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A Novel, One-Pot Preparation of *N*-Methyl-α-Amino Acid Dipeptides from Oxazolidinones and Amino Acids

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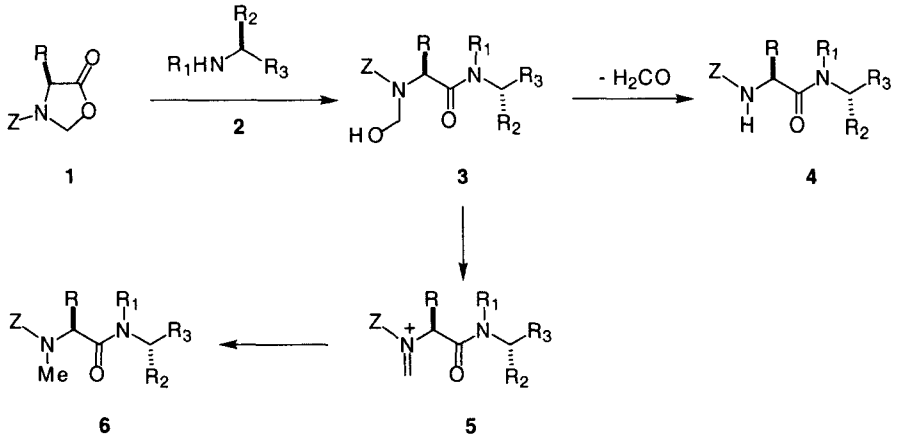
Abstract: A new synthetic method has been developed to prepare *N*-methyl dipeptides in one-pot directly from oxazolidinones. Treatment of oxazolidinone **1** with an amino ester yields an intermediate *N*-hydroxymethyl dipeptide **3**, which is treated with TFAA and triethylsilane to give *N*-methyl dipeptide **6** in good yield. The reaction parameters which were explored include the rate of oxazolidinone ring opening, the stability of **3**, and the optimum solvent and acid for conversion of **3** to **6**.

We are interested in the use of oxazolidinones for the preparation of dipeptides which contain *N*-methyl-α-amino acids. Typically, *N*-methyl dipeptides are prepared by first synthesizing the *N*-methyl amino acid[1] followed by coupling to a second amino acid derivative although the solid phase *N*-methylation of peptides is known.[1g] While oxazolidinones have been used to synthesize dipeptides[2] and *N*-methyl-α-amino acids,[1e,f] they have not been employed for the direct preparation of dipeptides containing *N*-methyl-α-amino acids. The formation of *N*-methyl dipeptides directly from oxazolidinones would simplify the synthesis since both the amino acid coupling and subsequent conversion to the *N*-methyl dipeptide could be done in one pot.

Scheme 1



As shown in Scheme 1, the reaction of an α-amino ester **2** with an oxazolidinone **1** proceeds *via* an intermediate *N*-hydroxymethyl dipeptide, **3**.[2] The ability to prepare *N*-methyl containing dipeptides **6** *via* this approach is dependent on the conversion of the hemi-aminal **3** to the immonium ion **5** followed by reduction to the

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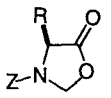
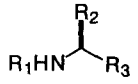
N-methyl dipeptide **6** rather than to the dipeptide **4**, the latter pathway a result of formaldehyde loss. The rate of formation of **4** from **3** is pH dependent with the fastest rates occurring at high pH.[3]



1

a R = H
b R = Me
c R = *i*-Pr
d R = Bn
e R = *i*-Bu
f R = Ph



2

a R_1 = H, R_2 = Me, R_3 = CO_2Et
b R_1 = H, R_2 = Bn, R_3 = CO_2Me
c R_1 = H, R_2 = CO_2Me, R_3 = Bn
d R_1 = Me, R_2 = H, R_3 = CO_2Et
e R_1 = R_2 = -C_4H_7-, R_3 = CO_2Me
f R_1 = H, R_2 = H, R_3 = Ph
g R_1 = H, R_2 = H, R_3 = CO_2t-Bu

The study of the preparation of dipeptides containing *N*-methyl-α-amino acids from oxazolidinones was begun by examining the rate of hemi-aminal formation. The oxazolidinones were prepared by a modification of the literature procedure.[4] The reaction of **1b** with *l*-alanine ethyl ester, **2a**, (2 equiv) was examined by HPLC, monitoring the disappearance of **1b** using Boc-benzylamine as an internal standard. At a reaction concentration of 3.5M in dichloromethane, the reaction is 80% complete after three hours and is complete after eight hours. While the steric environment of the oxazolidinone does not affect reaction with benzylamine, it does affect the rate of ring opening by α-amino esters. For example, 30-60% of **1c** is recovered after reaction with α-amino esters at 3.5M after 24 h while no **1b** is recovered under the same reaction conditions.

The stability of hemi-aminal **3** was examined next. Following a rapid silica gel plug filtration, the *N*-hydroxymethyldipeptide **3ba** is isolated as a solid upon treatment of **1b** with **2a**. Prolonged exposure of **3ba** to silica gel leads to the formation of the dipeptide **4ba**. Hemi-aminal **3ba** also displays thermal instability as determined by a variable temperature NMR experiment in d_6-DMSO. None of the dipeptide **4ba** is detected at rt while 9%, 24%, and 67% is present upon heating to 60°C, 90°C, and 120°C, respectively. Therefore, we generally avoided the isolation of the hemi-aminals and employed reaction temperatures at or below rt.

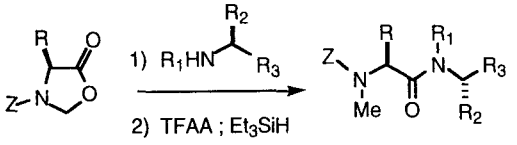
The ability to isolate **3ba** readily allowed a study of optimum reaction conditions for the conversion to **6ba**. Trifluoroacetic acid and triethylsilane were employed first as these reagents were used by Friedinger[1c] for the preparation of *N*-methyl-α-amino acids from oxazolidinones and by Grieco[5] for the preparation of *N*-methyl peptides from azanorbornene derivatives *via* an immonium ion intermediate. The reaction of **3ba** with trifluoroacetic acid (1.5 equiv) and triethylsilane (10 equiv) in chloroform[2a] is insensitive to the order of addition and to the reaction temperature (rt or 0°C). The solvent choice is important with methylene chloride providing the highest yields of **6ba** and ethereal solvents giving only **4ba**. However, even using methylene chloride, about 10% of **4ba** is formed.

Having determined that methylene chloride is the optimum solvent for the preparation of **6**, we then studied the effect that acids have on the conversion to **6**. Oxazolidinone **1b** was treated with two equivalents of

2a in methylene chloride at 3.5M. After stirring at room temperature overnight, the reaction mixture was diluted to 1.75M with methylene chloride and cooled in an ice bath. The mixture was treated with acid (2 equiv) and triethylsilane (2 equiv). The reaction is sensitive to the type of acid employed. A comparison of acetic, trichloroacetic, and trifluoroacetic acids reveals that **6ba** and **4ba** are formed in the following ratios: 0:100, 78:22, and 80:20. Unfortunately, some **4** is produced in all cases. We were, however, able to avoid the formation of **4** by employing TMSOTf or more conveniently TFAA as the additive. Presumably, the oxygen of the hemi-aminal is acylated by TFAA resulting in the facile formation of **5** due to the good leaving group ability of trifluoroacetate. The immonium ion is then rapidly reduced by Et_3SiH to give **6**. The reaction is much cleaner with TFAA than with acetic anhydride which yields a complex reaction mixture.

A variety of *N*-methyl containing dipeptides were formed using this novel procedure as shown in Table 1.[6] The by-product **4** is absent from these reactions as long as good quality TFAA is used. A number of α-amino

Table 1. Direct Preparation of Dipeptide 6 from 1.



1 6

Entry	R	R_1	R_2	R_3	Yield (%)
6ba	Me	H	Me	COOEt	96
6bb	Me	H	Bn	COOMe	86
6bc	Me	H	COOMe	Bn	90
6bd	Me	Me	H	COOEt	89
6be	Me	-C_4H_7-		COOMe	92
6bf	Me	H	H	Ph	81
6ca	*i*-Pr	H	Me	COOEt	66
6cb	*i*-Pr	H	Bn	COOMe	29
6cc	*i*-Pr	H	COOMe	Bn	54
6cd	*i*-Pr	Me	H	COOEt	43
6cf	*i*-Pr	H	H	Ph	70
6da	Bn	H	Me	COOEt	90
6de	Bn	-C_4H_7-		COOMe	91
6dg	Bn	H	H	COO*t*-Bu	74
6ea	*i*-Bu	H	Me	COOEt	90
6ed	*i*-Bu	Me	H	COOEt	94
6fa	Ph	H	Me	COOEt	77

esters can be successfully employed in this dipeptide formation including proline and sarcosine. Good yields of dipeptide **6dg** are obtained using glycine *t*-butyl ester with an additional 9% dipeptide being formed as the free acid. All of the dipeptides are formed in good yield with the exception of those formed from **1c** where the oxazolidinone ring opening is slow. The yield of **6cc** is improved to 54% (compared to 29% for **6cb**) merely by increasing the reaction time for the ring opening from 24 to 48h. The reaction proceeds without racemization as

determined by comparison of the ^{1}H and ^{13}C NMR spectra of **6bb** and **6bc**, **6cb** and **6cc**, and by the optical rotation of **6cf**.[7,8] This method allows the efficient preparation of *N*-methyl amino acid dipeptides since it is possible to couple the amino acids and prepare the *N*-methyl carbamate in one pot.

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References and Notes

1. (a) Dorow, R. L.; Gingrich, D. E. *J. Org. Chem.* **1995**, *60*, 4987. (b) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327. (c) Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314. (d) McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915. (e) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem.* **1983**, *48*, 77. (f) Luke, R. W. A.; Boyce, P. G. T.; Dorling, E. K. *Tetrahedron Lett.* **1996**, *37*, 263. (g) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.
2. (a) Hiskey, R. G.; Jung, J. M. *J. Am. Chem. Soc.* **1963**, *85*, 578. (b) Belshaw, P. J.; Meyer. S. D.; Johnson, D. D.; Romo, D.; Ikeda, Y.; Andrus, M.; Alberg, D. G.; Schultz, L. W.; Clardy, J.; Schreiber, S. L. *Synlett* **1994**, 381. (c) Itoh, M. *Chem. Pharm. Bull.* **1969**, *17*, 1679. (d) Micheel, F.; Meckstroth, W. *Chem. Ber.* **1959**, *92*, 1675. (e) Micheel, F.; Haneke, H. *Chem. Ber.* **1959**, *92*, 309. (f) Micheel, F.; Thomas, S. *Chem. Ber.* **1959**, *90*, 2906. (g) Micheel, F.; Haneke, H. *Chem. Ber.* **1962**, *95*, 1009. (h) King, G. A. III; Sweeney, J. G. *Organic Prep. and Procedures* **1997**, *29*, 177.
3. Kahns, A. H.; Friis, G. J.; Bundgaard, H. *Bioorganic and Medicinal Chem. Lett.* **1993**, *3*, 809.
4. (a) Ben-Ishai, D. *J. Am. Chem. Soc.* **1957**, *79*, 5736. (b) The oxazolidinones were prepared by adding 3 equiv of trioxane and 0.6 equiv of *p*-toluenesulfonic acid to the *N*-Cbz-α-amino acid in toluene. The slurry was refluxed for 4 h giving a homogeneous solution which was worked-up following Ben-Ishai's procedure.
5. Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746.
6. All new dipeptides were fully characterized by ^{1}H and ^{13}C NMR, MS, IR, rotation, and combustion analysis.
7. Filira, F.; Di Bello, C.; Veronese, A. C.; D'Angeli, F. *J. Org. Chem.* **1972**, *37*, 3265.
8. All of our attempts to determine the chiral integrity of the dipeptides by HPLC have been unsuccessful to date.