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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. © 1999 Elsevier Science Ltd. All rights reserved.

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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 (LiClO₄) 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'=CH₃) and 2d [R,R= (CH₂)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=(CH₂)₄] gave the expected

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Entry	Substrate	Nucleophile	Product (yield %) ^b
		отмя	$\begin{pmatrix} 0 & R' \\ 0 & H \\ 0 & 0 \end{pmatrix}$
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)
			R'
		OTMS	O R
		\prec	
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)
			$\begin{array}{c} & & \\$
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
	O C OH	C COTMS	$\begin{pmatrix} 0 \\ - \\ 0 \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\$
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 $(42)^{h}$

Table. Reaction of allylic alcohols 2 with silyl enol ethers in the presence of LiClO₄^a

^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 LiClO₄ (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 CH₃CN at -40 to -20°C. ^d Isolated as a mixture of diastereomers separated by flash chromatography. ^e Flus 25% of the product of nucleophilic attack at the tertiary carbon of the allylic system. ^g Crude product, pure according to ¹H and ¹³C 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 ¹³C NMR experiments.⁸



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 rearragement.



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.



When allylic alcohols 2a, and 1,2-bis(trimethylsilyloxy)cyclobut-1-ene were treated with 1.2 equiv of BF₃ etherate at -70°C for 30 min, cyclobutanone 6a was isolated in high yield (90-95%). Exposing the reaction mixture to excess BF₃ etherate in CH₂Cl₂ for 16 h at room temperature led to enone 14 (40% yield from 2). On the other hand, subjecting 6a to trifluoroacetic acid in CH₂Cl₂ 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

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- 8. All new compounds were fully characterized by their spectroscopic and analytical data. Selected compounds: **10a**: IR (CCl₄) v_{max} 3585, 3512, 1787 cm⁻¹. ¹H NMR (200MHz,CDCl₃) 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. ¹³C NMR (50.3 MHz, CDCl₃) δ 210.5 (C), 140.8 (C), 123.7 (CH), 96.3 (C), 64.4 (CH₂), 63.7 (CH₂),41.7 (CH₂), 41.1 (C), 24.7 (CH₂), 20.9 (CH₃), 19.5 (CH₃) ppm. **12a**: IR (CCl₄) v_{max} 1697, 1752 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ 1.11 (t, J=2Hz, 2H), 1.14 (t, J=2Hz, 2H), 1.20 (s, 6H), 4.10-4.30 (m, 4H) ppm. ¹³C NMR (50.3 MHz, CDCl₃) δ 1.40-(C), 66.1 (CH₂), 48.3 (C), 30.9 (C), 22.3 (CH₃), 13.0 (CH₂) ppm. **13c**: IR (CCl₄) v_{max} 1722 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ 1.40-1.60 (m, 4H), 1.75-2.10 (m, 8H), 4.00-4.40 (m, 4H) ppm. ¹³C NMR (50.3 MHz, CDCl₃) δ 214.3, 106.4 (C), 65.8 (CH₂), 63.0 (C), 36.4 (CH₂), 34.2 (C), 27.3 (CH₂), 17.8 (CH₂) ppm.
- 9. X-Ray crystal data : Crystals of 15, C11H₁₆O₄ 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)Å³; Z =2; dcalc =1.319g/cm³; µ=0.9cm⁻¹; F(000) =228. A total of 3299 unique reflexions were recorded in the range 2*≤ 20 ≤ 60.0° of which 852 were considered as unobserved (F² < 3.0σ(F²)), 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, R₀₀=0.061, G.O.F.=1.28.
- Under these conditions, cyclobutanone derivatives prepared by the reaction of ketones and their acetals with 1,2bis(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.