Isocyanates, Part 4.[10] Convenient Phosgene-Free Method for the Synthesis and Derivatization of Enantiopure α-Isocyanato Carboxylic Acid Esters

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Abstract: A novel phosgene-free procedure for the synthesis of α-isocyanato carboxylic acid esters starting from α-amino acid esters has been achieved. The isocyanates are obtained enantiomerically pure (> 99% ee) by a DMAP-catalyzed isocyanation with di-*tert*-butyl dicarbonate, which proceeds in 10 min at room temperature. *In situ* derivatization of the isocyanates by reaction with amines and alcohols affords the corresponding enantiopure ureas and carbamates.

Isocyanates of α-amino acid esters represent useful chiral building blocks for enantioselective synthesis.[1] The standard method for the synthesis of α-isocyanato carboxylic acid esters involves reaction of the amino acid ester hydrochlorides with either gaseous phosgene[2,3] or a solution of phosgene in toluene in the presence of pyridine.[4] Both procedures suffer from the drawback that highly toxic phosgene is used as reagent. We recently reported a novel phosgene-free synthesis of alkyl- and arylisocyanates by a DMAP-catalyzed[5] reaction of the corresponding amines with di-*tert*-butyl dicarbonate, $(Boc)_2O$, which proceeds in 10 min at room temperature.[6] This method has now been used for the direct racemization-free conversion of amino acid esters into their corresponding isocyanates and provides some very promising applications to protecting group chemistry as well as an access to enantiopure starting materials for asymmetric synthesis.

Using our previously developed standard set of reaction conditions, a broad range of α-amino acid esters are converted into the α-isocyanato carboxylic acid esters **1** in high yields without racemization (Table 1). The isolation of the isocyanates of α-amino acid esters was achieved by low-temperature chromatography (see Experimental Procedure). As observed before with alkyl- and arylamines, we noted that sterically hindered amino groups give rise to better yields of the corresponding isocyanates. Thus, L-valine methyl ester and L-isoleucine methyl ester afforded better yields than L-phenylalanine methyl ester and L-leucine methyl ester. L-Alanine methyl ester was transformed into the isocyanate **1a** in 49% yield, while the isocyanate of glycine ethyl ester had to be transformed to the urea derivative by trapping with an amine in order to get moderate yields (*vide infra*). Even bulky alkyl groups in the ester moiety are beneficial: L-phenylalanine *tert*-butyl ester provided significantly better yields than L-phenylalanine methyl ester or allyl ester. The synthesis of α-isocyanato carboxylic acid esters was also performed by using catalytic amounts of DMAP. However, these reactions were not optimized. The isocyanate **1g** with an additional stereogenic center was obtained as a single diastereoisomer, indicating that the isocyanation occurs without racemization. The α-isocyanato carboxylic acid esters **1** were shown to be enantiomerically pure by the following evidences: 1. comparison of the values for the optical rotation with literature values (Table 1), 2. reaction of the isocyanates with enantiopure (*S*)-1-phenylethylamine to the corresponding diastereomerically pure urea derivatives, and 3. conversion of the isocyanates to known carbamate-protected amino acid derivatives and subsequent comparison of the optical rotation values.

The conversion of the α-amino acid esters into the urea derivatives **2** was achieved by *in situ* reaction of the intermediate α-isocyanato carboxylic acid esters **1** with either benzylamine or (*S*)-1-phenylethylamine (Table 2), following the previously described procedure.[8] Using this method the isocyanates don't need to be isolated and even derivatives of isocyanates which are volatile or highly reactive under the reaction conditions are readily available. The urea derivative **2a** could be isolated by addition of benzylamine after transformation of

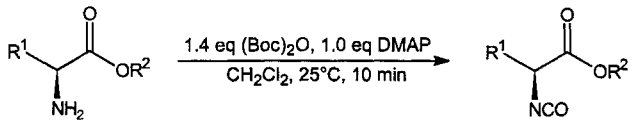

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Table 1. Synthesis of enantiopure α-isocyanato acid esters **1** from α-amino acid esters

	R^1	R^2	**1**, Yield [%]	$[\alpha]_D^{20}$ [a]	$[\alpha]_D^{20}$ (c, solvent) Ref.
a	Me	Me	49	–29.3°	—
				–16.4° [c]	–8.7° (1.8, $CHCl_3$) [7]
b	CH_2Ph	Me	56 (48) [b]	–79.4°	+71.9° (21°C, neat) [4]
c	CH_2Ph	$CH_2CH{=}CH_2$	55	–92.3°	—
d	CH_2Ph	*t*Bu	95	–29.5°	—
e	*i*Pr	Me	91 (72) [b]	–23.9°	–21.1° (19°C, neat) [4]
				–24.7° [d]	–11.8° (1.5, $CHCl_3$) [7]
f	*t*Bu	Me	82	–41.4°	–36.1° (21°C, neat) [4]
g	(*S*)-*s*Bu	Me	90	–9.2°	–4.3° (19°C, neat) [4]

[a] c = 1, DMF; unless otherwise noted. [b] Catalytic reaction: 1.1 equiv. $(Boc)_2O$, 0.1 equiv. DMAP, CH_2Cl_2, 25°C, 10 min. [c] c = 1.8, $CHCl_3$. [d] c = 1.5, $CHCl_3$.

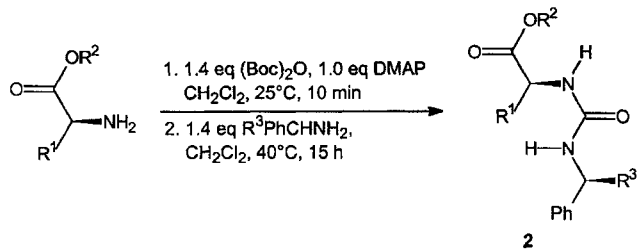

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Table 2. Synthesis of enantiopure ureas **2** from α-amino acid esters

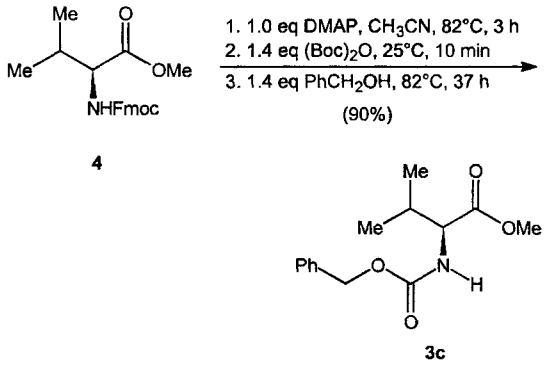
	R^1	R^2	R^3	**2**, Yield [%]	$[\alpha]_D^{20}$ [a]
a	H	Et	H	39	—
b	Me	Me	H	83	+3.8°
c	CH_2Ph	Me	H	97	+57.4°
d	CH_2Ph	Me	Me	95	+52.3°
e	CH_2Ph	*t*Bu	Me	94	+41.9°
f	*i*Pr	Me	H	99	+16.0°
g	*i*Pr	Me	Me	99	−10.4°

[a] c = 1, $CHCl_3$.

glycine ethyl ester into ethyl isocyanatoacetate. Addition of enantiopure (*S*)-1-phenylethylamine to the intermediate α-isocyanato carboxylic acid esters provided the diastereomerically pure urea derivatives **2d**, **2e**, and **2g**. Careful 500 MHz ^1H NMR analysis of these products confirmed by the absence of the signals for a second diastereoisomer that the isocyanates **1** were formed without partial racemization. Based on the sensitivity of this analytical method,[4,9] it can be followed that the α-isocyanato carboxylic acid esters **1** obtained by our method have an enantiomeric purity of more than 99% ee.

The addition of alcohols subsequent to the DMAP-catalyzed reaction of amines with di-*tert*-butyl dicarbonate provides the corresponding carbamates.[10] Carbamate protecting groups, like Moc, Boc, Cbz, and Aloc, are often used in peptide chemistry.[11] In the present study the Cbz- and Aloc-protected amino acid esters **3** were prepared from the amino acid esters by addition of benzyl alcohol or allyl alcohol to the intermediate α-isocyanato carboxylic acid esters **1** (Table 3). Comparison of the values for the optical rotation of the known compounds with literature values[12] confirmed again that no racemization occurred during the isocyanation process.

On the basis of these results we developed a novel high-yield amino acid ester protecting group transformation of the Fmoc moiety. The Fmoc protecting group is known to be removed under basic reaction conditions.[11] In the present investigation this was achieved using DMAP and combined with the isocyanate synthesis by addition of di-*tert*-butyl dicarbonate. Thus, *N*-Fmoc L-valine methyl ester **4** was deprotected on treatment with DMAP in acetonitrile at reflux, then transformed into methyl (*S*)-2-isocyanato-3-methylbutanoate **1e** by addition of $(Boc)_2O$, and converted to the Cbz-protected L-valine methyl ester **3c** ($[\alpha]_D^{20}$ = −21.3°, c = 1 in MeOH) by reaction with benzyl alcohol (Scheme 1). This novel one-pot conversion of Fmoc-protected amino acids into other carbamate-protected amino acids is general and potentially useful for peptide chemistry.



4 3c

Scheme 1

Under the usual reaction conditions (DMAP, $(Boc)_2O$, CH_2Cl_2, 10 min at room temperature) L-tryptophan methyl ester **5** was converted to the intermediate *N*-Boc-protected (*S*)-methyl 3-(indol-3-yl)-2-isocyanatopropanoate **6** and then cyclized *in situ* with concomitant loss of the *N*-Boc protecting group to the enantiopure β-carboline derivative **7** ($[\alpha]_D^{20}$ = +89.9°, c = 1 in DMF) by addition of an excess of trifluoroacetic acid (Scheme 2). The β-carboline derivative **7** represents a potentially useful chiral starting material for the enantioselective synthesis of indole alkaloids.[13] By careful low-temperature chromatography on silica gel (gradient elution with pentane/diethyl ether at −30°C) after the isocyanation process, compound **6** could be isolated and characterized. Subsequent Pictet-Spengler analogous cyclization to **7** was achieved on treatment with trifluoroacetic acid and thus confirmed the course of the reaction as depicted in Scheme 2.

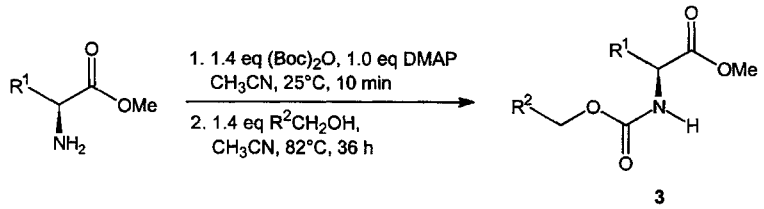


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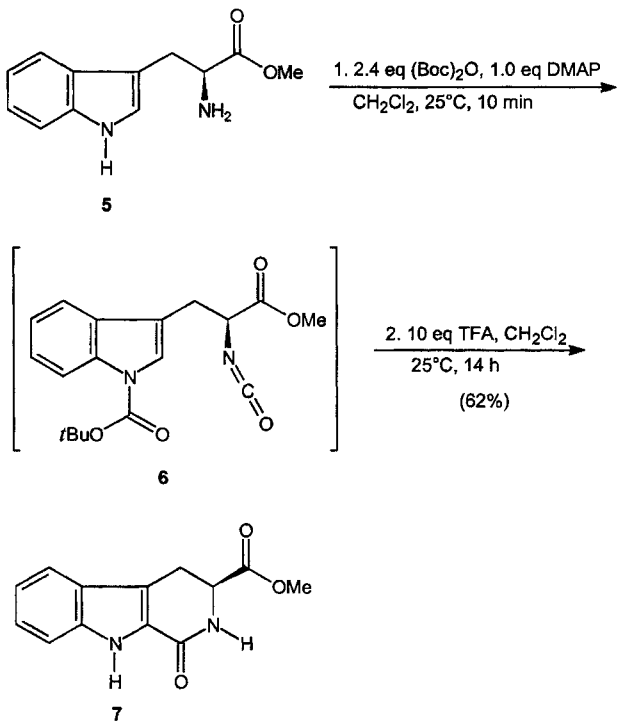
Table 3. Synthesis of enantiopure carbamate-protected α-amino acid esters **3**

	R^1	R^2	**3**, Yield [%]	$[\alpha]_D^{20}$ [a]	$[\alpha]_D^{20}$ [a], Ref.
a	Me	Ph	87	−35.2°	−33.0° [12a], −36.5° [12b]
b	CH_2Ph	Ph	90	−17.0°	−17.1° [12b]
c	*i*Pr	Ph	95	−20.9°	−21.9° [12b], −18.9° [12c]
d	*i*Pr	$CH{=}CH_2$	89	−26.3°	—

[a] c = 1, MeOH.



Scheme 2

In conclusion, a novel phosgene-free method for the conversion of α-amino acid esters into α-isocyanato carboxylic acid esters without racemization at the chiral center has been accomplished. The transformation opens up the way to the synthesis of amino acid-derived enantiopure building blocks which are also of potential utility as chiral ligands in asymmetric catalysis.[14]

Experimental Procedures

All reactions were performed in anhydrous solvents.

1d: A solution of L-phenylalanine *tert*-butyl ester (316 mg, 1.43 mmol) in dichloromethane (2 ml) was added to a solution of di-*tert*-butyl dicarbonate (436 mg, 2.0 mmol) and DMAP (174 mg, 1.43 mmol) in dichloromethane (2 ml) and the reaction mixture was stirred for 10 min at room temperature. Subsequent flash chromatography (pentane/diethyl ether 30:1 to 5:1) of the reaction mixture on silica gel at –30°C provided **1d** (334 mg, 95%) as a colorless liquid. $[\alpha]_D^{20}$ = –29.5° (c = 1 in DMF); IR (neat): ν = 2262 (NCO), 1737, 1395, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 3.01 (dd, *J* = 13.8 , 7.5 Hz, 1 H), 3.11 (dd, *J* = 13.8, 4.9 Hz, 1 H), 4.13 (dd, *J* = 7.5, 4.9 Hz, 1 H), 7.23 (m, 2 H), 7.30 (m, 3 H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 27.89 (3 CH_3), 39.89 (CH_2), 59.16 (CH), 83.56 (C), 127.30 (CH), 127.42 (NCO), 128.51 (2 CH), 129.46 (2 CH), 135.84 (C), 169.53 (CO).

3c: A solution of *N*-Fmoc-L-valine methyl ester **4** (200 mg, 0.57 mmol) in acetonitrile (6 ml) was treated with a solution of DMAP (69 mg, 0.57 mmol) in acetonitrile (2 ml) and refluxed for 3 h. After cooling to room temperature, a solution of di-*tert*-butyl dicarbonate (173 mg, 0.79 mmol) in acetonitrile (3 ml) was added and the reaction mixture was stirred for 10 min at room temperature. Then a solution of benzyl alcohol (86 mg, 0.79 mmol) in acetonitrile (3 ml) was added and the reaction mixture was stirred for 37 h at 82°C. Removal of the solvent and flash chromatography (hexane/ethyl acetate 30:1 to 10:1) of the residue on silica gel afforded **3c** (135 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ = –21.3° (c = 1 in MeOH); IR (neat): ν = 3353 (br), 1723 (br), 1525, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 2.16 (m, 1 H), 3.73 (s, 3 H), 4.31 (dd, *J* = 9.1, 4.8 Hz, 1 H), 5.11 (s, 2 H), 5.37 (d, *J* = 9.1 Hz, 1 H), 7.29-7.36 (m, 5 H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 17.48 (CH_3), 18.91 (CH_3), 31.21 (CH), 52.12 (CH_3), 58.96 (CH), 66.96 (CH_2), 128.10 (2 CH), 128.14 (CH), 128.48 (2 CH), 136.19 (C), 156.19 (CO), 172.54 (CO).

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References and Notes

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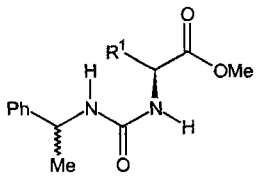

2d / 2d': R^1 = CH_2Ph

2g / 2g': R^1 = *i*Pr

Reaction of the isocyanates **1b** and **1e** with racemic 1-phenylethylamine afforded the ureas **2d/2d'** and **2g/2g'** as 1 : 1 diastereoisomeric mixtures. In the 500 MHz ^1H NMR spectra of these diastereoisomers the signals of the methyl esters were clearly separated in $CDCl_3$ solution (**2d/2d'**: δ = 3.627/3.644; **2g/2g'**: δ = 3.659/3.687). Addition of 1% of the corresponding 1 : 1 diastereoisomeric mixture to diastereomerically pure **2d** and **2g**, obtained from enantiopure (*S*)-1-phenylethylamine (*cf.* Table 2), gave a diastereoisomeric mixture of 99% de. In these mixtures of 99% de, the signal of the methyl ester of the minor diastereoisomer could be observed in the 500 MHz ^1H NMR spectrum.[4]

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