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# Enol Esters as Intermediates for the Facile Conversion of Amino Acids into Amides and Dipeptides

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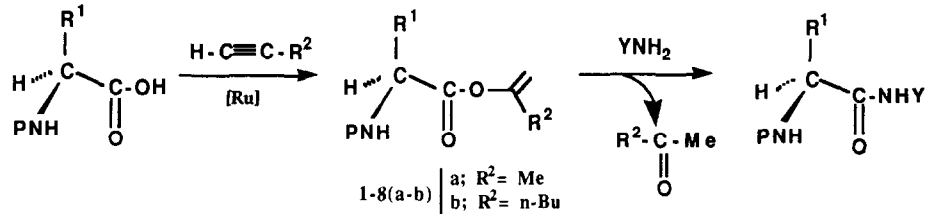
***Abstract:*** *N-Protected amino enol esters are easily transformed at room temperature into amino amides, and in the presence of potassium cyanide as catalyst, into tertiary amides and dipeptides.*

α-Amino amides are useful intermediates for the access to biologically active substances[1-4]. The amides P-NHCH(R)$CONH_2$ are used for the preparation of optically active geminal amino amides either *via* Hofmann rearrangement[1] or by condensation with an aldehyde and benzotriazole followed by aminolysis[2]. They are also key substrates for the enzyme resolution of amino acids using L-specific aminopeptidases[3]. Amino acid amides are usually prepared from amino nitrile derivatives[3a], amino acid chlorides[3b] or preferably mixed anhydrides resulting from the reaction of chloroformate with *N*-protected amino acids[1,4] The latter strategy is commonly used for the two-step transformation of *N*-protected amino acids into dipeptides. Mild and effective methods of preparation of dipeptides are currently sought after, such as the high pressure reaction of *N*-protected amino acids with amino acid salts[5] or the use of bromo-tris(dimethylamino)phosphonium hexafluorophosphate (BROP)[6].

We report here a simple route to amides and dipeptides based on the catalytic synthesis of enol esters followed by mild acylation of ammonia, amines and α-aminoesters (1).



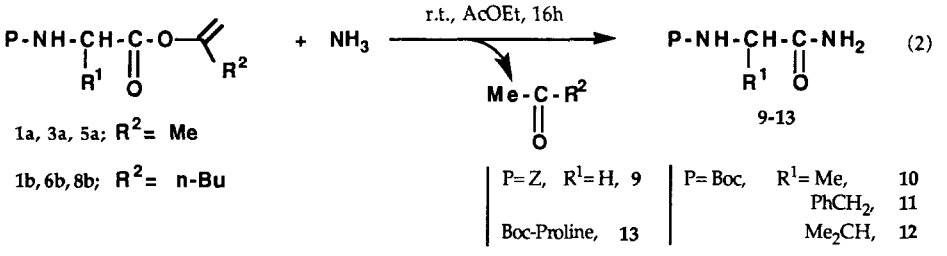

(1)

P: *tert*-BuOCO- (Boc) or $PhCH_2OCO$- (Z)

Z-Gly(**1a,b**), Z-Ala(**2b**), Boc-Ala(**3a**), Z-Phe(**4b**), Boc-Phe(**5a**), Boc-Val(**6b**), Z-Pro(**7b**), Boc-Pro(**8b**)

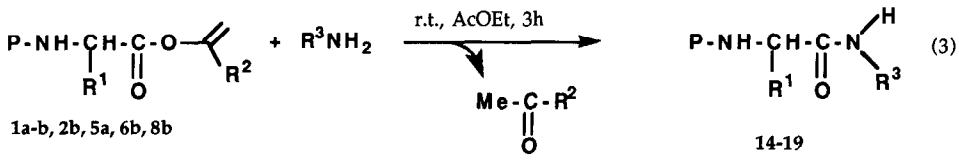
We have recently reported that ruthenium(II) complexes are efficient catalyst precursors for the addition of *N*-protected amino acids to propyne without racemisation to produce enol esters of type **a** ($R^2$= Me)[7]. We have now found that enol esters **1-8b** ($R^2$= n-Bu) can also be obtained in 60-80% yield by addition of the corresponding *N*-protected amino acids to hex-1-yne in the presence of catalytic amounts of $RuCl_2(PPh_3)(p\text{-cymene})$[8]. This reaction takes place without racemisation since after hydrolysis of the enol ester **2b** ($[\alpha]_D^{20}$= - 28°; c= 1, EtOH), the recovered Z-Ala-OH is identical to the starting *N*-protected amino acid as indicated by optical rotation.

The enol esters of type **a** or **b** react at room temperature with ammonia in ethyl acetate to give the simple *N*-protected α-amino amides (2). In a typical example, a 5 ml solution of ethyl acetate containing 1.49 g (5 mmol.) of hex-1-en-2-yl-Boc-prolinate **8b** was saturated by bubbling gaseous ammonia, and the mixture was stirred overnight (16 h) at room temperature. After evaporation, the amide **13** was isolated in 65% yield. The amino amides **9-12** were obtained in a similar way from enol esters **1a**, **3a**, **5a** and **6b** in 83, 80, 72 and 69% yield, respectively (2). α-Amino amides **9**, **10** and **11** were white solids recrystallized from $CH_2Cl_2/Et_2O$ mixtures, whereas **12** and **13** were oily compounds. When the ester **1b**, dissolved in ethyl acetate, was treated for 4 h with a stoichiometric amount of ammonia provided by a 7 N solution of $NH_3$ in methanol, a 85% yield of the amide **9** was obtained. The formation of amides **9-13** takes place without significant racemisation for compound **10** ($[\alpha]_D^{20}$= - 41°; c= 2, EtOH) on hydrolysis affords Boc-Ala-OH as the pure starting enantiomer.




It clearly appears that enol esters **1a, 1b, 3a, 5a, 6b** and **8b** are considerably activated with respect to their ethyl analogs. For example, ethyl-N-ethylprolinate treated in methanol with $NH_3$ afforded only 39% of the corresponding primary amide after 38 h at 50 °C[9].

The direct synthesis of functional amides was also possible under very mild conditions starting from hydroxy or unsaturated primary amines. When 5.5 mmol. of ethanolamine were allowed to react with 5 mmol. of enol esters **1a**, **6b** and **8b** at room temperature in 5 ml of ethyl acetate, the ethanolamides **14-16** were isolated in 90, 92 and 75% yield, respectively. Under similar conditions, allylamine gave the *N*-allylamides **17**, **18** and **19** in 87, 85 and 84% yield, by reaction with the esters **1b**, **2b** and **5a** (3).




1a-b, 2b, 5a, 6b, 8b

14-19 (3)

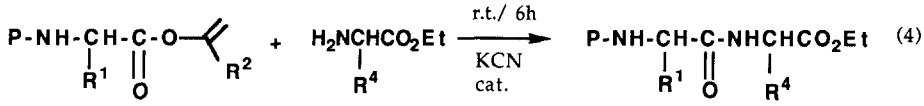
$R^3$= $CH_2CH_2OH$, **14** (Z-Gly), **15** (Boc-Val), **16** (Boc-Pro)

$R^3$= $CH_2CH{=}CH_2$, **17** (Z-Gly), **18** (Z-Ala), **19** (Boc-Phe)

The amide formation is mild and clean, and takes place only with elimination of acetone or hexan-2-one from enol esters of type **a** or **b**.

The acylation of secondary amines and α-amino esters under the above conditions did not take place, even on heating in the presence of usual activating agents like dimethylaminopyridine (DMAP), imidazole or KI. The use of KCN as catalyst has allowed us to quantitatively convert enol amino esters **a** and **b** into tertiary amides and dipeptides at room temperature. Högberg et al. had already shown that ethyl carboxylates could be fairly activated towards the acylation of secondary amines ($Me_2NH$) in the presence of catalytic amounts of KCN at 50 °C[9]. Thus, 5.5 mmol. of piperidine reacted at room temperature with 5 mmol. of the enol esters **1b** or **2b**, in the presence of KCN (10 mol %) as catalyst, in 5 ml of tetrahydrofuran to give the amides **20** and **21** in 77 and 75% yield respectively. Morpholine reacted the same way to afford the amides **22** (80%) and **23** (72%) when the enol esters **1b** and **7b** were used.

Dipeptide derivatives Z-GlyGlyOEt (**24**), Z-AlaGlyOEt (**25**), Z-AlaPheOEt (**26**) and Z-PheGlyOEt (**27**) were prepared at 20-25 °C in 96, 80, 85 and 78% isolated yield, respectively, by treatment of 5 mmol. of the appropriate enol ester **1b**, **2b** or **4b** with 5 mmol. of glycine or phenylalanine ethyl ester hydrochlorides in the presence of 10% KCN and $Et_3N$ (5.5 mmol.), in 10 mL of ethyl acetate for 6 h (4).




1b, 2b, 4b

24-27 (4)

P= Z | $R^4$= H, **24** ($R^1$= H), **25** ($R^1$= Me), **27** ($R^1$= $CH_2Ph$)

P= Z | $R^4$= $PhCH_2$; **26** ($R^1$= Me)

It should be noticed that only the dipeptide **24** could be formed in very good yield (96%), at room temperature even without potassium cyanide. The dipeptides **24-27** were purified by recrystallization from $CH_2Cl_2/Et_2O$/hexane mixtures and their optical rotations were in good agreement with those cited in the literature[10]. For compound **26**, obtained in 85% yield from **2b**, the presence of only one diastereoisomer was confirmed by NMR.

The catalytic synthesis of enol esters from α-amino acids and hex-1-yne avoids the use of harmful products like phosgene derivatives, generally used for the activation of the carboxylic function of α-amino acids, and these enol esters allow clean and mild acylations giving as by-product, only a ketone easy to remove.

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