Tetrahedron Letters, Vol. 34, No. 30, pp. 4837-4840, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Single-Step Synthesis of 4-Hydroxycyclopentenones from 3-Ethoxycarbonyl-2-oxo-propylidenetriphenylphosphorane and Glyoxals

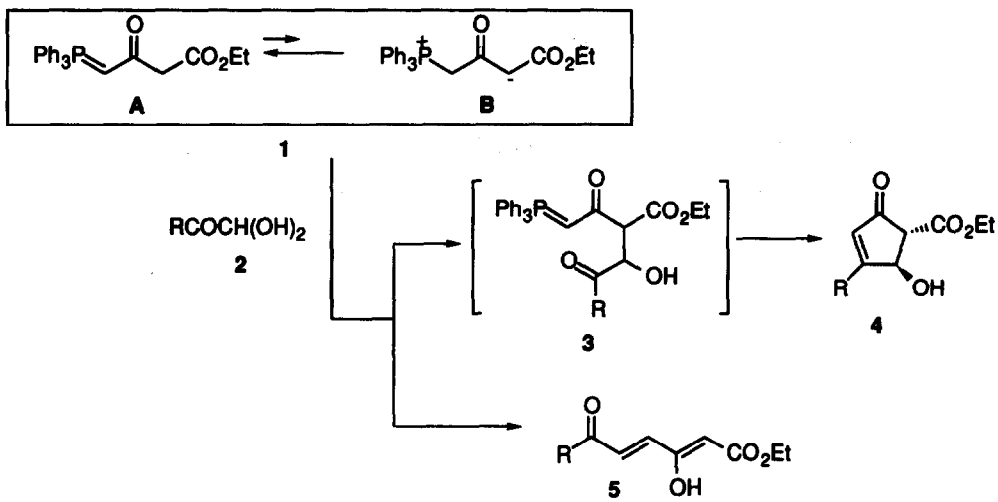
Minoru Hatanaka,* Yasuhiro Tanaka, Yuichiro Himeda[1] and Ikuo Ueda*
The Institute of Scientific and Industrial Research, Osaka University,
Mihogaoka, Ibaraki, Osaka 567, Japan

Abstract: *3-Ethoxycarbonyl-2-oxo-propylidenetriphenylphosphorane undergoes a [3+2]-annulation reaction with a variety of glyoxals to give 4-hydroxycyclopentenones in good to moderate yields.*

Formation of five-membered carbocycles attracts continuous interest of organic chemists.[2] Several phosphoranes are provided as efficient annulation reagents for the construction of 5-membered carbocyclic ring.[3] We have also demonstrated that the [3+2]-annulation reaction using allylidenetriphenylphosphorane and α-haloketones may be used to advantage for the regioselective preparation of the substituted cyclopentadienes[4] and cyclopentenones.[5] In this reaction the allylidenephosphorane takes part as a bifunctional reagent *via* alkylation at the γ-position of the phosphorane and subsequent intramolecular Wittig reaction. It is also known that 2-oxoalkylidenetriphenylphosphoranes show ambident character and especially in the presence of base react with α,β-unsaturated aldehydes to give cyclohexenones.[6] However, the synthetic utility of these phosphoranes in annulation reactions has been little explored. Here we report that 3-ethoxycarbonyl-2-oxo-propylidenetriphenylphosphorane undergoes a [3+2]-annulation reaction with glyoxals under very mild and neutral conditions, providing a single step synthesis of 4-hydroxycyclopentenones.

When 3-ethoxycarbonyl-2-oxo-propylidenetriphenylphosphorane (**1**) was treated with 4-chlorophenylglyoxal hydrate (**2a**) in THF at room temperature for 24 h, the *trans* 4-hydroxycyclopentenone **4a** was obtained in 73% yield together with 15% yield of the normal Wittig product **5a**. In the presence of 1 equiv of NaH, the yield of **4a** was reduced to 23%. This is sharply contrast to the fact that the known annulation with α,β-unsaturated aldehydes gives better yields of cyclohexenones in the presence of base such as NaH and NaOH *via* the carbanion formation at the γ-position of the phosphorane **1**.[6] The ratio of **4a** to **5a** largely depended on the solvent used (Table 1). In the aprotic

solvents both **4a** and **5a** were obtained in all cases and increasing polarity of the solvent trended to prefer the formation of the cyclopentenone **4a**. Finally we found that alcohols were solvents of choice and in methanol or ethanol **4a** was obtained exclusively in good yield.

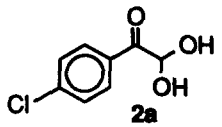
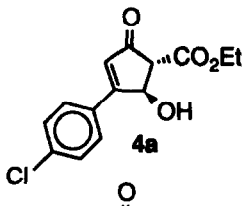
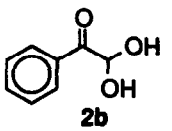
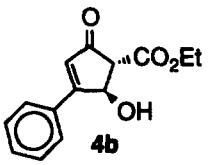
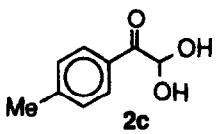
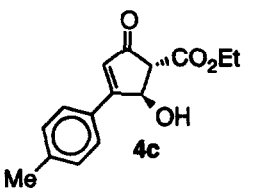
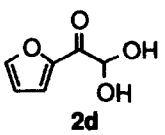
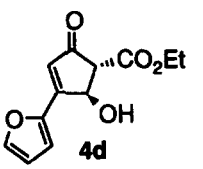
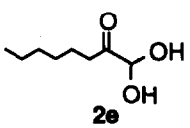
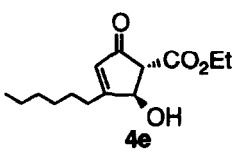
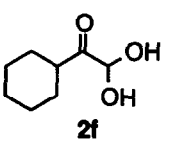
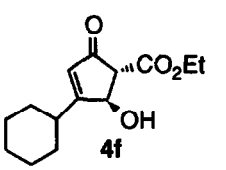


As can be seen from Table 1, the annulation reaction is applicable to a variety of glyoxals.[7] Arylglyoxals gave good yields of the *trans* 4-hydroxycyclopentenones. Alkylglyoxals also underwent annulation reaction to give the corresponding *trans* 4-hydroxycyclopentenones. In all cases the normal Wittig products **5** were not obtained when the reactions were carried out in methanol or ethanol.

A possible mechanism for the annulation reaction is outlined above. It appears from no requirement of an additive base that the annulation of the phosphorane **1** with glyoxals bases on the ambident character of the phosphorane. The tautomeric form **1B** in low equilibrium concentration may take part in an initial Aldol reaction at the γ-position of the phosphorane and the resulting aldol **3** is trapped effectively by the following intramolecular Wittig reaction to furnish the 4-hydroxycyclopentenone **4**.[8] Predominant formation of **4** in the polar medium seems to be mainly due to the increasing equilibrium concentration of **1B**.[9]

The annulation reaction was carried out by the simple procedure. In a typical run, a solution of the phosphorane **1** (390 mg, 1.0 mmol) in methanol (20 ml) was added dropwise to a stirred solution of 4-chlorophenylglyoxal hydrate (**2a**, 187 mg, 1.0 mmol) in methanol (10 ml) and the stirring was continued at room temperature for 24 h. Evaporation of the solvent and flash chromatography of the remaining residue gave the 4-hydroxycyclopentenone **4a** (244 mg, 87%).[10]

Table 1 . Synthesis of 4-Hydroxycyclopentenones.

Substrate	Product [a]	Condition [b]	Yield (%) [c]
 **2a**	 **4a**	THF MeCN DMF EtOH MeOH	73 [d] 79 [e] 77 [f] 80 87
 **2b**	 **4b**	MeOH	79
 **2c**	 **4c**	MeOH	70
 **2d**	 **4d**	MeOH	69
 **2e**	 **4e**	MeOH EtOH	43 53
 **2f**	 **4f**	EtOH	45

[a] All compounds showed analytical and spectroscopic data consistent with the assigned structures. [b] All reactions were carried out in the depicted solvent at room temp. for 24 h. [c] Isolated yield. [d] 15% of the Wittig product **5a** was isolated (ratio of **4a** to **5a** : 4.8/1). [e] 8% of **5a** was isolated (ratio of **4a** to **5a** : 9.8/1). [f] 6% of **5a** was isolated (ratio of **4a** to **5a** : 12.8/1).

In summary, we have developed an efficient [3+2]-annulation sequence for the synthesis of 4-hydroxycyclopentenones. This approach can provide the preparation of a wide variety of cyclopentenones by the extremely simple procedure from the phosphorane **1** and readily available glyoxals.

References and Notes

1. Present address: Department of Molecular Engineering, National Institute of Materials and Chemical Research, Higashi 1, Tsukuba, Ibaraki 305, Japan.
2. (a) For excellent reviews, see: Ramaiah, M. *Synthesis*, **1984**, 529. Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. Little, R. D. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds., Pergamon, Oxford, 1991, Vol. 5, 239-270. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset., J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438. (d) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. (e) Beak, P; Burg, D. A. *J. Org. Chem.* **1989**, *54*, 1647. (f) Tamao, K.; Kobayashi, K.; Ito, *J. Am. Chem. Soc.* **1988**, *110*, 1286. (g) Y. Buchwald, S. L.; Lum, R. T.; Fisher, R. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, *111*, 9113. (h) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336. (i) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514. (j) Mathau , J. *J. Chem. Soc., Chem. Commun.* **1990**, 1264. (k) Ejiri, S.; Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 8707.
3. Fuchs, P. L., *J. Am. Chem. Soc.* **1974**, *96*, 1607. Marino, J. P.; Ferro, M. P., *J. Org. Chem.* **1981**, *46*, 1828. Altenbach, H.-J. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 940. Bestmann, H. J.; Schade, G.; Schmid, G. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 822. Piers, E.; Abeysekera, B. *Can. J. Chem.* **1982**, *60*, 1114.
4. Hatanaka, M.; Himeda, Y.; Ueda, I. *J. Chem. Soc. Chem. Commun.* **1990**, 526.
5. Hatanaka, M.; Himeda, Y.; Ueda, I. *Tetrahedron Lett.* **1991**, *32*, 4521.
6. Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. *J. Org. Chem.* **1983**, *48*, 788. Pietrusiewicz, K. M.; Salammonczyk. I. *J. Org. Chem.* **1988**, *53*, 2837.
7. For preparation of alkylglyoxals, see: Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215.
8. The stereochemical results might be explained in terms of the easy enolization of the β-keto ester moiety in the intermediate **3**. The subsequent Wittig cyclization could undergo through the stable conformer.
9. Reichardt, C., *Solvents and Solvent Effects in Organic Chemistry*, 2 ed., VCH, Weinheim, 1988.
10. Spectral data for **4a**: ^{1}H NMR ($CDCl_3$, 360 MHz,) δ 1.33 (t, J=7.1 Hz, 3H), 2.48 (d, J=7.0 Hz, 1H), 3.56 (d, J=2.5 Hz, 1H), 4.27 (q, J=7.1 Hz, 2H), 5.74 (dd, J=7.0, 2.5 Hz, 1H), 6.46 (d, J=1.0 Hz, 1H), 7.44-7.48 (m, 2H), 7.68-7.72 (m, 2H); IR (KBr) 3400, 1730, 1670, 1595 cm^{-1}. colorless needles, mp. 115.0-116.2 °C.

(Received in Japan 17 March 1993)