JOC Article

pubs.acs.org/joc

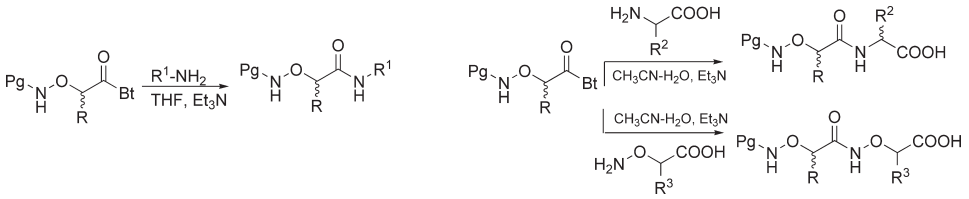
Efficient Preparation of Aminoxyacyl Amides, Aminoxy Hybrid Peptides, and α-Aminoxy Peptides

Alan R. Katritzky,*[,‡] Ilker Avan,[‡,§] and Srinivasa R. Tala[‡]

[‡]*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, and* [§]*Department of Chemistry, Anadolu University, 26470, Eskişehir, Turkey*

katritzky@chem.ufl.edu

Received July 24, 2009



N-(Pg-α-aminoxy acids) **1a**−**g** are converted to *N*-(Pg-α-aminoxyacyl)benzotriazoles **2a**−**g**, which react under mild conditions with amines, α-amino acids/α-dipeptides, and α-aminoxy acids to give aminoxyacyl amides **3a**−**g**, (**3e** + **3e**′), and (**3g** + **3g**′), aminoxy hybrid peptides **4a**−**h**, (**4a** + **4a**′), **6a**−**d**, **9a**−**e**, (**9a** + **9a**′), and (**9b** + **9b**′), and α-aminoxy peptides **10a**,**b** in good yields without racemization.

Introduction

In peptidomimetic foldamer chemistry, *β*-peptides have been applied widely in biomolecular design.[1] Unlike α-peptides, short *β*-peptides can fold into well-defined secondary structures, such as helices, sheets, and turns. Since *β*-peptides have excellent stability toward proteases,[2] they are widely used as backbone-modified amino acids in drug design. α-Aminoxy acids are analogues of *β*-amino acids in which the *β*-carbon atom is replaced by an oxygen atom. An α-aminoxy acid is more rigid than its corresponding *β*-amino acid,[3a] and aminoxy amide bonds are resistant to enzymatic degradation; therefore, α-aminoxy acids have been explored as peptidomimetics.[3b]

α-Aminoxy peptides have attracted considerable interest as novel foldamers[4] because of their unusual conformations and interesting bioactivities.[5] Aminoxy peptides may feature strong intramolecular hydrogen bonds between adjacent residues in peptidomimetic foldamers.[6] For example, peptides consisting of α-aminoxy acids can possess eight-membered-ring intramolecular hydrogen bonds (α N−O turns),[7] and peptides consisting of *β*-aminoxy acids can possess nine-membered-ring intramolecular hydrogen bonds (*β* N−O turns).[5e] Oligomers of homochiral α- or *β*-aminoxy acids can form helical structures consisting of consecutive N−O turns (1.8_8 and 1.7_9 helices, respectively).[8] *β*-Sugar aminoxy peptides exhibited rigid ribbon-like secondary structures composed of 5/7 bifurcated intramolecular hydrogen bonds.[6a] Hybrid peptides of an α-aminoxy acid provided robust 12/10-mixed helices.[9]

(1) (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (b) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015–2022.

(2) (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B. *Helv. Chim. Acta* **1996**, *79*, 913–941. (b) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734–739. (c) Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445–455. (d) Hintermann, T.; Seebach, D. *Chimia* **1997**, *51*, 244–247.

(3) (a) Wu, Y.-D.; Wang, D.-P.; Chan, K. W. K.; Yang, D. *J. Am. Chem. Soc.* **1999**, *121*, 11189–11196. (b) Briggs, M. T.; Morley, J. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2138–2143.

(4) (a) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011. (b) Yang, D.; Zhang, D.-W.; Hao, Yu.; Wu, Y.-D.; Luo, S.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 6719–6722. (c) Li, X.; Yang, D. *Chem. Commun.* **2006**, 3367–3379.

(5) (a) Jimenez-Castells, C.; De la Torre, B. G.; Gallego, R. G.; Andreu, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5155–5158. (b) Carrasco, M. R.; Nguyen, M. J.; Burnell, D. R.; Maclaren, M. D.; Hengel, S. M. *Tetrahedron Lett.* **2002**, *43*, 5727–5729. (c) Carrasco, M. R.; Brown, R. T. *J. Org. Chem.* **2003**, *68*, 8853–8858. (d) Vanderesse, R.; Thevenet, L.; Marraud, M.; Boggetto, N.; Reboud, M.; Corbier, C. *J. Peptide Sci.* **2003**, *9*, 282–299. (e) Yang, D.; Zhang, Y.-H.; Li, B.; Zhang, D.-W.; Chan, J. C.-Y.; Zhu, N.-Y.; Luo, S.-W.; Wu, Y.-D. *J. Am. Chem. Soc.* **2004**, *126*, 6956–6966.

(6) (a) Chandrasekhar, S.; Rao, C. L.; Reddy, M. S.; Sharma, G. D.; Kiran, M. U.; Naresh, P.; Chaitanya, G. K.; Bhanuprakash, K.; Jagadeesh, B. *J. Org. Chem.* **2008**, *73*, 9443–9446. (b) Chen, F.; Song, K.-S.; Wu, Y.-D.; Yang, D. *J. Am. Chem. Soc.* **2008**, *130*, 743–755.

(7) (a) Yang, D.; Ng, F.-F.; Li, Z.-J.; Wu, Y.-D.; Chan, K. W. K.; Wang, D.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9794–9795. (b) Yang, D.; Qu, J.; Li, B.; Ng, F.-F.; Wang, X.-C.; Cheung, K.-K.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **1999**, *121*, 589–590.

(8) Yang, D.; Qu, J.; Li, W.; Zhang, Y.-H.; Ren, Y.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **2002**, *124*, 12410–12411.

(9) Sharma, G. V. M.; Manohar, V.; Dutta, S. K.; Subash, V.; Kunwar, A. C. *J. Org. Chem.* **2008**, *73*, 3689–3698.

Published on Web 10/15/2009 DOI: 10.1021/jo901612j

Peptides containing α-aminoxy acids are good receptors for anions because of the acidity of their aminoxy amide protons.[10] A compound derived from an α-aminoxy acid has been used as an effective chemical shift reagent for measuring the ee of carboxylic acids;[11a] another compound derived from an α-aminoxy acid forms chloride channels to mediate chloride ion transportation across cell membranes.[11b]

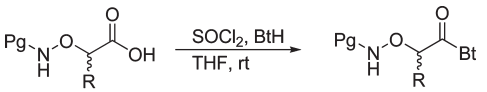
Published methods for the preparation of aminoxy acid derivatives and aminoxy peptides include (i) combinations of coupling reagents such as Bop-HOBt-NEM, HBTU-HOBt-NEM, DIC-HOAt;[12] EDCl-HOBt, EDCl-HOAt;[6a] TBTU/HOBt/DIEA;[13] HOBt, BOP, DIEA;[14] *i*BuOCOCl/NMM;[5d] DIC/HOBt;[15] (ii) activated esters;[16,17] and (iii) α-amino diazoketone.[18] These methods often involve longer reaction times[13] and N-diacylation products[16] and give low yields.[15] Hence, there is a need for a mild and efficient general method to prepare aminoxyacyl amides, aminoxy hybrid peptides, and aminoxy peptides.

N-Acylbenzotriazoles are stable, mostly crystalline compounds and easy to handle. These *N*-acylbenzotriazoles are advantageous for N-, O-, C-, and S-acylation,[19] especially where the corresponding acid chlorides are unstable or difficult to prepare.[19l,m] *N*-Fmoc-(α-aminoacyl)benzotriazoles and their Boc- and Cbz- analogues enabled the preparation of chiral di-, tri-, and tetrapeptides in good yields from natural amino acids in solution phase with complete retention of chirality.[19b,20] Recently, we have also prepared peptide alcohols in good yields using *N*-protected (α-aminoacyl)benzotriazoles and *N*-protected (α-dipeptidoyl)benzotriazoles.[21] Herein, we describe a new method for the preparation of aminoxyacyl amides, aminoxy hybrid peptides, and aminoxy peptides by using *N*-protected (α-aminoxyacyl)benzotriazoles **2**.

Results and Discussion

Preparation of *N*-Pg(α-aminoxyacyl)benzotriazole 2a−g. *N*-Protected (α-aminoxy) acids **1b−g** were synthesized from either corresponding α-bromocarboxylic acids or α-hydroxycarboxylic acids and were well characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis. The complete reaction procedure and the characterization data of *N*-protected (α-aminoxy)acids **1b−g** are given in the Supporting Information. *N*-Pg(α-aminoxy) acid **1a** was obtained from a commercial source. *N*-Pg(α-aminoxyacyl)benzotriazoles **2a−g** have been prepared by treatment of *N*-Pg(α-aminoxy) acids **1a−g** with 4 equiv of 1*H*-benzotriazole and 1 equiv of thionyl chloride in THF at room temperature in 56−89% yields (Scheme 1, Table 1). Products **2a−g** were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis.

SCHEME 1. Preparation of *N*-Pg(α-aminoxyacyl)benzotriazoles 2a−g



1a–g **2a–g**, 56-89%

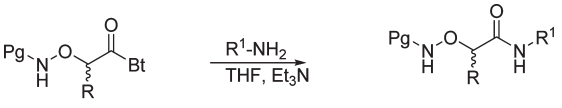
TABLE 1. Preparation of *N*-Pg(α-aminoxyacyl)benzotriazoles 2a−g

entry	Pg: protecting group	R	**2**, yield[a] (%)	mp (°C)
1	*tert*-butoxycarbonyl (Boc)	H	**2a**, 67	114−115
2	phthalimide (Phth)	H	**2b**, 75	155−157
3	phthalimide (Phth)	Me	**2c**, 56	145−147
4	benzyloxycarbonyl (Cbz)	H	**2d**, 66	86−87
5	Cbz	Me	**2e**, 58	oil
6	Cbz	$CH(CH_3)_2$	**2f**, 89	oil
7	Cbz	Ph	**2g**, 77	oil

[a]Isolated yield.

Preparation of *N*-Pg(α-aminoxyacyl)amides 3a−g, (3e + 3e′), and (3g + 3g′). α-Aminoxyacylamides also exhibit intramolecular hydrogen bonds between adjacent residues (α N−O turns) in peptidomimetic foldamers.[6b,7a] *N*-Pg(α-aminoxyacyl) amides **3a−g**, (**3e**+**3e′**), and (**3g**+**3g′**) were obtained by reaction between *N*-Pg(α-aminoxyacyl)benzotriazoles **2a**,**b**,**d−f** and the corresponding amines in THF at room temperature in the presence of triethylamine in 38−78% yields (Scheme 2, Table 2). Products **3a−g**, (**3e**+**3e′**), and (**3g**+**3g′**) were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis. Retention of enantiopurity of product **3g** was confirmed by chiral HPLC using a Whelk-O1 column (with detection at 254 nm, a flow rate of 1.0 mL/min, and MeOH as the eluting solvent). The diastereomer **3g** showed a single retention-time peak in chiral HPLC at 3.46, while its corresponding diastereomeric mixture (**3g**+**3g′**) showed two peaks at 3.46 and 5.68.

SCHEME 2. Preparation of *N*-Pg(α-aminoxyacyl)amides 3a−g, (3e+3e′), and (3g+3g′)



2a-b, 2d-f **3a–g, (3e+3e'), (3g+3g')**, 38–78%

Synthesis of α-Aminoxy Hybrid Peptides. α-Aminoxy hybrid peptides are defined as including at least one

(10) Yang, D.; Li, X.; Sha, Y.; Wu, Y.-D. *Chem.—Eur. J.* **2005**, *11*, 3005–3009.
(11) (a) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996–7997. (b) Li, X.; Shen, B.; Yao, X.-Q.; Yang, D. *J. Am. Soc. Chem.* **2007**, *129*, 7264–7265.
(12) Lee, M.; Lee, J.; Baek, B.; Shin, I. *Synlett* **2003**, 325–328.
(13) Thevenet, L.; Vanderesse, R.; Marraud, M.; Didierjean, C.; Aubry, A. *Tetrahedron Lett.* **2000**, *41*, 2361–2364.
(14) Baek, B.; Lee, M.; Kim, K.-Y.; Cho, U.-I.; Boo, D. W.; Shin, I. *Org. Lett.* **2003**, *5*, 971–974.
(15) Shin, I.; Park, K. *Org. Lett.* **2002**, *4*, 869–872.
(16) Dulery, V.; Renaudet, O.; Dumy, P. *Tetrahedron* **2007**, *63*, 11952–11958.
(17) Foillard, S.; Rasmussen, M. O.; Razkin, J.; Boturyn, D.; Dumy, P. *J. Org. Chem.* **2008**, *73*, 983–991.
(18) Yang, D.; Zhang, Y.-H.; Li, B.; Zhang, D.-W. *J. Org. Chem.* **2004**, *69*, 7577–7581.
(19) (a) Katritzky, A. R.; Angrish, P.; Hur, D.; Suzuki, K. *Synthesis* **2005**, 397–402. (b) Katritzky, A. R.; Angrish, P.; Suzuki, K. *Synthesis* **2006**, 411–424. (c) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720–5723. (d) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210–8213. (e) Katritzky, A. R.; Wang, M. Y.; Yang, H. F.; Zhang, S. M.; Akhmedov, N. G. *ARKIVOC* **2002**, *viii*, 134–142;. (f) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *ARKIVOC* **2005**, *vii*, 36–55;. (g) Katritzky, A. R.; Tala, S. R.; Singh, S. K. *Synthesis* **2006**, 3231–3237. (h) Katritzky, A. R.; Chen, Q.-Y.; Tala, S. R. *Org. Biomol. Chem.* **2008**, *6*, 2400–2404. (i) Katritzky, A. R.; Singh, A.; Haase, D. N.; Yoshioka, M. *Arkivoc* **2009**, *viii*, 47–56;. (j) Katritzky, A. R.; Tala, S. R.; Abo-Dya, N. E.; Abdel-Samii, Z. K. *Synthesis* **2009**, 1708–1714. (k) Katritzky, A. R.; Tala, S. R.; Abo-Dya, N. E.; Gyanda, K.; El-Gendy, B.; E-D, M.; Abdel-Samii, Z. K.; Steel, P. J. *J. Org. Chem.* **2009**, *74*, 7165–7167. (l) Katritzky, A. R.; Belyakov, S. A. *Aldrichim. Acta* **1998**, *31*, 35–46. (m) Katritzky, A. R.; Li, J.; Xie, J. *Tetrahedron* **1999**, *55*, 8263–8293. (n) Katritzky, A. R.; Angrish, P.; Todadze, E. *Synlett* **2009**, 2392–2411.
(20) (a) Katritzky, A. R.; Kazuyuki, S.; Singh, S. K. *Synthesis* **2004**, 2645–2652. (b) Katritzky, A. R.; Chen, Q.-Y.; Tala, S. R. *Chem. Biol. Drug. Des.* **2009**, *73*, 611–617.
(21) Katritzky, A. R.; Abo-Dya, N. E.; Tala, S. R.; Gyanda, K.; Abdel-Samii, Z. K. *Org. Biomol. Chem.* **2009**, DOI: 10.1039/b905730g.

TABLE 2. Preparation of *N*-(Pg)-aminoxy Acid Amides 3a−g, (3e+3e′), and (3g+3g′)

entry	2	amine	3, yield[a] (%)	mp (°C)
1	Boc-AOGly-Bt, **2a**	isopropylamine	**3a**, 74	67−68
2	Boc-AOGly-Bt, **2a**	*c*-hexylamine	**3b**, 62	137−139
3	Cbz-AOGly-Bt, **2d**	*c*-hexylamine	**3c**,78	69−70
4	Phth-AOGly-Bt, **2b**	*p*-methoxyaniline	**3d**, 38	210−211
5	Cbz-AOGly-Bt, **2d**	L-2-methylbenzylamine	**3e**, 67	oil
6	Cbz-AOGly-Bt, **2d**	DL-2-methylbenzylamine	(**3e**+**3e′**), 73	oil
7	Cbz-L-AOAla-Bt, **2e**	*p*-methoxyaniline	**3f**, 56	31−32
8	Cbz-L-AOVal-Bt, **2f**	L-2-methylbenzylamine	**3g**, 67	96−97
9	Cbz-L-AOVal-Bt, **2f**	DL-2-methylbenzylamine	(**3g**+**3g′**), 58	oil

[a]Isolated yield. [b]AO stands for aminoxy in the nomenclature for aminoxy compounds throughout the paper.

TABLE 3. α-AO-α-hybrid Dipeptides 4a−h and (4a+4a′)

entry	2	amino acid	product 4, yield[a] (%)	mp (°C)
1	Cbz-AOGly-Bt, **2d**	L-Phe-OH	Cbz-AOGly-L-Phe-OH, **4a**, 51	oil
2	Cbz-AOGly-Bt, **2d**	DL-Phe-OH	Cbz-AOGly-DL-Phe-OH, (**4a**+**4a′**), 56	oil
3	Cbz-L-AOAla-Bt, **2e**	L-Phe-OH	Cbz-L-AOAla-L-Phe-OH, **4b**, 61	33−34
4	Cbz-L-AOAla-Bt, **2e**	L-Trp-OH	Cbz-L-AOAla-L-Trp-OH, **4c**, 72	128−130
5	Cbz-L-AOAla-Bt, **2e**	L-Leu-OH	Cbz-L-AOAla-L-Leu-OH, **4d**, 78	oil
6	Cbz-L-AOVal-Bt, **2f**	L-Phe-OH	Cbz-L-AOVal-L-Phe-OH, **4e**, 69	126−127
7	Cbz-L-AOVal-Bt, **2f**	L-Trp-OH	Cbz-L-AOVal-L-Trp-OH, **4f**, 66	26−27
8	Cbz-AOGly-Bt, **2d**	L-Cys-OH	Cbz-AOGly-L-Cys-OH, **4g**, 66	oil
9	Cbz-L-AOAla-Bt, **2e**	L-Cys-OH	Cbz-L-AOVal-L-Cys-OH, **4h**, 61	oil

[a]Isolated yield.

TABLE 4. Preparation of α-AO-α,α-hybrid Tripeptides 6a−d

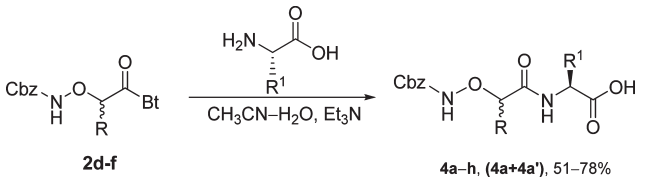
entry	2	dipeptide, 5	product 6, yield[a] (%)	mp (°C)
1	Cbz-AOGly-Bt, **2d**	Gly-L-Phe-OH	Cbz-AOGly-Gly-L-Phe-OH, **6a**, 81	oil
2	Cbz-AOGly-Bt, **2d**	Gly-L-Leu-OH	Cbz-AOGly-Gly-L-Leu-OH, **6b**, 70	oil
3	Cbz-L-AOAla-Bt, **2e**	Gly-L-Phe-OH	Cbz-L-AOAla-Gly-L-Phe-OH, **6c**, 50	63−64
4	Cbz-L-AOVal-Bt, **2f**	Gly-L-Phe-OH	Cbz-L-AOVal-Gly-L-Phe-OH, **6d**, 67	123−124

[a]Isolated yield.

α-aminoxy acid residue and at least one natural amino acid residue. We have prepared α-AO-α-hybrid dipeptides **4a**−**h** and (**4a**+**4a′**), α-AO-α,α-hybrid tripeptides **6a**−**d**, and α,α-AO-hybrid dipeptides **9a**−**d** and (**9a**+**9a′**).

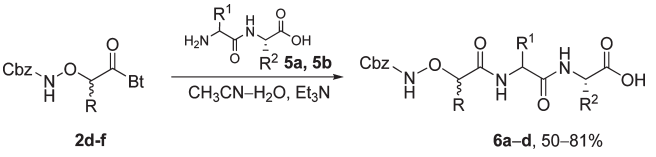
Preparation of α-AO-α-hybrid dipeptides 4a−h and (4a+4a′). α-AO-α-Hybrid dipeptides **4a**−**h** and (**4a**+**4a′**) were prepared by treatment of *N*-(Pg-aminoxyacyl)benzotriazoles **2d**−**f** and the corresponding amino acids in CH_3CN-H_2O in the presence of triethylamine at room temperature in 51−78% yields (Scheme 3, Table 3). Products **4a**−**h** were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis. Retention of enantiopurity of α-AO-α-hybrid dipeptides **4a** and (**4a**+**4a′**) was supported by chiral HPLC analysis using a Chirobiotic T column (detection at 254 nm, flow rate 1.0 mL/min, and MeOH as eluent). α-AO-α-hybrid dipeptide **4a** showed a single retention-time peak in chiral HPLC analysis at 3.15, while the corresponding enantiomeric mixture (**4a**+**4a′**) showed two peaks at 2.89 and 3.69.

SCHEME 3. α-AO-α-hybrid Dipeptides 4a−h and (4a+4a′)



Preparation of α-AO-α,α-hybrid tripeptides 6a−d. α-AO-α,α-hybrid tripeptides **6a**−**d** were prepared by treatment of *N*-Pg(α-aminoxyacyl)benzotriazoles **2d**−**f** with unprotected dipeptides **5a**,**b** in CH_3CN-H_2O in the presence of triethylamine in 50−81% yields (Scheme 4, Table 4).

SCHEME 4. Preparation of α-AO-α,α-hybrid Tripeptides 6a−d



Preparation of α,α-AO-hybrid Dipeptides 9a−e, (9a+9a′), and (9b+9b′). α,α-AO-hybrid dipeptides **9a**−**e**, (**9a**+**9a′**), and (**9b**+**9b′**) were obtained by treatment of *N*-Pg(α-aminoacyl)benzotriazole **7a**−**c** and the corresponding aminoxy acids **8a**,**b** (details about preparation of compounds **8a**,**b** are given in the Supporting Information) in CH_3CN-H_2O (3:1) in the presence of triethylamine at room temperature in 44−90% yields (Scheme 5, Table 5). All products **9a**−**e**, (**9a**+**9a′**), and (**9b**+**9b′**) were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis. The enantiomeric purity of

SCHEME 5. Preparation of α,α-AO-hybrid Dipeptides 9a−e, (9a+9a′), and (9b+9b′)

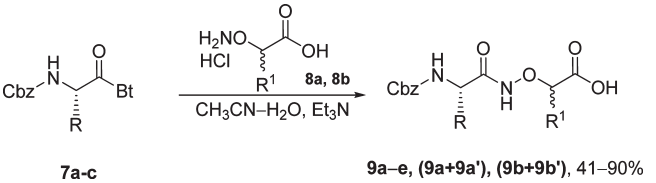


TABLE 5. Preparation of α,α-AO-hybrid Dipeptides 9a−e, (9a+9a′), and (9b+b′)

entry	7	8	product 9	yield[a] (%)	mp (°C)
1	Cbz-L-Ala-Bt, **7a**	AOGly-OH, **8a**	Cbz-L-Ala-AOGly-OH, **9a**	61	24−25
2	Cbz-DL-Ala-Bt, (**7a**+**7a′**)	AOGly-OH, **8a**	Cbz-DL-Ala-AOGly-OH, (**9a**+**9a′**)	71	24−25
3	Cbz-L-Phe-Bt, **7b**	AOGly-OH, **8a**	Cbz-L-Phe-AOGly-OH, **9b**	90	121−122
4	Cbz-DL-Phe-Bt, (**7b**+**7b′**)	AOGly-OH, **8a**	Cbz-DL-Phe-AOGly-OH, (**9b**+**9b′**)	72	145−146
5	Cbz-L-Met-Bt, **7c**	AOGly-OH, **8a**	Cbz-L-Met-AOGly-OH, **9c**	81	87−88
6	Cbz-L-Phe-Bt, **7b**	L-AOAla-OH, **8b**	Cbz-L-Phe-L-AOAla-OH, **9d**	44	38−39
7	Cbz-L-Met-Bt, **7c**	L-AOAla-OH, **8b**	Cbz-L-Met-L-AOAla-OH, **9e**	73	127−128

[a]Isolated yield.

TABLE 6. Preparation of α-Aminoxy Dipeptides 10a and 10b

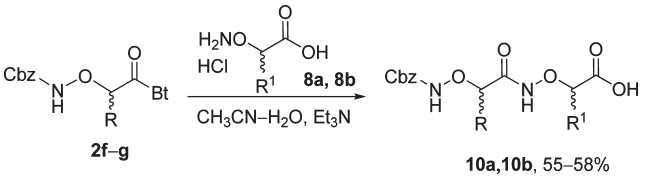
entry	2	8	product **10**, yield[a] (%)
1	Cbz-L-AOVal-Bt, **2f**	AOGly-OH, **8a**	Cbz-L-AOVal-AOGly-OH, **10a**, 58
2	Cbz-L-AOMan-Bt, **2g**	L-AOAla-OH, **8b**	Cbz-L-AOMan-L-AOAla-OH, **10b**, 52

[a]Isolated yield.

α,α-AO-hybrid dipeptides **9b** and (**9b**+**9b′**) was supported by chiral HPLC analysis using a Chirobiotic T column (detection at 254 nm, flow rate 0.6 mL/min, and MeOH−H_2O (7:3) as eluent). α,α-AO-hybrid dipeptide **9b** showed a single peak in HPLC analysis at 4.74, while the corresponding enantiomeric mixture (**9b**+**9b′**) showed two peaks at 4.10 and 5.32.

Preparation of α-Aminoxy Dipeptides 10a,b. α-Aminoxy dipeptides **10a**,**b** were prepared in 55−58% yields by reaction of *N*-(Pg-aminoxyacyl)benzotriazoles **2f**,**g** with the corresponding aminoxy acids **8a**,**b** in CH_3CN-H_2O (3:1) in the presence of triethylamine at ambient temperature (Scheme 6, Table 6). Products **10a**,**b** were characterized by ^1H NMR, ^{13}C NMR, and elemental analysis.

SCHEME 6. Preparation of α-Aminoxy Dipeptides 10a and 10b



In comparison with literature methods, our method has the following advantages: (i) utilization of milder reaction conditions, (ii) shorter reaction times, (iii) better yields, (iv) use of inexpensive, easily synthesizable *N*-(Pg-α-aminoxyacyl)benzotriazole reagents for peptide coupling, (v) coupling without protecting the carboxylic acid group, (vi) no N-diacylation products, and (vii) avoids racemization.

Conclusions

In conclusion, a mild and an efficient general method for the preparation of α-aminoxyacylamides, α-aminoxy hybrid peptides, and α-aminoxy peptides has been developed by reacting *N*-(Pg-α-aminoxyacyl)benzotriazoles with amines, α-amino acids, peptides, and α-aminoxy acids. All of the α-aminoxy derivatives were obtained under mild reaction conditions in good yields and with no racemization.

Experimental Section

Melting points are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz apparatus in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. The data are reported as follows: chemical shift in parts per million (ppm, δ units) and spin−spin coupling J (Hz). DMF was dried and distilled over CaH_2, whereas THF was used after distillation over Na/benzophenone.

General Preparation of *N*-(Pg-aminoxyacyl)benzotriazole (2). Thionyl chloride (1.2 mmol) was added to a solution of benzotriazole (4.16 mmol) in anhydrous THF (5 mL) at 0 °C, and the reaction mixture was stirred for 20 min at same temperature. *N*-(Pg)-aminoxyacetic acid (1.0 mol) dissolved in anhydrous THF (3 mL) was added dropwise to the mixture. After being stirred for 4 h at 0 °C, the reaction mixture was allowed to warm to room temperature. After 1 h, the white precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (25 mL), and the solution washed with saturated Na_2CO_3 solution (3 × 10 mL) and then saturated brine solution and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford *N*-(Pg-aminoxyacyl)benzotriazoles (**2**).

Boc-AOGly-Bt (2a): White microcrystals (67%); mp 115−116 °C; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9H), 5.54 (s, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.96 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 74.6, 82.7, 114.1, 120.6, 126.8, 130.9, 131.0, 146.0, 156.4, 168.3. Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.07; H, 5.69; N, 18.59.

General Preparation of *N*-(Pg)-aminoxy Acid Amides (3). Amine (1 equiv) and triethylamine (1 molar equiv) in THF (2 mL) were added to a stirred solution of *N*-(Pg-aminoxyacyl)benzotriazole (**2**) (1 molar equiv) in THF (4 mL) dropwise at 0 °C, and the mixture was stirred for 2 h at room temperature. After evaporation of THF, EtOAc (20 mL) was added to the solution, which was washed with saturated Na_2CO_3 solution (3 × 10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude amides.

***tert*-Butyl 2-(Isopropylamino)-2-oxoethoxycarbamate (3a)[13].** The crude product was recrystallized from diethyl ether−hexanes to give white microcrystals (74%): mp 67−68 °C; ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.6 Hz, 6H), 1.49 (s, 9H), 4.00−4.20 (m, 1H), 4.27 (s, 2H), 7.51 (s, 1H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 28.1, 41.0, 76.1, 83.0, 157.8, 167.8. Anal. Calcd for $C_{10}H_{20}N_2O_4$: C, 51.71; H, 8.68; N, 12.06. Found: C, 52.09; H, 8.90; N, 12.12.

General Preparation of α-AO-α-hybrid Dipeptides 4 and α-AO-α,α-hybrid Tripeptides 6. The unprotected amino acids (1.5 mmol) and triethylamine (2.0 mmol) were dissolved in a minimum amount of water. Acetonitrile (3 mL) was added, and the solution was cooled to 0 °C. A solution of *N*-(Pg-aminooxyacyl)benzotriazole (**2**) (1 mmol) in acetonitrile (4 mL) was added dropwise over 10 min at 0 °C and the resulting solution stirred for 4 h at 10 °C. After evaporation of THF, EtOAc (20 mL) was

added, and the mixture was washed with 4 N HCl solution (3 × 15 mL) and brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude product **4** or **6**.

Cbz-AOGly-L-Phe-OH (4a). The residue was purified by column chromatography [EtOAc−hexanes (from 1:3 to 1:1)] to give an oil (51%): $[\alpha]_D^{23} = -9.0$ (*c* 1.00, CH_3OH); ^1H NMR ($CDCl_3$) δ 3.02 (dd, J = 14.0 Hz, 8.3 Hz, 1H), 3.25 (dd, J = 14.0 Hz, 4.9 Hz, 1H), 4.28 (s, 2H), 4.76−4.89 (m, 1H), 5.11 (s, 2H), 7.14−7.30 (m, 5H), 7.33 (s, 5H), 7.72 (br s, 1H), 8.08 (s, 1H), 8.23 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.3, 53.6, 68.5, 75.8, 127.2, 128.6, 128.8, 128.9, 129.4, 135.1, 136.2, 158.5, 169.8, 174.5. Anal. Calcd for $C_{19}H_{20}N_2O_6.H_2O$: C, 58.46; H, 5.16; N, 7.18. Found: C, 58.76; H, 5.42; N, 7.38.

Cbz-AOGly-Gly-L-Phe-OH (6a). The residue was recrystallized from diethyl ether−hexanes to give white hydroscopic microcrystals, (81%): mp 29−31 °C; $[\alpha]_D^{23} = +7.1$ (*c* 1.00, CH_3OH); ^1H NMR ($CDCl_3$) δ 2.92 (br s, 1H), 3.04 (br s, 1H), 3.76 (br s, 1H), 3.83 (br s, 1H), 4.22 (br s, 2H), 4.67 (br s, 1H), 5.00 (br s, 2H), 6.92−7.36 (m, 12H), 8.04 (s, 1H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.4, 42.8, 53.8, 68.4, 75.9, 127.3, 128.3, 128.6, 128.8, 128.9, 129.6, 135.3, 136.1, 158.6, 169.8, 170.5, 173.8. Anal. Calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79. Found: C, 58.57; H, 5.28; N, 9.60.

General Preparation of α,α-AO-hybrid Dipeptides 9. α-Aminoxy acid hydrochloric acid salts **8** (1.5 mmol) and triethylamine (3.5 mmol) were dissolved in minimum amount of water. Acetonitrile (3 mL) was added, and the solution was cooled to 0 °C. A solution of *N*-(Pg-aminoacyl)benzotriazole (**7**) (1 mmol) in acetonitrile (3 mL) was added dropwise over 10 min at 0 °C, and the resulting solution was stirred for 4 h at 10 °C. The reaction was monitored by TLC [EtOAc−hexanes (1:1)]. The solvent was evaporated under vacuum. The mixture was diluted with EtOAc (20 mL), washed with 4 N HCl solution (3 × 15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude product **9**.

Cbz-L-Ala-AOGly-OH (9a). The residue was purified by column chromatography [EtOAc−hexanes (from 1:3 to 1:1)] to obtain a sticky oil (61%): $[\alpha]_D^{23} = -27.8$ (*c* 1.00, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 6.9 Hz, 3H), 4.31−4.51 (m, 1H), 4.51 (s, 2H), 5.06 (d, J = 12.3 Hz, 1H), 5.13 (d, J = 12 Hz, 1H), 5.59 (d, J = 8.4 Hz, 1H), 7.26−7.45 (m, 6H), 10.42 (br s 1H); ^{13}C NMR ($CDCl_3$) δ 18.3, 48.0, 68.0, 73.3, 128.3, 128.7, 128.8, 135.6, 156.7, 171.2, 171.9. Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 53.08; H, 5.72; N, 9.19.

General Preparation of α-Aminoxy Dipeptides 10. α-Aminoxy acid hydrochloric acid salts (**8**) (1.5 mmol) and triethylamine (3.5 mmol) were dissolved in a minimum amount of water. Acetonitrile (3 mL) was added, and the solution was cooled to 0 °C. A solution of *N*-(Pg-aminoxyoacyl)benzotriazole (**2**) (1 mmol) in acetonitrile (3 mL) was added dropwise over 10 min at 0 °C, and the resulting solution was stirred for 4 h at 10 °C. After the solvent was evaporated under vacuum, EtOAc (20 mL) was added, and the mixture was washed with 3 N HCl solution (3 × 15 mL) and brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude product **10**.

Cbz-L-AOVal-AOGly-OH (10a). The residue was an oily mixture of **10a** (80%) and **1f** (20%): $[\alpha]_D^{23} = -56.0$ (*c* 1.00, CH_3OH); (data from the mixture) ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 2.18−2.30 (m, 1H), 4.19 (d, J = 4.2 Hz, 1H), 4.43 (d, J = 17.4 Hz, 1H), 4.54 (d, J = 17.4 Hz, 1H), 5.17 (d, J = 11.7 Hz, 1H), 5.24 (d, J = 12.0 Hz, 1H), 7.32−7.42 (m, 5H), 8.17 (s, 1H), 11.64 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7, 18.9, 30.9, 69.0, 75.1, 91.2, 128.6, 128.7, 128.8, 128.9, 129.0, 134.7, 159.5, 171.1, 172.0; HRMS $[M + Na]^+$ found 363.1175, theoretical for $C_{15}H_{20}N_2O_7 \cdot Na^+$ 363.1163.

Acknowledgment. We thank Dr. C. D. Hall for helpful discussions.

Supporting Information Available: Materials and methods; general procedure for preparation of *N*-protected aminoxy acids **1b**−**g** and their characterization data; characterization data of **2b**−**2g**, **3b**−**g**, (**3g**+**3g′**), (**4a**+**4a′**)−**4h**, **6b**−**d**, (**9a**+**9a′**)−**9e**, and **10b**, ^1H NMR, ^{13}C NMR spectra of compounds and chiral HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.