Pergamon

Tetrahedron Letters 44 (2003) 373–377

TETRAHEDRON
LETTERS

Conjugated elimination versus [1,2]-Wittig rearrangement of unsaturated diox(ol)anes

Loïc Lemiègre,[a] Thomas Regnier,[a] Jean-Claude Combret[b] and Jacques Maddaluno[a,*]

[a] *Laboratoire des Fonctions Azotées & Oxygénées Complexes, IRCOF, Université de Rouen, 76821 Mont St Aignan Cedex, France*

[b] *Laboratoire des Sciences et Méthodes Séparatives, IRCOF, Université de Rouen, 76821 Mont St Aignan Cedex, France*

Received 4 October 2002; accepted 2 November 2002

Abstract—A set of unsaturated dioxanes and dioxolanes has been prepared in three steps from acetoxy-1-isoprene. When reacted with two equivalents of *t*-BuLi in THF, these compounds provided, under various conditions, a mixture of two types of 1,3-dienes. The first one, derived from a conjugated elimination reaction resulting in the heterocycles opening, is relatively unstable but could be trapped as an acrylate. The second one resulted probably from a [1,2]-Wittig rearrangement. The competition between these two reactions has been observed for both dioxanes and dioxolanes (but not for acyclic acetals) and is the object of a strong temperature effect, the Wittig rearrangement being favored over the elimination at room temperature. A difference between kinetic and thermodynamic deprotonation sites is proposed to be at the origin of this competition on the base of both experimental and theoretical results. © 2002 Elsevier Science Ltd. All rights reserved.

Albeit the object of less attention than its [2,3] counterpart, the [1,2]-Wittig rearrangement is a useful synthetic process that remains a reaction of experimental[1] and theoretical[2] interests. Because it is a convenient source of carbon–carbon bonds, its asymmetric version has also been extensively investigated, and high e.e. have been obtained lately thanks to enantioselective chiral-base induced processes.[3] Good advantage has also been taken of acetals in this reaction, in particular for the synthesis of *C*-glycosides,[1a,4] and the influence of substrate structure and conditions on this particular case has been subjected to in-depth studies.[5]

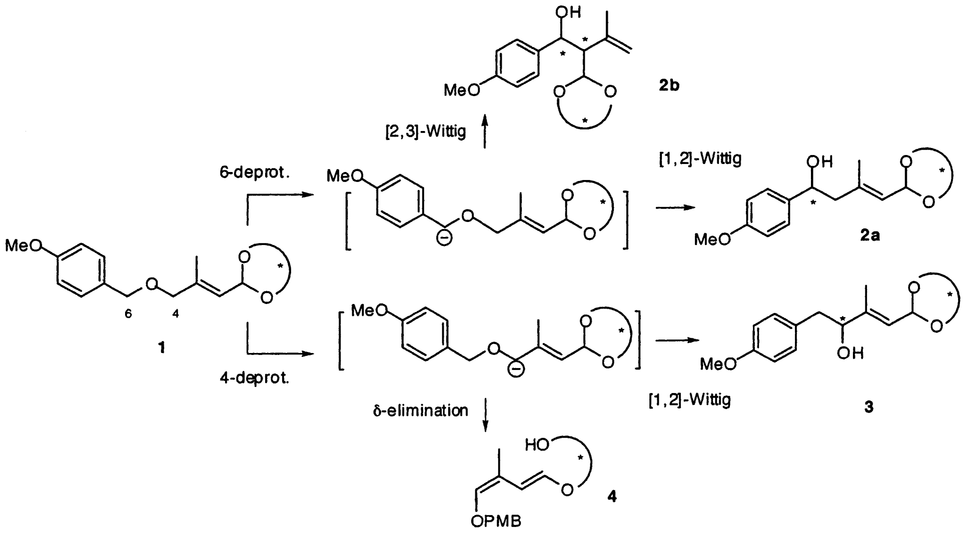


Figure 1.

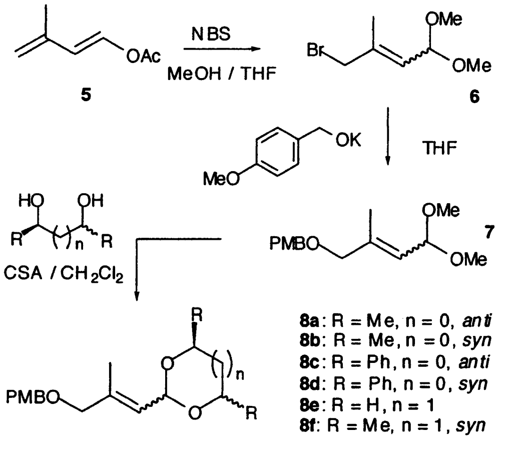
---

* Corresponding author.

PII: S0040-4039(02)02568-6

The propensity of α,β-unsaturated acetals to undergo conjugated eliminations upon deprotonation is well known and offers a handy access to functionalized 1,3-dienes.[6] However, these carbanions can also be candidates to the [1,2]- or [2,3]-Wittig rearrangements (Fig. 1). A substrate such as **1** carries indeed two possible deprotonation sites (C^4 and C^6). While the carbanion at C^6 is likely to undergo either a [1,2]- or [2,3]-Wittig rearrangement, yielding **2a** and **2b**, respectively, that at C^4 can provides the [1,2]-Wittig or the δ-elimination products **3** and **4**, respectively. Defining conditions favoring, at will, one of these pathways over the others could be of obvious synthetic interest. We also contemplated that introducing a remote C_2-symmetrical group could influence the diastereoselectivity of the rearrangement through an inductor not directly involved in the reaction.[7] This would increase the synthetic potential of these substrates since: (i) the protected aldehyde function is preserved after the transposition; (ii) a broad and rapid tuning of the selectivity can be easily undertaken thanks to the relatively large set of chiral diols commercially available. We present in this communication our preliminary findings about the influence of a few parameters on the chemioselectivity.

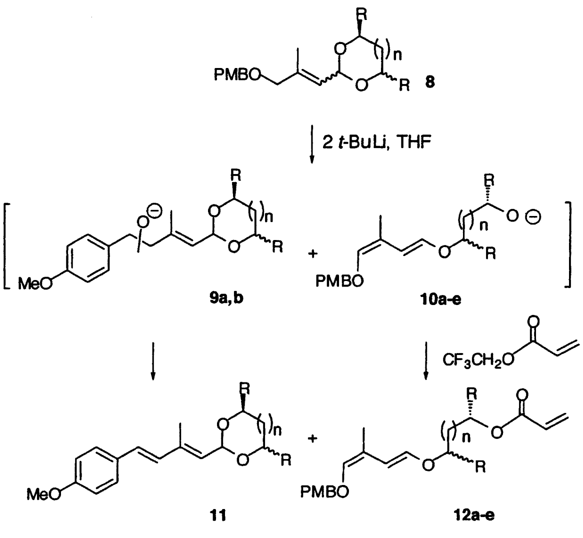
The unsaturated C_2-symmetrical dioxanes and dioxolanes necessary to this study have been prepared from isoprenylacetate **5** and NBS in THF/MeOH (Scheme 1), following the efficient protocol of Venturello et al.[8,9] The bromoacetal **6**, obtained as a ≈75:25 E/Z mixture, was then substituted by potassium *p*-methoxybenzyl alcoholate and the methyl acetal **7** underwent transacetalization reacting it with the diols retained in methylene chloride in the presence of catalytic amounts of camphorsulfonic acid (CSA).[6a] Six cyclic acetals **8a–f** were thus prepared in medium to reasonable overall yields (49–87%), the configuration of their double bond remaining unchanged during these steps. Substrates **8a–d** were designed to probe the sensitivity of the reaction to dioxolane structural features, while achiral **8e**,**f** have been considered as easy-to-prepare benchmarks for their dioxanic counterparts.



Scheme 1.

Reacting acetals **8** in THF with 2 equiv. of *t*-BuLi led to two types of 1,3-dienes. The first one (**10**) was obviously derived from the conjugated elimination/ring opening sequence that could be anticipated on the basis of previous results, while the second one (**11**) was bearing a *p*-methoxyphenyl substituent. This product results more than likely from the dehydration of an intermediate alcohol **9**, itself derived from a [1,2]-Wittig rearrangement[10,11] (Scheme 2). This unexpected reaction could not be dodged even under basic work-up conditions, rendering perfectly vain any attempt of diastereocontrol, but leaving all its interest to the control of the competitive pathways. The alcohols **10** are relatively sensitive and could not be efficiently isolated by chromatography over silica gel. We found the direct trapping of the intermediate alcoholates by trifluoroethyl acrylate furnishes the corresponding esters **12** in good yields (up to 70%).[12] On a stereochemical point of view, the dienic part of **12** adopts the expected[6c,d] (1E,3Z) configuration.

The sensitivity of these competitive reactions to experimental conditions has been evaluated and the results are gathered in Table 1. The three first entries concern-



Scheme 2.

Table 1. Elimination versus Wittig in THF (Scheme 2)

Entry	SM	R	*n*	Conf.	*T* (°C)	**9**/**10**
1	**8a**	Me	0	*anti*	−78	<5:95
2	**8a**	Me	0	*anti*	−40	33:67
3	**8a**	Me	0	*anti*	0	67:33
4	**8b**	Me	0	*syn*	0	13:87
5	**8b**	Me	0	*syn*	20	67:33
6[a]	**8b**	Me	0	*syn*	20	0:100
7	**8c**	Ph	0	*anti*	20	0:100
8	**8d**	Ph	0	*syn*	0	0:100
9	**8e**	H	1	–	0	0:100
10	**8e**	H	1	–	20	49:51
11	**8f**	Me	1	*syn*	20	58:42
12	**7**	–	–	–	20	<5:95

[a] 2 equiv. of TMEDA were added to the medium.

ing the *anti* dioxolane **8a** indicate that the [1,2]-Wittig rearrangement, leading to **9** then to diene **11**, is dramatically favored when increasing the temperature, even on a relatively small 20°C range. However, the conditions of entry 3 are associated with a chemical yield in **11** that remains, after flash chromatography, as low as 37%. Comparing entries 3 and 4 show that the *syn* dioxolane **8b** is more prone to an elimination than its *anti* counterpart **8a**. This can be related to the strain undergone by the five-membered heterocycle bearing two *syn* 4,5-substituents. Interestingly, an opposite effect is described in literature for 4,6-disubstituted dioxanes: *anti* isomers open more easily than their triequatorial *syn* counterparts (Fig. 2).[13]

The dioxolane derived from the *meso* butanediol isomer has been employed in entries 4–6, in an attempt to probe the sensitivity of these reactions to the exact structure of the acetal. The same alteration of the chimioselectivity in favor of the Wittig rearrangement was observed with temperature, a 67:33 ratio being obtained at room temperature, in an identically poor yield (38%). Entry 6 shows that the addition of 2 equiv. (with respect to the substrate) of tetramethylethylenediamine (TMEDA) to the medium renders the reaction elimination-selective. The yield in **12** then reaches values in the 70% range. This result can be related to a significant alteration of the solvation and/or aggregation[14] of the original allyllithium intermediate by the diamine, that would suppress an eventual reversibility of this elimination by preventing the back-addition of the alcoholate on the dienic system. Entries 7 and 8 further indicate the sensitivity of this system to structural parameters since the acetals **8c**,**d**, derived from hydrobenzoin, yields selectively, between 0 and 20°C, the ring-opening products **10c**,**d**. The case of dioxanes has been evaluated in entries 9–11. With the 1,3-propanediol derived dioxane **8e**, the same temperature effect is noted. It is worthy of note that at 20°C, the 2,4-pentanediol derivative **8f** provides more or less the same ratio between the competitive reactions (compare entries 5 and 11). However, the dioxanes seem more fragile under these conditions, since the isolated yields after chromatography on silica gel are extremely low (≈10%). Finally, the acyclic ketal **7** turned out to be elimination-selective, giving an efficient access to the corresponding dienol ether (entry 12), in line with previous results.[6,15]

Let us now consider the mechanistic implications of these observations. Since we were not able to isolate neither the original carbanion (quenching the reaction medium with Bu_3SnCl) nor the alcoholate(s) **2b** and/or **3** deriving from the two possible [1,2]-Wittig rearrangements (with TMSCl), it was not easy to determine the pathways followed by the system. Preventing the benzylic deprotonation was thus attempted resorting to cumbersome acetal **16** (Scheme 3). This latter was prepared in 51% yield condensing the potassium alcoholate of **14** (obtained from *p*-methoxybenzophenone **13** and an excess methyllithium in 35% yield) on allylic bromide **15** (itself obtained in 91% from **6**). However, **16** is unreactive toward *t*-BuLi and the starting material was recovered quantitatively. The steric hindrance due to the *gem*-dimethyl group is possibly responsible for the inaccessibility of the allylic protons to the base.

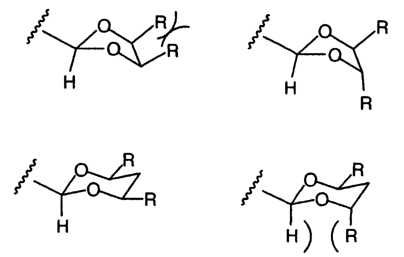
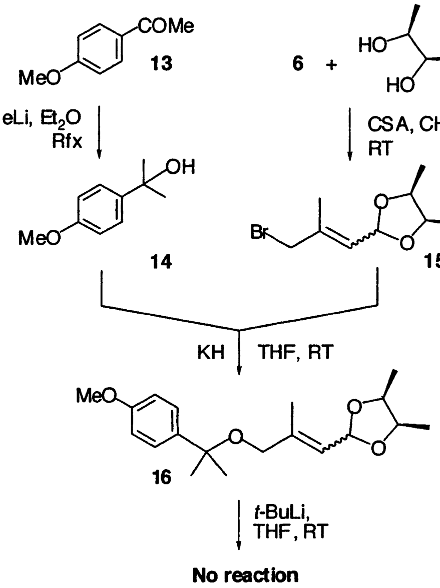


Figure 2. Steric strains in *syn* and *anti* dioxolanes and dioxanes.



Scheme 3.

We next tried to evaluate the relative stabilities of the two C^4/C^6 delocalized carbanions from a semiempirical theoretical point of view. We are well aware that the figures we can get from such calculations are quantitatively meaningless since they do not take into account the cation (Li^+) nor the solvent (THF), and are limited to the AM1 level. In addition, these computations can obviously provide only with thermodynamic data. However, even qualitative indications on the general behavior of these systems could help to improve the discussion. The resulting optimized anions are displayed on Figure 3(A,B), respectively. The energy values show that the C^6 anion is more stable by ≈2.5 kcal/mol, suggesting a higher thermodynamical acidity of this position.

This energy difference, together with the data in Table 1, suggest that the competition between δ-elimination and [1,2]-Wittig rearrangement could stem from the difference between C^4/C^6 deprotonation sites. The low temperature conditions (−78°C, entry 1) would favor the kinetic C^4 carbanion that would mainly evolve

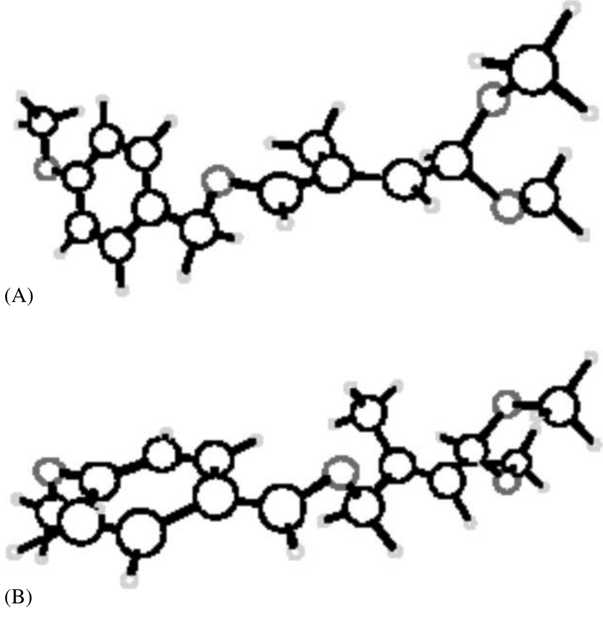


Figure 3. (A) AM1 optimized C^4 anion ($E=2.533$ kcal/mol); (B) AM1 optimized C^6 anion ($E=0.000$ kcal/mol).

along the eliminative pathway, while higher temperatures would lead preferentially to a C^6 carbanion that could only undergo the Wittig steps. In such a case an (intramolecular?) C^4/C^6 carbanion interchange would be required that remains to be demonstrated.

In conclusion, the above results indicate that the reaction of α,β-unsaturated diox(ol)anes with *t*-BuLi triggers a competition between the conjugated elimination reaction and the [1,2]-Wittig rearrangement. Depending mainly on the temperature, one or the other of these two pathways becomes exclusive or preponderant. We have been unable yet to establish, on experimental grounds, if these two reactions stem from a same lithiated intermediate or not. Conclusions are particularly difficult to draw from the experiments in Table 1 since both the regioselectivity of the deprotonation and the relative stabilities of the various diox(ol)anes considered certainly influence the kinetic of the two reactions. However, the temperature effect and the results of semiempirical calculations suggest that the allylic deprotonation could take place under kinetic control while the benzylic proton abstraction would rather happen under thermodynamic conditions. Experiments to confirm or invalidate these hypotheses are currently underway.

Acknowledgements

L.L. is grateful to the MRT for a Ph.D. fellowship. We thank Dr. Jean-Erik Ancel (Rhône-Poulenc Industrialisation) for generous samples of acetoxyisoprene.

References

1. Recent examples: (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4500; (b) Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.-H.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4502; (c) Katritzky, A. R.; Fang, Y. *Heterocycles* **2000**, *53*, 1783; (d) Kitagawa, O.; Momose, S.-I.; Yamada, Y.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **2001**, *42*, 4865; (e) Barluenga, J.; Fananas, F. J.; Sanz, R.; Marcos, C.; Trabada, M. *Org. Lett.* **2002**, *4*, 1587.
2. Inter alia: (a) Antoniotti, P.; Tonacchini, G. *J. Org. Chem.* **1998**, *63*, 9756; (b) Jursic, B. S. *Int. J. Quantum Chem.* **1999**, *73*, 299; (c) Sheldon, J. C.; Taylor, M. S.; Bowie, J. H.; Dua, S.; Chia, C. S. B.; Eichinger, P. C. H. *J. Chem. Soc., Perkin Trans. 2* **1999**, 333.
3. Recent contributions in the field: (a) Maleczka, R. E.; Geng, F. *J. Am. Chem. Soc.* **1998**, *120*, 8551; (b) Tomooka, K.; Yamamoto, K.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3741.
4. (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317; (b) Tomooka, K.; Kikuchi, M.; Igawa, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 1917.
5. (a) Gärtner, P.; Letschnig, M. F.; Knollmüller, M.; Völlenkle, H. *Tetrahedron: Asymmetry* **1999**, *10*, 4811; (b) Gärtner, P.; Letschnig, M. F.; Knollmüller, M.; Mereiter, K. *Tetrahedron: Asymmetry* **2000**, *11*, 1003.
6. (a) Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045; (b) Maddaluno, J.; Gaonac'h, O.; Le Gallic, Y.; Duhamel, L. *Tetrahedron Lett.* **1995**, *36*, 8591; (c) Martin, C.; Maddaluno, J.; Duhamel, L. *Tetrahedron Lett.* **1996**, *37*, 8169; (d) Deagostino, A. M.; Maddaluno, J.; Mella, M.; Prandi, C.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 881; (e) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1998**, *63*, 5110; (f) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1999**, *64*, 9348.
7. A comparable concept relying on protected diols has been put forward recently by Maleczka and Geng (Ref. 3a).
8. (a) Deagostino, A.; Balma Tivola, P.; Prandi, C.; Venturello, P. *Synthesis* **1999**, 1841. Experimental details are given in: (b) Bataille, C.; Bégin, G.; Guillam, A.; Lemiègre, L.; Lys, C.; Maddaluno, J.; Toupet, L. *J. Org. Chem.* **2002**, *67*, 8054.
9. For another access to these compounds see Ref 6a.
10. A [1,2]-Wittig/β-elimination competition, as well as a temperature effect is reported by Gärtner et al. (Ref. 5b).
11. No [2,3]-Wittig rearrangement was observed on acetals **8** by contrast with similar unsaturated aminals that yield significant amounts of the corresponding products: Blanchard, N.; Mangeney, P., unpublished results.
12. Details on the conditions providing ester **11**, a useful triene for intramolecular Diels–Alder reactions, are described in Lemiègre, L. Ph.D. Thesis, Université de Rouen, 2002 and will be published later on.
13. (a) Caballero, M.; Garcia-Valverde, M.; Pedrosa, R.; Vicente, M. *Tetrahedron: Asymmetry* **1996**, *7*, 219; (b) Ballini, R.; Bosica, G.; Cossu, S.; De Lucchi, O.; Peluso,

P. *Tetrahedron* **2001**, *57*, 4461.

14. Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.
15. (a) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061; (b) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694; (c) Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 519; (d) Fujiwara, S.; Katsumura, S.; Isoe, S. *Tetrahedron Lett.* **1990**, *31*, 691; (e) Venturello, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1032; (f) Deagostino, A.; Prandi, C.; Venturello, P. *Tetrahedron* **1996**, *52*, 1433.