Chemistry of Heterocyclic Compounds, Vol. 48, No. 2, May, 2012 (Russian Original Vol. 48, No. 2, February, 2012)

ETHYL 5-AMINO-3-OXO-1,2-DIHYDRO-1*H*-PYRAZOLE-1-CARBOXYLATE IN THE SELECTIVE SYNTHESIS OF PARTIALLY HYDROGENATED PYRAZOLO[3,4-*b*]PYRIDIN-3-ONES

P. S. Lebed'[1]*, N. G. Mozgovaya[1], P. O. Kos[1], and M. V. Vovk[1]

Ethyl 5-amino-3-oxo-1,2-dihydro-1H-pyrazole-1-carboxylate undergoes selective cyclocondensation with 1,3-dicarbonyl compounds or their synthetic equivalents to give ethyl 3-oxo-1,2-dihydropyrazolo[3,4-b]pyridine-1-carboxylates which are readily converted to their 1-unsubstituted analogs.

Keywords: 5-amino-1-ethoxycarbonyl-1,2-dihydro-1*H*-pyrazol-3-one, 5-aminopyrazol-3-one, 1,3-dicarbonyl compounds, pyrazolo[3,4-*b*]pyridin-3-ones, cyclocondensation.

Partially hydrogenated pyrazolo[3,4-*b*]pyridin-3-ones are a biologically important and promising type of fused heterocyclic system. They include compounds with pronounced antispasmodic [1], antidepressant [2], and cytotoxic [3] activity and are also able to inhibit hormone-sensitive lipases [4, 5].

Two routes have been reported for the construction of this system: annelation of a pyrazole ring to a 2-functionalized nicotinic acid derivatives [6, 7] or the condensation of 5-amino-1,2-dihydro-3*H*-pyrazol-3-one (**1**) with 1,3-dicarbonyl compounds. With the availability of reagents in mind, the second route is the more acceptable even though the presence in the molecule of compound **1** of three nucleophilic centers is generally a cause of nonselective cyclocondensation so forming, along with the target dihydropyrazolopyridinones, some pyrazolo[1,5-*a*]pyrimidine derivatives due to participation of the 1-NH and 5-NH_2 groups in the reaction.

As a result of the aminodihydropyrazolone **1** reaction with ethyl acetylpyruvate in acetic acid, there has previously been obtained a mixture of ethyl 3-oxo-2,3-dihydropyrazolo[3,4-*b*]pyridine-4-carboxylate (80% yield) and the corresponding 2,3-dihydropyrazolo[1,5-*a*]pyrimidin-2-one (10% yield) [8]. However, in many attempts to reproduce this reported method we have found that the content of the latter product is not less than 25-30%. When the same reaction was carried out by us without solvent at 120ºC by another known method [9] it was possible to prepare the target product in a yield no higher that 20%. According to the data in [8, 10] the result of condensation of compound **1** with 3-oxobutanal or 1,3-diketones in acetic acid or hydrochloric acid medium is the formation in all cases of a mixture of the corresponding dihydropyrazolo[3,4-*b*]pyridine and dihydropyrazolo[1,5-*a*]pyrimidine. At the same time it was found that the use of the sodium or potassium salt of

*To whom correspondence should be addressed, e-mail: p_lebed@rambler.ru.

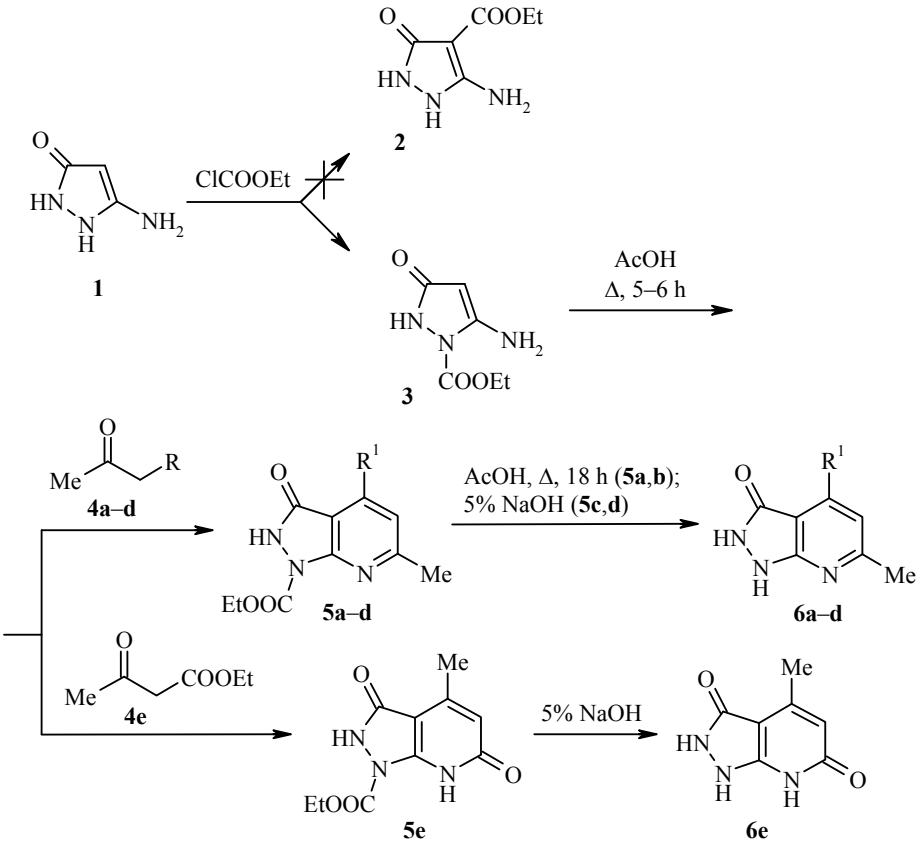
[1]Institute of Organic Chemistry, Ukraine National Academy of Sciences, 5 Murmanska St., Kyiv 02094, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 390-394, February, 2012. Original article submitted September 30, 2010; revision submitted May 16, 2011.

pyrazolone **1** gave high yields of 2,3-dihydropyrazolo[3,4-*b*]pyridin-3-ones [10-13]. However, the sodium salt proved ineffective in the reaction with acetoacetic ester. A satisfactory yield of the corresponding dihydropyrazolo[3,4-*b*]pyridinedione was achieved only by carrying out the condensation in hydrochloric acid [8, 10, 14, 15].

The data given above shows that development of a general, regiospecific method for the preparation of partially hydrogenated pyrazolo[3,4-*b*]pyridin-3-ones is a very important goal. For its solution, we have studied the possibility of protecting the nucleophilic center at atom N-1 in compound **1** by a COOEt group with subsequent condensation of the ethoxycarbonyl derivative obtained with a series of active methylene compounds.

It has previously been reported that reaction of compound **1** with ethyl chloroformate occurs at the C-4 atom to give the ethyl 5-amino-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (**2**) [16]. We have found that the reaction under the conditions given in [16] occurs at the N-1 atom to form the ethyl 5-amino-3-oxo-2,3-dihydro-1*H*-pyrazole-1-carboxylate (**3**) and this is confirmed by ^{1}H NMR spectroscopic data. Hence the ^{1}H NMR spectrum contains a singlet signal for H-4 proton at 4.63 ppm and a broad signal at 6.50 ppm for the NH_2 group. The ^{13}C NMR spectrum shows a characteristic signal for the C-4 atom at 75.6 ppm.



4 a R = $CH(OMe)_2$, **b** R = COMe, **c** R = $COCF_3$, **d** R = COCOOEt;
5, 6 a R^1 = H, **b** R^1 = Me, **c** R^1 = CF_3, **5d** R^1 = COOEt, **6d** R^1 = COOH

Study of the reaction of compound **3** with compounds **4a-e** (with an active methylene group) has shown that it can be successfully used in a regiospecific synthesis of both known and novel dihydropyrazolo[3,4-*b*]-pyridin-3-ones. Hence in the cases of its cyclocondensation with 3-oxobutanal acetal **4a** and with acetylacetone (**4b**), ^{1}H NMR and chromato-mass spectrometric analyses have shown that six-hour refluxing of the reagents in acetic acid gives both the 1-ethoxycarbonyl-substituted compounds **5a,b** in 10-15% yields and also their decarboxylation products **6a,b**. A further 18-hour refluxing of the reaction mixture allows the latter to be

obtained in 50-53% yields. In the case of the trifluoroacetylacetone **4c**, the ester **5c** formed does not undergo decarboxylation under the conditions given and its conversion to compound **6c** (in 89% yield) requires refluxing for 0.5 h in 5% aqueous NaOH solution. Similarly the ethyl acetylpyruvate **4d** gives an 83% yield of diester **5d**, alkaline treatment of which gives the acid **6d** in almost quantitative yield. The reported reaction can be regarded as a novel and convenient method for the preparation of 6-alkyl-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acids. Use of the 1-ethoxycarbonyl-substituted compound **3** in reaction with the acetoacetate **4e** has preparative value when compared with the analog unsubstituted at N-1 since the 2,3,6,7-tetrahydropyrazolo[3,4-*b*]pyridine-3,6-dione **5e** is formed virtually pure and is readily hydrolyzed using 5% NaOH to give the target compound **6e** in 96% yield.

Hence preliminary *N*(1)-acylation of 5-amino-1,2-dihydropyrazol-3-one using chloroformate is an efficient variant which increases the selectivity of its reaction with 1,3-dicarbonyl compounds or their synthetic equivalents.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 and 125 MHz, respectively) using DMSO-d_6 with TMS as internal standard.

The starting compound **1** was prepared using method [17].

Ethyl 5-amino-3-oxo-2,3-dihydro-1*H*-pyrazole-1-carboxylate (3) was prepared by method [16]. Yield 56%; mp 155-157ºC (mp 155-160ºC [16]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.0, CH_3); 4.30 (2H, q, *J* = 7.0, CH_2); 4.63 (1H, s, H-4); 6.50 (2H, br. s, NH_2); 10.19 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.0 (CH_3); 62.7 (CH_2); 75.6 (C-4); 150.5 (C=O); 153.0 (C-5); 165.2 (C=O).

Pyrazolo[3,4-*b*]pyridine-1-carboxylic Acid Derivatives 5c-e (General Method). A mixture of compound **3** (2.5 mmol) and trifluoroacetylacetone (**4c**), ethyl acetylpyruvate (**4d**), or acetoacetic ester (**4e**) (2.5 mmol) was refluxed in glacial acetic acid (8 ml) for 5-6 h. The corresponding precipitated product **5** obtained on cooling was filtered off, washed with water, dried, and recrystallized from ethanol.

Ethyl 6-Methyl-3-oxo-4-trifluoromethyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (5c). Yield 81%; mp 177-178ºC. IR spectrum, ν, cm^{-1}: 1735 (C=O), 1760 (C=O), 3350 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.72 (3H, s, 6-CH_3); 4.43 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.67 (1H, s, H-5); 12.26 (1H, br. s, NH). Found, %: C 45.71; H 3.47; N 14.50. $C_{11}H_{10}F_3N_3O_3$. Calculated, %: C 45.68; H 3.49; N 14.53.

Diethyl 6-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-1,4-dicarboxylate (5d). Yield 83%; mp 221-222ºC (decomp.). IR spectrum, ν, cm^{-1}: 1690 (C=O), 1760 (C=O), 3450 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.42 (6H, m, $CH_2C\underline{H}_3$); 2.71 (3H, s, 6-CH_3); 4.44 (4H, m, $C\underline{H}_2CH_3$); 7.51 (1H, s, H-5); 11.74 (1H, br. s, NH). Found, %: C 53.17; H 5.17; N 14.31. $C_{13}H_{15}N_3O_5$. Calculated, %: C 53.24; H 5.16; N 14.33.

Ethyl 4-Methyl-3,6-dioxo-2,3,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (5e). Yield 48%; mp 237-239ºC (decomp.). IR spectrum, ν, cm^{-1}: 1675 (C=O), 1725 (C=O), 3345 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.39 (3H, s, 4-CH_3); 4.36 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.21 (1H, s, H-5); 11.49 (1H, br. s, NH). Found, %: C 50.59; H 4.59; N 17.70. $C_{10}H_{11}N_3O_4$. Calculated, %: C 50.63; H 4.67; N 17.71.

6-Methyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-ones (6a,b) (General Method). A mixture of compound **3** (0.43 g, 2.5 mmol) and 3-oxobutanal dimethylacetal (**4a**) or acetylacetone (**4b**) (2.5 mmol) was refluxed in glacial acetic acid (8 ml) for 24 h. The solvent was evaporated and the residue was recrystallized from ethanol.

6-Methyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-one (6a). Yield 53%; mp 278-280ºC (mp 282-283ºC [8]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.49 (3H, s, 6-CH_3); 6.21 (1H, d, *J* = 7.9, H-4); 6.90 (1H, d, *J* = 7.9, H-5); 11.36 (2H, br. s, NH). Found, %: C 56.39; H 4.78; N 28.15. $C_7H_7N_3O$. Calculated, %: C 56.37; H 4.73; N 28.17.

4,6-Dimethyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-one (6b). Yield 50%; mp > 300ºC (mp 355ºC [8, 10]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, CH_3); 2.51 (3H, s, CH_3); 6.67 (1H, s, H-5); 11.16 (2H, br. s, NH). Found, %: C 58.91; H 5.59; N 25.72. $C_8H_9N_3O$. Calculated, %: C 58.89; H 5.56; N 25.75.

6-Methyl-4-trifluoromethyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-one (6c), 6-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic Acid (6d), 4-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine-3,6(2*H*,7*H*)-dione (6e) (General Method). A suspension of compound **5c-e** (1.4 mmol) in 5% aqueous NaOH solution (10 ml) was refluxed for 0.5 h, cooled, acidified with dilute HCl solution to pH 5, and the precipitate formed was filtered off, washed with water, and dried.

6-Methyl-4-trifluoromethyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-one (6c). Yield 89%; mp 253-254ºC (mp 255-256ºC [11]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.61 (3H, s, 6-CH_3); 7.27 (1H, s, H-5); 11.09 (1H, br. s, NH); 12.48 (1H, br. s, NH). Found, %: C 44.26; H 2.80; N 19.33. $C_8H_6F_3N_3O$. Calculated, %: 44.25; H 2.79; N 19.35.

6-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic Acid (6d). Yield 95%; mp > 300ºC. IR spectrum, ν, cm^{-1}: 1650 (C=O), 1680 (C=O), 3410 (N–H), 3480 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (3H, s, CH_3); 7.30 (1H, s, H-5). Found, %: C 49.73; H 3.67; N 21.70. $C_8H_7N_3O_3$. Calculated, %: C 49.75; H 3.65; N 21.75.

4-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine-3,6(2*H*,7*H*)-dione (6e). Yield 96%; mp > 300ºC (mp > 300ºC [8, 10]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, 4-CH_3); 5.78 (1H, s, H-5); 11.11 (2H, br. s, NH). Found, %: C 50.88; H 4.30; N 25.41. $C_7H_7N_3O_2$. Calculated, %: C 50.91; H 4.27; N 25.44.

REFERENCES

1. E. G. Paronikyan, S. N. Sirikanyan, A. S. Noravyan, R. G. Paronikyan, and I. A. Dzhagatspanyan, *Khim.-Farm. Zh.*, **35**, No. 1, 9 (2001).
2. R. M. Schelkun and P.-W. Yuen, US Pat. Appl. 2006116376.
3. M. Manpadi, P. Y. Uglinskii, S. K. Rastogi, K. M. Cotter, Y.-S. C. Wong, L. A. Anderson, A. J. Ortega, S. Slambrouck, W. F. A. Steelant, S. Rogelj, P. Tongwa, M. Y. Antipin, I. V. Magedov, and A. Kornienko, *Org. Biomol. Chem.*, **5**, 3865 (2007).
4. G. Zoller, S. Petry, G. Muller, H. Heuer, and K.-H. Bar-Inghaus, WO Pat. Appl. 2005073199.
5. G. Zoller, S. Petry, G. Muller, H. Heuer, and K.-H. N. Tennagels, US Pat. Appl, 2008287448.
6. A. Chandra Sheker Reddy, B. Narsaiah, and R. V. Venkataratnam, *Synth. Commun.*, **27**, 2217 (1997).
7. Z. A. Kalme, B. Roloff, Yu. E. Pelcher, Yu. Yu. Popelis, F. Hagen, and G. J. Duburs, *Khim. Geterotsikl. Soedin.*, 1218 (1992). [*Chem. Heterocycl. Compd.*, **28**, 1031 (1992)].
8. R. Balicki, *Pol. J. Chem.*, **57**, 1251 (1983).
9. P. Papini, S. Checchi, and M. Ridi, *Gazz. Chim. Ital.*, **87**, 931 (1957).
10. J.-L. Imbach, R. Jacquier, and J.-L. Vidal, *Bull. Soc. Chim. Fr.*, 1929 (1970).
11. R. Balicki and P. Nantka-Nemirski, *Pol. J. Chem.*, **54**, 2175 (1980).
12. E. C. Taylor and J. W. Barton, *J. Am. Chem. Soc.*, **81**, 2448 (1959).
13. W. Ried and E. U. Kocher, *Justus Liebigs Ann. Chem.*, **647**, 116 (1961).
14. G. Zoller, S. Petry, G. Muller, H. Hever, and K.-H. N. Tennagels, WO Pat. Appl. 2007110216.
15. R. Balicki, *Pol. J. Chem.*, **56**, 711 (1982).
16. P. Papini, S. Checchi, and M. Ridi, *Gazz. Chim. Ital.*, **84**, 769 (1954).
17. B. Graham, H. D. Porter, and A. Weissberger, *J. Am. Chem. Soc.*, **71**, 983 (1949).