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# Reductive Homocondensation of Benzylidene- and Alkylidenepyruvate Esters by a $P(NMe_2)_3$-Mediated Tandem Reaction

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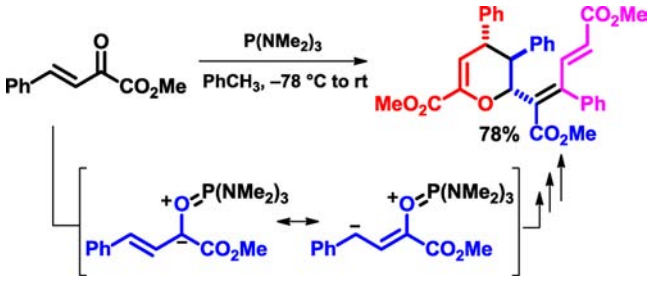
## ABSTRACT




**A reductive homocondensation of *E*-benzylidenepyruvate esters mediated by $P(NMe_2)_3$ is described. The transformation, initiated by the Kukhtin–Ramirez addition of the phosphorus reagent to the vinyl-substituted α-dicarbonyl substrate, proceeds via a resonance delocalized oxyphosphonium dienolate intermediate to provide access to diverse oxygenated heterocycles as a function of the substituent.**

Trivalent phosphorus derivatives are known to undergo an addition reaction with α-dicarbonyl compounds to give 1:1 adducts (Kukhtin–Ramirez reaction).[1] The products of this event, formulated as either dioxaphospholene **1** or oxyphosphonium enolate **1′** (Scheme 1), have been the subject of extensive structural investigation[1c,d,2] and have been shown to undergo a variety of reactions of both synthetic and mechanistic interest.[3−7] For instance, treatment of **1**/**1′** with electrophilic reagents may give rise to alkoxyphosphonium intermediates **2**, which in turn themselves may serve as electrophiles toward nucleophilic displacement (Scheme 1).[8] The resultant reactivity of intermediates **1**/**1′** has been exploited to effect epoxidation,[4] cyclopropanation,[5] formal S–Cl insertion,[6] and X–H functionalization (X = O, N) reactions.[7]

We considered the possibility of extending this basic reactivity by vinylogy.[9] In outline, Kukhtin–Ramirez addition of vinyl-substituted keto ester **3** with a trivalent phosphine reagent would generate oxyphosphonium

(1) (a) Kukhtin, V. A. *Dokl. Akad. Nauk SSSR* **1958**, *121*, 466. (b) Ramirez, F. *Pure Appl. Chem.* **1964**, *9*, 337. (c) Ramirez, F. *Acc. Chem. Res.* **1968**, *1*, 168. (d) Osman, F. H.; El-Samahy, F. A. *Chem. Rev.* **2002**, *102*, 629.

(2) (a) Ramirez, F.; Desai, N. B. *J. Am. Chem. Soc.* **1963**, *85*, 3252. (b) Ramirez, F.; Patwardhan, A. V.; Kugler, H. J.; Smith, C. P. *Tetrahedron Lett.* **1966**, *7*, 3053.

(3) (a) Ramirez, F.; Desai, N. B. *J. Am. Chem. Soc.* **1960**, *82*, 2652. (b) Ramirez, F.; Bhatia, S. B.; Smith, C. P. *J. Am. Chem. Soc.* **1967**, *89*, 3026. (c) Ramirez, F.; Bhatia, S. B.; Smith, C. P. *J. Am. Chem. Soc.* **1967**, *89*, 3030. (d) Lathourakis, G. E.; Litinas, K. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 491. (e) Zhang, W.; Shi, M. *Chem. Commun.* **2006**, 1218.

(4) (a) Mark, V. *J. Am. Chem. Soc.* **1963**, *85*, 1884. (b) Newman, M. S.; Blum, S. *J. Am. Chem. Soc.* **1964**, *86*, 5598. (c) Ramirez, F.; Gulati, A. S.; Smith, C. P. *J. Org. Chem.* **1968**, *33*, 13. (d) Muller, A. J.; Nishiyama, K.; Griffin, G. W.; Ishikawa, K.; Gibson, D. M. *J. Org. Chem.* **1982**, *47*, 2342. (e) Liu, X.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 4560.

(5) (a) Corre, E.; Foucaud, A. *J. Chem. Soc. D* **1971**, 570. (b) Fauduet, H.; Burgada, R. *Synthesis* **1980**, 642.

(6) (a) Harpp, D. N.; Mathiaparanam, P. *J. Org. Chem.* **1971**, *36*, 2540. (b) Harpp, D. N.; Mathiaparanam, P. *J. Org. Chem.* **1972**, *37*, 1367.

(7) Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10605.

(8) Burger, K. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: London, 1979; pp 467–510.

(9) (a) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1. (b) Krishnamurthy, S. *J. Chem. Educ.* **1982**, *59*, 543. (c) Bruneau, P.; Taylor, P. J.; Wilkinson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2263.

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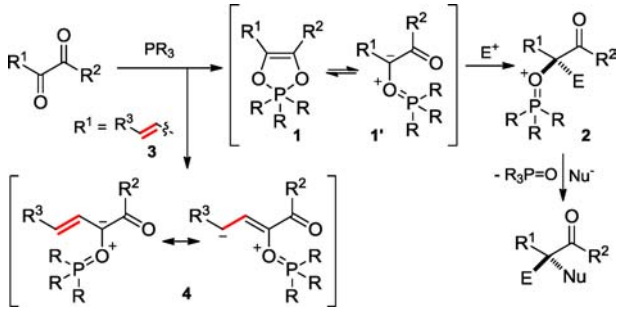
dienolate adduct **4**, wherein a formal negative charge would be delocalized over both α- and γ-positions with respect to the ester moiety (Scheme 1). In analogy to the reactivity of canonical dienolate intermediates,[10] we considered the possibility of engaging the γ-nucleophilicity of **4**, thereby leading to new transformations. Here, we report a P(III)-mediated reductive homocondensation reaction of unsaturated keto esters emanating from intermediate **4** that evidence this proposed γ-nucleophilicity.[11,12]

**Scheme 1.** Vinylogation of Kukhtin–Ramirez Redox Adducts



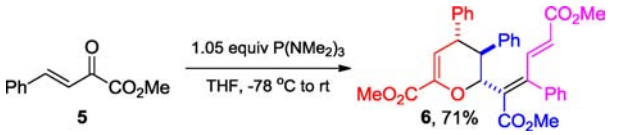
As a point of departure, we investigated the reaction of methyl *E*-benzylidenepyruvate **5** with tris(dimethylamino)-phosphorus under typical Kukhtin–Ramirez conditions. Specifically, $P(NMe_2)_3$ was added to a solution of substrate **5** at −78 °C in tetrahydrofuran. Upon warming, the formation of dihydropyran **6** was observed (Scheme 2). This product, whose structure was confirmed by single-crystal X-ray analysis, corresponds to a reductive trimerization of substrate **5**; it is isolated as a single diastereoisomer. In surveying this reactivity, we have found that tris(dimethylamino)phosphorus is uniquely suited to this transformation; trimethyl phosphite by contrast is not an effective promoter (Table 1, entry 2). A range of solvents were found to be serviceable, but reactions performed in toluene were found to be highest yielding (Table 1, entry 5). Consistent with the stoichiometry of the trimerization process, which requires the consumption of two molecules of tris(dimethylamino)phosphorus for each molecule of dihydropyran formed, the use of 0.7 equiv of $P(NMe_2)_3$ relative to the benzylidenepyruvate substrate was found to only minimally impact the observed yield.

(10) (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Soriente, A.; De Rosa, M.; Villano, R.; Scettri, A. *Curr. Org. Chem.* **2004**, *8*, 993. (c) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (d) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43. (e) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

(11) The γ-nucleophilicity of allylic ylides is reported; see: (a) Dauben, W. G.; Ipaktschi, J. *J. Am. Chem. Soc.* **1973**, *95*, 5088. (b) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1974**, *39*, 821. (c) Padwa, A.; Brodsky, L. *J. Org. Chem.* **1974**, *39*, 4199. (d) Moorhoff, C. M. *Synlett* **1997**, 126. (e) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Zhu, C.-Y.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408. (f) Zhu, B.-H.; Zhou, R.; Zheng, J.-C.; Deng, X.-M.; Sun, X.-L.; Shen, Q.; Tang, Y. *J. Org. Chem.* **2010**, *75*, 3454.

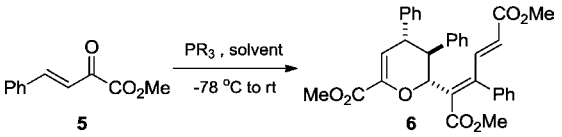
(12) For a related γ-nucleophilic intermediate, see: Winkler, T.; Bencze, W. L. *Helv. Chim. Acta* **1980**, *63*, 402.

**Scheme 2.** Reductive Trimerization of **5** with $P(NMe_2)_3$



As shown in Scheme 3, a range of *E*-benzylidenepyruvate esters with variations on both the ester group and the aryl motif are suitable substrates. Substitution of the aryl ring only modestly affects the reaction outcome, and yields of the trimerization reaction across both electron-deficient (**9**–**11**) and electron-rich (**12**–**13**) substrates are good. The yield of the corresponding furanyl derivative (**14**) by contrast is significantly diminished. In all cases investigated, the products, which contain three stereocenters and two unsymmetrical acyclic double bonds, are formed as a single observable stereoisomer.

**Table 1.** Screening of Reaction Conditions



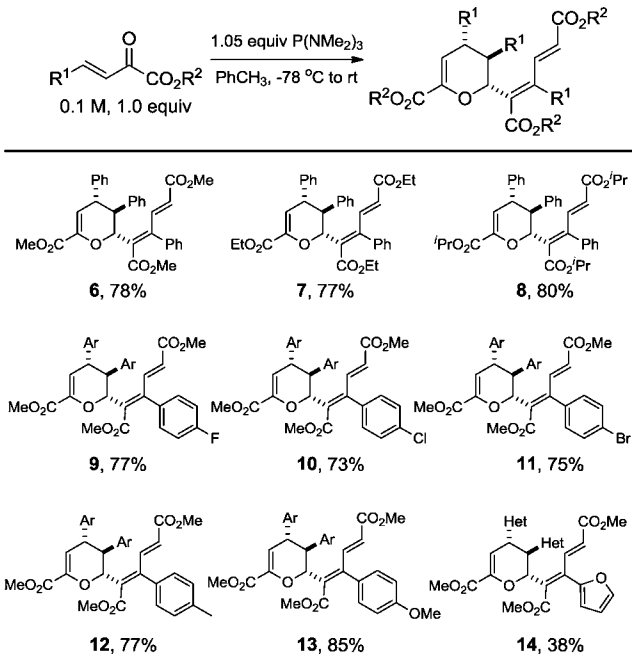
| entry | $PR_3$ | solvent | yield (%)[a] |
|---|---|---|---|
| 1 | $P(NMe_2)_3$, 1.05 equiv | THF | 71 |
| 2 | $P(OMe)_3$, 1.05 equiv | THF | <5% |
| 3 | $P(NMe_2)_3$, 1.05 equiv | $Et_2O$ | 70 |
| 4 | $P(NMe_2)_3$, 1.05 equiv | $CH_2Cl_2$ | 51[b] |
| 5 | $P(NMe_2)_3$, 1.05 equiv | $PhCH_3$ | 78 |
| 6 | $P(NMe_2)_3$, 0.70 equiv | $PhCH_3$ | 74 |

[a] Isolated yield. [b] Undetermined byproducts were observed.

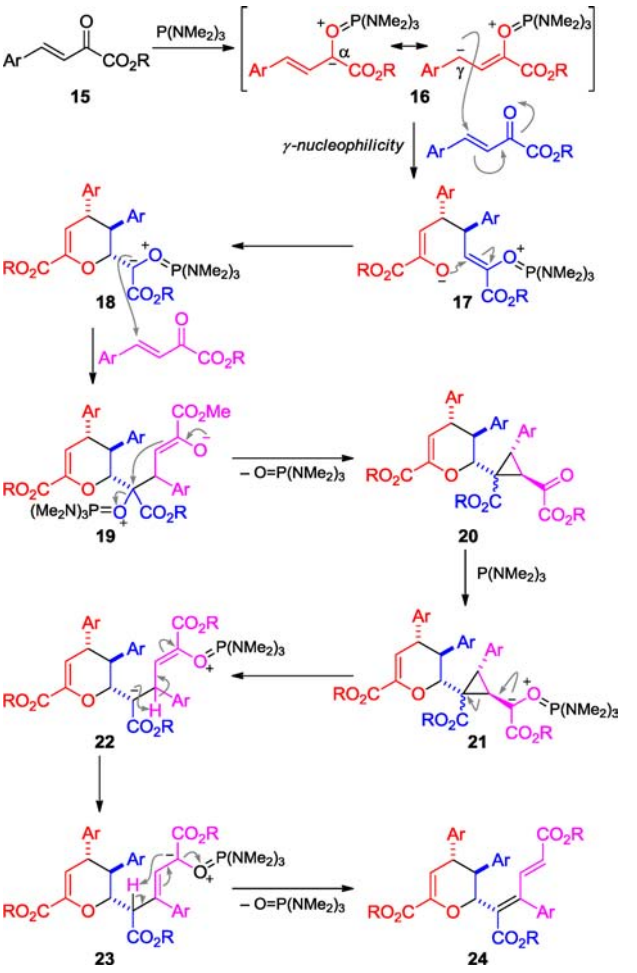
A mechanistic proposal consistent with the observed stereoselective reductive trimerization of *E*-benzylidenepyruvate esters is offered in Scheme 4.[13] The sequence is initiated by the Kukhtin–Ramirez addition of tris-(dimethylamino)phosphorus to the unsaturated keto ester substrate **15** giving oxyphosphonium dienolate intermediate **16**.[1] Subsequent conjugate addition of the nucleophilic γ-position[10–12] of **16** to an additional equivalent of substrate **15**, followed by intramolecular oxycyclization, would then give dipolar intermediate **18**. The *trans* stereochemistry about the newly formed C–C bond would be expected to be controlled by nonbonding steric interactions in the stepwise process. This sequence of events would regenerate a reactive oxyphosphonium enolate, which could then be expected to engage a third equivalent of **15** to produce **20** via stepwise polar cyclopropanation.[5]

(13) For deoxygenations by P(III) reagents, see: Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: London, 1979; pp 295–350.

**Scheme 3.** Scope of $P(NMe_2)_3$-Mediated *E*-Benzylidenepyruvate Ester Reductive Condensation




**Scheme 4.** A Proposed Pathway for the Reductive Trimerization

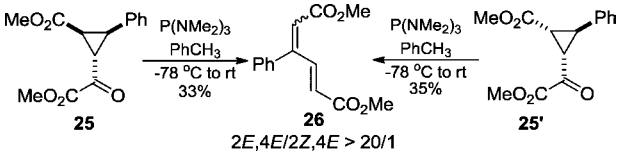



The keto ester moiety of **20** is itself susceptible to the Kukhtin–Ramirez addition with tris(dimethylamino)-phosphorus. Ring opening of the push–pull cyclopropyl intermediate **21** and final elimination then lead to the formation of **24**, terminating the trimerization sequence.[14,15]

In order to validate the terminal steps of this mechanistic sequence, we synthesized cyclopropyl α-keto ester **25**[16] and found that exposure to $P(NMe_2)_3$ gave diene **26** with a *E*/*Z* ratio greater than 20:1 (Scheme 5), albeit in low isolated yield. The diastereomeric cyclopropyl α-keto ester **25′** converges on the same result.

Consistent with this mechanistic proposal, the γ-nucleophilicity of oxyphosphonium dienolates **4** may be attenuated by increasing the steric congestion at that position. For instance, when the sterically hindered mesityl substrate **27** is reacted with 1.05 equiv of $P(NMe_2)_3$, a single diastereoisomer of the formal [4 + 1] cycloadduct **30** was isolated from the reaction in 61% yield. The relative configuration of the two stereocenters in **30** was confirmed by single-crystal X-ray analysis (Scheme 6). After initiation by the Kukhtin–Ramirez condensation of **27** with $P(NMe_2)_3$, a nucleophilic attack from the less hindered α-position of oxyphosphonium dienolate **28** to the second molecule of **27** affords intermediate **29**, which would finally cyclize to the dihydrofuran derivative **30** via a staggered transition state minimizing steric interactions (Scheme 6).

**Scheme 5**



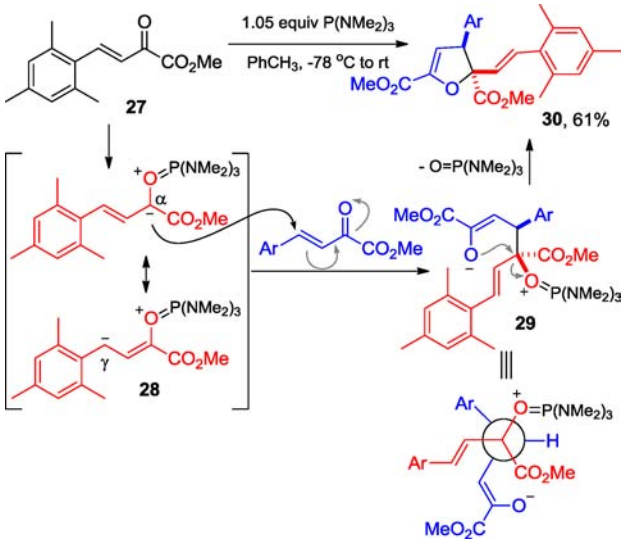

Reactions of alkylidene pyruvate esters with $P(NMe_2)_3$ differ from their benzylidene counterparts. The reaction of ethyl (*E*)-neopentylidenepyruvate (**31**) with $P(NMe_2)_3$ gives a mixture of 2,5-dihydrooxepin **32**[17] along with vinylcyclopropane **33** in moderate yield (Scheme 7). Presumably, absent of any benzylic stabilization, the Kukhtin–Ramirez adduct arising from the reaction of **31** and

(14) Sequential cyclopropanation/ring opening of electron-deficient double bonds activated by phosphoranes with electrophilic iron carbenoids has been reported; see: (a) Wang, S. R.; Zhu, C.-Y.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2009**, *131*, 4192. (b) Wang, P.; Ling, L.; Liao, S.-H.; Zhu, J.-B.; Wang, S. R.; Li, Y.-X.; Tang, Y. *Chem.—Eur. J.* **2013**, DOI: 10.1002/chem.201204182.

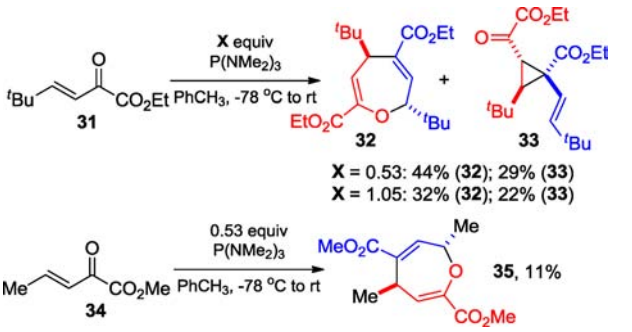
(15) For examples of ring opening of donor–acceptor-substituted cyclopropanes, see: (a) Doyle, M. P.; Van Leusen, D. *J. Am. Chem. Soc.* **1981**, *103*, 5917. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

(16) Preparation of **25** and **25′**: Rasmy, O. M.; Vaid, R. K.; Semo, M. J.; Chelius, E. C.; Robey, R. L.; Alt, C. A.; Rhodes, G. A.; Vicenzi, J. T. *Org. Process Res. Dev.* **2006**, *10*, 28.

**Scheme 6.** Reductive Dimerization of **27**




**Scheme 7.** Reaction of Alkylidenepyruvate Esters with $P(NMe_2)_3$




$P(NMe_2)_3$ does not exhibit significant $\gamma$-nucleophilicity, with the reaction instead emanating from the α-nucleophilic character. Methyl (*E*)-ethylidenepyruvate (**34**) behaves similarly (albeit with low yield), indicating that the preference for α-nucleophilic reactivity is not steric in origin.

In summary, the reaction of benzylidenepyruvate esters with $P(NMe_2)_3$ initiates a reductive homocondensation, leading to diverse oxygenated hetereocyclic products depending on the substitution of the starting substrate. Mechanistically, this reaction can be understood as proceeding via initial formation of oxyphosphonium dienolate intermediates by the Kukhtin–Ramirez reaction. The observation of the $\gamma$-nucleophilicity of oxyphosphonium dienolate intermediates and the notable effect of substituents on α-/$\gamma$-nucleophilicity modulation offers the potential for new synthetic transformations initiated by the Kukhtin–Ramirez reaction. Investigations aimed at the interception of the oxyphosphonium dienolate intermediates evidenced here with external electrophilic reagents are underway.

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**Supporting Information Available.** Detailed experimental procedures, analytical data of all new compounds, and X-ray data in CIF format for **6** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Both dihydrooxepins **32** and **35** and vinylcyclopropane **33** were isolated as single diastereomers, with tentative stereochemical assignment as shown in Scheme 7 based on the assumption that **32** is derived from the *cis*-diastereoisomer (the keto ester moiety relative to vinyl group) of **33** via a hetero-Cope rearrangement.

The authors declare no competing financial interest.