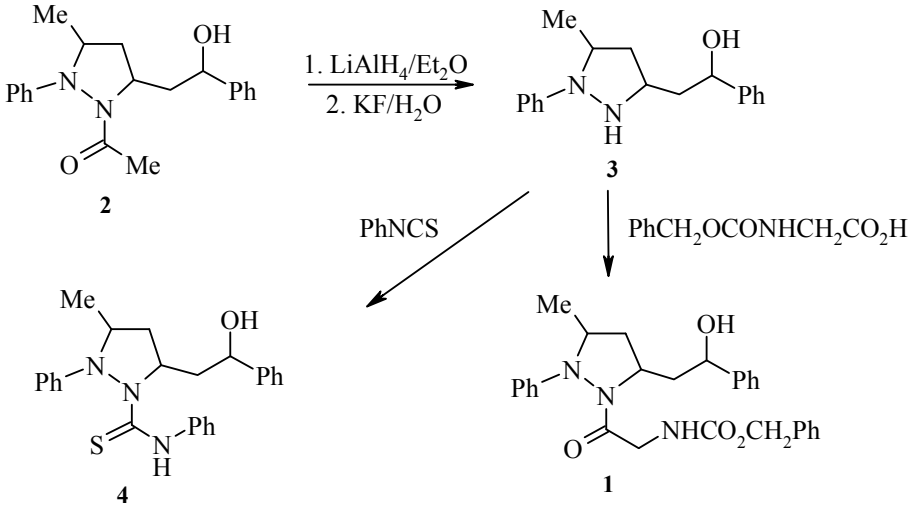
Chemistry of Heterocyclic Compounds, Vol. 44, No. 3, 2008

A NEW METHOD FOR THE SYNTHESIS OF PYRAZOLIDINES WITH N-AMINO ACID SUBSTITUTENTS

L. A. Sviridova[1], G. A. Golubeva[1], A. N. Tavtorkin[2], and K. A. Kochetkov[2]

Keywords: amino acids, pyrazolidines, acylation.

Pyrazolidine derivatives with an amino acid substituent at the ring nitrogen atom are very promising as fibrinogen receptors antagonists but the method for their synthesis from amino acid hydrazides is extremely limited [1]. We have found that 1-glycylpyrazolidine **1** may be obtained from 1-acetyl-5-(2-hydroxy-2-phenylethyl)-3-methyl-2-phenylpyrazolidine (**2**), which is readily available [2]. A well-known method involving the action of lithium aluminum hydride under mild conditions usually employed for simple amides and hydrazides was used to remove the acetyl protective group [3]. The resultant unstable cyclic phenylhydrazine **3** converts to give phenylisothiocarbamoyl derivative **4** in high yield.



* Dedicated to A. A. Akhrem on the occasion of his ninety-fifth birthday.

[1]M. V. Lomonosov Moscow State University, Chemistry Faculty, Moscow 119992, Russia; e-mail: svirid@org.chem.msu.ru. [2]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 119991, Russia; e-mail: const@ineos.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 474-475, March, 2008. Original article submitted February 6, 2008.

 0009-3122/08/4403-0368

We were able to carry out the reaction of **3** with N-benzyloxycarbonylglycine under mild conditions only by using the Mukaiyama method [4], which permits the preparation of other amino acid derivatives similar to **1**. All the reported methods for the acylation of amino acids did not give positive results.

The IR spectra were taken on a UR-20 spectrometer for vaseline mulls. The ^{1}H NMR spectra were taken on a Bruker-Avance 600 spectrometer at 600 MHz in $CDCl_3$.

5-(2-Hydroxy-2-phenylethyl)-3-methy-1-phenylthiocarbamoyl-2-phenylpyrazolidine (4). **C**ompound **2** (100 mg, 0.31 mmol) was added to saturated solution of $LiAlH_4$ (29 mg, 0.2 ml) in ether (1 mmol) at 0°C in a dry nitrogen stream and then stirred for 30 min at this temperature. Then, saturated aqueous KF solution (0.5 ml) was added dropwise. Ether (1 ml) was added and the mixture was stirred at room temperature for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with ether (3 x 1 ml). The organic phases were combined, dried over potassium carbonate, and evaporated to give cyclic phenylhydrazine **3** as an oil.

Phenyl isothiocyanate (0.04 ml, 0.33 mmol) was added to a solution of crude compound **3** in ether (0.5 ml) and left in an inert atmosphere. The precipitate formed was washed with ether to give 94 mg (73%) compound **4**, mp 165-166°C. IR spectrum, ν, cm^{-1}: 3278 (OH), 3390 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, d, *J* = 6.4, 3-CH_3); 1.75 (1H, m, α-H); 2.02 (1H, m, H-4); 2.22 (1H, m, H'-4); 2.68 (1H, m, α-H'); 3.82 (1H, d, *J* = 4.6, OH); 4.23 (1H, m, H-3); 4.95 (1H, m, CHOH); 5.45 (1H, m, H-5); 7.00-7.44 (15H, m, Ar). Found, %: C 71.94; H 6.46; N 10.05. $C_{25}H_{27}N_3OS$. Calculated, %: C 71.91; H 6.52; N 10.06.

1-(N-Benzyloxycarbonylglycyl)-5-(2-hydroxy-2-phenylethyl)-3-methyl-2-phenylpyrazolidine (1). A solution of 2-chloro-1-methylpyridinium iodide (79 mg, 0.31 mmol), benzyloxycarbonylglycine (70 mg, 0.33 mmol) and N-methylmorpholine (0.07 ml, 0.62 mmol) in methylene chloride (2 ml) was added to pyrazolidine **3** (obtained according to the previous procedure from compound **2** (0.31 mmol), and left in an inert atmosphere for 3 h. The solvent was distilled off and the residue was subjected to chromatography on a silica gel column with gradient elution from 1:10 to 1:1 ethyl acetate-hexane to give 80 mg (55%) **1** as an oil. IR spectrum, ν, cm^{-1}: 1657 (CO amide), 1722 (CO carbamate), 3347 (NH), 3417 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, d, *J* = 6.6, 3-CH_3); 1.91 (2H, m, α-H, H-4); 2.13 (1H, dd, *J* = 11.8, *J* = 7.4, H'-4); 2.54 (1H, m, α-H'); 3.84 (1H, dd, *J* = 18.5, *J* = 4.4, NCOC$\underline{H}_2$NH); 4.19 (1H, m, H-3); 4.44 (1H, dd, *J* = 18.5, *J* = 5.3, NCOC$\underline{H}'_2$NH); 4.69 (1H, m, H-5); 4.90 (1H, dd, *J* = 9.7, *J* = 3.5, CHOH); 5.16 (1H, d, *J* = 2.6, $CH_2C_6H_5$); 5.72 (1H, br. s, NCO$CH_2N\underline{H}$); 7.01-7.44 (15H, m, Ar). Found, %: C 70.23; H 6.75; N 8.33. $C_{28}H_{31}N_3O_4$. Calculated, %: C 71.02; H 6.60; N 8.87.

REFERENCES

1. G. K. Vertelov, Author's Abstract of Chemical Candidate's Dissertation, Moscow State University, Moscow (2004), 20 pp.
2. L. A. Sviridova, A. N. Tavtorkin, and K. A. Kochetkov, in: *Abstracts of the International Conference on Heterocyclic Chemistry Dedicated to Prof. A. N. Kost on the Occasion of his Ninetieth Birthday* [in Russian], Moscow (2005), p. 279.
3. S. Hanessian, *Tetrahedron Lett.*, 1549 (1967).
4. E. Baki, K. Saigo, and T. Mukaiyama, *Chem. Ind.*, 1163 (1975).