A Simple and Convenient Synthesis of *N*-Formyl Amino Acid Esters Under Mild Conditions

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A variety of amino acid ester hydrochlorides react with cyanomethyl formate at room temperature to give the *N*-formyl amino acid esters in good yields and without racemization.

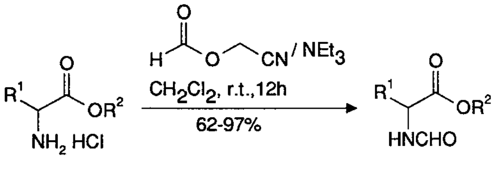
One of the most useful and versatile functional groups to be introduced into an organic molecule is the formyl group. A number of formylating methods and formylating agents have been reported (cf. Ref.[1–4]). Formyl compounds have been widely used for the protection of amino and hydroxy groups.[5] Thus, *N*-formyl amino acid esters are useful in peptide synthesis, especially in enzymatic synthesis in aqueous media.[6] *N*-Formylation of amino acid *tert*-butyl esters are important, because the products are readily converted into isocyano acid *tert*-butyl esters, which are used as starting materials in four component condensations.[7] Standard *N*-formylation by formic acid and acetic anhydride[8,9] proved incompatible with *tert*-butyl groups.

N-Formyl amino acid esters can be obtained from amino acid esters by reaction with: formic acid and acetic anhydride,[8,9] in situ formed formic anhydride,[10] activated aryl formate,[11,12] chloral followed by elimination,[13] enol formates,[14] trialkyl orthoformates,[7] or *N*-(diethylcarbamoyl)-*N*-methoxyformamide.[15]

Despite the usefulness of the reagents mentioned above there are several factors in some cases limiting their application, for example thermal instability, formation of undesirable or toxic byproducts, difficult accessibility or the application of expensive catalysts for the preparation of the formylating agent (cf. ref.[3,14] and lit. cited therein).

Recently, we reported the use of cyanomethyl formate as a new, easily prepared and convenient formylating agent for amines and alcohols with high *N*-selectivity.[4] We report here a simple *N*-formylation procedure for the preparation of *N*-formyl amino acid esters **2** using cyanomethyl formate, which accomodates chirality and functionality.

The procedure can be used directly on hydrochlorides of amino acid methyl, ethyl, benzyl and *tert*-butyl esters **1a–n**. The reaction is carried out at room temperature within 12 hours furnishing the compounds **2a–n** in good to excellent yields and in high optical purity (ee ≥ 99 %) (Table). The *tert*-butyl esters **1k–n** are formylated without special care to give the corresponding *N*-formyl compounds **2k–n** in 78–88 % yield. Serine gave only the *N*-formylated product **2i**. In all cases, the formylations proceed without any catalysts.



1a-n **2a-n**

Table. *N*-Formylated Amino Acid Esters **2a–n** Prepared

Product	Parent Amino Acid	R^1	R^2	Yield[a] (%)	bp/mbar (°C) or mp (°C) (solvent)	$[\alpha]_D^{20}$ found	$[\alpha]_D^{20}$ reported	^{1}H NMR (CDCl$_3$) δ (CHO)
2a	L-Ala	Me	Me	62	80–90/0.12	– 34.65 (c = 0.6, EtOH)	– 34.60 (c = 0.6, EtOH)[13]	8.18
2b	L-Leu	*i*-Bu	Me	84[b]	80–95/0.09	– 43.52 (c = 1, MeOH)	– 43.50 (c = 1, MeOH)[13]	8.14
2c	D-Leu	*i*-Bu	Me	86[b]	90–105/0.40	+ 43.34 (c = 1, MeOH)	–	8.14
2d	L-Phe	PhCH$_2$	Me	94[c]	175–180/29	+ 85.10 (c = 1, CH$_2$Cl$_2$)	+ 86.37 (c = 1, CH$_2$Cl$_2$)[13]	8.11
2e	D-Phe	PhCH$_2$	Me	97[c]	175–180/29	– 84.18 (c = 1, CH$_2$Cl$_2$)	–	8.11
2f	L-Phe	PhCH$_2$	Et	82	135–150/0.12	+ 81.67 (c = 1.78, CHCl$_3$)	–[d]	8.17
2g	L-Glu	EtO$_2$C(CH$_2$)$_2$	Et	85	120–130/0.10	+ 27.28 (c = 1.92, CHCl$_3$)	–[e]	8.23
2h	L-Val	*i*-Pr	Et	87	80–95/0.12	– 53.99 (c = 2.08, H$_2$O)	–[f]	8.27
2i	L-Ser	HOCH$_2$	PhCH$_2$	85	87–90 (toluene)	– 18.50 (c = 2, EtOH)	– 18.20 (c = 2, EtOH)[10]	8.15
2j	L-Val	*i*-Pr	PhCH$_2$	92	175–180/0.08	– 40.10 (c = 2, EtOH)	– 40.20 (c = 2, EtOH)[10]	8.25
2k	L-Leu	*i*-Bu	*t*-Bu	78[b]	150–160/0.05	– 50.07 (c = 2, EtOH)	– 49.90 (c = 2, EtOH)[10]	8.20
2l	D-Leu	*i*-Bu	*t*-Bu	88[b]	110–115/0.08	+ 49.90 (c = 2, EtOH)	–	8.20
2m	L-Phe	PhCH$_2$	*t*-Bu	88	155–160/0.08	+ 16.19 (c = 0.7, EtOH)	+ 15.97 (c = 0.7, EtOH)[9]	8.11
2n	L-Val	*i*-Pr	*t*-Bu	81	67–75 (hexane)	– 33.38 (c = 2, EtOH)	– 33.70 (c = 2, EtOH)[10]	8.25

[a] Yield of pure, isolated product; purity confirmed by ^{1}H NMR.
[b] Enantiomeric excess was determined by ^{1}H NMR (500 MHz, CDCl$_3$) using Eu(tfc)$_3$ as shift reagent: ee ≥ 99 %.
[c] Enantiomeric excess was determined using HPLC analysis (Chiralpak, EtOH): ee ≥ 99 %.
[d] ^{13}C NMR (main rotamer): δ = 171.24 (CO$_2$Et), 160.85 (CHO), 135.68, 129.33, 128.52, 127.14 (C-aryl), 61.66 (OCH$_2$), 51.92 (C-N), 37.79 (Ph$\underline{\text{C}}$H$_2$), 14.07 (CH$_3$).
[e] ^{13}C NMR (main rotamer): δ = 172.78, 171.53 (CO$_2$Et), 161.15 (CHO), 61.84, 60.77 (OCH$_2$), 50.35 (C-N), 30.25, 27.35 (CH$_2$), 14.17, 14.13 (CH$_3$).
[f] ^{13}C NMR (main rotamer): δ = 171.58 (CO$_2$Et), 160.99 (CHO), 61.33 (OCH$_2$), 55.52 (C-N), 31.16 [CH(CH$_3$)$_2$], 18.83, 17.49, 14.08 (CH$_3$).

In conclusion, the *N*-formylation of amino acid ester hydrochlorides **1**, including *tert*-butyl esters, is carried out in dichloromethane at ambient temperature in a simple operation using cyanomethyl formate.

Melting points were determined with a Boetius apparatus and are corrected. ^{1}H NMR spectra were measured at 300 MHz on a Varian Unity 300 or at 500 MHz on a Varian Unity 500 with TMS as internal standard. ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer in $CDCl_3$; internal standard: HMDS (δ: 1.9). Optical rotations were measured on a Perkin-Elmer polarimeter 241. All amino acid ester hydrochlorides were purchased from Bachem-Biochemica GmbH and used without further purification.

N-Formyl Amino Acid Esters 2a–n; General Procedure:

The amino acid ester hydrochloride **1** (4 mmol) and cyanomethyl formate (0.34 g, 4 mmol) were dissolved in CH_2Cl_2 (6 mL) and cooled in an ice-bath to 0 °C. Then, a solution of Et_3N (0.55 mL, 4 mmol) in CH_2Cl_2 (1 mL) was added. After 12 h at r.t., CH_2Cl_2 (43 mL) was added. Finally, the mixture obtained was washed with brine (3 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by distillation or crystallization (Table).

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