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A FACILE AND GENERAL SYNTHESIS OF 4-HYDROXYCYCLOPENTENONES

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Various rethrolones were prepared in good yields simply from 2,5-disubstituted furans. The electrooxidation of 2,5disubstituted dihydrofurans gave 2,5-dimethoxy-2,5-disubstituted dihydrofurans. Hydrolysis of electrooxidation products with ion enchange-resin, followed by the treatment with base gave rethrolones. Furthermore, this method was applicable for the synthesis of 2-alkyl-4-hydroxycyclopentenone.

We wish to report a remarkably simple synthetic method of 4-hydroxycyclopentenones, some of which have been known to be the essential component of some useful insecticides.¹ Furthermore, this method may indicate a wide potentiality in the syntheses of the related compounds of prostaglandins.



2,5-Dimethoxydihydrofurans (3) were easily obtained by the anodic methoxylation² of the corresponding 2,5-disubstituted furans (2) prepared from 2-methylfuran (1) and alkyl bromide according to the method of Ramanthan.³

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Compounds 3 were hydrolyzed at room temperature for an hour in the presence of acidic ion-exchange resin (Amberlite 120B). The resin was removed by filtration, and the treatment of the filtrate with 1% aqueous sodium carbonate at 100°C for two hours gave the 4-hydroxycyclopentenones (4)⁴ as the exclusive products. Results are shown in Table I. All products were identified by the elemental and spectroscopic analyses and/or by the comparison with authentic samples.

	Table	I. Isolated	Yield	(웅)	and Bo	oiling Point	(°C/mmHg) of	2, 3, and 4
		R	۲ 2	Yiel (%) 3	4 ^{b,c}	2	Boiling Poin (°C/mmHg) 3	4 ^{b,c}
a		Н	a	59	44		63/25	100-110/0.2
ь		CH ₂ CH ₃	78	78	55	135-138	58- 60/3	115-120/0.2
С		CH ₂ CH ₂ CH ₃	84	71	59	155-157	70- 72/5	130-140/0.2
đ		CH ₂ CH=CH ₃	70	68	54	152-153	115-117/28	135-140/0.25
е		cis and trans ^d CH ₂ CH=CHCH ₃	72	71	85	67- 69/11	122/15	110-115/0.15

a. Commercially available.

b. Isolated with column chromatography. 4e was isolated with preparative thin-layer chromatography.

c. The isolated yields of the intermediates cis- $5a^5$ and cis- $5e^6$ are 98 and 96%, respectively.

d. Mixture.

In the course of the conversion of **3** to **4**, the intermediary formation of cisdiketone (cis-5) and hydroxycyclopentenone (6) was observed by VPC analysis, and furthermore, cis-5a and $6a^7$ (yield, 67%) were isolated and transformed to the final product, **4**a. The yields were 43% from cis-5a and 75% from **6**a.

The acid-catalyzed hydrolysis of 2,5-dialkoxydihydrofuran (3) may yield both cis- and trans-1,4-diketone (cis-5 and trans-5), though the ratio of the stereoisomers would depend on the nature of acid catalyst.⁸ The treatment of 3a (1.0g) with acidic ion-exchange resin (Amberlite 120B) (0.5g) in aqueous solution for 30 minutes gave only cis-5a (0.694g) which cyclized to 6a (0.465g), while the cyclization of trans-5a generated by the hydrolysis of 3a with dilute sulfuric acid did not take place. There would be two possible pathways in the cyclization of trans (R#H). One of them is the formation of the compound of type 6 and the

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compound of type 7 may be yielded by another route in which the proton abstraction from 5 takes place on the methyl group as shown below.



The cyclization of cis-5 was, however, completely regiospecific and the formation of the compound of type 7 or the rearranged product of 7 was not detected. The isomerization of 6 to 4 may involve the intervention of diol (8),⁹ though the formation of this compound was not observed in the present reaction.¹⁰



Hydroxycyclopentenones of type **9** may be synthesized from mono substituted furans by this new method. For example, 2-propyl-4-hydroxycyclopentenone¹¹ was prepared from butylfuran in an overall yield of 37%.



In principle, there would be no particular restriction as to the structure of the group R in this reaction.¹² Thus, the combination of this new method with the reported reaction¹³ would give a wide potentiality in the syntheses of the related compounds of prostaglandins. The study on the syntheses of some of the latter compounds is in progress.

References and Notes

- (1) Representative synthetic reports for rethrolones;
 - (a) M. S. Schechter, N. Green, and F. B. Laforge, J. Am. Chem. Soc., 71, 3165 (1949);
 - (b) R. F. Romanet and R. H. Schlessinger, J. Am. Chem. Soc., <u>96</u>, 3701 (1974), and references cited therein;
 - (c) R. A. Ellison, Synthesis, <u>1973</u>, 397.
- (2) Electrooxidation of furan (0.05mole) was accomplished in methanol (50cc) containing sodium methoxide (0.5g). The electrode was carbon rod. The electricity passed was 2.5F/mole. P. Nedenskov, N. Elming, J. T. Nielsen, and N. Clauson-Kass, Acta Chem. Scand., 9, 17 (1955).
- (3) Methylfuran (0.2mole) was added at -25°C with stirring to a solution of buthyllithium (0.2mole) in THF (180cc) and stirring was continued for 4hr at -15°C. To this solution was added alkyl halide (0.2mole) diluted with THF (20cc). Stirring was continued over night at room temperature.
 V. Ramanthan and R. Levine, J. Org. Chem., 27, 1216 (1962).
- (4) 4a-e: ir; 1680cm⁻¹, nmr(δ_{TMS}ppm, in CCl₄); 2.15(s., 3H, methyl)
- (5) cis-**5**a: nmr(δ_{TMS}ppm, in CCl₄); 2.18(s., 6H), 6.10(s., 2H).
- (6) dis-5e: nmr(δ_{TMS} ppm, in CCl₄); 1.63(d., 3H), 2.30(s., 3H), 1.90-2.70(m., 4H), 5.35(m., 2H), 6.08(s., 2H).
- (7) 6a: nmr(^δ_{TMS}ppm, in CCl₄); 1.46(s., 3H), 2.40(s., 2H) 5.96(d., 1H), 7.40(d., 1H).
- (8) J. Levisalles, Bull. Soc. Chim. Fr., 1957, 997.
- (9) Although the stereochemical requirement in a similar rearrangement of hydroxycyclopentenone was recently reported by Stork et al.,¹³ the study on the mechanism of the rearrangement of 6 to 4 is currently in progress.
- (10) The formation of a compound supposed to be an intermediate was observed with gas chromatographic analysis, though isolation of the sufficient amount of this compound for the analysis of structure was impossible.
- (11) 9: nmr(δ_{TMS}ppm, in CCl₄); 0.90(t., 3H). 1.50(m., 2H), 2.00-3.10(m., 4H), 4.92(m., 1H) 7.30(m., 1H).
 10: nmr(δ_{TMS}ppm, in CCl₄); 0.89(t., 3H), 1.50(m., 4H), 2.55(t., 2H), 6.05(d. d., 1H), 6.81(d., 1H), 10.20(d., 1H).
- (12) R group should not be hydroxyl group. T.Shono and Y. Matsumura, Tetrahedron Lett., 1976, 1363.
- (13) G. Stork, C. Kowalski, and G. Garcia, J. Am. Chem. Soc., <u>97</u>, 3258 (1975).

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