Studies of Unusual Amino Acids and Their Peptides. XV. The Chemistry of *N*-Carboxymethyl Amino Acids. III. The Synthesis of *N*-Tosyl-*N*-carboxymethyl Amino Acid Derivatives by *N*-Alkoxycarbonylmethylation

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Synopsis. The alkoxycarbonylmethylation of the amide nitrogen of *N*-tosyl amino acid esters with iodoacetic acid esters in the presence of silver(I) oxide in *N*,*N*-dimethylformamide afforded the corresponding *N*-tosyl-*N*-carboxymethyl amino acid esters in good yields without racemization of the amino acids.

Previous publications[1,2] from this laboratory have dealt with the first systematic investigation regarding the preparation and properties of *N*-carboxymethyl (Cm-) amino acids and their derivatives, especially their peptides. On the synthetic routes adopted, a Cm-amino acid[3] (or its ester) was at first prepared from the corresponding parent amino acid, and then converted to an appropriate *N*-protected intermediate for further derivation. As a possible alternative, we examined the carboxymethylation of the amide nitrogen of *N*-protected amino acid derivatives for preparing Cm-amino acid derivatives.

The *N*-alkylation of tosylamides, which has often been used as a preparative reaction, may also be applicable to *N*-alkoxycarbonylmethylation. Attempts to react *N*-tosyl amino acids with methyl iodoacetate in aqueous alkaline solutions,[4] however, were unsuccessful. On the other hand, the *N*-alkoxycarbonylmethylation of an *N*-tosyl amino acid ester (**1**) with an iodoacetic acid ester (**2**) in the presence of silver(I) oxide[5] yielded an *N*-tosyl Cm-amino acid derivative (**3**).

$$\underset{\mathbf{1}}{\text{Tos-AA-OR}^1} + \underset{\mathbf{2}}{\text{ICH}_2\text{CO}_2\text{R}^2} \xrightarrow{\text{Ag}_2\text{O}} \underset{\mathbf{3}}{\text{Tos-}\overset{\text{OR}^2}{\overset{|}{\text{C}}}\text{mAA-OR}^1}$$

TABLE 1. *N*-ALKOXYCARBONYLMETHYLATION OF *N*-TOSYL AMINO ACID ESTERS

Product **3**				Yield[a]	$[\alpha]_D^{25}$ (MeOH)	TLC,
	AA	R^1	R^2	%		R_f[b]
3a	Ala	Me	Me	76	−54.7° (*c* 0.79)	0.44
3b	Asp(OMe)	Me	Me	71	−24.7° (*c* 1.0)	0.37
3c	Glu(OMe)	Me	Me	65	−55.7° (*c* 0.90)	0.35
3d[c]	Gly	Me	Me	73	—	0.36
3e[c]	Ile	Me	Me	83	−60.7° (*c* 1.0)	0.54
3f[c]	Leu	Me	Me	76	−46.0° (*c* 1.0)	0.53
3g	Phe	Me	Me	74	−13.7° (*c* 0.65)	0.52
3h	Val	Me	Me	82	−70.5° (*c* 1.0)	0.52
3i	Ala	Bzl	Bzl	72	−34.3° (*c* 0.92)	0.62
3j	Phe	Bzl	Bzl	63	−9.1° (*c* 1.0)	0.67
3k	Val	Bzl	Bzl	67	−38.3° (*c* 0.65)	0.68
3l	Ala	Bzl	Me	63	−34.5° (*c* 1.0)	0.51
3m	Phe	Bzl	Me	65	−5.3° (*c* 0.90)	0.56
3n	Val	Bzl	Me	73	−39.9° (*c* 1.2)	0.56

a) Isolated yield. b) Benzene–EtOAc (3:1). c) Obtained as crystals: **3d**, mp 100—101 °C ($CHCl_3$–hexane); **3e**, mp 47—49 °C (cyclohexane); **3f**, mp 60—61 °C (cyclohexane).

An investigation of the conditions for this reaction employing methyl *N*-tosylalaninate and methyl iodoacetate revealed that the best yield was obtained using the reactants in an 8:2:1 molar ratio (ICH_2CO_2Me/Ag_2O/Tos-Ala-OMe) in *N*,*N*-dimethylformamide (DMF) after 24 h at room temperature. As can be seen from Table 1, several *N*-tosyl Cm-amino acid methyl esters (**3a—h**) were thus prepared from the methyl esters of *N*-tosyl monoamino mono- and dicarboxylic acids as substrates in a 70—80% isolated yield under the above reaction conditions. All the compounds, except **3d**, **3e**, and **3f**, were obtained as oils. Their homogeneity was demonstrated by elemental analyses, TLC on silica gel, and ^1H NMR spectral data. In the NMR spectra the absorption attributable to the methylene protons in the *N*-alkoxycarbonylmethyl group appeared at δ=3.8—4.4, in many cases as an AB quartet with J=18—19 Hz.

The above reaction conditions were also applicable to cases where R^1 on **1** and/or R^2 on **2** were groups other than the methyl group (**3i—n**). The Cm-amino acid derivatives carrying two different ester groups, such as **3l—n**, are practically useful intermediates for further derivation. When an *N*-tosyl amino acid itself was used as a substrate instead of its ester, *O*-alkoxycarbonylmethylation occurred simultaneously with the *N*-alkoxycarbonylmethylation. The analytical and spectral data were compatible with the assigned structures (**4**) of the products (Table 2, **4a—c**).

$$\text{Tos-}\overset{\text{OMe}}{\overset{|}{\text{C}}}\text{mAA-OCH}_2\text{CO}_2\text{Me}$$
4

The specific rotation of the *N*-tosyl Cm-amino acid dimethyl ester (**3a**, **3g**, or **3h**) prepared by the present method was in good accordance with that of a sample prepared by esterification with diazomethane of the corresponding *N*-tosyl Cm-amino acid synthesized previously.[2] Furthermore, the *N*-tosyl Cm-amino acid prepared by the catalytic hydrogenation of its dibenzyl ester (**3i** or **3k**) was identical in its specific rotation

TABLE 2. METHOXYCARBONYLMETHYLATION OF *N*-TOSYL AMINO ACIDS

Product **4**		Yield[a]	$[\alpha]_D^{25}$	TLC,
	AA	%	(MeOH)	R_f[b]
4a	Ala	66	−37.3° (*c* 0.67)	0.38
4b	Phe	73	−9.0° (*c* 1.6)	0.48
4c	Val	72	−68.4° (*c* 1.4)	0.49

a) Isolated yield. b) Benzene–EtOAc (3:1).

with an authentic sample.[2] These results indicate that no appreciable racemization occurred during *N*-alkoxycarbonylmethylation. In addition, since the yields for *N*-tosylation of free Cm-amino acids were rather low,[2] the present route to *N*-tosyl Cm-amino acid derivatives is a convenient alternative for preparing compounds containing Cm-amino acids.

The *N*-alkoxycarbonylmethylation of *N*-benzyloxycarbonyl amino acid esters would not proceed smoothly under the above conditions, nor even at an elevated temperature, in contrast to the corresponding *N*-methylation.[5]

Experimental

Optical rotations were measured with a JASCO DIP-4 polarimeter. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-24B spectrometer. TLC and preparative TLC were performed on Merck Kieselgel 60 F_{254} and Kieselgel GF_{254} (Type 60), respectively. All new compounds (**3a—n** and **4a—c**) gave satisfactory microanalysis (C, H, N ±0.3%).

General Procedure for the N-*Alkoxycarbonylmethylation of* N-*Tosyl Amino Acids and Their Esters.* *Methyl* N-*Tosyl*-N-*(methoxycarbonylmethyl)alaninate (**3a**)*: A solution of Tos-Ala-OMe (130 mg, 0.5 mmol) and ICH_2CO_2Me (800 mg, 4 mmol) in DMF (4 ml) was stirred at room temperature with Ag_2O (232 mg, 1 mmol) in the dark for 24 h. The reaction mixture was filtered, and the filtrate was mixed with $CHCl_3$, washed with 5% $Na_2S_2O_3$ and water, and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a syrup, which was chromatographed on preparative layers of silica gel with benzene-EtOAc (49:1); yield, 125 mg (76%); syrup, $[\alpha]_D^{25}$ −54.7° (*c* 0.79, MeOH).

Methoxycarbonylmethyl N-*Tosyl*-N-*(methoxycarbonylmethyl)alaninate (**4a**)*: Tos-Ala (130 mg, 0.5 mmol) was reacted with ICH_2CO_2Me (800 mg, 4 mmol) in the presence of Ag_2O (464 mg, 2 mmol) in DMF (4 ml) for 36 h. After a work-up similar to the above, the final purification was performed by preparative TLC with benzene-EtOAc (9:1); yield, 130 mg (66%); syrup, $[\alpha]_D^{25}$ −37.3° (*c* 0.67, MeOH).

Preparation of the Dimethyl Esters from N-*Tosyl Cm-amino Acids by Treatment with Diazomethane.* *Tos-CmAla-OMe*: Tos-CmAla[2] (215 mg) was dissolved in EtOAc and treated with an ethereal solution of CH_2N_2 as usual. Purification by preparative TLC with benzene-EtOAc (49:1) afforded a syrup; yield, 219 mg (93%); $[\alpha]_D^{25}$ −55.2° (*c* 1.0, MeOH).

Tos-CmPhe-OMe ($[\alpha]_D^{25}$ −13.2° (*c* 0.66, MeOH)) and Tos-CmVal-OMe ($[\alpha]_D^{25}$ −70.8° (*c* 0.96, MeOH)) were prepared from Tos-CmPhe[2] and Tos-CmVal,[2] respectively, in the same manner as above.

N-*Tosyl Cm-amino Acids Prepared by Catalytic Hydrogenation of Their Dibenzyl Esters.* *Tos-CmVal*: **3k** (285 mg) was hydrogenated in dioxane (15 ml) in the presence of 5% Pd-C (140 mg). After the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in ether and extracted with 5% $NaHCO_3$. The extracts were combined, washed with ether, and acidified with 4 M HCl (1 M=1 mol dm^{-3}) to pH 2. The turbid mixture was extracted with EtOAc. The extracts were combined, washed with water, and dried over Na_2SO_4. Evaporation of the solvent afforded crystals; yield, 140 mg (76%); mp 179.5—181 °C (EtOAc-hexane), $[\alpha]_D^{25}$ −55.4° (*c* 0.70, MeOH). Lit,[2] mp 179.5—181 °C, $[\alpha]_D^{25}$ −55.6° (*c* 1.0, MeOH).

Tos-CmAla was prepared from **3i** in the same manner as above; $[\alpha]_D^{25}$ −33.2° (*c* 0.62, MeOH). Lit,[2] $[\alpha]_D^{25}$ −33.7° (*c* 0.82, MeOH).

^{1}H NMR Spectra (CDCl$_3$) of Products, 3 and 4. **3a**: δ=1.31 (3H, d), 2.39 (3H, s), 3.47 (3H, s), 3.62 (3H, s), 3.95 and 4.12 (2H, ABq), 4.36 (1H, q), 7.19 and 7.65 (4H, ABq).

3b: δ=2.40 (3H, s), 2.7—3.0 (2H, 4 peaks), 3.50 (3H, s), 3.55 (3H, s), 3.59 (3H, s), 4.02 (2H, s), 4.68 (1H, *t*-like), 7.21 and 7.65 (4H, ABq).

3c: δ=1.6—2.8 (4H, m), 2.40 (3H, s), 3.47 (3H, s), 3.61 (3H, s), 3.69 (3H, s), 3.92 and 4.19 (2H, ABq), 4.46 (1H, q), 7.25 and 7.69 (4H, ABq).

3d: δ=2.40 (3H, s), 3.61 (6H, s), 4.16 (4H, s), 7.25 and 7.65 (4H, ABq).

3e: δ=0.7—1.0 (6H, m), 1.1—2.0 (3H, m), 2.39 (3H, s), 3.41 (3H, s), 3.64 (3H, s), 3.86 (1H, d), 4.00 and 4.30 (2H, ABq), 7.22 and 7.70 (4H, ABq).

3f: δ=0.83 and 0.86 (6H, 2× d), 1.1—2.0 (3H, m), 2.40 (3H, s), 3.47 (3H, s), 3.69 (3H, s), 4.11 (2H, s), 4.38 (1H, *t*-like), 7.26 and 7.72 (4H, ABq).

3g: δ=2.36 (3H, s), 2.86 and 2.99 (2H, *d*-like), 3.30 (3H, s), 3.59 (3H, s), 4.11 and 4.13 (2H, 2× *s*-like), 4.42 (1H, *t*-like), 7.04 (5H, s), 7.12 and 7.61 (4H, ABq).

3h: δ=0.85 and 0.96 (6H, 2× d), 1.5—2.2 (1H, m), 2.39 (3H, s), 3.37 (3H, s), 3.57 (3H, s), 3.83 (1H, d), 3.84 and 4.20 (2H, ABq), 7.17 and 7.63 (4H, ABq).

3i: δ=1.35 (3H, d), 2.32 (3H, s), 4.04 and 4.27 (2H, ABq), 4.60 (1H, q), 4.89 (2H, s), 5.10 (2H, s), 7.1—7.35 (10H, m), 7.10 and 7.67 (4H, ABq).

3j: δ=2.34 (3H, s), 2.95 and 3.07 (2H, *d*-like), 4.30 (2H, s), 4.62 (1H, *t*-like), 4.73 (2H, s), 5.11 (2H, s), 6.9—7.35 (17H, m), ~7.65 (2H, half of ABq).

3k: δ=0.83 and 0.94 (6H, 2× d), 1.6—2.3 (1H, m), 2.33 (3H, s), 4.01 (2H, d), 4.08 and 4.39 (2H, ABq), 4.74 and 4.88 (2H, ABq), 5.08 (2H, s), 7.1—7.35 (10H, m), 7.09 and 7.70 (4H, ABq).

3l: δ=1.39 (3H, d), 2.35 (3H, s), 3.66 (3H, s), 4.01 and 4.23 (2H, ABq), 4.54 (1H, q), 4.91 (2H, s), 7.23 (5H, s), 7.16 and 7.68 (4H, ABq).

3m: δ=2.33 (3H, s), 2.96 and 3.08 (2H, *d*-like), 3.62 (3H, s), 4.23 (2H, s), 4.63 (1H, *t*-like), 4.77 (2H, s), 6.85—7.3 (10H, m), 7.16 and 7.65 (4H, ABq).

3n: δ=0.86 and 0.97 (6H, 2× d), 1.6—2.3 (1H, m), 2.35 (3H, s), 3.60 (3H, s), 4.01 (1H, d), 4.02 and 4.32 (2H, ABq), 4.78 and 4.92 (2H, ABq), 7.13 and 7.69 (4H, ABq), 7.24 (5H, s).

4a: δ=1.39 (3H, d), 2.38 (3H, s), 3.64 (6H, s), 3.99 and 4.08 (2H, 2× *s*-like), 4.36 (2H, s), 4.48 (1H, q), 7.18 and 7.65 (4H, ABq).

4b: δ=2.38 (3H, s), 3.0—3.2 (2H, 4 peaks), 3.64 (6H, s), 4.21 (2H, s), 4.37 (2H, s), 4.71 (1H, *t*-like), 7.12 (5H, s), 7.17 and 7.68 (4H, ABq).

4c: δ=0.93 and 1.04 (6H, 2× s), 1.7—2.3 (1H, m), 2.40 (3H, s), 3.63 (3H, s), 3.68 (3H, s), 4.06 (1H, d), 4.02 and 4.26 (2H, ABq), 4.26 and 4.43 (2H, ABq), 7.22 and 7.74 (4H, ABq).

References

1) T. Miyazawa, *Bull. Chem. Soc. Jpn.*, **53**, 2555 (1980).
2) T. Miyazawa, *Bull. Chem. Soc. Jpn.*, **53**, 3661 (1980).
3) The amino acid derivatives used here are all of the L-configuration. The following abbreviations are used for Cm-amino acids and their derivatives: CmAA for a Cm-amino acid derived from an amino acid (AA), and X^1-CmAA-X^3 for its derivative (X^1-NCHCO-X^3). Abbreviations given by the IUPAC-IUB Commission (*J. Biol. Chem.*, **247**, 977 (1972)) are used throughout.
4) *Cf.* E. Fischer and W. Lipschitz, *Ber.*, **48**, 360 (1915).
5) *Cf.* R. K. Olsen, *J. Org. Chem.*, **35**, 1912 (1970).