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The Conversion of Carboxylic Acids to Keto Phosphorane Precursors of 1,2,3-Vicinal Tricarbonyl Compounds

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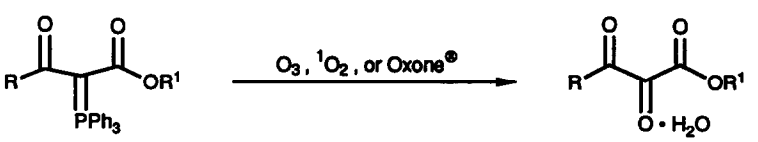
Abstract: *Acyl phosphoranylidines react with acid chlorides or anhydrides in the presence of bis(trimethylsilyl)acetamide (BSA), or couple directly with carboxylic acids activated by EDCI to give keto phosphoranes* ***1****.*

Keto phosphoranes of the type **1** are versatile intermediates in the synthesis of a variety of functionalized systems. As reported by Cooke,[1] reductive removal of the triphenylphosphine group[2] gives β-keto esters, vinyl derivatives undergo Michael addition of nucleophiles followed by trapping with electrophiles to form alkyl substitution products, and thermolysis provides access to substituted acetylenes.[3] More recently, there has been heightened interest in keto phosphoranes as precursors of the vicinal tricarbonyl system which is incorporated in the macrocylic immunosuppressants, such as FK-506[4] and rapamycin.[5] In our current work, we have shown that such tricarbonyl units, readily prepared by oxidation of **1** with ozone, singlet oxygen, or Oxone®, are useful intermediates in a variety of synthetic applications.[6]

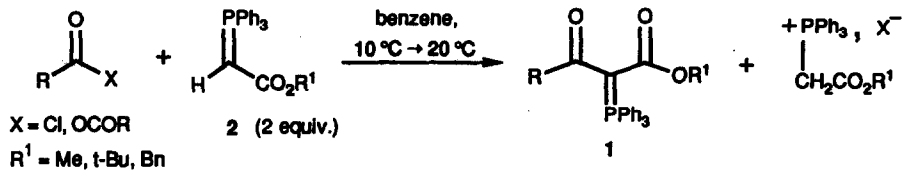


1

R = alkyl, aryl
R^1 = Me, t-Bu, Bn

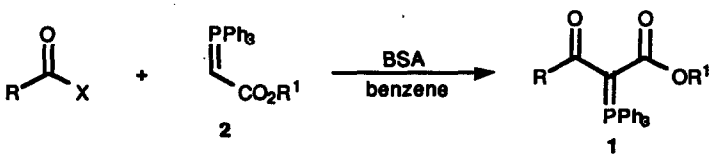
Synthesis of keto ylides **1** has previously been achieved by the reaction of an acid chloride (or anhydride) with two equivalents of the appropriate (triphenylphosphoranylidine) acetate **2**[1], in which the second equivalent of ylide functions as a proton acceptor (Scheme 1). This procedure suffers from two limitations: (i) competitive ketene formation as has been observed in several cases[7] and (ii) the wasteful consumption of a second equivalent of ylide **2**.

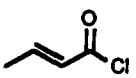
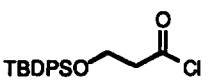
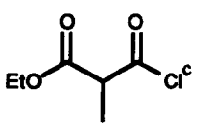
Scheme 1



We have now developed two modifications which overcome these problems and provide milder conditions for carrying out the coupling reaction in the presence of acid-sensitive functional groups. In one procedure, the use of the proton scavanger, bis(trimethylsilyl)acetamide (BSA) eliminates the need for the second equivalent of ylide, providing an efficient and general alternative to the earlier method. Table 1 lists the outcome of a number of BSA-promoted coupling reactions.

Table 1. Formation of Keto Ylides 1 using BSA[a]

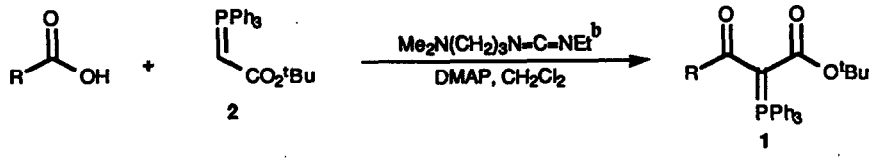


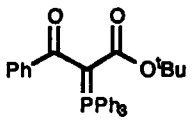
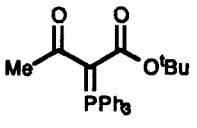
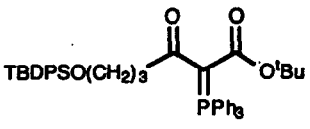
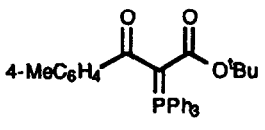
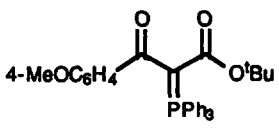
RCOX	R^1	Yield %
$(MeCO)_2O$	Me	98
$(PhCO)_2O$	Me	91
MeCOCl	t-Bu	87
n-BuCOCl	t-Bu	69
ArCOCl[b]	t-Bu, Bn	88-96
	Me	84
	t-Bu	78
	t-Bu	78

(a) The acid chloride or anhydride (1 mmol) is added dropwise to a solution of ylide (1 mmol) and BSA (1.2 mmol) in benzene (15 mL) at 10°C over 5 min. and then stirred at room temperature for 2 h. (b) Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-methoxycinnamyl. (c) No reaction is observed when the reaction is attempted in the absence of BSA.

In a second modification, we have recently discovered that carbodiimide coupling reagents permit mild, one-step syntheses of these ylide precursors directly from the carboxylic acids. In particular, the addition of the peptide coupling reagent, EDCI[8] to a series of representative carboxylic acids in the presence of ylide 2 affords phosphorane derivatives 1 in good yields (Table 2).

Table 2. Direct Conversion of Carboxylic Acids to Keto Ylides[a]

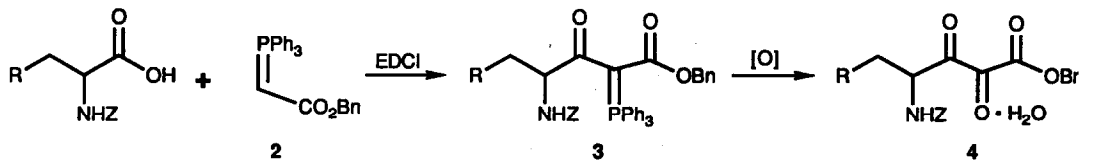


R	Product	Yield %
Ph		79
Me		76
TBDPSO(CH2)3		71
4-MeC6H4		62
4-MeOC6H4		61

(a) To a solution of the carboxylic acid (1 mmol) and the ylide (1 mmol) in methylene chloride (15 mL) is added EDCI (1 mmol) and DMAP (catalytic) at 0°C. The mixture is then allowed to reach room temperature, and stirring is continued for 2-24 h. (b) EDCI, commercially available as the hydrogen chloride salt.

In one application of this procedure, we have prepared keto ylides 3 from N-protected peptido carboxylic acids. Oxidative cleavage[9] of these intermediates[10] then yields the tricarbonyl derivatives 4 (Scheme 2). It is anticipated that, like trifluoromethyl ketones[11] or α-keto esters[12], these highly electrophilic tricarbonyl products will form covalent linkages with serine or other donor residues of enzymes, and, accordingly, show promise as enzyme inhibitors.[13]

Scheme 2



2 3 4

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