

## Synthesis of Cyanoketophosphoranes, Precursors of $\beta$ -Amino- $\alpha$ -keto-esters from UNCAs.

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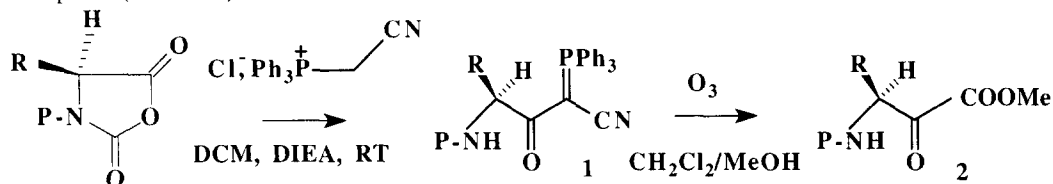
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**Abstract:** Cyanomethylene triphenylphosphoranes of N-protected amino acids were synthesized from the corresponding N-urethane protected  $\alpha$ -amino acid N-carboxyanhydrides (UNCAs) by reaction with cyanomethyltriphenylphosphonium chloride in good yields. These compounds are precursors of  $\alpha$ -keto esters which are candidates for mimicking the tetrahedral transition state in enzyme inhibitors. © 1998 Elsevier Science Ltd. All rights reserved.

The interest of  $\alpha$ -keto esters and  $\alpha$ -keto amides has been demonstrated in peptide sequences by their potential activity as inhibitors of proteolytic enzymes such as serine and cysteine proteases.<sup>1,2,3</sup> Their biological activity has been attributed to the presence of the electron-deficient  $\alpha$ -keto group which is equivalent of the carbonyl group of  $\alpha$ -fluorinated keto-inhibitors.  $\alpha$ -keto esters are readily hydrated in the presence of water as shown by NMR studies,<sup>4</sup> suggesting that these inhibitors mimic the tetrahedral transition state involved in the proteolysis process between the enzyme and its substrate. The synthesis of  $\alpha$ -keto esters was recently achieved by cleavage of cyano keto phosphoranes with ozone in the presence of nucleophiles.<sup>5</sup>

The high reactivity of N-protected  $\alpha$ -amino acid N-carboxyanhydrides (UNCAs) is well established. We have shown they are able to react with Wittig derivatives<sup>6</sup> to yield the corresponding phosphoranes which can be oxidized by ozone to prepare vicinal tricarbonyl compounds, as described by Wasserman.<sup>7</sup> We report here the reactivity of UNCAs with cyanomethyltriphenylphosphonium chloride. The resulting compounds **1** are interesting precursors of  $\alpha$ -keto esters **2** which can be easily obtained by ozonolysis in the presence of nucleophiles (Scheme 1).



**Scheme 1.** Synthesis of  $\beta$ -amino- $\alpha$ -keto-esters from UNCAs and cyanomethylphosphonium chloride.

The experimental conditions using UNCAs are very simple. The reaction was performed at room temperature to yield the desired compounds **1** in good yields as shown in Table 1. In a typical experiment, Boc-Ile-NCA (5 mmol) was dissolved in DCM (20 mL) and placed under stirring. Cyanomethyltriphenylphosphonium chloride (5 mmol) was added to the mixture at room temperature; then diisopropylethylamine (DIEA) (5 mmol) was added. After 45 min the solvent was concentrated *in vacuo* and

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the mixture dissolved in diethyl ether (100 mL), washed with 5% sodium hydrogensulfate (2 x 20 mL), saturated sodium bicarbonate (2 x 20 mL) and brine. After drying over sodium sulfate, the solvent was evaporated under *vacuo* to yield the desired product which is dried under *vacuo* overnight. When necessary, a flash chromatography on silica gel was performed with ethyl acetate/hexane as eluent system. All compounds were checked by reverse phase HPLC on a C18 analytical column and by T.L.C. for their homogeneity and were characterized by mass spectrometry and  $^1\text{H}$  NMR spectroscopy.

The cyanomethylene triphenylphosphoranes **1** were submitted to ozonolysis to yield  $\beta$ -amino- $\alpha$ -keto esters **2** (Table 1). The reaction was performed in a mixture of methanol and dichloromethane (7/3: v/v) at -78°C. Compounds were subjected to an ozone stream and ozonolysis was continued for 5 min after the apparition of an intense blue coloration. The reaction mixture was then purged with argon and the solvents evaporated under *vacuo*. The desired compounds were obtained after drying in *vacuo*. When necessary, a silica gel chromatography was performed with ethyl acetate/hexane as eluent system.

UNCAs	R	Compound 1: Yield (%)	Compound 2: Yield (%)
Z-Ala	$\text{CH}_3$	76	68
Z-Val	$\text{CH}(\text{CH}_3)_2$	71	75
Z-Leu	$\text{CH}_2\text{-CH}(\text{CH}_3)_2$	87	60
Boc-Asp(OBzl)	$\text{CH}_2\text{-CH}_2\text{-COOBzl}$	70	71
Z-Phe	$\text{CH}_2\text{-}\Phi$	77	55
Boc-Leu	$\text{CH}_2\text{-CH}(\text{CH}_3)_2$	65	50
Boc-Ile	$\text{CH}(\text{CH}_3)\text{-CH}_2\text{-CH}_3$	90	60

Table 1. Synthesis of  $\beta$ -amino- $\alpha$ -keto-esters from UNCAs.

The usefulness of the reaction of UNCAs with cyanomethylphosphonium chloride was demonstrated by the simple synthesis of various N-protected cyanoketophosphoranes (Boc or Z) from the corresponding UNCAs. Once again the excellent reactivity of UNCAs is shown together with simple experimental conditions. N-protected cyanoketophosphoranes were obtained in fairly good conditions and yields. These compounds were then oxidized by ozonolysis to reach N-protected  $\beta$ -amino- $\alpha$ -keto esters which are of interest for peptide and combinatorial chemistry.

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