Tetrahedron Letters, Vol. 33, No. 30, pp. 4279-4282, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

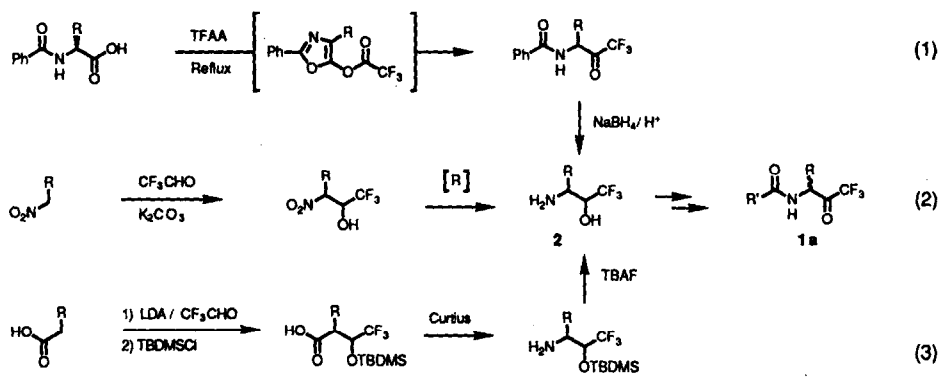
A Method For The Stereoselective Synthesis of Peptidyl Trifluoromethyl Ketones

Philip D. Edwards

Department of Medicinal Chemistry, ICI Pharmaceuticals Group,
A Business Unit of ICI Americas Inc., Wilmington, Delaware 19897

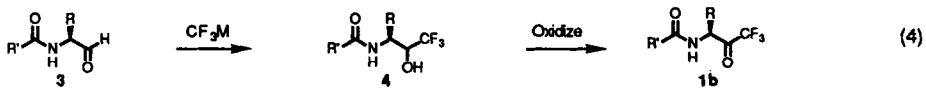
Abstract: A method is described for the stereoselective preparation of peptidyl trifluoromethyl ketones which is centered around the addition of trifluoromethyl zinc iodide to a peptidyl aldehyde. Oxidation of the resulting alcohol with selected oxidants affords the corresponding ketone in greater than 99% isomeric purity.

Peptidyl trifluoromethyl ketones (TFMKs; eg. **1a**) are an important class of inhibitors of hydrolytic enzymes including serine,[1] aspartyl,[2,3] metallo-,[2e] and cysteine proteinases.[1e,4] While a large number of methods have been developed for the preparation of simple alkyl TFMKs,[5] only three approaches for introducing the trifluoromethyl ketone functionality into a peptide backbone have been reported: a modified Dakin-West reaction employing trifluoromethyl acetic anhydride[6] (eq 1); a Henry reaction between a nitro alkane and fluoral[7,8] (eq 2); and the condensation of the dianion of substituted acetic acids with fluoral followed by a Curtius rearrangement[3] (eq 3). With all three approaches, a peptide backbone is appended to the amino group of amino alcohol **2**, and the resulting peptidyl trifluoromethyl alcohol (TFMA) oxidized to the corresponding TFMK **1a**.



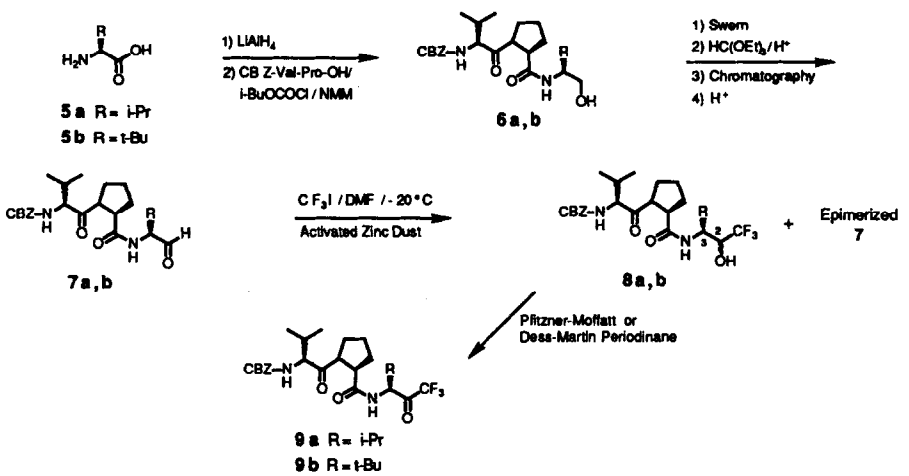
As part of our structure-activity studies on the inhibition of human leukocyte elastase (HLE) by peptidyl TFMKs, it became necessary to prepare isomerically pure TFMKs of known absolute stereochemistry. Common to all three processes described above is the addition of an achiral carbanion to a trifluoromethyl

carbonyl derivative in the crucial carbon-carbon bond forming step. As a result, the ketones **1a** produced by these methods are 1:1 mixtures of epimers at the stereogenic center alpha to the ketone carbonyl group. We therefore pursued a conceptually different approach and investigated the addition of a trifluoromethyl anion equivalent to a peptidyl aldehyde (eq 4). The success of this method for preparing isomerically pure TFMKs **1b** required that both the trifluoromethyl anion addition and subsequent alcohol oxidation be effected stereospecifically.



(4)

While pentafluoroethyl and higher homologous perfluoroalkyl anions can be readily generated and employed synthetically,[9] the trifluoromethyl anion is unstable and decomposes rapidly.[9a,10] This problem can be circumvented by generating the trifluoromethyl anion in the presence of the substrate. For the preparation of simple alkyl and aryl trifluoromethyl carbinols from aldehydes, several reagent systems have been successfully employed to produce trifluoromethyl anion equivalents: $CF_3TMS/TBAF$,[11] CF_3I/Zn,[12] $CF_3I/SnCl_2$,[13] (trialkylsilyl)(trifluoromethyl)diazenes,[14] and electrochemical trifluoromethylation.[15] However, none of these procedures has previously been applied to the construction of peptidyl trifluoromethyl alcohols. We have found that the CF_3I/Zn system can be used to prepare peptidyl TFMAs stereoselectively.



Aldehyde **7a** was prepared in a straightforward manner from L-valine thereby establishing the absolute stereochemistry of the stereogenic center alpha to the aldehydic carbonyl group as the natural *S* configuration. As a result of minor amounts of epimerization during its preparation, **7a** was a 95:5 mixture of *S/R* epimers.[16] When a mixture of peptidyl aldehyde **7a**, CF_3I, and zinc was sonicated at room temperature according to the procedure of Kitazume and Ishikawa[12d,f] only a 5-10% yield of the desired TFMA **8a** was produced. The remainder of the reaction mixture consisted of epimerized aldehyde **7a**. It was hypothesized

that under the conditions of sonication the CF_3ZnI rapidly decomposed to a basic by-product which converted the aldehyde to an enolate, thereby precluding the aldehyde from further reaction. In order to improve the life-time of the CF_3ZnI reagent, the reaction was run at -20°C and activated zinc was used to eliminate the need for sonication. These modifications resulted in a 50% isolated yield of the desired alcohol **8a**. Again, the only other component of the reaction mixture was epimerized aldehyde.

In a typical experiment, a solution of trifluoromethyl iodide (100 mmol) in DMF (25 ml) at -40°C was added over 2-3 h via a dry ice/acetonitrile cooled addition funnel to a -20°C mixture of aldehyde (5 mmol) and activated zinc[17] (100 mmol) in DMF (75 ml). After stirring for an additional 1 h at -20°C, the clear solution was warmed to room temperature, partitioned between water and ethyl acetate, acidified with 1N HCl, and the aqueous phase extracted with several portions of ethyl acetate. The combined organic extracts were washed with 20% NaOH and brine, dried (K_2CO_3/Na_2SO_4, 1:1) and the solvents evaporated. The crude trifluoromethyl alcohols **8** were purified by flash chromatography on silica gel.[18]

The trifluoromethyl alcohol **8a** was a mixture of all four possible diastereomers (HPLC analysis[16]). The two major isomers accounted for 95-92% of the mixture, both before and after purification. The *relative* stereochemistry of alcohols **8a** was assigned by HPLC correlation with the individual syn and anti diastereomeric pairs of **8a** independently prepared from the diastereomerically pure syn and anti amino alcohols **2**.[8] The *absolute* stereochemistry of the stereogenic center at C_3 of the two major isomers was derived from L-valine and therefore had the *S* configuration. Thus, these two isomers were assigned as (3*S*,2*S*)-*syn*-**8a** and (3*S*,2*R*)-*anti*-**8a**. The ratio of syn to anti (3*S*)-**8a** was 1:6. The anti product is that predicted to be the major isomer by Cram's cyclic chelation model.[19] 5-7% of the epimeric (3*R*)-**8a** alcohols was present. The ratio of 3*S*/3*R* epimers was about the same in the alcohol **8a** as in the starting aldehyde **7a**. This is consistent with the hypothesis that incomplete conversion of aldehyde to trifluoromethyl alcohol is the result of the aldehyde's conversion to an unreactive enolate. If the enolate were generated under equilibrating conditions, the product alcohol would have a higher percentage of the 3*R* epimers than in the starting aldehyde. Further support for this theory comes from an experiment wherein the reaction mixture was quenched with d_4-acetic acid. As determined by MS and ^1H NMR, the recovered epimerized aldehyde had virtually complete incorporation of a deuterium atom at C_3. A control experiment in which aldehyde **7a** in DMF was treated with d_4-acetic acid and subjected to the standard work-up did not result in either epimerization or deuterium incorporation.

A number of oxidants will convert the peptidyl TFMAs into the corresponding ketones.[3,5-8] Most cause extensive epimerization of the stereogenic center alpha to the ketone carbonyl. The Dess-Martin periodinane[20] was previously shown to oxidize TFMAs without epimerization.[8b] In addition, a modification of the Pfitzner-Moffatt oxidation[21] has also been found to be useful in this respect. Thus, treatment of alcohol **8a** (0.2 mmol) with dichloroacetic acid (0.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2 mmol) in DMSO (2 ml) and toluene (2 ml) afforded ketone **9a** with an isomeric purity of 90-95% prior to purification. Following chromatography, the peptidyl TFMK **9a** was isolated in 70% yield in greater than 99% isomeric purity. Enzyme inhibition studies confirmed that **9a**, which possessed the natural *S* configuration at C_3, was the biologically active epimer with a K_i of 0.8 nM against HLE (the 3*R* epimer of **9a** had a $K_i > 150$ nM [8b]).

This is the only method reported to allow for the preparation of single isomers of peptidyl TFMKs of defined stereochemistry. In addition, this process can be used to prepare TFMKs which are not readily

accessible by other approaches. For example, when the substituent "R" in amino alcohol **2** is a bulky group such as tert-butyl, the routes described in equations 1-3 may be problematic. In contrast, the aldehyde **7b**, readily prepared from L-tert-leucine **5b**, was smoothly converted to TFMA **8b** in 85% yield. Oxidation of **8b** with periodinane afforded the tert-butyl trifluoromethyl ketone **9b** in 72% yield as an 85:15 mixture of C_3 epimers, the major isomer presumably having the *S* configuration.

In summary, the methodology presented here allows for the preparation of peptidyl trifluoromethyl ketones of defined absolute stereochemistry. The success of this process with the tripeptides in this study indicates it should be generally applicable to the stereoselective synthesis of a variety of peptidyl trifluoromethyl alcohols and ketones. In addition, access is afforded to analogues which are not readily available by other technologies. These compounds will serve as important probes of enzymatic catalysis and inhibition.

References and Notes:

1. Skiles, J. W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K. G.; Mauldin, S. C.; Vitous, J.; Mui, P. W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S. M.; Possanza, G.; Keirns, J.; Letts, G.; Rosenthal, A. S. *J. Med. Chem.*, **1992**, *35*, 641-662, and references therein.
2. (a) Thaisrivongs, S.; Pals, D. T.; Turner, S. R. *ACS Symp. Ser.*, **1991**, *456*, 163-174; (b) Christianson, D. W.; Lipscomb, W. N. *Acc. Chem. Res.*, **1989**, *22*, 62-69; (c) Teater, C.; Grobelny, D.; Galardy, R. E. *Biochem. Biophys. Res. Comm.*, **1988**, *153*, 773-778; (d) Christianson, D. W.; Lipscomb, W. N. *J. Am. Chem. Soc.*, **1986**, *108*, 4998-5003; (e) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry*, **1985**, *24*, 1813-1817.
3. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.*, **1988**, *29*, 4665-4668.
4. (a) Giordano, C.; Gallina, C.; Consalvi, V.; Scandurra, R. *Eur. J. Med. Chem.*, **1989**, *24*, 357-362; (b) Smith, R. A.; Copp, L. J.; Donnelly, S. L.; Spencer, R. W.; Krantz, A. *Biochemistry*, **1988**, *27*, 6568-6573.
5. For a recent review see Begue, J.-P.; Bonnet-Delpon, D. *Tetrahedron*, **1991**, *47*, 3207-3258.
6. (a) Kolb, M.; Neises, B.; Gerhart, F. *Liebigs Ann. Chem.*, **1990**, 1-6; (b) Kolb, M.; Neises, B. *Tetrahedron Lett.*, **1986**, *27*, 4437-4440; (c) Kolb, M.; Barth, J.; Neises, B. *ibid*, 1579-1582.
7. Imperiali, B.; Abeles, R. H. *Tetrahedron Lett.*, **1986**, *27*, 135-138.
8. (a) Schwartz, J. A.; Stein, M. M.; Wildonger, R.A.; Edwards, P. D.; Trainor, D. A. *U.S. Patent* 4 910 190, **1990**; (b) Andisik, D. A.; Bergeson, S. H.; Edwards, P. D.; Stein, M. M.; Trainor, D. A.; Wolanin, D. J. Tenth American Peptide Symposium, (Abstracts), Washington University, St. Louis, MO, 1987.
9. (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds, 2nd Ed.*; Ellis Horwood Ltd.: Chichester, 1976; pp. 358-405; (b) References 12-16 of reference 11a below.
10. Pierce, O. R.; McBee, E. T.; Judd, G. F. *J. Am. Chem. Soc.*, **1954**, *76*, 474-478; (b) Haszeldine, R. N. *J. Chem. Soc.*, **1954**, 1273-1279; *ibid.* **1953**, 1748-1757.
11. (a) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.*, **1991**, *56*, 984-989; (b) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A.; *J. Am. Chem. Soc.*, **1989**, *111*, 393-395.
12. (a) Tordeux, M.; Francese, C.; Wakselman, C. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 1951-1957; (b) Kitazume, T.; Ikeya, T. *J. Org. Chem.*, **1988**, *53*, 2349-2350; (c) Francese, C.; Tordeux, M.; Wakselman, C. *J. Chem. Soc. Chem. Commun.*, **1987**, 642-643; (d) Kitazume, T.; Ishikawa, T. *J. Am. Chem. Soc.*, **1985**, *107*, 5186-5191; (e) O'Reilly, N. J.; Maruta, M.; Ishikawa, N. *Chem. Lett.*, **1984**, 517-520; (f) Kitazume, T.; Ishikawa, N. *ibid*, **1981**, 1679-1680.
13. Kitazume, T., Ishikawa, N. *Chem. Lett.*, **1981**, 1337-1338.
14. Hartkopf, U.; de Meijere, A. *Angew. Chem. Int. Ed. Engl.*, **1982**, *21*, 443.
15. (a) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.*, **1991**, *56*, 2-4; (b) Sibille, S.; Mcharek, S.; Perichon, J. *Tetrahedron*, **1989**, *45*, 1423-1428; Sibille, S.; d'Incan, E.; Leport, L.; Perichon, J. *Tetrahedron Lett.*, **1986**, *27*, 3129-3132.
16. The isomeric ratio of aldehyde **7a** was determined by integration of the aldehydic proton in the ^{1}H NMR spectrum. The isomeric ratios of TFMAs **8** and TFMKs **9** were determined by HPLC analysis : ODS C-18 column; water/acetonitrile eluent.
17. Technical grade zinc dust was washed with 20% HCl then with distilled water until neutral; the activated zinc was washed with acetone, ether, and dried under vacuum: see Frankenfeld, J. W.; Werner, J. J.; *J. Org. Chem.*, **1969**, *34*, 3689-3691.
18. Compounds **7a**, **7b**, **8a**, **8b**, **9a** and **9b** had ^{1}H NMR, MS, and CHN analysis consistent with the assigned structures.
19. Eliel, E. L. "Application of Cram's Rule: Addition of Achiral Nucleophiles to Chiral Substrates." In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press.: New York, 1983; Vol. 2, pp. 125-155.
20. (a) Dess, D. B., Martin, J. C. *J. Am. Chem. Soc.*, **1991**, *113*, 7277-7287; (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.*, **1983**, *48*, 4155-4156; (c) The Dess-Martin periodinane is potentially explosive: see Plumb, J. B.; Harper, D. J. C&EN, July 16, 1990, p. 3.
21. Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.*, **1987**, *30*, 1617-1622.

(Received in USA 11 March 1992)