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INTRAMOLECULAR WITTIG REACTIONS WITH ESTERS: A NOVEL SYNTHESIS OF 2,3-DIHYDROFURANS.[1]

William G. Dauben and David J. Hart

Department of Chemistry, University of California, Berkeley, CA 94720

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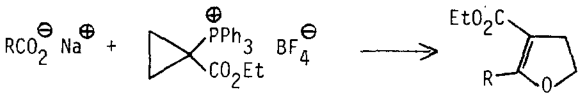
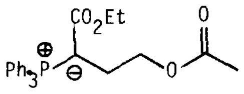
Ylids generated by treatment of vinyl,[2] butadienyl,[3] and cyclopropylphosphonium salts[4,5] with nucleophiles have been used widely in the preparation of carbocyclic and heterocyclic compounds.[6] The use of carboxylic acid salts as nucleophiles has not been reported. We have found that sodium carboxylates (1) react with carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (2)[5] to give in high yields 5-substituted-4-carbethoxy-2,3-dihydrofurans.[7]



1 2 3

For example, when an HMPT solution of sodium formate and phosphonium salt 2 was allowed to stir at room temperature for 24 hr, a 56% yield of 3 (R = H) was obtained after chromatography on silica gel. A similar treatment of 2 with sodium acetate produced no dihydrofuran; instead a 48% yield of 3-acetoxy-1-carbethoxypropylidenetriphenylphosphorane (4)[8] was obtained. This ylid 4 upon heating in refluxing chloroform for 39 hr was converted into 3 (R = CH_3). Alter-



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natively, when a mixture of sodium acetate (4 mmol) and 2 (1 mmol) in 10 ml of chloroform was heated under reflux for 39 hr, the dihydrofuran 3 (R = CH_3) was directly obtained in 86% yield. These results demonstrate that the reaction proceeds via attack of the carboxylate anion on the geminally activated cyclopropane[9] followed by an intramolecular Wittig reaction at the resulting ester carbonyl group.

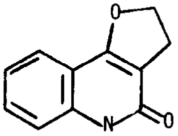
Several examples of Wittig reactions between esters and stabilized phosphoranes have been reported.[10] With the exception of formate esters, the success of these reactions has been attributed to the presence of strong electron withdrawing groups adjacent to the ester carbonyl. The present results demonstrate that carbonyl activation is not necessary in intramolecular Wittig reactions at ester carbonyl groupings. The results of the reaction between 2 and a variety of sodium carboxylates are summarized in Table 1.

TABLE 1

REACTION OF SODIUM CARBOXYLATES WITH 2.

1	YIELD OF 3[a,b]	CONDITIONS[d]
R = H	56%	HMPT, 24 hr, 25°
R = H	81%	$CHCl_3$, 144 hr, reflux
R = CH_3	86%	$CHCl_3$, 39 hr, reflux
R = FCH_2	83%	$CHCl_3$, 46 hr, reflux
R = Ph	93%	$CHCl_3$, 66 hr, reflux
R = PhCH=CH	70%[c]	$CHCl_3$,90 hr, reflux

(a) Isolated yields; (b) All compounds exhibited spectral and analytical or exact mass spectral data consistent with the assigned structure; (c) mp 63-64°; (d) chloroform stabilized with ethanol or pure chloroform were used without effect on yield.



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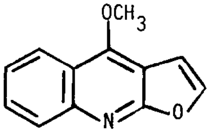

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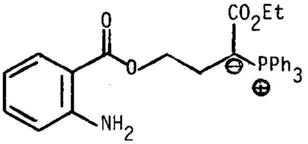

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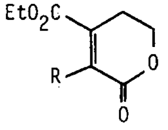
This intramolecular Wittig sequence has been utilized to synthesize **5**,[11] a key intermediate in one synthesis of the furoquinoline alkaloid dictamnine (**6**).[12] A mixture of **2** and sodium anthranilate was heated in refluxing chloroform (12 hr) to yield ylid **7** in 50% yield.[13] A tetrachloroethylene solution of the ylid was heated at 120° for 24 hr to give **5** in 46% yield.[14]

The reaction of α-ketoacid salts with **2** also was briefly investigated. When sodium pyruvate was allowed to react with **2** in refluxing chloroform, a 5:1 mixture of **3** (R = CH_3CO)[15] and **8** (R = CH_3),[16] respectively, was produced in 70% yield. To our knowledge, this result represents the first example of a phosphorane reacting selectively with an ester in the presence of a ketone. The inactivation of the ketone carbonyl group by enolization is probably not a contributing factor since carbomethoxymethylenetriphenylphosphorane reacted, exothermically, with ethyl pyruvate in chloroform to give a 70% yield of a 3:1 mixture of mesaconate **9** and citraconate **10**, respectively.[17] No products from reaction at the ester carbonyl were observed. On the other hand, treatment of **2** with sodium glyoxalate monohydrate[18] gave a high yield of dihydro-α-pyrone **8** (R = H).[19] Therefore, it appears that an interplay between carbonyl electrophilicity and steric factors involved in ring formation governs the course of the reaction.



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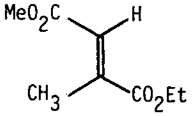

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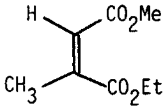

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8. mp 114-119°; nmr ($CDCl_3$) δ 0.73 (t, 3), 1.82 (s, 3), 2.27 (d of t's, J = 17, 7, 2), 3.83 (q, 2) 4.00 (t, 2) 8.00 (m, 15).
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12. M.F. Grundon and N.H. McCorkindale, *J. Chem. Soc.*, 2177 (1957).
13. mp 167-168°; nmr ($CDCl_3$) δ 0.70 (m, 3), 2.40 (d of t's, J = 18, 6, 2), 3.90 (m, 2H), 4.30 (t, 2) 5.73 (broad s, 2), 6.63 (m, 2), 7.60 (m, 17).
14. mp 280-281° (lit.[11] 280-284°).
15. nmr (CCl_4) δ 1.25 (t, J = 7, 3) 2.33 (s, 3) 2.90 (t, J = 10, 2) 4.07 (q, J = 7, 2) 4.47 (t, J = 10, 2).
16. nmr (CCl_4) δ 1.37 (t, J = 7, 3) 2.17 (t, J = 1.5, 3) 2.63 (broad t, J = 6, 2) 4.23 (q, J = 7Hz, 2) 4.40 (t, J = 6, 2).
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