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# THE PREPARATION OF α,β-ACETYLENIC KETONES BY CONDENSATION OF LITHIUM ACETYLIDES WITH LACTONES

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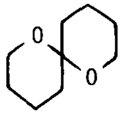
We have been examining synthetic approaches to spiroketal rings of types 1 and 2, structural units common to a wide variety of natural products including steroid sapogenins,[2] oligomycins,[3] milbemycins,[4] and many polyether antibiotics, *e.g.*, monensin[5] and antibiotic A23187.[6] During the course of this work we discovered that 1 eq. of the lithium salt of the THP[7] or trityl[8] ethers of 4-hydroxy-1-butyne (3a and 3b, respectively) added cleanly to δ-valerolactone to provide 71% and 99% isolated yields of α,β-acetylenic ketones 4a and 4b, respectively. Since the addition of organolithium reagents to esters often proceeds past the ketone stage and since the reported syntheses of α,β-acetylenic ketones did not include acylations of acetylide anions with lactones,[9] we decided to explore the scope of this reaction. Specifically, we examined the additions of the lithium salts of 4-trityloxy-1-



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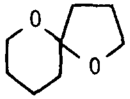

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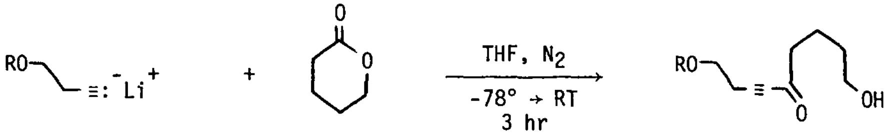
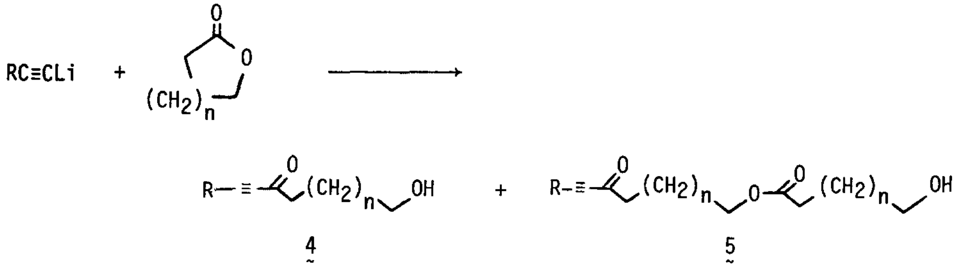


3a R = THP
3b R = $\emptyset_3$C

4a R = THP 71%
4b R = $\emptyset_3$C 99%

Table 1. Yields of Products of the Reaction of Lithium Acetylides with Lactones[a]



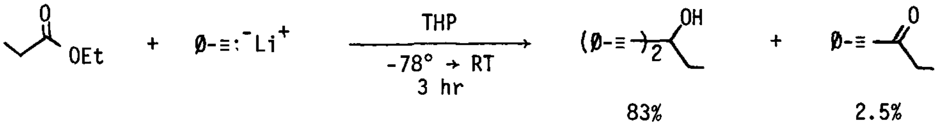
| R | n | % 4 | % 5 |
|---|---|---|---|
| n-Bu | 1 | 63 (4c) | - |
| | 2 | 80 (4d) | - |
| | 3 | 38 (4e) | 19 (5a) |
| $\phi_3COCH_2CH_2$ | 1 | 52 (4f) | - |
| | 2 | 99 (4b) | - |
| | 3 | 31 (4g) | 18 (5b) |
| $C_6H_5$ | 1 | 68 (4h) | - |
| | 2 | 99 (4i) | - |
| | 3 | 31 (4j) | 22 (5c) |

[a] All products are new compounds which had i.r., n.m.r., and mass spectra in accord with the assigned structures. Elemental formulae were determined from high resolution mass spectra, and agreed with the calculated exact masses by ±0.005 amn. All yields are of isolated products, homogeneous on TLC.

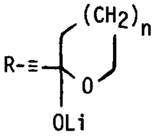
butyne, 1-hexyne, and phenylacetylene to γ-butyrolactone, δ-valerolactone, and ε-caprolactone, and our results are summarized in the accompanying table.

The general experimental procedure[10] used is as follows: A stirred solution of 5.0 mmole lactone in 35 ml dry THF at -78° under $N_2$ was treated dropwise with 25 ml of a 0.20 M solution of lithium acetylide in THF. The dry ice bath was removed, and the reaction mixture stirred 3 h, during which time the solution warmed to room temperature and turned yellow. The reaction was quenched with 60 ml satd aq $NH_4Cl$, the layers separated, and the aqueous phase washed with 60 ml $Et_2O$. The combined organic phases were dried with $Na_2SO_4$ and reduced to an oil which was chromatographed using $Et_2O$/hexane mixtures on silica gel columns or thick layer plates.

Examination of the accompanying table reveals that δ-valerolactone provided excellent yields of acetylenic ketones 4d, 4b and 4i in all three cases, while γ-butyrolactone provided more modest, but nevertheless acceptable, yields of α,β-ynones 4c, 4f and 4h. Although δ-caprolactone condensations apparently proceeded in uniformly poor yields, the desired products, 4e, 4g and 4j, were accompanied in all cases by approx. 20% of ynone esters 5a-c. Hence, the combined yields of products of monoaddition of alkynyl lithiums to ε-caprolactone are 49-53%. Under identical conditions, lithium phenylacetylide adds twice to ethyl propionate forming 83% isolated yield of carbinol 6 and only 2.5% of ketone 7. Although we have provided no confirmatory evidence, the yields of ketone appear to reflect the expected order of stability of the intermediate ketal alkoxides 8, *i.e.*, in ring size, 6>5>7>>acyclic.



6 7



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We are currently pursuing the generalization of this reaction and its use in preparing spiroketals of varying ring sizes.

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## References

1. Current address: Stevens Institute of Technology, Department of Chemistry, Castle Point Station, Hoboken, N. J. 07030.
2. See for example J. Elks, "Steroid Saponins and Sapogenins," Chapt. 18 of *Rodd's Chemistry of Carbon Compounds, Vol. IIE,* Elsevier Publ. Co., Amsterdam, 1971, pp. 1-53.
3. G. T. Carter, Ph.D. Thesis, University of Wisconsin, Madison, 1976; M. von Glehn, R. Norrestam, P. Kierkegaard, L. Maron, and L. Ernster, *FEBS Lett.*, 20, 267 (1972); W. F. Prouty, R. M. Thompson, H. K. Schnoes, and F. M. Strong, *Biochem. Biophys. Res. Comm.*, 34, 511 (1969).
4. A. Aoki, R. Fukuda, T. Nakayabu, K. Ishibashi, C. Takeichi, and M. Ishida (Sankyo Company Ltd.), U. S. Patent 3,998,699, Dec. 21, 1976; A. Aoki, *et al.* (Sankyo Co. Ltd.), Japan Kokai, 75-29,742, March 25, 1975; H. Mishima, M. Kurabayashi, C. Tamura, S. Sato, H. Kuwano, and A. Saito, *Tet. Lett.*, 1975, 711.
5. A. Agtarap, J. W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, 89, 5737 (1967); M. Pinkerton and L. K. Steinrauf, *J. Mol. Biol.*, 49, 533 (1970); W. K. Lutz, F. K. Winkler, and J. D. Dunitz, *Helv. Chim. Acta,* 54, 1103 (1971).
6. M. O. Chaney, P. V. Demarco, N. D. Jones, and J. L. Occolowitz, *J. Am. Chem. Soc.*, 96. 1932 (1974).
7. E. H. R. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 1950, 230.
8. Prepared by reaction of 1.0 g (14.3 mmole) 3-butyne-1-ol with 4.38 g (15.7 mmole) trityl chloride in 40 ml 1:1 dry pyridine/$CH_2Cl_2$ for 3 days at room temperature.

Product was isolated by pouring the reaction mixture into 200 ml ice cold water extracting with ether, drying with $Na_2SO_4$, evaporating solvent, and azeotroping the solid residue with benzene. Pure trityl ether was prepared by chromatography on 100 g silica gel (eluted with petroleum ether, bp 30-60°) and recrystallizing twice from hexane, to yield 3.02 g (70%) colorless crystals, mp 108-110°C. Spectral data were in accord with the proposed structure. Calc. for $C_{23}H_{20}O$: C, 88.46%; H, 6.41%. Found: C, 88.71%; H, 6.57%.

9. $\alpha,\beta$-Acetylenic ketones have been prepared by oxidation of the corresponding alcohol and by nucleophilic additions of Cu, Ag, and Cd acetylides to acyl halides (J. F. Normant and M. Bourgain, *Tet. Lett.*, 1970, 2659; M. W. Logue and G. L. Moore, *J. Org. Chem.*, 40, 131 [1975]; O. G. Yashina, T. V. Zarva, T. D. Kaigorodova, and L. I. Vereshchagin, *Zh. Org. Khim.*, 4, 2104 [2032 in English translation] [1968]; R. B. Davis and D. H. Scheiber, *J. Am. Chem. Soc.*, 78, 1675 [1956]) or by addition of Li acetylides to acyl anhydrides (R. Finding, G. Zimmermann, and U. Schmidt, *Monatsh.*, 102, 214 [1971]) or by $AlCl_3$ catalyzed acylation of trimethylsilylated acetylenes with acyl halides (L. Birkofer, A. Ritter, H. Uhlenbrauck, *Ber.*, 96, 3280 [1963]).
10. All materials were commercial samples of reagent grade and were used as received. Dry THF was distilled under $N_2$ immediately before use from sodium benzophenone ketyl. Lithium acetylides were prepared by addition at -78° under $N_2$ of 1.02 eq BuLi in hexane to a THF solution of the acetylene and allowing the mixture to warm to RT. The acetylides were generally used immediately after preparation, but could be stored for several weeks without effect on subsequent reaction. All yields are of isolated products.