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Conjugate-Elimination on Unsaturated Acetals: A One-Step Route to Functionalized 1,3-Dienes.

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Abstract: γ-Functionalized α,β-unsaturated dimethyl acetals undergo a methanol δ-elimination upon basic treatment, leading to 1,4-disubstituted 1,3-dienes in good yields and, in several cases, with high stereocontrol of the newly formed double bonds.

Because of their wide applicability to the synthesis of natural products[1], among which the very important classes of terpenoids and carotenoids, the chemistry of functionalized building blocks bearing a 4 or 5 carbon atom backbone is the object of a sustained attention[2]. The continuous interest of our group in the field[3] recently led us to propose a method giving way to a set of 4-substituted 1-phenylthio-1,3-dienes[4] and unsaturated ketene dithioacetals[5]. Their dienic structure endows these synthons with interesting properties in cycloaddition reactions[6]. Our earlier papers described the easy elimination taking place on α,β-unsaturated acetals[7] bearing a thiophenyl group in the δ-position, eventually followed by a subsequent addition reaction. This preliminary report.now extends our original investigations to other hetero-substituted unsaturated acetals.

All α,β-unsaturated acetals considered in this work have been readily prepared from chloroacetal **1**[8] (Equation 1). A smooth nucleophilic substitution indeed takes place on this substrate with all thiolates, phenates, phosphonates or amines tested here. These reactions have been performed either in a biphasic process (ArSH or ArOH, aqueous sodium hydroxide/THF: method A) or by refluxing **1** in an excess (5 to 10 eq.) of the nucleophilic agent, in solution or neat (HNR_2 or $P(OEt)_3$: method B)[9]. In all cases, yields are almost quantitative. Compound **1** is available as a 75:25 E/Z mixture and in all cases studied in this work, the stereochemical ratios remained virtualy unaltered after substitution of the halogen atom.

Low temperature addition of strong bases solutions (R-Li, KHMDS, t-BuOK) to the acetals **2** followed by a temperature increase trigers in most cases a δ-elimination reaction, characterized by a strong darkening of the reaction medium. The isoprenoid-type structures we are dealing with in this work can undergo an initial deprotonation either on the methylene or on the methyl vinylic group (leading to dienes **3** or **4**, respectively, Eq. 1 and Table 1). NMR analysis of the crude reaction mixture indicate that, in general, the dienes **3** and/or **4** are obtained nearly pure and can be used without any further purification. If needed, a flash-chromatography of the oil obtained can be performed on silicagel in presence of 1% triethylamine but yields are then substantially lower. Actually, dienes **3** are more sensitive to hydrolysis than corresponding **4** which can thus be purified efficiently.

(Eq. 1)

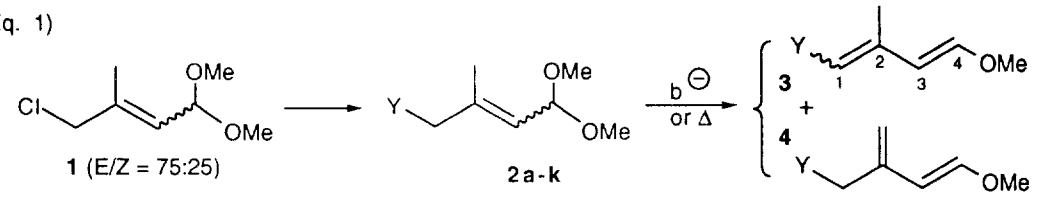


Table 1. Elimination reactions on functionalized α,β-unsaturated acetals **2**.

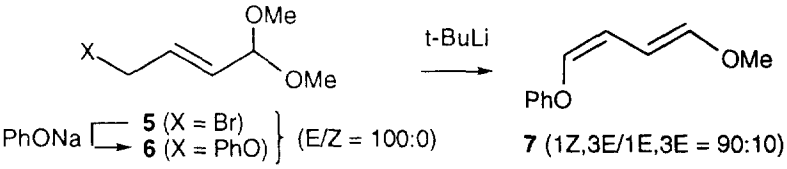
Entry	Substrate **2** #	Y	Conditions	**3** : **4**	Yd (%)	1E,3E/1Z,3E ratio for **3**[a]	Ref
1	**2a**	Ph-S	THF, n-BuLi (1 eq.), -70 to 20°C (20 min).	100:0	90	85:15	4a
2	**2b**	2,6-Me_2-C_6H_4-S	Et_2O, t-BuLi (1 eq.), -70 to 20°C (30 min).	38:62	95	73:27	4c
3	**2c**	2,6-Cl_2-C_6H_4-S	ibid	100:0	29[b]	> 95:5	4c
4	**2d**	Ph-O	ibid	100:0	94	≈10:90	4c
5	**2e**	Me_2N	Et_2O, t-BuLi (2 eq.), -78 to 37°C (4h).	0:100	95	-	
6	**2e**		Tol, n-BuLi, (2 eq.), -78 to 110°C (8h).	50:50	66	> 95:5	
7	**2e**		Tol, MeLi (2 eq.), -78 to 100°C (3h).	44:56	60	> 95:5	
8	**2f**	Et_2N	Et_2O, n-BuLi (2 eq.), -78 to 37°C (2h) or RT (18h).	30:70	94	>95:5	
9	**2f**		THF, KHMDS (2.6 eq.),-70 to 20°C (1h).	0:100	40[c]	-	
10	**2g**	$(i\text{-}Pr)_2N$	Et_2O, n-BuLi (2.2 eq.), -78 to 37°C (3h).	-	0[d]	-	13
11	**2h**	$(i\text{-}Bu)_2N$	Et_2O, n-BuLi (2.3 eq.), -78 to 37°C (1h).	0:100	92	-	
12	**2i**	2-Pipecolino	Et_2O, n-BuLi (2 eq.), -78 to 37°C (2h).	25:75	95	>95:5	
13	**2j**	Morpholino	Et_2O, t-BuLi (1.8 eq.), -78 to 37°C (2h).	36:64	67	>95:5	
14	**2j**		Et_2O, n-BuLi (1.6 eq.), -78 to 37°C (2h)	30:70	29[e]	>95:5	
15	**2k**	$(EtO)_2PO$	THF, t-BuOK (1.2 eq.), -78°C (1h30)	100:0	94	>95:5	14b
16	-	H	Pentane, t-BuLi (1.3 eq.), -5°C (3h)	-	80	100% E	7

[a] Ratios for **3** only (**4** is pure E).
[b] 67% **2c** recovered (E/Z = 100:0).
[c] 60% **2f** recovered (E/Z = 66:33).
[d] **2g** recovered unaltered.
[e] 70% **2j** recovered (E/Z = 100:0).

The presence of an electronegative substituent Y should favor the more substituted diene **3**; but this electronic effect can be balanced by steric umpairements reinforcing the kinetic[10] acidity of the methyl protons and thus promoting the less substituted ("exo") diene **4**. Because of the selective deprotonation in α of the sulfur atom (entries 1-3), our original works on the thiophenyl-substituted acetal **2a** had been restricted to the "endo" type dienes **3a**.[4a,c,6] The same regioselective reaction takes place on the phenoxy (**2d**, entry 4), or phosphonato (**2k**, entry 15) derivatives.

On a stereochemical point of view, the 3-4 enol ether double bond of **3** is always obtained under its single E form; on the other hand, the configuration of the 1-2 bond depends on its substitution pattern. Noteworthy is the dramatic reversal observed when going from arylthioether **2a-c** to arylether acetal **2d**: the major products in entries 1-3 are the 1E,3E dienes **3a-c** while row 4 indicates a selective access to 1Z,3E dienol diethers **3d**. Similarly, acetal **6**, which provides access to the butadienoid serie and has been prepared (method A) from bromoacetal **5** obtained itself under the pure E configuration following a two-step procedure from crotonaldehyde[4a,c,11], leads to the corresponding linear diene **7** (Equation 2) mainly under its 1Z,3E configuration (90%). The origin of this sensitivity to the heteroatom poses a conundrum that we are, for the moment, at a loss to untangle; it probably has to be considered in relation with the poor Li^+ chelation ability of sulfur when compared to oxygen.[12]

(Eq. 2)



As expected, cumbersome substituents alter the regioselectivity of the deprotonation reaction. Such is the case with the o,o'-dimethylphenylthio apendage (**2b**, entry 2), leading to a **3b/4b** mixture, while its dichloro equivalent **2c** restricts the reaction to the only Z acetal, as proved by the selective recovering of the starting material under its pure E configuration (entry 3). The same observation has been made with the morpholino acetal **2j** (entry 14). Dialkylamino substituents in general extend the competition between deprotonation sites, as can be seen from results about acetals **2e-j** (entries 5-14). The selectivity, while clearly depending on the respective bulkiness of the alkyl groups borne by the amino moiety and that of the base itself, tends to be in favor of the "exo" dienes **4** (entries 5, 7-9, 11-13). Comparison between entries 5 and 9 on one hand and 11 on the other also illustrates the symmetrical influence of base and substrate bulkiness, both cases providing a total "exo" selectivity by opposite means. The upper limit to bulkiness seems to be reached with the di-isopropylamino group[13] which remains inert under standard deprotonation conditions (entry 10). Let us last underline that these basic conditions favorably compare to thermal cracking of chloro **1** or thiophenylacetals **2a** which similarly yields the conjugate elimination but do not afford control on the 1,2 double bond (1E,3E/1Z,3E ≈ 50:50).[4c,14a]

In conclusion, these results indicate that a large set of 1,4-difunctionalized dienes **3** and **4** is at reach of a δ-elimination reaction based on readily prepared substituted acetals **2**. Depending on the substituent, "endo" (**3**) or "exo" (**4**) dienes may be prepared selectively. Extensions to other unsaturated acetals and synthetic applications for these functional isoprenoid and butadienoid synthons as well as mechanistic studies to check the possible influence of E/Z configuration in **2** on the **3/4** ratios are currently in progress in our group.

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8. Chloroacetal **1** is an industrial intermediate.
9. See Ref. 4a,c and 6 for experimental details. Following procedures were found convenient in this work:
   - *Method A*: phenol (22.2g, 0.24mol) disolved in 100ml aqueous soda (2.7N) was added to 420mg of chloroacetal **1** (10.0g, 61mmol) in 50ml THF. After 48h stirring at RT, the organic layer was recovered, washed with distilled water then dried ($MgSO_4$) and evaporated to yield **2d** (13.3g, Yd = 98%).
   - *Method B*: diethylamine (50ml, 0.48mol) was added to neat chloroacetal **1** (16.5g, 0.1 mol) and the mixture warmed up to reflux overnight.[13] The precipitate was then filtered off, the organic phase washed with distilled water, dried ($MgSO_4$) and evaporated, directly yielding aminoacetal **2f** (19.1g, Yd = 95%).
10. This kinetic aspect was checked on aminoacetals by treating the 30:70 **3f/4f** mixture obtained in entry 8 by 2.6 eq. KHMDS in THF, as described in entry 9. The **3f/4f** ratio remained unchanged. Complementarily, addition of 2.0 eq. of n-BuLi at RT to a 100% **4f** ether solution (entry 9), did not yield any **3f** neither.
11. Rhône-Poulenc Industrie, French Patent n° 7700855 (1977).
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13. The efficient preparation of acetal **2g** under method B conditions requires excessively long heating at reflux of $(i\text{-Pr})_2NH$ (>1 month). This may be shortened to 4 days at 150°C in a sealed tube (92% yield).
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