ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 5, pp. 787–789. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © Z.R. Valiullina, F.A. Gimalova, L.V. Spirikhin, M.S. Miftakhov, 2017, published in Zhurnal Organicheskoi Khimii, 2017, Vol. 53, No. 5, pp. 772–773.

SHORT COMMUNICATIONS

Unusual Course of "Enolate-Imine" Condensation in Approach to β-Lactams

Z. R. Valiullina, F. A. Gimalova, L. V. Spirikhin, and M. S. Miftakhov*

Ufa Institute of Chemistry, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Russia
**e-mail: bioreg@anrb.ru*

Received December 7, 2016

Abstract—In reaction of methyl (*E*)-3-(methoxycarbonyl)methylimino-2,2-dimethylpropanoate with enolate of ethyl 3-hydroxybutanoate an abnormal reaction product was isolated, 2-methyl 4-ethyl-(2S*,3S*,4S*,5S*)-3-methyl-5-(2-methyl-1-methoxy-1-oxopropan-2-yl)pyrrolidine-2,4-dicarboxylate.

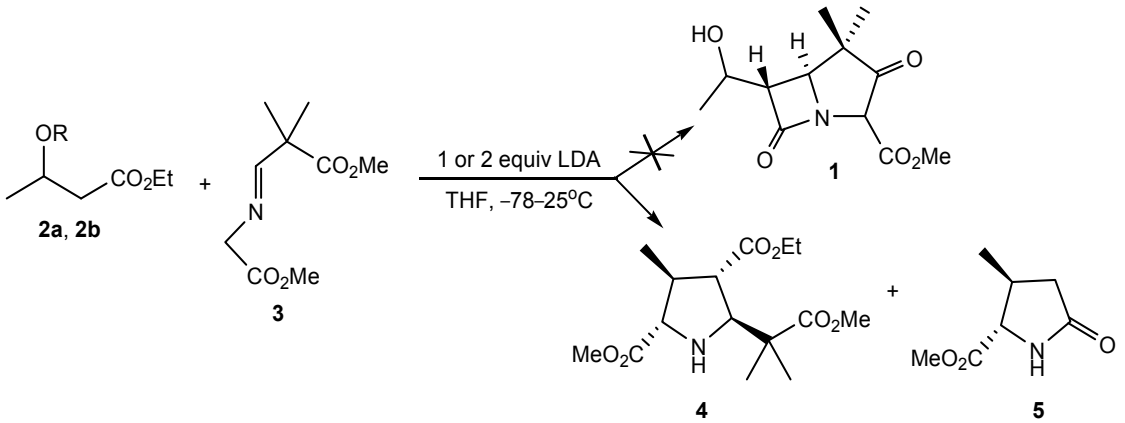
DOI: 10.1134/S1070428017050220

Antibiotics of β-lactam series although are known for a long time, nowadays still are the most demanded for treating bacterial infections [1–3]. The design and construction of new modified structures is the proverbial approach to overcome the global problem of bacterial resistance to drugs [4, 5]. Aiming at development of a tandem version of the approach to carbapenems **1** we studied the reaction of enolate generated from compound (±)-**2a** under the action of 1 equiv of LDA, with imine **3** under standard conditions (THF, –78°C) [6].

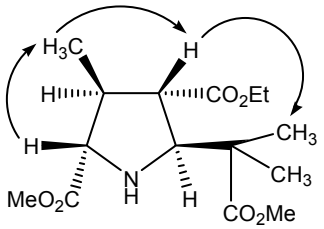
The product of reaction between equimolar quantities of enolate and imine, the expected β-lactam derivative, was planned to treat without isolation in a one-pot procedure with more 1 equiv of LDA and to obtain compound **1**. Yet at the condensation of imine **3** with 1 equiv of enolate generated from compound **2a** an abnormal reaction product was isolated: (±)-*all-trans*-pyrrolidine **4** and a minor product **5** of glycine ester coupling with enolate.

Note that in the reaction of the imine **3** with enolate arising at treating alcohol **2b** with 2 equiv of LDA we also isolated pyrrolidine **4**. Evidently the formation of compound **4** is favored by the presence of the activated CH_2 group in the structure of imine **3**, since at the lack of such group reactions of imines with compound **2** under the effect of LDA occur by the common scheme giving β-lactams [6].

Structures of compounds **4** and **5** were proved by spectral methods. The stereochemistry of compound **4** was suggested basing on the data of NOE-experiments (see the figure).



R = $SiMe_2Bu$-*t* (**a**), H (**b**).



NOE-interactions in compound **4**.

Methyl (*E*)-2,2-dimethyl-3-[(methoxycarbonyl)-methylimino]propanoate (3). To a solution of 0.58 g (4.62 mmol) of methyl glycinate hydrochloride in 1 mL of water was added a solution of 0.95 g (6.93 mmol) of K_2CO_3 in 4 mL of water. The mixture was stirred for 5 min, methyl glycinate was extracted with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$, filtered off, and evaporated. The residue was added to a solution of 0.40 g (3.08 mmol) of methyl 2,2-dimethyl-3-oxopropanoate [7] in toluene and the mixture was boiled till the end of water liberation. The reaction mixture was washed with brine, dried with $MgSO_4$, evaporated, and the residue was additionally dried for 5 h in a vacuum (2 mm Hg) at 20°C. Yield 0.40 g (70%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 s (6H, CH_3), 3.71 s (3H, CO_2Me), 3.72 s (3H, CO_2Me), 4.21 s (2H, CH_2), 7.79 s (1H, =CH). ^{13}C NMR spectrum, $CDCl_3$, δ, ppm: 22.64 (CH_3), 51.96 and 52.21 (OCH_3), 47.82 (C^2), 61.18 (CH_2N), 170.19 ($\underline{C}O_2Me$), 170.57 (CH=N), 175.0 ($\underline{C}O_2Me$). Found, %: C 53.95; H 7.63; N 7.02. $C_9H_{15}NO_4$. Calculated, %: C 53.72; H 7.51; N 6.96.

Reaction of ethyl 3-*tert*-butyl(dimethyl)sililoxy]-butanoate (2a) and compound (3). To a solution of 0.11 g (1.10 mmol) of *i*-Pr_2NH in 5 mL of anhydrous THF at –78°C under an argon atmosphere was added 0.47 mL (1.00 mmol) of 2.1 N solution of BuLi. The reaction mixture was stirred for 20 min at –10°C, then at –78°C 0.25 g (1.00 mmol) of compound **2a** was added dropwise. The mixture was stirred for 1.5 h at –20°C, then the reaction mixture was cooled to –78°C and 0.20 g (1.00 mmol) of imine **3** solution in 1 mL of anhydrous THF was added dropwise. The reaction mass was stirred for 1.5 h at –20°C, then at room temperature it was treated with saturated water solution of NH_4Cl (4 mL). The reaction product was extracted with ethyl acetate, the combined organic extracts were washed with brine and dried with $MgSO_4$. On distilling off the solvent in a vacuum and purifying the residue by column chromatography on SiO_2 (eluent petroleum ether–ethyl-acetate, 95 : 5→1 : 1) we isolated 0.09 g (30%) of compound **4**, 0.02 g (13%) of compound **5**, and 0.05 g of unreacted compound **2a**.

2-Methyl 4-ethyl (2*S,3*S**,4*S**,5*S**)-3-methyl-5-(2-methyl-1-methoxy-1-oxopropan-2-yl)pyrrolidine-2,4-dicarboxylate (4).** IR spectrum, cm^{-1}: 2979, 2907, 1733, 1178. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 d (3H, CH_3, *J* 6.9 Hz), 1.24 t (3H, CH_3, *J* 7.1 Hz), 1.30 s (3H, CH_3), 1.32 s (3H, CH_3), 2.57–2.63 m (2H, CH), 3.33 d (1H, H^2, *J* 5.8 Hz), 3.35 d (1H, H^5, *J* 6.3 Hz), 3.68 s (3H, OCH_3), 3.77 s (3H, OCH_3), 4.00 d.d (1H, OCH_2, *J* 7.1, 3.7 Hz), 4.06 d.d (1H, OCH_2, *J* 7.2, 3.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.84 (CH_3), 20.02 (CH_3), 23.68 (CH_3), 24.37 (CH_3), 43.63 (C^4), 51.85 and 52.11 (OCH_3), 53.39 (C^3), 60.63 (OCH_2), 67.44 (C^2), 68.59 (C^5); 173.09, 173.71, 176.40 ($2CO_2Me$, CO_2Et). Mass spectrum, *m/z* (I_{rel}, %): 316 $[M + H]^+$ (100). Found, %: C 57.35; H 7.87; N 4.52. $C_{15}H_{25}NO_6$. Calculated, %: C 57.13; H 7.99; N 4.44.

Methyl (2*S,3*S**)-3-methyl-5-oxopyrrolidine-2-carboxylate (5).** IR spectrum, cm^{-1}: 3349–3112, 2960, 1731, 1691, 1672, 1212. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 d (3H, CH_3, *J* 6.5 Hz), 2.03 q (1H, H^4, *J* 10.0 Hz), 2.55 m (2H, H^3, H^4), 3.70 d (1H, H^2, *J* 5.2 Hz), 3.75 s (3H, OCH_3), 6.63 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.04 (CH_3), 34.02 (C^3), 37.88 (C^4), 52.47 (OCH_3), 62.41 (C^2), 172.13 and 177.11 (CO_2, CONH). Mass spectrum, *m/z* (I_{rel}, %): 199 $[M + MeCN]^+$ (100), 158 $[M + H]^+$ (40).

IR spectra were recorded on a spectrophotometer IR Prestige-21 Shimadzu from thin film. ^{1}H and ^{13}C NMR spectra were registered of spectrometers Bruker AM-300 at operating frequencies 300.13 and 75.47 MHz and Bruker Avance-500 at operating frequencies 500.13 and 125.77 MHz respectively, internal reference TMS. Mass spectra were taken on an instrument LCMS-2010EV (Shimadzu). Elemental analysis of synthesized compounds was carried out on a CHN-analyzer Evro EA-2000. The reaction progress was monitored by TLC on Sorbfil plates (Russia), spots visualized by adding solution of anisaldehyde and sulfuric acid in ethanol followed by heating at 120–150°C. The products of synthesis were isolated by column chromatography on silica gel (30–60 g of adsorbent per 1 g of compound).

ACKNOWLEDGMENTS

In the study the equipment was used of the Center of joint usage of the Ufa Institute of Chemistry, Russian Academy of Sciences.

The study was carried out under the financial support of the Russian Science Foundation (project no.15-13-00039).

REFERENCES

1. Hart, D.J. and Ha, D.-Ch., *Chem. Rev*., 1989, vol. 89, p. 1447. doi 10.1021/cr00097a003
2. Fu, N. and Tidwell, T.T., *Tetrahedron*, 2008, vol. 64, p. 10465. doi 10.1016/j.tet.2008.08.028
3. Brandi, A., Cicchi, S., and Cordero, F.M., *Chem. Rev*., 2008, vol. 108, p. 3988. doi 10.1021/cr800325e
4. Orbegozo, T., Burel, F., Jubault, P., and Pannecoucke, X., *Tetrahedron*, 2013, vol. 69, p. 4015. doi 10.1016/j.tet.2013.02.043
5. Betts, J.W., Phee, L.M., Abdul Momin, M.H.F., Umland, K.-D., Brem, J., Schofield, C.J., and Wareham, D.W., *Med. Chem. Commun*., 2016, vol. 7, p. 190. doi 10.1039/C5MD00380F
6. Georg, G.I., Kant, J., and Gill, H.S., *J. Am. Chem. Soc*., 1987, vol. 109, p. 1129. doi 10.1021/ja00238a023
7. Tanimoto, S., Kokubo, T., Oida, T., and Ikehira, H., *Synthesis*, 1982, p. 723. doi 10.1055/s-1982-29913