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Efficient Masking of *p*-Benzoquinone in Nitrone Cycloaddition Chemistry

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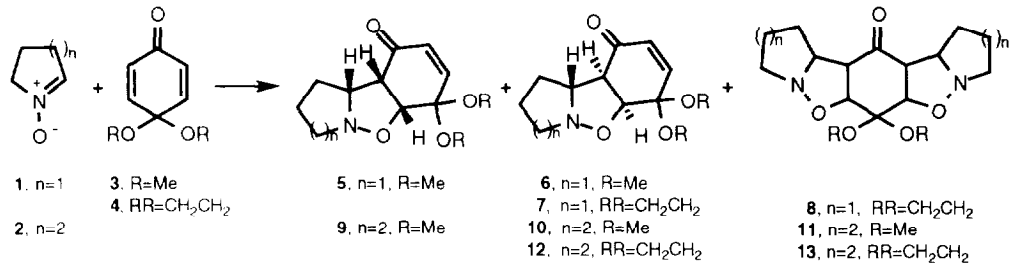
Abstract - 1,3-Dipolar cycloadditions of five and six membered cyclic nitrones to *p*-benzoquinone monoketals have shown poor chemo- and stereoselectivity. To overcome these problems, a highly efficient strategy has been set up based on the temporary conjugate addition of thiophenol to the dipolarophile.

For years *p*-benzoquinone derivatives have been considered as interesting target molecules, probably because of their important role in bioorganic redox reactions. Several examples have been published in which *p*-benzoquinones acted as a dipolarophile in front of different kind of 1,3-dipoles, including nitrile ylides,[1] nitrile oxides,[2] diazoalkanes,[3] phenyl azide,[4] azomethine ylides[5] and nitrile sulfides,[6] but the regio- and stereoselectivity of these reactions remain still uncertain. The reactivity of several *p*-benzoquinones towards nitrones has been studied previously and the yields of cycloadducts were always extremely low, probably due to the ocurrence of complicated redox processes between reactants and products.[7] Moreover, depending on the substitution of the starting quinone, the aromatization of the primary adducts can easily take place, obscuring the stereochemical information of the process. Quite often, the use of mono- and bisketals of quinones has shown to be effective to overcome reactivity and/or selectivity problems presented by the corresponding unprotected quinones.[8] We therefore decided to investigate the reactivity of *p*-benzoquinone monoketals towards cyclic nitrones, as a part of a more general study in which other 1,2-disubstituted electron-deficient olefins are also included.[9] A preliminary account of this investigation is reported in the present letter.

We carried out the prospective studies with nitrones **1**[10] and **2**[11] and *p*-benzoquinone monoketals **3**[12] and **4**[12b,13] (Scheme 1). Some significant results are collected in the Table.[14] The reaction of nitrone **1** with dimethylketal **3** gave a mixture of *endo*, **5**, and *exo*, **6**, 1:1 cycloadducts in a moderate overall yield, while with the ethyleneketal **4** the *exo* 1:1 adduct, **7**, was isolated in 18% yield, along with a considerable amount of a 2:1 cycloadduct, **8**. The cycloadditions of nitrone **2** gave better yields of identifiable products. For this nitrone the *exo* selectivity appears to be high for both ketals, although the quantities of 2:1 cycloadducts, **11** and **13**, also increased, even when larger excesses of ketal were employed. The assignment of the *exo* or *endo* stereochemistry to the 1:1 cycloadducts was not always trivial because of the complicated conformational behaviour of some of these compounds, due to the slow inversion of the nitrogen lone pair.

Nevertheless, comparison of their ^{1}H and ^{13}C NMR spectra with those of related compounds previously prepared and carefully studied by our group[9a,9b] allowed us to establish their stereochemistry as depicted in Scheme 1.



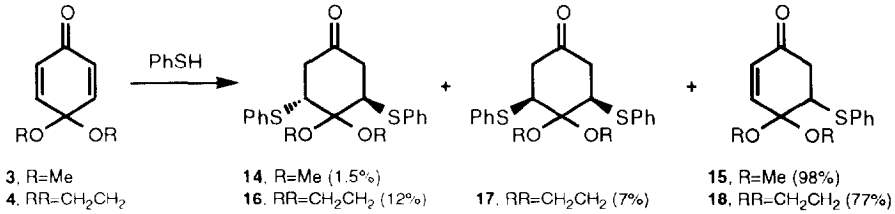
Scheme 1

nitrone	ketal	solvent, temperature, time	[nitrone]:[ketal]	product (% yield)
1	**3**	toluene, 110 °C, 8 h	1:2	**5** (12), **6** (21)
1	**4**	toluene, 110 °C, 4.5 h	1:1.7	**7** (18), **8** (24)[a]
2	**3**	methanol, 20 °C, 5 days	1:1.8	**9** (1), **10** (51), **11** (30)
2	**4**	chloroform, 20 °C, 7 days	1:4	**12** (24), **13** (39)

[a] A regioisomeric 1:1 cycloadduct was also isolated in a 16% yield.

In view of the poor chemoselectivity observed, we decided to protect one the double bonds of the quinone monoketal dipolarophile previously to the cycloaddition reaction.

Foster and Payne described that treatment of monoketal **3** with a catalytic amount of LiOH in a thiophenol solution gave the product of double conjugate addition, **14**, in excellent yield.[15] It occurred to us that the temporary addition of one equivalent of thiophenol could be a convenient way to protect one of the double bonds of the quinone monoketal and, at the same time, the phenylthio group may somehow influence the stereochemical course of the subsequent cycloaddition. Also, the introduction of chirality in the dipolarophile could be later on useful to accomplish an overall enantioselective process.

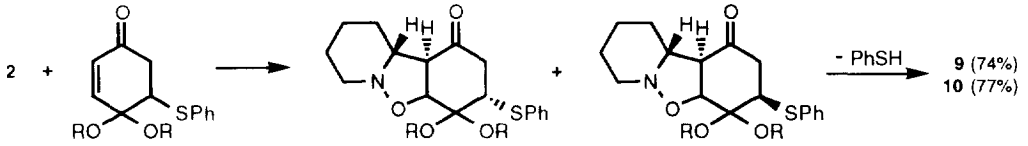


Scheme 2

We therefore performed the reactions of ketals **3** and **4** with 0.5 eq of thiophenol under thermodynamically controlled conditions (cat. LiOH, $CHCl_3$, reflux, 5 h) and we obtained the products of single conjugate addition, **15** and **18**, in very good yields[16] (Scheme 2).

Nitrone **2** was used to study the 1,3-dipolar cycloaddition to the phenylthio derivatives (Scheme 3). Its addition to **15** ($CHCl_3$, reflux, 24 h) gave a *ca.* 1:1 mixture of two cycloadducts, to which we tentatively assign the stereochemistries *exo-anti*, **19**, and *exo-syn*, **20**, in 81% overall yield. Curiously, the addition of **2** to **18** ($CHCl_3$, reflux, 5.5 h) showed higher selectivity and it proceeded quantitatively to give a major cycloadduct **21**, assigned as *exo-anti*, in 98% yield, along with a small percentage of the *exo-syn* isomer **22**.

The pair of diastereoisomers **19/20** was correlated with the corresponding olefinic cycloadduct **9**, previously obtained in the cycloaddition of nitrone **2** to the dienic ketal **3**. This transformation was efficiently performed by treatment of a mixture of **19** and **20** with Ac_2O/pyridine at 70 °C for 21 h. This elimination of thiophenol promoted by base proceeded in better yield (74%) than the alternative pyrolytic elimination of the corresponding sulfoxides. In a similar way, compound **21** was converted into the olefinic cycloadduct **10** in a 77% yield. In this way the *exo* relative stereochemistry of all these compounds was confirmed.



15, R=Me
18, RR=CH_2CH_2

19, R=Me (39%)
21, RR=CH_2CH_2 (98%)

20, R=Me (42%)
22, RR=CH_2CH_2 (2%)

Scheme 3

The above results indicated that the presence of a phenylthio group at the β-carbonyl position of the spirocyclic monoketal was very effective in controlling the diastereoselectivity of the nitrone cycloaddition. Therefore, access to enantiopure derivative **18** was most desirable. We attempted the direct resolution of racemic **18** by liquid chromatography using cellulose triacetate (15-25 μm from Merck) as chiral stationary phase. Ethanol/water (96/4, 150 ml/h) was used as elution solvent through a column of 200 x 25 mm and a very good enantioselection factor α=2.52 was found. The first enantiomer eluted had an optical rotation value of $[\alpha]_D^{20}$=-72.1 (*c*=1.90, $CHCl_3$) and the second had $[\alpha]_D^{20}$=+71.8 (*c*=1.70, $CHCl_3$). Preparative runs were performed on 100 mg samples and both enantiomers were recovered in yields around 85%.

Compound (+)-**18** was then treated with excess of nitrone **2** ($CHCl_3$, reflux, 6 h) and a single adduct (+)-**21** with $[\alpha]_D^{20}$=+13.2 (*c*=2.35, $CHCl_3$) was obtained in 79% yield. Then the base promoted elimination of thiophenol in the standard conditions gave (-)-**12** with $[\alpha]_D^{20}$=-27.7 (*c*=0.65, $CHCl_3$).

In summary, we have set up a methodology that allows the use of a *p*-benzoquinone synthetic equivalent in a nitrone dipolar cycloaddition by efficiently masking one of each pair of functional groups, the carbonyl and the double bond, through ketalization and transient conjugate addition of thiophenol. An optically pure synthetic equivalent of *p*-benzoquinone has been readily obtained in both enantiomeric forms by direct resolution, providing an enantioselective version of this methodology. We are now extending the same strategy to other types of reactions. A full account of this work will be reported elsewhere.

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