Synthesis of α-CH_2-X Functionalized Tryptophan Methyl Ester

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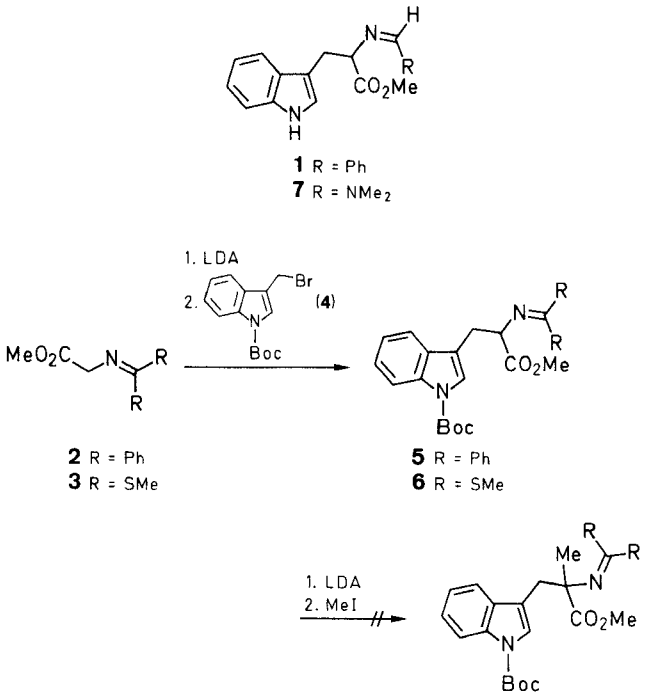
A short and efficient synthesis of α-CH_2-X functionalized tryptophan methyl ester (methyl 2-amino-3-(1*H*-indol-3-yl)propionate) is described, by alkylation of methyl 2-isocyano-3-(1*H*-indol-3-yl)propionate with a range of functionalized alkyl halides.

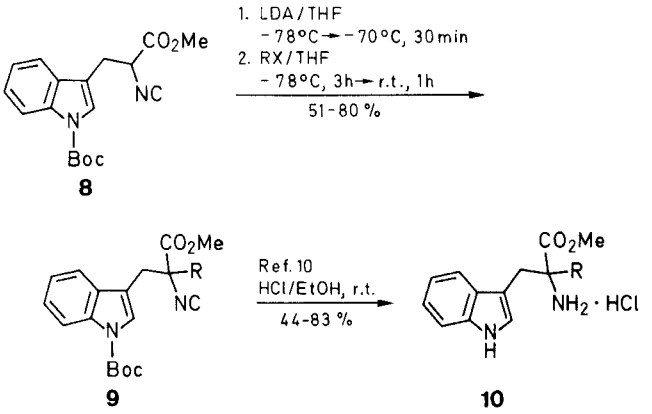
α-Methyl α-amino acids are of current interest in medicinal chemistry as surrogates for the corresponding proteinogenic amino acids, and their incorporation into polypeptides with biological activity.[1] Various methods for the synthesis of α-methyl α-amino acids have been described.[2] However, α-CH_2-X functionalized derivatives are uncommon,[3] and such derivatives of tryptophan are unknown.[4] We report here a short and efficient route to α-CH_2-X functionalized tryptophan methyl ester.

Alkylation of the anion formed by lithiation of methyl 2-(*N*-benzylideneamino)-3-(1*H*-indol-3-yl)propionate **(1)** with methyl iodide has been previously described as a route to racemic methyl 2-amino-3-(1*H*-indol-3-yl)-2-methylpropionate.[3] However, in our hands higher alkyl and functionalized alkyl halides either failed to react under these conditions or gave poor yields. Furthermore, intermolecular allylation of benzylideneamino derivatives of various amino acid esters was also unsuccessful.[4] Steric hindrance was suggested as a possible reason for these results. The Schiff bases **2** and **3** have also been used for the preparation of other α-substituted amino acids by double alkylation.[5] We have found that **2** and **3** could be monoalkylated with 3-bromomethyl-*N*-tert-butoxycarbonylindole **(4)** to give *N*-diphenylmethylene and *N*-[bis(methylthio)methylene]amino derivatives **5** and **6**, but attempted dialkylation failed, even with methyl iodide (Scheme A). The amidine ester **7**[6] also failed to give the α-methyl derivative under these conditions.



Scheme A

However, we have now found that the isonitrile method of Schöllkopf[7-9] can successfully be used in a short, efficient synthesis of a range of α-CH_2-X functionalized tryptophan esters. Methyl 2-isocyano-3-(1*H*-indol-3-yl)-propionate **(8)** is readily prepared from methyl 2-formylamino-3-(*N*-tert-butoxycarbonylindol-3-yl)propionate by dehydration with triphosgene. Lithiation of isocyanide **8** and reaction with a range of electrophiles gave the 2-substituted isocyano esters **9** in good chemical yield (Table). Hydrolysis of the isocyano esters **9** was achieved by stirring with ethanolic hydrochloric acid at room temperature, under which conditions the indole *N*-Boc protecting group was also removed. The resulting off-white amino acid methyl ester hydrochlorides **10** could be converted without further purification directly into their N^{α}-Boc derivatives in good overall yields (44–83%).[10]



9, 10	R	9, 10	R
a	Me	**e**	$CH_2CO_2CH_2Ph$
b	$CH_2CH{=}CH_2$	**f**	$CH_2CH_2CO_2CH_2Ph$
c	$CH_2C{\equiv}CH$	**g**	$CH_2CH_2CH(OCH_2CH_2O)$
d	CH_2CN	**h**	$CH_2CH_2OCH_2CH_2OMe$

Scheme B

The results described here show that for the first time alkylation of the isocyanide derived from tryptophan followed by hydrolysis is a very efficient route to α-CH_2-X functionalized tryptophan derivatives. The isocyanide method is suggested as applicable for the synthesis of a wide range of novel α-substituted amino acids. Extension of this methodology to the synthesis of optically active α-CH_2-X functionalized tryptophan is in progress.

Melting points were determined using a Reichart Thermovar hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AM 300 spectrometer; chemical shifts were

Table. Functionalized Tryptophan Methyl Esters **9** Prepared

Product	Yield (%)	mp[a] (°C)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)[c]
9a[d]	73	oil	$C_{19}H_{22}N_2O_4 \cdot 0.75H_2O$ (342.4)	1.66 (s, 9H, $3CH_3$), 1.71 (s, 3H, CH_3), 3.35 (d, AB, 1H, J = 16, H-β), 3.43 (d, AB, 1H, J = 16, H-β), 3.70 (s, 3H, OCH_3), 7.18–7.32 (m, 2H, H-5, H-6), 7.52 (d, 1H, J = 7, H-7), 7.59 (s, 1H, H-2), 8.13 (d, 1H, J = 7, H-4)
9b	74	oil	$C_{21}H_{24}N_2O_4$ (368.4)	1.63 (s, 9H, $3CH_3$), 2.60 (dd, ABX, 1H, J = 14, 7, CH_2CH), 2.76 (dd, ABX, 1H, J = 14, 7, CH_2CH), 3.22 (d, AB, 1H, J = 15, H-β), 3.34 (d, AB, 1H, J = 15, H-β), 3.65 (s, 3H, OCH_3), 5.24 (m, 2H, $=CH_2$), 5.88 (m, 1H, CH), 7.20–7.33 (m, 2H, H-5, H-6), 7.52 (d, 1H, J = 8, H-7), 7.59 (s, 1H, H-2), 8.13 (d, 1H, J = 8, H-4)
9c	80	71.5–72.5	$C_{21}H_{22}N_2O_2$ (366.4)	1.67 (s, 9H, $3CH_3$), 2.34 (dd, ABX, 1H, J = 3, 3, $CH{\equiv}C$), 2.85 (dd, ABX, 1H, J = 17, 3, $CH_2C{\equiv}$), 2.95 (dd, ABX, 1H, J = 17, 3, $CH_2C{\equiv}$), 3.40 (s, 2H, H-β), 3.69 (s, 3H, OCH_3), 7.22–7.34 (m, 2H, H-5, H-6), 7.54 (d, 1H, J = 8, H-7), 7.61 (s, 1H, H-2), 8.13 (d, 1H, J = 8, H-4)
9d	63	91.5–92.5	$C_{20}H_{21}N_3O_4$ (367.4)	1.68 (s, 9H, $3CH_3$), 2.98 (d, AB, 1H, J = 17, CH_2CN), 3.07 (d, AB, 1H, J = 17, CH_2CN), 3.44 (d, AB, 1H, J = 15, H-β), 3.47 (d, AB, 1H, J = 15, H-β), 3.76 (s, 3H, OCH_3), 7.25–7.34 (m, 2H, H-5, H-6), 7.50 (d, 1H, J = 7, H-7), 7.62 (s, 1H, H-2), 8.13 (d, 1H, J = 7, H-4)
9e	80	oil	$C_{27}H_{28}N_2O_6 \cdot 0.5H_2O$ (471.5)	1.67 (s, 9H, $3CH_3$), 2.93 (d, AB, 1H, J = 17, CH_2CO_2), 3.25 (d, AB, 1H, J = 17, CH_2CO_2), 3.27 (d, AB, 1H, J = 16, H-β), 3.37 (d, AB, 1H, J = 16, H-β), 3.60 (s, 3H, OCH_3), 5.13 (d, AB, 1H, J = 14, CH_2Ph), 5.15 (d, AB, 1H, J = 14, CH_2Ph), 7.20–7.36 (m, 7H, $5H_{arom}$, H-5, H-6), 7.49 (d, 1H, J = 8, H-7), 7.61 (s, 1H, H-2), 8.13 (d, 1H, J = 8, H-4)
9f	74	oil	$C_{28}H_{30}N_2O_6 \cdot 0.75H_2O$ (490.0)	1.68 (s, 9H, $3CH_3$), 2.24–2.71 (m, 4H, $(CH_2)_2CO_2$), 3.23 (d, AB, 1H, J = 15, H-β), 3.38 (d, AB, 1H, J = 15, H-β), 3.63 (s, 3H, OCH_3), 5.12 (s, 2H, CH_2Ph), 7.20–7.36 (m, 7H, $5H_{arom}$, H-5, H-6), 7.51 (d, 1H, J = 8, H-7), 7.59 (s, 1H, H-2), 8.13 (d, 1H, J = 8, H-4)
9g[e]	80	88.5–89.5	$C_{23}H_{27}N_2O_6$ (427.5)	1.67 (s, 9H, $3CH_3$), 1.96–2.30 (m, 4H, $2CH_2$), 3.20 (d, AB, 1H, J = 14, H-β), 3.37 (d, AB, 1H, J = 14, H-β), 3.64 (s, 3H, OCH_3), 3.94 (m, 4H, $2OCH_2$), 4.92 (t, 1H, J = 4, CH), 7.20–7.32 (m, 2H, H-5, H-6), 7.51 (d, 1H, J = 8, H-7), 7.59 (s, 1H, H-2), 8.12 (d, 1H, J = 8, H-4)
9h[e]	51	oil	$C_{23}H_{30}N_2O_6 \cdot 0.25H_2O$ (435.0)	1.67 (s, 9H, $3CH_3$), 1.98 (m, 1H, CH_2CH_2O), 2.49 (m, 1H, CH_2CH_2O), 3.24 (d, AB, 1H, J = 14, H-β), 3.37 (d, AB, 1H, J = 14, H-β), 3.43–3.70 (m, 12H, $2OCH_3$, $CH_2OCH_2CH_2$), 7.20–7.33 (m, 2H, H-5, H-6), 7.54 (d, 1H, J = 8, H-7), 7.60 (s, 1H, J = 8, H-2), 8.13 (d, 1H, H-4)

[a] Uncorrected, measured with a Reichart Thermovar apparatus.
[b] Satisfactory microanalysis obtained: C ±0.4, H ±0.4, N ±0.3.
[c] Recorded on a Bruker AM300 Spectrometer.
[d] Using methyl iodide.
[e] Cosolvent HMPT.

recorded in ppm downfield from TMS. Silica gel used for chromatography was Kieselgel-60 (230–400 mesh) (E. Merck AG, Darmstadt, Germany). Mass spectra were recorded using a Finnegan 4500 spectrometer. Microanalysis was obtained from C, H and N Analysis, Leicester, UK.

Alkylation of Methyl 2-Isocyano-3-(1*H*-indol-3-yl)propionate (8); General Procedure:

The isocyanide **8** (0.657 g, 2 mmol) is dissolved in THF (10 mL) and the solution is cooled to −78 °C under an atmosphere of Ar. A solution of LDA (2.2 mmol) is added dropwise to the stirred solution at such a rate that the temperature does not exceed −70 °C. After 30 min stirring at this temperature, the functionalized alkyl bromide (2.2 mmol) dissolved in THF (5 mL) is added slowly. After a further 3 h, the mixture is allowed to warm to r.t. and is stirred for a further hour. The solvent is evaporated *in vacuo*, the residue dissolved in H_2O and extracted with Et_2O (3 × 25 mL). The combined organic layer are dried ($MgSO_4$), filtered and evaporated to dryness. The crude mixture is chromatographed on Merck Kieselgel 60 with Et_2O/hexane mixtures to give the alkylated product **9** (Table).

Hydrolysis of the isocyanides **9** is achieved by stirring in ethanolic HCl as described in reference 8.

Received: 11 August 1989; revised: 5 December 1989

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