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Phthalimidesulfenyl Chloride Part 6[1]. The First Example of an α-Oxothione Acting as Heterodiene: Synthesis of 2,3-Dihydro-1,4-Oxathiines.

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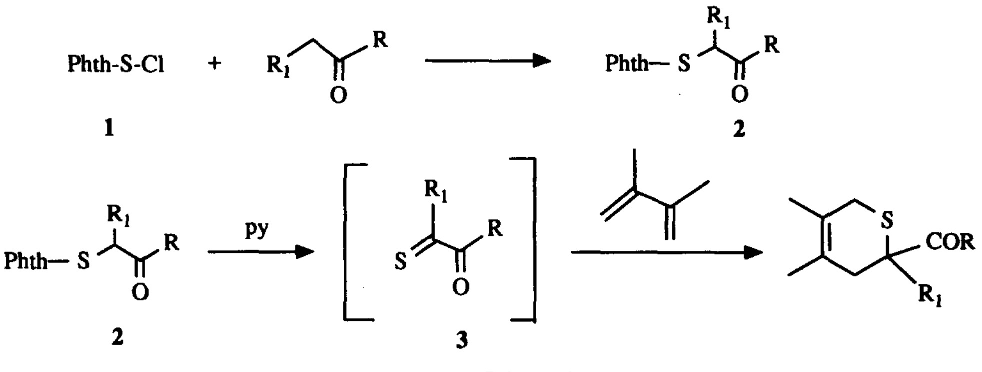
Key Words: *Phthalimidesulfenyl chloride, α-oxo-thione, vinyl ethers, heterodiene, cycloaddition, 2,3-dihydro-1,4-oxathiines.*

Abstract: α-α'*-Dioxothione 3a acts as heterodiene undergoing 4+2 cycloaddition reactions with enol ethers with the regiospecific formation of 2,3-dihydro-1,4-oxathiines 5 in good yields. The reaction is very simple and quite general. Using this reaction the thiosugar derivative 5e has been also prepared.*

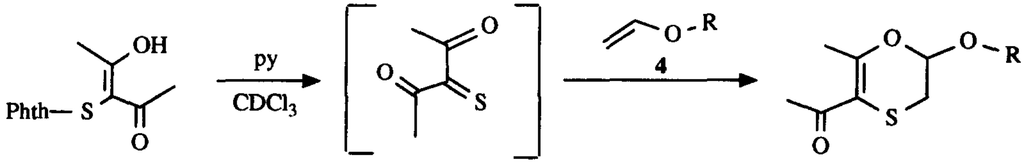
Thiocarbonyl compounds have been successfully employed in the synthesis of complex structures[2], as well as for the construction of new carbon-carbon bonds[3].

We have recently shown that phthalimidesulfenyl chloride **1** reacts with enolizable ketones or silyl enol ethers to give α-substituted ketones **2**, and that the latter can easily generate the corresponding thione derivatives **3** which have been trapped by electron rich 1,3-dienes in a classical 4+2 cycloaddition reaction[1] (Scheme 1).



Scheme 1

In this communication we report that the α-oxothione **3a** (R=Me, R_1=COMe) can also act as heterodiene in reactions with electron-rich alkenes, e.g. enol ethers, to give rise to 2,3-dihydro-1,4-oxathiine derivatives[4]. The reaction is simply accomplished by adding pyridine to a $CDCl_3$ solution of **2a** and the vinyl ether **4** at room temperature (Scheme 2).



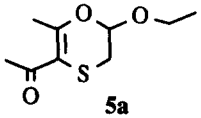
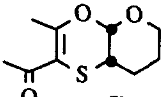
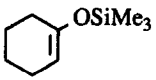
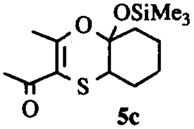
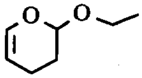
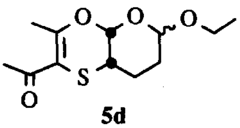
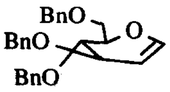
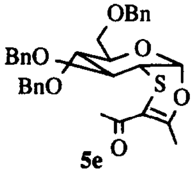
Scheme 2

The reaction progress, monitored by ^{1}H n.m.r., indicates that the formation rate of the heterocycle is dependent upon the nature of enol ether **4**, and the relative ratio of the reagents.

The crude reaction mixture is washed with saturated NH_4Cl, the solvent is removed, and the resulting mixture extracted with *n*-pentane in order to separate the insoluble phthalimide. Isolation of the cycloadduct **5** is then accomplished by flash chromatography.

I.R. spectra and ^{1}H and ^{13}C n.m.r. data strongly support the proposed structures of the cycloadducts **5a-e**[5,6]. Yields of the products synthesized and reaction conditions are reported in the Table.

Table. Reaction of thione **3a** with enol ethers **4a-e** and pyridine[a]

Enol Ether	Cycloadduct	Reaction Time (h)	Yields[b] (%)
 **4a**	 **5a**	2	80
 **4b**	 **5b**	20	90
 **4c**	 **5c**	40	80
 **4d**	 **5d**	22	67[c]
 **4e**	 **5e**	168	88[d]

[a] The reagents (**3a**:**4**:py=1:2:3 molar ratio) were mixed at room temperature.

[b] Isolated yields. [c] Isolated as 80:20 mixture of diastereoisomers.

[d] Ratio **3a**:**4e**:py=2:1:6 ; yield is calculated on the converted **4e**.

These data show that the reaction is strictly regiospecific and highly stereoselective. Indeed *ab initio* molecular calculations[7] indicate a most favorable interaction between the LUMO of the thione and the HOMO of the enol ether and show higher coefficients on the C=S bond of the LUMO of **3a** and on the β-carbon of the HOMO of a model vinyl ether. Thus the reaction might be an inverse electron demand 4+2 cycloaddition, perhaps with a high polar character.

Moreover it has been possible to demonstrate by MO calculations[7] that conformer A is only about 2 Kcal/mol lower in energy than conformer B (Scheme 3). We speculate that form B is required for the cycloaddition to succeed.

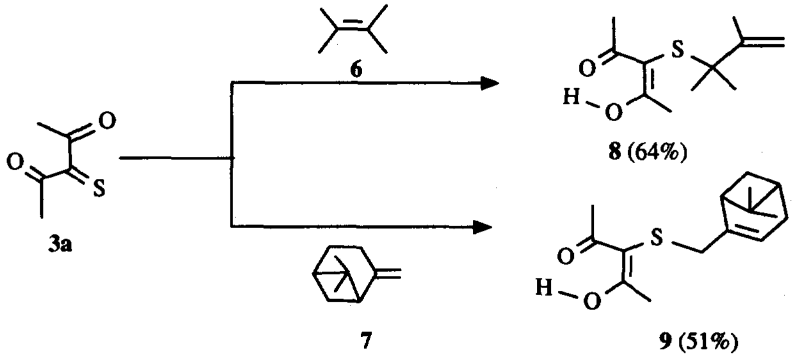
A

Scheme 3

B

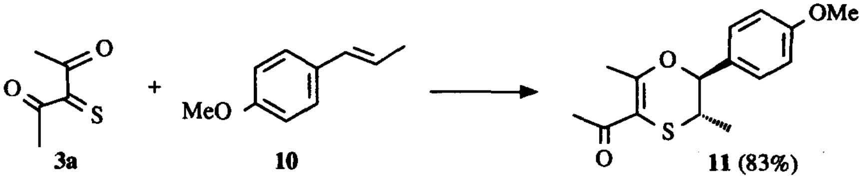
A remarkable stereoselectivity is exhibited by the reaction of **3a** with the dihydropyran **4d** (80 : 20 diastereomeric ratio), while the reaction of **3a** with tri-*O*-benzyl glucal **4e** gives a single stereoisomer to which was assigned the structure shown in the Table[8].

We have also examined the reactivity of **3a** towards 2,3-dimethyl-2-butene **6** and (-)-β-pinene **7**. In both cases we observed only a selective *ene* reaction[9] with the formation of sulfides **8** and **9** respectively (Scheme 4).



Scheme 4

On the other hand the reaction of **3a** with *trans*-anethole **10**, an alkene where cycloaddition and *ene* reaction might compete, gave the cycloadduct **11** as unique product (Scheme 5).



Scheme 5

This result indicates that the two possible reaction paths are evenly balanced and that small modifications of the alkene structure can drive the reaction in a specific way.

A more detailed study on this matter and in particular the effect of both oxothione and alkene structure on reactivity is being currently investigated in these laboratories.

ACKNOWLEDGMENTS.

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2. Vedejs, E; Reid, J. G. *J. Org. Chem.* **1987**, *52*, 4269-4274.
3. Metzener, P. *Synthesis*, **1992**, 1185-1199.
4. To our knowledge only one report describing the synthesis of these heterocycles has been published: Asinger, F.; Saus, A.; Offermanns, H.; Scherberich, P. *Liebigs Ann. Chem.* **1971**, *753*, 151-168.
5. Relevant spectroscopic data for compound **5a** are as follows: ^1H n.m.r: 5.26 (X part of an ABX system, 1H); 4.02-3.85 and 3.77-3.61 (AB part of an ABX_3 system, 2H); 2.97-2.77 (AB part of an ABX system, 2H, J_{AB}=13.0 Hz); 2.30 (s, COMe, 3H); 2.28 (s, 3H); 1.26 (t, X_3 part of an ABX_3 system, 3H, J_{AX}=J_{BX}=7.1 Hz) δ. ^{13}C n.m.r.: 195.62 (s, COMe); 158.03 (s, vinylic); 105.41 (s, vinylic); 96.56 (s, O-CH-O); 64.79 (t, O-CH_2); 29.67 (q, CH_3-CO); 28.63 (t, S-CH_2); 22.07 (q, CH_3-=); 15.04 (q, CH_3-CH_2) δ. I.R.: 2978-2928 (C-H stetc.); 1673 (C=O strect.); 1562 (C=C stretc.); 1246 (C-O stretc.) cm^{-1}. Mass Spectrum (M/z, %): 202 ($M^{+\cdot}$, 27%); 160 (M-42, 32%), 72 (M-130, 57%), 43 (100%). Elemental Analysis: Calculated for $C_9H_{14}O_3S$: C 53.44%, H 6.98%; Found: C 53.56%, H 7.19%. All other compounds synthesized show correct elemental analysis and consistent spectral data.
6. *Cis* junction in compounds **5b** and **5d** is strongly supported by the ^3J values between hydrogens at C-9 and C-10 which are 2.7 Hz for **5b** and 2.4 and 2.9 Hz for the major and the minor diastereisomer of **5d** respectively.
7. *Ab initio* molecular calculation have been performed with the SPARTAN program at 3-21G* level.
8. Assignement has been possible using the ^3J value between the hydrogens laying in position 1, 2 and 3: the values of 3.0 Hz for J_{H1-H2} and 10.3 Hz for J_{H2-H3} are as expected for an equatorial-axial-equatorial arrangement of the hydrogens.
9. a) Bladon, C. M.; Ferguson, I. E. G.; Kirby, G. W.; Lochead, A. W.; McDougall, D. C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1541-1545; b) Kirby, G. W.; McGregor, W. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3175-3181; c) Snider, B. B.; Hrib, N. J.; Fuzesi, L. *J. Am. Chem. Soc.* **1976**, *98*, 7115-7117.

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