A Novel Four-Component Synthesis of N-Substituted Amino Acid Esters

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Abstract: A library of *N*-substituted amino acid esters was synthesized using a solid phase bound organic isocyanide that provides a C1 synthon to the final molecule. This novel four-component, onepot reaction delivers the final products in acceptable yields with high purities of the crude reaction products, facilitating the final purification. The preparation of the isocyano resin is also described the intermediates being controlled by ATR-spectroscopy.

Key words: multi-component reaction, amino acids, polymer-supported synthesis, combinatorial chemistry, Lewis acids

The discovery of novel synthetic routes towards amino acid derivatives is an area of continued interest and creativity of organic chemists. The Strecker three-component reaction, a corner stone amino acid synthesis procedure using aldehydes, amines and cyanide, has been an early example of multi-component reactions in organic chemistry. Improved multi-component variants of this reaction have been introduced since, using trimethylsilylcyanide together with lanthanide triflates as Lewis acid catalyst,¹ or using carbon monoxyde as the source of the carboxylic acid carbon atom under palladium catalysis instead of Strecker's cyanide.² Exploring other compound classes that can replace the cyanide or carbon monoxyde and comprising a nucleophilic carbon atom allowed for discovery of novel three-component reactions, for example reacting alkynes³ or α -alkenyl boronic acids⁴ with a suitable carbonyl and amine component.

Similar to carbon monoxide, organic isocyanides contain a carbon atom in a monodentate, C^{II} oxidation state. Thus, it seemed reasonable to investigate, whether isocyanides could be used as an equivalent of Strecker's cyanide anion.

The Ugi-type four-component addition of isocyanides with aldehydes and amines in methanol usually yields α -amino acid amides **2** through a postulated imino-ether intermediate **1** (Scheme 1).⁵

On the other hand, it is known that the aqueous cleavage of imino-ethers depends on reaction conditions, yielding in most cases the respective amides as above, or, more rarely, carboxylic acid esters.⁶ Combining this alternative imino-ether cleavage towards carboxylic acid esters with the Ugi-four component reaction, we developed a novel procedure for the synthesis of *N*-substituted α -amino acid esters using aldehydes, alcohols, amines and solid-phase bound isocyanides. Polymer bound isocyanide was obtained from aminomethyl polystyrene or TentaGel-NH₂ through treatment with formic acid/acetic anhydride and subsequent dehydration of the polymer bound formamide with tosylchloride/pyridine.⁷ The completion of the formylation was followed by the Kaiser-test⁸ and ATR-IR spectroscopy (Figure 1).

The conversion of the formamide to the polymer bound isocyanide was determined by reacting the polymer with a tenfold excess of *N*-benzylidene aniline and Fmoc-glycine in methanol/dichlormethane = 1:1. The Fmoc-group



Scheme 1 Mechanism of the synthesis of *N*-substituted α -amino acids methyl esters using polymer bound isocyanide; PS = polystyrene resin.

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Figure 1 ATR-IR spectra of isocyanide resin formation: Spectrum A shows the starting aminomethyl polystyrene resin, spectrum B the carbonyl band of the respective formamide 1674 cm⁻¹, and spectrum C the isocyanide band at 2145 cm⁻¹. It is also seen that the isocyanide formation was not complete as revealed by the still prevalent carbonyl band in spectrum C. A = aminomethyl polystyrene, B = formamidomethyl polystyrene, C = isocyanomethyl polystyrene, 1 = carbonyl band, 2 = isocyanide band. A Thermo Nicolet Nexus instrument with the ATR unit Smart DuraSampIIR was used.

was cleaved and quantified according to Meienhofer.⁹ The loading of the polymer was calculated to be 0.61 mmol/g.

In the uncatalyzed reaction, using a polymer bound isocyanide derived from aminomethyl polystyrene resin, we did not obtain any observable product **3** in solution. Therefore, we tested the effect of several Lewis acid catalysts and various reaction conditions. From all catalysts tested [Yb(OTf)₃, InCl₃, ZnCl₂, FeCl₃, BF₃·Et₂O], only boron trifluoride etherate gave significant amounts of the



Figure 2 ATR-IR spectrum of the intermediate iminoether: Spectrum A shows the starting isocyanomethyl polystyrene, spectrum B the polymer bound iminoether intermediate after reaction with the imine, an alcohol and boron trifluoride etherate. In the spectrum B the isocyanide band at 2145 cm⁻¹ disappeared and a new band at 1701 cm⁻¹ for the C=N stretch vibration of the iminoether is visible. The ether C-O-C band is visible at 1058 cm⁻¹. Spectrum A = isocyanomethyl polystyrene, spectrum B = polymer bound iminoether intermediate, 1 = isocyanide band, 2 = CN-band, 3 = C-O-C-band

expected *N*-substituted α -amino acid methyl esters **3** when using methanol as the alcohol component. The formation of the iminoether **1** could be observed by ATR-IR-spectroscopy (Figure 2).

This imino-ether is than cleaved by a acetone/water mixture to the corresponding *N*-alkyl, *N*-aryl- or *N*-hetaryl amino acid methyl ester **3** (Scheme 1). The respective byproduct α -amino acid amide **2** would remain bound on solid support, allowing for a facile separation of the desired products.¹⁰

Table 1 Yields and Purities (in Parenthesis) of the *N*-Substituted α -Amino Acids Methyl Esters Obtained from the Boron Trifluoride Catalyzed Reaction of Methanol and Cyanomethyl Polystyrene with the Corresponding Aldehydes and Amines after Subsequent Treatment with Water^a

Starting Materials	⟨ → ⊣ [°] _H	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	CI-	, ≻K ^o	⟨S→CO H	N H
	56 (95)	24 (88)	53 (94)	53 (82)	19 (92)	32 (68)
O-NH2	15 (96)	20 (40)	15 (94)	45 (95)	16 (45)	30 (91)
CI-NH2	64 (94)	-	56 (97)	40 (94)	21 (95)	28 (92)
→NH₂	Traces	Traces	Traces	Traces	Traces	18.3 (23)
NH ₂	24 (30)	_	27 (28)	Traces	_	20 (62)
	34 (96)	42 (94)	29 (97)	18 (93)	Traces	19 (90)

^a Yields were calculated based on the loading of the resin, purities were determined by reversed phase HPLC [Agilent 1100 HPLC-system, YMC ODS-A column, 50×2 mm with guard column 10×2 mm; detector wavelength: 220 nm; flow: 0.6 mL/min; gradient: 0 min (10% acetonitrile, 80% water, 10% 0.1 M HCOOH), 2.5 min (90% acetonitrile, 10% 0.1 M HCOOH), 4 min (90% acetonitrile, 10% 0.1 M HCOOH), 6 min (10% acetonitrile, 80% water, 10% 0.1 M HCOOH)].

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Both yields and purities of the final products were significantly higher when the aldehyde and amine were precondensed to the respective imine and solid phase bound isocyanide, boron trifluoride etherate and alcohol were added sequentially, as compared to a true four-component reaction protocol. Out of 36 tested aldehyde-amine combinations, 17 crude reaction products were obtained with a purity higher than 90% (Table 1).

While aliphatic amines gave only poor results, aromatic amines yielded the respective products in both satisfactory yields and purities. Using the more water compatible isocyano-TentaGel instead of the isocyanomethyl polystyrene resin, both yields and purities of the crude reaction products could be improved by about twofold for unsatisfactory cases as *N*-benzyl phenyl-glycine methylester and *N*-benzyl 4-chlorophenyl-glycine methyl ester, giving 53.5% (61% purity) and 44.5% yield (65% purity), respectively. Replacing methanol with isopropanol and 5-phenylpentanol as the hydroxy component yielded in similarly satisfactory results.

In summary, the described reaction sequence provides a novel and facile, four-component synthesis route to unnatural amino acid esters. Remarkably, only the carbon atom of the polymer bound isocyanide, which acts as a C1 synthon, appears in the final product. The use of other nucleophiles like amines or C-nucleophiles that could replace the alcohol in the described process above is under current investigation.

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- (10) Synthesis of N-(4-Methoxyphenyl)-(R,S)-valine methylester: 0.044 mL Isobutyraldehyde (0.48 mmol) and 60 mg *p*-anisidine (0.48 mmol) were dissolved in 2 mL dry dichloromethane and 50 mg molecular sieves (0.4 nm) was added. The reaction mixture was stirred at room temperature for one hour. The molecular sieve was filtered off and 0.195 mL dry methanol (4.8 mmol), 0.183 mL boron trifluoride etherate (1.44 mmol) and 400 mg isocyanomethyl polystyrene (0.24 mmol) were added together with 2 mL dry dichloromethane. The reaction mixture was shaken at room temperature for two hours. The resin was filtered off and washed twice with dry dichloromethane and dry acetone. The cleavage was performed by shaking the resin with a mixture of acetone/water = 4:1 for 4 h at room temperature. The resin was filtered off and washed several times with acetone. The combined filtrates were combined and the solvent was evaporated, yielding 22.8 mg N-(4methoxyphenyl)-(R,S)-valine methylester as a yellow oil (40% yield, calculated based on the loading of the resin). Satisfactory analytical data were obtained. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ (ppm) 1.00 [d, ³*J*(H,H) = 6.3 Hz, 3 H, CH₃CH], 1.09 [d, ${}^{3}J$ (H,H) = 6.3 Hz, 3 H, CH₃CH], 2.33 (m, 1 H, CH₃CHCH₃), 3.72 (s, 3 H, CH₃O), 3.79 (s, 3 H, CH₃O), 4.06 (m, 1 H, CHNH), 6.88 [d, ${}^{3}J$ (H,H) = 8.6 Hz, 2 H, ArH], 7.43 [d, ${}^{3}J(H,H) = 8.6$ Hz, 2 H, ArH]. ${}^{13}C$ NMR (100 MHz, CDCl₃, 25 °C): δ(ppm) 16.3 CH₃CH), 19.5 (CH₃CH), 28.4 (CH₃CH), 53.1 (CH₃O), 55.5 (CH₃O), 71.4 (CHNH), 115.2 (m-CAr), 124.7 (i-CAr), 125.6 (o-CAr), 160.5 (p-CAr), 167.0 (CO).