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LETTERS

1,4-Dioxene in Organic Synthesis: Substitution Reactions of 2-(1,4-Dioxenyl)-alkanol. Unusual Formation of Spirocyclopropane Derivatives.

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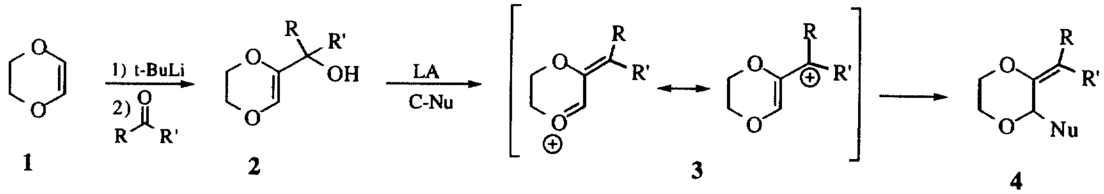
Abstract: Substitution reactions of allylic alcohols **2** with various C-nucleophiles are described; in particular, 1,2-bis(trimethylsilyl)oxy)-cyclobutene in the presence of a Lewis acid leads to cyclobutanone derivatives which undergo an unusual acid-induced rearrangement affording spirocyclopropane structures.

Keywords: 2,3-dihydro-1,4-dioxin, lithium perchlorate, allylic alcohols, nucleophilic substitution, spirocyclopropane.

1,4-dioxene (2,3-dihydro-1,4-dioxin) **1** was found to be a valuable reagent for C-C bond formation with simultaneous introduction of oxygenated functionalities.[1,2] In particular, addition of dioxenyllithium to ketones and aldehydes leads to allylic alcohols **2**,[3] which may be transformed into a variety of functionalized compounds *via* e.g. dehydration, oxidation or hydrolysis.[4] In order to extend the utility of this synthon, the behaviour of these allylic alcohols towards nucleophilic displacement reactions was studied. We assumed that these compounds would undergo substitution reactions by carbon nucleophiles in the presence of a Lewis acid resulting in a new carbon-carbon bond formation. This transformation, which is assisted by the neighboring dioxene ring, probably proceeds *via* the oxocarbenium intermediates **3**. By analogy with earlier reports on such reactions,[5] we expected the nucleophilic attack to occurs mainly at the less substituted end of the allylic system to afford derivatives of structure **4**.



Exposure of allylic alcohols **2** to various silyl enol ethers in the presence of lithium perchlorate ($LiClO_4$) in ether[5,6] or a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in acetonitrile,[7] led to substitution products in high yields (Table). With 1-(trimethylsilyloxy)-cyclohexene and 2-(trimethylsilyloxy)-propene, regioisomers **4** were obtained exclusively (entries 1-6, 8) or as the major products (entry 7). In contrast, when trimethylsilyloxyfuran or 1,2-bis(trimethylsilyloxy)cyclobut-1-ene were used, the nucleophilic attack proceeded either at the tertiary carbon or at the less hindered side of the allylic system depending upon the structure of the allylic alcohol. Thus, the reaction of 1,2-bis(trimethylsilyloxy)cyclobut-1-ene with **2a** ($R=R'=CH_3$) and **2d** [$R,R=(CH_2)_5$] gave exclusively the product of nucleophilic attack at the more substituted side **7a** and **7d** respectively in quantitative yield (entries 9 and 12). In contrast, **2b** and **2c** led to the regioisomers **6b** and **6c**. With trimethylsilyloxyfuran, allylic alcohols **2a** and **2c** [$R,R=(CH_2)_4$] gave the expected

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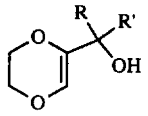
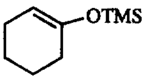
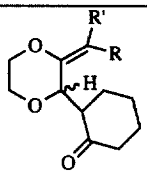
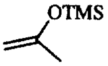
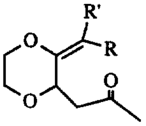
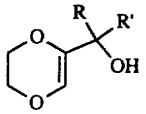
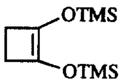
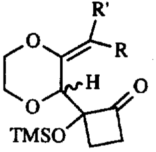
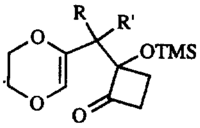
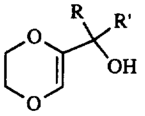
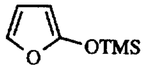
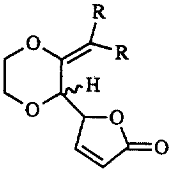
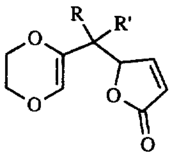
Table. Reaction of allylic alcohols 2 with silyl enol ethers in the presence of $LiClO_4$[a]

Entry	Substrate	Nucleophile	Product (yield %)[b]	
			 (c)	
1	**2a** R=R'= CH_3		**4a** (91)	
2	**2b** R=CH_3, R'=Ph		**4b** (90)	
3	**2c** R=R'=$(CH_2)_4$		**4c** (86)	
4	**2d** R=R'=$(CH_2)_5$		**4d** (80)[d]	
5	**2e** R=R'=$(CH_2)_6$		**4e** (96)	
				
6	**2b** R=CH_3, R'=Ph		**5b** (94)[e]	
7	**2d** R=R'=$(CH_2)_5$		**5d** (70)[f]	
8	**2e** R=R'=$(CH_2)_6$		**5e** (94)	
				
9	**2a** R=R'= CH_3		——	**7a** (quant)[g]
10	**2b** R=CH_3, R'=Ph		**6b** (quant)[g]	——
11	**2c** R=R'=$(CH_2)_4$		**6c** (quant)[g]	——
12	**2d** R=R'=$(CH_2)_5$			**7d** (quant)[g]
				
13	**2a** R=R'= CH_3		**8a** (80)[h]	—
14	**2c** R=R'=$(CH_2)_4$		**8c** (82)[h]	—
15	**2d** R=R'=$(CH_2)_5$		**8d** (42)[h] +	**9d** (42)[h]

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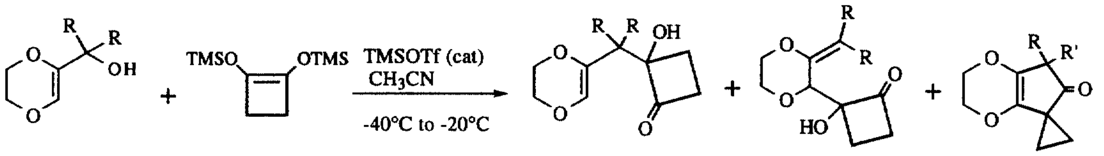
[a] Typical procedure: To a stirred solution of the substrate (1 mmol) and the trimethylsilyl enol ether (1.5 mmol) in ether (4 mL) cooled to 0°C, was added in one portion $LiClO_4$ (1.25g, 12 mmol). The ice bath was removed and the mixture stirred at rt until the disapearence of the starting material (tlc). Water was added and the product extracted with ether and purified by flash chromatography. [b] Yield of isolated, purified products . [c] This yield was obtained when the reaction was performed with TMSOTf (5%) as Lewis acid in CH_3CN at -40 to -20°C. [d] Isolated as a mixture of diastereomers separated by flash chromatography. e Isolated as a mixture of isomers Z and E (5:1 ratio) separated by flash chromatography. [f] Plus 25% of the product of nucleophilic attack at the tertiary carbon of the allylic system. [g] Crude product, pure according to ^1H and ^{13}C NMR spectra. [h] Isolated as a unseparable mixture of diastereomers.

regioisomers **8a** and **8c** respectively in 80 and 82% yield (Table). Under the same conditions, **2d** [R,R=$(CH_2)_5$] afforded a 1:1 mixure of regioisomers **8d** and **9d** in 84% combined yield (entry 15). In the presence of a catalytic amount of TMSOTf as Lewis acid in acetonitrile, allylic alcohols **2** reacted with 1,2-bis(trimethylsilyloxy)cyclobut-1-ene to afford, besides the expected cyclobutanone derivatives **10** or **11**, the spirocyclopropane compounds **12a-c** in 5% to 18.5% yield. The structure of these compounds was deduced on the basis of their spectroscopic data, in particular ^1H and ^{13}C NMR experiments.[8]

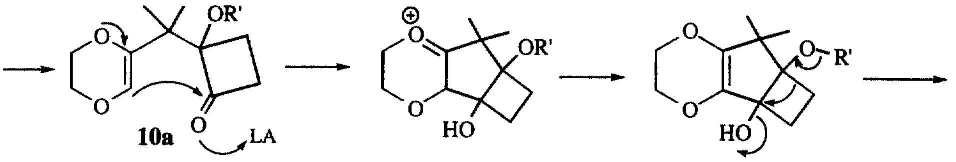


2a R = CH_3
2b R,R = $(CH_2)_5$
2c R,R = $(CH_2)_4$

10a 67%	______	**12a** 5%
10b 51%	______	**12b** 18.5%
______	**11c** 70%	**12c** 13.5%

The formation of **12**, which presumably proceeds through **10** or **11**, can be rationalized as illustrated in the following scheme for the case of **2a**.The Lewis acid chelation at the carbonyl group is followed by the formation of the five-membered ring and subsequent pinacol-like rearrangement.

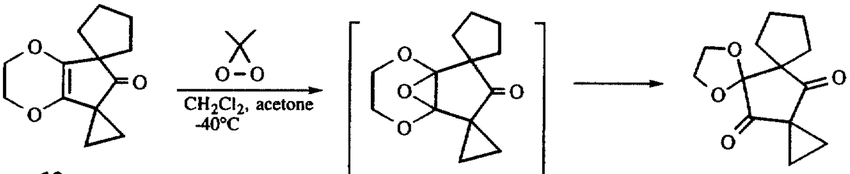
2a



10a

12a

Oxidation of **12** with dimethyldioxirane furnished the trispirocyclopropane derivative **13c**[8] in nearly quantitative yield. This result, which is in agreement with previous observations,[1b] provides a strong argument for the structure of **12**.

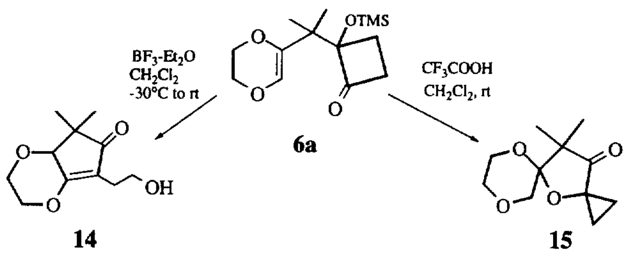


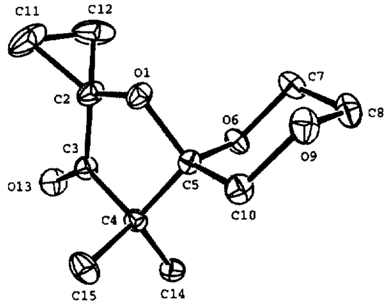
12c

13c

When allylic alcohols **2a**, and 1,2-bis(trimethylsilyloxy)cyclobut-1-ene were treated with 1.2 equiv of BF_3 etherate at -70°C for 30 min, cyclobutanone **6a** was isolated in high yield (90-95%). Exposing the reaction mixture to excess BF_3 etherate in CH_2Cl_2 for 16 h at room temperature led to enone **14** (40% yield from **2**). On the other hand, subjecting **6a** to trifluoroacetic acid in CH_2Cl_2 for 1h at room temperature gave the spirocyclopropyltetrahydrofuran **15** in 73% yield. The structure of this compound was assigned on the basis of spectroscopic data and confirmed by X-ray crystallographic analysis.[9] Under these conditions, it is reasonable to assume that the protonation of the dioxene ring occured first followed by the formation of the tetrahydrofuran ring and the pinacol-like rearrangement to afford **15**.

It is worthy of note that in all cases the reaction proceeded with *cyclobutane ring contraction* in concert with cyclization, and no cyclobutanone ring expansion products were isolated.[10]





ORTEP drawing of **15**

In summary, allylic alcohols **2** easily undergo sustitution reaction with various silyl enol ether under mild conditions affording 2,3-disubstituted 1,4-dioxanes in high yields. The ability to employ these allylic alcohols directly is also significant, since it obviates the need to prepare activated derivatives. With 1,2-bis(trimethylsilyloxy)cyclobut-1-ene, an unusual rearrangement leading to spirocyclopropane structures was observed.

References and Notes

1. For recent studies on the use of dioxene in synthesis, see : (a) Hanna, I.; Prangé, T.; Zeghdoudi, R. *Tetrahedron Lett.* **1996**, *37*, 7013-7016. (b) Baylon, C.; Hanna, I. *Tetrahedron Lett.* **1995**, *36*, 6475-6478. (c) Hanna, I. *Tetrahedron Lett.* **1995**, *36*, 889-892
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8. All new compounds were fully characterized by their spectroscopic and analytical data. Selected compounds: **10a**: IR (CCl_4) ν_{max} 3585, 3512, 1787 cm^{-1}. ^1H NMR (200MHz,$CDCl_3$) δ 1.00 (s, 3H), 1.06 (s, 3H), 1.60-1.95 (m, 2H), 2.50-2.90 (m, 2H), 3.87-4.00 (m, 4H), 5.92 (s, 1H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 210.5 (C), 140.8 (C), 123.7 (CH), 96.3 (C), 64.4 (CH_2), 63.7 (CH_2),41.7 (CH_2), 41.1 (C), 24.7 (CH_2), 20.9 (CH_3), 19.5 (CH_3) ppm. **12a**: IR (CCl_4) ν_{max} 1697, 1752 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (t, J=2Hz, 2H), 1.14 (t, J=2Hz, 2H), 1.20 (s, 6H), 4.10-4.30 (m, 4H) ppm. ^{13}C NMR (50.3MHz, $CDCl_3$) δ 134.6 (C), 66.1 (CH_2), 48.3 (C), 30.9 (C), 22.3 (CH_3), 13.0 (CH_2) ppm. **13c**: IR (CCl_4) ν_{max} 1722 cm^{-1}. ^1H NMR (200 MHz,$CDCl_3$) δ 1.40-1.60 (m, 4H), 1.75-2.10 (m, 8H), 4.00-4.40 (m, 4H) ppm. ^{13}C NMR (50.3 MHz,$CDCl_3$) δ 214.3, 106.4 (C), 65.8 (CH_2), 63.0 (C), 36.4 (CH_2), 34.2 (C), 27.3 (CH_2), 17.8 (CH_2) ppm.
9. X-Ray crystal data : Crystals of **15**, $C_{11}H_{16}O_4$ were grown from a petroleum ether solution of the compound. Data were collected at -150 ± 0.5K on an Enraf Nonius CAD4 diffractometer using Mo Kα (λ = 0.71073Å) radiation and a graphite monochromator. The crystal structure was solved and refined using the Enraf Nonius MOLEN package. The compound crystallises in space group P-1(Å 2), a=5.820(1)Å, b=8.402(1)Å, c=11.801(1)Å, α=87.86(1)°, β=87.56(1)°, γ=68.05(1)°; V=534.54(7)$Å^3$; Z =2 ; dcalc =1.319g/cm^3; μ=0.9cm^{-1}; F(000) =228. A total of 3299 unique reflexions were recorded in the range 2°$\leq 2\theta \leq$ 60.0° of which 852 were considered as unobserved ($F^2 < 3.0\sigma(F^2)$), leaving 2447 for solution and refinement. Direct methods yielded a solution for all atoms. The hydrogen atoms positionnal and isotropic thermal parameters were refined in the final stages of least-squares while using anisotropic temperature factors for all other atoms. A non-Poisson weighting scheme was applied with a p factor equal to 0.08. The final agreement factors were R=0.038, R_ω=0.061, G.O.F.=1.28.
10. Under these conditions, cyclobutanone derivatives prepared by the reaction of ketones and their acetals with 1,2-bis(trimethylsilyloxy)cyclobut-1-ene undergo acid-mediated rearrangement to 1,3-cyclopentanediones: Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759-1773. Wu, Y.-J;; Burnel, D. J. *Tetrahedron Lett.* **1988**, *29*, 369-4372.