(Cyanomethylene)phosphoranes as Novel Carbonyl 1,1-Dipole Synthons: An Efficient Synthesis of α-Keto Acids, Esters, and Amides

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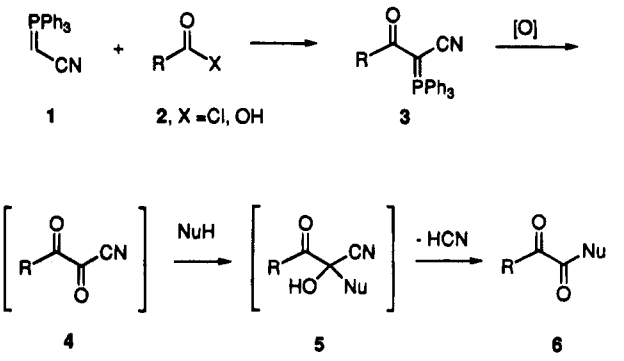
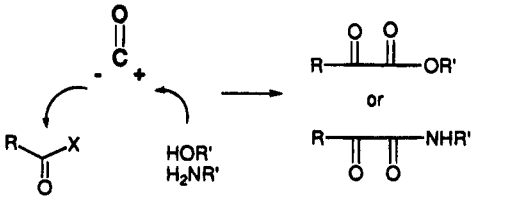
Summary: Carboxylic acids react with (cyanomethylene)triphenylphosphorane in the presence of EDCI to form cyano keto phosphoranes. The resulting ylides may then be oxidatively cleaved with ozone to form α,β-diketo nitriles. These highly electrophilic products may then be converted *in situ* to α-keto acids, esters, and amides.

There has been increasing interest in peptidyl α-keto esters and α-keto amides in connection with their activity as potent inhibitors of proteolytic enzymes such as the serine and cysteine proteases.[1] These compounds also show promising inhibition of leukotriene A_4 hydrolase[2] and chymase.[3] The biological activity of these inhibitors has been attributed to the presence of the electron-deficient α-keto group, which is similar in reactivity to the carbonyl group of α-fluorinated ketone inhibitors[4] and the α- or β-carbonyl group in vicinal tricarbonyls.[5] NMR studies have indicated that α-keto esters and amides are readily hydrated in the presence of water,[1b,2a] suggesting that these inhibitors either form tetrahedral adducts with donor residues at the enzyme active site or exist as *gem*-diols bound to these sites. In other work, Bey has reported an X-ray diffraction study of α-chymotrypsin incubated with a peptidyl α-keto ester showing that the serine hydroxyl group actually undergoes transesterification with the ester residue of the inhibitor.[6,7] More recent interest in α-keto amides stems from their occurrence in natural products, such as the cyclotheonamides,[8] orbiculamide A,[9] and the keramamides.[10]

Scheme 1



Scheme 2



Peptidyl α-keto esters are generally prepared by the oxidation of α-hydroxy esters,[11] which are derived from the hydrolysis of cyanohydrins[12] or α-hydroxy trithioorthoformic esters.[13] Alternatively, these esters may be prepared by the Dakin–West reaction of N-acylated amino acids with oxalyl chloride[14] or by the oxidation of keto vinyl ethers.[15] In a like manner, α-keto amides are mostly obtained from amidation of α-hydroxy esters or acids, followed by oxidation. Of the above methods, most lack generality or suffer from lengthy procedures.

We envisaged a more versatile strategy for the formation of α-keto acids, esters, or amides based on the use of the (cyanomethylene)triphenylphosphorane (**1**) in coupling reactions with carboxylic acids. The ylide **1**, readily accessible either by dehydrohalogenation of a phosphonium salt[16] or by the reaction of methyltriphenylphosphorane with 4-methylphenyl cyanate,[17] has long been used in the Wittig reaction with aldehydes or ketones to

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Scheme 3

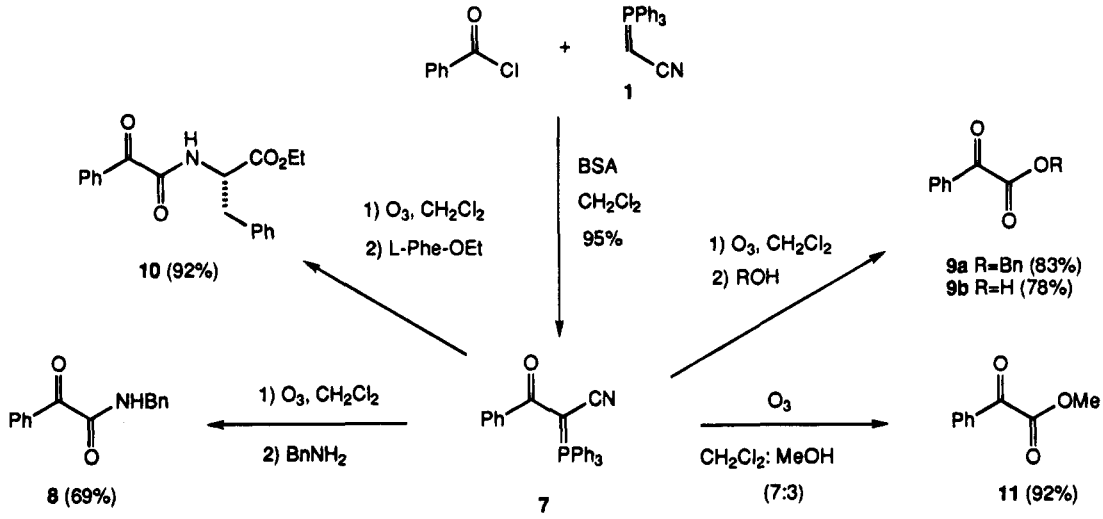
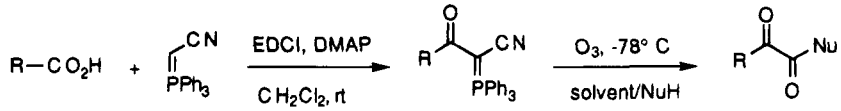


Table 1. Synthesis of α-Keto Acids, Esters, and Amides from Carboxylic Acids



entry	RCO_2H **12**	ketocyano ylide **13**	yield (%)	solvent/NuH	α-keto acid, esters, and amides[a] **14**	yield (%)
1	Cbz-HN-$(CH_2)_{11}$-CO_2H (**12a**)	**13a**	78	(7:3) CH_2Cl_2–MeOH	**14a** (Nu = OMe)	83
2	HO-$(CH_2)_{11}$-CO_2H (**12b**)	**13b**	*b*	(7:3) CH_2Cl_2–MeOH	**14b** (Nu = OMe)	85
3	Boc-Phe-OH (**12c**)	**13c**	80	CH_2Cl_2/(4/1) THF–H_2O[c]	**14c** (Nu = OH)[d]	74
4	Boc-Phe-OH (**12c**)	**13c**	80	(7:3) CH_2Cl_2–MeOH	**14d** (Nu = OMe)	89
5	Cbz-Gly-Gly-OH (**12e**)	**13e**	59	(7:3) CH_2Cl_2–MeOH	**14e** (Nu = OMe)	74
6	Cbz-Ala-Gly-Gly-OH (**12f**)	**13f**	64	(7:3) CH_2Cl_2–MeOH	**14f** (Nu = OMe)	88
7	Boc-Phe-OH (**12c**)	**13c**	80	CH_2Cl_2/Phe-OEt[c,e]	**14g** (Nu = Phe-OEt)	63
8	Boc-Phe-OH (**12c**)	**13c**	80	CH_2Cl_2/Leu-OMe[c,f]/$^iPr_2NEt$	**14h** (Nu = Leu-OMe)	58

[a] A general procedure for keto esters and amides follows: A solution of **13** in CH_2Cl_2 (or 7/3) CH_2Cl_2–MeOH) (ca. 0.1 M) was ozonized at −78 °C until the color of the solution remained blue (or yellow-blue). After the solution was purged with N_2 to remove the excess O_3, the nucleophile (1.1 equiv) was introduced at −78 °C. After 0.5 h at −78 °C, the solvent was removed and the residue was further either by silica gel chromatography or by trituration in (5/4) benzene–hexanes followed by recrystallization to afford the product (see refs 26 and 27). [b] Yield for protection of **12b** and coupling with **1** was 60%. For deprotection with fluoride, yield was 74%. [c] The nucleophile was added after excess ozone was removed. [d] This compound was purified by acid–base extraction (1 N NaOH–EtOAc–3 N HCl–EtOAc). [e] The free amino ester was used. [f] The amino ester hydrogen chloride salt was used.

form α,β-unsaturated nitriles. It is also known to react with electrophiles such as alkyl halides, esters, and acyl halides to yield substituted cyano phosphoranes and cyano keto phosphoranes.[18] We have now found that these cyano keto phosphoranes **3** undergo ready oxidation to the highly electrophilic vicinal diketo nitriles **4** which can be trapped by reaction with nucleophiles to give transient intermediates **5.** These cyanohydrins undergo facile elimination of hydrogen cyanide to form α-keto acids, esters, and amides **6**, as illustrated in Scheme 1.

In the above reaction sequence, the cyano ylide **1** may be viewed as a carbonyl 1,1-dipole equivalent[19] reacting first as a nucleophile and then, after oxidation of the carbon–phosphorus double bond in the ylide intermediate, as a powerful electrophile (Scheme 2).

Following up on the early work of Bestmann[20] and then Cooke,[21] who showed that keto ylides could be reacted with esters or acyl halides to form α,α′-diketo ylides, we found that the coupling of keto ylides with acyl chlorides could take place on a 1:1 molar basis using BSA as a proton sponge. Moreover, the coupling with the corresponding carboxylic acid could be accomplished directly in the presence of EDCI.[5,22] These conditions can now be applied to the formation of stable cyano keto ylides **3** from cyano ylide **1**. In the following example, we illustrate the use of ylides of type **3** in the formation of α-keto esters and amides using the specific case of **7** (**3**, R = Ph).[23]

Ozonolysis of **7** in anhydrous CH_2Cl_2 at −78 °C (Scheme 3) yielded an unstable diketo nitrile (**4**, R = Ph) which underwent decomposition on warming to room temperature. If, however, excess ozone was removed at −78 °C and benzyl amine added *in situ*, the intermediate could be trapped and converted to the α-keto amide **8** (69%). Similar reactions were observed when the diketo

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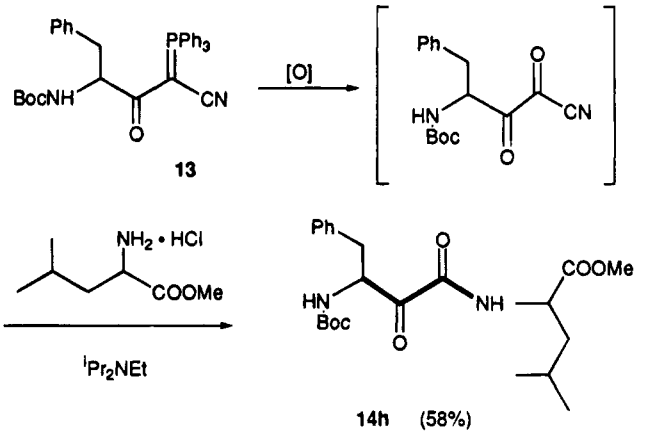
nitrile was trapped with other nucleophiles such as benzyl alcohol, water, or L-phenylalanine ethyl ester, leading to **9a**, **9b**, and **10**, respectively. Although the reaction with amines proceeded completely within a few minutes at −78 °C, the reaction with alcohols generally required excess quantities of the nucleophile and longer reaction times. In any case, formation of α-keto esters could be effected more easily and in one step by carrying out the ozonolysis in a mixture containing both CH_2Cl_2 and the alcohol as illustrated in the efficient formation of the methyl ester **11** (92%).[24,25]

The synthesis of α-keto esters and amides is summarized in Table 1. As shown in entries 3−8, the methodology may be applied to the formation of peptidyl α-keto acids, esters and amides. Thus, an amino acid **12c**, a dipeptide **12e** and a tripeptide **12f** undergo direct coupling with cyano ylide **1** to afford cyano ylides **13** which may be readily converted to the α-keto acid **14c** and esters **14d**, **14e**, and **14f**.[26,27] The α-diketo functionality may also be inserted between two amino acid units (entries 7 and 8). Here, either a free amino ester (entry 7) or an amino ester salt in the presence of a Hunig's base (entry 8) reacts as the nucleophile, leading, in good yields, to **14g** and **14h** (Scheme 4).[27,28]

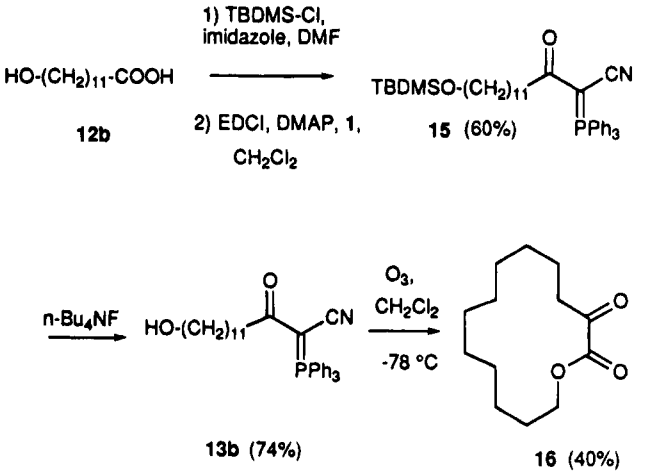
This procedure appears to have a particularly interesting application in the synthesis of α-keto macrolides. As shown in Scheme 5, the hydroxy cyano ylide **13b** was prepared from the hydroxy acid **12b** by protection of the ω-hydroxyl, coupling with ylide **1** to form **15**, and then deprotection. Ozonolysis of **13b** in a highly dilute CH_2Cl_2 solution yielded the 14-membered α-keto lactone **16**.

In conclusion, we have shown that the (cyanomethylene)phosphorane **1** may be used as a powerful carbonyl 1,1-dipole equivalent through a facile sequence resulting in the insertion of a carbonyl group α to a carboxylate derivative. This strategy, which may be applied to the synthesis of peptidyl α-keto esters and amides, has also shown promise in the preparation of α-keto macrolides. Current efforts in this laboratory are focused on the further applications of this methodology to the formation of α-keto esters, amides and related cyclic systems which show promise as enzyme inhibitors.

Scheme 4



Scheme 5



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Supplementary Material Available: Experimental details and spectroscopic data for all new compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(25) Use of tetra n-butylammonium oxone for the conversion of **7** to **11** was also effective (87% yield), but required a longer time at room temperature. For the preparation of TBA-oxone see: Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532.

(26) The di- and tri-peptidyl α-keto esters **14e**, **14f** were difficult to purify by silica gel chromatography. They were isolated by filtration after trituration with a (5/4) benzene−hexanes solvent system to remove the side product, triphenylphosphine oxide.

(27) We are exploring the possibility of epimerization during both coupling and oxidation stages in the conversion of **12** to **14**. These experiments, which will be reported in a further account, are being conducted using chiral lanthanide NMR shift reagents (Sweeting, L. M.; Crans, D. C.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2273) and/or Moser acid derivatives (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543). We have observed that the proton NMR spectra of compounds **14g** and **14h** show only one major diastereomer, indicating that no substantial epimerization occurred during the coupling and oxidation procedures.

(28) These two α-keto amides (**14g** and **14h**) were found to be equilibrating on silica gel between hydrated and anhydrous forms. The anhydrous α-keto amides can be obtained by crystallization of these two mixtures in a hexane/ether or petroleum ether/ether solvent system after silica gel chromatography.