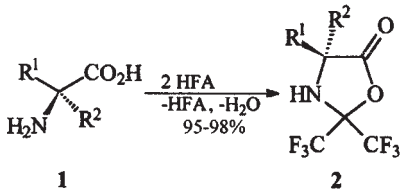
An Efficient Synthesis of *N*-Methylamino Acids and Some of Their Derivatives

Jan Spengler, Klaus Burger*
Department of Organic Chemistry, University of Leipzig, Talstr. 35, D-04103 Leipzig, Germany
Fax +49(341)9736599; E-mail: burger@organic.orgchem.uni-leipzig.de
Received 12 August 1997

N-Methylamino acid derivatives are obtained in high yield by a stereoselective one-pot procedure from hexafluoroacetone protected amino acids via *N*-chloromethylation and treatment with triethylsilane/trifluoroacetic acid.

α-*N*-Methylamino acids are constituents of various peptides and depsipeptides isolated from plant strains, microorganisms and marine species. Some of these are pseudopeptides like cyclosporine,[1] dolastatin,[2] didemnin[3] etc. exhibiting highly interesting therapeutic profiles.[4] Incorporation of α-*N*-methylamino acids into strategic positions of peptides leads to an enhanced proteolytic stability, to an increase in lipophilicity and to profound conformational changes.[5] Therefore, they are valuable building blocks for the synthesis of peptidomimetics and combinatorial chemistry. Furthermore, certain α-*N*-methylamino acids themselves have been found to be biologically active in their own right.[6] Consequently, a number of synthetic routes to optically pure α-*N*-methylamino acids have been developed.[4, 7, 8]

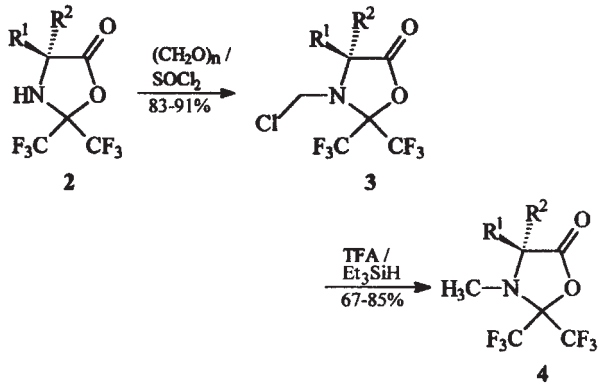
Recently we have shown that hexafluoroacetone (HFA) is a useful reagent for the simultaneous protection of the amino and the carboxylic group of α-amino acids.[9] The protected carboxylic group turned out to be stabile against a wide range of electrophilic reagents, however, the carboxylic group is activated towards nucleophiles. Therefore, deprotection of the carboxylic group and the α-amino group can be achieved simultaneously under mild conditions. Nucleophilic ring opening reactions of the oxazolidinones are always coupled with the deprotection of the α-amino group.



1 2

Scheme 1

We now report on a preparatively simple stereoconservative route to α-*N*-methylamino acid derivatives starting from hexafluoroacetone protected α-amino acids **2**. In a three component condensation compound **2**, paraformaldehyde and thionyl chloride react - without any solvent - to give the α-*N*-chloromethyl compounds **3** in nearly quantitative yield. The progress of the reaction can be monitored by ^{19}F NMR spectroscopy. Compounds **3** were treated without further purification with triethylsilane/trifluoroacetic acid.[10] The transformation **3** $\rightarrow$ **4** is an exothermic process. Purification of **4** can be achieved by fractional distillation under reduced pressure. In the case of the low boiling compound **4a** diphenylmethylsilane instead of triethylsilane was used for the transformation of the *N*-chloromethylamino into the α-*N*-methylamino acid derivatives. The 2,2-bis(trifluoromethyl)-3-methyl-1,3-oxazolidin-5-ones **4** can be stored in the refrigerator without decomposition over weeks.



2 3 4

Scheme 2

Since compounds **4** are carboxylic group activated species they can be readily transformed into acid hydrochlorides, ester hydrochlorides and hydroxamic acids, respectively.

α-Amino hydroxamic acid derivatives are a class of amino acid analogs of current interest.[11] To our knowledge α-*N*-methylamino hydroxamic acids have not been described so far.

Solvents were purified and dried prior to use. Reagents were used as purchased. Melting points (uncorrected) were determined on a Boetius hot plate. Optical rotations were measured on a Polartronic polarimeter (Schmidt & Haensch) in a 5 cm cell. For C, H, N analyses a CHNO-Rapid-Elemental-Analyser (Hereaus) was used. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV) or by GC/MS on a HP5890 MSD spectrometer. IR spectra were obtained using a Specord spectrometer (Carl Zeiss, Jena). ^{1}H (200.041 or 300.075 MHz), ^{13}C (50.305 or 75.462 MHz) and ^{19}F NMR (188.205 or 282.33 MHz) spectra were recorded on a Varian Gemini 2000 or a Varian Gemini 300 spectrometer. TMS was used as reference standard for ^{1}H and ^{13}C NMR spectra (internal) and TFA for ^{19}F NMR spectra (external).

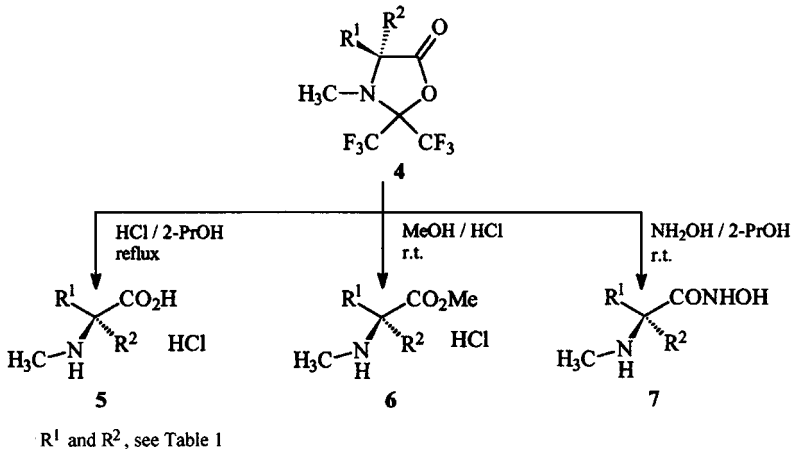
3-Chloromethyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones 3; General Procedure:

A mixture of 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones[12] **2** (20 mmol) and paraformaldehyde (1.20 g, 40 mmol) was stirred in $SOCl_2$ (5 mL) at 60°C until gas evolution ceased (l-5 h). The progress of the reaction was monitored by ^{19}F NMR spectroscopy. After removal of the excess of $SOCl_2$, the residue was distilled in vacuo. The reaction mixture of **3** can be used without any purification for N-methylation to give **4** (Table 1).

Table 1. Compounds **2–4** Prepared

Product[a]	R^1	R^2	NR	Yield (%)	bp (°C)/Torr	$[\alpha]_D^{25}$ (*c*, $CHCl_3$)	IR (film) ν C=O (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)		^{13}C NMR ($CDCl_3$/TMS), δ				^{19}F NMR ($CDCl_3$), δ[b]
								NR	H-4	NR	C-4	C-2	C-5	CF_3
2a	CH_3	H	H	98	54/12	+14.4 (1.3)	1823	3.00 (br s)	4.01 (m)	–	50.9	88.8 (m)	172.8	–2.97 (br s)
2b	$(CH_3)_2CH$	H	H	98	74/13	–2.22 (4.1)	1823	2.95 (br s)	3.86 (t, *J*=4.8)	–	60.1	88.4 (m)	170.8	–2.71 (q, *J*=8.3) –2.38 (q, *J*=8.3)
2c	$(CH_3)_2CHCH_2$	H	H	95	85/15	–3.81 (4.2)	1818	2.98 (d, *J*=7.0)	3.87 (m)	–	63.0	88.5 (m)	172.1	–2.82 (br s)
2d	H	Ph	H	95	72/0.3	–68.3 (2.4)	1825	3.42 (d, *J*=6.0)	4.99 (d, *J*=6.4)	–	68.7	88.4 (m)	170.0	–2.55 (q, *J*=8.0) –2.36 (q, *J*=8.0)
3a	CH_3	H	CH_2C1	83	65/11	+30.9 (1.1)	1844	5.22 (d, *J*=12.2) 5.39 (d, *J*=12.2)	4.22 (q, *J*=6.4)	58.1	61.0	88.5 (m)	169.1	–0.65 (q, *J*=8.7) 3.23 (q, *J*=8.7)
3b	$(CH_3)_2CH$	H	CH_2C1	87	88–90/8	+35 (1.0)	1841	5.18 (d, *J*=12.2) 5.38 (d, *J*=12.2)	4.10 (d, *J*=3.2)	58.5	69.6	87.4 (m)	167.4	0.74 (q, *J*=7.7) 3.46 (q, *J*=7.7)
3c	$(CH_3)_2CHCH_2$	H	CH_2C1	87	42/0.36	+105 (1.7)	1844	5.20 (d, *J*=12.4) 5.37 (d, *J*=12.4)	4.18 (m)	58.6	73.3	87.7 (m)	169.0	–0.33 (q, *J*=9.0) 3.48 (q, *J*=9.0)
3d	H	Ph	CH_2C1	91	65–67/0.01	–209 (1.5)	1848	4.87 (d, *J*=12.1) 5.35 (d, *J*=12.1)	5.15 (s)	57.9	69.6	87.5 (m)	166.6	0.54 (q, *J*=9.0) 3.46 (q, *J*=9.0)
4a	CH_3	H	CH_3	67	53/12	+32 (1.02)	1843	2.72 (q, *J*=1.6)	3.59 (d, *J*=6.6)	32.5	66.3	89.9 (m)	170.8	–1.29 (q, *J*=8.0) 4.24 (q, *J*=8.0)
4b	$(CH_3)_2CH$	H	CH_3	75	87/23	+36 (1.06)	1837	2.70 (m)	3.45 (d, *J*=2.0)	32.3	64.3	88.9 (m)	167.7	–0,68 (q, *J*=7.7) 4.38 (q, *J*=7.7)
4c	$(CH_3)_2CHCH_2$	H	CH_3	85	89–90/21	+44 (2.3)	1840	2.70 (q, *J*=2.2)	3.55 (t, *J*=4.8)	33.2	69.3	90.0 (m)	170.6	–1.02 (q, *J*=8.0) 4.37 (q. *J*=8.0)
4d	H	Ph	CH_3	83	44–46/0.05	120 (1.1)	1847	2.68 (q, *J*=2.3)	4.54 (s)	33.3	65.5	89.9 (m)	167.7	–0.50 (q, *J*=7.6) 4.25 (q, *J*=7.6)

[a] Satisfactory microanalyses obtained: C+ 0.46, H ± 0.43, N ± 0.35,
[b] CF_3CO_2H was used as the external standard.



Scheme 3

Table 2. Compounds **5** Prepared

Product	Yield (%)	mp (°C)		$[\alpha]_D$		^{1}H NMR (D_2O/TMS), δ, J (Hz)		^{13}C NMR (D_2O/TMS), δ		
		found	reported	found	reported	NCH_3	H-2	NCH_3	C-2	CO_2H
5a	84	146–152	165.5–166[13]	+5.9[a]	+5.77[13]	2.59 (s)	3.82 (m)	31.1	56.8	172.5
5b	70	143–145	149[14]	+29[b]	+25.5[14]	2.59 (s)	3.63 (m)	2.9	67.4	171.1
5c	95	139–142	–	+20.5[c]	+21.6[8]	2.58 (s)	3.76 (m)	34.5	62.6	174.6
5d	81	209–211	241[15]	–108[d]	–87[15]	2.47 (s)	4.78 (s)	31.2	64.6	170.7

[a] c=6, H_2O.
[b] c=2, EtOH.
[c] c=9, H_2O.
[d] c=1.49, 1 N HCl.

Table 3. Compounds **6** Prepared

Product	Yield (%)	mp (°C)		$[\alpha]_D$		^{1}H NMR ($CDCl_3$/TMS), δ, J (Hz)			^{13}C NMR ($CDCl_3$/TMS), δ			
		found	reported	found	reported	NCH_3	OCH_3	H-2	NCH_3	OCH_3	C-2	C=O
6a	71	82–83	82[16]	+1[a]	–3[16]	2.61 (s)	3.70 (s)	3.97 (m)[b]	31.2	54.1	56.7	171.1[b]
6b	72	139–141	140–141[17]	+35[c]	+30[18]	2.77 (t, J=5.4)	3.85 (s)	3.60 (m)	33.2	53.3	67.6	167.8
6c	75	131	127–128[19]	+34[d]	+31.4[20]	2.68 (s)	3.78 (s)	3.74 (m)	34.4	56.5	62.5	173.4
6d	87	169–173	155–156[21]	–132[e]	–	2.61 (t, J=5.2)	3.77 (s)	4.95 (m)	31.0	53.1	64.4	168.5

[a] c=2, EtOH.
[b] Recorded in D_2O.
[c] c=1, EtOH.
[d] c=1, EtOH.
[e] c=1, 1 N HCl.

Table 4. Compounds **7** Prepared

Product	Yield (%)	mp (°C)	$[\alpha]_D^{25}$	^{1}H NMR, δ, J (Hz)		^{13}C NMR, δ			IR (KBr) ν C=O (cm^{-1})	MS (m/z) M^+
				NCH_3	H-2	NCH_3	C-2	C=O		
7a	85	149–l52	–20[d]	2.33 (s)	3.27 (m)[b]	33.8	56.5	170.7[c]	1645	118
7b	91	172–173	+30[e]	2.51 (s)	3.16 (m)[b]	34.9	68.9	168.2[b]	1620	146
7c	79	186–187	+40[f]	2.15 (s)	2.76 (m)[c]	34.0	59.4	170.7[c]	1619	160
7d	72	179	–140[g]	2.17 (s)	3.89 (s)[c]	34.9	66.1	169.7[c]	1623	180

[a] Satisfactory microanalyses obtained: C ± 0.11, H ± 0.39, N ± 0.24.
[b] Recorded in D_2O.
[c] Recorded in DMSO-d_6.
[d] c=1, H_2O.
[e] c=1, 1 N HCl.
[f] c=1, 3 N HCl.
[g] c=1, 1 N HCl.

2,2-Bis(trifluoromethyl)-3,4-dimethyl-1,3-oxazolidin-5-one (4a): To a mixture of **3a** (5.7 g, 20 mmol) and diphenylmethylsilane (4.8 g, 24 mmol), was added CF_3CO_2H (4 mL) with stirring. An exothermal reaction started immediately! The mixture was stirred until gas evolution ceased (0.5 h). Then the volat[1]le compounds were distilled off (0.05 Torr/25 °C) and collected in a trap at –196°C. The distillate was dissolved in CH_2Cl_2 (50 mL), treated with ice / water mixture (2 × 25 mL) and satd $NaHCO_3$ solution until the organic phase was neutral. After drying ($MgSO_4$) and evaporation of the solvent the residue was distilled in vacuo (Table 1).

2,2-Bis(trifluoromethyl)-3-methyl-1,3-oxazolidin-5-ones 4b–4d; General Procedure:
To a mixture of **3** (20 mmol) and Et_3SiH (2.8 g, 24 mmol) was added CF_3CO_2H (4 mL) with stirring. An exothermic reaction started immediately! The mixture was stirred until gas evolution ceased (0.5 h) and distilled in vacuo (Table 1).

***N*-Methylamino Acid Hydrochlorides 5a–5d; General Procedure:**
A mixture of oxazolidinone **4** (10 mmol), 2-propanol (5 mL) and 3 N HCl (5 mL) was refluxed for 12 h. After complete hydrolysis of **4** (^{19}F NMR analysis) the mixture was evaporated to dryness in vacuo. The residue was triturated with Et_2O and the crystalline product was filtered and washed with Et_2O (Table 2).

***N*-Methylamino Acid Methyl Ester Hydrochlorides 6; General Procedure:**
Oxazolidinone **4** (10 mmol) was dissolved in a saturated solution of HCl gas in anhyd MeOH (5 mL) and stirred overnight. After completion of the reaction (^{19}F NMR analysis) the mixture was evaporated to dryness and the residue triturated with Et_2O to afford **6** as a white solid. After filtration and washing with Et_2O the ester hydrochlorides **6** were obtained in analytically pure form (Table 3).

α-*N*-Methylamino Hydroxamic Acids 7; General Procedure:
A solution of **4** (10 mmol) in 2-propanol (5 mL) was treated with an aqueous solution of hydroxylamine (1 mL, 50 %). After an induction period (10 min–5 h), compounds **7** crystallized, which were filtered and washed with Et_2O (Table 4).

We gratefully acknowledge the financial support from the Hermann Schlosser Stiftung, Deutsche Forschungsgemeinschaft and Fond der Chemischen Industrie. We thank Degussa AG and Hoechst AG, Frankfurt / Main for providing chemicals. This project is associated to an INTAS Network.

(1) Wenger, R. M. *Helv. Chim. Acta* **1984**, *67*, 502.
(2) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Dufresne, C,; Bates, R. B.; Schmidt, J. M.; Cerny, R. L.; Kizu, H. *J. Org. Chem*. **1990**, *55*, 2989.
Bates, R. B.; Brusoe, K. G.; Burns, J. J.; Caldera, S.; Cui, W.; Gangwar, S.; Gramme, M.R.; McClure, K. J.; Rouen, G. P.; Schadow, H.; Stessman, C. C.; Taylor, S. R.; Vu, V. H.; Yarick, G.V.; Zhang, J.; Pettit, G. R.; Bontems, R. *J. Am. Chem. Soc.* **1977**, *119*, 2111.
Pettit, G. R.; Kamano, Y.; Herald, C. L.; Fujii, Y.; Kizu, H.; Boyd, M. R.; Boettner, F. E.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J. C.; Michel, C. *Tetrahedron* **1993**, *49*, 9151.
(3) Jouin, P.; Poncet, J.; Dufour, M.-L.; Pantaloni, A.; Castro, B. *J. Org. Chem*. **1989**, *54*, 617.
Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett*. **1984**, *25*, 2935.
Li, W.-R.; Jouillé, M. M. In *Studies in Natural Products Chemistry, Vol. 10, Stereoselective Synthesis (Part F)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1992**, pp 241-302.
Ramanjulu, I. M.; Ding, X.; Joullié, M. M. *J. Org. Chem*. **1997**, *62*, 4961.
(4) Chruma, J. J.; Sames, D.; Polt, R. *Tetrahedron Lett*. **1997**, *38*, 5085.
(5) Ovchinnikov, Y. A.; Ivanov, V. T. *Tetrahedron* **1975**, *31*, 2177.
(6) Sangster, A. W.; Thomas, S. E.; Tingling, N. L. *Tetrahedron* **1975**, *31*, 1135.
Paruszewski, R.; Rostafinska-Suchar, G.; Strupinska, M.; Jaworski, P.; Stables, J. P. *Pharmazie* **1996**, *51*, 145.
Okamoto, K.; Quastel, J. H. *Br. J. Pharmacol*. **1977**, *59*, 551; *Chem. Abstr*. **1977**, *87*, 78729.
(7) Muller, D.; Zeltser, I.; Bitan, G.; Gilon, C. *J. Org. Chem*. **1997**, *62*, 411.
Luke, R. W.; Boyce, P. G. T.; Dorling, E. K. *Tetrahedron Lett.* **1996**, *37*, 263.
O'Donnell, M. J.; Bruder, W. A.; Daugherty, B. W.; Lui, D.; Wojciechowski, K. *Tetrahedron Lett*. **1984**, *25*, 3651.
Olsen, R. A. *J. Org. Chem*, **1970**, *35*, 1970.
Oppolzer, W.; Cintas-Moreno, P.; Tamura, O. *Helv. Chim. Acta* **1993**, *76*, 187.
Coulton, S.; Moore, G. A.; Ramage, R. *Tetrahedron Lett*. **1976**, *44*, 4005.
Cheung, S. T.; Benoiton, N. L. *Can. J. Chem*. **1977**, *55*, 906.
Grieco, P. A.; Bahsas, A. *J. Org. Chem*. **1987**, *52*, 5746.
Dorow, R. L.; Gingrich, D. E. *J. Org. Chem*. **1995**, *60*, 4986.
Ebata, M.; Takahashi, Y.; Otsuka, H. *Bull. Chem. Soc. Jpn* **1966**, 39, 2535.
Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *43*, 327.
Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314.
(8) Fischer, E.; v. Mechel, L. *Ber. Dtsch. Chem. Ges*. **1916**, *49*, 1355.
(9) Pires, R.; Fehn, S.; Golubev, A.; Winkler, D.; Burger, K. *Amino Acid*s **1996**, *11*, 301, and literature cited therein.
(10) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem*. **1983**, *48*, 77.
Colvin, E. W. *Silicon in Organic Synthesis*, Butterworths: London, **1981**.
(11) Bihofsky, R.; Levinson, B. L.; Loewi, R. C.; Erhardt, P. W.; Polokoff, M. A. *J. Med. Chem*. **1995**, *38*, 2119.
Tamaki, K.; Ogita, T.; Tanzawa, K.; Sugimura, Y. *Tetrahedron Lett*. **1993**, *34*, 683.
Floyd, C. D.; Lewis, C. D.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett*. **1996**, *37*, 8045.
(12) Weygand, F.; Burger, K.; Engelhardt, K. *Chem. Ber*. **1966**, *99*, 1461.
(13) Fischer, E.; Lipschitz, W. *Ber. Dtsch. Chem. Ges*. **1915**, *48*, 369.
(14) Cook, A. H.; Cox, S. F.; Farmer, T. H. *J. Chem. Soc*. **1949**, 1024.
(15) Araga, T.; Saito, T.; Kotage, H. *Nippon Kagaku Zasshi* **1965**, *86*, 111; *Chem. Abstr*. **1965**, *62*, 16365.
(16) Portnova, S. L.; Bystrov, V. F.; Tsetlin, V. I.; Ivanov, V. T.; Ovchinnikov, Y. A. *Zh. Obshch. Khim*. **1968**, *38*, 428; *Chem. Abstr.* **1968**, *69*, 107048.
(17) Shemyakin, M. M.; Ovchinnikov, Y. A.; Ivanov, V. T.; Kiryushkin. A. A. *Tetrahedron Lett*. **1962**, 301.
(18) Coste, J.; Frerot, E.; Jouin, P. *J. Org. Chem*. **1994**, *59*, 2437.
(19) Shemyakin, M. M.; Ovchinnikov, Y. A.; Ivanov, V. T.; Kiryushkin, A. A. *Tetrahedron* **1963**, *19*, 581.
(20) Suganu, H.; Higaki, K.; Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 231.
(21) Klosa; J. *Arch. Pharm*. (Weinheim, Ger.) **1952**, *285*, 401.