the mixture was cooled at 0 °C. Filtration of the precipitated product followed by washing with ether afforded **5** (285 mg, 84%) as a crystalline monohydrochloride salt. Recrystallizaton from methanol gave the analytical sample, mp >280 °C. UV λ_{max} (pH 1) 271 nm (ϵ 14620), 234 (ϵ 17850); λ_{min} (pH 1) 250 (ϵ 8000); λ_{max} (pH 7) 269 (ϵ 8920), 230 (ϵ 22460); λ_{min} (pH 7) 249 (ϵ 6000); λ_{max} (pH 13) 285 (ϵ 6920), 257 (ϵ 6620), 223 (ϵ 23540); λ_{min} (pH 13) 271 (ϵ 6120), 249 (ϵ 6450).

Anal. Calcd for $C_{11}H_{14}N_4O_5{\cdot}HCl$: C, 41.45; H, 4.74; N, 17.58. Found: C, 41.45; H, 4.85; N, 17.50.

Acknowledgment. We are indebted to Dr. Jack J. Fox for his continued interest. We also thank Ms. Iris Wempen for her valuable assistance in the preparation of synthetic precursors and Mr. Marvin Olsen for recording the NMR spectra.

Registry No. **1**·HCl, 74458-08-5; **3**·HCl, 84649-09-2; **4**·HCl, 84649-10-5; **5**·HCl, 84649-11-6; **6**α, 84710-19-0; **6**β, 84710-20-3; **7**α, 84710-21-4; **7**β, 84710-22-5; **8**α, 84649-12-7; **8**β, 84710-23-6; **9**α, 84649-13-8; **9**β, 84710-24-7; **10**α, 84649-14-9; **10**β, 84649-15-0; **11**α, 74458-06-3; **12**α, 84649-16-1; **12**β, 84649-17-2; **14**, 84649-18-3; **15**, 77691-00-0; **16**, 83060-69-9; **17**, 84649-19-4; **18**, 84649-20-7; **19**, 84649-21-8; **20**, 84649-22-9; **21**, 84649-23-0; **22**, 84649-24-1; **23**, 84649-25-2; **24**, 84649-26-3; **27**, 84680-83-1; **28**, 84649-27-4; benzoyl isothiocyanate, 532-55-8; triethyl orthoformate, 122-51-0; *N,N'*-thiocarbonyldiimidazole, 6160-65-2; glycine ethyl ester hydrochloride, 623-33-6; formamidine acetate, 3473-63-0.

(3-Carbethoxy-2-oxopropylidene)triphenylphosphorane. A Reagent for "3 + 3" Cyclohexenone Annulation[1]

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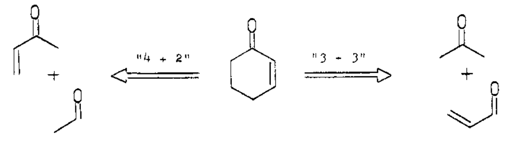
Received May 17, 1982

The development of a new cyclohexenone annulation reaction of general scope which utilizes α,β-unsaturated aldehydes and (3-carbethoxy-2-oxopropylidene)triphenylphosphorane is reported.

The cyclohexenone system has been a target of innumerable synthetic endeavors for years.[2] In a retrosynthetic analysis of cyclohexenones,[3] "4 + 2" and "3 + 3" disconnections are ultimately designated as the two principal approaches to these compounds (Scheme I). In sharp contrast to the "4 + 2" annulation reaction which is commonly known as the Robinson annulation[4] and which has proven extraordinarily useful in synthetic practice,[2,5] the "3 + 3" annulation of cyclohexenones has rarely been addressed as an alternative.[6] From the many compounds which are likely to compose a pair of reactants suitable for a "3 + 3" annulation reaction, esters of acetoacetic acid and α,β-unsaturated aldehydes stand out for their simplicity and ready accessibility. However, only a few individual examples of the synthesis of cyclohexenones directly from these substrates could be found in the literature.[7] We reasoned, therefore, that rendering such a route to cyclohexenones general would possess considerable synthetic utility.

Scheme I



It has recently been shown[8,9] that the introduction of a terminal phosphorus substituent into the ethyl acetoacetate molecule produced a synthetically attractive equivalent of this simple unit. Such a γ-phosphorylated ethyl acetoacetate, e.g., **1**, was found to form a dianion under relatively mild conditions and then to react with aldehydes and ketones exclusively at its phosphorylated terminus to give δ,γ-unsaturated β-keto esters with a simultaneous removal of the auxiliary phosphorus grouping.[8,9] The reaction of **1** with conjugated aldehydes[8] followed exactly the same pattern (eq 1). Apparently the reaction between the two harder centers of these ambident reactants competed favorably with other possible reaction paths. It was therefore logical to expect that a replacement of the highly nucleophilic phosphonate carbanion of **1** with the more delocalized ylide group[10] (such as in **2**) would

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(1) Presented in part at the International Conference of Phosphorus Chemistry, Durham, NC, June 1–5, 1981.

(2) For an excellent review of annulation, see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(3) Corey, E. J.; Johnson, A. P.; Long, K. *J. Org. Chem.* **1980**, *45*, 2051.

(4) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.

(5) Gawley, R. E. *Synthesis* **1976**, 777.

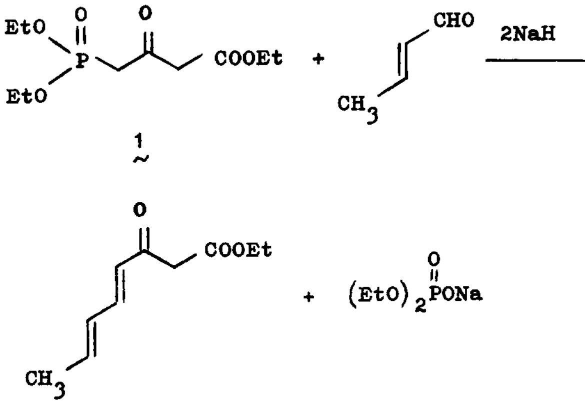
(6) For a recent example, see: Martin, S. F.; Desai, S. *J. Org. Chem.* **1977**, *42*, 1664.

(7) For some mostly two-step preparations, see: (a) Kryshtal, G. V.; Kulganek, V. V.; Kucherov, V. F.; Yanovskaya, L. A. *Synthesis* **1979**, 107. (b) Bohlmann, F.; Przewosky, K. *Chem. Ber.* **1964**, *97*, 1176. (c) Mousseron, M.; Jacquier, R.; Fontaine, A.; Zagdoun, R. *Bull. Soc. Chim. Fr.* **1954**, *21*, 1246. (d) Meyer, W. L.; Sigel, C. W.; Hoff, R. J.; Goodwin, T. E.; Manning, R. A.; Schroeder, P. G. *J. Org. Chem.* **1977**, *42*, 4131.

(8) Bodalski, R.; Pietrusiewicz, K. M.; Monkiewicz, J.; Koszuk, J. *Tetrahedron Lett.* **1980**, *21*, 2287.

(9) van der Goorbergh, J. A. M.; van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 3621.

0022-3263/83/1948-0788$01.50/0



(1)

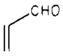
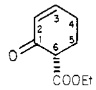
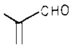
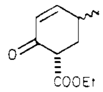
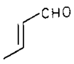
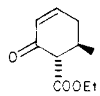
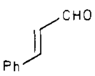
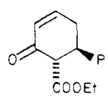
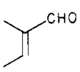
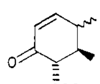
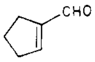
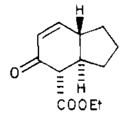
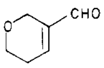
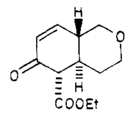
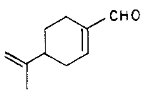
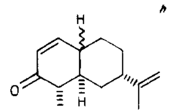
markedly alter this pattern[11] and might even create a situation in which, in such a reaction, the enolate (α) addition across the conjugated double bond would precede the Wittig olefination.[12,15] Scheme II illustrates this concept.

The reaction sequence outlined in Scheme II could thus be considered as a route to the cyclohexenone system. Most importantly, however, it could provide a convenient access to 6-carbalkoxycyclohex-2-en-1-ones which are otherwise difficult to prepare. The utilization of this simple method for the synthesis of 6-carbethoxycyclohex-2-en-1-ones from the α,β-unsaturated aldehydes and the synthetic equivalent of ethyl acetoacetate **2** is reported herein.

The ylide **2**,[16] a yellow-orange air-stable solid [mp 103 °C; ^{31}P NMR (CDCl$_3$) δ 14.6] was conveniently prepared from ethyl γ-bromoacetoacetate and triphenylphosphine by using the published procedure.[16] This reagent was found to react smoothly, in the presence of added base,[17] with a variety of α,β-unsaturated aldehydes **3** to give carbethoxycyclohexenones **5** in fair yields (Table I).

An examination of the data in Table I reveals that the reaction is reasonably general and that both acyclic and cyclic enals may be employed with equal success. It is also evident that in some cases high stereoselectivity can be achieved. In each of the products studied the carbethoxy group and the neighboring 5-alkyl substituent were found to occupy pseudoequatorial positions. The analogous behavior of the 5-Ph substituent (entry 4) seems to reflect similar steric requirements of the phenyl group in this position.[20]

Table I

entry	starting enal **3**	cyclohexenone **5**[a]	yield,[b] %
1			21
2		 [c]	25
3		 [d]	55[e]
4			62
5		 [c]	31
6			35
7		 [f]	50
8[g]		 [h]	30

[a] Satisfactory ^{1}H NMR, ^{13}C NMR, and mass spectral data were obtained for all compounds. Ratios of isomeric products were determined from the pertinent ^{1}H and ^{13}C NMR spectra. Stereochemical conclusions were based mainly on vicinal interproton coupling data derived from the analysis of the well-separated H-3 and H-6 resonances.[22] [b] The figures given represent unoptimized yields of isolated materials. [c] 1:1 mixture of the two isomers. [d] Product of isomeric purity greater than 90%. [e] The yield in this synthesis was increased to 83% when the ester ethyl group in **2** was replaced with a bulky menthyl group. [f] Containing ca. 8% of the cis isomer. [g] The synthesis carried out in the presence of 15-crown-5. [h] Mixture of two isomers in a 8:3 ratio; see ref 22 and 23 for some additional stereochemical details.

One interesting aspect of this study should be mentioned here: aprotic conditions and the presence of an excess of a base during the course of the reaction are prerequisite to its successful completion. This infers that, in fact, it is the intermediate enolate **4**, and not its conjugate acid, which undergoes the internal Wittig reaction as visualized in Scheme II.[21]

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(10) A lower reactivity of phosphoranes toward carbonyl groups as compared with their P(O)-stabilized counterparts is well documented. See for example: (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (b) Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1976**, 825.

(11) Cf.: Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1974**, *39*, 821.

(12) Recent findings by Bohlmann and Zdero[13] substantiate considerably this expectation. Some (3-carbomethoxyallylidene)triphenylphosphoranes were found to produce cyclohexadienes upon treatment with α,β-unsaturated aldehydes[13] while only acyclic polyene products were obtained when the corresponding phosphonates were used as substrates.[14]

(13) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1973**, *106*, 3779.

(14) (a) van den Tempel, P. J.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 293. (b) Corey, E. J.; Katzenellenbogen, J. A.; Roman, S. A.; Gilman, N. W. *Tetrahedron Lett.* **1971**, 1821. (c) Edwards, J. A.; Schwarz, V.; Fajkos, J.; Maddox, M. L.; Fried, J. H. *Chem. Commun.* **1971**, 292. Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984.

(15) A number of reactions of similar type, combining the Michael and Wittig reactions of some allylidenetriphenylphosphoranes have recently appeared: (a) Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1971**, *54*, 1767. (b) Dauben, W. G.; Ipaktschi, J. *J. Am. Chem. Soc.* **1973**, *95*, 5088. (c) Dauben, W. G.; Hart, D. J.; Ipaktschi, J.; Kozikowski, A. P. *Tetrahedron Lett.* **1973**, 4425. See also ref 5, 6, and 12.

(16) Serratosa, F.; Sole, E. *Ann. Real Soc. Espan. Fis. Quim., Ser. B* **1966**, *62*, 431; *Chem. Abstr.* **1967**, *66*, 2623.

(17) The most effective base for promoting this transformation was, in our hands, an excess of sodium hydride (2 equiv) followed by the addition of a few drops of water. Annulation did not proceed to a detectable extent without added water. When D_2O was used in place of H_2O, no deuterium incorporation resulted. It can reasonably be assumed that a complex base consisting of NaH–NaOH acted as the effective base[18] in the above transformations.[19]

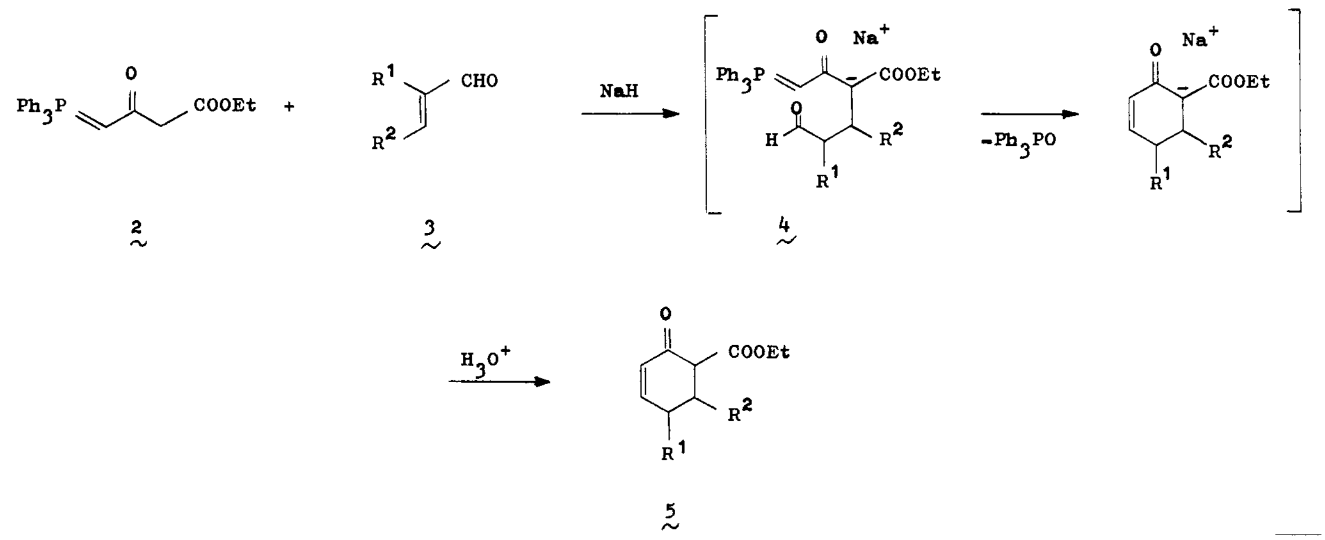
(18) For a detailed discussion on the analogous NaH–RONa complex bases see: Caubiere, P. *Top. Curr. Chem.* **1978**, *73*, 105.

(19) An additional promoting influence of 15-crown-5 was also observed (see Table I, entry 8).

(20) For a series of 6-carbethoxy-3,5-diarylcyclohex-2-en-1-ones obtained by the analogous "3 + 3" coupling of **1** with a series of chalcones, a pseudoequatorial orientation of the 5-aryl substituent was uniformly evidenced by ^{1}H NMR: Bodalski, R.; Pietrusiewicz, K. M.; Monkiewicz, J.; Koszuk, J. *Pol. J. Chem.*, in press.

(21) More detailed discussion on this and other aspects of the chemistry of ylides stabilized by a keto ester enolate substituent will be presented elsewhere: Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R., manuscript in preparation.

Scheme II



A general experimental procedure is as follows. To a stirred solution of the ylide **2** (4 mmol) in THF (35 mL) was added an equimolar amount of the appropriate α,β-unsaturated aldehyde **3**, and the resulting solution was warmed to about 35 °C. After the addition of an excess (8 mmol) of sodium hydride followed by a small amount (1–3 drops) of water, cautiously added, the reaction mixture was stirred at that temperature. When the ylide was completely consumed (TLC), usually after 0.5–1 h, the reaction mixture was acidified with dilute HCl and then partitioned between ether and brine. The aqueous phase was further extracted with ether, and the combined ethereal extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude cyclohexenones **5** thus obtained were purified by short-column chromatography (silica gel; CCl_4–ether, 5:1).

In conclusion, the one-step procedure described here provides convenient and, in large part, stereoselective access to a diversity of structurally different cyclohexenones featuring an *unsubstituted* double bond conjugated with a β-keto ester functionality. It should add to the arsenal of synthetic methods of potential utility in the total synthesis of natural products. Further studies along this line are underway.

Acknowledgment. We are indebted to Professor E. L. Eliel for the gift of perillaldehyde and we thank Professor J. Michalski for his kind interest in this work.

Registry No. **2**, 13148-05-5; **2** menthyl ester, 84254-78-4; **3** (R^1 = H; R^2 = H), 107-02-8; **3** (R^1 = CH_3; R^2 = H), 78-85-3; **3** (R^1 = H; R^2 = CH_3), 4170-30-3; **3** (R^1 = H; R^2 = Ph), 104-55-2; **3** (R^1 = CH_3; R^2 = CH_3), 1115-11-3; **3** (R^1, R^2 = $(CH_2)_3$), 6140-65-4; **3** (R^1, R^2 = $CH_2OCH_2CH_2$), 13417-49-7; **3** (R^1, R^2 = $CH_2CH_2CH(C(Me){=}CH_2)CH_2$), 2111-75-3; **5** ($R^1$, R^2 = H), 3400-80-4; **5** (R^1 = Me; R^2 = H) (isomer 1), 84254-67-1; **5** (R^1 = Me; R^2 = H) (isomer 2), 84254-68-2; **5** (R^1 = H; R^2 = Me), 84254-69-3; **5** (R^1 = H; R^2 = Ph), 84254-70-6; **5** (R^1, R^2 = Me) (isomer 1), 84254-71-7; **5** (R^1, R^2 = Me) (isomer 2), 84366-80-3; **5** (R^1, R^2 = $CH_2CH_2CH_2$), 84254-72-8; **5** (R^1, R^2 = $CH_2OCH_2CH_2$), 84254-73-9; **5** (R^1, R^2 = $CH_2CH_2CH(C(Me){=}CH_2)CH_2$) (isomer 1), 84254-74-0; **5** (R^1, R^2 = $CH_2CH_2CH(C(Me){=}CH_2)CH_2$) (isomer 2), 84254-75-1; **5** (R^1, R^2 = $CH_2OCH_2CH_2$) (cis isomer), 84254-76-2; **5** (R^1 = H; R^2 = Me) menthyl ester, 84254-77-3.

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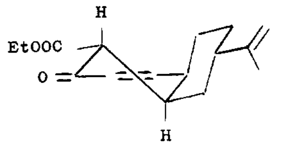
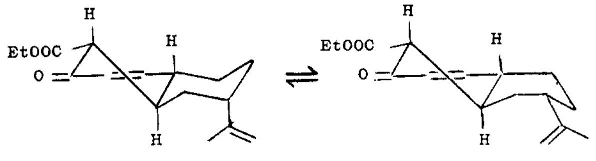
(22) Observation of $^3J_{H\text{-}5,H\text{-}6} \geq 10$ Hz led to the assignment of pseudoaxial disposition for both coupled nuclei in relevant cases. Also, values of 0–1.5 and ~5 Hz found for $^3J_{H\text{-}3,H\text{-}4}$ allowed for the assignment of pseudoaxial and pseudoequatorial position, respectively, for the proton H-4 in question: Jackman, L. M.; Sternhell, S. "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1969; Chapter 4-2.

(23) Distinct signals of methylene protons δ 4.70 (br s) and δ 4.83 (unresolved m) in the ^1H NMR spectra of the major and the minor isomers, respectively, suggested equatorial and axial orientations of isopropenyl groups and allowed final formulation of the exact structure of both isomers.[24] It should be noted that the stereochemistries observed apparently resulted from the stereoelectronically controlled axial attack of anion of **2** on the conjugated double bond of perillaldehyde. Analogous axial attack of *tert*-butyl acetoacetate anion has been recorded.[7d] In contrast, in similar additions diethyl malonate anion strongly favored an equatorial approach.[25]



major



minor

(24) Humber, D. C.; Pinder, A. R. *J. Org. Chem.* **1966**, *31*, 4188.

(25) Abramovitch, R. A.; Singer, S. S.; Rogić, M. M.; Struble, D. L. *J. Org. Chem.* **1975**, *40*, 34.