Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8469-8472, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10282-9

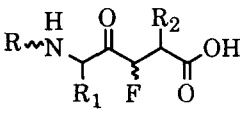
A Short, Efficient Synthesis of Monofluoro Ketomethylene Peptide Isostere Core Units

Robert V. Hoffman* and James E. Saenz

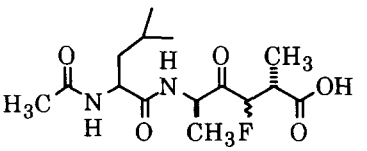
Department of Chemistry and Biochemistry
New Mexico State University
Las Cruces, NM 88003-0001

Abstract: Monofluoro ketomethylene peptide isosteres can be prepared by a four step sequence from carboxylic acids in satisfactory overall yields (30-60%). Fluorine is introduced by electrophilic fluorination of a β-ketoester enolate with SelectFluor™.

The use of α-fluorinated ketone groups in peptidase inhibitors often increases the inhibition constants dramatically because the hydrated form, in which the α-fluoroketones exist in aqueous solution, serves as a transition state analog for the tetrahedral intermediate in proteolysis[1] and/or can form a tetrahedral hemiacetal function with an active site nucleophile (usually serine).[2] In most previous studies either a trifluoromethyl or difluoroalkyl ketone has been used as the electrophilic carbonyl group (and often it is situated at the end of a peptide chain).



1



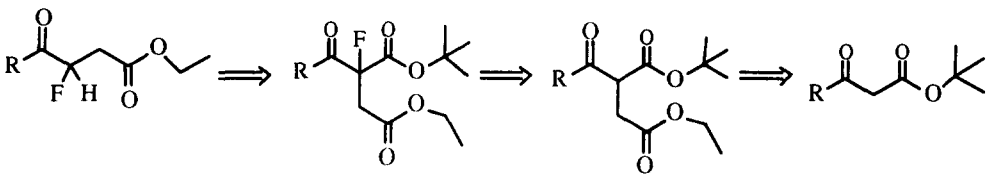
2

Monofluorinated ketomethylene peptide isosteres such as **1** are of potential interest as peptidase inhibitors for the following reasons. First, there should be a significantly greater fraction of the non-hydrated ketonic form present (≈ 50% [2c]) thus it would be possible to compare the binding behavior with difluoroketomethylene peptide isosteres,[2e] which are fully hydrated, and analogous ketomethylene peptide isosteres, which are unhydrated in aqueous solution. Second the electrophilic carbonyl group can be incorporated in a peptide chain so that binding both at P_1 and P_2 sites as well as P'_1 and P'_2 sites can contribute to the binding. This would be particularly useful for proteases with extended binding regions.[3] Finally it is important to determine if placement of the α-fluoroketone in the peptide chain reduces the irreversible inhibition noted for monofluoromethyl ketones[2d] due to increased steric crowding around the carbon to which fluorine is attached.

Monofluoroketomethylene peptide isosteres haven't been studied to any great extent because they are difficult to make. To our knowledge only a single example of **2** has been reported in the literature.[4] The synthesis of this compound , which utilizes XeF_2 fluorination of a silyl enol ether derivative of a ketomethylene peptide isostere, requires many steps (12) and suffers from the same problems seen in the syntheses of other ketomethylene peptide isosteres which use homoenolate equivalent nucleophiles to construct the 3,4-bond.

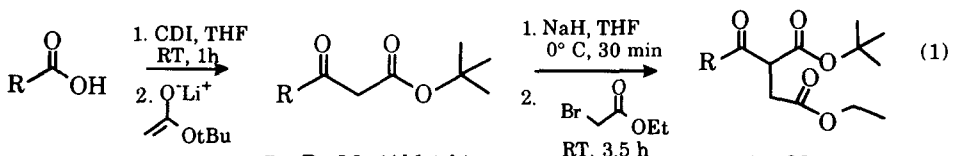
Based on our previous syntheses of ketomethylene peptide isosteres[5] and a related synthesis of a pyrenophorin precursor,[6] it was envisioned that a short route to monofluorinated ketomethylene peptide isosteres might be developed utilizing electrophilic fluorination of tricarbonyl intermediate **4**, which itself could be prepared from a β-ketoester **5** (Scheme 1). In this report, a series of monofluoroketomethylene peptide isostere core units **1** were prepared from β-ketoesters **5** in good yields demonstrating the validity of this strategy.

Scheme 1



1 **3** **4** **5**

A series of *t*-butyl β-ketoesters **5** was prepared by the CDI mediated addition of lithio *t*-butyl acetate to carboxylic acids in generally high yields.[7] Without further purification the crude products **5** were converted to the enolate with NaH and alkylated with ethyl bromoacetate to give keto diesters **4** (58-87%) (eq 1).[5] The products **4** were easily purified by Kugelrohr distillation.



(1)

5a, R= Me (Aldrich)
5b, R= $CH_2CH(CH_3)_2$ (77%)
5c, R=C_6H_{11} (60%)
5d, R= Ph (87%)
5e, R=Bn (63%)
5f, R= CH_2CH_2Ph (84%)

4a, 82%
4b, 58%
4c, 87%
4d, 83%
4e, 58%
4f, 84%

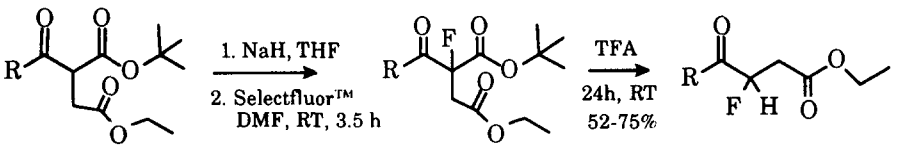
In order to determine the best fluorination protocol, several electrophilic fluorinating agents were examined. 2-Carboethoxycyclopentanone, used as a typical β-ketoester substrate, was treated with N-fluoropyridinium triflate **6**,[8] N-fluoropyridinium pyridine heptafluorodiborate complex **7**,[9] or SelectFluor™ **8**[10] under various conditions suggested in the literature for each

reagent. Depending on the conditions, either the enol form (Lewis acid catalysis), the silyl enol ether (Et_3N, TMSCl), or the enolate (NaH) derivative was the reacting species. The results collected in Table 1 demonstrate unequivocally that conversion to the enolate (NaH) and treatment with SelectFluor™ is a superior method for the introduction of fluorine into β-ketoesters.

Table 1. Fluorination of 2-Carboethoxycyclopentanone with Various Electrophilic Fluorinating Agents.

Reagent	Conditions	Yield of **3a** (%)
6	$ZnCl_2$, $C_2H_2Cl_4$, reflux 72 h	47
6	a. NaH, 15min, b. **6**, 0° C, 1 h	78
6	a. TMSCl, Et_3N, b. **6**, $C_2H_4Cl_2$, reflux, 1 h	20
7	$ZnCl_2$, $C_2H_4Cl_2$, reflux 72 h	42
7	BF_3 etherate, $C_2H_4Cl_2$ reflux	0
8	a. NaH, THF, 0°C, 30min b. **8**, DMF, RT, 3.5 h	91
8	a. TMSCl, Et_3N b. **8**, RT, 6h	82

Tricarbonyl esters **4a-f** were converted to their enolates and fluorinated with SelectFluor™ to produce fluorinated products **3a-f** in excellent yields (eq 2). Decarboxylation of **3a-f** in TFA gave monofluoro γ-ketoesters **1a-f** in good yields. These are the core units of monofluoro ketomethylene peptide isosteres.



4a-f

3a, 91%
3b, 97%
3c, 94%
3d, 83%
3e, 95%
3f, 87%

1a, 52%
1b, 57%
1c, 75%
1d, 72%
1e, 68%
1f, 72%

(2)

For the purposes of method development, the reaction products were isolated and purified at each step (eq 1, 2).[11] However in practice, carboxylic acids were converted via β-ketoesters **5** to fluorination substrates **4** which were purified easily by bulb to bulb distillation. Then fluorination and decarboxylation of **4** were carried out sequentially without purification to produce **1**, which was purified by bulb to bulb distillation.

In summary an effective synthesis of monofluoroketomethylene peptide isostere core units **1** has been developed. The preparation requires only four steps from commercially available carboxylic acids, is experimentally simple and proceeds in satisfactory overall yields (30-60% for four steps).

Acknowledgement: This work was supported by a grant from the National Science Foundation (CHE 9520431). JES was an undergraduate research participant supported by the NSF. The authors would like to thank Air Products and Chemicals for a generous gift of SelectFluor™.

References and Notes

1. For example: a. Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry*, **1985**, *24*, 1813. b. Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.*, **1986**, *29*, 2080. c. Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.*, **1987**, *30*, 1617. d. Hong, W.; Dong, L.; Cai, Z.; Titmas, R. *Tetrahedron Lett.*, **1992**, *33*, 741. e. Damon, D. B.; Hoover, D. J. *J. Am. Chem. Soc.*, **1990**, *112*, 6439.
2. For example: a. Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, R. E., Jr.; Meyer, E. F., Jr.; Trainor, D. A. *J. Am. Chem. Soc.*, **1989**, *111*, 3368. b. Edwards, P. D.; Meyer, E. F., Jr.; Vijayalakshmi, J.; Tuthill, P. A.; Andisik, D. A.; Gomes, B.; Strimpler, A. *J. Am Chem. Soc.*, **1992**, *114*, 1854 and references therein. c. Imperiali, B.; Abeles, R. H. *Biochemistry*, **1986**, *25*, 3760.
3. Rich, D. H. in "Comprehensive Medicinal Chemistry", Sammes, P.G., Ed., Pergamon Press, Oxford, U.K., 1990, pp 391-441.
4. Garrett, G. S.; Emge, T. J.; Lee, S.C.; Fischer, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.*, **1991**, *56*, 4823.
5. Hoffman, R. V.; Kim, H.-O. *Tetrahedron Lett.*, **1992**, *33*, 3579.
6. Hoffman, R. V. ; Patonay, T.; Nayyar, N.; Tao, J., *Tetrahedron Lett.*, **1996**, *37*, 2381
7. Harris, B. D.; Jouillé, M. M. *Tetrahedron*, **1988**, *44*, 3489.
8. Umemoto, T.; Fukami, S.; Tomizawa, F.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.*, **1990**, *112*, 8563.
9. Poss, A. J.; Van Der Puy, M.; Nalewajek, D.; Shia, G. A.; Wagner, W. J.; Frenette, R. L. *J. Org. Chem.*, **1991**, *56*, 5962.
10. Lal, G. S. *J. Org. Chem.*, **1993**, *58*, 2791.
11. Products **5b-f**, **4a-f**, **3a-f**, and **1a-f** were characterized by ^{1}H nmr, ^{13}C nmr, and IR spectra and the final products **1a-f** gave satisfactory elemental analysis (± 0.4%)

(*Received in USA* 28 *July* 1997; *accepted* 24 *September* 1997)