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A MILD AND DIRECT OXIDATION OF DIENOL THIOETHERS INTO KETENE DITHIOACETALS.

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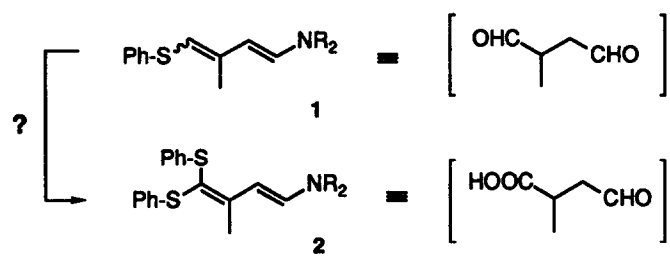
Abstract: *Functionalized dienol thioethers reacts with 3 eq. of thiophenol at room temperature in presence of dioxygen to give directly corresponding ketene dithioacetals in high yields.*

Because of their implication in the synthesis of terpenic and related natural compounds, the chemistry of functionalized building blocks with a 4 or 5 carbon atom backbone has been largely developed[1] and remains an area of intensive work[2]. In this context, we have recently proposed[3] a method providing a versatile access to 4-substituted 1-phenylthio-1,3-dienes, among which dienamines **1**. These synthons may be considered as formal equivalents of 2-methyl-butane dial (Scheme 1) in which the two aldehydes are protected as two groups of very different chemical sensitivity, *viz* the enol thioether and the enamine one. Since both acid and aldehyde functions are encountered in terpenic systems, searching for a route to building blocks bearing masked forms of a carboxylic acid could turn out to be a rewarding effort.

Scheme 1.



We thought a polyfunctional compound such as **2** could thus be an interesting synthon since it both retains the labile enamine group and features a ketene dithioacetal[4]; this latter, which is a function of many synthetic possibilities as recently underlined by Kolb[5], may preserve even in relatively harsh conditions the immanent acid moiety[6]. However, the simple conversion of the enol thioether function directly into the ketene dithioacetal one is unknown, and literature does not provide, to our knowledge, a smooth method to perform such an oxidation, especially in presence of the relatively fragile enamine group[7]. The set of functionalized enol

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phenylthioethers **1a-c**, prepared from haloacetals **3a** or **3b**[8] has thus been treated by thiophenol in presence (or absence) of dioxygen. Depending on substrate and reaction conditions, we have found the expected double addition[9a] (leading to **6**) to compete with the oxidation into ketene dithioacetal **2**, as presented on Scheme 2. Results are summarized in Table 1.

Scheme 2.

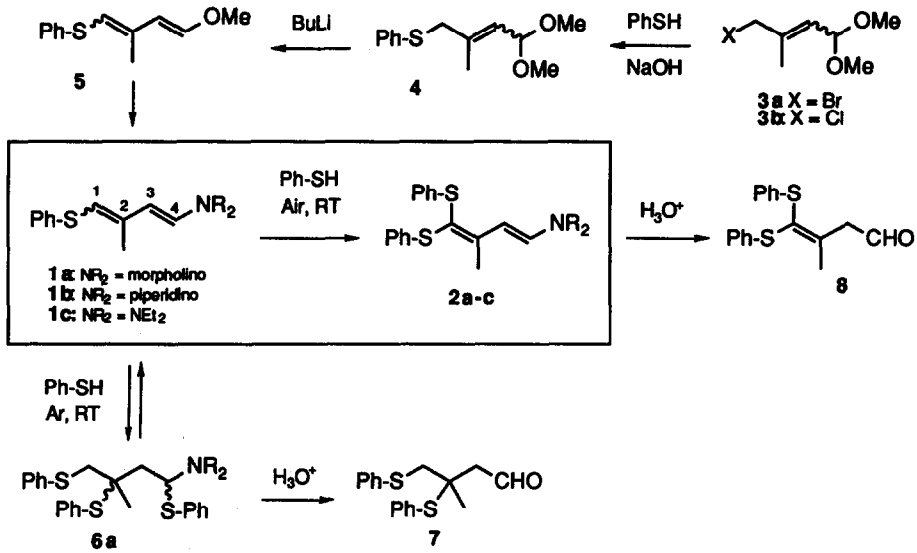


Table 1. Reactions of thioenol ethers at room temperature with 3 eq. of aromatic thiols in THF.

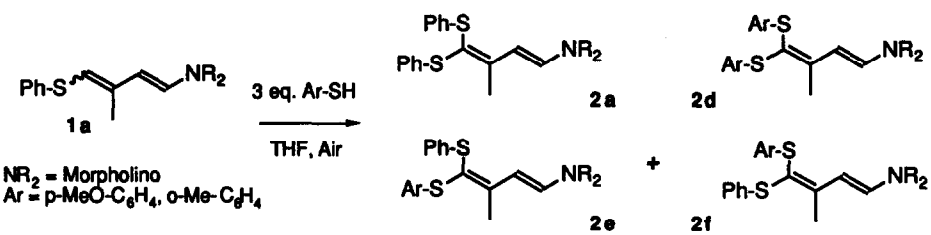
Entry	Substrate	Conditions	Reaction	Product	Yield (%)[a]
1	**1a**[b]	Ph-SH air, 24h	Oxidation	**2a**	>90
2	**1a**[b]	Ph-SH Ar or N_2, 24h	Addition	**6a**	>70
3	**1b**[b]	Ph-SH air, 48h	Oxidation	**2b**	>90
4	**1c**[b]	Ph-SH air, 48h	Oxidation	**2c**	>90
5	**1a**[b]	p-MeO-C_6H_4-SH air, 24h	Oxidation	**2a+2d+2e+2f**[c] (15:25:30:30)[d]	>90
6	**1a**[b]	o-Me-C_6H_4-SH air, 48h	Oxidation	**2a+2d+2e+2f**[c] (15:25:30:30)[d]	>90

[a] yields based on ^1H NMR spectroscopic analysis.
[b] prepared as a 1E,3E:1Z,3E = 50:50 mixture[3a,c].
[c] determined from NMR and MS analysis.
[d] correlation between ratios and products not established for (2d-f).

It is worth emphasizing that all dienamines **1** we have considered are converted in high yields, in 24h in presence of air, into the corresponding ketene dithioacetals **2**. The clear involvement of dioxygen as the original oxidizing agent indeed appears when comparing entries 1 and 2. While the oxidation is the almost single reactional pathway in presence of air, working under an inert atmosphere makes the double addition the major route, leading in this latter case only to saturated **6a** in absence of any diastereo-selectivity on this compound (d.e. ≈ 0%). Identity of these products has been established on the basis of 200 MHz NMR analysis and hydrolysis (1N HCl, RT) of **6a** and **2a** into corresponding aldehydes **7** and **8**, respectively (Scheme 2). On the other hand, simply stirring **6a** for 24h in THF solution under air leads quantitatively to the same ketene dithioacetal **2a**, strongly suggesting that the addition reaction is reversible while the oxidation one is irreversible in these conditions[10]. The selective hydrolysis of the enamine group in **2a** illustrates the ease with which the two functions may independently be unblocked, as required for convenient application of this synthon.

Use of other aromatic thiols has yielded results summarized in Scheme 3 and Table 1. A mixture of the four possible ketene dithioacetals was obtained with p-methoxybenzenethiol or o-thiocresol, in ratios depending on relative proportions of reagents and time (entries 5 and 6). Formation of symmetrical ketene dithioacetals **2a** and **2d** is specially noteworthy since treatment of **2a** by 3 eq. p-thioanisol leads to recovering of the starting material only, indicating that aryl-thio exchange takes place before the oxidation step. Bulky o,o'-dichlorothiophenol is sluggish and leads to three oxidation products only, while 2-mercaptopyridine remains inert after 6 days. We also report the absence of reaction of **1a** with t-butylthiol which is not only due to the large pK_a difference between alkyl and aryl thiols (4.5 pK units)[9b] since addition of 10% p-toluenesulfonic acid to the medium does not improve reactivity. This may be related to the easier oxidation of thiophenol when compared to t-butylthiol[9c].

Scheme 3.



From a stereochemical point of view, both (1E,3E) and (1Z,3E) stereoisomeric forms of dienamines **1**[3] appear reactive and the enamine double bond C_3-C_4 geometry is recovered since ketene dithioacetals **2** are in each case obtained as pure E compounds, as deduced from the 13.5-14Hz measured coupling constants[11] Mechanistically, our results are to be considered in relation to those by Oswald, Griesbaum and Hudson concerned with radical co-oxidation of conjugated simple diolefins with thiols by dioxygen[12] and to those of Yoshida et al[13] dealing with the transformation of single enol thioethers.into α-phenylthio carbonyl compounds by oxygenation in the presence of thiophenol. Likewise in our case disulfides are not the active species in this reaction since treating dienamine **1a** with various amounts of diphenyl or di-t-butyl disulfide in absence of air and, eventually, in presence of acids or bases leads mainly to recovering of the starting material. This same result was observed using 3 eq. of sodium thiophenate in a mixture of THF and ethanol.

We think the preliminary results presented here constitutes an unprecedented access to the ketene

dithioacetal function and apply to synthons particularly well suited to terpen synthesis. Further work devoted to applications and better mechanistic understanding of this new reaction are currently pursued in our laboratory.

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7. See Ref. 4a for the only related example.
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10. **2a** may stand for instance a 24 h long 254 nm irradiation in THF at 35°C without decomposition.
11. Data for **2a**: ^{1}H NMR (200MHz, $CDCl_3$): δ(ppm): 2.33 (3H, s), 3.08 (4H, broad t, J = 5.0Hz), 3.70 (4H, broad t, J = 5.0Hz), 6.33 (1H, d, J = 13.9Hz), 6.56 (1H, d, J = 13.9Hz), 7.18 (10H, m). ^{13}C NMR (50MHz, $CDCl_3$): δ(ppm): 17.6, 48.2, 65.9, 100.4, 111.2, 124.9, 125.1, 126.8, 126.9, 127.1, 127.5, 128.4, 128.7, 137.0, 137.6, 144.0, 153.8. HRMS for $C_{21}H_{23}NOS_2$: m/z 369.1221, found 369.1234. Attempt to chromatography **2a** on silica gel led mainly to aldehyde **8**.
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