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Environmentally benign process for the synthesis of *N*-formyl amino acid esters

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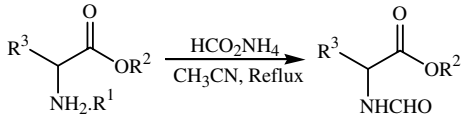
Abstract—Several amino acid ester hydrochlorides were reacted with ammonium formate to give *N*-formyl amino acid esters in good yields.

A potentially useful protecting group, which can be introduced on the amine functionality is the formyl group.[1] *N*-Formyl amino acid derivatives are useful in peptide chemistry.[2] Moreover, dehydration of formamides can give isocyano derivatives, which are useful glycine equivalents.[3] The formyl group in combination with a *tert*-butyl ester group is useful in preparing highly functionalized peptide derivatives.[4] Generally, *N*-formyl amino acid esters are prepared from the corresponding amino esters using orthoformates[5] and various other formylating agents.[6] However, many of these methods involve reagents that are either toxic or expensive. Although orthoformates are commercially available, they are prepared from chloroform, which is not a favorable starting material from an environmental point of view. Herein, we report ammonium formate as an efficient formylating agent for the synthesis of *N*-formyl amino acid esters (Scheme 1).



R^1 = HCl, PTSA

R^2 = Et, Me, *tert*-Bu, CH_2Ph

R^3 = H, Me, *i*-Pr, *i*-Bu, Allyl

Scheme 1.

The reaction of amino acid ester hydrochlorides with ammonium formate in dry acetonitrile at reflux gave the *N*-formyl derivatives in good yields. Generally, the formylation reaction requires 8–12 h for completion. The results are summarized in Table 1.

Moreover, we found that optically pure amino acid ester hydrochlorides react to give the corresponding *N*-formyl derivatives without racemization. The specific rotation values for these samples are comparable to the literature values[5] as given in Table 2.

It is noteworthy to mention that standard *N*-formylation by other methods is incompatible with *tert*-butyl groups,[8] although DCC was used in combination with formic acid to formylate glycine *tert*-butyl ester hydrochloride.[9] However, the use of ammonium formate gave *N*-formyl glycine *tert*-butyl ester in good yield. In the literature, it was reported that primary amines did not give formylation using ammonium formate.[10] Surprisingly, in our hands all the amino acid esters gave the formylated products in good yields.

In conclusion, we have developed a simple and useful methodology for the preparation of *N*-formyl amino acid esters using the inexpensive, readily available, and environmentally acceptable reagent ammonium formate.

Typical experimental procedure for the N-formylation: To a stirred solution of glycine ethyl ester hydrochloride salt (5 g, 35 mmol) in dry acetonitrile (35 mL) was added anhydrous ammonium formate (4.6 g, 73 mmol). The resultant heterogeneous reaction mixture was refluxed

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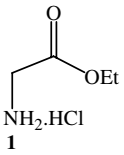
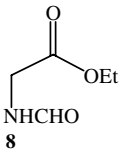
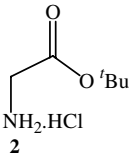
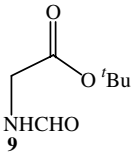
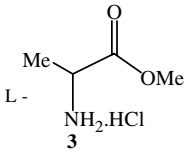
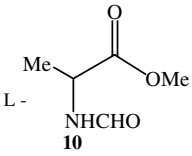
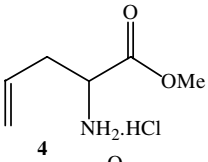
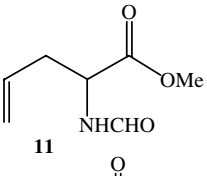
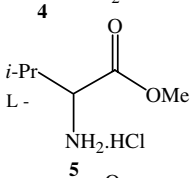
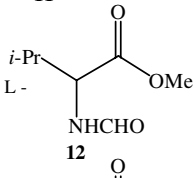
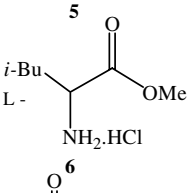
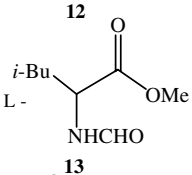
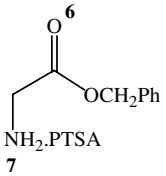
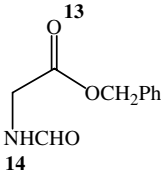
Table 1. The *N*-formylated derivatives prepared

Starting material	*N*-Formyl derivatives	Yield (%)
 **1**	 **8**	91
 **2**	 **9**	86
 **3**	 **10**	81
 **4**	 **11**	66
 **5**	 **12**	84
 **6**	 **13**	88
 **7**	 **14**	63

All the compounds except **11** are known and physical properties agree with literature. The spectral data for **11** is given in Ref. 7. Compound **4** is a racemic mixture.

for 12 h. The solvent was evaporated and the reaction mixture was diluted with water, extracted with ethyl acetate, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was chromatographed on a silica gel column. Elution of the column with 50% ethyl acetate/petroleum ether gave the pure *N*-formyl glycine ethyl ester (4.16 g, 91% yield) as a colorless liquid.

Table 2. List of $[\alpha]_D^{20}$ values for the optically active *N*-formyl derivatives prepared

N-Formyl derivatives	Observed value $[\alpha]_D^{20}$	Literature value[5] $[\alpha]_D^{20}$
10	−36.6 (*c* 0.6, EtOAc)	−34.6 (*c* 0.6, EtOAc)
12	−23.73 (*c* 1.98, EtOH)	−23.24 (*c* 1.98, EtOH)
13	−44.28 (*c* 2.1, EtOH)	−43.8 (*c* 2.1, EtOH)

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References and notes

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7. Spectral data for compound **11**:
   ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1H), 6.23 (br s, 1H), 5.68–5.63 (m, 1H), 5.20–5.12 (m, 2H), 4.80 (m, 1H), 3.78 (s, 3H), 2.66–2.60 (m, 2H).
   ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 160.6, 131.9, 119.7, 52.7, 50.4, 36.5.
   IR (neat): ν_{max} = 3440 (NH), 1745 (ester), 1658 (formyl) cm^{-1}. HRMS (QTOF): *m/z* for $C_7H_{11}NO_3Na$ (M+Na), calcd: 180.0637. Found: 180.0640.
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