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Enantioselective Oxidation of Thioethers[1]: an Easy Route to Enantiopure C_2 Symmetrical *bis*-Methylsulfinylbenzenes

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Dedicated to Professor A I. Meyers on the occasion of his 60th birthday

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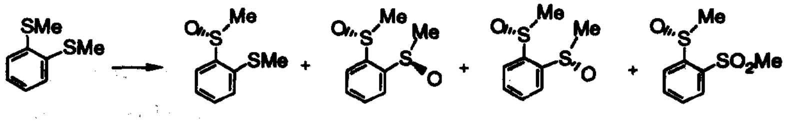
Abstract: The direct oxidation of *bis*-methylthioethers **1** by *t*-butyl hydroperoxide, titanium tetra-*iso*-propilate, and (+)-diethyltartrate, affords the almost enantiomerically pure *dl bis*-methylsulfinylbenzenes **2** (e.e.≥99%) in a process which is also characterized by a very high diastereoselectivity.

The availability of optically pure compounds containing two or more homochiral functionalities is a rather attractive synthetic achievement for a series of reasons, the most obvious one being the possibility to use reduced amounts of material.[2,3,4] On the other hand, the preparation of such compounds, which can be used as chiral auxiliaries and in many other asymmetric reactions, is intrinsically complicated by the presence of more stereogenic centers on the molecule, leading to the formation of several diastereoisomers. Accordingly, highly stereoselective synthetic procedures are needed.[5]

In this communication we present an example of such a procedure aimed at obtaining 1,2, 1,3 and 1,4-*bis*-methylsulfinylbenzenes **2a**, **2b** and **2c**, rather appealing materials in asymmetric synthesis,[6] *via* direct enantioselective oxidation of the corresponding methyl thioethers **1** by the modified Sharpless reagent [Ti(IV)/(+)-diethyltartrate/*t*-butyl hydroperoxide= 1:4:2] developed a few years ago in our laboratories.[7]

The *bis*-methylthiobenzenes **1**, obtained by reaction of the corresponding sodium dithiolates with dimethylsulfate, were oxidized by using two different substrate/oxidant ratios. A first set of experiments was carried out with an excess of the substrate over the oxidant (Sub:Ti(IV):(+)-DET:TBHP = 8:1:4:2) so that the enantioselectivity of the first oxidative step could be measured. In the second set, an excess of the oxidant (Sub:Ti(IV):(+)-DET:TBHP = 1:1:4:2) was used, in order to obtain the *bis*-sulfoxides as the major products. In both cases the reactions were carried out until complete disappearance of the oxidant. The general scheme of the process, together with the results obtained with 1,2-*bis*-methylthiobenzene **1a** taken as a representative example, are collected in Table 1.[8,9] Under the conditions of an excess of the oxidant one may predict that the *mono*-sulfoxide **3a**, two diastereomeric *bis*-sulfoxides, *i.e.* the *dl* pair **2a** and the *meso* compound **4a**, and the sulfoxide-sulfone **5a**, respectively, should be formed.

Table 1.



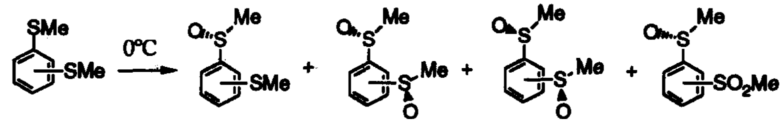
1a 3a 2a 4a 5a

Sub:Ti(IV):(+)DET:TBHP	Temp. °C	Time hs	3a % ^{a}(e.e.,%^{b})	*dl*-2a %^{a} (e.e.,%^{b})	*meso*-4a %^{a}	5a %^{a} (e.e.,%^{b})
8:1:4:2	-20	16	80.1 (90)	19, 5 (99)	0.4	--
1:1:4:2	-20	144	3.3 (18)	93.0 (99)	1.8	1.8 (88)
8:1:4:2	0	16	83.3 (94)	16.0 (98)	0.7	--
1:1:4:2	0	66	3.9 (20)	91.6 (99)	2.2	2.7 (88)

a. determined *via* ^{1}H NMR on the crude material; b. determined *via* ^{1}H NMR on the products purified by flash chromatography in the presence of (+)-S or (-)-R-1-(9-anthryl)-2,2,2-trifluoroethanol or (-)-R-*N*-(3,5-dinitrobenzoyl-α-phenylethylamine.[10]

The model compound **1a** was oxidized either at -20°C, *i. e.* the standard temperature, or at 0°C, providing almost identical results.[11] Therefore, the other reactions with 1,3 and 1,4-*bis*-methylbenzenes **1b** and **1c** were run at 0°C, in order to accelerate the oxidation. The pertinent results are reported in Table 2.[8,9]

Table 2.



1 3 2 4 5

1b= 1,3-*bis*-methylthiobenzene; 1c= 1,4-*bis*-methylthiobenzene

#	Sub:Ti(IV):(+)DET:TBHP	Time hs	3 % ^{a}(e.e.,%^{b})	*dl*-2 %^{a} (e.e.,%^{b})	*meso*-4 %^{a}	5, %^{a} (e.e.,%^{b})
1b	8:1:4:2	16	94.5 (78)	4.3 (n.d.)	1.2	--
1b	1:1:4:2	65	11.3 (96)	49.4 (>99)	7.3	32.0 (79)
1c	8:1:4:2	16	92.4 (75)	6.2 (96)	1.4	--
1c	1:1:4:2	68	8.4 (89)	48.5 (>99)	5.4	37.7 (85)

a. determined *via* ^{1}H NMR on the crude material; b. determined *via* ^{1}H NMR on the products purified by flash chromatography in the presence of (+)-S or (-)-R-1-(9-anthryl)-2,2,2-trifluoroethanol or (-)-R-*N*-(3,5-dinitrobenzoyl-α-phenylethylamine.[10]

The data reported in the Tables show that all the *bis*-sulfoxides **2** are produced with a very high degree of enantioselection (e.e.$\geq$99%.) These results are not unexpected in the light of the finding that the first oxidative step is already highly enantioselective (e.e.= 94, 78 and 75% for **3a**, **3b** and **3c** respectively). In fact, under the hypothesis that the second oxidative step is not affected by the presence of the first stereogenic sulfinylic group, one might calculate that the diastereo and the enantioselections of the second process should reach values of ca. 94: 6 for **2a** : **4a** (e.e.$_{2a}$= 99.8%), 80:20 for **2b** : **4b** (e.e.$_{2b}$= 97%) and 78:22 for **2c**: **4c** (e.e.$_{2c}$= 96%) respectively.[12] Whereas the enantioselections experimentally found agree with those calculated, the diastereomeric excesses are much higher than those predicted by assuming that the two oxidation steps are not related. Accordingly, it may be suggested that a synergism takes place between the sulfinylic group already present in the molecule and the asymmetric oxidant. Such an effect strongly favors the formation of the *dl bis*-sulfoxides **2** over the achiral *meso* derivatives **4**. Furthermore, in such an effect, proximity factors appear to play a role. In particular, in the oxidation of 1,2-*bis*-methylthiobenzene **1a** the ratio between compounds *dl* **2a** and *meso* **4a** is remarkably higher (98:2) than those found for 1,3- and 1,4-derivatives **1b** and **1c** (87:13 and 90:10, respectively).

Finally, the oxidation of compound **1a** is much more selective than that of **1b** and **1c** as far as the distribution of products with a different degree of oxidation state **3**, **2**+ **4** and **5** is concerned. In particular the *bis*-sulfinylic compounds (+)-**2a** and **4a** account for 94% of the all recovered products, whereas for the substrates **1b** and **1c**, together with **2** and **4**, appreciable amounts of **3** and **5** are obtained. This finding is somehow unexpected and its implications deserve further consideration. At any rate, also for these compounds, the main products are always the *dl bis*-methylsulfinylbenzenes (+)-**2b** and (+)-**2c**.

The extension of the reported procedure to *poly*-methylsulfinylbenzenes as well as the synthetic scope of the resulting *bis*-sulfoxides **2** are currently under investigation.

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References and Notes

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8. Satisfactory spectroscopic data were obtained for all compounds reported. The yields ranged from 70 to 80%, based on the oxidant.

9. Data for: (+)-**2a** : (toluene), mp 165-167°C, $[\alpha]_D^{25}$=+455.9 (c=0.9, chloroform), e.e.>99%; (+)-**3a** : oil, $[\alpha]_D^{25}$=+331.1 (c=1.0, chloroform), e.e.=94%; **4a** was not isolated; (+)-**5a**: mp 186-188°C, $[\alpha]_D^{25}$=+216.6 (c=1.0, chloroform) e.e.>99%; (+)-**2b** and **4b** were not isolated; (+)-**3b**: oil, $[\alpha]_D^{25}$=+92.2 (c=1.0, chloroform), e.e.= 78%; (+)-**5b** : mp 145-148°C, $[\alpha]_D^{25}$=+81.5 (c=0.6, chloroform), e.e.= 79%; (+)-**2c** and **4c** were not isolated; (+)-**3c** : mp 60-62°C, $[\alpha]_D^{25}$=+142.4 (c=0.7, chloroform), e.e.= 75%; (+)-**5c**: mp 162-165°C, $[\alpha]_D^{25}$=+94.9 (c=1.0, chloroform), e.e.= 85%.
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11. The enantioselectivity of our asymmetric oxidant is slightly effected by the temperature. Conte, V.; Di Furia, F.; Licini, G.; Modena, G.; Sbampato, G. "Titanium Promoted Enantioselective Oxidation of Thioethers and Synthetic Applications" in "*Dioxigen Activation and Homogeneous Catalytic Oxidation*", pp. 385-394, Simandi, L.I. Ed., Elsevier Science Publisher B.V., Amsterdam, The Nederlands (1991).
12. If the two process were independent, one should obtain the *bis*-sulfoxides with a ratio (+)-**2**: **4**: (-)-**2**=x^2: 2x: 1, where the enantioselection of the first step is (+)-**3**:(-)-**3**=x: 1.[2,3]

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