Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 260–261

Mendeleev Communications

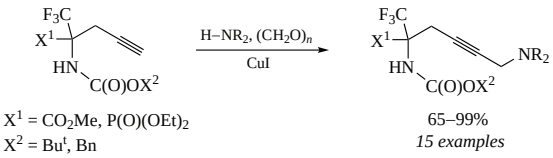
Synthesis of α-CF_3-substituted γ,δ-didehydro lysine derivatives

Anna N. Philippova, Daria V. Vorobyeva, Tamara P. Vasilyeva, Artur K. Mailyan, Pavel S. Gribanov and Sergey N. Osipov*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: osipov@ineos.ac.ru

DOI: 10.1016/j.mencom.2022.03.036

An efficient and selective access to novel α-CF_3-substituted γ,δ-didehydro lysine derivatives and their phosphorus analogues has been developed *via* the Cu-catalyzed Mannich reaction of α-amino α-propargyl α-trifluoromethyl carboxylates or phosphonates with different secondary amines and paraformaldehyde.



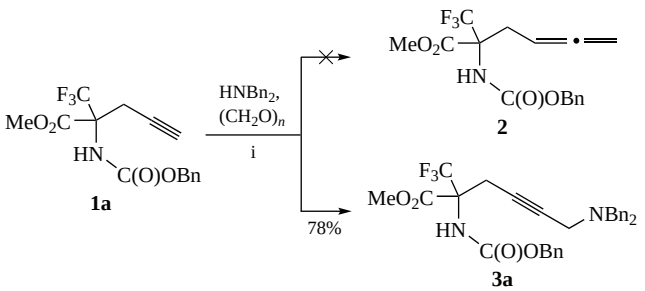
Keywords: α-amino carboxylates, α-amino phosphonates, Mannich reaction, γ,δ-didehydro lysine, hydrogenation.

Unsaturated α-amino acid derivatives have gained a considerable attention in the field of biological and medicinal chemistry.[1] Due to diverse reactivity of the multiple bonds they serve as important building blocks for the incorporation of the different functional and imaging groups by, *e.g.*, metal-catalyzed transformations.[2] These compounds are often used in peptide chemistry to induce new properties *via* the restriction of their side-chain flexibility.[3] Among them, α-propargylated α-amino acids and their derivatives attract a particular interest because they are the common motifs in a range of biologically active compounds.[4]

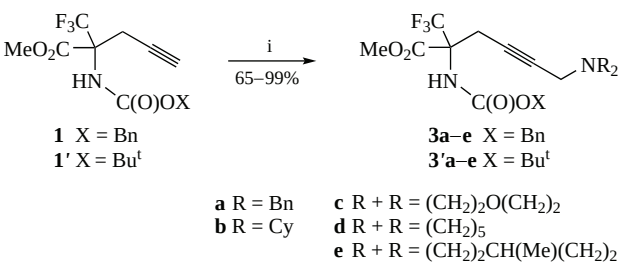
At the same time, α-fluoromethyl α-amino acids constitute a special family of amino acids, which can act as highly selective inhibitors of a number of important decarboxylases with a broad spectrum of interesting biological activities.[5] One of the most striking examples is D,L-α-difluoromethyl ornithine (eflornithine) applied for the treatment of African sleeping disease, the pneumonia associated with acquired immune deficiency syndrome (AIDS), and to treat excessive facial hair growth (hirsutism) in women as well.[6] Therefore, the development of new representatives of α-fluoromethyl α-amino acids including their unsaturated derivatives is of great interest.

We have recently described an efficient method for the preparation of α-CF_3-substituted dehydro ornithine derivatives based on CuI-catalyzed hydroamination of trifluoromethyl-containing α-allenyl α-amino carboxylates with aliphatic amines.[7] Now we report on the convenient synthesis of novel α-CF_3-substituted γ,δ-didehydro lysine derivatives *via* the Mannich reaction of orthogonally protected α-propargyl α-amino acids with paraformaldehyde and secondary amines under Lewis acid catalysis (see also Online Supplementary Materials, Figure S1). In the course of our ongoing studies on the development of new efficient methods for the preparation of fluorinated amino acids bearing unsaturated substituents[8] in their structure including allenyl groups[9] we commenced our investigation with the reaction of easily accessible *N*-Cbz protected α-propargyl α-CF_3-α-amino ester **1**[8(a)] with paraformaldehyde in the presence of dibenzyl amine and CuI in a hope to access allene **2** under typical Crabbe reaction[10] conditions. However, instead of allene **2** the corresponding amino alkyne **3a** has been isolated as a result of the Mannich-type transformation (Scheme 1). All our further attempts to redirect the reaction towards allene formation varying different amines, Cu^I-catalysts and solvents failed. Despite this, given the importance of fluorinated ornithine and lysine derivatives, we decided to study a scope and limitation of the found Mannich reaction that has just few applications in amino acid chemistry to date.[11]

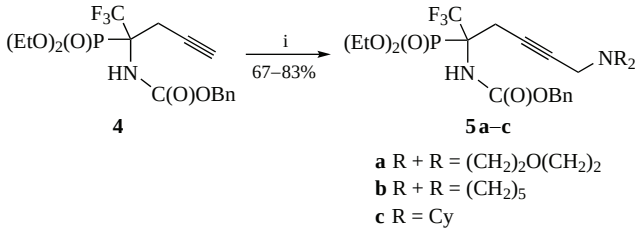
Thus, orthogonally protected α-propargyl α-CF_3-α-amino esters **1** (*N*-Cbz) and **1′** (*N*-Boc) were involved in Mannich reaction with different secondary amines under optimum conditions found for the preparation of **3a**, namely, by heating of amino ester acetylene in dioxane at 90 °C with 2.5 equiv. of paraformaldehyde, double excess of amine and 30 mol% of CuI. In all studied cases, the reaction goes to the completion within



Scheme 1 *Reagents and conditions*: i, CuI (30 mol%), 1,4-dioxane, 90 °C, 16 h.



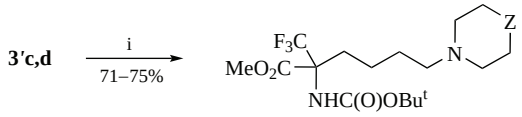
Scheme 2 *Reagents and conditions*: i, HNR_2, $(CH_2O)_n$, CuI (30 mol%), 1,4-dioxane, 90 °C, 16 h.



4 **5a–c**

a R + R = $(CH_2)_2O(CH_2)_2$
b R + R = $(CH_2)_5$
c R = Cy

Scheme 3 *Reagents and conditions*: i, HNR_2, $(CH_2O)_n$, CuI (30 mol%), 1,4-dioxane, 90 °C, 16 h.



6a,b

a Z = O
b Z = CH_2

Scheme 4 *Reagents and conditions*: i, H_2 (1 atm), Pd/C, methanol, room temperature, 24 h.

16 h to afford new α-CF_3-substituted γ,δ-didehydro lysine derivatives **3a**–**e** and **3′a**–**e** in good to excellent yields (Scheme 2).

α-Amino phosphonates are currently under extensive investigation in medicinal chemistry as important surrogates of the corresponding α-amino acids.[12] For this reason, we performed the reaction of available α-propargyl α-amino phosphonate **4**[13] with morpholine, piperidine and dicyclohexylamine using the conditions found for amino ester analogues **1** and **1′**. As a result, new phosphorus analogues of α-CF_3-γ,δ-didehydro lysine **5a**–**c** were obtained in good yields after the purification by flash chromatography (Scheme 3).

To demonstrate one of the possible synthetic applications of the compounds obtained, typical catalytic hydrogenation of the triple bond of compounds **3′c**,**d** was accomplished to yield the corresponding lysine derivatives **6a** and **6b** (Scheme 4).

In summary, we have developed an efficient and selective access to novel α-CF_3-substituted γ,δ-didehydro lysine derivatives and their phosphorus analogues *via* the Cu^I-catalyzed Mannich reaction of trifluoromethyl-containing α-propargyl α-amino carboxylates or phosphonates with different secondary amines and excess of paraformaldehyde. We anticipate that this strategy may provide a new method for the synthesis of valuable functionalized CF_3-containing compounds with great potential for the application in amino acid and peptide chemistry.

This work was supported by the Russian Foundation for Basic Research (grant no. 20-33-90233). The NMR studies were performed with the financial support from the Ministry of Science and Higher Education of the Russian Federation using the equipment of Center for molecular composition studies of INEOS RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.036.

References

1 (*a*) F. P. J. T. Rutjes, L. B. Wolf and H. E. Schoemaker, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4197; (*b*) S.-S. Jin and M.-H. Xu, *Adv. Synth. Catal.*, 2010, **352**, 3136; (*c*) Y. Masuda, C. Maruyama, K. Kawabata, Y. Hamano and T. Doi, *Tetrahedron*, 2016, **72**, 5602; (*d*) R. Wu, S. Liu, Y. Liu, Y. Sun, X. Cheng, Y. Huang, Z. Yang and Z. Wu, *Eur. J. Med. Chem.*, 2019, **183**, 111730.

2 J. Kaiser, S. S. Kinderman, B. C. J. van Esseveldt, F. L. van Delft, H. E. Schoemaker, R. H. Blaauw and F. P. J. T. Rutjes, *Org. Biomol. Chem.*, 2005, **3**, 3435.

3 M. A. Jones, A. D. Hislop and J. S. Snaith, *Org. Biomol. Chem.*, 2006, **4**, 3769.

4 (*a*) L. Peng, Z. He, X. Xu and C. Guo, *Angew. Chem., Int. Ed.*, 2020, **59**, 14270; (*b*) A. H. K. Al Temimi, P. B. White, M. J. M. Mulders, N. G. A. van der Linden, R. H. Blaauw, A. Wegert, F. P. J. T. Rutjes and J. Mecinović, *Chem. Commun.*, 2020, **56**, 3039; (*c*) G. de Bruin, E. J. van Rooden, D. Ward, C. Wesseling, A. M. C. H. van den Nieuwendijk, C. A. A. van Boeckel, C. Driessen, A. F. Kisselev, B. I. Florea, M. van der Stelt and H. S. Overkleeft, *Eur. J. Org. Chem.*, 2017, 5921.

5 (*a*) R. Smits, C. D. Cadicamo, K. Burger and B. Koksch, *Chem. Soc. Rev.*, 2008, **37**, 1727; (*b*) J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes and B. Koksch, *Chem. Rev.*, 2019, **119**, 10718.

6 (*a*) C. J. Bacchi, B. Goldberg, J. Garofalo-Hannan, D. Rattendi, P. Lyte and N. Yarlett, *Biochem. J.*, 1995, **309**, 737; (*b*) S. R. Perrin, W. Hauck, E. Ndzie, J. Blehaut, O. Ludemann-Hombouger, R.-M. Nicoud and W. H. Pirkle, *Org. Process Res. Dev.*, 2007, **11**, 817; (*c*) F. Raul, *Biochem. Soc. Trans.*, 2007, **35**, 353; (*d*) M. Köckinger, T. Ciaglia, M. Bersier, P. Hanselmann, B. Gutmann and C. O. Kappe, *Green Chem.*, 2018, **20**, 108.

7 A. N. Philippova, D. V. Vorobyeva, F. Monnier and S. N. Osipov, *Org. Biomol. Chem.*, 2020, **18**, 3274.

8 (*a*) G. T. Shchetnikov, A. S. Peregudov and S. N. Osipov, *Synlett*, 2007, **1**, 136; (*b*) G. T. Shchetnikov, M. A. Zotova, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Eur. J. Org. Chem.*, 2010, 1587; (*c*) A. K. Mailyan, I. M. Krylov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Eur. J. Org. Chem.*, 2013, 5353; (*d*) D. V. Vorobyeva, D. A. Petropavlovskikh, I. A. Godovikov, S. E. Nefedov and S. N. Osipov, *Eur. J. Org. Chem.*, 2021, 1883.

9 (*a*) D. V. Vorobyeva, A. K. Mailyan, A. S. Peregudov, N. M. Karimova, T. P. Vasilyeva, I. S. Bushmarinov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Tetrahedron*, 2011, **67**, 3524; (*b*) A. K. Mailyan, I. M. Krylov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Synlett*, 2011, **16**, 2321; (*c*) A. K. Mailyan, A. S. Peregudov, P. H. Dixneuf, C. Bruneau and S. N. Osipov, *J. Org. Chem.*, 2012, **77**, 8518.

10 (*a*) P. Rona and P. Crabbé, *J. Am. Chem. Soc.*, 1969, **91**, 3289; (*b*) P. Crabbé, H. Fillion, D. André and J.-L. Luche, *J. Chem. Soc., Chem. Commun.*, 1979, 859.

11 (*a*) M. Periasamy, P. O. Reddy and N. Sanjeevakumar, *Tetrahedron: Asymmetry*, 2014, **25**, 1634; (*b*) A. C. A. Jansen, R. J. M. Weustink, K. E. T. Kerling and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 1969, **88**, 819; (*c*) L. W. Bieber and M. F. da Silva, *Tetrahedron Lett.*, 2004, **45**, 8281.

12 (*a*) V. D. Romanenko and V. P. Kukhar, *Chem. Rev.*, 2006, **106**, 3868; (*b*) M. Ordonez, F. J. Sayago and C. Cativiela, *Tetrahedron*, 2012, **68**, 6369; (*c*) E. D. Naydenova, P. T. Todorov and K. D. Troev, *Amino Acids*, 2010, **38**, 23; (*d*) F. Orsini, G. Sello and M. Sisti, *Curr. Med. Chem.*, 2010, **17**, 264; (*e*) D. Zhao and R. Wang, *Chem. Soc. Rev.*, 2012, **41**, 2095.

13 D. V. Vorobyeva, N. M. Karimova, T. P. Vasilyeva, S. N. Osipov, G. T. Shchetnikov, I. L. Odinets and G.-V. Röschenthaler, *J. Fluorine Chem.*, 2010, **131**, 378.

Received: 30th August 2021; Com. 21/6672