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METALATION REACTIONS. IX. DILITHIATION OF AROMATIC THIOETHERS

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Summary: Direct dimetalation of aromatic thioethers gives with good yield the dilithiated species 3, 4, 17, 18, 25, 26. The first four species allowed the simultaneous introduction of an electrophile in the thiomethyl group and in the ring,while the last two species undergo disubstitution in the ring.

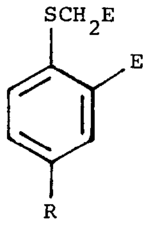
Many metalation reactions with organolithium reagents have shown that some substituents of the aromatic ring direct the metal atom in the *ortho* position[1,2]. It is thus possible to prepare isomer free *ortho* disubstituted compounds. On the other hand, reports on direct dimetalation are very scarce even though dilithiated compounds prepared by metal-halogen or metal-metal exchange are quite common[1,3-7]. Direct dimetalation has been so far reported only for aromatic ethers[8,9] and amides[10-12].

In this communication we report the direct dimetalation of aromatic thioethers[13]. This reaction is of synthetic importance since it makes it possible the introduction in a single stage of two electrophilic groups in strategic points of the molecule otherwise accessible only *via* multistep reactions. Moreover, these reactions are different with respect to those of the corresponding ethers[9].

According to the reaction products of the dimetalation reaction, the thioethers examined in this report can be divided in three classes: *i)* (methylthio)-benzenes unsubstituted or substituted with groups of none or very limited *ortho* directing ability; *ii)* (methylthio)benzenes substituted with *ortho* directing groups more efficient than thioalkyls; *iii)* (alkylthio)benzenes with the alkyl group different from methyl.

Representative results are summarized in Table.

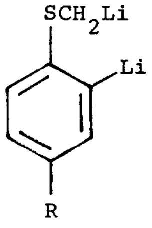
Metalation of thioethers of the first group makes possible the simultaneous introduction of two functional groups in the molecule, the reactive sites being the methylthio carbon and the annular carbon atom *ortho* to the thioethereal function[14]. Thus, metalation of compounds 1 and 2 through the dianion intermedia-



1,2

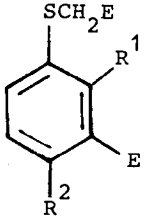
5-14

1: R=E=H
2: R=Me, E=H
5: R=H, E=COOH
6: R=H, E=Me
7: R=H, E=$C_6H_5CH_2$
8: R=H, E=CH_2=CH-CH_2
9: R=H, E=Me_3Si
10: R=H, E=CHO
11: R=H, E=C_6H_5CO
12: R=H, E=$C_6H_5CH(OH)$
13: R=Me, E=COOH
14: R=E=Me



3,4

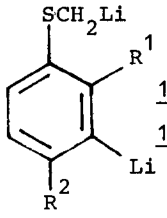
3: R=H
4: R=Me



15,16

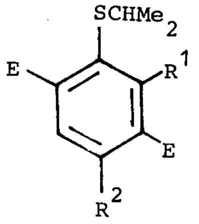
19-22

15: R^1=E=H, R^2=OMe
16: R^1=OMe, R^2=E=H
19: R^1=H, R^2=OMe, E=COOH
20: R^1=H, R^2=OMe, E=CH_2=CH-CH_2
21: R^1=OMe, R^2=H, E=COOH
22: R^1=OMe, R^2=H, E=CH_2=CH-CH_2



17,18

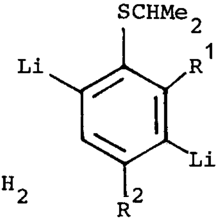
17: R^1=H, R^2=OMe
18: R^1=OMe, R^2=H



23,24

27-30

23: R^1=E=H, R^2=OMe
24: R^1=OMe, R^2=E=H
27: R^1=H, R^2=OMe, E=COOH
28: R^1=H, R^2=OMe, E=CH_2=CH-CH_2
29: R^1=OMe, R^2=H, E=COOH
30: R^1=OMe, R^2=H, E=CH_2=CH-CH_2



25,26

25: R^1=H, R^2=OMe
26: R^1=OMe, R^2=H

tes 3 and 4 yields, following treatment with various electrophiles, the products 5-14.

Thioethers of the second group can be simultaneously functionalized at the thiomethyl carbon and at the annular carbon atom *ortho* to the other more efficient *ortho*-directing group. Metalation of compounds 15 and 16 yield in fact, Table: Reaction of 3, 4, 17, 18, 25 and 26 with Electrophiles

Entry	Electrophile	Product[a]	Yield, %[b]	Mp(bp)°C
3	CO_2	5	68	118-120[c]
3	MeI	6	59	65-66/2 mm
3	$C_6H_5CH_2Br$	7	58	151-153/1.5 mm
3	CH_2=CH-CH_2Br	8	61	168-170/30 mm
3	Me_3SiCl	9	72	145-147/17 mm
3	$HCONMe_2$	10	50	102-103[d]
3	C_6H_5COCl	11	54	115-117[d]
3	C_6H_5CHO	12	51	160-161/1 mm
4	CO_2	13	65	197-198[e]
4	MeI	14	63	68-70/1 mm
17	CO_2	19	72	126-127[c]
17	CH_2=CH-CH_2Br	20	57	130-132/1.5 mm
18	CO_2	21	67	167-168[c]
18	CH_2=CH-CH_2Br	22	55	118-120/1.5 mm
25	CO_2	27	75	219-220[c]
25	CH_2=CH-CH_2Br	28	58	120-121/1.5 mm
26	CO_2	29	62	170-171[c]
26	CH_2=CH-CH_2Br	30	60	95-96/1 mm

[a] All new compounds show analytical and spectral (IR, ^1H and ^{13}C NMR) data fully consistent with the proposed structures. [b] Yields correspond to chromatographically pure materials. [c] Recrystallized from EtOH/H_2O. [d] Recrystallized from EtOH. [e] Recrystallized from chloroform.

after treatment with electrophiles of the corresponding dianions 17 and 18, the products 19-22.

Metalation of substrates of the third group can be performed only when the aromatic ring is substituted with very efficient *ortho*-directing groups. Thioethers 23 and 24 can be in fact easily dilithiated yielding first the intermediates 25 and 26 and subsequently the products 27-30. On the other hand, dimetalation of (isopropylthio)benzene proved to be impossible; only the known monolithiated specie was obtained, which yields, after carbonation, the 2-(isopropylthio)benzoic acid[15,16].

It should also be noticed that, owing to the facile desulphuration of thioethers by Ni-Raney[17,18] the latter reactions can be used to prepare 2,5-disubstituted alkoxybenzenes, as shown by the formation of the 2-methoxyterephthalic acid from 27 or 29. Moreover, this result suggests that substitution of the alkoxy group with other efficient *ortho*-directing groups for lithiation, permits the preparation of a number of 1,2,5-trisubstituted benzene derivatives.

The investigation in this area is still in progress in our laboratory (i.e. the possibilities of reacting the dianionic species with one equivalent of an electrophile, the introduction of two different electrophiles, etc.).

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13. The thioethers were metalated with 2.2 equiv of *n*-BuLi/2.2 equiv TMEDA/hexane/25°C and then treated with excess of electrophiles.
14. Direct dilithiation of methoxybenzene was not observed; the dimetalation product was prepared by a stepwise monometalation sequence[9]. Moreover, the metalation on alkoxy group was not detected.
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