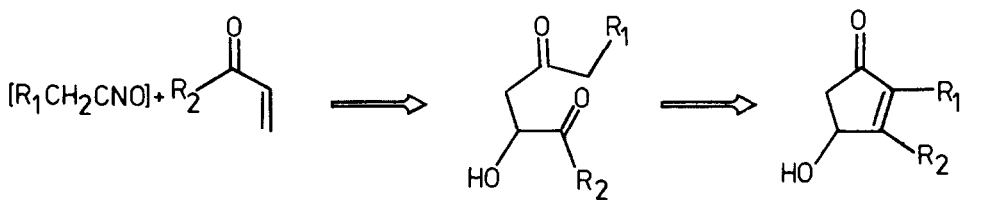
Tetrahedron Letters,Vol.24,No.33,pp 3443-3446,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A SHORT SYNTHESIS OF γ-HYDROXYCYCLOPENTENONES

Dennis P. Curran[1]
Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Abstract. A facile synthesis of γ-hydroxycyclopentenones is described involving olefin-nitrile oxide cycloaddition, isoxazoline reduction, and intramolecular aldol cyclization. Applications toward rethrolones and important prostanoid synthons are presented.

γ-Hydroxycyclopentenones have frequently served as synthetic targets by which methods for five-membered ring formation are illustrated.[2] One of the most common modes of cyclopentenone ring formation has involved intramolecular aldol condensation (Eq. 1). This route, in turn, has served as a vehicle by which 1,4-diketone synthesis is illustrated. The many routes to 2-hydroxy-1,4-diketones (I) frequently employ reversed electron polarity concepts for carbon-carbon bond formation. By nature, this approach involves appropriate introduction of activating groups followed by subsequent unmasking of desired functionalities. We now wish to report a different strategy which results in an unusually facile three step synthesis of γ-hydroxycyclopentenones via the intramolecular aldol route.[3]



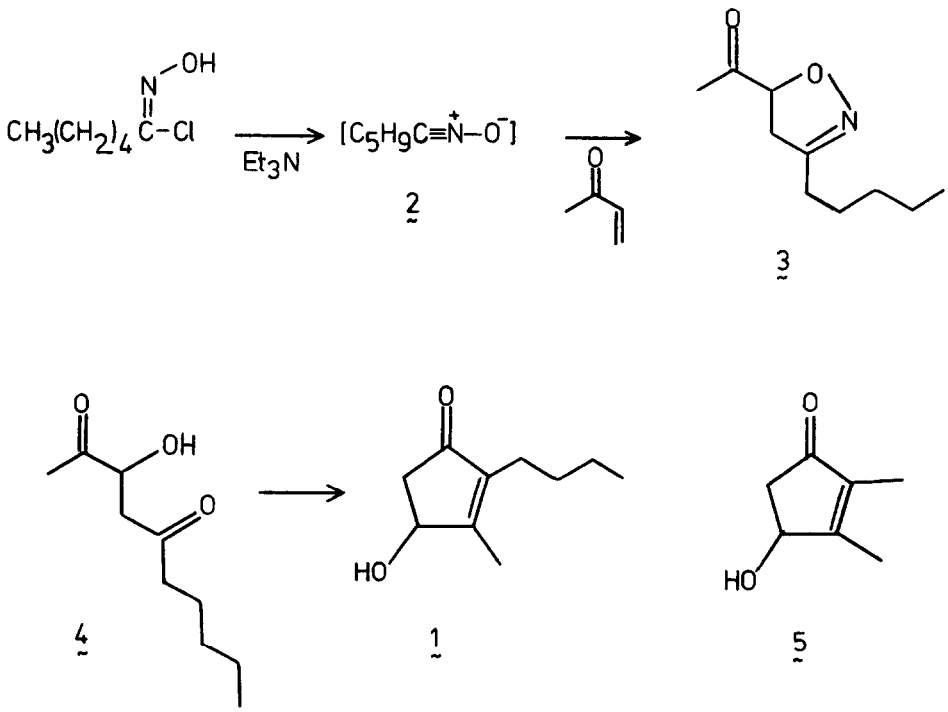
Eq. 1

I

Rethralones are the alcohol components of the insecticidal pyrethrin esters.[4] Scheme I outlines our general strategy as applied to the synthesis of dihydrocinerolone 1. Generation of nitrile oxide 2 by dehydrohalogenation of hexanaldoxime chloride in the presence of methyl vinyl ketone [Et_3N, Et_2O, -20° to RT] resulted in [3+2] dipolar cycloaddition to produce isoxazoline 3 in 92% yield.[5] The hydroxy-1,4-diketone was then uncovered by employment of our recently developed conditions for reductive transformation of Δ^2-isoxazolines to β-hydroxy ketones.[6] Thus, exposure of 3 to W-2-Raney-nickel (H_2 gas, 5/1 MeOH/H_2O, 10 eq $B(OH)_3$, 1.5h, 25°C) produced sensitive hydroxy-1,4-diketone 4 in 90% crude yield. Compound 4 was directly cyclized under standard conditions (NaOH, H_2O, EtOH, 25°C)[7a] to give (±) dihydrocinerolone

(1)[7b] in 61% yield from 2. The overall yield for this three step synthesis is then 56%. In a similar fashion, 4-hydroxy-2,3-dimethyl-2-cyclopenten-1-one (5) was produced in 35% overall yield from methyl vinyl ketone and nitropropane.[8] In each case, the intramolecular aldol cyclization is the lowest yielding step. Extensive optimization of these yields has not been investigated.

Scheme I

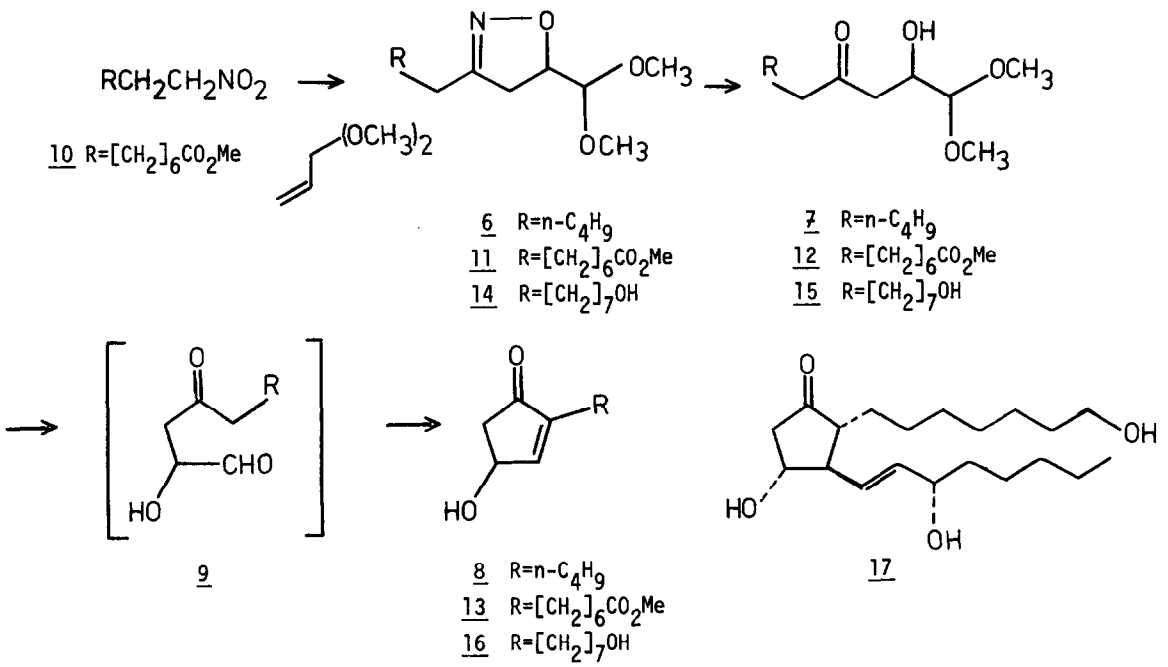


This efficient strategy takes advantage of a mild cycloaddition reaction for formation of the requisite carbon-carbon bond and the development of our new reduction conditions allows for the general employment of Δ^2-isoxazolines as heterocyclic aldol equivalents.[6] The mildness of these reduction conditions involving boric acid (pH ~5.5 to 6) is underscored by the high yield production of 4. The use of other additives lead to extensive decomposition of this sensitive molecule.

A slightly different protocol was developed for the synthesis of the 3-unsubstituted system which requires an acrolein equivalent as a cycloaddition partner.[9] Cycloaddition of nitrohexane with acrolein dimethyl acetal under the Mukaiyama conditions[10] produced 6 in 82% yield. After reduction as above (90%), 7 was directly cyclized in aqueous THF (12h, 40°C) using Rexyn 300, a mixed acid-base ion exchange resin. γ-Hydroxycyclopentenone 8[11] was directly isolated in 41% yield. These conditions, developed by Stowell and Hauck,[12] may involve acid catalyzed acetal hydrolysis to 9 followed by base catalyzed aldol cyclization. As such the use of the sensitive aldehyde grouping is avoided, without addition of any extra steps. Again, extensive optmization of the cyclization conditions was not explored.

In a similar manner, important intermediates for the conjugate addition approach to prostaglandins[13] may be prepared. Employment of readily available nitroester 10[14] in the cycloaddition reaction gave 11 (75%). Although reduction proceeded without event, hydroxy ketone 12 did not cyclize to form the PGE_1 precursor 13 under the reaction conditions. However, careful reduction of 11 with 2.0 equivalents of diisobutylaluminum hydride (THF, -78°C) produced alcohol 14 in nearly quantitative yield. After reduction to 15 (87%), Rexyn 300 promoted cyclization then gave (±) 16 in 53% yield (10/1, THF/H_2O, 6h reflux, based on 66% conversion of 15). It is of interest to note that conjugate addition of appropriate side chains to (R)-16 has been shown to produce PGE_1 carbinols 17 which show marked selectivity in biological activity as compared to PGE_1.[15]

Scheme II



It can be seen that this strategy is one of the shortest, most straightforward routes for the production of γ-hydroxycyclopentenones. In addition to brevity and mildness of reaction conditions, other advantages include employment of readily available starting materials and inexpensive reagents and efficient use of all functionality present. Although it may be difficult to introduce absolute chirality due to likely epimerization in the cyclization step, the overall sequence is so short and simple as to make resolution a viable alternative.[16,17]

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM 31678-01), for support of this work. Mr. Christopher Fenk is also thanked for valuable preliminary experiments.

References

1. Recipient of a Dreyfus Foundation Grant for Newly Appointed Young Faculty in Chemistry, 1981-1986.

2. Ellison, R. A. Synthesis, (1973), 397. T.-L. Ho Syn. Comm. (1974) 4, 265.

3. A similar strategy involving silyl nitronate cycloaddition, elimination to form the isoxazoline, and $TiCl_3$ reduction, has recently been reported. Anderson, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G.; Acta. Chem. Scand. (1982) B36, 1.

4. "Pyrethrum, the Natural Insecticide" ed. J. E. Casida, Academic Press, New York (1973).

5. For a review on the chemistry of nitrile oxides see: Grundmann, C.; Grünanger, P. "The Nitrile Oxides", Springer-Verlag, New York, 1971.

6. Curran, D. P. J. Amer. Chem. Soc. (1982) 104, 4024. Curran, D. P. J. Amer. Chem. Soc. (1983), 105, 0000. See also, Kozikowski, A. P.; Adamczyk, M. Tetrahedron Lett. (1982) 23, 3123.

7. a) Crombie, L.; Hemesley, P.; Pattenden, G. J. Chem. Soc. C (1969), 1016. b) Woessner, W. D.; Ellison, R. A. Tetrahedron Lett. (1972) 3735.

8. This β-hydroxy ketone was cyclized with K_2CO_3 in methanol. See ref. 3.

9. We were not successful in obtaining the requisite cycloadducts directly from acrolein.

10. Mukaiyama, T.; Hoshino, T. J. Amer. Chem. Soc. (1960) 82, 5339.

11. Cooper, G. K.; Dolby, L. J. Tetrahedron Lett. (1976), 4675.

12. Stowell, J. C.; Hauck, H. F., Jr. J. Org. Chem. (1981) 46, 2428.

13. Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis" Academic Press, New York, 1977.

14. Prepared from commercially available azealic acid mono methyl ester by 1) 1eq BH_3, THF, 2) MsCl, Et_3N, 3) NaI, acetone, 4) $AgNO_2$, Et_2O.

15. Kluender, H. C.; Peruzzotti, G. P. Tetrahedron Lett. (1977), 2063. Arndt, H. C., Gardiner, P. J.; Hong, E.; Kluender, H. C.; Myers, C.; Woessner, W. D. Prostaglandins (1978) 16, 67. See also Gill, M.; Richards, R. W. Aust. J. Chem. (1981), 34 (1063).

16. All new compounds exhibited satisfactory spectral and physical data.

17. An elegant approach to prostaglandins via intramolecular nitrile oxide cycloadition is being investigated by A. P. Kozikowski and P. Stein (personal communication) see: Kozikowski, A. P.; Stein, P. D. J. Amer. Chem. Soc. (1982) 104, 4023. For β-side chain elaboration via nitrile oxide cycloaddition see: Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Simoni, D.; Guarneri, M.; Candolti; C. J. Org. Chem. (1980) 45, 3141.

(Received in USA 13 May 1983)