Preprint Title	A study on the synthesis of *β*-amino acids: the first synthesis of a bicyclic hemiaminal (3,3-dimethyl-1-(2,4,5-trifluorophenyl) tetrahydro-3*H*,5*H*-oxazolo[3,4-c] [1,3] oxazin-5-one)
Authors	Ozlem Gundogdu, Ertan Sahin and Yunus Kara
Publication Date	21 Apr 2020
Article Type	Letter
Supporting Information File 1	Supporting info for BJOC.docx; 498.4 KB
ORCID® iDs	Ozlem Gundogdu - https://orcid.org/0000-0002-6943-9674; Yunus Kara - https://orcid.org/0000-0001-7552-9425

A study on the synthesis of *β*-amino acids: the first synthesis of a bicyclic hemiaminal (3,3-dimethyl-1-(2,4,5-trifluorophenyl) tetrahydro-3*H*,5*H*-oxazolo[3,4-c] [1,3] oxazin-5-one)

Özlem Gündoğdu*[1], Ertan Şahin‡[2], Yunus Kara*[2]

[1]*Vocational School of Kaman, Ahi Evran University, 40100 Kırşehir, Turkey*

[2]*Department of Chemistry, Atatürk University, 25240 Erzurum, Turkey*

ogundogdu@atauni.edu.tr : yukara@atauni.edu.tr

Abstract

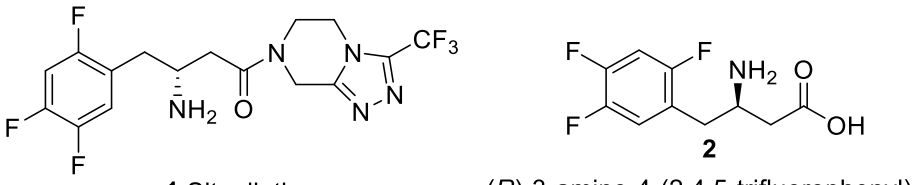
We synthesized (4*S*)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(2,4,5-trifluorophenyl) oxazolidin-2-one and examined its Pd/C-catalyzed hydrogenation reaction. The condensation and rearrangement reaction of acetone with (4*S*)-4-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-5-(2,4,5-trifluorophenyl)oxazolidin-2-one resulted in the formation of a hemiaminal structure containing a fused oxazine-oxazole ring, whose exact configuration was determined by X-ray crystal analysis. A mechanism was proposed to explain the formation of the fused oxazine-oxazole ring, which has a hemiaminal structure.

Keywords

Hemiaminal, cyclic urethane, vicinal amino-alcohol, oxazine ring, oxazole ring

Introduction

The synthesis of amino acids still represents a great challenge and they are seen as target molecules due to their biological and toxicological properties. *β*-Amino acids are key components of many natural compounds. Thus, they are one of the most important classes of compounds in synthetic and medicinal chemistry [1-4]. The *β*-amino acids do not participate in the protein structure but are involved as secondary metabolites in biochemical processes. Amino acids are systematically added to peptide drugs to increase their stability and incur conformational biases [5-7]. It is well known that the use of *β*-amino acids in peptides improves their metabolic lability and therefore enhances their stability against proteolytic degradation [8-11]. *β*-Peptides have thus been used to mimic natural peptide-based drugs in medicinal and pharmacological studies. For example, sitagliptin containing the *β*-amino acid unit is known as dipeptidyl peptidase IV (DPP-IV) enzyme [12-13]. Many methods have been developed for the synthesis of the amino acid unit of sitagliptin in the literature (Fig. 1) [14]. In our previous studies we developed new methods for the synthesis of *β*-amino and *β*-hydroxy acids [15-18].



1 Sitagliptin

2

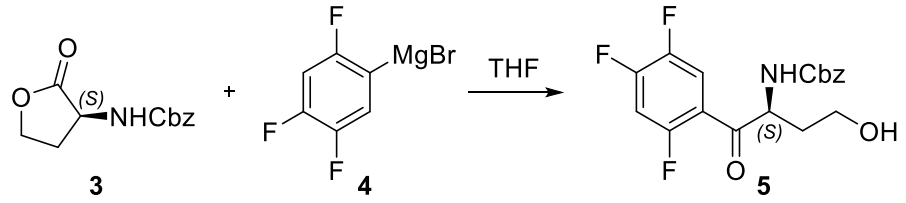
(*R*)-3-amino-4-(2,4,5-trifluorophenyl) butanoic acid

Figure 1. Structure of sitagliptin and *β*-amino acid.

Very recently, we also reported the synthesis of *γ*-keto-*β*-amino acids *via* the ring-opening reaction of homoserine lactone, which is readily available from (*S*)-methionine [19]. Following on from the study of the synthetic applications of the ring-opening reaction of homoserine lactone with Grignard reagent, further reactions of the ring opening products were performed for the synthesis of *β*-amino acid derivatives in these studies. As part of our current studies on the synthesis of amino acid derivatives from readily available building blocks, herein we report interesting results obtained from the reduction reaction of amino keto-alcohol derivative and their transformation.

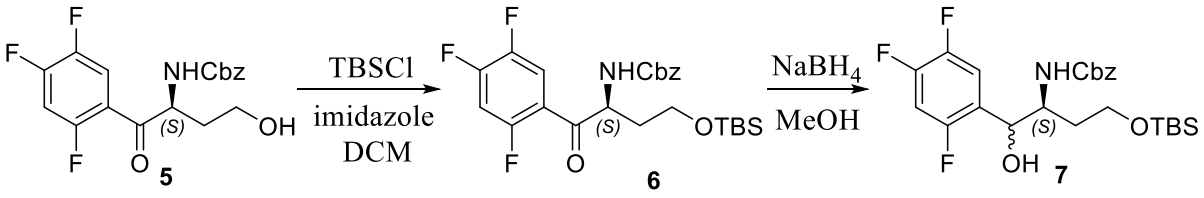
Results and Discussion

Our synthesis of *N-Cbz*-(*S*)-homoserine lactone (**3**) started from (*S*)-methionine using a known method reported in the literature [20-21]. Then the reaction of 2,3,5-triflorophenylmagnesium bromide with *N-Cbz*-(*S*)-homoserine lactone at room temperature gave an amino-keto alcohol derivative (Scheme 1). The product was then isolated and purified through column chromatography and characterized by ^{1}H and ^{13}C NMR spectra. Thus, benzyl (*S*)-(4-hydroxy-1-oxo-1-(2,4,5-trifluorophenyl)butan-2-yl) carbamate (**5**) was obtained in 80% yield in this reaction (Scheme 1).



Scheme 1. Synthesis of benzyl (*S*)-(4-hydroxy-1-oxo-1-(2,4,5-trifluorophenyl) butan-2-yl) carbamate (**5**).

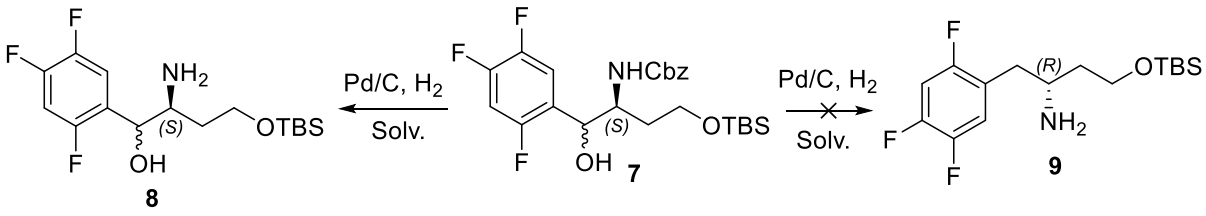
Thus, amino-keto alcohol **5**, the precursor compound of homophenylalanine, was synthesized by this methodology. For the synthesis of homophenylalanine, we decided to reduce amino-keto alcohol **5** to amino diol **8** or amino alcohol **9**. It is well known that H_2/Pd (in catalytic reduction) and metal hydrides are very useful reduction reagents. Firstly, the primary hydroxyl of amino-keto alcohol **5** was protected with *tert*-butyl-diphenylsilyl (TBDPS) to give silyl ether **6**. Subsequently, silyl ether **6** was reacted with $NaBH_4$ to give benzylic alcohols **7** in high yield as a mixture of diastereoisomers (Scheme 2).



Scheme 2. Synthesis of benzylic alcohols **7**.

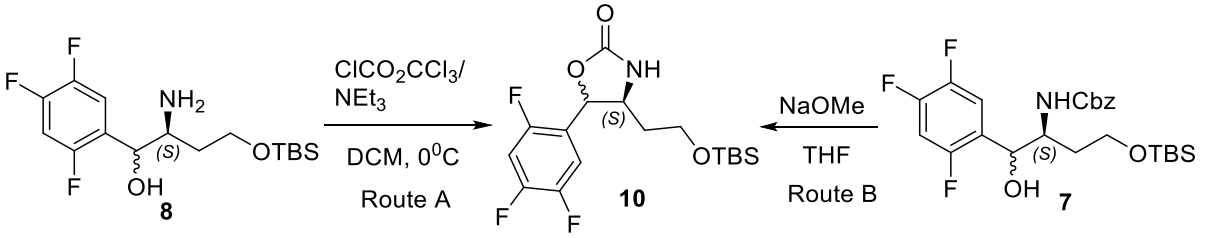
For practical reasons, the diastereomeric alcohols **7** were not isolated but directly subjected to a further reaction. The reduction of the benzylic OH group was carried out by various methods [22]. One of these methods was direct Pd/C catalyzed

hydrogenation of benzylic ketones or alcohols. However, this methodology was not suitable to reduce the benzylic OH group of **7**. However, compound **8** was obtained by removal of the protecting group (*Cbz*-) from **7** in this reaction (Scheme 3).



Scheme 3. Pd/C catalyzed hydrogenation of benzylic alcohols **7**.

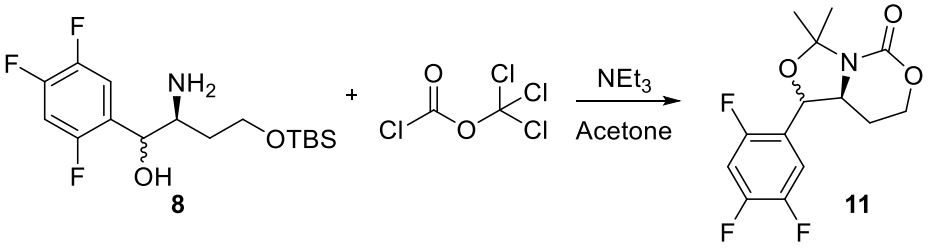
Therefore, we planned to use a different modification for the reduction reaction of benzyl alcohol. The reduction reactions of the urethane ring containing the benzylic group are known in the literature. During this reaction, the reduction product is formed by the release of carbon dioxide from the molecule. In this context, we synthesized benzylic urethane **10** using two methods. First, the ketone was subjected to direct hydrogenation to give amino alcohol **8**. Next, amino alcohol **8** was converted to benzylic urethane **10** with trichloroacetyl chloride in the presence of NEt_3 in 55% yield. Second, benzyl alcohol **7**, which contains a protecting *Cbz*-group, was reacted with $NaOCH_3$ to give benzylic urethane **10** in 60% yield (Scheme 4).



Scheme 4. Synthesis of benzylic urethane **10**.

As can be seen from Scheme 4, we used DCM as the solvent for the synthesis of the urethane ring. We obtained urethane with an average yield (55%). In order to increase the amount of product formed, the synthesis of the urethane ring was examined in different solvents. When using acetone, a very interesting rearrangement product including two methyl groups and a different urethane ring was obtained in the urethane synthesis reaction of amino alcohol **8** in acetone (Scheme 5). After separation, the ^1H

and ^{13}C NMR spectroscopic data indicated that a product different from what was expected was formed. The ^{1}H NMR spectra interestingly showed two methyl and two different methylene protons. In addition, three different carbon signals, i.e., quaternary, tertiary, and carbonyl carbon, appeared in the ^{13}C-NMR spectra. In particular, the presence of two methyl groups and one saturated quaternary carbon in the ^{1}H and ^{13}C NMR indicate that acetone reacts with molecule **10** and any molecule. On the other hand, butyl and phenyl protons belonging to the silyl group were not seen in the ^{1}H NMR spectra.



Scheme 5. Synthesis of the hemiaminal **11**.

Although the ^{1}H and ^{13}C NMR spectra support the formation of an acetal ring and a different urethane ring, to gain more insight about the compound **11**, we decided to confirm its exact structure by single-crystal X-ray diffraction techniques [23].

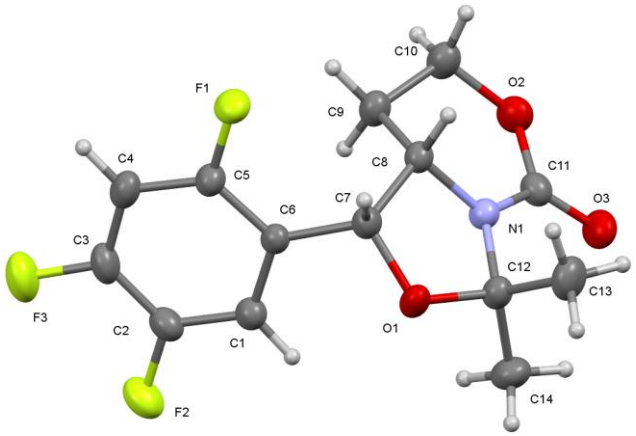


Figure 2a

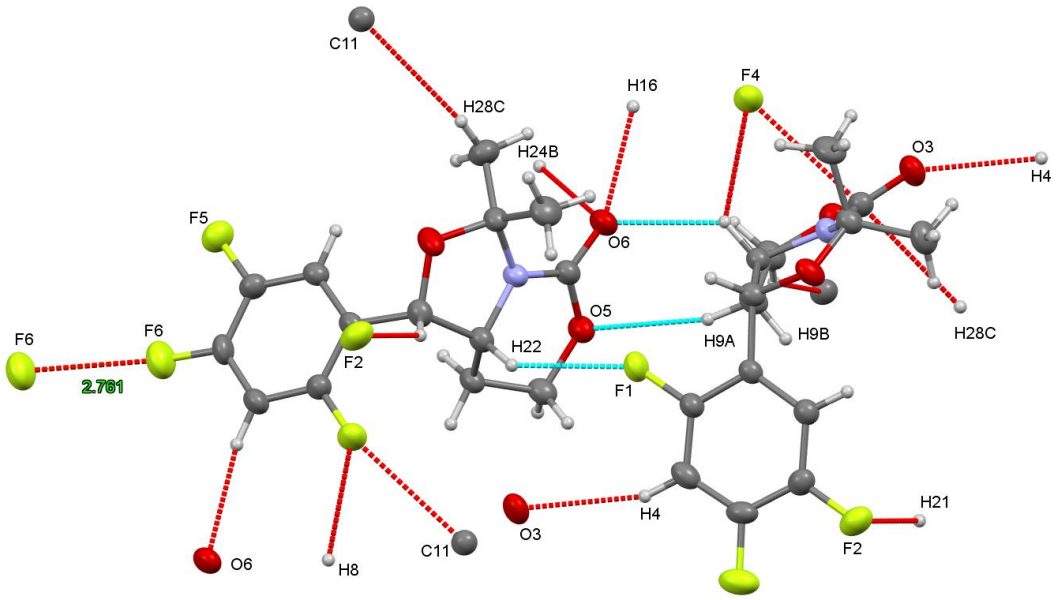


Figure 2b

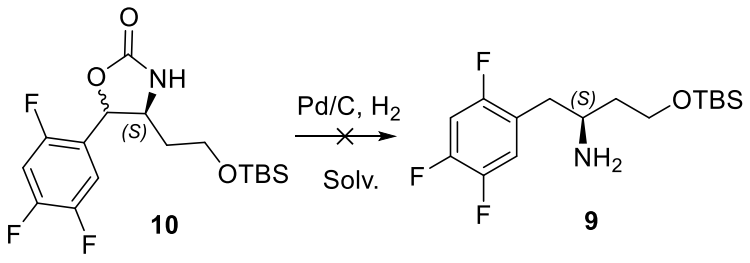
Figure 2. (**a**) Molecular structure of the compound **11**. Thermal ellipsoids are shown at the 40% probability level. (**b**) Racemic mixture of the molecule **11** with the intermolecular short-contact interactions, dotted lines indicate contacts shorter than the sum of the vdW radii.

We performed X-ray structure analysis of the molecule 3,3-dimethyl-1-(2,4,5-trifluorophenyl)tetrahydro-3*H*,5*H*-[1,3]oxazolo[3,4-c][1,3]oxazin-5-one (**11**) to identify the conformation and possible interactions (Fig. 2a). The structure has a racemic form and crystallizes in the triclinic centrosymmetric space group *P*-1 with two enantiomers in the unit cell**.** There are two molecules in the asymmetric unit and their circumference of each one is different (Fig. 2b). The C–F (flourobenzen) distances are in the typical single bond range [1.353(3)–1.359(3) Å]. The C11 = C10 double bond is 1.323(3) Å. and the C–N bonds are between 1.365–1.471(3) Å. Deviation from planarity of the molecule is due to significant steric effects and intermolecular interactions. For both enantiomers, oxazine hetereocycle has a half-chair conformation, maximum deviation from mean-plane for atom C9 is -0.332 Å. Conformation of oxazolidine, a nonplanar five-membered saturated ring; four of its ring atoms lie in one plane and the remaining atom N1 lies outside that plane is in envelope form (deviation from mean-plane for atom N1 is -0.153 Å). In the oxazine and oxazolidine hererocycles the bond lengths of N3-C9 = 1.3334(3) Å and C8-C7 =1.378(4) Å are in the range of typical single bond values. The C11-N1 bond length is 1.353 (2) Å which is in between the value of a single

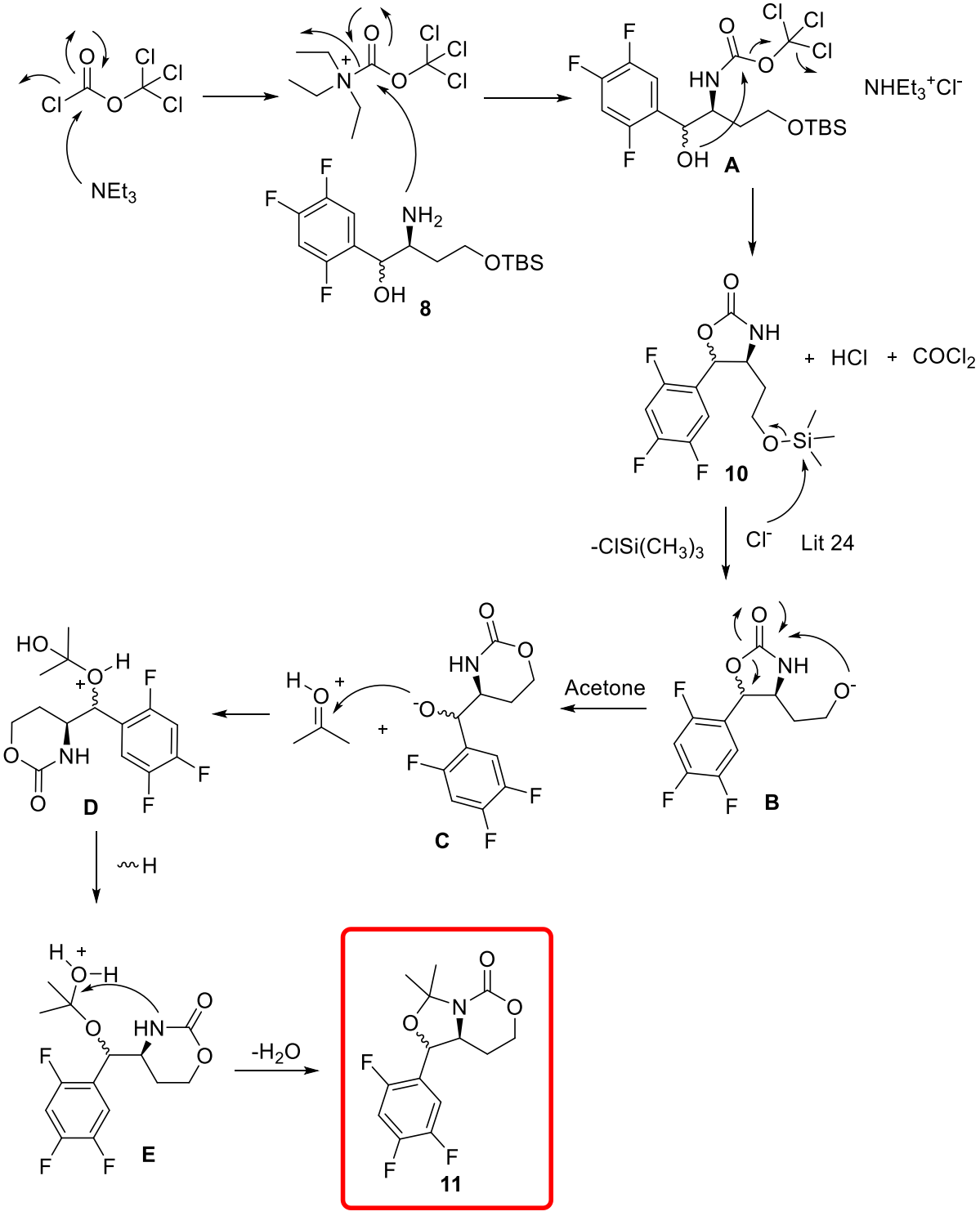
and double C-N bond. Also O2-C11 1.355(3) Å bond is significantly shorter than the O2-C10 1.433 Å single bond indicating a partial delocalization of the electron density over the oxazine heterocycle. The fact that the carbonyl functional group is attached to the bicyclic heterocycle significantly affects the structure. The structure contains four asymmetric carbon atoms and the stereogenic centers are as follows: C7(*R*), C8(*S,*), C21(*S*), C22(*R*). The shortest intramolecular F···F separation 2.761(3) Å is found between the same enantiomers and is below the sum of van der Waals radii for fluorine atoms (2.94 Å).

Based on the structure of the product, we propose the reaction mechanism shown in Scheme 7. The formation of the product takes place through three different reactions in one pot: *i*) removal of the silyl ether group, *ii*) degradation of the urethane ring, and *iii*) formation of a new urethane ring and a new hemiaminal ring. During this reaction, after removal of the silyl ether group with chloride anion (Cl^-) [24] and opening of the urethane ring, a cyclic six-membered urethane and five-membered hemiaminal are formed. Thus, the synthesis of the hemiaminal structure containing the fused oxazine-oxazole ring is performed.

In the second step, the synthesized benzylic urethane **10** was submitted to Pd-C catalyzed hydrogenation to give its reduction product **9**. The reduction reaction of urethane **10** was examined in different solvents such as ethanol, methanol, ethyl acetate, and chloroform. However, this methodology was unsuccessful in reducing the benzylic OH group of **10** (Scheme 6). Additionally, the Pd-C catalyzed hydrogenation reaction was examined at 25 °C for 10 h in a Parr apparatus, but the desired reduction product **9** was not formed and the molecule was degraded in this condition.



Scheme 6. Pd-C catalyzed hydrogenation reaction of **10**.



Scheme 7. Reaction mechanism for 3,3-dimethyl-1-(2,4,5-trifluorophenyl) tetrahydro-3*H*,5*H*-oxazolo[3,4-c] [1,3] oxazin-5-one

Conclusion

For the first time, we synthesized a five-membered urethane (**10**), a β-amino acid precursor compound. We demonstrated the condensation reaction of acetone to the system of benzylic urethane **10**. We obtained the hemiaminal structure containing the fused oxazine-oxazole ring and determined the reaction mechanism of the acetalization product **11**. Such an acetalization reaction is a unique example for the formation of an oxazine-oxazole ring.

The chemical transformations of amino-keto alcohol **5** and urethane ring **10** to the related compounds are currently under investigation. We think that this simple and straightforward method will find application in the synthesis of pharmacologically important β-amino acid derivatives.

Experimental

General

All reagents and substrates were purchased from commercial sources and used without further purification. Solvents were purified and dried by standard procedures before use. 1H and 13C NMR spectra were recorded on Varian 400 and Bruker 400 spectrometers. Elemental analysis were performed on a Leco CHNS-932 instrument. M.p. was measured with Gallenkamp melting point devices. X-Ray: Rigaku R-AXIS RAPID IP diffractometer. HR-MS: electron spray technique (M+/M-) from the soln. in MeOH (Waters LCT PremierTM XE UPLC/MS TOF (Manchester, UK)).

Synthesis of (3,3-dimethyl-1-(2,4,5-trifluorophenyl)tetrahydro-3*H*,5*H*-oxazolo [3,4-c] [1,3] oxazin-5-one (11)

To a magnetically stirred solution of (2*R*)-2-amino-4-((tert-butyldimethylsilyl)oxy)-1-(2,4,5-trifluorophenyl)butan-1-ol (**8**) (156 mg, 0.44 mmol) in acetone (20 mL) were added NEt_3 (0.12 mL, 0.89 mmol) and $ClCO_2CCl_3$ (0.05 mL, 0.44 mmol) in N_2 atm at 0 °C. The mixture was stirred at the same temperature for 2 h. The reaction was monitored by TLC. The solvent was evaporated. EtOAc (5 mL) was added and the

mixture was washed with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with saturated NH_4Cl (20 mL) and dried (Na_2SO_4). The product mixture was purified by silica gel column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ δ 7.39 – 7.27 (m, 1H), 7.04 – 6.93 (m, 1H), 5.59 (d, *J* = 7.8 Hz, 1H), 4.32 – 4.17 (m, 3H), 1.94 (s, 3H), 1.78 – 1.69 (m, 1H), 1.59 (s, 3H), 1.36–1.26 (m, 1H) **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.39, 115.96, 115.79, 115.73, 105.72, 105.51, 105.25, 95.79, 72.50, 66.55, 56.02, 26.81, 24.71, 24.47 **IR (neat) (cm^{-1}):** 2954, 2930, 2885, 2858, 1766, 1632 m.p: 140-144.

Acknowledgements

The authors are indebted to Department of Chemistry and Atatürk University for financial support. This research was supported by the Scientific and Technological Research Council of Turkey (TÜBİTAK-114Z170).

References

1. Juaristi, E.; Soloshonok, V. A. *Enantioselective synthesis of β-amino acids* John Wiley & Sons, Inc., New Jersey **2005**.

2. Cole, D. C. *Tetrahedron,* **1994**, *50*, 9517-9582.

3. Nussbaum, F. V. and Spiteller, P. β-Amino Acids in Nature. Highlights in Bioorganic Chemistry, 2005, (1.5.) 63-89.

4. Seki, M.; Shimizu T.; Matsumoto, K. *J. Org. Chem.,* **2000**, *65*, 1298-1304.

5. Moumne, R.; Lavielle, S; Karoyan, P. *J. Org. Chem.,* **2006,** 71, 3332-3334

6. Romanens, A. and Bélanger, G. *Organic letters,* 2015, 17, 2, 322-325.

7. Karoyan, P.; Sagan, S.; Lequin, O.; Quancard, J.; Lavielle, S.; Chassaing, G. *Targets Heterocycl. Syst*., **2004**, 8, 216-273.

8. Seebach, D.; Matthews, J. L. *Chem. Commun.,* 1997, 21, 2015-2022.

9. Adessi, C.; Soto, C. *Curr. Med. Chem.,* **2002**, 9, 963-978.

10. Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.,* **1999**, 6, 905-925.

11. Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chemistry biodiversity,* **2004**, 1, 1111-1239.

12. Thornbery, N. A.; Weber, A. E. *Curr. Top. Med. Chem.,* **2007**, *7*, 557-568.

13. Aschner, P. Kipnes, M. S. Lunceford, K. Sanchez, M. Mickel, C. Williams-Herman, D. E. *Sitagliptin Study, Diabetes Care,* **2006**, *29*, 2632-2637.

14. Sun, G. F.; Cai, Z. Y.; Zhou, W. C. *Chinese J. Pharm.,* **2008**, *39*, 383-386.

15. Fistikci, M.; Gundogdu, O.; Aktas, D.; Secen, H.; Sahin, M. F.; Altundas, R.; Kara, Y. *Tetrahedron,* **2012**, *68*, 2607-2610.

16. Köse, A.; Gündoğdu, Ö.; Aktaş, D.; Fıstıkçı, M.; Secen, H.; Altundas, R.; Kara, Y. *Helvetica Chimica Acta*, **2015**, 98, 260-266.

17. Aktaş, D.; Fıstıkçı, M.; Gündoğdu, Ö.; Secen, H.; Sahin, M. F.; Altundas, R.; Kara, Y. *Helvetica Chimica Acta*, **2015**, 98,1127-1131.

18. Anil, D.; Altundas, R.; Kara, Y. *Synthetic Communications,* **2019**, 49(6), 852–858.

19. Gündoğdu, Ö.; Turhan, P.; Köse, A. Altundas, R.; Kara, Y. *Tetrahedron: Asymmetry,* **2017,** 28(9), 1163-1168.

20. Boyle, P. H.; Davis, A. P.; Dempsey, K. J.; Hosken, G. D. *Tetrahedron: Asymmetry,* **1995**, *6*, 2819-2828.

21. Seki, M.; Matsumoto, K. *Tetrahedron Lett.,* **1996**, *37*, 3165-3168.

22. Dobmeier, M.; Herrman, J. N.; Lenoir, D.; Köning, B. *Beilstein J. Org. Chem.,* **2012**, *8*, 330.

23. Sheldrick, G. M. SHELXS-97, SHELXL-97 Program for Crystal Structure Solution and refinement, University of Gottingen, Germany Göttingen, **1997**.

24. Farras, J.; Serra, C.; Ilarrasa, J. *Tetrahedron Letters,* **1998**, 39, 327-330.