The use of cyclohexyl isocyanide in the esterification of *N*-benzoyl α-amino acids derivatives

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The *N*-benzoyl of α,β–dehydroamino acids that were obtained by condensation of *N*-benzoylglycine and an aldehyde, were esterified with an alcohol in high yield using cyclohexyl isocyanide to activate the carboxylic acid under neutral conditions.

Keywords: cyclohexyl isocyanide, esterification, α-amino acids, *α,β*-dehydro-*α*-amino acids, alcohols

The synthesis of *α,β*-dehydro-*α*-amino acids is important in the context of peptide-derived chemotherapeutics.[1–4] The substitution of proteinogenic α-amino acids by *α,β*-dehydro-*α*-amino acid residues usually affects markedly the physiological activity of peptides, changing their secondary structure and increasing their resistance to protease catalyzed hydrolysis.[5–7] The hydrogenation of *α,β*-dehydro-*α*-amino acids using Wilkinson-type chiral catalysts is one of the general methods for the enantioselective synthesis of α-amino acids.[1,2,8–11] α,β-Dehydro-α-amino acid derivatives have been obtained by the Wittig reaction, starting from easily accessible N-acyl-α-triphenylphosphonioglycinates as precursors of ylides[12] or by the Wadsworth–Emmons variant.[13–16]

The addition reactions to isocyanides has been of particular interest. For example the reaction of hydrogen halides to isocyanides at low temperatures has been reported to produce haloimines.[17] The reaction of organic acids, such as Meldrum's acid[18] or 1,1,1-trifluoro-2,3-pentandiones,[19] with isocyanides has also been reported. Isocyanides react with two equivalents of carboxylic acids to afford the corresponding carboxylic acid derivatives.[17] Recently it has been reported that the reaction of isocyanides with sulfonic acids lead to the corresponding sulfonamides.[20] A similar reaction was also reported between isocyanides and carboxylic acids in methanol as solvent to yield the corresponding carboxamides.[21]

Isocyanides alone have been shown to activate phosphoric acid derivatives in pyridine. [22] Esterification of *α*-amino acid derivatives has also been reported.[26–28]

Results and discussion

In this paper, we report the synthesis of α-substituted α-amino esters starting from the natural amino acids, glycine and (±)valine.

The amino group of glycine was protected with the benzoyl group as *N-ben*zoyl glycine **3**. The 2-phenyl-4*H*-oxazol-5-one (**4**), was condensed with an aldehyde to form the oxazolones **5** which was then hydrolysed to the corresponding acids **6**.

The acids **6** were treated with cyclohexyl isocyanide in different alcohols as solvent as shown in Scheme 1. These reaction afforded a simple route for the synthesis of *N*-acyl-*α,β*-dehydro-*α*-amino acid esters **7** under neutral condition in high yield. The reaction of *N*-benzoyl glycine or (±)valine **1a** under the same conditions afforded *N*-acyl-α-substituted *α*-amino acid esters **8**.

When the acid **6** was added to different alcohols as a solvent in the absence of cyclohexyl isocyanide, no product was detected.

Compounds **5a**, **6a** and **7a** were known and our m.p. and ^{1}H NMR spectroscopic data of compounds are in agreement with previously reported NMR data.[12,23–25,29,31]

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Compounds **6b**,**c**, **7b–f** and **8** were all new compounds and their structures were deduced from their elemental analyses and spectral data.

An X-ray crystallographic study has shown[29] that the stereochemistry of the double bond that was formed during condensation of **3** with the aldehydes has the Z-configuration in **6**.

The ^{1}H NMR spectra of products **7a–f** revealed the restricted rotation around the carbon–carbon double bond and with the ^{13}C NMR spectra were consistent with the presence of only one isomer (*Z*-isomer). Thus the NMR spectra were in agreement with the proposed structures.[30]

The ^{1}H NMR spectrum of compound **8** exhibited one sharp line at δ = 3.79 ppm for the proton of methoxy group. The NH was coupled with methine proton to give a doublet ($^3J_{HH}$ = 8.5 H_Z) at 6.63 ppm. After addition of D_2O the signal assigned to the NH proton disappeared. The two methyl groups are diastereotopic and showed distinct signals in the NMR spectra of compound **8** (Scheme 2). Two doublets ($^3J_{HH}$ = 6.5 Hz) at 1.00 and 1.02 ppm and multiplets at 2.29 ppm were observed for the two methyl groups protons and methine proton respectively. The other methine proton resonates at 4.80 ppm as a double doublet ($^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.5 Hz). The aromatic protons resonate between 7.27 and 7.82 ppm as multiplets. Two signals were observed for the methyl groups at 17.97 and 19.67 ppm in the ^{13}C NMR spectrum of compound **8**. The methine carbons resonated at 34.44 and 57.45 ppm. Four signals were observed between 127.07 and 134.29 ppm for aromatic carbons and the carbonyl carbons were observed at 167.38 and 172.67 ppm. The IR spectrum of compound **8** also supported the suggested structure. Strong absorption bands were observed at 3335, 1741 and 1641 cm^{-1} respectively for the NH, ester and amide groups.

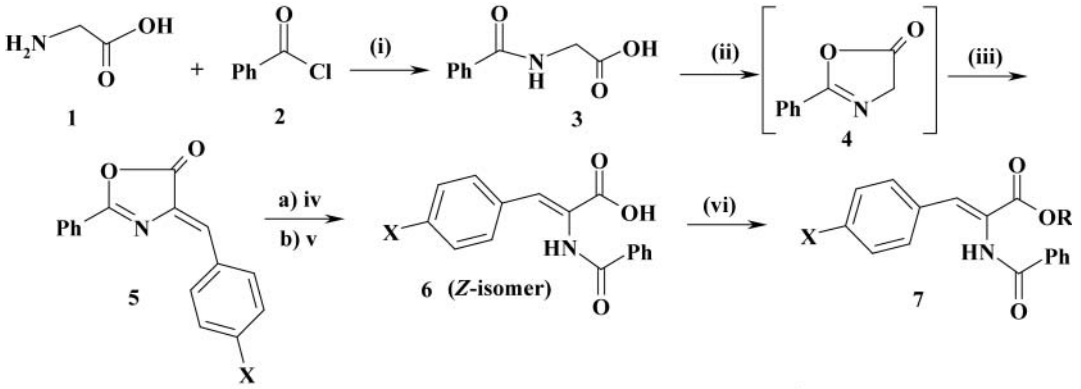
On the basis of the well established chemistry of isocyanides[32–35] the formation of compound **8** can be rationalised as shown in Scheme 3. Protonation of cyclohexyl isocyanide by the carboxyl group followed by the nucleophilic addition of the conjugate anion **10** on the nitrilium cation **11** led to the iminoester **12**. Cyclisation of **12** gave intermediate **13**. Nucleophile attack on **13** produced **8**.

The present method has the advantage that the reaction is performed under neutral conditions, and the components can be mixed without any activation or modification.

In summary, we report that three-component reaction between *N*-benzoyl *α,β*-dehydro-*α*-amino acid derivatives or N-bezoylamino acids and cyclohexyl isocyanide in different alcohols as solvent, afforded a simple route for synthesis of *N*-acyl-*α,β*-dehydro-*α*-amino acid esters.

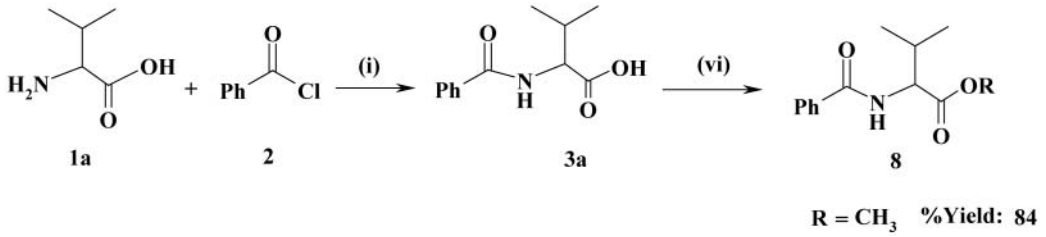
Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010

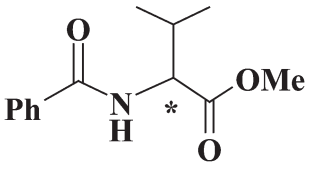


7	X	R	%Yield *
b	Cl	CH_3	92
c	NO_2	CH_3	89
d	NO_2	C_2H_5	91
e	Cl	t-Bu	78
f	Cl	Bz	80

* Isolated yields

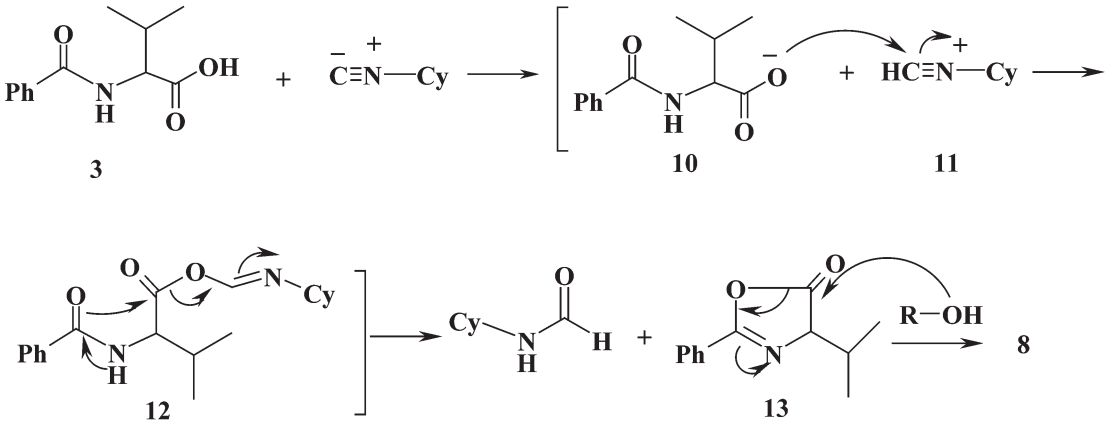


Scheme 1 Reagents and conditions: (i) NaOH(10%), HCl; (ii) Ac_2O/ AcO^-; (iii) ArCHO; (iv) NaOH/ H_2O/ CH_3OH; (v) H^+/H_2O; (vi) Cyclohexyl isocyanide/ROH, reflux, 1h.



Scheme 2 Compound **8** is racemic.

CHNS-O analyser at the analytical laboratory of the Islamic Azad University Yazd branch. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.



Scheme 3 Suggested mechanism for formation compound **8**.

Preparation of compounds **7b–f***; general procedure*
To a magnetically stirred solution of **6** (2 mmol) in 10 mL alcohol was added dropwise cyclohexyl isocyanide (2 mmol) The reaction mixture was then stirred for 1 h at reflux temperature. The solvent was evaporated at reduced pressure. The residue was precipitated, filtered and washed with diethyl ether to give the pure product **7**. Compound **3**, **5** and **6** were prepared as previously described in the literature.[29] Compounds **5a**, **6a** and **7a** were known compounds.[12,23–25,29,31]

Preparation of compounds **8***; general procedure*
To a magnetically stirred solution of the *N*-benzoyld of α-amino acids **3a** (2 mmol) in 10 mL alcohol was added dropwise cyclohexyl isocyanide (2 mmol) The reaction mixture was then stirred for 1 h at reflux temperature. The solvent was removed under reduced pressure and the residue was purified by silica-gel column chromatography using hexane-ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product **8**.

Compound **5a** had a m.p. 161–163 °C (lit. 165–166 °C), **6a** had a m.p. 180–182 °C (lit. 185–186 °C) and **7a** had a m.p. 145–147 °C (lit. 162–163 °C).

2-Benzoylamino-3-(4-chlorophenyl)acrylic acid (**6b**): Yellow powder, m.p. 191–193 °C, IR (KBr)(ν_{max}, cm^{-1}): 3211 (NH); 1655 (C=O, amide). Anal. Calcd for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; N, 4.64. Found: C, 63.52; H, 4.14; N, 4.73%. MS (*m/z*, %): 301 (M^+, 5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (1 H, s, $CH_{olefinic}$), 7.31–7.88 (9H, m, aromatic), 7.90 (1H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 123.94, 129.09, 129.36, 129.57, 130.56, 131.15, 132.70, 133.08, 133.92, 135.77 (10C olefinic and aromatic), 165.69 and 166.45 (2C=O).

2-Benzoylamino-3-(4-nitrophenyl)acrylic acid (**6c**): Yellow powder, m.p. 168–170 °C, IR (KBr)(ν_{max}, cm^{-1}): 3217 (NH); 1650 (C=O, amide). Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.71; H, 3.99; N, 9.07%. MS (*m/z*, %): 312 (M^+, 11). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (1 H, s, $CH_{olefinic}$), 7.42–8.37 (9H, m, aromatic), 8.15 (1H, s, NH).^{13}C NMR (125.8 MHz, $CDCl_3$): δ 123.85, 127.73, 128.22, 128.74, 129.19, 130.31, 132.90, 133.55, 141.69, 147.78 (10C olefinic and aromatic), 165.88 and 166.04 (2C=O).

Methyl 2-(benzamido)-3-(4-chlorophenyl)acrylate (**7b**): Yield: 92%; yellow powder, m.p. 160–162 °C, IR (KBr)(ν_{max}, cm^{-1}): 3220 (NH); 1725 (C=O, ester); 1643 (C=O, amide). Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.78; H, 4.29; N, 4.52%. MS (*m/z*, %): 315 (M^+, 8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (3H, s, OCH_3), 7.38 (1 H, s, $CH_{olefinic}$), 7.25–7.84 (9H, m, aromatic), 7.96 (1H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 53.32 (OCH_3), 124.59, 127.91, 129.22, 129.24, 130.77, 131.34, 132.76, 132.95, 133.83, 135.63 (10C olefinic and aromatic), 165.87 (C=O amide), 166.17 (C=O ester).

Methyl 2-(benzamido)-3-(4-nitrophenyl)acrylate (**7c**): Yield: 89%; yellow powder, m.p. 173–175 °C, IR (KBr)(ν_{max}, cm^{-1}): 3215 (NH); 1725 (C=O, ester); 1643 (C=O, amide). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.43; H, 4.24; N, 8.72%. MS (*m/z*, %): 326 (M^+, 5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 7.40 (1 H, s, $CH_{olefinic}$), 7.39–8.07 (9H, m, aromatic), 8.69 (1H, s, NH).^{13}C NMR (125.8 MHz, $CDCl_3$): δ 53.48 (OCH_3), 123.94, 127.52, 128.06, 128.41, 129.14, 130.45, 132.85, 133.62, 141.46, 147.64 (10C olefinic and aromatic), 165.74 (C=O amide), 165.94 (C=O ester).

Ethyl 2-(benzamido)-3-(4-nitrophenyl)acrylate (**7d**): Yield: 91%; yellow powder, m.p. 168–170 °C, IR (KBr)(ν_{max}, cm^{-1}): 3225 (NH); 1719 (C=O, ester); 1652 (C=O, amide). Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.40; H, 4.89; N, 8.33%. MS (*m/z*, %): 340 (M^+, 10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (3H, t $^3J_{HH}$ = 7 Hz, CH_3), 4.39 (2H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.53 (1 H, s, $CH_{olefinic}$), 7.48–8.17 (9H, m, aromatic), 8.23 (1H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.66 (CH_3), 63.05 (OCH_2), 123.96, 126.54, 126.82, 127.85, 129.36, 130.23, 133.06, 133.67, 141.84, 147.64 (10C olefinic and aromatic), 165.17 (C=O amide), 165.34 (C=O ester).

Tert-butyl 2-(benzamido)-3-(4-chlorophenyl)acrylate (**7e**): Yield: 78%; yellow powder, m.p. 196–198 °C, IR (KBr)(ν_{max}, cm^{-1}): 3211 (NH); 1729 (C=O, ester); 1640 (C=O, amide). Anal. Calcd for $C_{20}H_{20}ClNO_3$: C, 67.13; H, 5.63; N, 3.91. Found: C, 67.35; H, 5.80; N, 4.09%. MS (*m/z*, %): 357 (M^+, 5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (9 H, s, CMe_3), 7.35 (1 H, s, $CH_{olefinic}$), 7.18–7.59 (9H, m, aromatic), 7.87 (1H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.12 (CMe_3), 83.35 ($OCMe_3$), 124.50, 127.84, 129.06, 129.33, 130.61, 131.49, 132.70, 132.97, 133.97, 135.48 (10C olefinic and aromatic), 165.64 (C=O amide), 166.14 (C=O ester).

Benzyl 2-(benzamido)-3-(4-chlorophenyl)acrylate (**7f**): Yield: 80%; yellow powder, m.p. 174–178 °C, IR (KBr)(ν_{max}, cm^{-1}): 3227 (NH); 1721 (C=O, ester); 1649 (C=O, amide). Anal. Calcd for $C_{23}H_{18}ClNO_3$: C, 70.50; H, 4.63; N, 3.57. Found: C, 70.31; H, 4.40; N, 3.76%. MS (*m/z*, %): 391 (M^+, 3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.05 (2H, s, OCH_2), 7.33 (1 H, s, $CH_{olefinic}$), 7.27–7.80 (14H, m, aromatic), 7.82 (1H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 66.63 (OCH_2), 124.47, 127.76, 128.09, 128.49, 128.68, 128.87, 129.00, 129.19, 129.26, 130.64, 131.31, 132.54, 132.85, 133.77, 135.51 135.70, (16C olefinic and aromatic), 165.57 (C=O amide), 166.09 (C=O ester).

Methyl 2-(benzamido)-3-methylbutanoate (**8**): Yield: 84%; white powder, m.p. 174–176 °C, IR (KBr)(ν_{max}, cm^{-1}): 3335 (NH), 1741 (C=O, ester), 1641 (C=O, amide). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.41; N, 5.80%. MS (*m/z*, %): 235 (M^+, 20). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 and 1.02 (6H, 2d, $^3J_{HH}$ = 6.5 Hz, $2CH_3$), 2.29 (1H, m, $CH(Me)_2$), 3.79 (3H, s, OCH_3), 4.80 (1H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.5 Hz, CH), 6.63 (1H, d, $^3J_{HH}$ = 8.5 Hz, NH), 7.27–7.82 (5H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 17.97 and 19.67 ($2CH_3$), 31.63 (CH), 52.25 (OCH_3), 57.41 (CHN), 127.07, 128.61, 131.73, 134.29 (4C aromatic), 167.38 (C=O amide), 172.67 (C=O ester).

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