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# A CONVENIENT SYNTHESIS OF SUBSTITUTED γ-PYRONES

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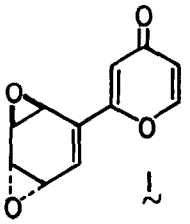
Summary: An efficient and general synthetic method for various 2-mono- and 2,6-disubstituted γ-pyrones has been developed. This utilizes the C-acylation (70-85%) of β-methoxy-α,β-enone lithium enolates 4 by acid chlorides 3 followed by the acid-catalyzed cyclization (>80%) of the resulting enols 5 to γ-pyrones 6.

A large number of natural products possessing a γ-pyrone moiety have been isolated from various sources.[1] Of particular interest as synthetic targets are γ-pyrone-cyclohexane epoxides such as LL-Z1220 1,[2] an antibiotic isolated from an unidentified fungal species, and tridachione 2,[3] a propionate-derived metabolite from a mollusk, Tridachiella diomedea.



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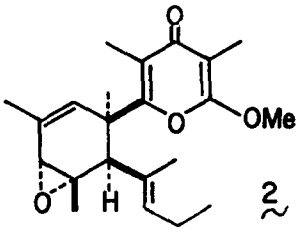


2

Although a variety of synthetic methods for γ-pyrones are available,[4] essentially all of them employ strongly acidic conditions for the cyclization of open-chain 1-aryl-[5] or 1-carbomethoxy-1,3,5-triketones,[6] followed by thermal decarboxylation in the latter case. These often proceed only in moderate yields. In connection with our synthetic efforts toward the acid- and heat-sensitive antibiotic LL-Z1220 1, we developed an efficient and mild method for the synthesis of alkyl- and/or aryl-substituted γ-pyrones which uses an acid chloride and a β-methoxy-α,β-enone as the building blocks.

The basic strategy undertaken is outlined below:

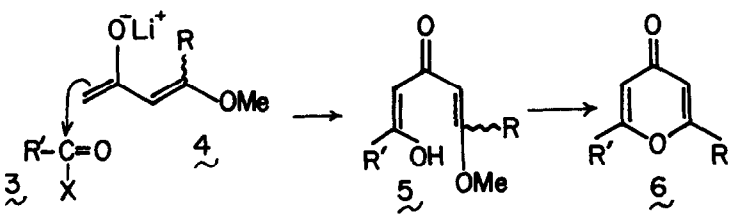
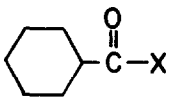
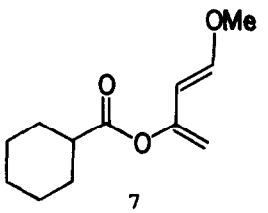
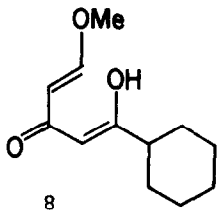


Table I. Acylation Reactions of the Anion 4[a] (R = H) with Cyclohexanecarboxylic Acid Derivatives.[b]



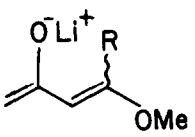


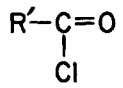


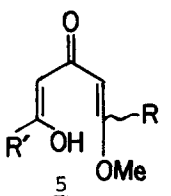
| | Yield (%)[c] | |
|---|---|---|
| | 7 | 8 |
| 9 X = -O-CO-O-i-Bu | 40 | -[d] |
| 10 X = -O-P(O)(OEt)$_2$ | 45 | - |
| 11 X =  | - | 67 |
| 12 X = -Cl | - | 75 |

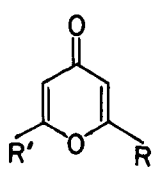
a. See Typical Procedure. For 9-11, the lithium enolate solution was added to these acid derivative solutions, whereas the acid chloride 12 solution was added to the former.
b. All reactions were carried out in dry THF under nitrogen initially at -78°C and gradually warmed up to room temperature and was kept at room temperature for 2 - 3 hrs.
c. Yields based on the material isolated by column chromatography or TLC.
d. The designation - in the Table indicates the absence of the corresponding product analyzed by NMR of the crude reaction mixture.

Table II. Synthesis of Substituted γ-Pyrones.









| entry | 4 | 3 | 5 | Yield (%)[a] 6 |
|---|---|---|---|---|
| 1. | R = H (E)[b] | R' = Me | 70 | 85 |
| 2. | R = H (E) | R' = $PhCH_2$ | 74 | 83 |
| 3. | R = H (E) | R' = t-Bu | 81 | 80 |
| 4. | R = H (E) | R' = c-$C_6H_{11}$ | 72 | 85 |
| 5. | R = H (E) | R' = Ph | 83 | 90 |
| 6. | R = Me (Z) | R' = Me | 55 | 65 |
| 7. | R = OMe | R' = Ph | 50[c] | 80 |

a. Yields based on isolated material which was >98% pure.
b. Stereochemistry of the enolate.
c. See text.

Typical Procedure: The solution of acid chloride (1 mmol) in 2 ML of dry THF was added, under nitrogen, to the solution of lithium enolate 4, prepared by the dropwise addition of 4-methoxy-3-buten-2-one (2 mmol) to 2 mmol of lithium bis(trimethylsilyl)amide[7] in 8 mL of THF at -78°C for 30 min. The mixture was gradually warmed up to room temperature and was kept at room temperature for 2 hrs. The reaction mixture was treated with saturated aqueous $NH_4Cl$ solution and was extracted with ether. The organic layer was washed with saturated aqueous NaCl solution, dried over sodium sulfate, and evaporated under reduced pressure providing the enol 5 whcih was purified by column chromatography or TLC

The enol 5 (1 mmol) in 10 mL of dry benzene was treated with two drops of trifluoroacetic acid at room temperature for 12 - 18 hrs. The mixture was then evaporated to dryness under vacuum, and was subsequently purified by column chromatography or TLC to give the γ-pyrone 6.

Acknowledgment: We thank the National Institutes of Health for support of this work.

References and Notes

1. Dean, F. M. "Naturally Occurring Oxygen Ring Compounds"; Butterworths: London, 1963; Chapter 4.
2. (a) Borders, D. B.; Shu, P.; Lancaster, J. E. J. Am. Chem. Soc. 1972, 94, 2540; (b) Borders, D. B.; Lancaster, J. E. J. Org. Chem. 1974, 39, 435; (c) Vogel, E.; Altenbach, H. J.; Schmidbauer, E. Angew. Chem. int. Ed. 1973, 12, 838.
3. (a) Ireland, C.; Faulkner, D. J.; Solheim, B. A.; Clardy, J. J. Am. Chem. Soc. 1978, 100, 1002; (b) Ireland, C.; Faulkner, D. J.; Finer, J. S.; Clardy, J. ibid. 1979, 101, 1275.
4. Livingstone, R. In "Rodd's Chemistry of Carbon Compounds"; Coffey, S. Ed.; Elsevier: Amsterdam, 1977; Vol. IV, Part E, Chapter 20.
5. Light, R. J.; Hauser, C. R. J. Org. Chem. 1960, 25, 538.
6. Dorman, L. C. J. Org. Chem. 1967, 32, 4105.
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