Pergamon

Tetrahedron Letters 39 (1998) 6889–6890

TETRAHEDRON LETTERS

Synthesis of Cyanoketophosphoranes, Precursors of β-Amino-α-keto-esters from UNCAs.

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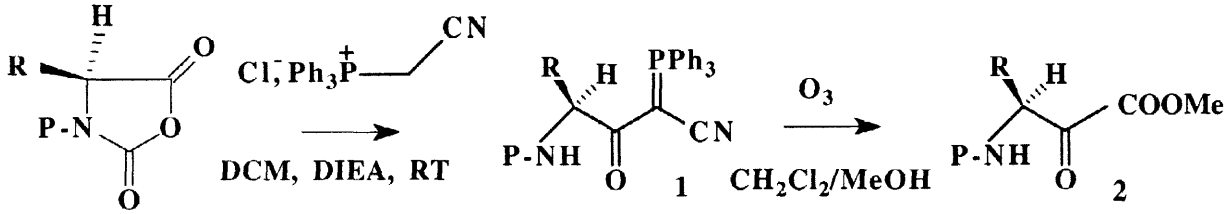
Received 17 June 1998; accepted 15 July 1998

Abstract: Cyanomethylene triphenylphosphoranes of N-protected amino acids were synthesized from the corresponding N-urethane protected α-amino acid N-carboxyanhydrides (UNCAs) by reaction with cyanomethyltriphenylphosphonium chloride in good yields. These compounds are precursors of α-keto esters which are candidates for mimicking the tetrahedric transition state in enzyme inhibitors.

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

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



Scheme 1. Synthesis of β-amino-α-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 mmoles) was dissolved in DCM (20 mL) and placed under stirring. Cyanomethyltriphenylphosphonium chloride (5 mmoles) was added to the mixture at room temperature; then diisopropylethylamine (DIEA) (5 mmoles) was added. After 45 min the solvent was concentrated in *vacuo* and

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0040-4039/98/$ - see front matter
PII: S0040-4039(98)01504-4

the mixture dissolved in diethyl ether (100 mL), washed with 5% sodium hydrogenosulfate (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}H NMR spectroscopy.

The cyanomethylene triphenylphosphoranes **1** were submitted to ozonolysis to yield β-amino-α-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	CH_3	76	68
Z-Val	$CH(CH_3)_2$	71	75
Z-Leu	CH_2-$CH(CH_3)_2$	87	60
Boc-Asp(OBzl)	CH_2-CH_2-COOBzl	70	71
Z-Phe	CH_2-Φ	77	55
Boc-Leu	CH_2-$CH(CH_3)_2$	65	50
Boc-Ile	$CH(CH_3)$-CH_2-CH_3	90	60

Table 1. Synthesis of β-amino-α-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 β-amino-α-keto esters which are of interest for peptide and combinatorial chemistry.

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