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Phthalimidesulfenyl Chloride Part 13.[1] 3,3'-Regioselective Thiofunctionalization of Atropisomeric 2,2'-Biphenols

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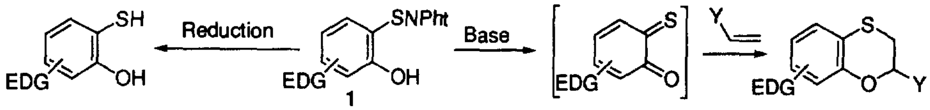
Abstract: Regioselective 3,3'-thiofunctionalization of atropisomeric biphenol **2** can be achieved using phthalimidesulfenyl chloride as the key reagent. The *bis*-thiophthalimide derivative **3** is the starting material for the preparation of linear (**7a-d**) and macrocyclic (**15a-d**) C_2 symmetric ligands containing the biphenyl moiety.

The biphenyl structure is present in several bioactive natural products most of which possess hydroxylated functionality and exhibit a range of biological activities and pharmacological effects.[2] Moreover, atropisomeric biphenyls are important tools in asymmetric synthesis and catalytic processes.[3] Despite the wide literature on the preparation of chiral hydroxylated biphenyls, examples of chiral biphenyl derivatives containing thiol or disulfide groups are extremely rare.[4] We have shown that the electrophilic aromatic substitution of various activated phenols with phthalimidesulfenyl chloride PhtNSCl (Pht=phthaloyl) occurs with complete regioselectivity to give the corresponding *ortho*-hydroxythiophthalimides **1** as unique regioisomers.[5,6] These species can be easily transformed into *ortho*-hydroxythiols by reduction of the sulfur-nitrogen bond,[5] or into *ortho*-thioquinones by base promoted elimination of the phthalimide[6] (Scheme 1). *Ortho*-thioquinones are reactive intermediates which can act as electron-poor hetero dienes with a large number of electron-rich dienophiles in synthetically useful,[6,7] inverse electron-demand, Diels-Alder reactions (Scheme1).



EDG = alkyl, OH, OR, fused aromatic; Pht = phthaloyl; Y = OR, SR, NRCOR', Ar

Scheme 1

The interesting transformations achieved through this electrophilic thiofunctionalization of phenols prompted us to investigate this chemistry in the case of atropisomeric C_2 symmetric biphenols like **2**. In this communication we describe our preliminary results on the sulfenylation reaction of atropisomeric hydroxylated biphenyls.

The reaction of 2.5 eq of phthalimidesulfenyl chloride with phenol **2** in dry chloroform at rt for 5h

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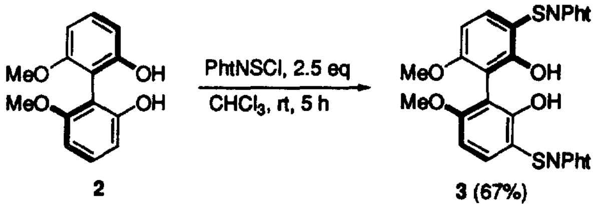
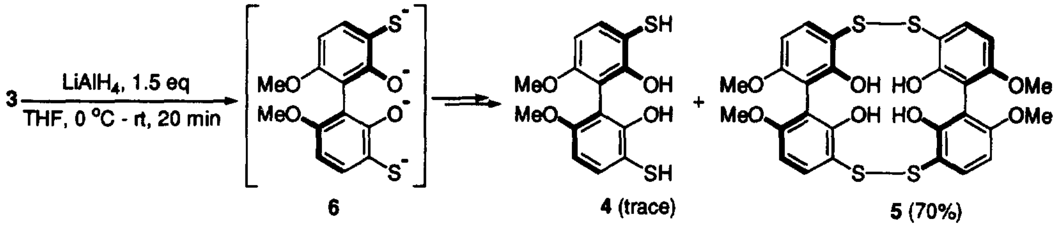
allowed the isolation[8] of the corresponding 3,3'-bisthiophthalimide 3 in 67% yield (Scheme 2).



Scheme 2

This easy double functionalization allowed to verify the potential of 3 for the synthesis of new C_2 symmetric sulfur containing compounds. As a first target, we tried to transform 3 into the corresponding bis-thiol 4 by hydride reduction of the sulfur-nitrogen bond.[5] Carrying out the reduction of 3 with 1.5 eq of $LiAlH_4$, compound 4 was obtained only as a minor component while disulfide 5 was isolated in 70% yield (Scheme 3).



Scheme 3

The formation of the disulfide linkage of 5 can be rationalised by nucleophilic attack[5,9] of the thiolate ions of 6 on the sulfenamidic sulfurs of 3, or alternatively, by auto-oxidation. Irrespective of the actual mechanism, we observed the formation of only a single dimeric disulfide 5, identified as the a*R*a*R*/a*S*a*S* diastereoisomer by X-Ray crystallography (Figure 1).

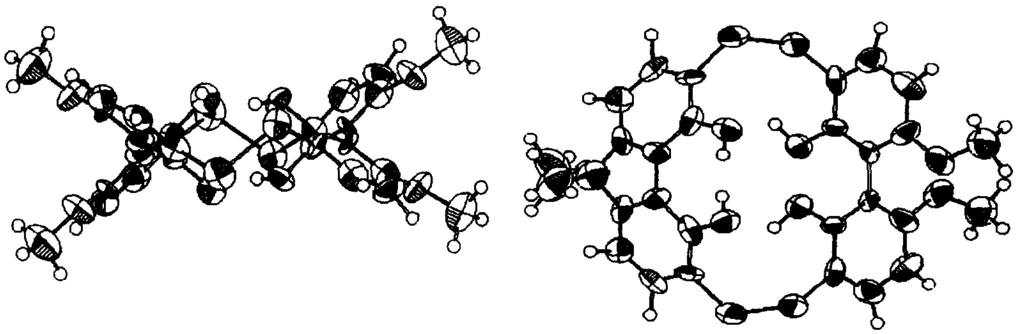
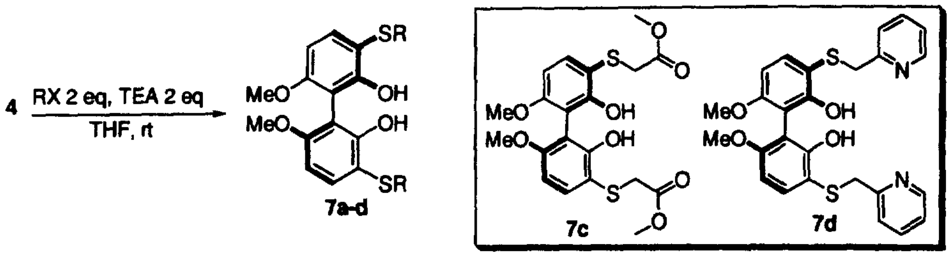


Figure 1: "Side" and "up" ORTEP views of disulfide 5

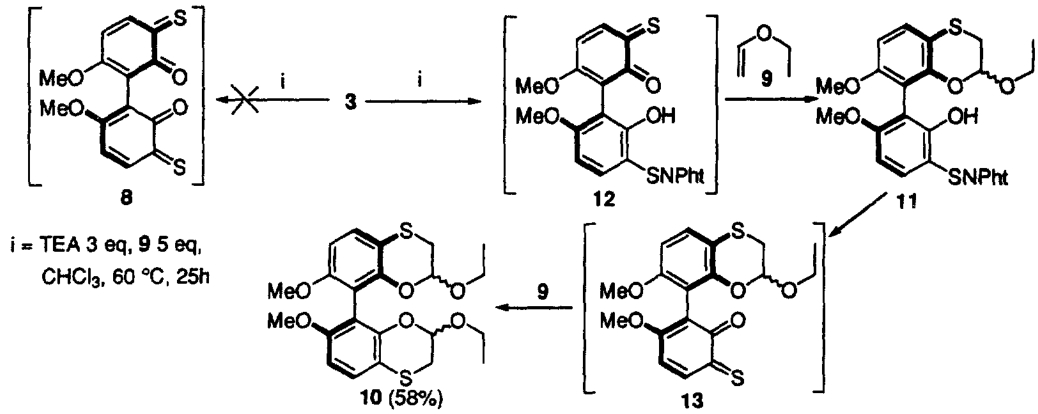
The synthesis of the bis-thiol 4 was achieved carrying on the reduction, under nitrogen, with an excess of $LiAlH_4$ (5.5 eq) on a suspension of 3 in dry THF through which nitrogen had been bubbled. Following this procedure, 4 was isolated in 82% yield as a white solid quite stable to air oxidation. This compound was reacted in the presence of triethylamine (TEA) with different alkyl halides to obtain the corresponding sulfides **7a-d** as reported in Scheme 4. Thus this reaction opens a simple way to compounds, like **7c** and **7d**, which can be seen as potential C_2 symmetric ligands (Scheme 4).



$7a$: R = CH_3; X = I, 82%; **7b**: R: CH_3OCH_2; X = Br, 80%
7c: R = CH_3OCOCH_2; X = Br, 79%; **7d**: R: 2-pyridyl-CH_2; X = Cl (TEA 4 eq.), 48%

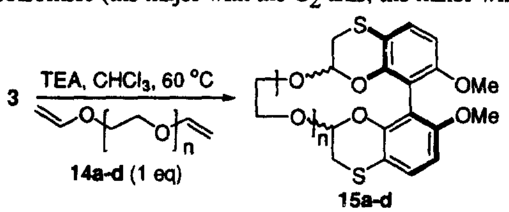
Scheme 4

As second goal we tried to use bis-thiophthalimide **3** as a precursor of the corresponding bis-*ortho*-thioquinone **8**. To verify this possibility the derivative **3** was heated at 60 °C in chloroform in the presence of 3 eq of TEA and 5 eq of ethyl vinyl ether (**9**) as trapping reagent.[6] After 25 h we could indeed isolate the cycloadduct **10** in 58% yield as a 1.7:1.7:1 mixture of the three possible diastereoisomers[10] (Scheme 5).



Scheme 5

Although compound **10** clearly derived from a double inverse electron demand Diels-Alder reaction, the bis-thione **8** was not the real intermediate of the process. In fact by quenching the reaction before the complete disappearance of **3** we could show, by ^{1}H NMR, the presence of compound **11**, bearing an oxathiin and a *o*-hydroxyphthalimide residue on the same biphenyl moiety, which suggests a stepwise reaction involving biphenylic mono-*o*-thioquinones **12** and **13** as intermediates (Scheme 5). Carrying on the reaction of **3** in the presence of TEA and bis-enol ethers **14a-d** (1 eq) we obtained crown ethers **15a-d** as a mixture of only two diastereoisomers (the major with the C_2 axis, the minor without) (Scheme 6).



	n	Yield (%)	Diast. Ratio
15a	1	80	3 : 1
15b	2	50	2.8 : 1
15c	3	52	2 : 1
15d	4	46	2.5 : 1

Scheme 6

When alkenes **14b-d** were used as dienophiles (n = 2, 3 and 4 respectively), monomeric cycloadducts

15 occurred with variable amount of by-products tentatively identified as the corresponding oligomers containing two or more biphenyl units and/or compounds deriving from a single process of cycloaddition[11] (Scheme 6). The high yields of monomers, as well as the diastereoselectivity obtained in these reactions can be rationalised considering that the poor solubility of **3**, used as suspension in chloroform, and the stepwise mode of the cycloaddition reaction, generated a pseudo-high dilution system.

The extension of this chemistry to the enantiopure biphenyl **2**[12] as well as the use of derivatives **7** and **15** in organic catalysis are under investigation in these laboratories.

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8. Purification of compound **3** can be achieved filtering off the impurities soluble in hot chloroform. Physical and spectroscopic data of **3** are as follows: white solid, mp 228-230 °C; ^{1}H nmr (200 MHz, $CDCl_3$): 8.25 (s, 2H, OH), 7.92-7.67 (m, 8H, Pht), 7.89 (d, 2H, J = 8.8 Hz, $H_{44'}$), 6.55 (d, 2H, J = 8.8 Hz, $H_{55'}$), 3.72 (s, 6H, OCH_3). Analysis Calc. for $C_{30}H_{20}N_2O_8S_2$: C 59.99, H 3.36, N 4.66. Found: C 59.50, H 3.36, N 4.59.
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10. Analysis of the ^{1}H nmr spectra of the crude reaction mixture indicates the absence of a C_2 axis (two different acetal protons) for one of the two major diastereoisomers.
11. The diastereoisomeric ratios, as well as the relative amount of the by-products, were measured by integration of the ^{1}H NMR signals of the crude reaction mixtures in C_6D_6. For compounds **15b-d** the spectra do not allow the exclusion of the presence of traces of the third stereoisomer.
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