Communications to the Editor

Trifluoromethyl-Substituted Imidazolines: Novel Precursors of Trifluoromethyl Ketones Amenable to Peptide Synthesis

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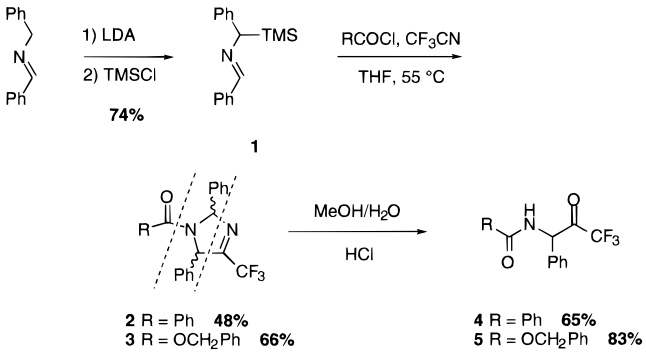
Trifluoromethyl ketones (TFMKs) have been shown to be potent inhibitors of a variety of esterases and proteases,[1] and peptidyl TFMKs have found specific applications as inhibitors of serine,[2] aspartic,[3] metallo,[4] and cysteine proteases.[5] Current approaches to synthesizing peptidyl TFMKs involve the oxidation of a trifluoromethyl alcohol precursor to the TFMK, which limits their use with amino acids having oxidizable residues.[6] In this communication we report a new approach to peptidyl TFMKs through a 1,3-dipolar cycloaddition reaction which produces trifluoromethyl-substituted Δ^3-imidazolines. These imidazolines, which act as latent forms of the TFMKs, can be manipulated by standard Fmoc-peptide synthesis methods and then hydrolyzed to peptidyl TFMKs under mild (nonoxidizing) acidic conditions.

Our approach to preparing the Δ^3-imidazoline heterocycle was modeled after a 1,3-dipolar cycloaddition reaction between an azomethine ylide (generated from an acyl chloride and an α-silylimine) and a dipolarophile,[7] a reaction which has been used for the preparation of related heterocycles.[8,9] The specific heterocycle we required as the TFMK precursor, a 4-trifluoromethyl-Δ^3-imidazoline, is conveniently prepared by 1,3-dipolar cycloaddition between the azomethine ylide and trifluoroacetonitrile.[10] Scheme 1 demonstrates our initial cycloaddition and hydrolysis studies with the simple α-silylimine **1**. Compound **1**[11] was prepared from *N*-benzylidinebenzylamine by benzylic deprotonation and silation with chlorotrimethylsilane. The reaction of **1** with either benzoyl chloride or benzyl chloroformate produced the *N*-protected Δ^3-imidazolines **2** and **3**.[12] These Δ^3-imidazolines were then cleaved by mild acid hydrolysis to yield the amino-protected phenylglycine TFMKs **4** and **5** in good yield.

Scheme 1



To demonstrate the usefulness of the Δ^3-imidazoline as a protected form of the TFMK, we incorporated it into a larger peptide. This was done conveniently using Carpino's carbamate-protected amino acid fluorides.[13] The amino acid fluorides required somewhat higher temperatures (75−80 °C) to initiate the cycloaddition, but they gave cleaner reactions and higher yields of the corresponding imidazolines. As shown in Scheme 2, the cycloaddition reaction involving Fmoc-Phe-F, benzylidinetrimethylsilylmethylamine,[7b] and trifluoroacetonitrile produced imidazoline **6** regioselectively in 70−77% yield. In one step, this approach produces the imidazoline as part of a pseudo dipeptide, which can then be readily hydrolyzed to the dipeptide TFMK **7**. More importantly, under standard Fmoc deprotection and peptide coupling conditions, imidazoline **6** could be converted to a pseudo tripeptide **8** and then hydrolyzed to give the tripeptide TFMK **9**, in 30% overall yield from the acid fluoride. Using the Fmoc protecting strategy in conjunction with the imidazoline as a protecting group for the ketone, one should be able to access peptidyl TFMKs of any size.[14]

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(1) For a review of uses and preparation of trifluoromethyl ketones, see: Bégué, J.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207−3258.

(2) Representative serine proteases. (a) Human neutrophil elastase: Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127−194. (b) α-Chymotrypsin: Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760−3767.

(3) Representative aspartic proteases. (a) HIV protease: Hodge, C. N.; Aldrich, P. E.; Fernandez, C. H.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Erickson-Viitanen S. *Antiviral Chem. Chemother.* **1994**, *5*, 257−262. (b) Pepsin: Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817. (c) Renin: Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. D. *J. Med. Chem.* **1993**, *36*, 2431−2447.

(4) Representative metallo proteases. (a) Angiotensin-converting enzyme: ref 3b. (b) Carboxypeptidase A: ref 3b

(5) Representative cysteine proteases. (a) Cathepsin G: Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M. Neises, B. Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394−407. (b) Cathepsin B: Smith, R. A.; Copp, L. J.; Donnelly, S. L.; Spencer, R. W.; Krantz, A. *Biochemistry* **1988**, *27*, 6568−6573.

(6) Methods for preparation of peptidyl TFMKs. (a) Stereoselective synthesis by CF_3ZnI addition to an isomerically pure peptidyl aldehyde: Edwards, P. D. *Tetrahedron Lett.* **1992**, *33*, 4279−4282. (b) Modified Dakin-West procedure: Kolb, M.; Barth, J.; Neises, B. *Tetrahedron Lett.* **1986**, *27*, 1579−1582. Kolb, M.; Neises, B. *Tetrahedron Lett.* **1986**, *27*, 4437−4440. (c) Henry reaction: Imperiali, B.; Abeles, R. H. *Tetrahedron Lett.* **1986**, *27*, 135−138. (d) Curtius rearrangement: Patel, D. V.; Gauvin, K. R.; Ryono, D. E. *Tetrahedron Lett.* **1988**, *29*, 4665−4668.

(7) (a) Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213−1216. (b) Achiwa, K.; Motoyama, T.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 3939−3945.

(8) For references on 1,3-dipolar cycloadditions, see: (a) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Vedejs, E. In *Advances in Cycloaddition;* Curran, D. P., Ed; JAI: Greenwich, CT, 1988. (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990; Chapter 6, pp 269−331. (d) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.9, pp 1069−1109. (e) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.10, pp 1111−1168.

(9) For reviews of azomethine ylides, see ref 8 and: Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981−1008.

(10) Trifluoroacetonitrile as a dipolarophile: (a) Kobayashi, Y.; Kumadaki, I.; Kobayashi, E. *Heterocycles* **1981**, *15*, 1223−1225. (b) Banks, R. E.; Thompson, J. *J. Fluorine Chem.* **1983**, *22*, 589−592.

(11) Popowski, E.; Franz, K. *Z. Chem.* **1979**, *19*, 103.

(12) Since trifluoroacetonitrile (bp −65 °C) is a gas, cycloaddition reactions were carried out in stainless steel sample cylinders which were sealed and placed in an oven at the appropriate temperature.

(13) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651−9652. Carpino, L. A.; Mansour, E. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611−2614.

(14) Although we have not explored peptide synthesis extensively using the C-terminal trifluoromethyl ketone protected as the Δ^3-imidazoline, it would appear to be generally useful with Fmoc *N*-terminal protection/acyl fluoride coupling, using acid labile groups (Boc and trityl) for side chain protection.

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Scheme 2

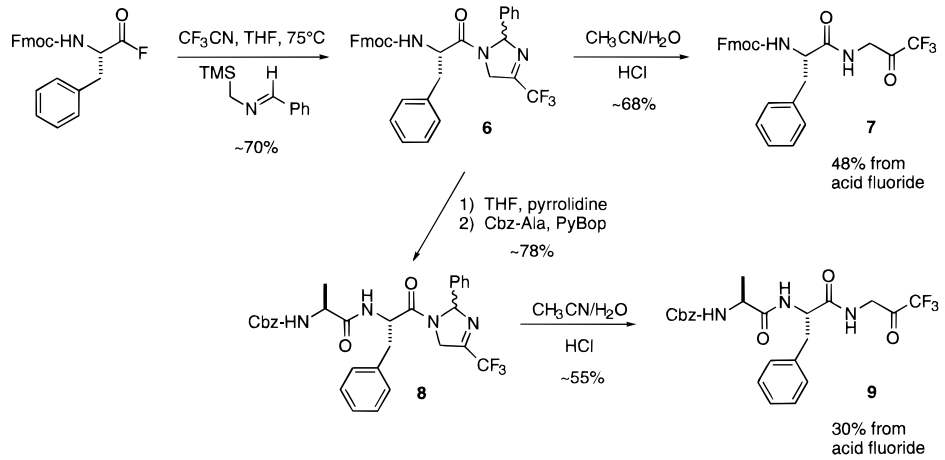

Table 1. Peptidyl TFMKs Prepared with the Structure R-AA^2-AA^1-CF_3

compound	R	AA^2	AA^1–CF_3	% overall yield from AA^2-F
10	Cbz	Gly	Phg-CF_3[a]	30
11	Cbz	Val	Phg-CF_3	29
7	Fmoc	Phe	Gly-CF_3	48
12	Fmoc	Phe	Phg-CF_3	36
9	Cbz-Ala	Phe	Gly-CF_3	30
13	Cbz-Ala	Met	Gly-CF_3	25
14	Cbz-Ala	Phe	Phg-CF_3	23
15	Cbz-Ala	Met	Phg-CF_3	26

[a] Phg-CF_3 = −NHCH(Ph)$COCF_3$.

A number of peptidyl TFMKs have been prepared by this method, some of which are listed in Table 1. Each of these compounds is composed of at least two amino acids and is described by the formula R-AA^2-AA^1-CF_3. In this formula, R is a protecting group or an additional protected amino acid, which was coupled to the AA^2 residue after cycloaddition. AA^2 originates as an amino acid fluoride (AA^2-F), and AA^1 is the residue formed during the cycloaddition. Numerous amino acids have been converted to the acid fluoride and used in the cycloaddition reaction, demonstrating the tolerance of the cycloaddition reaction to a variety of acid fluoride initiators. Some examples are glycine (**10**), alanine (not shown), valine (**11**), and phenylalanine (**7**). Finally, incorporation of methionine (a thioether residue) into peptidyl TFMKs **13** and **15** demonstrates the compatibility of oxidizable moieties with this synthetic approach to TFMKs.[14]

It should be noted that in all of the TFMKs prepared, no attempt was made to control the stereochemistry of AA.[1] As a result, the phenylglycine-derived TFMKs are isolated as a mixture of two diastereomers. This is not necessarily a serious drawback, since it is known that the stereogenic center α to the ketone carbonyl of a TFMK readily epimerizes under very mild conditions, even in blood.[15] It should also be noted that isolating TFMKs **9** and **13** as single diastereomers indicates that the AA^2 stereogenic center does not epimerize significantly during the formation of the acid fluoride or during the 1,3-dipolar cycloaddition.

Thus, we have developed an efficient method to prepare 4-trifluoromethyl-substituted Δ^3-imidazolines and incorporate them into peptides. The imidazoline serves as both a synthetic precursor to a TFMK and as a protecting group for the ketone during Fmoc-based peptide synthesis. The imidazolines can be readily hydrolyzed with mild acid to afford peptidyl TFMKs. We have also demonstrated that this method is amenable to oxidizable substrates. The one limitation is with AA^1, where only phenylglycine- and glycine-derived TFMKs are presently described. This limitation arises from the difficulty of preparing appropriately substituted α-silylimines and is being addressed in current studies.[16]

Acknowledgment. We are grateful for support of this research through a grant from the National Institutes of Health (PHS 5R01CA25836). This paper is dedicated to Nelson J. Leonard on the occasion of his 80th birthday.

Supporting Information Available: Detailed experimental procedures and characterization of all numbered compounds as well as other intermediates (10 pages). See any current masthead page for ordering and Internet access instructions.

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(15) P. D. Edwards, Zeneca Pharmaceuticals, personal communication.

(16) In order for this Δ^3-imidazoline approach to be generally applicable to the synthesis of peptidyl trifluoromethyl ketones with any substituent at the AA^1 position, it would be necessary to have a general method for the synthesis of substituted α-silylimines. Also, if unsymmetrical α-silylimines and/or azomethine ylides are utilized, it is necessary for the cycloaddition reaction to operate with appropriate regioselectivity, so that the desired substituent would become attached to the C-5 vs the C-2 positions. From our present studies, it appears that the α-silylimine synthesis can be generalized (C. W. Derstine and J. A. Katzenellenbogen, unpublished results), and, at least in the one unsymmetrical case we studied (ca. synthesis of **6**), that the cycloaddition can be quite regioselective, although it is not yet certain how selective the cycloaddition will be with the more complex unsymmetrical disubstituted α-silylimines.