Reactions of Phosphorus Compounds. XIV. A General Synthesis of 2,5-Dihydrofurans

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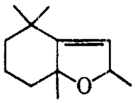
The preparation of 2,5-dihydrofurans, substituted in the 2 and/or 3 position, from α-hydroxy ketones employing vinyltriphenylphosphonium bromide as the cyclization reagent is reported.

Previously we have shown that vinyltriphenylphosphonium bromide (V)[1] is a unique reagent in preparative organic chemistry. It has been used in a general chain extension reaction,[2] and in a number of cyclization reactions affording high yields of pyrrolizines,[3] dihydroquinolines,[4] 2H-1-benzopyrans,[5] and cycloalkenes.[6]

We now wish to make a complete report[7] of our work on the synthesis of 2,5-dihydrofurans from α-hydroxy ketones and vinyltriphenylphosphonium bromide V. The parent 2,5-dihydrofuran and 2,5- or 3,4-substituted 2,5-dihydrofurans (*i.e.*, symmetrically substituted species) have been prepared in high yields generally by dehydration of 1,4-dihydroxybutene-2 or its derivatives[8,9] or by the dehydrohalogenation of substituted tetrahydrofurans.[10]

The syntheses, described herein, thus provide unique new supplements to the known general procedure for the preparation of dihydrofurans. The 2,5-dihydro furans with substituents in the 2,3 positions sometime occur in natural products. Many carotenoids,[11] for instance, mutatochrome, flavochrome, flavoxanthin, auroxanthin, and others, contain the moiety I in their structure. The parent 7-oxabicyclo[4.3.0]-$\Delta^{1(9)}$-nonene (II) has been prepared from adipoin and the vinyl salt V in 46% yield thus providing access to carotenoidlike structures *via* this new technique.



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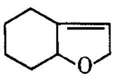
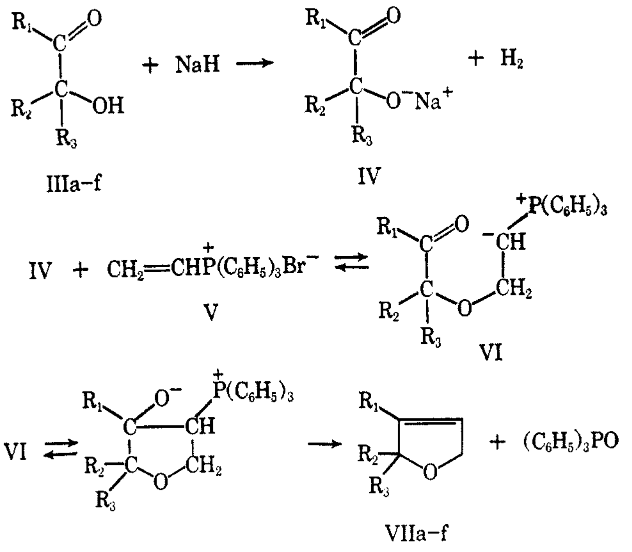


II

A general equation for the procedure is depicted in Scheme I.

SCHEME I



a, $R_1 = C_6H_5$; $R_2 = R_3 = H$
b, $R_1 = R_2 = C_6H_5$; $R_3 = H$
c, $R_1 = R_2 = R_3 = C_6H_5$
d, $R_1 = CH_3$; $R_1 = R_2 = H$
e, $R_1 = R_2 = CH_3$; $R_3 = H$
f, $R_1 = R_2 = R_3 = CH_3$

The sodium salts of adipoin and the hydroxy ketones IIIa–f were prepared by reaction with sodium hydride in anhydrous ether followed generally by addition of the salt, V, and dimethylformamide. Reaction at room temperature or with heating followed by work-up gave the product. In the case of IIf, however, the yields of the expected 2,2,3-trimethyl-2,5-dihydrofuran (VIIf) were minuscule. The yields of VIIf were increased to 26% by isolation of the salt IVf followed by its reaction as an intimately blended mixture of the salt IVf with the vinyl salt V under reduced pressure.

It was found that the purity of the starting materials critically affected the yields. The lower yields of the alkyl-substituted species undoubtedly can be attributed to the ability of the hydroxy ketone to dehydrate, to increased steric hindrance, and to decreased positive nature of the carbon of the carbonyl site. No optimization of yields was attempted; however, it was found that the preparation of 2,3-diphenyl-2,5-dihydrofuran (VIIb) increased from 35 to 50% on increasing the reaction temperature from room temperature to 80°. In this last experiment a second solid product was obtained of indeterminate structure which is under examination and will be reported on at a later date.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord 137 and nmr spectra on a Varian A-60A analytical nmr spectrometer, using tetramethylsilane as a standard. All melting points are uncorrected and were obtained on a Fisher-Johns melting point apparatus. Analyses were done by Microanalysis Inc., Wilmington, Del.

General Preparation of 2,5-Dihydrofurans.—Except in the case IIf, all the products were obtained according to the following general procedure.

The sodium salt of the β-hydroxybutanone was prepared by addition of an equimolar amount of sodium hydride (55% disper-

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(1) E. E. Schweizer and R. D. Bach, *J. Org. Chem.*, **29**, 1746 (1964); *Org. Syn.*, in press.

(2) E. E. Schweizer, L. D. Smucker, and R. Votral, *J. Org. Chem.*, **31**, 467 (1966).

(3) E. E. Schweizer and K. K. Light, *ibid.*, **31**, 870 (1966).

(4) E. E. Schweizer and L. D. Smucker, *ibid.*, **31**, 3146 (1966).

(5) E. E. Schweizer, *J. Am. Chem. Soc.*, **86**, 2744 (1964); D. Monaco and J. Liehr, unpublished results.

(6) E. E. Schweizer and G. J. O'Neill, *J. Org. Chem.*, **30**, 2082 (1965).

(7) An initial disclosure was made earlier on the preparation of compound VIIe. See ref 5.

(8) W. Reppe, *Ann.*, **596**, 111 (1955).

(9) A. I. Blomquist and C. S. Marvel, *J. Am. Chem. Soc.*, **55**, 1662 (1933).

(10) J. Colonge and P. Garnier, *Compt. Rend.*, **222**, 803 (1946).

(11) See P. Karrer and E. Jucker, "Carotenoids," Elsevier Publishing Co., New York, N. Y., 1950.

TABLE I

$$\text{IIIa–f} + \text{V} \xrightarrow[\text{solvent}]{\text{base}} \text{VIIa–f} + (C_6H_5)_3PO$$

III, mole	NaH, mole	Temp, °C	Time	VII (% yield)	Bp, °C (mm)	Anal., % Calcd C	H	Found C	H
IIIa, 0.103	0.104[a]	Room–80	4 days 2 days	VIIa (28)	95–97 (0.4)	82.16	6.90	82.09	6.65
IIIa, 0.0875	0.079	Room–60	45 hr 3 hr	VIIb (50)[b]	Mp 79–80	86.40	6.30	86.15	6.22
IIIc, 0.0438[c]	0.042	Room–60	45 hr 3 hr	VIIc (71)	Mp 106–107	88.56	6.08	88.62	5.98
IIId, 0.088	0.079	Room–60	12 hr 36 hr	VIId (7)[d]	83–5 (1 atm)	71.39	9.58	70.22	9.54
IIIe, 0.175	0.153	Room	48 hr	VIIe (39)	104 (1 atm)	73.43	10.27	73.09	10.29
IIIf, 0.09	0.08	Fusion under vacuum		VIIf (26)	117–118 (1 atm)	74.95	10.78	74.70	10.94
Adipoin, 0.088	0.079	Room–90	2 days 36 hr	II (46)	74–75 (10.5)	77.30	9.74	77.37	9.88

[a] $LiNH_2$ was used. [b] A second product analyzed for $C_{34}H_{29}PO_2$, mp 217–219°. [c] Prepared according to S. F. Acree [*Ber.*, **37**, 2758 (1940)]. [d] The infrared spectrum was identical with that reported by M. A. Gianturco, P. Friedel, and V. Flanagan [*Tetrahedron Letters*, **23**, 1851 (1965)].

sion in mineral oil[12]) in 50 ml of ether. After the vessels had been thoroughly dried, the reaction was carried out under dry nitrogen atmosphere. After stirring for 0.5 hr an equimolar amount of salt V[1] was added all at once. Dimethylformamide (DMF) (100 ml) was then added dropwise to the mixture. After 0.5 hr the solution had developed the red color characteristic of an ylide which then gradually disappeared upon stirring at room temperature or at an elevated temperature for about 2 days. The reaction was quenched by adding 300 ml of water. The product was obtained by extracting the mixture with ether, drying, and concentrating and distilling if the compound is a liquid. In case the product is solid, the concentrated ether solution was taken up in methanol. The dihydrofuran then precipitated out from the methanolic solution and could be recrystallized from methanol. The triphenylphosphine oxide could be found to a small extent in the ether solution. The rest could be obtained by extracting the reaction mixture with methylene chloride, concentrating, and crystallizing.

New compounds were characterized by their analyses and infrared spectra and nmr spectra. The amounts of the reagents and reaction conditions employed may be found in Table I; the data given by infrared and nmr spectra are listed in Table II.

2,5-Dihydro-2,2,3-trimethylfuran (VIIf).—2,5-Dihydro-2,2,3-trimethylfuran was prepared according to the following method. Compound IIf (0.99 mole) was added to 0.08 mole of NaH in 100 ml of ether. This mixture was stirred until gas evolution abated. The sodium salt was filtered under nitrogen cover, washed with ether, and dried overnight at room temperature. The dried salt was blended intermittently with 0.081 mole of salt V and heated under vacuum until the product distilled into a trap. The product was mixed with benzene which could be separated from dihydrotrimethylfuran (VIIf) by distillation on a Nester-Faust spinning-band column. It boiled at 117–118°.

Registry No.—II, 15377-92-1; VIIa, 15377-93-2; VIIb, 15377-94-3; VIIc, 15377-95-4; VIId, 1708-31-2; VIIe, 15377-97-6; VIIf, 15377-98-7.

TABLE II

Product	Infrared bands, cm^{-1}		Nmr Chemical shift (δ), ppm	Multiplicity	Area	Proton assignment
VIIa	685 (s)	1075 (s)	4.40–4.75	multiplet	4	CH_2's
	740 (s)	2850 (s)	5.82	quadruplet	1	$=CH$
	900 (s)		7.00	singlet	5	C_6H_5
VIIb	690 (s)	1065 (s)	4.82	multiplet	2	CH_2
	750 (s)	1250 (m)	6.08	multiplet	1	$HC<$
	840 (s)	2900 (m)	6.30	doublet	1	$=CH$
			7.20	split doublet	10	C_6H_5
VIIc	695 (s)	1060 (s)	4.80	doublet	2	CH_2
	755 (s)	1440 (s)	6.24	triplet	1	$=CH$
	800 (s)	1480 (s)	7.05–7.50	multiplet	15	C_6H_5
	1030 (m)					
VIId	895 (s)	1380 (m)				
	940 (s)	1680 (m)	[a]			
	970 (s)	2900 (s)				
	1075 (s)					
VIIe	865 (s)	1440 (s)	1.12	doublet	3	$H_3CC<$
	935 (s)	1680 (m)	1.61	triplet	3	$CH_3C=$
	1030 (s)	2800 (s)	4.45	multiplet	3	CH_2, $HC<$
	1090 (s)	2950 (s)	5.47	triplet	1	$=CH$
VIIf	845 (s)	1420 (m)	1.10	singlet	6	$(CH_3)_2C<$
	935 (m)	1440 (m)	1.15	multiplet	3	$CH_3C=$
	1050 (s)	2880 (s)	4.29	multiplet	2	$CH_2<$
	1170 (m)	2950 (s)	5.25	quadruplet	1	$=CH$
	1340 (m)					
II	829 (m)	1330 (s)	1.0–2.7	multiplet	8	$-(CH_2)_4-$
	880 (s)	1440 (s)	4.40	multiplet	3	CH_2, $CH<$
	990 (s)	2850 (s)	5.27	doublet	1	$=CH$
	1050 (s)	2950 (s)				
	1080 (s)					

[a] Insufficient material available to enable running of both ir and nmr spectral determinations.

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[12] Obtained from Metal Hydrides, Inc., Beverly, Mass.