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Nucleophilic addition to 3,4-*cis*-diacetyl-1,2,3,4-tetramethyl-1-cyclobutene: remarkably fast intramolecular hemiketalization

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Abstract—Reduction of 3,4-*cis*-diacetyl-1,2,3,4-tetramethyl-1-cyclobutene **1** with $NaBH_4$ yielding 2-hydroxyoxolanes **2a** and **2b** with complete diastereoselectivity at the anomeric carbon atom suggests that a highly stereoselective intramolecular hemiketalization process leading to the formation of the 2-hydroxyoxolane unit is much faster than the attack of the second molecule of the nucleophile on the second carbonyl group. Further reduction of **2a** at 0 °C gives selectively the *meso*-diol **3a**. Reaction of **1** with MeLi or MeMgBr also involves the participation of the adjacent carbonyl, thereby yielding hydroxyoxolane **5a** selectively. A mechanistic rationale is proposed on the basis of the relative energies of all isomeric hemiketals, **2a–d** and **5a** and **b**, (calculated by the PM3 method) and the relative stabilities of the conformers of **1** (calculated by the MM2 method).

The reduction of 1,4-diketones is of considerable interest because it leads to 'many unexpected and usually inaccessible compounds; the product variety and distribution depends on both the conformation and electronic environment of the carbonyl groups.[1] This statement published 30 years ago is still valid despite huge progress made in the last three decades in the theory and methodology of reduction.

As an additional and clear-cut example, we report herein the preliminary results of the reduction of 3,4-*cis*-diacetyl-1,2,3,4-tetramethyl-1-cyclobutene **1** with $NaBH_4$. Extension of the above methodology covering carbon nucleophiles was also examined by the reaction of **1** with MeMgI and/or MeLi.

Reduction of diketone **1** with an equimolar amount of $NaBH_4$ (−30 °C, MeOH) afforded two hemiketals, **2a** (46%) and **2b** (32%), as the primary products. It should be noted that four isomeric compounds **2a–d** are possible together with the diols **3a–c** (Scheme 1). However, only a minute amount of diol **3a** was observed in the ^{1}H NMR spectrum of the crude products.

When a large molar excess (8-fold) of $NaBH_4$ was used and the reaction was run at 0 °C, the yield of diol **3a** increased at the expense of hemiketal **2a**. Thus, the isolated yields of **2a**, **2b** and **3a** were 19%, 36% and 28%, respectively. Examination of NMR spectra (^{1}H, ^{13}C) of the crude reaction product showed the absence of other resonances that could be assigned to the starting diketone, the isomeric hemiketals **2c**, **2d** or diols **3b**, **3c**.

It is noteworthy that hemiketal **2a** undergoes further reduction to **3a** with $NaBH_4$, while **2b** is inert (Scheme 2).

In order to examine the behaviour of **1** on treatment with other nucleophiles, the reactions with MeMgBr and MeLi were performed. The addition of MeMgBr to diketone **1** afforded only hemiketal **5a** (Scheme 3), despite using a 5-fold excess of the reagent. The reaction at room temperature was completed after 40 min, and **5a** was isolated in 87% yield. Essentially the same result was obtained when the reaction time was extended to 6 days although the isolated yield of **5a** was somehow lower (81%). The reaction of **1** with MeLi (−70 °C; 5-fold excess) also afforded only **5a** (64% yield). In both

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Keywords: Reduction; Diketone; 2-Hydroxyoxolane; $NaBH_4$; Hemiketalization.

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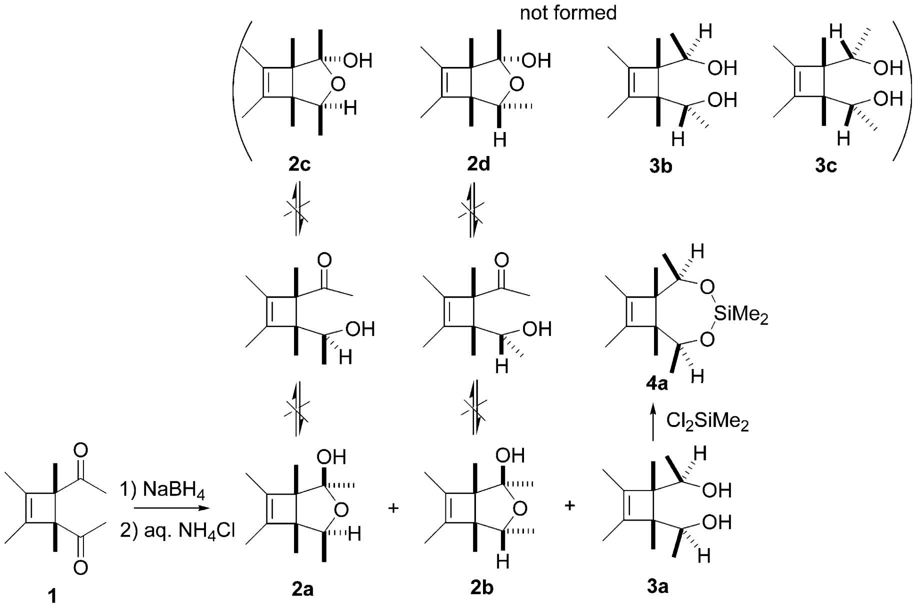
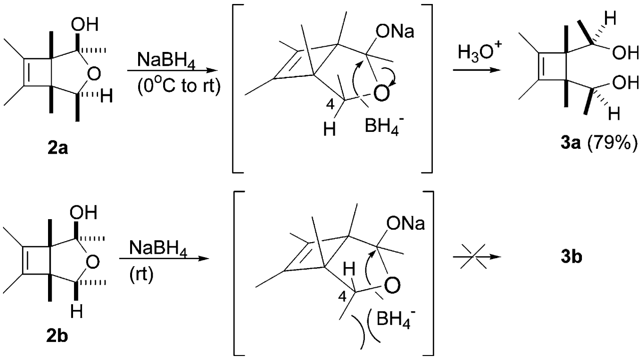


	2a	2b	3a
		Yield [%]	
1 eq. NaBH$_4$ (-30°C)	46	32	traces
8 eq. NaBH$_4$ (0°C)	19	36	28

Scheme 1.

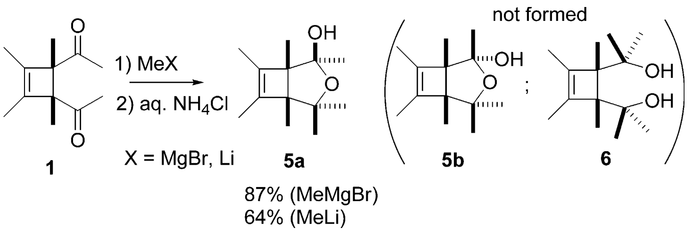


Scheme 2.

cases the formation of hemiketal **5b** and diol **6** (Scheme 3) was not observed.

The structures of all compounds and especially the configurations at the anomeric carbon atoms were established by 1D (^{1}H, ^{13}C) and 2D (NOESY, HETCOR, COLOC) NMR experiment. The multiplicities of the carbon resonances were recognised by the DEPT editing techniques. Six resonances in the carbon spectrum of the diol **3a** suggested C_s symmetry (point group), which was apparently consistent with its structure. The same, however, could apply to the structure of **3c** (Scheme 1). In order to distinguish between these two possibilities, we obtained the bicyclic compound **4a** by the reaction of diol **3a** with Cl_2SiMe_2 (Scheme 1). The NOE of the methyl groups 'fixed' in this way on one side of the ring with methyl groups attached to the adjacent carbon atoms, as indicated in the formula, was the proof of the structure of diol **3a**. Diagnostic NOE-s of **2a**, **2b**, **4a**, **5a** are shown in Figure 1.

The 2-hydroxyoxolane system is very common, in particular in carbohydrate chemistry, and furanoses are sugars of great theoretical and practical interest.[2] It is, therefore, surprising that formation of hemiketals or acetals incorporating such a system, by the nucleophilic addition of hydrides or organometallics to 1,4-dicarbonyls has been reported in just a few papers.[3,4] Some other nucleophiles are also known to undergo addition in a similar fashion.[5] The 2-hydroxyoxolane system is well known to exist as an equilibrium mixture of open and closed forms (Scheme 1), thereby making the formation of two anomeric 2-hydroxyoxolane products quite



Scheme 3.

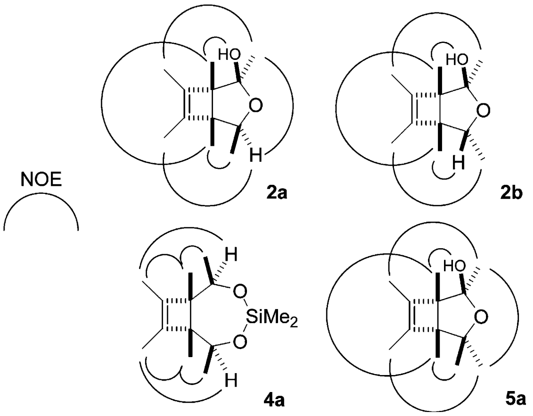


Figure 1. Diagnostic NOE effects found in NOESY spectra.

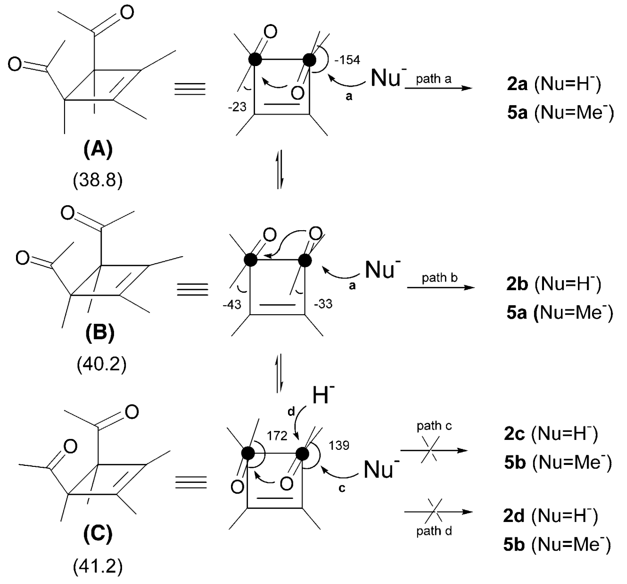
common.[5h,6a–f] The reduction of 2-hydroxyoxolane systems with NaBH$_4$ is also an interesting problem in organic synthesis but, nevertheless, no comprehensive study on this subject has been reported.[7] Examples of the synthesis of 2-hydroxyoxolane systems with high stereoselectivity at the anomeric carbon are limited either to cases where acyl groups are fixed as parts of the ring system[3a,4,5g] or where an additional stabilising factor, like an intramolecular hydrogen bond, is involved.[8] In this context, complete diastereoselectivity at the anomeric carbon atom leading to 2-hydroxydioxolane derivatives **2a**, **2b**, **5a** and stereoselective formation of diol **3a** is particularly interesting.

To achieve complete diastereoselectivity at the anomeric carbon atom the reversible hemiketalization process via open keto-hydroxy intermediate must be excluded (Scheme 1). Consistently, the calculations of heat of formation for all possible isomeric 2-hydroxyoxolanes, **2a–d** and **5a** and **b**, performed using the semiempirical PM3 method (Table 1), predicted that among anomeric pairs: **2a**, **2c**; **2b**, **2d** and **5a**, **5b**; isomers **2c**, **2d** and **5b** are thermodynamically more stable. Thus, the less stable isomers **2a**, **2b**, **5a** can be formed only in a kinetically controlled process. Moreover **5a** remains unchanged upon stirring with EtONa in EtOH at rt for 1 day. These observations suggest that no reversible hemiketalization takes place during the reaction of diketone **1**.

In order to explain the fact that of the four possible isomers **2a–d**, only two **2a**, **b** are formed, the conformation of **1** was considered. Strain energy and dihedral angles calculated by using MM2 method are presented in Scheme 4. Although three conformers A–C represent three energetic minima in a global energetic surface, the contribution of conformer A (two acyl groups are antiparallel) must be very high (the lowest strain energy) and in contrast, the contribution of conformer C (parallel oxygen-down alignment) must be very low due to steric (Me–Me) and electrostatic (O–O) repulsion (the highest strain energy). As depicted in Scheme 4, the attack on the conformer A by a nucleophile ion from the less hindered face is followed by a rapid participation of the adjacent carbonyl group (path a). Subsequent protonation by acidification results in formation of hemiketal **2a** (Nu=H$^-$) or **5a** (Nu=Me$^-$). In a similar fashion, only isomeric hemiketal **2b** is expected to be obtained from conformer B (parallel oxygen-up alignment) (path b). The stereoisomers **2c**, **d** (Nu=H$^-$), **5b** (Nu=Me$^-$) are not produced, since they could be formed from only conformer C (path c, d), which does not exist at all or is present in a very low rotameric population. These results lead us to deduce that complete diastereoselection at the anomeric carbon atom is a result of a very rapid intramolecular hemiketalization of the oxyanion, derived from an attack of the nucleophile on the carbonyl group, leading to 2-hydroxyoxolane unit.

Table 1. Relative heat of formation (kcal/mol) of isomeric compounds **2a–d** and **5a** and **b** calculated by the PM3 method

Compound	2a	2b	2c	2d	5a	5b
Δ*H*	−87.3	−87.3	−87.6	−87.8	−91.2	−92.5



Scheme 4. Strain energy (in parenthesis—kcal/mol) and dihedral angles (deg) calculated by MM2 method.

As shown before, hemiketal **2a** is easily reduced by NaBH$_4$ to give diol **3a**, while under the same conditions isomeric hemiketal **2b** remains intact. This remarkable difference in the reduction of **2a** and **2b** with NaBH$_4$ can be explained as follows.[9] In methanol, the attack of BH$_4^-$ on **2a** seems to occur from the less hindered *endo* face, yielding *meso*-diol **3a**. In the case of **2b**, however, the approach of BH$_4^-$ from the same direction is significantly suppressed by the methyl group at C-4 (Scheme 2). The lack of reactivity of **5a** toward diols with an excess of MeLi or MeMgBr seemed to support the hypothesis of no occurrence of the reversible hemiketalization process and again indicate a significant role of steric factors in 2-hydroxydioxolane ring opening.

In conclusion, we have demonstrated the synthesis of the 2-hydroxydioxolane unit with unusual complete diastereoselectivity at the anomeric carbon atom, achieved by the action of H^- and Me^- nucleophiles on 3,4-*cis*-diacetyl-1,2,3,4-tetramethyl-1-cyclobutene (**1**). As a reversible chemiketalization process was excluded, we concluded that after non-selective addition of the nucleophile to the carbonyl group at the first stage, the subsequent process leading to formation of 2-hydroxyoxolane ring was much faster than the attack of the second molecule of the nucleophile on the second carbonyl carbon atom. Selective formation of the *meso*-diol **3a** is a result of the opening of 2-hydroxydioxolane ring by hydride anion in stereocontrolled fashion. A study on the scope and limitations of the reactivity of **1** towards other nucleophiles is under way.

Supplementary data

Description of analytical and synthetic methods, yields and physical data of compounds **2a**, **2b**, **3a**, **4a**, **5a** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.037.

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