Synthesis of *N*-Methylamino Acid Derivatives from Amino Acid Derivatives using Sodium Hydride/Methyl Iodide[1]

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Reaction of *N*-acetyl-, *N*-benzoyl-, and *N*-carbobenzoxy derivatives of aliphatic amino acids with sodium hydride/methyl iodide in tetrahydrofuran containing dimethylformamide at 80° gave the corresponding *N*-methylamino acid methyl esters as oils in high yields. Saponification of these gave the *N*-protected-*N*-methylamino acids, and decarbobenzoxylation gave the *N*-methylamino acid methyl ester hydrobomides. The products are essentially optically pure and free of unmethylated amino acid derivative.

On fait réagir, à 80 °C dans le tétrahydrofuranne contenant de la diméthylformamide, les dérivés *N*-acétyle-, *N*-benzoyle-, ou *N*-carbobenzoxyle d'acides aminés avec de l'iodure de méthyle en présence d'hydrure de sodium et l'on obtient, avec d'excellents rendements, les esters méthyliques des dérivés *N*-méthylamino correspondants qui se présentent sous forme d'huile. La saponification de ces esters conduit aux acides aminés portant sur l'azote un groupe méthyle et un groupe protecteur; leur décarbobenzoxylation conduit aux bromhydrates des esters méthyliques des acides aminés *N*-méthylés. Les produits sont essentiellement optiquement purs et exempts de produits non méthylés.

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The preparation of derivatives of optically active *N*-methylamino acids presents many obstacles. Optically pure *N*-methylamino acids are not readily accessible; no method has been described for establishing their optical purity; *N*-methylamino acids are difficult to determine because they react slowly with ninhydrin; and their derivatives are not easy to make because *N*-methylamino acids are generally less reactive than are amino acids. We report here a new and simple one or two step synthesis of optically pure *N*-methylamino acid derivatives from commercially available starting materials. The method involves the *N*-methylation of *N*-acyl- or *N*-carbobenzoxyamino acids with methyl iodide and sodium hydride.[3] The determination of *N*-methylamino acids and their optical purity has been described elsewhere (3).

Methylation of aromatic amides has been achieved using methyl iodide (4–7) or dimethyl sulfate (8) in the presence of alkali. Alkylation of aliphatic amides (7, 9) and lactams (9) has been similarly achieved. Methylation of sulfonamides (10) has provided a route to *N*-methylamino acids (11). The more recent permethylation of peptides using silver oxide/methyl iodide (12), a reagent previously used for the methylation of a lactam (13), suggested consideration of this reagent for an approach to the synthesis of *N*-methylamino acid derivatives. Sodium hydride, however, was investigated in preference on the basis of the reports of its use for the alkylation of amides (14) and urethanes (15).[4]

N-Carbobenzoxyleucine in tetrahydrofuran (THF) was treated with sodium hydride/methyl iodide under various conditions, and the reaction mixture was analyzed for amino acids with an amino acid analyzer[5] after suitable deprotection. Representative results of these and subsequent experiments with other leucine derivatives appear in Table 1. The best yield (96%) of *N*-methylleucine was obtained using the reactants in an 8:3:1 molar ratio (MeI/NaH/R-Leu) after 24 h at 80 °C

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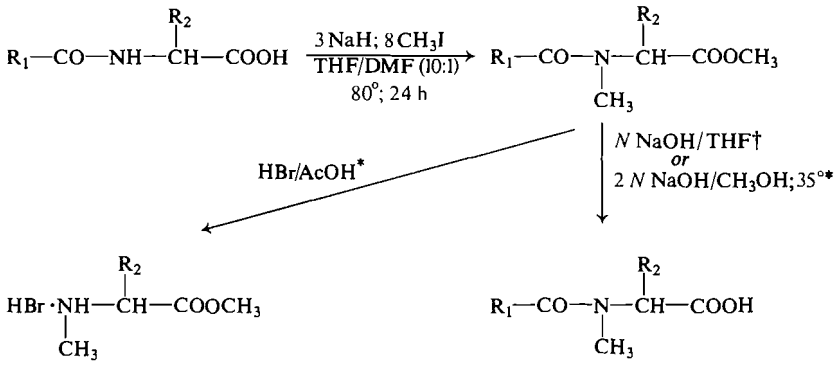
[3]A preliminary account of this work has been presented (1). Complete details of all aspects of this work are described in the Ph.D. thesis of J.R.C. Sodium hydride/methyl iodide has since been used for the permethylation of peptides for sequencing by mass spectrometry (2).

[4]A synthesis of *N*-methylamino acid derivatives using silver oxide/methyl iodide has since appeared (16).

[5]We have found that α-*C*-methyl- and *N*-methylamino acids can be determined satisfactorily with a Beckman amino acid analyzer if a half-normal eluting buffer flow rate is used. Under these conditions, the ninhydrin color constants are 10–30 times those obtained using the normal flow rate (3).



SCHEME 1. R_1 = CH_3, C_6H_5, $C_6H_5CH_2O$; R_2, corresponding to the amino acids in Table 2; (*) for R_1 = $C_6H_5CH_2O$; (†) for R_1 = CH_3, C_6H_5.

TABLE 1. Methylation of leucine derivatives with sodium hydride/methyl iodide*

	Amino acid recovered (yield, %)†		
Derivative	MeLeu	Leu	Total
Cbz	96	1.1	97
Cbz‡	46	39	85
Cbz§	32	0.6	33
Cbz‖	54	1.0	55
Boc	86	3.0¶	89
Boc**	37	28	65
Bz	96	0.1	96
Ac	88	0.7	89
For	95	4.0	99
Tos	61	4.0	65††

*Standard conditions: MeI/NaH/R-Leu (8:3:1 mol). NaH added to a solution of R-Leu (1 mmol) and MeI in THF/DMF (10:1). Mixture was placed on an oil bath at 80 °C for 24 h.
†Determined with an amino acid analyzer (3) after deprotection.
‡Reactant ratio: 4:2:1 mol.
§DMF replaced by dimethylsulfoxide as solvent.
‖MeI added after heating R-Leu and NaH for 10 min.
¶Same value obtained in a duplicate experiment.
**MeI added after leaving R-Leu and NaH at room temperature until hydrogen evolution had ceased.
††Low total believed due to difficulty with deprotection.

in the presence of dimethylformamide (DMF), and unexpectedly when the sodium hydride was added to the mixture after the methyl iodide had been added and not before.

In experiments on a preparative scale (Scheme 1), *N*-acetyl-, *N*-benzoyl-, and *N*-carbobenzoxy-amino acids were methylated to give the corresponding *N*-methylamino acid methyl esters whose i.r. curves were characterized by a sharp absorption band at 1735–1740 cm^{-1} (ester carbonyl), and the absence of bands at 3280 and 1520 cm^{-1} (—NH stretch and amide II bands, respectively). The esters were isolated as oils by extraction into ether and were therefore contaminated with the paraffin oil from the sodium hydride dispersion. Saponification of the *N*-acyl-*N*-methylamino acid esters in *N* NaOH/THF gave the *N*-acyl-*N*-methylamino acids in satisfactory yield. Similar treatment of the *N*-carbobenzoxy-*N*-methylamino acid esters gave very low yields of the corresponding acids. Good yields were finally obtained using warm 2 *N* NaOH/methanol. Removal of the carbobenzoxy group from the esters with hydrogen bromide in acetic acid gave the *N*-methylamino acid methyl esters as hydrobromides. After one recrystallization, these esters contained less than 0.1% of the unmethylated amino acid ester. An aliquot of one preparation of L-MeLeu-OMe·HBr was hydrolyzed before the crystallization step, and was shown to contain not more than 1% (the limit of detection) of the D-isomer by the method described elsewhere (3). Similarly, crystalline L-MePhe prepared from the carbobenzoxy derivative, and the hydrolysis product of Ac-L-MeLeu were also shown to be optically pure. However, preparations of Ac-MePhe were found to be partially or completely racemized. It is known that phenylalanine derivatives are more susceptible to base-catalyzed racemization than are most other amino acids (19). The properties of the derivatives prepared are recorded in Table 2. The i.r. curves of all compounds have been recorded.[3]

Experimental

Materials and Methods

Methyl iodide and DMF were obtained from Fisher Scientific Co. The DMF was purified by shaking over KOH pellets, then over CaO, followed by distillation (151–154°/753 mm) (20). The THF was the J. T. Baker product containing butylated hydroxytoluene as stabilizer.

TABLE 2. Properties of derivatives of *N*-methyl-L-amino acids

Compound*	Yield† (%)	Melting point (°C)	$[\alpha]_D^{25}$‡	Analysis							
				Formula	Molecular weight	Calculated			Found		
						C	H	N	C	H	N
Bz-MeAla	57	133	−31.7	$C_{11}H_{13}NO_3$	207.2	63.8	6.3	6.8	64.1	6.6	6.9
Bz-MeLeu	74	135–137	−54.8	$C_{14}H_{19}NO_3$	243.3	67.4	7.7	5.6	67.7	7.6	5.7
Ac-MeAla§	7	110–112	−50.0	$C_6H_{11}NO_3$	145.2	49.6	7.6	9.7	50.5	7.4	10.2
Ac-MeVal§	73	112–114	−144.3	$C_8H_{15}NO_3$	173.2	55.5	8.7	8.1	55.4	8.6	8.2
Ac-MeIle	39	121.5–122.5	−135.4	$C_9H_{17}NO_3$	187.2	57.7	9.2	7.5	58.0	8.7	7.4
Ac-MeLeu·H_2O	60	83–85‖	+34.5	$C_9H_{19}NO_4$	205.25	52.7	9.3	6.8	53.4	9.5	7.1
Ac-MePhe¶	50			$C_{12}H_{15}NO_3$	221.25	65.1	6.8	6.3	64.7	7.2	6.5
Cbz-MeAla§	65	65–66	−29.2	$C_{12}H_{15}NO_4$	237.25	60.7	6.4	5.9	61.2	6.5	5.8
Cbz-MeVal	65	semi-solid**									
Cbz-MeIle	55	oil									
Cbz-MeLeu	40	73–74	−26.1	$C_{16}H_{23}NO_4$	279.3	64.5	7.6	5.0	64.7	7.4	4.8
Cbz-MePhe	82	oil									
MeAla-OMe·HBr	82	109–109.5	−5.7	$C_5H_{12}NO_2Br$	198.1	30.3	6.1	7.1	29.6	6.0	6.8
MeVal-OMe·HBr	61	127–128	+17.0	$C_7H_{16}NO_2Br$	226.1	37.2	7.1	6.2	37.3	7.4	5.8
MeIle-OMe·HBr	56	126.5–127.5	+23.8	$C_8H_{18}NO_2Br$	240.15	40.0	7.6	5.8	40.2	7.6	5.8
MeLeu-OMe·HBr	65	105–106	+17.5	$C_8H_{18}NO_2Br$	240.15	40.0	7.6	5.8	40.3	7.7	5.8
MePhe-OMe·HBr	81	132–133	+37.3	$C_{11}H_{16}NO_2Br$	274.2	48.2	5.9	5.1	48.4	6.1	5.3

*Esters were crystallized once from methanol–ether; all other derivatives, from water except where indicated.
†Based on the *N*-protected amino acid used for the methylation.
‡In DMF; $c = 1$ for acetyl and benzoyl derivatives; $c = 2$ for others.
§Crystallized from ethyl acetate – petroleum ether. Literature m.p. 62–64.5°; $[\alpha]_D^{28}$ −31° (c, 2 in AcOH (16)).
‖The m.p. 107–108° after drying at 65°.
¶Racemized.
**Literature m.p. 69° (17, 18).

Sodium hydride was a 50% dispersion in oil obtained from BDH Chemicals. The amino acids were purchased from General Biochemicals, Chagrin Falls, Ohio. The *N*-carbobenzoxyamino acids were synthesized by the usual procedure of Bergmann and Zervas (21), with the phenylalanine derivative being purified as described (22). The *N*-benzoyl- and *N*-acetylamino acids were prepared by standard procedures as described for each amino acid in the treatise by Greenstein and Winitz (23). The optical purity of the *N*-acetylamino acids was verified.

The DMF and THF were dried immediately before use by adding sodium hydride dispersion (0.2 g/10 ml solvent) and filtering under suction after shaking for 2 min. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter using a 1 dm tube. Melting points were taken by the capillary method and are uncorrected. All evaporations were carried out under reduced pressure using a rotary evaporator. Compounds melting above 100° were dried for analysis by heating at 65° under vacuum over P_2O_5 for 2 h.

N-Acyl- and N-Carbobenzoxy-N-methylamino Acid Methyl Esters

To a solution of *N*-acyl- or *N*-carbobenzoxyamino acid (0.020 mol) in THF/DMF (10:1; 55 ml)[6] were added methyl iodide (10.0 ml; 0.160 mol) and sodium hydride dispersion (2.88 g; 0.060 mol of NaH) (*caution*) *in that order*. A reflux condenser protected with a drying-tube (Drierite) was mounted on the flask which was then placed in an 80 °C wax-bath for 24 h. The solvent was removed under vacuum, ether (25 ml) was added, and the evaporation was repeated (to remove the methyl iodide). The residue was distributed between ether (100 ml) and water (25 ml). The ether layer was washed with water (25 ml), dried ($MgSO_4$), and evaporated to give two clear immiscible oils[7] (one is the oil from the sodium hydride dispersion). All products gave satisfactory i.r. analyses at this stage.

N-Acyl- and N-Carbobenzoxy-N-methylamino Acids

The suspension of oils described above was saponified by stirring in the presence of 80 ml of *N* NaOH/THF (1:1) for 30 min for the *N*-acyl derivatives and 60 ml of 2 *N* NaOH/methanol (1:2) at 35 °C for 3 h for the *N*-carbobenzoxy derivatives. The THF and methanol were evaporated off, the remaining aqueous solution was washed with ether (2 × 20 ml), cooled (0°), and brought to p*H* 2 with 4 *N* HCl. The product was extracted into ethyl acetate (3 × 40 ml), the combined extracts were dried ($MgSO_4$), and the solvent was removed by evaporation. The residue was crystallized as indicated in Table 2.

[6]This solvent volume was used for 0.01 to 0.03 mol quantities.

[7]The product is sometimes slightly colored due to the presence of iodine. We have recently found that washing with aqueous potassium iodide solution removes the color.

N-Methylamino Acid Methyl Ester Hydrobromides

To an *N*-carbobenzoxy-*N*-methylamino acid methyl ester obtained as described above was added 37% HBr in acetic acid and the mixture was left at room temperature for 2 h. The mixture was evaporated to an oil which was dissolved in water (25 ml). The solution was washed with ether (2 × 10 ml), and then evaporated to dryness. The residue was dried overnight under vacuum over P_2O_5, and crystallized from methanol–ether.

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