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1-(Phenylthio)- and 1-(Phenylsulfoxide)-4-Alkoxy-Butadienes, a New Class of Chiral Dienes.

Odile Gaonac'h, Jacques Maddaluno, Gérard Plé, Lucette Duhamel*.

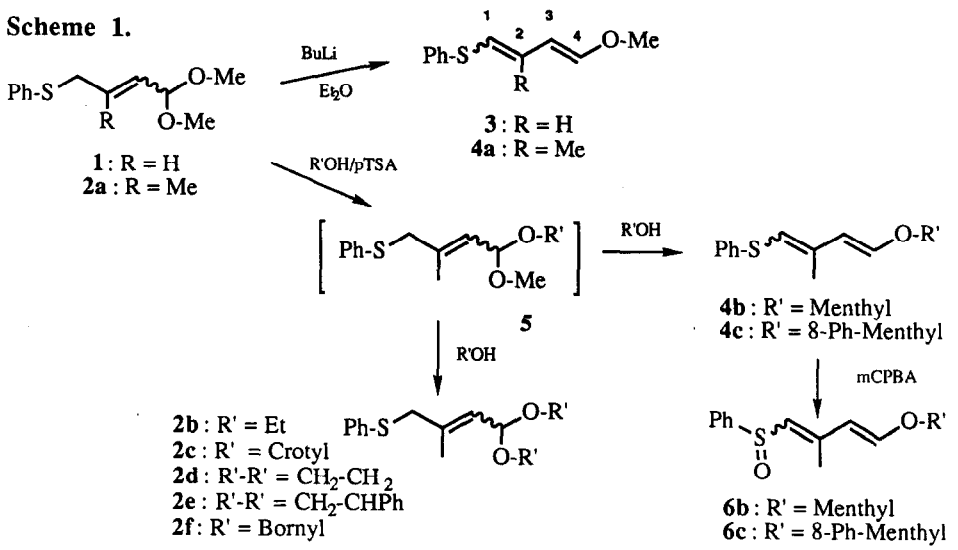
Laboratoire Associé au CNRS n°464, Faculté des Sciences et Techniques de Rouen, BP 118, F-76134 Mont Saint Aignan (France).

Key Words: acid-catalyzed transacetalization; chiral dienol ethers; thioether oxidation; π-stacked structure.

Abstract: Trans-acetalization of the methyl acetal of 3-methyl-4-(phenylthio)-but-2-enal 2a in acidic medium leads to the expected trans-acetals 2b-f or their γ-elimination products (i.e. 4-alkoxy-2-methyl-1-(phenylthio)buta-1,3-dienes 4), depending on the nature of the selected alcohol. Both types of compounds may be easily oxidized into the expected sulfoxides 6. The menthyloxy and phenyl-8-menthyloxy sulfides 4b,c and sulfoxides 6b,c have been prepared.

Despite their generally difficult synthetic access due to control of both regio and stereoselectivity[1], 1,4-disubstituted 1,3-dienes are synthons of special interest in organic chemistry as key partners in the widely employed Diels-Alder cycloaddition reaction[2]. We have recently reported[3] the synthetic utility of the methyl acetals of 4-(phenylthio)-but-2-enal **1** and 3-methyl-4-(phenylthio)-but-2-enal **2a** as precursors of 1,4-disubstituted dienol ethers **3** and **4a**. We wish now to present i) the ability of structure **2a** to be trans-acetalized in an acidic medium, leading to either trans-acetals **2b-f** or directly to their elimination products **4**, depending on the nature of the alcohol used, and thus allowing a simple one-step access to 1,4-disubstituted dienol ethers **4**; ii) the easy oxidation of later compounds into sulfoxides **6**.

Scheme 1.



Our recent results about the reactivity of methyl acetals of 4-(phenylthio)-but-2-enal **1** and 3-methyl-4-(phenylthio)-but-2-enal **2a** in the presence of alkyl lithium reagents or lithium amides to give access to dienol ethers **3** and **4a**, respectively, led us to apply trans-acetalization reactions to starting methyl acetal **2a** in an attempt to get access to a larger set of substituted dienol ethers. Thus, compound **2a** in ether has been exposed to different alcohols in presence of a trace of dry p-toluenesulfonic acid (pTSA)[4]; the results are gathered in Table 1. While small primary alcohols such as dry ethanol or crotyl alcohol (entries 1 and 2) or 1,2-diols such as glycol or phenyl glycol (entries 3 and 4) give the expected trans-acetals **2b-e**, tertiary alcohols remain ineffective (entry 8). It is specially worth emphasizing that bulky secondary alcohols may either partially trans-acetalize (entry 5)[6] or lead, through γ elimination of alcohol, to corresponding dienol ethers (entries 6 and 7). This same phenomenon may be observed on the original acetal **2a** and takes also place in the presence of unreactive tertiary alcohols (entry 9). Purification of the products is achieved by flash chromatography on silica gel, adding 1% triethylamine to the eluant; yields in isolated acetals are generally good while dienol ethers **4** tend to decompose on silica or florisil. Nevertheless, thin layer chromatography as well as mass spectrometry performed on the crude reaction mixture suggest formation of **4** to be much more efficient than indicated by isolated yields[7]. We then decided to directly oxidize the dienes **4** into sulfoxides **6**. This operation converts the electrodonating sulfur into an electron withdrawing group[8], leading in our case to push-pull type dienes generally regarded as highly regioselective partners in cycloaddition reactions[9]. As expected in such situations[10], one equivalent of m-chloroperbenzoic acid (mCPBA) efficiently oxidizes the thioethers **4** within a few minutes at room temperature into corresponding sulfoxides **6**. These compounds resist definitely better to chromatography.

Table 1. Trans-acetalization of **2a** in Various Alcohols.

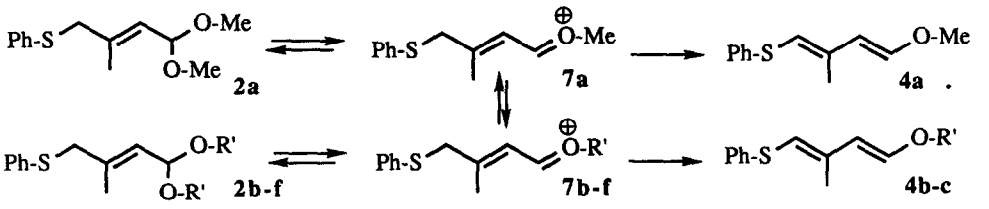
Entry	Alcohol (eq.)	Product	Yield(%)[a]	Stereochemistry
1	EtOH (100)[b]	Trans-acetal (**2b**)	72	E:Z = 75:25
2	CH_3-CH=CH-CH_2OH (15)	Trans-acetal (**2c**)	45	E:Z = 75:25
3	Glycol (1.4)	Trans-acetal (**2d**)	68	E:Z = 75:25
4	Phenylglycol (1.5)	Trans-acetal (**2e**)	65	E:Z = 75:25
5	L-(-)-Borneol (3 or 15)[c]	Trans (**2f**) + mixed (**5f**) acetal	-	E:Z = 75:25
6	L-(-)-Menthol (3)	Enol ether (**4b**)	43[d]	1E3E:1E3Z = 50:50
7	(-)-8-Phenylmenthol (3)	Enol ether (**4c**)	35[d]	1E3E:1E3Z = 50:50
8	t-BuOH (3)	Starting material (**2a**)	-	-
9	Ph_3COH (3)	Enol ether (**4a**)	45[d]	1E3E:1E3Z = 50:50

[a] Yields after flash chromatography.
[b] Used as solvant.
[c] See Note 6.
[d] Yield calculated on corresponding sulfoxide **6**.

From a stereochemical point of view, high field NMR and NOE experiments have shown that the original E/Z ratio of the methyl acetal **2a** (Z:E = 75:25) is preserved when the simple trans-acetalization step takes place. On the other hand the eventual elimination process leads, in all cases studied here, to total control of the enol ether 3-4 bond in absence of any stereoselectivity for the thioenol ether 1-2 double bond (1E,3E:1Z,3E = 50:50). Furthermore, the 360 MHz NMR spectra indicate that sulfur oxidation of asymmetric enol ethers **4b** and **4c** occurs without any diastereoselectivity, as measured from careful integration of the H^3 signals.

These results prompt us to think that this trans-acetalisation process takes place through the generally admitted[11] intermediate oxoniums **7**, according to three possible paths (Scheme 2). The outcome of the reaction may then depend on the bulkiness of R' that could, while making reaction of **7** with surrounding alcohol cumbersome, drive this carbocation to dienol ether **4b-c** through the γ elimination of a proton rendered possible by the phenylthio group activation.

Scheme 2.



There are few examples of asymmetric dienes reported in the litterature[12]; indeed, the relative conformational flexibility of a butadiene-type structure makes the facial selectivity control from a remote chiral auxiliary difficult. Comparison of the chemical shifts between asymmetric dienol ethers **4b** and **4c** or **6b** and **6c** is likely to provide an evaluation of a possible intramolecular π-stacking effect taking place between the butadiene and phenyl ring moieties of **4c** or **6c**[13]. Results are presented in Table 2.

Table 2. Chemical Shifts (ppm, in C_6D_6) of Dienol Ethers **4b,c** and Sulfoxides **6b,c**.

	Ph-S, O-Menthyl **4b**		Ph-S, O-Ph-Menthyl **4c**		
	Z,E	E,E	Z,E	E,E	Δδ(E,E)
H^1	5.82	6.00	5.82	6.01	-0.01
H^3	6.81	5.98	6.67	5.86	-0.12
H^4	6.60	6.43	6.38	6.23	-0.20
Me^5	1.76	1.96	1.77	1.94	-0.02

	Ph-S(=O), O-Menthyl **6b**		Ph-S(=O), O-Ph-Menthyl **6c**		
	Z,E	E,E	Z,E	E,E	Δδ(E,E)
H^1	5.82	6.02	5.81	6.01/5.99[a]	-0.01/-0.03[a]
H^3	6.90	5.57/5.56[a]	6.65/6.59[a]	5.44/5.37[a]	-0.13/-0.19[a]
H^4	6.58/6.57[a]	6.50	6.34	6.30/6.27[a]	-0.20/-0.23[a]
Me^5	1.49	1.95	1.48	1.95	0.00

[a] : the mCPBA oxidation of sulfur leads to a mixture of diastereoisomers for **6b** and **6c**.

An upfield shift decreasing along the isoprenylic chain of **4c** and **6c** takes place as reported for menthyl and aryl-8-menthyl crotonates[13], supporting the hypothesis of the contribution of a stacked conformer to chemical shifts of both **4c** and **6c**. Furthermore, the magnitude of this effect compares very nicely to those reported for related menthyl/phenyl-8-menthyl enol and dienol ethers[14]. This phenomenon, which has been proposed as being at the origin of the excellent diastereofacial selectivity observed with phenyl-8-menthyl esters[14,15] makes compounds **4c** or **6c** interesting candidates to study the origin of asymmetric induction in cycloaddition reactions.

In conclusion, the acidic procedure described constitutes a new and expeditious synthetic access to a series of 1,4-difunctionalised chiral 1,3-dienes; scope and limitations of this class of compounds are currently under investigation in our laboratory.

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6. Warming **2a** to reflux of ether for 2h with 15 equivalents of borneol leads to a mixture of trans acetal (**2f**) and corresponding bornyl dienol ether (compound **4** with R'=bornyl).
7. For instance, dienol ethers **4b** and **4c** may be trapped *in situ* by cycloaddition with tetracyanoethylene at room temperature, leading to expected cycloadducts in about 65% overall yield.
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