AMBIPHILIC REACTIVITY OF 1,1-DIMETHOXYACETONE

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Summary: Trialkylsilyloxyallyl cations 2 with a π-donating methoxy substituent at the allylic termini are generated from nonhalogenated substrates via treatment of 5b-e with Lewis acids. 2 undergoes stereo- and regioselective cycloaddition with furans yielding 2-methoxy-8-oxabicyclo[3.2.1] oct-6-en-3-ones. Cycloadduct 7 is converted to 2-methoxytropone 14 and thus represents an efficient entry into tropolonoid systems.

In connection with our continuing interest in developing synthetic methodology targeted towards construction of polyoxygenated natural products, we embarked on a systematic investigation of the α-anionic and ambiphilic chemistry of α,α-dialkoxy ketones 1. We felt that compounds such as 1 would provide the appropriate functionality needed for direct and efficient introduction of synthetically manipulatable bifunctional carbonyls through an anionic reactivity mode, while the ambiphilic reactivity mode would provide rapid access into oxygenated seven membered rings via [4π + 2π] cycloaddition reactions. The ambiphilic pathway (Scheme I) features a departure from conventional methods of generating oxyallyl cations and allows direct access to the relatively unexplored chemistry of *heteroatom stabilized oxyallyl cations* 2.

Scheme I. Ambiphilic Reactivity of α,α-Dialkoxyketones.

a: R^1 = H, R^2 = Me
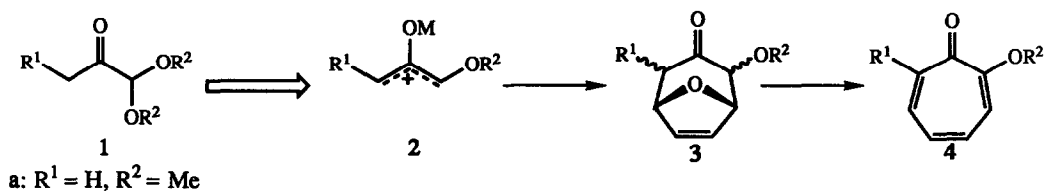
While the synthetic utility[1] of oxyallyl cations as a viable route to seven membered rings has been amply demonstrated, additional synthetic manipulations are usually necessary in order to obtain highly oxygenated systems. We wish to report preliminary findings concerning the latent ambiphilic reactivity of 1a (R^1 =H, R^2 =Me) via trialkylsilyl enol ethers 5b-e. These undergo cycloadditions with furans and the resulting oxabicycles are valuable as key intermediates in constructing the α-tropolone ring system. To our knowledge only an isolated case involving the enolate chemistry of 1a has been reported in the literature,[2] while the latent ambiphilic reactivity of 1a or substances derived from it has not been explored.
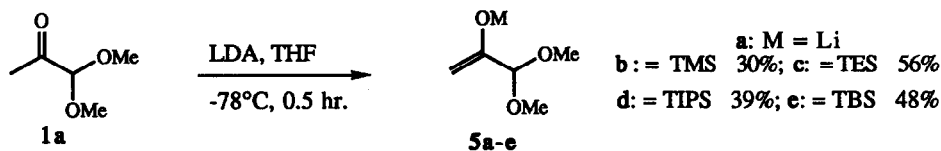
The silyl enol ethers **5b-e** were prepared by the reaction of enolate **5a** with the corresponding trialkylsilyl chlorides.[3d] The fact that enolization of **1a** with LDA occurred smoothly is significant, since it is well known that treatment of α-alkoxy and α,α-dialkoxy ketones with LDA results in facile and extensive carbonyl reduction.[3]
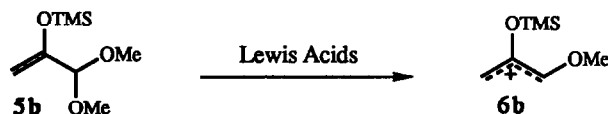
We anticipated that Lewis acid induced carbon oxygen bond cleavage of **5b** would result in the formation of trimethylsilyloxyallyl cation **6b**. This approach allows facile entry into oxyallyl cations from readily accessible *nonhalogenated substrates* and provides the opportunity to investigate the reactivity effects of *stabilizing electron releasing heteroatoms substituted at the allylic termini*. Subsequently, we found that addition of appropriate Lewis acids to a solution containing **5b** and suitable furans at -78 °C gave [3 + 4] cycloadducts. This represents the first example of *trialkylsilyloxyallyl cations stabilized by a π-donor heteroatomic substituent*.[4]

Cycloaddition of **6b** with furan, 2-methylfuran, 2,5-dimethylfuran and cyclopentadiene gave good to excellent yields of the corresponding cycloadducts. Furan and 2,5-dimethylfuran give solely one stereoisomer (**7** and **11** respectively) while 2-methylfuran yields exclusively one regio- and stereoisomer (**10**). The stereoselectivity of the cycloaddition diminishes considerably to a 3 : 1 *endo* to *exo* (**12** : **13**) isomeric ratio when cyclopentadiene replaces furan as the 4π component.[5] Structural assignment of the oxabicycles indicates that all the adducts have an equatorial /*endo* α-methoxy group. The characteristic 5.0 Hz coupling constant for the exo-proton, H_a is observed and is in agreement with previously published data.[4,5] In addition, H_a, in **10** is a singlet, while H_b is doublet of doublets with coupling constants of 5.0 and 15.0 Hz and H_c is a doublet with J = 15.0 Hz implying that the regioisomer obtained is the one depicted in Scheme II. This regioselectivity is opposite to what Föhlisch reported and suggest that cycloaddition under our reaction conditions is mechanistically different. A complete mechanistic explanation concerning the stereo- and regioselectivity will be offered and discussed after cycloaddition results from functionalized derivatives of **2** are obtained, e.g. M = TMS, R^1 = methyl, phenyl, methoxy and carboethoxy and R^2 = methyl.

A typical cycloaddition reaction procedure involves the addition of 1 mmol of TMSOTf to a 2.5 mmol solution of silyl enol ether and 2.5 mmol of diene in 2.5 ml of nitroethane at -78 °C for three hours, followed by quenching with aq. NaHCO₃ and methylene chloride extraction. The reaction also proceeds smoothly, with no decrease in product yields, on a ten fold reaction scale.

Scheme II. Ambiphilic Reactivity of α,α-Dimethoxyacetone **1a.**[a]
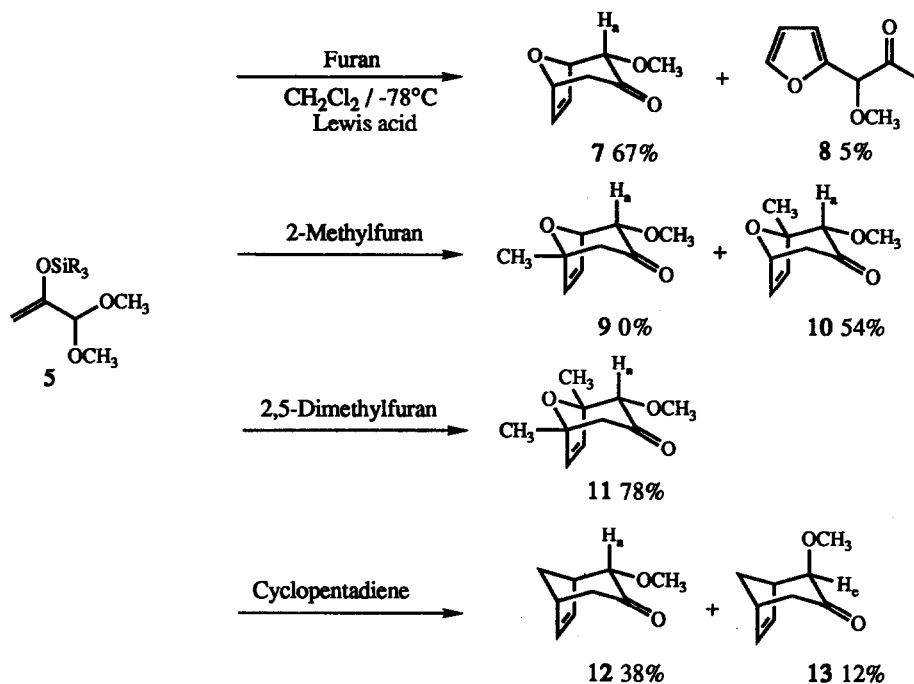
a) Isolated yields of **7** - **13** after flash chromatography and HPLC on silica.

The cycloaddition reaction is successfully promoted in a stoichiometric fashion by a variety of Lewis acids including TMSOTf, SnBr$_4$, SnCl$_4$, TiCl$_4$, SbCl$_5$, BCl$_3$, and Ph$_3$C$^+$BF$_4^-$. However, when Sn(OAc)$_4$, SnCl$_2$, ZnBr$_2$ or AgBF$_4$ are used no cycloadducts are obtained. In these cases the starting materials are recovered unchanged. These results suggest that the oxidation state, counteranion and oxophilicity of the Lewis acid are important parameters in determining their ability to promote this reaction. TMSOTf is effective in both stoichiometric and catalytic modes. Amounts as low as 2.5 mole % of TMSOTf have been found to induce cycloaddition.

Increasing the equivalents of diene used from one to five does not dramatically alter the reaction yields, except when 2-methylfuran is used as the diene. In this case extensive polymerization results when two or more equivalents are used. Various solvents such as CH$_2$Cl$_2$, THF, MeNO$_2$, and EtNO$_2$ can be used. In CH$_2$Cl$_2$ and THF cycloaddition with furan gave cycloadduct **7** along with side product **8**, while cycloadditions performed in polar nitroalkane solvents give cycloadducts uncontaminated with **8**. Variation of the silyl group from TMS to TES, TIPS or TBS did not change the stereochemical outcome of the cycloaddition with furan in CH$_2$Cl$_2$.

8-Oxabicyclo[3.2.1]oct-6-en-3-ones have been used as key intermediates in natural product syntheses,[1] so we anticipated that 2-methoxy-8-oxabicyclo[3.2.1] oct-6-en-3-ones could also serve as intermediates for the synthesis of certain classes of oxygenated natural products. Thus, using the recently reported one step procedure for troponization,[6] cycloadduct **7** was converted readily into 2-methoxytropone **14**, which is itself a key intermediate in several natural product syntheses.[7]
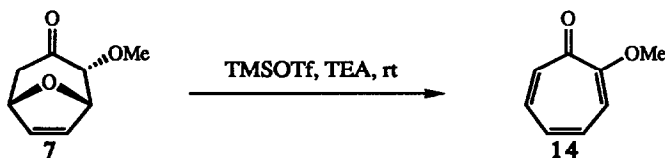
This two step approach facilitates direct entry into naturally occurring tropolonoid systems e.g. thujaplicins, colchicinoids and polyoxygenated tropolones, some of which exhibit significant biological activity.[8]

In summary, trialkylsilyloxyallyl cations **2** with a π-donating heteroatomic substituent at the allylic termini, have been generated under Lewis acidic conditions. They react with furans stereo- and regioselectively to yield oxabicycles which can be readily converted into tropolonoid systems. Additional research is currently underway to develop the latent ambiphilic reactivity of α,α-dialkoxy ketones and explore their synthetic potential for construction of oxygenated hetero- and carbocycles.

References
1) (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Barbosa, L. C. de A.; Mann, J. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 177.
2) Ito, M.; Tsutomu, I.; Kiyoshi, T. *Chem. Pharm. Bull.* **1986**, *34*, 4346.
3) (a) Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057 and references therein. (b) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1979**, *44*, 1798. (c) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43* 2601. (d) The reaction yield of **5b** was increased to 70% by using a nonaqueous workup procedure and subsequent purification by vacuum distillation.
4) (a) For a report of a species related to **5**, see Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Kashammer, D. *Chem. Ber.* **1988**, *121*, 1585. (b) For a report on alkoxy-substituted allyl cations that shows a different [4π + 2π] reactivity pattern, see Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P. *J. Am. Chem. Soc.* **1987**, *109*, 2182. (c) Satisfactory ^{1}H NMR, ^{13}C NMR, IR and HRMS data were obtained for silyl enol ethers **5b-e** and cycloadducts **7, 10, 11, 12** and **13**.
5) (a) Hoffmann, H. M. R. *Angew. Chem. Inter. Ed. Engl.* **1984**, *23*, 1. (b) Hoffmann, H. M. R. *Angew. Chem. Inter. Ed. Engl.* **1973**, *12*, 819. (c) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765. (d) Noyori, R.; Shimizu, F.; Fukuta, K.; Takaya, H.; Hayakawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5196.
6) Barbosa, L. C. de A.; Mann, J.; Wilde, P. D. *Tetrahedron* **1989**, *45*, 4619.
7) (a) Greene, A. E.; Teixeira, M. A.; Barreiro, E.; Cruz, A.; Crabbé, P. *J. Org. Chem.* **1982**, *47*, 2553. (b) Pasto, D. J. In *Organic Photochemistry*; Chapman, O. L., Ed.; Marcel Dekker: New York, 1967; pp 161-170. (c) Takeshita, H.; Mori, A.; Kusaba, T. *Synthesis* **1986**, 578.
8) (a) Nozoe, T. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 232. (b) Pietra, F. *Chem. Rev.* **1973**, *73*, 293. (c) Banwell, M. G.; Herbert, K. A.; Buckleton, J. R.; Clark, G. R.; Rickard, C. E. F.; Lin, C. M.; Hamel, E. *J. Org. Chem.* **1988**, *53*, 4945. (d) Capraro, H.-G.; Brossi, A. In *The Alkaloids*, Brossi, A., Ed.; Academic Press: Orlando, Florida, 1984; pp 1-70. (e) Sugawara, K.; Ohbayashi, M.; Shimizu, K.; Hatori, M.; Kamei, H.; Konishi, M.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 862.