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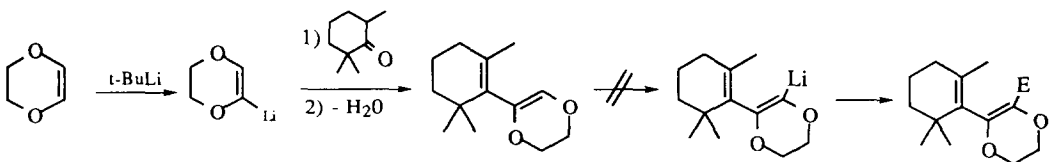
1,4-Dioxene in Organic Synthesis: Introduction of a Second Carbon-Carbon Bond with Simultaneous Opening of the Dioxene Ring

Issam Hanna

Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau Cedex, France

Abstract: *Treatment of the acetal 5, readily prepared from 2,6,6-trimethyl-2-(1,4-dioxenyl)-1-cyclohexene 3, with carbon nucleophiles in the presence of Lewis acid leads to the formation of a new carbon-carbon bond with simultaneouus cleavage of the dioxene ring.*

Earlier disclosures from this laboratory have demonstrated the utility of 1,4-dioxene (2,3-dihydro-1,4-dioxin) **1** in the formation of carbon-carbon bonds with rapid elaboration of useful functional groups.[1] Thus, allylic alcohols, easily obtained from 2-lithio-5,6-dihydro-1,4-dioxin **2** and ketones or aldehydes, undergo dehydration to afford substituted 2-vinyl-dioxenes.[2] In particular, 2,6,6-trimethyl-1[2-(1,4-dioxenyl)]-1-cyclohexene **3**, prepared from 2,2,6-trimethylcyclohexanone, appeared to be a useful springboard for the synthesis of terpenes and related substances.[2,3] Starting from this compound, we have recently described a methodology for the early introduction of the C-6 and C-7 oxygenated groups in the A,B ring system of forskolin.[4] As part of synthetic studies towards polyoxygenated natural products, we required a general method for the introduction of a *second* carbon-carbon bond with simultaneous opening of the dioxene ring and release of the oxygenated functionalities. To this end, the behaviour of lithiated derivative **4** towards carbon electrophiles was first examined. According to early reports related to metallation of cyclic vinyl ethers[5] including 1,4-dioxene, we assumed that deprotonation of **3** with strong lithiating agents should preferably occur at the position adjacent to the oxygen atom leading to **4**. Instead, treatment of **3** with strong bases (*t*-BuLi, *n*-BuLi-*t*-BuOK, *sec*-BuLi-TMEDA, PhLi-HMPA) followed by Bu_3SnCl gave rise to the dioxene ring-cleavage compounds as majors products (Scheme 1).[3,6]

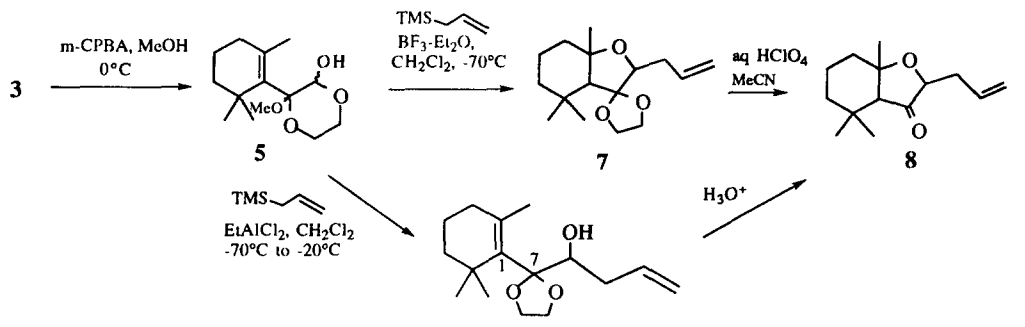


1 **2** **3** **4**

Scheme 1

To circumvent this problem, introduction of the new carbon-carbon bond on the dioxene moiety was then envisaged from acetal **5**. Lewis acid mediated addition of carbon nucleophiles to acetals has become a widely used reaction for the formation of carbon-carbon bonds.[7] In particular, an important contribution has been the development of allylsilanes in the stereoselective allylation of carbohydrates derivatives.[8] We anticipated that acetal **5** would also behave as an electrophile in the allylsilane-induced C-C bond formation. This communication discloses the preliminary results.

Oxidation of **3** with *m*-chloroperbenzoic acid (*m*-CPBA) in methanol at 0°C afforded **5** as a mixture of diastereomers in 70% yield.[9] This white cristalline compound, which is stable at room temperature, was allowed to react with allyltrimethylsilane in CH_2Cl_2 in the presence of BF_3-Et_2O. The reaction gave product **7** as a mixture of diastereomers. The structure of **7** was assigned on the basis of its spectroscpic data, and confirmed by acid hydrolysis to **8** (Scheme 2).



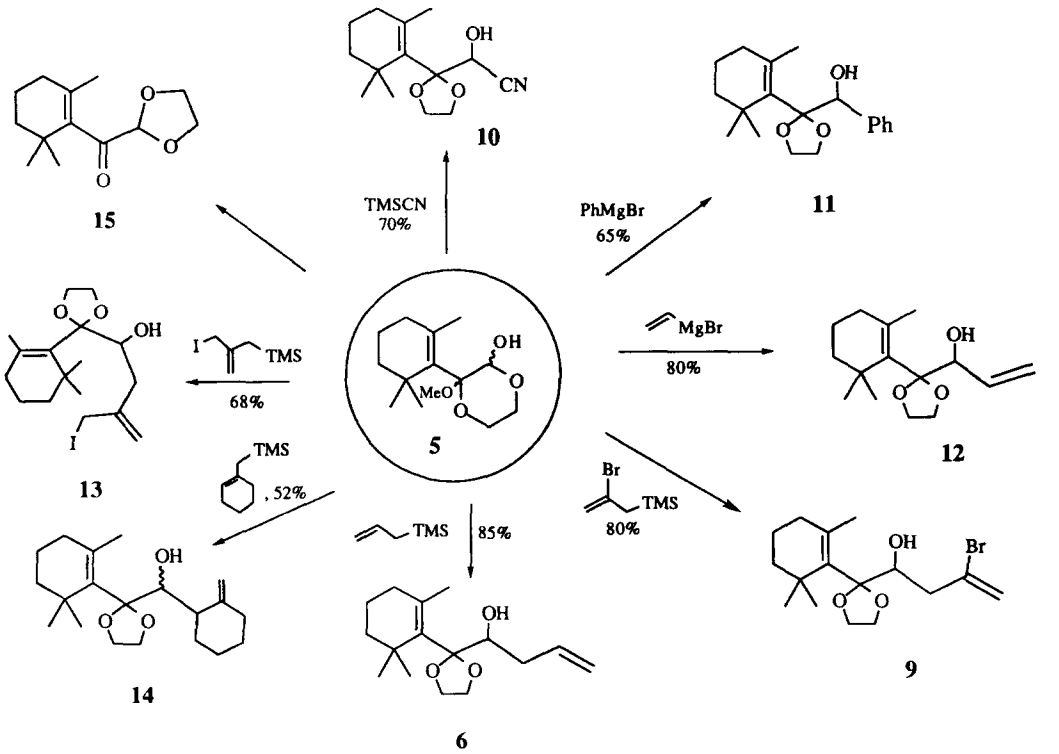
Scheme 2

Formation of **7** undoubtedly occurs *via* cyclization of the initially formed adduct **6** caused by the presence of adventitious protons.[10] Indeed, when the reaction was carried out in acetonitrile, a more basic solvent than CH_2Cl_2, compoud **6** was isolated as the sole product. However, ethylaluminum dichloride, a proton scavenger Lewis acid[11], in CH_2Cl_2 was found to be the most effective reagent and gave **6** in 85% yield.

As shown in Scheme 3, the reaction worked with various types of nucleophiles. Thus, the addition of bromoallyltrimethylsilane, 3-iodo-2[(trimethylsilyl)methyl]-propene[12] and cyanotrimethylsilane proceeded smoothly to give, as expected, products **9**, **13** and **10** respectively, in good yield. With 1-[(trimethylsilyl)-methyl]cyclohexene[13], the adduct **14** was isolated in 52% yield as a mixture of separable diastereomers in a 1.6 : 1 ratio. In the same way, phenyl and vinyl Grignard reagents produced compouds **11** and **12** in good yield. However, trimethylsilyl enol ethers [e.g. 1-(trimethylsilyloxy)cycloxene or 2-(trimethylsilyloxy)furan] failed to react with **5**, and compound **15** was isolated as the major product.

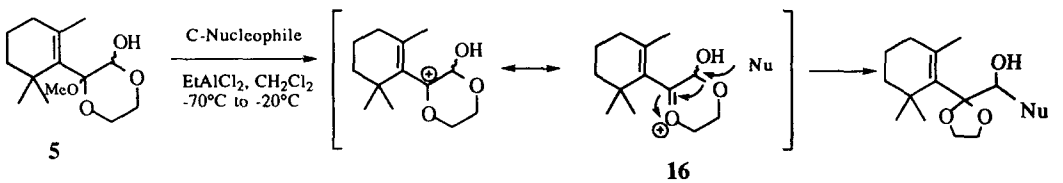
A typical procedure is as follows: to a stirred solution of **5** (128 mg, 0.5 mmol) and C-nucleophile (1 mmol) in dry CH_2Cl_2 (4 mL) at -70°C was added $EtAlCl_2$ (1 mmol) and the mixture allowed to warm to -20°C. The reaction was monitored by TLC until complete conversion. The reaction mixture was then quenched with

water, extracted with ether and dried over $MgSO_4$. After evaporation of the solvent, the pure products[14] were isolated by flash chromatography [SiO_2, AcOEt/petroleum ether (1:4 v/v)].



Scheme 3. Reaction of **5** with carbon nucleophiles

This reaction probably proceeds via the oxocarbenium intermediate **16** which arises from Lewis acid complexation and ionization of the methoxy group.[16] At this stage, the formation of the final product could be reasonably explained in terms of addition of the nucleophile to the hemiacetal part with concomitant migration of the C-O bond in the dioxenyl moiety as shown in Scheme 4.



Scheme 4

In conclusion, we have found that treatment of acetal **5**, readily prepared from 2,6,6-trimethyl-2-(1,4-dioxenyl)-1-cyclohexene **3**, with carbon nucleophiles in the presence of Lewis acid leads to the formation of a new carbon-carbon bond with simultaneouus cleavage of the dioxene ring. Application of this method to the total synthesis of natural products is in progress in our laboratory.

References and Notes

1. For a review of the chemistry of 1,4-dioxene, see: Fétizon, M.; Goulaouic, P.; Hanna, I. *Heterocycles*, **1989**, *28*, 521-527.
2. Fétizon, M.; Goulaouic, P.; Hanna, I.; Prangé, T. *J. Org. Chem.* **1988**, *53*, 5672-5679.
3. Blanchot, V.; Hanna, I. *Synth. Commun.* **1991**, *21*, 563-568.
4. Blanchot-Courtois, V.; Fétizon, M.; Hanna, I. *Tetrahedron Lett.* **1992**, *35*, 5061-5064.
5. Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997-4006.
6. For recent examples on competing metallation of substituted dihydropyran see: Imanieh, H.; Quayle, P.; Voaden, M.; Conway, J.; Street, S.D. A.*Tetrahedron Lett.* **1992**,*33*,543-546. Friesen, R. W.; Stwino, C. F.; Daljeet, A. K.; Kolaczewska, A. *J. Org. Chem.* **1991**, *56*, 1944-1947. Barber, C.; Jarowicki, K.; Kocienski, P. *Synlett* **1991**, 197-198.
7. Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043-1054.
8. For recent rviews see: (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545-8599. (b) Fleming, I. in *Comprehensive organic Synthesis*, Eds.: Trost, B. M.; Fleming, I.; Heathcock, C. H, Pergamon, Oxford, **1991**,*Vol. 2* pp 563-593 .
9. For a similar regioselective oxidation of the dioxenyl moiety see: Fétizon, M.; Goulaouic, P.; Hanna, I. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1107-1110.
10. In fact, it is very difficult to prepare anhydrous proton-free BF_3. See: Olah, G. A., *Friedel-Crafts chemistry*, pp. 219-224, Wiley, New York **1973**. Protons are also produced from the reaction of BF_3-Et_2O with the hydroxyl group of the hemiacel **5**.
11. Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, R. C.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927-3934.
12. Trost, B. M.; Curran, D. P *J. Am. Chem. Soc.* **1981**, *103*, 7380-7381
13. Hayashi,T.; Fujima,T.; Okamoto,Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001-1003.
14. All new compouds have been fully characterized by IR, ^1H, ^{13}C NMR and mass specroscopy. It is worthy of note that some of these products (e.g. **6**, **9**, **10** and **11**) appeared as a mixture of two atropoisomers giving separated signals in ^1H and ^{13}C NMR at room temperature. This obviously reflected a restricted rotation about the C1(sp^2) - C7(sp^3) bond.[15]

    10: Colorless oil as a mixture of atropoisomers in 3:1 ratio; IR (CCl_4): ν_{max} 3615, 3518, 2936, 2870, 2359, 1681, 1457, 1311, 1186, 1126, 1085, 1034 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): major δ 5.20 (s, 1H, C*H*OH), 3.95-3.79 (m, 4H), 2.60 (br. s, 1H, CHO*H*), 1.85-1.84 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H); minor δ 5.38 (s, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): major δ 20.0 (CH_2), 26.0 (CH_3), 26.5 (CH_3), 30.1 (CH_3), 34.9 (C), 39.9 (CH_2), 41.4 (CH_2), 61.4 (CH_2), 65.8 (CH), 72.6 (CH_2), 89.6 (C), 118.4 (C), 130.3 (C), 139.4 (C); minor δ 20.3 (CH_2), 26.3 (CH_3), 27.2 (CH_3), 30.1 (CH_3), 35.3 (C), 39.9 (CH_2), 41.4 (CH_2), 61.4 (CH_2), 67.0 (CH), 73.3 (CH_2), 89.6 (C), 117.0 (C), 131.5 (C), 138.0 (C).
15. For a review on the atropisomerism see: Oki, M. in *Topic in stereochemistry* Eds.: Allinger, N. L.; Eliel, E. L.; Wilen, S. H. John Wiley, New York, **1983**, *vol 14*, pp 1-83.
16. For a recent report on the evidence for an oxocarbenium ion intermediate in Lewis acid mediated reactions of acetals see: Sammakia, T.; Smith, R. S. *J. Am. chem. Soc.* **1994**, *116*, 7915-7916.

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