Furan Synthesis by Reaction of α-Hydroxy Ketones with β-Ethoxyvinyltriphenylphosphonium Salts

Summary: Compounds **1**, **2**, or **3**, which generate or are vinylphosphonium salts bearing a leaving group in the β position, react with acyloins in the presence of base to afford good yields of 2-ethoxy-2,5-dihydrofurans and, from these, furans upon mild acid treatment.

Sir: Our interest in developing effective methods for the synthesis of furans with the substitution patterns found in natural products[1-4] has led us to explore an extension of the chemistry of vinylphosphonium salts, which have been amply documented as useful reagents by Schweizer.[5] We have found that use of vinylphosphonium salts which incorporate a β leaving group, or their precursors, such as the readily prepared salts **1**,[6] **2**,[7] or **3**,[8] can lead by reaction with α-hydroxy ketones in the presence of base to good yields of furans, *via* isolable 2-ethoxy-2,5-dihydrofurans. Scheme I illustrates the probable course of reaction of benzoin with **1**, which serves overall as an acetylene transfer reagent.

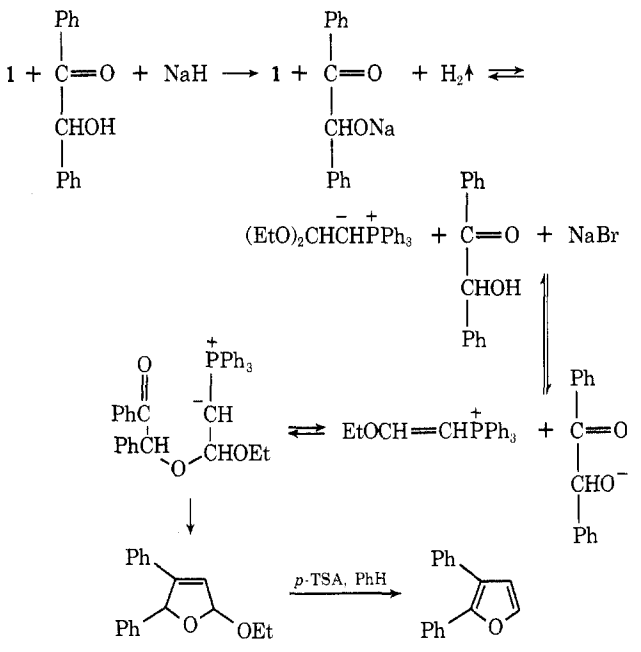
$(EtO)_2CHCH_2P^+Ph_3Br^-$ (**1**) $\qquad$ $EtOCH{=}CHP^+Ph_3I^-$ (**2**)

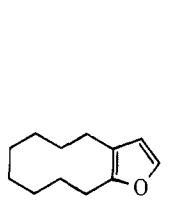
$EtOCH{=}C(CH_3)P^+Ph_3I^-$ (**3**)

Reagent **1**, prepared by the reaction of triphenylphosphine with bromoacetaldehyde diethyl acetal[9] according to Swan and Wright,[6] thus afforded 2,3-diphenylfuran[10] in 74% yield and afforded furan **4** in 61% yield from sebacoin.[11] Reagent **2**, prepared by O-alkylation[7] of α-formylmethylidenetriphenylphosphorane,[12] afforded 75% 2,3-diphenylfuran from benzoin and 70% **5** from **6**.[13]

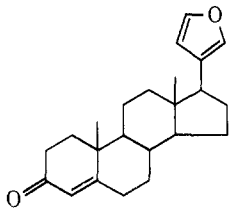
Preparation of a reagent analogous to **1** or **2** with a methyl substituent on the carbon adjacent to phosphorus

Scheme I

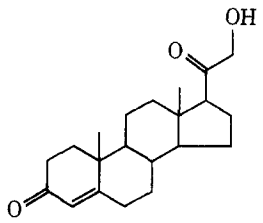




4



5



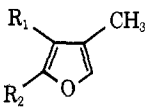
6

was of particular interest because it would offer the possibility of facile construction of furans with the substituent pattern shown in **7**, which is prevalent among natural products.[14] Attempted alkylation of triphenylphosphine with 2-bromopropanal diethyl acetal[15] and attempted alkylation of **1** with base and methyl iodide both failed to yield **8**. The desired homolog of **2**, reagent **3**, was obtained, however, by O-ethylation of α-formylethylidenetriphenylphosphorane,[12] as shown in Scheme II.

Scheme II

$$Ph_3P + CH_3CH_2I \longrightarrow Ph_3P^+CH_2CH_3I^- \xrightarrow[EtOOCH]{n\text{-BuLi},} Ph_3PC(CH_3)CHO \xrightarrow[EtI]{} \mathbf{3}$$

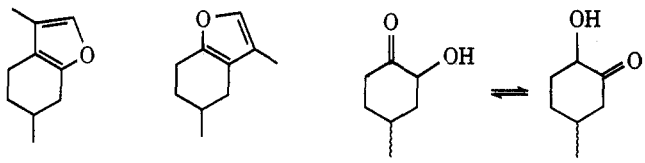
Reaction of **3** with benzoin afforded 71% of the anticipated furan **9**. However, the steroidal acyloin **6** yielded no furan with **3**, in striking contrast to its behavior with **2**. Inspection of Dreiding models shows that the Michael adduct of **6** with **3** has severe steric hindrance to formation of the Wittig betaine in all available conformations, whereas the adduct of **6** with **2** does have a conformation which would permit cyclization.



7, R_1, R_2 = alkyl
9, R_1, R_2 = Ph

$(EtO)_2CHCH(CH_3)P^+Ph_3Br^-$ (**8**)

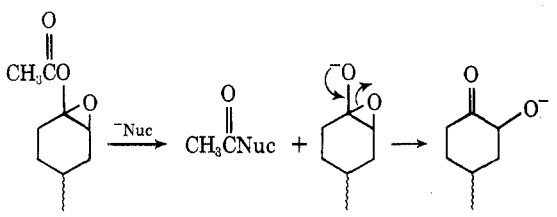
A more serious limitation to this furan synthesis was discovered when attempts were made to use reagent **3** to prepare menthofuran (**10**). 4-Methylcyclohexanone was converted to an acyloin both by hydrolysis[16] of its monobromination product and by thallium nitrate oxidation.[17] Hydroxy ketone prepared by either method, as crude oily product or redistilled from solid dimer, gave under all conditions tried a mixture (~1:1) of **10**[18] and its isomer **11**.[19] The well-known, facile acyloin isomerization was apparently occurring during the preparation and/or use of the hydroxy ketone, resulting in formation of **10** and **11** from a mixture of **12** and **13**. In all the cases previously cited the acyloin was either symmetrical or one (*e.g.*, **6**) in which one isomer was favored at equilibrium.



10 11 12 13

To circumvent this isomerization problem, we attempted to generate and trap the specific acyloin anion putatively generated by reaction of epoxyacetate **14**[20] with nucleophilic reagents, as shown in Scheme III. Treatment of **14** with various amounts of butyllithium followed by 3 afforded no furan, although the formation of 56% 5-methylnonan-5-ol plus 15% hexan-2-one in one reaction suggested that at least the initial stages of the desired reaction sequence were occurring. Treatment of **14** with sodium ethoxide in an aprotic medium afforded 30% of the familiar mixture of **10** and **11**. Efforts to overcome this acyloin isomerization limitation to the furan synthesis are in progress, as are studies of the use of β-alkoxyvinylphosphonium salts in the synthesis of other heterocycles.

Scheme III



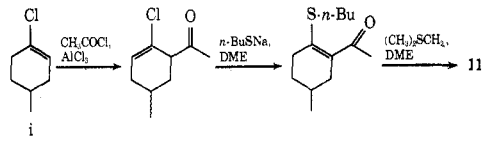
14

Typical Procedure for Furan Synthesis. The following procedure is suitable for any of the three phosphonium salt reagents. A mixture of 0.300 g (6.5×10^{-4} mol) of **2**, 0.025 g (5.5×10^{-4} mol) of a 50% mineral oil dispersion of sodium hydride, and 0.165 g (5×10^{-4} mol) of **6** in 25 ml of anhydrous dimethoxyethane was stirred for 72 hr at room temperature under nitrogen until tlc no longer showed **6**. The mixture was filtered and evaporated, and the residue was dissolved in 50 ml of benzene to which was then added a pinch of *p*-toluenesulfonic acid and 4 g of Linde 4A Molecular Sieves. This mixture was heated at reflux for 2 hr and filtered rapidly through 20 g of Florisil, which was then washed with five 30-ml portions of ether. The filtrates were evaporated and the residue was purified by preparative layer chromatography on silica gel which had been treated with potassium hydroxide[21] to afford 0.113 g (70%) of **5**: mp 117–119°; ir (KBr) 6.0, 6.2, 11.5, and 11.55 μ; nmr ($CDCl_3$) 0.55 (s), 0.7–2.8 (m), 1.2 (s), 5.8 (s, 1), 6.25 (s, 1), and 7.1–7.4 ppm (m, 2).

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

References and Notes

(1) D. L. Storm and T. A. Spencer, *Tetrahedron Lett.*, 1865 (1967).
(2) S. T. Murayama and T. A. Spencer, *Tetrahedron Lett.*, 4479 (1969).
(3) T. A. Spencer, R. A. J. Smith, D. L. Storm, and R. M. Villarica, *J. Amer. Chem. Soc.*, **93**, 4856 (1971).
(4) M. E. Garst and T. A. Spencer, *J. Amer. Chem. Soc.*, **95**, 250 (1973).
(5) E. E. Schweizer, A. T. Wehman, and D. M. Nycz, *J. Org. Chem.*, **38**, 1583 (1973), and previous papers in this series.
(6) J. M. Swan and S. H. B. Wright, *Aust. J. Chem.*, **24**, 777 (1971). These workers also prepared $EtOCH{=}CHP^+Ph_3Br^-$
(7) J. P. Snyder and H. F. Bestman, *Tetrahedron Lett.*, 3317 (1970).
(8) All new (unreferenced) compounds were characterized by ir and nmr spectra and by combustion analysis (solids) or high resolution mass spectroscopy (liquids).
(9) Aldrich Chemical Co., Milwaukee, Wis.
(10) A. Padwa and R. Hartman, *J. Amer. Chem. Soc.*, **88**, 3759 (1966).
(11) N. L. Allinger, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 840.
(12) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1266 (1961).
(13) Steraloids, Inc., Pawling, N. Y.
(14) See, *e.g.*, T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds, Vol. II Terpenes," Academic Press, New York, N. Y., 1972.
(15) Pfaltz and Bauer, Inc., Flushing, N. Y.
(16) P. D. Bartlett and G. F. Woods, *J. Amer. Chem. Soc.*, **62**, 2933 (1940).
(17) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Org. Chem.*, **37**, 3381 (1972).
(18) Identified by comparison with **10** purchased from the source cited in ref 15.
(19) Furan **11** was also prepared for purposes of identification by the following route: i [prepared by the method of M. S. Newman, G. Fraenkel, and W. N. Kirn, *J. Org. Chem.*, **28**, 1851 (1963)] → **11**.



i

(20) A. L. Draper, W. J. Heilman, W. E. Schaefer, H. J. Shine, and J. N. Shoolery, *J. Org. Chem.*, **27**, 2727 (1962).
(21) E. Stahl, "Thin-layer Chromatography," Academic Press, New York, 1965, pp 36, 37.

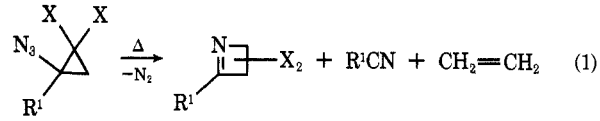
Department of Chemistry **Michael E. Garst**
Dartmouth College **Thomas A. Spencer***
Hanover, New Hampshire 03755

Received November 6, 1973

Stereochemical Aspects of the Photochemical and Thermal Fragmentation of Cyclopropyl Azides[1]

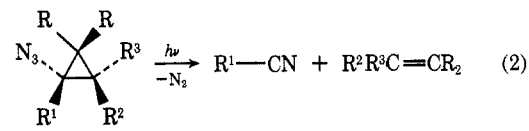
Summary: Photolysis of cyclopropyl azides results in high yields of nitrile and olefin derived from fragmentation of the cyclopropane ring in contrast to their thermal decomposition which leads to 1-azetine and/or fragmentation; both the photochemical and the thermal fragmentation are stereospecific.

Sir: Several examples[2-4] of the thermal decomposition of cyclopropyl azides **1** have recently been reported. In most of these cases formation of the ring-expanded 1-azetine predominates with minor amounts of nitrile and olefin present (eq 1). The availability of stereochemically pure



(1)

1



(2)

1a, R^1 = Ph; R^2 = R^3 = H; R = Cl
b, R^1 = Me; R^2 = Me; R^3 = H; R = Cl
c, R^1 = Me; R^2 = H; R^3 = Me; R = Cl
d, R^1 = R^2 = R^3 = Me; R = H
e, R^1 = Ph; R^2 = R^3 = Me; R = H

cyclopropyl azides[5] led us to investigate their photochemical and thermal fragmentation. The effect of ring substituents and determination of the stereochemistry of the resultant olefins provide an insight into the scope and mechanism of these reactions.

Concurrently with the thermolysis of **1**,[2] we investigated the photolysis of azides **1a–e** (sealed tube) at 3500 Å. Only the corresponding nitriles and olefins in yields of ~90% were obtained. No 1-azetines could be observed in the pmr spectra of the products.[6] This is in sharp contrast to