile; at this point the oxygen atom is available for coordination with the second lithium cation, so that the site of reaction is again that in ortho to the alkoxy group.

Both positions in ortho to the alkoxy group being eventually substituted, the sulphur atom directs further lithiation in ortho to the alkylthio substituent. Trilithiation reactions will be reported in the future.

Methyl substituted (alkylthio)benzenes undergo direct dimetalation only with the thiomethyl derivatives. While the meta and para derivatives (**79** and **93**) are attacked at the thiomethyl carbon and at the ortho ring carbon, the ortho derivative **68**[12] is lithiated at the thiomethyl and at the methyl carbons.

On the contrary, higher (alkylthio)methylbenzenes homologues can be only monolithiated even in excess of organolithium reagent. The absence of thioalkyl metalation is due to the destabilization of the thioalkyl carbanion induced by the additional methyl groups.[20] Thus, the metalation is directed in ortho by the thioalkyl group but, since sulphur, like oxygen, can coordinate only one molecule of organolithium reagent, only one of the two ortho positions can react. However, after reaction with an electrophile the functionalized compounds possess an alkylthio group capable again of coordination which can direct further lithiation into the ring ortho position or into the ortho methyl substituent.

It is also noteworthy that annular metalation of the meta (alkylthio)-alkylbenzenes **79** and **88** occurs almost exclusively in para to the methyl group. This would be in agreement with the disactivating power of alkyl substituents, the ortho position being the most affected;[1] steric effects cannot however be completely excluded.[19]

The reported results indicate that lithiation of thioethers is a useful "one-flask" procedure to prepare sulphur-containing products, or other derivatives without the alkylthio group which has been removed after its use as an orienting group. Moreover, a silylation reaction protects the site which is first lithiated. The trimethylsilyl group can be removed later, thus permitting a further expansion of the number of different products conveniently prepared with this procedure. A good example is the preparation of **33** which has a carboxylic group in ortho to the thioalkylic group whose further desulphuration to **34** allows the preparation of a product in which the carboxylic group is in meta to the alkoxy group.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage microscope and are uncorrected. Infrared spectra were taken on a Perkin-Elmer (Model 1310) spectrophotometer. ^{1}H NMR spectra were taken on a Varian EM 360A spectrometer with tetramethylsilane as internal reference. The following abbreviations are used to describe the signal multiplicity: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; br: broad. Gas chromatographic analyses were carried out with a Carlo Erba Fractovap (Model 4200) gas-chromatograph equipped with a flame ionization detector and a 5 m Apiezon L capillary column. Mass spectra were recorded at 70 eV with a "Hitachi" Perkin-Elmer RMU-6D spectrometer, by use of the direct-inlet system. The GC/MS analyses were performed with a Finnigan 1020 GC/MS instrument fitted with a capillary column. Microanalyses were carried out with a Carlo Erba (Model 1106) elemental analyzer.

Commercially available reagent-grade starting materials and solvents were used. Solutions of n-butyllithium in hexane were obtained from the Aldrich Chemical Company and were analyzed by the Gilman double titration method before use.[21] TMEDA was obtained from the Aldrich Chemical Company and distilled from calcium hydride before use. Hexane was distilled from lithium aluminum hydride.

Starting materials

(Methylthio)benzene (**1**) was obtained from Janssen Chimica. 2-(Methylthio)- (**11**), 2-(isopropylthio)- (**23**), 3-(methylthio)- (**35**), 3-(isopropylthio)- (**40**), 4-(methylthio)- (**49**) and 4-(isopropylthio)-1-methoxybenzene (**59**), 2-(isopropylthio)- (**72**), 3-(methylthio)- (**79**), 3-(isopropylthio)- (**88**) and 4-(isopropylthio)-1-methyl-benzene (**96**) were prepared by published methods starting from the corresponding arenethiols and dimethylsulphate or 2-bromopropane.[17,22-27]

Authentic samples

(Ethylthio)benzene (**4b**), 2,2'-dithiobisbenzoic acid (**10**), methoxybenzene (**17**), 2-methyl- (**16**), 3-methyl- (**28**), 2,6-dimethyl- (**47b**) and 2,4-dimethyl-1-methoxybenzene (**48b**), 2-methoxy- (**22**), 3-methoxy- (**34**), 2-methyl- (**87**), 3-methyl- (**78**) and 4-methyl-benzoic acid (**86**) and phenylacetic acid (**77**) were purchased from the Aldrich Chemical Company.

1-Phenyl-2-(phenylthio)ethanone (**4a**), 1-(ethylthio)-2-methyl- (**3b**), 1-methyl-2-(methylthio)- (**5b**), 1-(ethylthio)-2-(phenylthio)- (**9d**), 1,2-bis-(buthylthio)- (**9e**) and 4-(ethylthio)-1-methoxy-benzene (**53**), 2-(ethylthio)- (**4c**) and 3-ethyl-2-methoxy-benzoic acid (**58**), 2-(methylthio)benzophenone (**5a**) [(2-methylphenyl)thio]- (**5c**) and [(3-methylphenyl)thio]-acetic acid (**81**), 2-methoxy- (**47a**) and 4-methoxy-isophtalic acid (**48a**) were prepared by published procedures.[9,14,15,23,26,28-35]

Sequential one-flask introduction of two different electrophiles on 2

a) **Reaction with benzoyl chloride-methanol**

To a vigorously stirred solution of 1 (4.5 g, 36 mmol), anhydrous TMEDA (9.2 g, 78 mmol) and anhydrous hexane (100 ml) cooled to 0°C a 1.2 M solution of n-butyllithium in hexane (65.8 ml, 79 mmol) was gradually added under nitrogen, and stirring was continued at room temperature for 12 h. The resulting solution of 2 was then cooled to -80°C and a solution of benzoyl chloride (5 g, 36 mmol) in anhydrous ethyl ether (20 ml) is gradually added under nitrogen. When the addition was complete the mixture was stirred at -80°C for 1 h. It was then treated at the same temperature with an excess of methanol. The mixture was then allowed to warm up, left at room temperature for 2 h, and poured into water, and the pH was adjusted to 5-6 by addition of 10% hydrochloric acid. The organic layer was separated, the aqueous layer extracted with ethyl ether, and the organic solutions combined and dried (Na_2SO_4). GLC examination of the ethereal solution showed two peaks, with retention times identical to those of authentic samples of **4a**, **5a**, in the ratio 70/30.

b) **Reaction with iodomethane-methanol**

To a vigorously stirred solution of 2, iodomethane (5.1 g, 36 mmol) was gradually added at 0°C. After the addition was completed the mixture was allowed to warm to room temperature and kept 12 h with stirring. It was then treated at 0°C with an excess of methanol. The following work-up was as described above. GLC examination of the ethereal solution showed four peaks, with retention times identical to those of authentic samples of **4b**, **5b**, in the ratio of 60/40.

c) **Reaction with iodomethane-carbon dioxide**

The solution obtained as previously described by reaction of 2 with iodomethane was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated successively with 10% aqueous sodium bicarbonate and then with ethyl ether. The alkali layer was separated, washed with ethyl ether, and then acidified with cold concentrated hydrochloric acid, extracted with ethyl ether, and dried (Na_2SO_4). A portion of this solution was treated with ethyl ether containing a 30% molar excess of diazomethane. The ethyl ether and excess diazomethane were allowed to evaporate off. The resulting methyl esters were analyzed by GLC, which gave two peaks with retention times identical to those of authentic sample of the methyl esters of **4c**, **5c**, in the ratio of 60/40.

Sequential, one-flask introduction of two different electrophiles on 1

a) **2-(Ethylthio)benzoic acid (4c).** - A solution of 1 (4.5 g, 36 mmol), anhydrous TMEDA (4.6 g, 39 mmol) and anhydrous hexane (100 ml) was treated dropwise at 0°C with n-butyllithium in hexane (33 ml, 39 mmol). The mixture was worked up as above described. The resulting solution of **6** was then cooled to

10°C, treated dropwise with iodomethane (5.1 g, 36 mmol), allowed to warm and left at room temperature for 4 h with stirring. A portion of this solution, analyzed by GLC, gave one peak with retention time identical to that of authentic sample of **4b**.

The above solution of **4b** was treated at 0°C with n-butyllithium in hexane (33 ml, 39 mmol). After the usual work-up, the resulting solution of **8a** was poured onto ca. 100 g of crushed solid carbon dioxide and worked-up in the same manner above described. The GLC analyses of the methyl esters from the sodium bicarbonate phase exhibited one peak. The component responsible for this peak was identified as **4c**. Yield 55%, mp 131°C (EtOH-water) (lit.[31] mp 131-132°C).

b) **1-(Ethylthio)-2-(trimethylsilyl)benzene (9a).** - A solution of **8a** (36 mmol), obtained as above described, was treated dropwise at 0°C with a solution of chlorotrimethylsilane (3.9 g, 36 mmol) in anhydrous ethyl ether (10 ml). When the addition was complete, the resulting mixture was allowed to warm and left at room temperature for 12 h with stirring. The reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with ethyl ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash-chromatography using petroleum ether (bp 40-70°)/ethyl ether (1:1) as eluent. Yield 63%; bp 156-158°C (28mm Hg); n_D^{21}= 1.5691. ^{1}H NMR ($CDCl_3$) δ: 0.3 (9H, s, $(C\underline{H}_3)_3Si$), 1.10 (3H, t, $C\underline{H}_3CH_2$), 2.70 (2H, q, $C\underline{H}_2$), 7.10 (4H, m, Ar-$\underline{H}$). $\underline{m}/\underline{z}$ 210 (M^+). (Found C, 62.58; H, 8.71; S, 15.07. $C_{11}H_{18}SSi$ requires C, 62.80; H, 8.62; S, 15.24).

The following compounds were similarly obtained from **8a** and iodomethane, iodoethane, dipropyldisulphide and diphenyldisulphide, respectively:

c) **1-(Ethylthio)-2-methylbenzene (3b).** - Yield 75%; bp 120-122°C (15mm Hg) (lit.[9] bp 65-66°C (2mm Hg)). ^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, t, $C\underline{H}_3CH_2$), 2.30 (3H, s, $ArC\underline{H}_3$), 2.90 (2H, q, $CH_3C\underline{H}_2$), 7.20 (4H, m, Ar-$\underline{H}$).

d) **1-Ethyl-2-(ethylthio)benzene (9b).** - Yield 71%; bp 126-128°C (15mm Hg) (lit.[16] bp 144°C (50mm Hg)). ^{1}H NMR ($CDCl_3$) δ: 1.20 (6H, m, $C\underline{H}_3$), 2.60 (2H, q, $ArC\underline{H}_2$), 2.95 (2H, q, $SC\underline{H}_2$), 7.15 (4H, m, Ar-$\underline{H}$).

e) **1-(Ethylthio)-2-(propylthio)benzene (9c).** - The crude product was distilled under reduced pressure. Yield 71%; bp 105-107°C (15mm Hg); n_D^{22}= 1.5508. ^{1}H NMR ($CDCl_3$): δ 0.9 (6H, m, $C\underline{H}_3$), 1.70 (2H, m, $SCH_2C\underline{H}_2$), 2.50 (4H, m, $SC\underline{H}_2$), 7.25 (4H, m, Ar-$\underline{H}$). $\underline{m}/\underline{z}$: 212 ($M^+$). (Found C, 62.04; H, 7.49; S, 30.01. $C_{11}H_{16}S_2$ requires C, 62.21; H, 7.60; S, 30.19).

f) **1-(Ethylthio)-2-(phenylthio)benzene (9d).** - Yield 61%; bp 162-163°C (12mm Hg) (lit.[14] bp 141-142°C (3mm Hg)). ^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, t, $C\underline{H}_3$), 2.85 (2H, q, $C\underline{H}_2$), 7.30 (9H, m, Ar-$\underline{H}$).

g) **1,2-Bis(butylthio)benzene (9e).** - A solution of **6**, obtained as above described, was treated dropwise at 0°C with a solution of 1-iodopropane (6.1 g,

36 mmol) in anhydrous ethyl ether (10 ml). When the addition was complete, the resulting mixture was allowed to warm and left at room temperature for 8 h with stirring. The reaction mixture was then treated at 0°C with n-butyllithium in hexane (33 ml, 39 mmol). After the usual work-up, the resulting solution of **8b** was treated dropwise at 0°C with a solution of dibutyldisulphide (6.4 g, 36 mmol) in anhydrous ethyl ether (10 ml). When the addition was complete, the resulting mixture was allowed to warm, left at room temperature for 12 h with stirring and worked-up in the same manner described for **9a**. Yield 62%; bp 140-141°C (1mm Hg). The IR and ^{1}H NMR spectra were identical with those of an authentic sample of **9e**.[15]

h) **2-[[(propylthio)methyl]thio]benzoic acid (9f)**. - A solution of **6**, obtained as above described, was treated dropwise at 0°C with a solution of dipropyldisulphide (5.4 g, 36 mmol) in anhydrous ethyl ether (10 ml). When the addition was complete, the resulting mixture was allowed to warm and heated for 24 h at reflux with stirring. The reaction mixture was then cooled and treated at 0°C with n-butyllithium in hexane (33 ml, 39 mmol). After the usual work-up, the resulting solution of **8c** was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was diluted with ethyl ether (50 ml) and water (100 ml) and the pH adjusted to 7 by addition of ammomium acetate. After the usual work-up, the crude product was purified by flash-chromatography using petroleum ether (bp 40-70°C)/ethyl ether (1:1) as eluent. Yield 58%; bp 145-147°C; n_D^{21}= 1.5820. IR (liquid film, cm^{-1}): 3450, 3050 (OH), 1715 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t, $C\underline{H}_3$), 1.55 (2H, m, $C\underline{H}_2CH_2S$), 2.55 (2H, t, $CH_2C\underline{H}_2S$), 3.60 (2H, s, $SC\underline{H}_2S$), 7.30 (4H, m, Ar-H), 7.90 (1H, s, br, COOH, D_2O exchanged). m/z 242 (M^+). (Found C, 54.30; H, 5.71; S, 26.23. $C_{11}H_{14}O_2S_2$ requires C, 54.51; H, 5.82; S, 26.46).

If the hydrolysis of the reaction mixture is performed with aqueous hydrochloric acid, the **2,2'-dithiobisbenzoic acid (10)** is obtained in 60% yield; mp 289-290°C undepressed in admixture with a sample of commercial product.

i) **2-[(2-hydroxy-2-methylbutyl)thio]benzoic acid (9g)**. - A solution of **6**, obtained as above described, was treated dropwise at 0°C with a solution of butanone (2.6 g, 36 mmol) in anhydrous ethyl ether (5 ml). When the addition was complete, the resulting mixture was allowed to warm and left at room temperature for 12 h with stirring. The reaction mixture was then treated at 0°C with n-butyllithium in hexane (33 ml, 39 mmol). After the usual work-up, the resulting solution of **8d** was poured onto ca. 100 g of crushed solid carbon dioxide and worked-up in the same manner described for **4c**. The crude product was purified by flash-chromatography with ethyl acetate as eluent. Yield 48%; mp 141-143°C. IR ($CHCl_3$, cm^{-1}): 3510, 3100 (OH), 1715 (C=O). ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, $C\underline{H}_3CH_2$), 1.60 (3H, s, C-$C\underline{H}_3$), 2.55 (2H, q, $CH_3C\underline{H}_2$), 3.65 (2H, s, $SC\underline{H}_2$), 4.50 (1H, s, br, OH, D_2O exchanged), 7.40 (4H, m, Ar-H), 9.45 (1H, s, br, COOH, D_2O exchanged). m/z 240 (M^+). (Found C, 59.70; H, 6.82; S, 13.19. $C_{12}H_{16}O_3S$ requires C, 59.97; H, 6.71; S, 13.34).

Sequential, one-flask introduction of two different electrophiles on 12

To a solution of **11** (5.5 g, 36 mmol), anhydrous TMEDA (9.2 g, 78 mmol) and anhydrous hexane (100 ml) cooled to 0°C a 1.2 M solution of n-butyllithium in hexane (65.8 ml, 79 mmol) was gradually added under nitrogen. The mixture was worked-up as described for **2** and then treated dropwise at 0°C with iodomethane (5.1 g, 36 mmol). After the usual work-up, the mixture was treated at 0°C with an excess of methanol. The mixture was then allowed to warm, left at room temperature for 2 h and poured into water. The organic layer was separated and the aqueous layer extracted with ethyl ether. The organic solutions were combined, dried (Na_2SO_4) and concentrated. GLC analysis of the residue showed two peaks, in the ratio 40/60. Identification of the components (**14** and **15**) responsible for these peaks was accomplished after desulphuration with Raney nickel.

A solution of these components (10 mmol) in 95% ethanol was refluxed 2 h with Raney nickel (2 g).[17] The mixture was filtered, evaporated and the residue diluted with ethyl ether. GLC gave two peaks with had retention times identical with those of authentic samples of **16** and **17**, in the ratio 40/60.

Sequential, one-flask introduction of two different electrophiles on 11

a) **3-(Ethylthio)-2-methoxybenzoic acid (21a).** - The reaction was performed as described for **4c**. The crude product was purified by flash-chromatography with ethyl acetate as eluent. Yield 51%; mp 84-86°C. IR ($CHCl_3$, cm^{-1}): 3520, 3210 (OH), 1740, 1700 (C=O). ^1H NMR ($CDCl_3$) δ: 1.20 (3H, t, $C\underline{H}_3CH_2$), 2.90 (2H, q, $CH_2\underline{H}_2$), 3.90 (3H, s, $OC\underline{H}_3$), 7.45 (3H, m, Ar-H), 9.90 (1H, s, br, COOH, D_2O exchanged). m/z 212 (M^+). (Found C, 56.35; H, 5.65; S, 14.98. $C_{10}H_{12}O_3S$ requires C, 56.58; H, 5.70; S, 15.10).

This compound after desulphuration gave **22** in 91% yield.

b) **1-methoxy-2-(trimethylsilyl)-6-(propylthio)benzene (21b).**- The reaction was performed as described for **9a** by using iodoethane and chlorotrimethylsilane as electrophiles. The crude product was distilled under reduced pressure. Yield 56%; bp 173-175°C (21mm Hg); n_D^{20}= 1.5421. ^1H NMR ($CDCl_3$) δ: 0.20 (9H, s, $(C\underline{H}_3)_3Si$), 0.95 (3H, t, $C\underline{H}_3CH_2$) 1.55 (2H, m, $CH_3C\underline{H}_2$), 2.65 (2H, t, $SC\underline{H}_2$), 3.75 (3H, s, $OC\underline{H}_3$), 6.90 (3H, m, Ar-H). m/z 254 (M^+). (Found C, 61.18; H, 8.63; S, 12.43. $C_{13}H_{22}OSSi$ requires C, 61.36; H, 8.72; S, 12.60).

Sequential, one-flask introduction of two different electrophiles on 24

The reaction was performed as described for **12**. GLC analysis of the residue showed two peaks in the ratio 48/52. Identification of the components (**26** and **27**) responsible for these peaks was accomplished after desulphuration. The products **16** and **28** were identified by comparison of their GLC retention times with those of authentic samples.

Sequential, one-flask introduction of two different electrophiles on 23

a) **4-Ethyl-3-methoxy-2-(isopropylthio)benzoic acid (32a).** - The reaction was performed as described for **4c** by using iodoethane and carbon dioxide as electrophiles. The crude product was purified by flash-chromatography with ethyl ether/hexane (20:1) as eluent. Yield 59%; n_D^{25}= 1.5148. IR ($CHCl_3$, cm^{-1}): 3520, 3120 (OH), 1720 (C=O). ^1H NMR ($CDCl_3$) δ: 1.30 (9H, m, $C\underline{H}_3$), 2.75 (2H, q, $C\underline{H}_2$), 3.55 (1H, m, C<u>H</u>), 3.90 (3H, s, $OC\underline{H}_3$), 7.50 (2H, m, Ar-<u>H</u>), 9.85 (s, br, COOH, D_2O exchanged). <u>m/z</u> 254 (M^+). (Found C, 61.20; H, 7.08; S, 12.43. $C_{13}H_{18}O_3S$ requires C, 61.39; H, 7.13; S, 12.60).

b) **3-Methoxy-4-(trimethylsilyl)-2-(isopropylthio)benzoic acid (32b).** - The reaction was performed as described for **4c** by using chlorotrimethylsilane and carbon dioxide as electrophiles. The crude product was distilled under reduced pressure. Yield 51%; bp 140-142°C (21mm Hg); n_D^{21}= 1.5527. IR ($CHCl_3$, cm^{-1}): 3520, 3200 (OH), 1735 (C=O). ^1H NMR ($CDCl_3$) δ: 0.25 (9H, s, $(C\underline{H}_3)_3Si$), 0.90 (6H, d, $(C\underline{H}_3)_2CH$), 3.50 (1H, m, C<u>H</u>), 3.60 (3H, s, $OC\underline{H}_3$), 7.20 (2H, m, Ar-<u>H</u>), 9.90 (1H, s, br, COOH, D_2O exchanged). <u>m/z</u> 298 (M^+). (Found C, 56.19; H, 7.36; S, 10.51. $C_{14}H_{22}O_3SSi$ requires C, 56.34; H, 7.43; S, 10.74).

3-Methoxy-2-(isopropylthio)benzoic acid (33). - A mixture of **32b** (0.5 g, 1.7 mmol), cesium fluoride (5.2 g, 34 mmol), dimethylformamide (20 ml) and water (2 ml) was refluxed for 24 h. The mixture was then poured into water and extracted with ethyl ether. The extract was carefully washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography with chloroform as eluent. Yield 81%; n_D^{20}= 1.5289. IR ($CHCl_3$, cm^{-1}): 3500, 3150 (OH), 1720 (C=O). ^1H NMR ($CDCl_3$) δ: 1.00 (6H, d, $(C\underline{H}_3)_2CH$), 3.55 (1H, m, C<u>H</u>), 3.70 (3H, s, $OC\underline{H}_3$). 7.30 (3H, m, Ar-<u>H</u>), 7.90 (1H, s, br, COOH, D_2O exchanged). <u>m/z</u> 226 (M^+). (Found C, 58.21; H, 6.17; S, 14.01. $C_{11}H_{14}O_3S$ requires C, 58.38; H, 6.24; S, 14.17).

This compound, after desulphuration gave **34** in almost quantitative yield.

One-step introduction of two electrophiles on 35

2-[(carboxymethyl)thio]-6-methoxybenzoic acid (37) . - A solution of **35** (5.5 g, 36 mmol), anhydrous TMEDA (9.2 g, 78 mmol) and anhydrous hexane (100 ml) was lithiated with 1.2 M solution of <u>n</u>-butyllithium in hexane (65.8 ml, 79 mmol) in the same manner described for **1** in order to prepare **36**. The resulting mixture was poured onto ca. 100 g of crushed solid carbon dioxide and worked-up as above described. The crude product obtained after acidification of the bicarbonate phase was purified by flash-chromatography using as eluent at first hexane alone and later hexane/ethyl acetate (3:1). Yield 45%; mp 152-153°C. IR (nujol, cm^{-1}): 3100 (OH), 1735, 1690 (C=O). ^1H NMR ($(CD_3)_2CO$) δ: 3.75 (1H, s, $SC\underline{H}_2$), 3.80 (3H, s, $OC\underline{H}_3$), 7.25 (3H, m, Ar-<u>H</u>), 8.90 (1H, s, br, COOH, D_2O exchanged), 9.50 (1H, s, br, COOH, D_2O exchanged). <u>m/z</u> 242 (M^+)

(Found C, 49.70; H, 4.20; S, 13.07. $C_{10}H_{10}O_5S$ requires C, 49.58; H, 4.16; S, 13.23).

Sequential, one-flask introduction of two different electrophiles on 36

The reaction was performed as described for **12**. GLC analyses of the residue showed two peaks in the ratio 65/35. Identification of the components (**38** and **39**) responsible for these peaks was accomplished after desulphuration. The products **16** and **17** were identified by comparison of their GLC retention times with those of authentic samples.

One-step introduction of two electrophiles on 40

The compound **40** was dilithiated and treated with solid carbon dioxide in the same manner described for **35**. The GLC analyses of the methyl esters from the sodium bicarbonate phase exhibited three peaks, in the ratio 80/13/7. Identification of the components (**44a**, **45a** and **46a**) responsible for these peaks was accomplished after desulphuration. The resulting products **47a** and **48a** (ratio 80/20) were identified by comparison of their GLC retention times with those of authentic samples.

Analogously, using iodomethane instead of carbon dioxide, **44b**, **45b**, **46b** were obtained in the ratio 78/15/7 (GLC). These compounds, after desulphuration, gave **47b** and **48b**, in the ratio 78/22, which were identified by comparison of their GLC retention times with those of authentic samples.

Sequential, one-flask introduction of two different electrophiles on 50

The reaction was performed as described for **12**. GLC analyses of the residue showed two peaks in the ratio 60/40. Identification of the components (**52** and **53**) responsible for these peaks was accomplished after desulphuration. The products **16** and **17** were identified by comparison of their GLC retention times with those of authentic samples.

Sequential, one-flask introduction of two different electrophiles on 49

3-Ethyl-2-methoxy-5-(methylthio)benzoic acid (57). - The reaction was performed as described for **32a**. The crude product was purified by flash-chromatography using chloroform as eluent. Yield 57%; n_D^{22}= 1.5805. IR ($CHCl_3$, cm^{-1}): 3315, 3050 (OH), 1750 (C=O). ^1H NMR ($CDCl_3$) δ: 1.20 (3H, t, $C\underline{H}_3CH_2$), 2.40 (3H, s, $SC\underline{H}_3$), 2.55 (2H, q, $C\underline{H}_2$), 4.00 (1H, s, $OC\underline{H}_3$), 7.35 (2H, m, Ar-$\underline{H}$), 8.50 (1H, s, br, COOH, D_2O exchanged). $\underline{m}/\underline{z}$ 226 (M^+). (Found C, 58.22; H, 6.18; S, 14.01. $C_{11}H_{14}O_3S$ requires C, 58.38; H, 6.24; S, 14.17).

After desulphuration **57** afforded **58** in 63% yield; mp 57-58°C (ligroin) (lit.[32] mp 58-59°C).

When the hydrolysis was performed after treatment with iodoethane, **1-ethyl-**

2-methoxy-5-(methylthio)benzene (55) was isolated. Yield 78%; bp 148-150°C (20mm Hg); n_D^{20}= 1.5642. ^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t, $C\underline{H}_3CH_2$), 2.35 (3H, s, $SC\underline{H}_3$), 2.50 (2H, q, CH_2), 3.70 (3H, s, $OC\underline{H}_3$), 6.95 (3H, m, Ar-H). (Found C, 65.75; H, 7.65; S, 17.38. $C_{10}H_{14}OS$ requires C, 65.89; H, 7.74; S, 17.59).

To a solution of **55** (6.5 g, 36 mmol), anhydrous TMEDA (4.6 g, 39 mmol) and anhydrous hexane (100 ml) a 1.2 M solution of n-butyllithium in hexane (33 ml 39.5 mmol) was gradually added with stirring at room temperature. After the usual work-up, the mixture was poured into ca 100 g of solid carbon dioxide and worked-up in the same manner above described to furnish **57** in 61% yield.

Sequential, one-flask introduction of two different electrophiles on 60

The reaction was performed as described for **12**. GLC analyses of the residue showed two peaks in the ratio 45/55. Identification of the components (**62** and **63**) responsible for these peaks was accomplished after desulphuration. The products **16** and **28** were identified by comparison of their GLC retention times with those of authentic samples.

Sequential, one-flask introduction of two different electrophiles on 59

3-Ethyl-2-methoxy-5-(isopropylthio)benzoic acid (67). - The reaction was performed as described for **32a**. The crude product was purified by flash-chromatography using chloroform as eluent. Yield 59%; mp 110-112°C (EtOH-water). IR ($CHCl_3$, cm^{-1}): 3450, 3120 (OH), 1685 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t, $C\underline{H}_3CH_2$), 1.25 (6H, d, $(C\underline{H}_3)_2CH$), 2.60 (2H, q, $C\underline{H}_2$), 3.20 (1H, m, C<u>H</u>), 3.95 (3H, s, $OC\underline{H}_3$), 7.55 (2H, m, Ar-H), 10.4 (1H, s, br, COOH, D_2O exchanged). m/z 254 (M^+). (Found C, 61.55; H, 7.20; S, 12.44. $C_{13}H_{18}O_3S$ requires C, 61.39; H, 7.13; S, 12.60).

After desulphuration **67** afforded **58** in 66% yield.

When the hydrolysis was performed after treatment with iodoethane **1-ethyl-2-methoxy-5-(isopropylthio)benzene (65)** was isolated. Yield 75%; bp 183-185°C (24mm Hg); n_D^{20}= 1.5430. ^{1}H NMR ($CDCl_3$) δ: 1.20 (9H, m, $C\underline{H}_3$), 2.55 (2H, q, $C\underline{H}_2$), 3.15 (1H, m, C<u>H</u>), 3.75 (3H, s, $OC\underline{H}_3$), 6.95 (3H, m, Ar-H). (Found C, 18.39; H, 8.51; S, 15.05. $C_{12}H_{18}OS$ requires C, 68.52; H, 8.62; S, 15.24).

The compound **65** was converted into **67** in the same manner described for **55**. Yield 59%.

Attempts to introduce in one-step two electrophiles into 72

A solution of **72** (6 g, 36 mmol), anhydrous TMEDA (9.2 g, 78 mmol) and anhydrous hexane (100 ml) was treated with 1.2 M solution of n-butyllithium in hexane (65.8 ml, 79 mmol) in the same manner above described. The resulting mixture was poured onto ca. 100 g of crushed solid carbon dioxide and worked-up as described for **37**. GLC analysis of the methyl esters of the mixture from the sodium bicarbonate phase showed two peaks in the ratio 53/47. Identifica-

tion of the components (methyl esters of **75** and **76**) responsible for these peaks was accomplished by desulphuration. In fact, after treatment with Raney nickel, the GLC analyses showed two peaks, with retention times identical to those of methyl esters of **77** and **78**.

The same results were obtained by using three, four o five moles of n-butyllithium per mole of **72**.

One-step introduction of one or two electrophiles on 79

A solution of **79** (5 g, 36 mmol), anhydrous TMEDA (4.6 g, 39 mmol) and anhydrous hexane (100 ml) was lithiated with 1.2 M solution of n-butyllithium in hexane (32.9 ml, 39.5 mmol). The resulting mixture was poured onto ca. 100 g of crushed solid carbon dioxide and worked-up in the usual manner. GLC analyses of the methyl esters of the mixture from the sodium bicarbonate phase showed one peak. The component responsible for this peak was identified as **[(3-methylphenyl)thio]acetic acid (81)**. Yield 61%; mp 66-67°C (EtOH-water) (lit.[26] mp 67-68°C).

This reaction was repeated using 78 mmol of TMEDA and 79 mmol of n-butyllithium. GLC analyses of the methyl esters from the sodium bicarbonate phase showed two peaks. The acidic mixture was identified as a mixture of **84** and **85** in the percentage ratio of 85/15. Total yield 78%. The IR spectrum shows at 3200 and 1700 cm^{-1} two bands characteristic of the OH and C=O groups, respectively. The ^1H NMR spectrum exhibited at δ 3.70 and 3.80 two signals attributed to SCH_2 groups in the percentage ratio of 85/15. GLC analyses of methyl esters obtained upon treatment of the acidic mixture with Raney nickel and then with diazomethane exhibited two peaks with retention times identical to those of authentic samples (methyl esters of **86** and **87**).

The major component, **2-[(carboxymethyl)thio]-4-methylbenzoic acid (84)**, was isolated by flash-chromatography using petroleum ether (bp 40-70°)/ethyl ether (1:1) as eluent. Yield 65%; mp 194-195°C. IR (KBr, cm^{-1}): 3200 (OH), 1700 (C=O). ^1H NMR ($(CD_3)_2CO$) δ: 2.35 (3H, s, $ArCH_3$), 3.70 (2H, s, SCH_2), 7.40 (3H, m, Ar-H), 7.75 (1H, s, br, COOH, D_2O exchanged), 9.35 (1H, s, br, COOH, D_2O exchanged). m/z 226 (M^+). (Found C, 53.15; H, 4.38; S, 14.02. $C_{10}H_{10}O_4S$ requires C, 53.08; H, 4.45; S, 14.17).

One-step introduction of one and attempts to introduce two electrophiles on 88

A solution of **88** (6 g, 36 mmol), anhydrous TMEDA (4.6 g, 39 mmol) and anhydrous hexane (100 ml) was treated with 1.2 M solution of n-butyllithium in hexane (32.9 ml, 39.5 mmol). The resulting mixture was poured onto ca. 100 g of crushed solid carbon dioxide and worked up in the usual manner. GLC analyses of the methyl esters of the mixture separated from the sodium bicarbonate phase showed two peaks in the percentage ratio of 95:5. Total yield 75%.

The components responsible for these peaks were identified as methyl esters of **91** and **92** after desulphuration. In fact, GLC analyses of methyl esters obtained upon treatment of the acidic mixture with Raney nickel and then with diazomethane exhibited two peaks with retention times identical to those of authentic samples (methyl esters of **86** and **87**). The major component, **4-methyl-2-(isopropylthio)benzoic acid (91)**, was isolated by flash-chromatography using petroleum ether (bp 40-70°)/ethyl ether (1:1) as eluent. Yield 70%; mp 130-131°C. IR (CCl_4, cm^{-1}): 3520, 3200 (OH), 1735, 1690 (C=O). ^1H NMR ($CDCl_3$) δ: 1.20 (6H, d, $(C\underline{H}_3)_2CH$), 2.40 (3H, s, $ArC\underline{H}_3$), 3.55 (1H, m, $C\underline{H}$), 7.45 (3H, m, Ar-$\underline{H}$), 10.80 (1H, s, br, COOH, D_2O exchanged). m/z 210 (M^+). (Found C, 62.90; H, 6.66; S, 15.08. $C_{11}H_{14}O_2S$ requires C, 62.82; H, 6.71; S, 15.25).

The same results were obtained by using two, three, four or five moles of n-butyllithium per mole of **88**.

One-step introduction of one and attempts to introduce two electrophiles on 96

The reaction was performed as described for **88** starting from **96** and equimolar amounts of n-butyllithium in hexane. GLC analyses of the methyl esters of the mixture from the sodium bicarbonate phase showed one peak. The component responsible for this peak was identified as **5-methyl-2-(isopropylthio)-benzoic acid (98a)**. Yield 55%; mp 106-108°C (EtOH-water). IR ($CHCl_3$, cm^{-1}): 3520, 3050 (OH), 1720, 1690 (C=O). ^1H NMR ($CDCl_3$) δ: 1.35 (6H, d, $(C\underline{H}_3)_2CH$), 2.40 (3H, s, $ArC\underline{H}_3$), 3.40 (1H, m, $C\underline{H}$), 7.60 (3H, m, Ar-$\underline{H}$), 9.70 (1H, s, br, COOH, D_2O exchanged). m/z 210 (M^+). (Found C, 62.65; H, 6.64; S, 15.13. $C_{11}H_{14}O_2S$ requires C, 62.82; H, 6.71; S, 15.25).

After desulphuration nickel **98a** afforded **78** in 71% yield.

The same result was obtained by using two, three, four or five moles of n-butyllithium per mole of **96**.

Sequential one-flask introduction of two different electrophiles on 96

5-Methyl-3-(trimethylsilyl)-2-(isopropylthio)benzoic acid (100). - The reaction was performed as described for **32b**. The crude product was purified by flash-chromatography using hexane/ethyl acetate (3:1) as eluent. Yield 55%; mp 108-110°C. IR ($CHCl_3$, cm^{-1}): 3510, 3100 (OH), 1690 (C=O). ^1H NMR ($CDCl_3$) δ: 0.35 (9H, s, $(C\underline{H}_3)_3Si$), 1.20 (6H, d, $(C\underline{H}_3)_2CH$), 2.20 (3H, s, $ArC\underline{H}_3$), 3.70 (1H, m, $C\underline{H}$), 7.30 (2H, m, Ar-$\underline{H}$), 9.85 (1H, s, br, COOH, D_2O exchanged). m/z 288 (M^+). (Found C, 58.17; H 9.70; S, 10.98. $C_{14}H_{22}O_2SSi$ requires C, 58.29; H, 9.77; S, 11.11).

ACKNOWLEDGEMENT

The financial support from C.N.R. (Rome) and from M.P.I. (Italy) is gratefully acknowledged.

REFERENCES

1. Wakefield, B.J. in "The Chemistry of Organolithium Compounds", Pergamon Press, Oxford, **1974**.
2. Gschwend, H.W.; Rodriguez, H.R. Org. React. (N.Y.) **1979**, 26, 1.
3. Vollhardt, J.; Gais, H.J.; Lukas, K.L. Angew. Chem. Int. Ed. Engl. **1985**, 24, 610.
4. Figuly, G.D.; Loop, C.K.; Martin, J.C. J. Am. Chem. Soc. **1989**, 111, 654, and references cited therein.
5. Block, E.; Eswarakrishman, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. J. Am. Chem. Soc. **1989**, 111, 658, and references cited therein.
6. Smith, K.; Lindsay, C.M.; Pritchard, G.J. J. Am. Chem. Soc. **1989**, 111, 665, and references cited therein.
7. Block, E.; Ofori-Okai, G.; Zubieta, J. J. Am. Chem. Soc. **1989**, 111, 2327.
8. Cabiddu, S.; Melis, S.; Piras, P.P.; Sotgiu, F. J. Organometal. Chem. **1979**, 182, 155, and references cited therein.
9. Cabiddu, S.; Floris, C.; Melis, S. Tetrahedron Lett. **1986**, 38, 4625.
10. Cabiddu, S.; Cancellu, D.; Floris, C.; Gelli, G.; Melis, S. Synthesis **1988**, 888.
11. Cabiddu, S.; Fattuoni, C.; Floris, C.; Gelli, G. Heterocycles **1988**, 27, 1679.
12. Cabiddu, S.; Floris, C.; Gelli, G.; Melis, S. J. Organometal. Chem., **1989**, 366, 1.
13. Gilman, H.; Webb, F.J. J. Am. Chem. Soc. **1940**, 62, 987.
14. Miller, B.; Hwa Han, C. J. Org. Chem. **1971**, 36, 1513.
15. Adams, R.; Reifschneider, W.; Ferretti, A. Organic Syntheses collect V, **1973**, 107.
16. Farbenfrabiken Bayer A.-G. Patent Chem. Abstr. **1962**, 56P, 3416d.
17. Cabiddu, S.; Melis, S.; Piras, P.P.; Secci, M. J. Organometal. Chem. **1977**, 132, 321.
18. Bernard, A.M.; Piras, P.P.; Plumitallo, A.; Melis, S.; Sotgiu, F. Gazz. Chim. Ital. **1982**, 112, 443.
19. Cabiddu, S.; Maccioni, A., Piras, P.P.; Plumitallo, A. Gazz. Chim. Ital. **1981**, 111, 123.
20. Cabiddu, S.; Melis, S.; Piras, P.P.; Sotgiu, F. J. Organometal. Chem. **1979**, 178, 291.
21. Gilman, H.; Haubein, A.H. J. Am. Chem. Soc. **1944**, 66, 1515.
22. Cabiddu, S.; Maccioni, A.; Secci, M.; Solinas, V. Gazz. Chim. Ital. **1969**, 99, 397.
23. Suter, C.M.; Hausen, H.L. J. Am. Chem. Soc. **1932**, 54, 4100.

24. Maccagnani, G.; Taddei, F. Boll. Sci. Fac. Ch. Ind. Bologna **1965**, 23, 381.
25. Casparic, J.; Vecera, M.; Jurecek, M. Chem. Listy **1958**, 52, 1720; Chem. Abstr. **1959**, 53, 7075d.
26. Tarbell, D.S.; Fukushima, D.K. J. Am. Chem. Soc. **1946**, 68, 1456.
27. Jones, I.V.; Tebby, J.C. Phosphorus Sulfur **1978**, 5, 57.
28. Long, M.L. J. Am. Chem. Soc. **1946**, 68, 2159.
29. Schellenberg, K.A.; Westheimer, F.H. J. Org. Chem. **1965**, 30, 1859.
30. Leandri, G.; Mangini, A.; Passerini, R. Gazz. Chim. Ital. **1943**, 84, 3.
31. Donleavy, J.J.; English, J. J. Am. Chem. Soc. **1940**, 62, 220.
32. Letsinger, R.L.; Schnizer, A.W. J. Org. Chem. **1951**, 16, 869.
33. Dalgliesh, C.E.; Mann, F.G. J. Chem. Soc. **1945**, 893.
34. Kruber, O. Chem. Ber. **1932**, 65, 1382.
35. Gray, R.; Bonner, J. J. Am. Chem. Soc. **1948**, 70, 1248.