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The Use of *N*-Urethane-protected *N*-Carboxyanhydrides (UNCAs) in Amino Acid and Peptide Synthesis

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Abstract: *N*-Urethane-protected *N*-carboxyanhydrides (UNCAs) are very reactive amino acid derivatives. They have been successfully used in peptide synthesis, in both solution and solid phase. We have demonstrated that UNCAs are interesting starting materials for the synthesis of various amino acid derivatives. Chemoselective reduction of UNCAs with sodium borohydride led the corresponding *N*-protected β amino alcohols. Reaction of UNCAs with Meldrum's acid, followed by cyclisation, yielded enantiomerically pure tetramic acid derivatives. Diastereoselective reduction of tetramic acid derivatives produced (4*S*,5*S*)-*N*-alkoxycarbonyl-4-hydroxy-5-alkylpyrrolidin-2-ones derived from amino acids, which after hydrolysis yielded statine and statine analogues. Tetramic acid derivatives could also be obtained by reaction of UNCAs with benzyl ethyl malonate in the presence of sodium hydride to yield γ-*N*-benzyloxycarbonylamino-β-oxodicarboxyl esters followed by hydrogenolytic deprotection and decarboxylation. UNCAs also reacted with phosphoranes to produce the ketophosphorane in excellent yields. Subsequent oxidation with oxone or with [bis(acetoxy)-iodo]-benzene produced vicinal tricarbonyl derivatives. These reactions usually proceeded smoothly and with high yields.

Keywords: β-amino-alcohols; statine; UNCAs; vicinal tricarbonyl compounds

The synthesis of peptides needs efficient activation and coupling techniques; hundreds of coupling reagents appeared in the literature and several new reagents such as BOP, HBTU and more recently HATU [1] are considered to be preferred reagents for rapid activation with minimal racemization and side reaction.

Preactivated *N*-protected amino acids like active esters eliminate the separate activation step and are, in principle, simpler for use. Recently, a new class of preactivated amino acids, the *N*-urethane-protected amino acid *N*-carboxyanhydrides (UNCAs) were introduced [2]. UNCAs proved their efficiency both in liquid and solid-phase peptide synthesis. In this paper, we report on the use of UNCAs for the synthesis of unusual amino acid derivatives, i.e. β-amino alcohols, tetramic acid derivatives (which are statine precursors) and β,γ-dicarbonyl amino acids. As in the case of peptide bond formation, reactions performed with UNCAs are very simple and rapidly go to completion.

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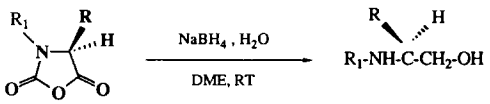
N-Protected β-Amino Alcohols from UNCAs

N-Protected β-amino alcohols are of great interest in the synthesis of peptide bond surrogates because

they are key intermediates in the synthesis of α-amino aldehydes by oxidation [3], which are potent inhibitors of proteases, and in the preparation of stereochemically defined 'methylene-oxy' dipeptides [4]. They can also be incorporated at the C-terminal end of hormones as in the case of enkephalins to achieve receptor selectivity [5]. *N*-protected β-amino alcohols are prepared by reduction of alkyl esters of amino acids [6, 7], and active esters of amino acids [8] with sodium borohydride. Recently we and others described an efficient synthesis of *N*-protected β-amino alcohols via the reduction of mixed anhydrides by sodium borohydride [9, 10]. We present here a convenient and attractive one-pot synthesis of β-amino alcohols by chemoselective reduction of *N*-protected amino acids *N*-carboxyanhydrides (UNCAs) with sodium borohydride (Figure 1). Various reduction conditions of the UNCAs have been tested but the simplest was found to be sodium borohydride in 1,2-dimethoxyethane in the presence of water.

The usefulness of this method was demonstrated by the synthesis of various *N*-protected β-amino alcohols (Z, Boc, Fmoc) (Table 1). The *tert*-butyl-ester or the benzyl ether used respectively for the protection of the carboxylic acid side chain of glutamic acid and for the phenol of tyrosine remained unaffected under the described reaction conditions [11].



R_1 = Boc, Fmoc, Z

R = amino acid side chains

Fig. 1 Reduction of UNCAs by sodium borohydride to yield to the corresponding alcohol.

All *N*-protected β-amino alcohols that were synthesized were homogeneous by thin-layer chromatography (TLC) and reversed-phase high-pressure liquid chromatography (HPLC) on a C_{18} analytical column. They were identified by mass spectrometry. No racemization could be detected as indicated by comparison of their $[\alpha]_D$ with those reported in the literature.

Synthesis of β-hydroxy γ-Amino Acids (Statine-like Derivatives) from UNCAs

Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA) is an unusual β-hydroxy γ-amino acid which was first discovered in pepstatin [12], a naturally occurring peptide antibiotic which functions as an unselective inhibitor of acid proteases such as renin, pepsin and cathepsin D. Statine analogues are also present in antiviral cytotoxic cyclodepsipeptides, didemnines, A, B, C and nordidemnines A, B C [13].

Statine and β-hydroxy γ-amino acid have been widely used for the synthesis of inhibitors of aspartyl proteases such as renin, a key enzyme in the renin–angiotensin system, and HIV. These β-hydroxy γ-amino acids are recognized to mimic the transition state structure of the substrate when interacting with the enzymes. Only the β-hydroxy γ-amino acids of the *syn* configuration are generally believed to adopt a suitable conformation for such an interaction. Several syntheses of *syn*- and *anti*-statine and β-hydroxy γ-amino acids have been reported [14]. Stereospecific syntheses of *syn*-statine and statine analogues were reported via stereocontrolled reduction of tetramic acids [15–19]. The key step of these syntheses is the stereoselective reduction of the *N*-alkyloxycarbonyl tetramic acids **3**. In fact, the

Table 1 Preparation of β-Amino Alcohols from Urethane-protected *N*-Carboxyanhydrides (UNCAs)

N-protected β-amino alcohols	Yield (%)	m.p. (°C)	$[\alpha]^{20}_D$ (*c* = 1, MeOH)	R.f.(A)[a]	R.f.(B)[a]
Z-Leu	80	oil	−21	0.57	0.64
Z-Ile	96	64	−14	0.57	0.60
Fmoc-Leu	90	130	−17	0.52	0.59
Fmoc-Glu(OtBu)	83	55–57	−10	0.42	0.59
Fmoc-Ile	89	108–110	−12	0.50	0.70
Fmoc-Trp	80	86–90	−26	0.21	0.44
Boc-Phe	91	96	−26	0.48	0.58
Boc-Tyr(Bzl)	87	108	−17	0.34	0.60

[a] (A) ethyl acetate/hexane 1 : 1; (B) dichloromethane/methanol 95 : 5.

stereoselectivity of the reduction is dependent on the substitution on the nitrogen; reduction of *N*-unsubstituted tetramic acids leads to a mixture of the epimeric alcohols [15, 20]. Optically pure tetramic acids are obtained from *N*-protected amino acids, Meldrum's acid. 4-*N*,*N*-dimethylaminopyridine and isopropenyl chlorofomate [17]. The reaction conditions are rather elusive and, as reported by the authors, any change in the procedure leads to lower yields. Alternatively, enantiomerically pure tetramic acids are also accessible by hydrogenolytic deprotection of 4-(benzyloxycarbonylamino)-3-oxocarboxylic acid esters [19]. Tetramic acids are also interesting intermediates for the synthesis of optically active γ-amino acid derivatives [19].

We have reported on a simple and stereoselective synthesis of chiral tetramic acid derivatives (**3**) (Fig. 2) [21]. The reaction of Meldrum's acid on the corresponding *N*-protected-*N*-carboxyanhydride **1** derivatives (UNCAs) in the presence of a tertiary amine (triethylamine TEA, *N*,*N*-diisopropylethylamine DIEA, *N*-methylmorpholine NMM, etc.), readily afforded a high yield of the adducts **2** in a few minutes. Any effort to purify these oily derivatives by column chromatography were unsuccessful. The crude materials were cyclized [16, 17] and yielded the corresponding enantiomerically pure tetramic acid derivatives (**3**) (Table 2). As previously described [16, 17], diastereoselective reduction of tetramic acids **3** produced (4*S*,5*S*)-*N*-alkoxycarbonyl-4-hydroxy-5-akylpyrrolidin-2-ones (**4**) derived from amino acids, which after hydrolysis yielded statine and statine analogues **5**. The usefulness of this method was demonstrated by the synthesis of a series of tetramic acid derivatives (**3**) starting from Z, Boc and Fmoc *N*-protected *N*-carboxyanhydrides (Table II). They were identified by mass spectrometry, ^{1}H-NMR spectroscopy and by comparison of their physical characteristics with those reported in the literature.

UNCAs were also able to react easily with malonic acid derivatives. The reaction of UNCAs with benzyl ethyl malonate in the presence of sodium hydride easily lead to γ-*N*-benzyloxycarbonylamino-β-oxodicarboxylic esters **6** (Fig. 3). The reaction proceeded in better yields using sodium hydride (50%) than with potassium carbonate (35%). The hydrogenolytic deprotection of **6** in the presence of 4-dimethylaminopyridine, followed by decarboxylation produced tetramic acid derivatives (**7**) which can be reduced into the corresponding pyrrolidin-2-one (**8**) as described in [19].

Reaction of UNCAs with Wittig Reagents

There has been considerable interest in small peptide substrates which incorporate a strongly electron-deficient group at the site of a scissile amide bond and thereby act as potent inhibitors of hydrolytic enzymes. Inhibition has been associated with the formation of a tetrahedral intermediate. Among functional groups in which the electrophilic reactivity of the carbonyl group is greatly enhanced, the vicinal tricarbonyl unit is a powerful acceptor. Vicinal tricarbonyl compounds are potential inhibitors of serine proteases [22] or starting materials for the synthesis of isoquinoline alkaloids [23], eudistomins [24], vicamine-related alkaloids [25], carbacephams [26] and highly substituted imidazoles [27]. In our

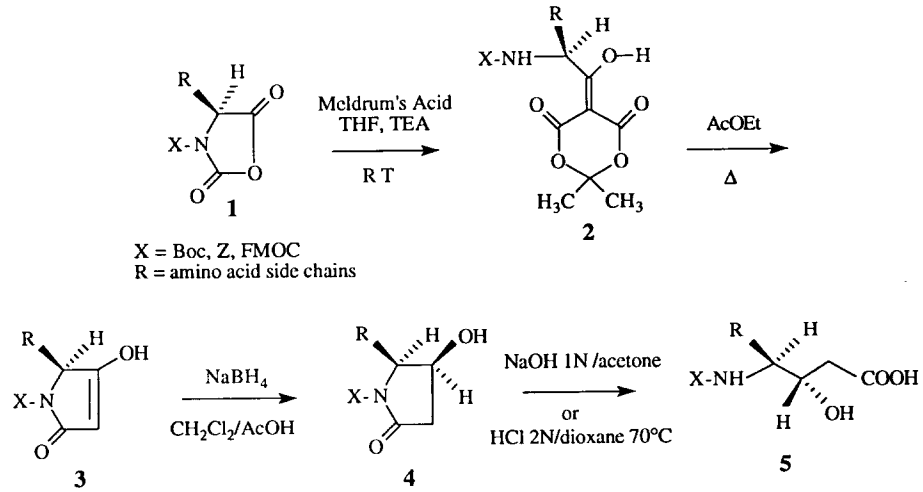
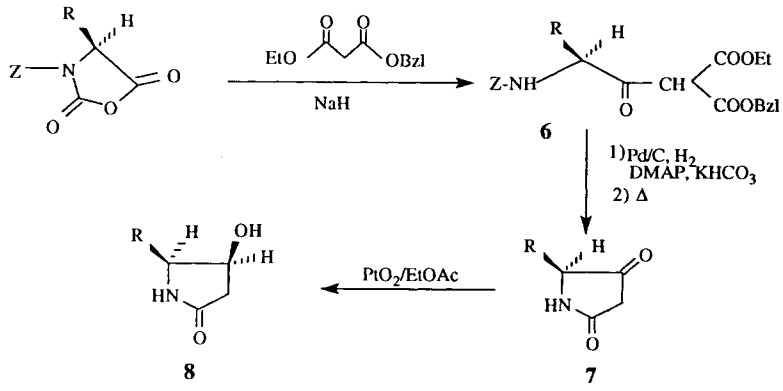


Fig. 2 Synthesis of tetramic acid derivatives **3** and statine analogues **5** from UNCAs.

Table 2 Characterization of Tetramic Acid Derivatives **3** Synthesized from UNCAs **1**

Tetramic acid derivatives **3**[a]	Yield[b] (%)	R.f.(A)[c]	R.f.(B)[c]	$[\alpha]_D^{20}$ (c ≈ 1 MeOH)
Fmoc-L-Phe	84	0.45	0.57	+104
Fmoc-L-Leu	79	0.54		+66
Fmoc-L-Val	63	0.61	0.68	+44
Fmoc-L-Lys(Boc)	75	0.52	0.80	+46
Boc-L-Leu	87	0.58	0.72	+101
Boc-L-Phe	80	0.37	0.49	+205
Boc-L-Trp(For)	60	0.37	0.35	+113
Z-L-Phe	82	0.35	0.55	+150
Z-L-Leu	76	0.51		+44
Z-L-Val	80	0.75	0.57	+54

[a] Identified by mass spectrometry and ^{1}H-NMR spectroscopy (250 MHz).
[b] Yields are expressed from the UNCAs.
[c] (A) Chloroform/methanol/acetic acid 180/10/5; (B) Ethyl acetate/hexane/acetic acid 7/3/1.

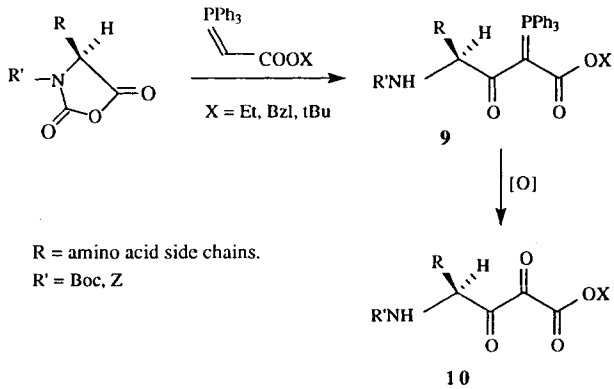


R = amino acid side chains

Z = benzyloxycarbonyl

Fig. 3 Synthesis of (4S,5S)-4-hydroxy-5-alkylpyrrolidin-2-one (**8**) from UNCAs.

recent studies on the chemistry of UNCAs, we have developed a mild, efficient reaction sequence for forming vicinal tricarbonyl compound derivative of amino acids. Figure 4 illustrates the general procedure by which the UNCAs are reacted with phosphoranes to produce the keto phosphorane **9** in excellent yields. These compounds can yield by subsequent oxidation with oxone or with [bis(acetoxy)-iodo]-benzene, to the vicinal tricarbonyl derivatives **10** (Fig. 4) as described by Wasserman and coworkers [28–31].



R = amino acid side chains.
R' = Boc, Z

Fig. 4 Synthesis of vicinal tricarbonyl compounds **10** from UNCAs.

General Comments

As shown in this paper, UNCAs are very reactive intermediates, which are useful in peptide synthesis and chemistry of amino acids. We and others have already proved the utility of UNCAs for the synthesis of biologically active peptides, both in solution and solid-phase peptide syntheses [32–34]. Difficult couplings of hindered amino acids were also successfully performed with UNCAs [35]. We have shown herein that UNCAs were also interesting intermediates in the chemistry of amino acids. They have proved their usefulness for the synthesis of *N*-protected β-amino alcohols, *N*-protected β-hydroxy γ-amino acids and vicinal tricarbonyl derivatives which are important synthetic intermediates in the synthesis of biologically active molecules.

The $NaBH_4$ reduction of UNCAs has allowed us to obtain in a one-step synthesis the corresponding β-amino alcohols in good yields (80–96%). The reaction proceeds without racemization and with a very simplified procedure (room temperature, no need to prepare the anhydride, easy recovery of the compound). This method seems to be valuable for the preparation of β-amino alcohols from Boc, Z or Fmoc *N*-carboxyanhydrides and to be compatible with various side chain protecting groups.

Furthermore, we have established that UNCAs can be used to obtain chiral *N*-protected tetramic acid derivatives which are important precursors of statine and β-hydroxy γ-amino acid as well as of optically active γ-amino acid derivatives. Using UNCAs is much more simple than the described synthesis involving preactivated *N*-protected amino acids, which in addition must be performed at a low temperature. In summary, this method (UNCAs, Meldrum's acid and tertiary amine) leads in a very simple manner to a variety of tetramic acid derivatives protected with Boc, Z, or Fmoc, without using expensive reagents.

We have also shown that malonate derivatives can react with UNCAs in the presence of sodium hydride. This reaction is also an attractive route for the synthesis of tetramic acid derivatives. Nevertheless in the reaction conditions that were studied, the use of Meldrum's acid in the presence of a tertiary amine and UNCAs leads to better yields than the reaction with malonate derivatives.

Another interesting reaction of the UNCAs is the condensation with Wittig reagents. The experimental procedures of these reactions are also very simple and high yields are obtained. This condensation can be performed with Fmoc, Z and Boc NCA derivatives and with various triphenylphosphoranylidenes. The resulting compounds are important intermediates for the synthesis of vicinal tricarbonyl amino acid derivatives which are potential biological active molecules.

All these reactions with UNCAs were performed without racemization of the amino acid derivatives, in good yields and in a very simple and efficient way. They are the expression of the high reactivity and simple use of UNCAs which undoubtedly will lead to various other attractive reactions.

EXPERIMENTAL PART

Melting points (m.p.) were taken on a Büchi apparatus in open capillary tubes and are reported uncorrected. Optical rotations were determined with a Perkin Elmer 141 polarimeter. Ascending TLC were performed on precoated plates of silica gel 60 F 254 (Merck) using the indicated solvent systems. Amino acid derivatives were located by UV light (254 nm), charring reagent or ninhydrin. Column chromatographies were performed with silica gel 60, 60–229 mesh, ASTM (Merck). ^{1}H-NMR spectra were recorded at 305 K on an AMX 360 Bruker spectrophotometer with chemical shifts reported in δ relative to the signal set to 2.5 p.p.m. Mass spectra were recorded on a Jeol JMS DX 100 and DX 300 spectrometer in a FAB-positive mode. All reagents were of analytical grade. All UNCAs were obtained from Propeptide, BP 12, 91710 Vert-Le-Petit, France. Abbreviations used were those recommended by the IUPAC–IUB Commission (*Eur. J. Biochem.*, 1984, *138*, 9–37).

Synthesis of *N*-Protected β-Amino Alcohols

A typical experiment which can be applied to Boc, Z and Fmoc derivatives is described below: Boc-L Phe-NCA (2.91 g, 10 mmoles) was dissolved in 1,2-dimethoxyethane (20 ml) and stirred at room temperature. A solution of sodium borohydride (0.57 g, 15 mmol) in water (5 ml) was added in one portion. A strong evolution of gas occurred and after 5–10 min the reaction was quenched by addition of water (200 ml). The expected alcohol (2.28 g, 91%) precipitated (entry 7, Table 1); it was collected by filtration and washed with water and hexane. In some cases, the expected compound did not precipitate as a solid; the reaction mixture was extracted with ethyl acetate (entries 1, 2, 4 and 6, Table 1), and the organic layer washed with water, dried over sodium sulphate and concentrated *in vacuo*. The physical characteristics

of the obtained *N*-protected β-amino alcohols are reported in Table I.

Synthesis of Boc-statine from Boc-L-Leu-NCA

As an example and a typical procedure, the reaction of Boc-L-Leu-NCA with Meldrum's acid, which leads to the statine derivative is described. Boc-L-Leu-NCA (2.5 g, 9.7 mmoles) was dissolved in THF (20 ml). Meldrum's acid (1.4 g, 9.7 mmoles) and TEA (3.03 g, 30 mmoles) were then added to the solution and the reaction mixture was stirred at room temperature. A strong evolution of gas occurred and after 25 min, the solvent was removed *in vacuo*.The residue was dissolved in ethyl acetate (250 ml) and then washed with 1 M potassium hydrogenosulphate, satured sodium bicarbonate and saturated sodium chloride solutions. The organic layer was dried over sodium sulphate and concentrated *in vacuo* to yield a white solid (3.1 g). This compound (3.1 g) was dissolved in ethyl acetate (100 ml) and refluxed for 90 min. After concentration of the solvent *in vacuo*, the oily residue was dissolved in a mixture of dichloromethane/acetic acid (9:1, 100 ml) and treated with sodium borohydride as previously described [16, 17], to yield after flash chromatography the corresponding pyrrolidin-2-one as a white solid (1.62 g, 65%). This compound (1 g, 3.9 mmoles) was dissolved in acetone (5 ml) and 1 M sodium hydroxide solution (2 ml) was added. After 2 h, the reaction mixture was slowly acidified with 1 M HCl to pH 3–4. The Boc-statine was precipitated by addition of water, filtered, washed with water and then hexane. After drying *in vacuo*, pure Boc-statine (810 mg, 75%) was obtained. The sample presented the same physical properties to those reported in the literature [16–19]. This typical procedure can be applied to various Boc-, Z- and Fmoc-NCA derivatives. Physical and analytical data of the obtained *N*-protected tetramic acid derivatives **3** are reported in Table II.

Synthesis of (4S,5S)-4-hydroxy-5-(sec-butyl)pyrrolidin-2-one (8) from Boc-L-Ile-NCA

As an example, the reaction of Z-Ile-NCA with benzyl ethyl malonate is described. Benzyl ethyl malonate (0.70 ml, 3.43 mmoles) was dissolved in anhydrous tetrahydrofuran (THF) (10 ml). Sodium hydride (0.048 g, 4.12 mmoles, 1.2 equivalents) was added, followed by Z-Ile-NCA (1 g, 3.43 mmoles). After 30 min, the reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (150 ml). The organic layer was washed with 1 M potassium hydrogenosulphate, saturated sodium bicarbonate and saturated sodium chloride. After drying of the organic layer on sodium sulphate, the solvent was evaporated *in vacuo*. The residue was purified on silica gel with an ethyl acetate/hexane (9/1) eluent system to yield 0.82 g (51%) of pure oily compound **6** (^{1}H-NMR ($CDCl_3$/TMS) δ p.p.m., 7.3 (s, 10H); 5.23 (s, 2H); 5.14 (s, 2H); 5.04 (s, 1H); 4.68 (m, 1H); 2.00 (m, 1H); 1.51 (m, 2H); 1.32 (m, 3H); 0.86 (m, 6H)]. This compound (0.41 g, 0.88 mmoles) was dissolved in dioxane (2 ml) and hydrogenated with 10% Pd/C in the presence of DMAP (0.03 g, 0.22 mmoles) and 1N potassium hydrogeno-carbonate (2.5 ml). After 16 h, the reaction mixture was filtered on celite, concentrated *in vacuo* and the residue dissolved in ethanol (5 ml). 5N sulphuric acid (0.69 ml) was added and the solution was refluxed for 1 h. After cooling and removal of the ethanol, the residue was dissolved in chloroform (100 ml), washed with water, dried on potassium sulphate and concentrated *in vacuo*. The desired compound (5S, 1'S)-5-(*sec*-butyl)pyrrolidin-2,4-dione (**7**) was crystallized in diethyl ether (60 mg, 44%, 1st crop). m.p. 103–108°C; MH^+ 156; ^{1}H-NMR ($CDCl_3$/TMS, δ p.p.m., J Hz); 8.33 (s, 1H, NH); 3.95 (d, 1H, CHα, J = 3.4); 2.99 (s, 2H, CH_2); 1.88 (m, 1H); 1.49–1.14 (m, 2H, CH_2); 1.03 (d, 3H, CH_3, J = 6.9); 0.42 (t, 3H, CH_3, J = 7.3). The corresponding (4S,5S)-4-hydroxy-5-(*sec*-butyl)pyrrolidin-2-one **8** was obtained by hydrogenation of compound **7** in the presence of PtO_2 at 30 bar H_2 for 24 h as described by Schmidt *et al.* [19].

Synthesis of *N*-benzyloxycarbonyl-L-valine Keto Ylide (9)

As a typical experiment we describe the reaction of Z-L-Val-NCA with ethyl (triphenylphosphoranylidene) acetate. Z-Val-NCA (1.0 g, 3.6 mmoles) was dissolved in dichloromethane (10 ml) and ethyl (triphenylphosphoranylidene) acetate (1.25 g, 3.6 mmoles) was added to the cooled solution. After 15 min the solvent was removed *in vacuo*, and the residue dissolved in ethyl acetate (150 ml). The organic layer was washed with 1 M potassium hydrogenosulphate, satured sodium bicarbonate and saturated sodium chloride, dried on sodium sulphate. After removal of the solvent *in vacuo*, the residue was purified by column chromatography to afford crystalline compound **9** (1.48 g, 71%). Physical and chemical characteristics are reported in Table III.

Table 3 Characterization of N-Protected Amino Acid Keto Ylides **9** Synthesized from UNCAs

UNCAs	m.p. (°C)	$(Ph)_3P{=}CH{-}COOR$	Yield (%) compound **9**	MH^+
Boc-Ala	153–155	R = Et	54[a,b]	520
Boc-Gly	182–184	R = Et	60[a,b]	506
Boc-Val	62–65	R = Et	55[a,b]	548
Z-Phe	164–165	R = Bzl	90[a]	692
Z-Ala	130–133	R = Et	35[a]	554
Z-Val	108–109	R = Et	71[a]	582
Z-Gly	134–136	R = Et	75[a]	540
Fmoc-Leu	75–80	R = Et	50[a]	684
Fmoc-Gly	105	R = Et	55[a]	628
Z-Phe	122–124	R = *t*Bu	67[a]	658

[a]: compound characterized by ^{1}H-NMR at 250 MHz.
[b]: compound characterized by ^{13}C-NMR at 250 MHz.

This type of reaction is very simple and can be performed with *N*-Fmoc, *N*-benzyloxycarbonyl, *N*-Boc NCA with various triphenylphosphoranylidenes. Physical and analytical characteristics of some of the compounds that were obtained are reported in Table III. These derivatives can be oxidized into vicinal tricarbonyl compounds as described by Wasserman [21–24, 28, 30, 31] or using [bis(acetoxy)-iodo]-benzene [36].

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