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Synthesis of Substituted 2-Cyclopenten-1-ones from Oxodithioesters *via* a Domino Process

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Abstract. Freshly prepared sulfines of δ-oxodithioesters underwent chemoselective addition of methyllithium to the electron poor sulfur atom of the thiocarbonyl moiety. Subsequent ring closure was effected by intramolecular addition of the carbanion, generated *in situ*, to the δ-carbonyl function leading to 2-cyclopenten-1-ones. While most described intramolecular procedures involve a base-catalysed cyclisation, our method is induced by an addition reaction. It is a new efficient synthesis of substituted 2-cyclopenten-1-ones *via* a domino process.

Cyclopentenones are the major structural feature of numerous natural products.[1] The biological importance[2] and the high diversity of cyclopentenoid molecules justify the intensity of research efforts devoted to their synthesis within the last decades. The most convergent synthesis of cyclopentenones is the Pauson-Khand reaction which consists of the co-cycloaddition of alkynes, alkenes and carbon monoxide.[3] Recently catalytic and asymmetric versions of this formal [2 + 2 + 1] cycloaddition have been developed.[3a,4] Other intermolecular coupling process have been described.[5] Another important strategy is the base-catalysed cyclisation of 1,4-dicarbonyl compounds. A large variety of precursors of such bifunctional molecules have been proposed: furans,[6] chiral bicyclic lactams,[7] β-ketophosphonates or α-phosphoryl sulfides,[8] nitroalkenes.[9,10] Acid-catalysed intramolecular process like the Nazarov cyclisation[11,12] and the polyphosphoric acid-ring closure of α-ethylenic esters[13] should also be mentioned.

We report here a novel synthesis of 2-cyclopenten-1-ones based on the *Umpolung* chemistry strategy. We have recently demonstrated that the reaction of enethiolisable sulfines, arising from the oxidation of dithioesters, with organolithiums was almost instantaneous at low temperature (−78°C or −100°C) and exclusively thiophilic,[14,15] affording stabilised dithioacetal oxide carbanions. The high electrophilic character of sulfines[16]

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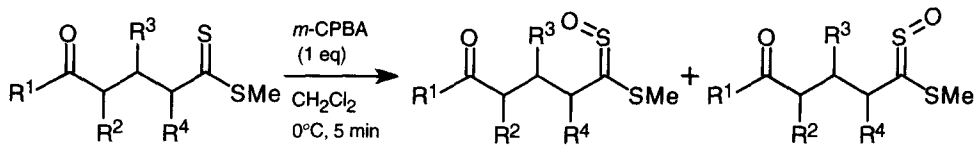
encouraged us to extend this reaction to molecules bearing a second electrophilic function (ketone) which would act as an internal trap of the carbanion generated *in situ* to achieve a ring closure.

Such a strategy was previously attempted with oxodithioesters as substrates and was shown to proceed only with non enethiolisable oxodithioesters.[17] Addition of organolithium or Grignard reagents to enethiolisable β-oxodithioesters selectively occured on the C=O function.[18]

The preparation of racemic δ-oxodithioesters **1a-d** has been previously described by our laboratory[19,20] and consists of the 1,4-addition of dithioester lithium enolates on conjugated ketones. This reaction is selective as no 1,2-adducts are formed and specific to thiocarbonyl compounds. Compounds **1a-d** were obtained with yields ranging from 71 to 80% after chromatography on silica gel. They were subjected to oxidation with 1 equivalent of *m*-CPBA in dichloromethane at 0°C and for only 5 minutes. The reaction was fully chemoselective (no Baeyer-Villiger oxidation) and afforded new sulfines **2a-d** (Scheme 1). We initially reported the direct oxidation of enethiolisable carbonyl compounds with *m*-CPBA.[21-23] These new examples demonstrate that it is an efficient and general process. The crude yields range from 94 to 98% (Table 1) and the estimated purity of the crude products is 95% according to the ^{1}H NMR spectra. In all cases but **2c** [(*E*)/(*Z*) = 60:40], only the (*E*) isomer – the kinetic product – was detected by ^{1}H NMR analysis, 1 hour after the reaction quench. Sulfines are usually not stable and decompose on chromatography columns. Compounds **2a-b** are the first sulfines stable enough to be purified by chromatography on silica gel (eluent=petroleum ether/ethyl acetate: 20/80). However some isomerisation was observed: (*E*)/(*Z*) evolved from 100/0 to 55/45 (**2a**) and 75/25 (**2b**).



1a: $R^1 = R^2 = Me$, $R^3 = R^4 = H$
1b: $R^1 = Me$, $R^2 = H$, $R^3 = Me$, $R^4 = H$
1c: $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Me$
1b: $R^1 = R^2 = -(CH_2)_3-$, $R^3 = Me$, $R^4 = H$

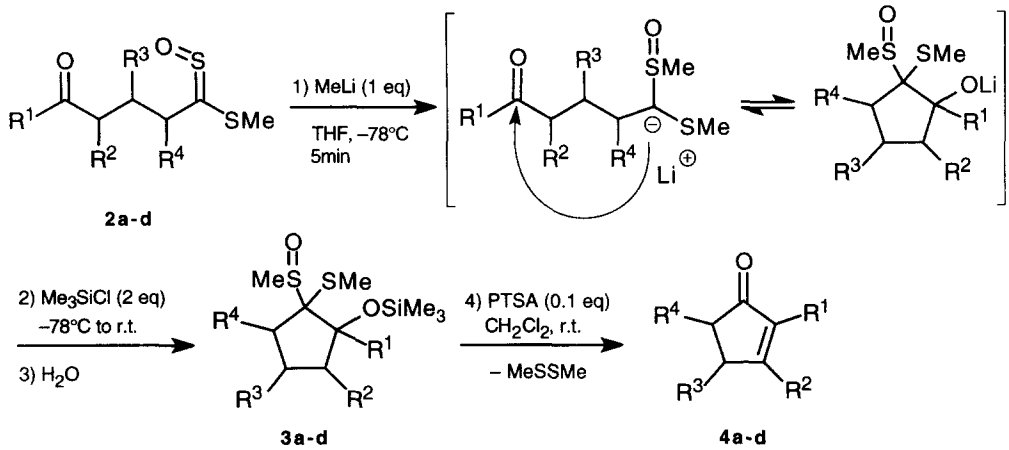
	(*E*)	(*Z*)
2a-b,d:	100	0
2c:	60	40

Scheme 1

Methyllithium (1eq) was added to a solution of freshly prepared oxodithioesters *S*-oxides **2a-d** in THF at –78°C. After 5 minutes, 2 equivalents of TMSCl were introduced. The reaction mixture was allowed to warm up to room temperature in 1 h and then hydrolysed. The cyclic silyl ethers **3a-d** were isolated as the sole products (80–95% crude yield).

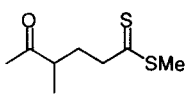
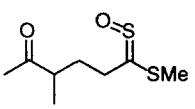
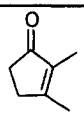
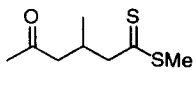
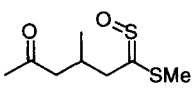
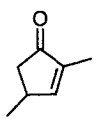
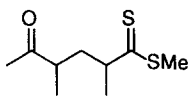
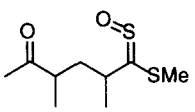
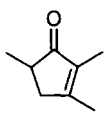
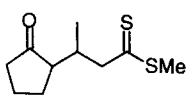
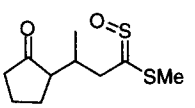
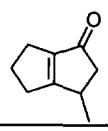
Compounds **3a-d** result from a domino process[24] involving 3 steps (Scheme 2): (i) Thiophilic addition of MeLi. (ii) Intramolecular addition of the stabilised dithioacetal oxide carbanion formed *in situ* on the C=O function. (iii) Silylation of the cyclic alcoholate. No reaction between the methyllithium and the carbonyl function occurs. The chemoselectivity of the first step gives further evidence of the high electrophilic character of sulfines. The TMSCl quench is crucial to prevent the formation of cyclohexenones (10–40%). This by-product probably arises from a 4-ketoaldehyde which results from the direct hydrolysis of the linear stabilised dithioacetal oxide. We noticed that the temperature of the hydrolysis step influenced the cyclopentenone/cyclohexenone ratio. This

observation suggests that the open chain carbanion and its cyclisation product are in equilibrium. The formation of the silyl ether enables complete conversion into the cyclised product.



Scheme 2

Table 1: Synthesis of Sulfines **2a-d** and 2-Cyclopenten-1-ones **4a-d**.

Oxodithioesters	**1**	Sulfines	**2**	Yield % (*)	Cyclopentenones	**4**[ref]	Yield %
	**1a**		**2a**	94 (38)		**4a**[13,25]	60
	**1b**		**2b**	97 (75)		**4b**[26,27]	40
	**1c**		**2c**	96		**4c**[28]	60
	**1d**		**2d**	98		**4d**[13]	44

*: yield after chromatography

Silyl ethers **3a-d** are not stable and spontaneously evolve into cyclopentenones **4a-d** by elimination of TMSOH or H_2O and dimethyl disulfide. Indeed, dithioacetal oxides are known to undergo spontaneous rearrangement into carbonyl function.[14,15] This transformation was accelerated by addition of a catalytic amount

(0.1 eq) of *p*-toluenesulfonic acid (PTSA). Total conversion was reached after 2 hours at room temperature in dichloromethane with a 75% crude overall yield.

As cyclopentenones **4a-d** are very sensitive towards polymerisation, their purification by distillation or chromatography on silica gel or alumina leads to partial decomposition (35% yield). Finally, they could be purified by filtration through alumina. The overall yields from the oxodithioesters **1a-d** (3 steps) range from 40 to 60% (Table 1). They are quite satisfactory when compared to those reported in the literature.

In summary, we have described an original synthesis of 2-cyclopenten-1-ones which does not involve a base-catalysed cyclisation process but an addition reaction. This new example of *Umpolung* chemistry should find application in the case of substrates bearing base-sensitive functional groups.

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