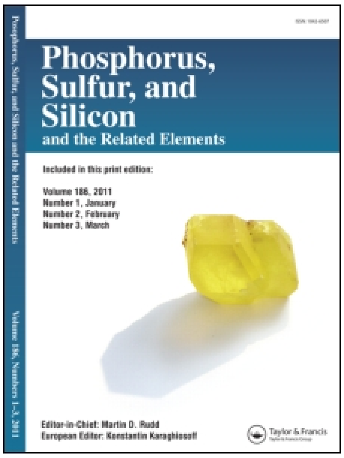

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# METALATION REACTIONS. PART XVII. DILITHIATION OF PHENYL ISOPROPYL SULPHONE

Maria G. Cabiddu[a]; Salvatore Cabiddu[a]; Claudia Fattuoni[a]; Costantino Floris[a]; Gioanna Gelli[a]; Stefana Melis[a]
[a] Dipartimento di Scienze Chimiche, Università Via Ospedale, Cagliari, Italy

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# METALATION REACTIONS. PART XVII. DILITHIATION OF PHENYL ISOPROPYL SULPHONE

MARIA G. CABIDDU, SALVATORE CABIDDU,* CLAUDIA FATTUONI
COSTANTINO FLORIS, GIOANNA GELLI and STEFANA MELIS
*Dipartimento di Scienze Chimiche, Università Via Ospedale, 72, I-09124, Cagliari, Italy*

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The general utility of dimetalation reactions of phenyl *iso*-propyl sulphone for the preparation of *ortho,alpha*-substituted aryl sulphones is described. All the products were obtained in satisfactory yields.

*Key words:* Alkyl aryl sulphones; metalations; polylithiations.

## INTRODUCTION

Direct lithiation of aromatic compounds is a process of considerable synthetic utility and a useful complement to halogen-metal exchange. The use of organolithium reagents may result in a significant reduction in the number of the operational steps with respect to more conventional routes. This factor leads to a greater use of organolithium chemistry.[1–5]

A large amount of literature reports data on the metalation of alkyl phenyl sulphones.[1,6–21] Di- or polymetalation of linear alkyl aryl sulphones usually leads to di- or poly-*alpha*-metalation.[8,11] Dimetalation of *tert*-butyl phenyl sulphone leads to di-*ortho,ortho*-metalation.[6,22] Dimetalation of *iso*propyl aryl sulphones was never attempted. Thus, we studied the direct (one-step) and one-pot dimetalation of phenyl isopropyl sulphone (**1**) in order to obtain an *alpha-ortho*-dimetalated sulphone. An intermediate of this kind allows the preparation of aryl *tert*-butyl type *ortho*-substituted sulphones, which are precursors of natural products.[23,24]

## RESULTS AND DISCUSSION

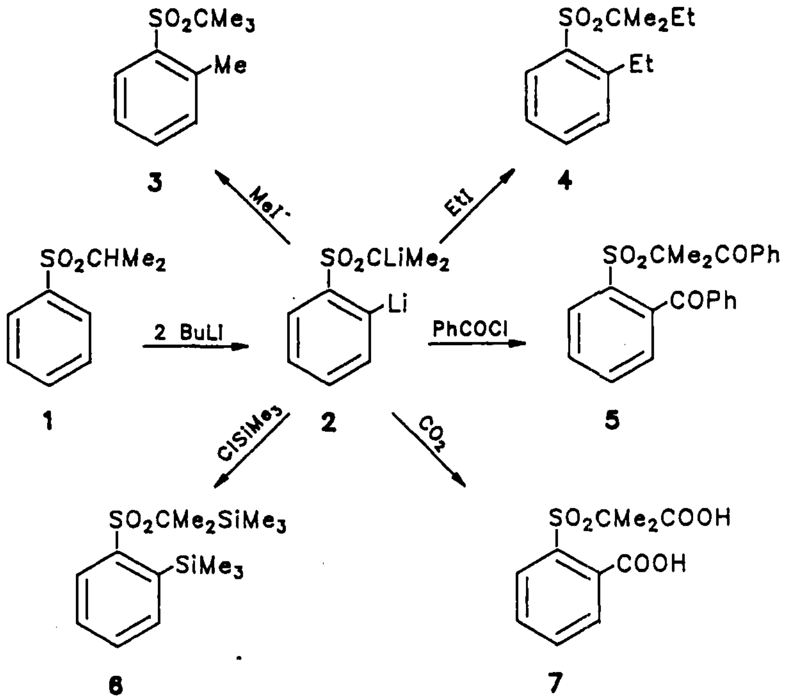
All reactions were performed by treating an ethereal solution of **1** with *n*-butyllithium in hexane. Lithiation intermediates were revealed by their reaction with electrophiles. All products were identified on the basis of analytical and spectral data.

Operating with two moles of organolithium per mole of **1** the dilithiated species **2** was obtained, where one of the two lithium atoms is bound to the methynic carbon atom and the other to the *ortho* ring carbon atom. Electrophilic quenching of **2** leads to products which are difficult to obtain through traditional routes; thus treatment of **2** with two equivalents of either iodomethane, or iodoethane, or benzoyl chloride, or chlorotrimethylsilane, or carbon dioxide gave the bifunctionalized derivatives **3–7** (Scheme 1) in satisfactory yields (54–77%).

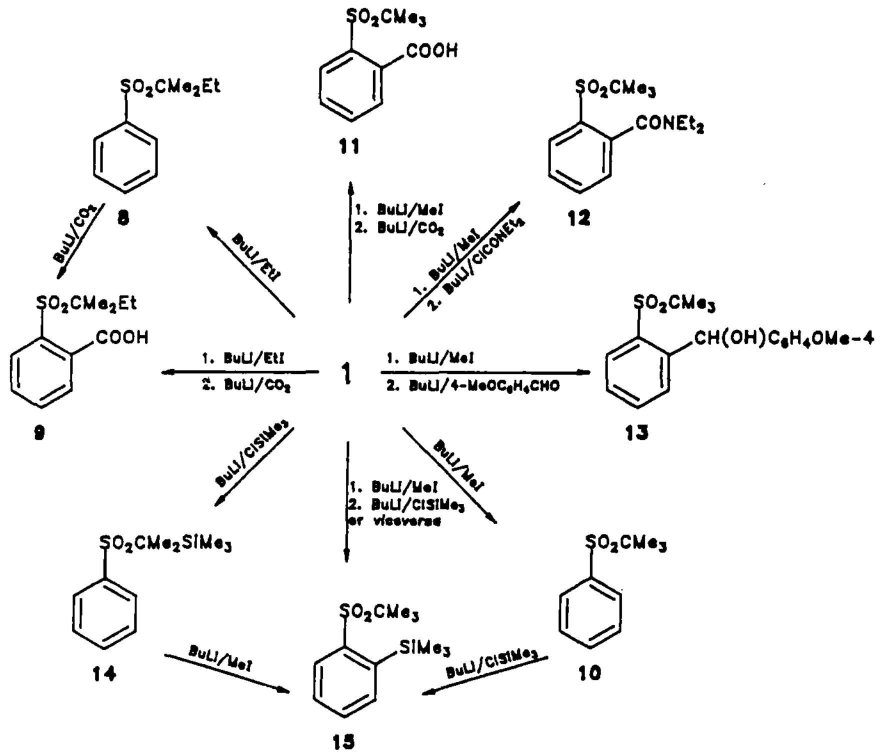
Two sequential (one-pot) monometalations allowed the introduction of two different electrophiles into the substrate: the first at the methynic carbon atom and the second at the *ortho* ring carbon atom (Scheme 2). Thus treatment of **1** with *n*-butyl-lithium/iodoethane followed by a second treatment with *n*-butyl-lithium/carbon dioxide gave the *ortho,alpha*-substituted products **9**. Analogously, the products **11–13** were obtained after a sequential, one-pot, treatment of **1** with *n*-butyllithium/iodomethane and, then, either with *n*-butyl-lithium/carbon dioxide, or *N,N*-diethylcarbamoyl chloride, or 4-methoxybenzaldehyde, respectively.

Monolithiation of **1** followed by treatment with chlorotrimethylsilane as electrophile yields the normal $\alpha$-substituted product **14**. However, monolithiation of this product, followed by treatment with iodomethane yields **15** where the trimethylsilyl group is in the *ortho* position. The same product **15** is obtained in a sequential, one-pot reaction with chlorotrimethylsilane either as first or second electrophile. Clearly the trimethylsilyl group of **14** migrates during the second lithiation process. The *alpha-ortho* shift of the trimethylsilyl group has been recently described by Fuchs *et al.*[21] The mobility of trimethylsilyl group in a lithiating mixture was also observed by Schlosser *et al.*[25]

The results show that our sulphone is a useful synthon to prepare regioselectively aryl alkyl sulphones. In fact, sulphones having in the alkyl moiety a tertiary carbon atom bound to either equal or different groups, and in the aromatic ring the *ortho*-position substituted with suitable groups are usually much more difficult or sometimes impossible to obtain by conventional methods.



**Scheme 1**



**Scheme 2**

## EXPERIMENTAL

The $^1$H NMR spectra were determined on a Varian VXR-300 spectrometer using tetramethylsilane as internal reference. IR spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer. Microanalyses were carried out on a Carlo Erba model 1106 Elemental Analyzer. Mass spectra were performed with a Hewlett-Packard 5989A mass spectrometer, using the direct-inlet system. 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 *n*-butyllithium in hexane were obtained from Aldrich Chemical Company and were analyzed by the Gilman double titration method before use.[26] Diethyl ether and tetrahydrofuran were dried by distillation from sodium benzophenone ketyl before use. Phenyl *iso*propyl sulphone (**1**) was prepared according to a published method.[27]

*General Procedure for the One-Step Introduction of Two Identical Electrophiles in* **1**. To a vigorously stirred solution of **1** (7.4 g, 40 mmol) and anhydrous diethyl ether (50 ml) a 1.6 M solution of *n*-butyllithium in hexane (73 ml, 88 mmol) was gradually added at room temperature under nitrogen, and stirring was continued at room temperature for almost 2 hours. The resulting solution of **2** was then cooled to −10°C and treated dropwise with the appropriate electrophile (88 mmol), allowed to warm and left at room temperature for almost 4 hours with stirring. The mixture was then hydrolyzed with water, and the pH adjusted to 5–6 by addition of 10% hydrochloric acid. The organic layer was separated, the aqueous layer extracted with diethyl ether, and the organic solutions combined, dried over sodium sulphate and the solvent evaporated *in vacuo*.

In this way, starting from iodomethane, iodoethane, benzoyl chloride and chlorotrimethylsilane, respectively, the following compounds were obtained:

*1-[(1,1-Dimethylethyl)sulphonyl]-2-methylbenzene* (**3**). Yield 68%; crystallized from ethanol, mp 98–99°C (lit.[17] 99–100.5).

*1-[(1,1-Dimethylpropyl)sulphonyl]-2-ethylbenzene* (**4**). Yield 64%; flash-chromatography (light petroleum), yellow oil; IR (liquid film): 1300, 1125 cm$^{-1}$ ($SO_2$); $^1$H NMR ($CDCl_3$): $\delta$ 0.85 (t, 3H, $C\underline{H}_3CH_2$), 0.95 (t, 3H, $C\underline{H}_3CH_2Ar$), 1.22 (s, 6H, $C\underline{H}_3C$), 1.78 (q, 2H, $CH_3C\underline{H}_2C$), 3.08 (q, 2H, $ArC\underline{H}_2$), 7.60 (m, 4H, Ar-$\underline{H}$); MS *m/z* 240 ($M^+$).
Anal. Calc'd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 64.87; H, 8.34; S, 13.20.

*[2-[(1-Methyl-1-benzoylethyl)sulphonyl]phenyl]phenylmethanone* (**5**). The solution of **2**, obtained as previously described in tetrahydrofurane solution, was added dropwise with stirring at −60°C to a solution of benzoyl chloride (88 mmol) in dry tetrahydrofuran. When the addition was complete the mixture was stirred at the same temperature for almost 0.5 hours, allowed to warm to room temperature with stirring and worked up in the same manner described above. Yield 58%; crystallized from ethanol, mp 215–217°C; IR ($CHCl_3$): 1725, 1680 (C=O), 1365, 1115 cm$^{-1}$ ($SO_2$); $^1$H NMR ($CDCl_3$): $\delta$ 0.98 (s, 3H, $CH_3$), 1.78 (s, 3H, $CH_3$), 7.73 (m, 14H, Ar-$\underline{H}$); MS *m/z* 392 ($M^+$).
Anal. Calc'd for $C_{23}H_{20}O_4S$: C, 70.38; H, 5.14; S, 8.17. Found: C, 70.27; H, 5.09; S, 7.99.

*[2-[[1-Methyl-1-(trimethylsilyl)ethyl]sulphonyl]phenyl]trimethylsilane* (**6**). Yield 77%; crystallized from light petroleum, mp 195–197°C; IR ($CHCl_3$): 1300, 1110 cm$^{-1}$ ($SO_2$); $^1$H NMR ($CDCl_3$): $\delta$ 0.38 (s, 18H, $C\underline{H}_3Si$), 0.81 (s, 6H, $(C\underline{H}_3)_2C$), 7.65 (m, 4H, Ar-$\underline{H}$). MS *m/z* 328 ($M^+$).
Anal. Calc'd for $C_{15}H_{28}O_2SSi_2$: C, 54.83; H, 8.59; S, 9.76. Found: C, 54.95; H, 8.65; S, 9.57.

*2-[(1-Carboxy-1-methylethyl)sulphonyl]benzoic Acid* (**7**). The solution of **2**, prepared as previously described, was poured onto *ca.* 100 g of crushed solid carbon dioxide. After 24 hours the residue was treated successively with 10% aqueous sodium hydroxide and then with diethyl ether. The alkali layer was separated, washed with diethyl ether and then acidified with cold concentrated hydrochloric acid. The crude product was filtered and crystallized from ethanol. Yield 73%; mp 188–190°C; IR (KBr): 3700, 3400 (OH), 1720 (C=O), 1320, 1110 cm$^{-1}$ ($SO_2$). $^1$H NMR ($(CD_3)_2CO$): $\delta$ 1.62 (s, 6H, $(C\underline{H}_3)_2C$), 7.82 (m, 4H, Ar-$\underline{H}$); MS *m/z* 272 ($M^+$).
Anal. Calc'd for $C_{11}H_{12}O_6S$: C, 48.52; H, 4.44; S, 11.78. Found: C, 48.35; H, 4.38; S, 11.59.

*General procedure for the sequential, one-pot introduction of two different electrophiles on* **1**. A 1.6 M solution of *n*-butyllithium in hexane (36.5 ml, 44 mmol) was gradually added under nitrogen at room temperature to a solution of **1** (40 mmol) in dry tetrahydrofuran (50 ml). The mixture was worked up as described above. The resulting solution was then cooled to 0°C, treated dropwise with the first electrophile (40 mmol) in dry tetrahydrofuran (10 ml), allowed to warm and left at room temperature for 4 hours with stirring. To this solution was added dropwise at −10°C *n*-butyllithium in hexane (36.5 ml, 44 mmol). When the addition was complete, the mixture was stirred at the same temperature for almost 0.5 hours and treated dropwise with the second electrophile (40 mmol) in dry tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for almost 0.5 hours, allowed to warm to room temperature with stirring and worked up in the same manner described above. In this manner the following compounds were obtained:

*2-[(1,1-Dimethylpropyl)sulphonyl]benzoic Acid* (**9**). Prepared using iodoethane as first electrophile and carbon dioxide as second one. In this reaction, after treatment with the first electrophile and successive metalation, the reaction mixture was poured onto *ca.* 100 g of crushed solid carbon dioxide and worked up in the same manner described for the preparation of (**7**). Yield 61%; crystallized from benzene, mp 119–120°C; IR (nujol): 3430–3050 (OH), 1730 (C=O), 1310, 1150 cm$^{-1}$ ($SO_2$); $^1$H NMR ($CDCl_3$): $\delta$ 0.92 (t, 3H, $C\underline{H}_3CH_2$), 1.32 (s, 6H, $C\underline{H}_3C$), 1.81 (q, 2H, $CH_3C\underline{H}_2$), 7.72 (m, 4H, Ar-$\underline{H}$), 10.15 (s, 1H, $COO\underline{H}$, $D_2O$ exchanged); MS *m/z* 256 ($M^+$).
Anal. Calc'd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29; S, 12.51. Found: C, 56.14; H, 6.20; S, 12.39.

If a portion of the reaction mixture was hydrolized before treatment with the second electrophile *[(1,1-dimethylpropyl)sulphonyl]benzene* (**8**) was obtained; yellow oil; IR (liquid film): 1300, 1130 cm$^{-1}$ ($SO_2$); $^1$H NMR ($CDCl_3$): $\delta$ 0.92 (t, 3H, $C\underline{H}_3CH_2$), 1.28 (s, 6H, $(C\underline{H}_3)_2C$), 1.75 (q, 2H, $CH_3C\underline{H}_2$), 7.75 (m, 5H, Ar-$\underline{H}$); MS *m/z* 212 ($M^+$).
Anal. Calc'd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10. Found: C, 62.15; H, 7.52; S, 14.97.

*2-[(1,1-Dimethylethyl)sulphonyl]benzoic Acid* (**11**). Prepared in the same manner described for **9** using iodomethane as first electrophile and carbon dioxide as second one. Yield 69%; crystallized from benzene, mp 173–175°C[22]. $^1$H NMR ($CDCl_3$): $\delta$ 1.27 (s, 9H, $CH_3$), 7.78 (m, 4H, Ar-$\underline{H}$), 9.30 (s, 1H, $COO\underline{H}$, $D_2O$ exchanged).

If a portion of the reaction mixture was hydrolyzed before the treatment with the second electrophile *[(1,1-dimethylethyl)-sulphonyl]benzene* (**10**) was obtained; mp 98–100°C (lit.[28] 98–99°C).

*2-[(1,1-Dimethylethyl)sulphonyl]-N,N-diethylbenzamide* (**12**). Prepared using iodomethane as first electrophile and diethylcarbamoyl chloride as second one. Yield 60%; crystallized from hexane/ethyl acetate, mp 68–70°C (lit.[17] 69°C).

*2-[(1,1-Dimethylethyl)-sulphonyl]-α-(4-methoxyphenyl)benzenemethanol* (**13**). Prepared using iodomethane as first electrophile and 4-methoxybenzaldehyde as second one. Yield 75%; flash-chromatography (chloroform), mp 138–140°C (lit.[17] 139–139.5°C).

*[2-[(1,1-Dimethylethyl)sulphonyl]phenyl]trimethylsilane* (**15**). Prepared using iodomethane as first electrophile and chlorotrimethylsilane as second one. Yield 78%; crystallized from diethyl ether/light petroleum, mp 99–100°C (lit.[17] 100–101°C).

The same result was obtained using chlorotrimethylsilane as first electrophile and iodomethane as second one. In this case, if a portion of the reaction mixture was hydrolized before the treatment with the second electrophile *trimethyl[1-(phenylsulphonyl)ethyl]silane* (**14**) was obtained; mp 77–78°C (lit.[21] 78°C).

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## REFERENCES

1. B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, 1974.
2. B. J. Wakefield, *Organolithium Methods*, Academic Press, London, 1988.
3. H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979).
4. V. Snieckus, *Chem. Rev.*, **90**, 879 (1990).
5. V. Snieckus, *Pure Appl. Chem.*, **62**, 2047 (1990).
6. F. M. Stoyanovich, R. G. Karpenko, G. I. Gorushkina and Ya. L. Gold'farb, *Tetrahedron*, **28**, 5017 (1972).
7. E. M. Kaiser, R. D. Beard and C. R. Hauser, *J. Organometal. Chem.*, **59**, 53 (1973).
8. A. Bongini, D. Savoia and A. Umani-Ronchi, *J. Organometal. Chem.*, **112**, 1 (1976).
9. R. Lett, G. Chassaing and A. Marquet, *J. Organometal. Chem.*, **111**, C17 (1976).
10. S. Melis, P. P. Piras and A. Plumitallo, *Rend. Sem. Fac. Sci. Univ. Cagliari*, **47**, 19 (1977); *Chem. Abstr.*, **89**, 109629a (1978).
11. A. Roggero, T. Salvatori, A. Proni and A. Mazzei, *J. Organometal. Chem.*, **117**, 313 (1979).
12. J. B. Baudin, M. Julia, C. Rolando and J. N. Verpeaux, *Tetrahedron Lett.*, **25**, 3203 (1984).
13. E. J. Madaj, D. M. Snyder and W. E. Truce, *J. Am. Chem. Soc.*, **108**, 3466 (1986).
14. H. J. Gais, J. Vollhardt, G. Hellmann, H. Paulus and H. J. Lindner, *Tetrahedron Lett.*, **29**, 1259 (1988).
15. H. J. Gais, G. Hellmann, H. Günther, F. Lopez, H. J. Lindner and S. Braun, *Angew. Chem. Int. Ed. Engl.*, **28**, 1025 (1989).
16. P. Charreau, M. Julia and J. N. Verpeaux, *J. Organometal. Chem.*, **379**, 201 (1989).
17. M. Iwao, T. Iihama, K. K. Mahalanabis, H. Perrier and V. Snieckus, *J. Org. Chem.*, **54**, 24 (1989).
18. P. Jankowski, S. Marczak, M. Masnyk and J. Wicha, *J. Organometal. Chem.*, **403**, 49 (1991).
19. F. Chemla, M. Julia, D. Uguen and D. Zhang, *Synlett.*, 501 (1991).
20. M. Julia, D. Uguen, J. N. Verpeaux and D. Zhang, *Synlett.*, 505 (1991).
21. M. Lamothe, M. B. Anderson and P. L. Fuchs, *Syn. Comm.*, **21**, 1675 (1991).
22. F. M. Soyanovich and B. P. Fedorov, *Angew. Chem. Int. Ed. Engl.*, **5**, 127 (1966).
23. P. D. Magnus, *Tetrahedron*, **33**, 2019 (1977).
24. P. L. Fuchs and T. F. Braish, *Chem. Rev.*, **86**, 903 (1986).
25. A. Mordini and M. Schlosser, *Chimia*, **40**, 309 (1986).
26. H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).
27. A. Ratajczak, F. A. L. Anet and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 2072 (1967).
28. V. N. Ipatieff, H. Pines and B. S. Friedman, *J. Am. Chem. Soc.*, **60**, 2731 (1938).