

HETEROCYCLIZATION OF VIC-SUBSTITUTED HYDROXAMIC ACID SALTS OF ACETYLENYL-PYRAZOLES: A NEW PROCEDURE FOR THE PREPARATION OF PYRAZOLO[3,4-*c*]PYRIDIN-7-ONES

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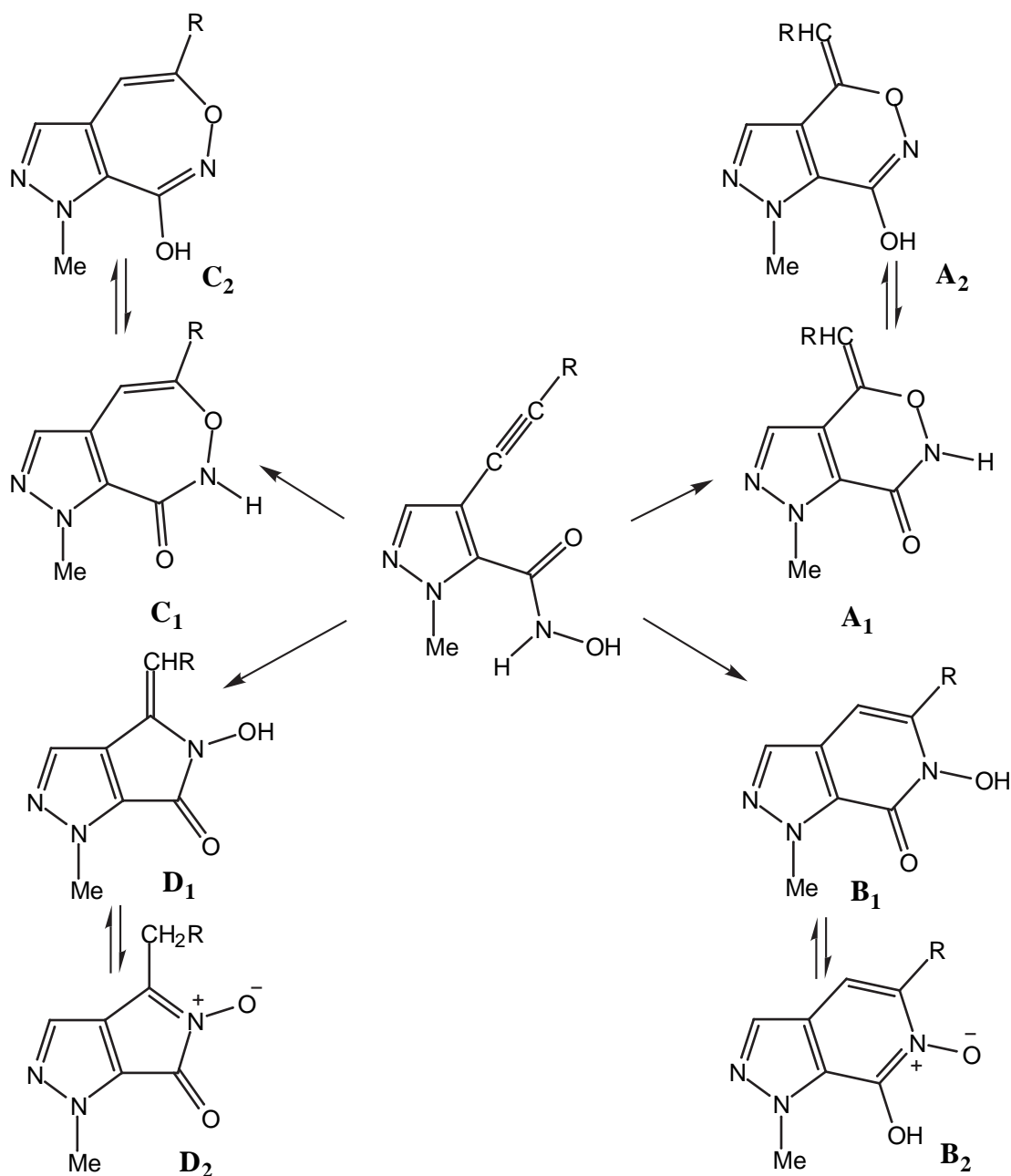
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Abstract– Procedures for the preparation of 5-substituted pyrazolo[3,4-*c*]pyridin-7-ones and 5-substituted 6-hydroxypyrazolo[3,4-*c*]pyridin-7-ones have been developed based on heterocyclization of *vic*-acetylenylpyrazolyhydroxamic acids under the influence of copper(I) salts in dimethylformamide or with organic bases in butanol or methanol.

One of the procedures for the synthesis of fused heterocyclic compounds involves cyclization of *ortho(vic)*-functionalized aryl- and hetarylacetylenes.¹⁻⁴ Previously, we have reported the cyclocondensation of hydrazides of *vic*-substituted acetylenylpyrazoles which lead to substituted six-membered *N*-aminolactam rings.⁵ In the present paper, we describe the cyclization of *vic*-substituted acetylenic derivatives of pyrazolyhydroxamic acids, a synthetic procedure previously unreported. To the best of our knowledge, this is the first example of a hydroxamic acid group (CONHOH) involved in a cyclization with an adjacent acetylenic group. The resulting pyrazolo[3,4-*c*]pyridin-7-ones belong to a class of compounds with biological properties as phosphodiesterase IV (PDE IV) inhibitors (useful for the treatment of asthma, cystic fibrosis, chronic bronchitis, cardiovascular and cerebrovascular diseases, peripheral blood vessel diseases and urogenital tract diseases).⁶ Sakamoto has reported a related reaction: the formation of carbolines and isoquinolines from the imines of *ortho*-ethynyl-carbaldehydes.^{7,8}

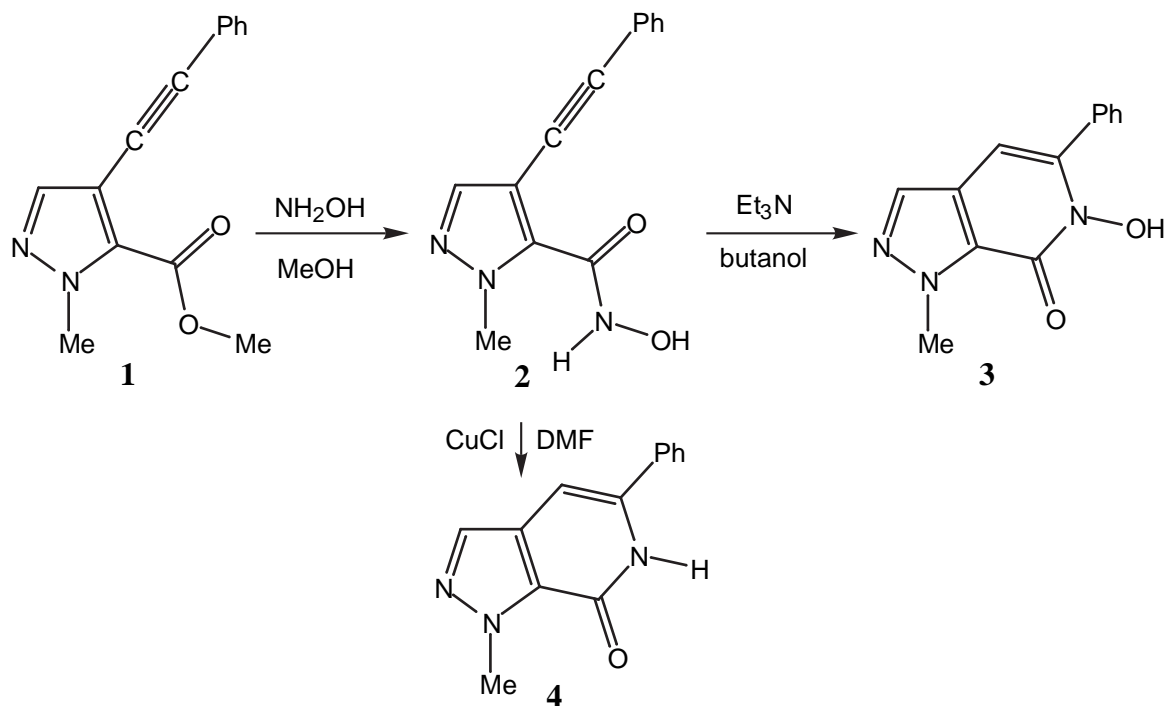
Heterocyclization of *vic*-acetylenylpyrazolyhydroxamic acids can afford at least four compounds (**A-D**), each of them presenting two tautomeric forms (either oxo/hydroxy or *N*-hydroxy/*N*-oxide). This is due to the possibility of an attack by both the N and the O atoms of the functional hydroxylamino group to the α - and β -carbon atoms of the triple bond (Scheme 1).



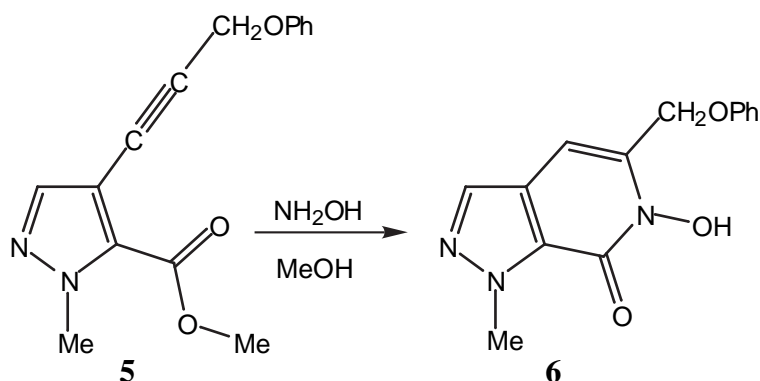
Scheme 1

The synthesis of the starting esters of pyrazole (**1**) (Scheme 2) and (**5**) (Scheme 3) was described in previous works.^{9,10} Hydroxamic acid (**2**) was prepared in 90 % yield by boiling the methyl ester of the corresponding 5-pyrazole carboxylic acid with an excess of hydroxylamine in methanol.

In general, it could be expected that the direction of cyclization of *vic*-acetylenylpyrazolyhydroxamic acids, which bear two (O and N) atoms exhibiting different nucleophilicity, can be controlled by the reaction conditions. The study of the heterocyclization of *vic*-acetylenylpyrazole-hydroxamic acids has allowed to find some regularities of this process.



Scheme 2



Scheme 3

The cyclization of hydroxamic acid (2) occurs in milder conditions (in comparison with the corresponding hydrazides) *i.e.* an organic base can be used instead of KOH. Thus, in the conditions (heating at reflux for 4 h in presence of triethylamine in butanol) for heterocyclization of the acetylenic derivative of hydroxamic acid with a phenyl fragment, the pyridine cycle is formed. The yield of δ -*N*-hydroxylactam (3) is about 50 %. It should be noted that the phenoxymethyl derivative (5) can undergo

ring closure more easily than the phenyl derivative (**1**). Even in the mild conditions of heterocyclization (in the presence of hydroxylamine) it is converted to compound (**6**). On the other hand, for the cyclization of **2**, a stronger base (triethylamine) is required. Possibly this is related to the opposite polarization of the triple bond under the influence of the phenyl and phenoxyethyl groups.

The reaction performed in the presence of copper(I) chloride in boiling DMF (Scheme 2) is rather unexpected. Although, as in the case of **3** formation, there is an attack by the amide nitrogen atom resulting in a 6-membered lactam (**4**) (20 %), the oxygen atom is lost in the final product (compare **3** and **4**). The fact that heterocyclization affords pyridones (**3**, **4** and **6**) rather than the oxygen containing rings (Scheme 1, **A** or **C**) is probably associated with the higher nucleophilicity of the N atom compared to the O atom.

From the above and our previous results,⁵ it can be concluded that the cyclization of acetylenic derivatives of pyrazolyhydroxamic acids and of the hydrazides of pyrazolecarboxylic acids affords exclusively fused pyrazolo[5.5] and [5.6] ring systems.

A comment about the tautomerism of **3**, **4** and **6**. In the solid state, the presence of a C=O band in IR spectrum indicates that all of them exist in the pyridone form (**3** and **6**: Scheme 1, **B1**). In CDCl₃, the results are not conclusive (for instance, the signal at 9.09 ppm of **4** could be an NH or an OH), but it is safe to assume that the tautomeric form is the same.¹¹

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EXPERIMENTAL

¹H NMR spectra were recorded on a Bruker AM-300 spectrometer. IR spectra were recorded on a Bruker IFS 66 spectrometer (KBr). Mass spectra were recorded on a Finnigan SSQ-710 instrument (direct inlet, EI, 70 eV, ionization chamber temperature 220-270 °C). Column chromatography was carried out on KSK silica gel (60-200 mesh). Melting points were determined with a Kofler apparatus.

Ethynylpyrazolecarboxylic acid methyl ester (**1**).⁹ A mixture of 2.86 g (10 mmol) of 1-methyl-4-iodopyrazole-5-carboxylic acid,¹² 1.28 g (12.5 mmol) of phenylacetylene, 20 mg of CuI and 40 mg of PdCl₂(PPh₃)₂ in 50 mL of Et₂NH was stirred at 50 °C under argon atmosphere up to disappearance of starting iodo derivative (TLC control). The reaction mixture was cooled and poured into ether, the inorganic salts were filtered off and the solution was evaporated under reduced pressure. The residue was

filtered through silica gel (height/diameter of the column: 2 x 3 cm). Compound (**1**) was crystallized from ethanol, yield 1.95 g, 75 %, mp 116-117 °C, *Anal.* Calcd for C₁₄H₁₂N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.06; H, 4.97; N, 11.33.

Hydroxamic acid of acetylenylpyrazole (**2**). In 15 mL of methanol was added 0.55g (24.0 mmol) of Na and 0.8 g (11.0 mmol) of hydroxylamine hydrochloride in 10 mL of methanol. The sodium chloride precipitate was filtered off. To the free hydroxylamine thus prepared, was added 1 g (4.0 mol) of the methyl ester of ethynylpyrazolecarboxylic acid (**1**). The reaction mixture was boiled for 15 min (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid was added (pH = 5-6). Precipitate **2** was filtered off and crystallized from water (0.9 g, 90 %), mp 67-68 °C; ν/cm^{-1} (KBr): 3448 (NH), 3350 (OH), 2200 (C≡C), 1637 (C=O); δ_{H} (CDCl₃) 1.90 (br, s, OH), 3.91 (s, N-CH₃), 7.52 (s, 3-H), 8.31 (s, NH), 7.3-7.4 (m, Ph); MS (70 eV) m/z: 241 [M⁺] (3.1), 28.0 (41.6), 44.0 (79.3), 124.2 (16.0), 128.1 (16.7), 196.0 (43.8), 197.1 (100.0); C₁₃H₁₁N₃O₂, Mw: found m/z 241.08524; calcd 241.08512. *Anal.* Calcd for C₁₃H₁₁N₃O₂: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.51; H, 4.29; N, 17.30.

Synthesis of 6-hydroxy-1-methyl-5-phenyl-1,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (**3**) by cyclization of the hydroxamic acid of phenylethynylpyrazole (**2**) with triethylamine. 0.2 g (0.8 mmol) of the hydroxamic acid (**2**) and 2 mL of triethylamine in 5 mL of butanol were boiled for 4 h (TLC control). The solvent was distilled off in a vacuum, the product (**3**) was recrystallized from ethanol (0.1g, 50%), mp 75-76°C; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3350 (OH), 1666 (C=O); δ_{H} (CDCl₃) 2.10 (br, s, OH), 4.15 (s, N-CH₃), 6.56 (s, 4-H), 7.60 (s, 3-H), 7.1-7.4 (m, Ph); MS (70 eV) m/z: 241 [M⁺] (1.68), 28.0 (48.26), 124.0 (28.26), 195.8 (41.65), 197.0 (100.0). C₁₃H₁₁N₃O₂, Mw: found m/z 241.08522; calcd 241.08512. *Anal.* Calcd for C₁₃H₁₁N₃O₂: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.81; H, 4.93; N, 17.56.

Synthesis of 1-methyl-5-phenyl-1,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (**4**) by cyclization of the hydroxamic acid of phenylethynylpyrazole (**2**) with CuCl. 0.5 g (2 mmol) of hydroxamic acid (**2**), 0.12 g CuCl (1.0 mmol) in 5 mL of dimethylformamide were boiled for 15 min in an atmosphere of argon (TLC control). The reaction mixture was cooled and poured into chloroform and then was washed with ammonia. Chloroform solution was dried with Na₂SO₄ and filtered through alumina (3 x 1.5 cm), the solvent was evaporated under reduced pressure. The product was recrystallized from ethanol (0.1 g, 20 %), mp 245-246 °C; ν/cm^{-1} (KBr): 3440 (NH), 1667 (C=O); δ_{H} (CDCl₃) 4.38 (s, N-CH₃), 6.70 (s, 4-H), 7.77 (3-H), 7.4-7.5 (m, Ph), 9.09 (NH); MS (70 eV) m/z: 225 [M⁺] (100.0), 28.0 (20.0), 77.1 (23.4), 104.1

(13.9), 273.9 (96.1), 226.0 (21.8). $C_{13}H_{11}N_3O$, Mw: found m/z 225.08989; calcd 225.09021. *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.17; H, 5.11; N, 18.79.

Synthesis of 6-hydroxy-1-methyl-5-phenoxyethyl-1,6-dihydropyrazolo[3,4-c]pyridin-7-one (**6**). In 20 mL of methanol was added 0.89 g (39.0 mmol) of Na, and 1.42 g (20.0 mmol) of hydroxylamine hydrochloride in 15 mL methanol. Precipitated sodium chloride was filtered off. To free hydroxylamine, was added 1.77 g (7 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid (**5**)¹⁰ and then heated 6 h at reflux (TLC control). Methanol was distilled off in a vacuum, the residue was dissolved in water and acetic acid was added (pH = 5-6). The precipitate of **6** was filtered off and recrystallized from ethanol (0.78 g 44 %), mp 209-210 °C; ν/cm^{-1} (KBr): 1656 (C=O), 3372 (OH); δ_H ($CDCl_3$) 2.15 (br, s, OH), 4.37(s, N-CH₃), 5.19 (s, CH₂), 6.73 (s, 4-H), 7.76 (s, 3-H), 6.9-7.3 (m, Ph); MS (70 eV) m/z: 271 [M^+] (6.3), 147.9 (16.1), 162.0 (11.4), 177.9 (100.0). $C_{14}H_{13}N_3O_3$, Mw: found m/z 271.09528; calcd 271.09568. *Anal.* Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.87; H, 5.12; N, 15.64.

REFERENCES AND NOTES

1. S. F. Vasilevsky and E. V. Tretyakov, *Liebigs Ann. Chem.*, 1995, 775.
2. S. F. Vasilevsky, E. V. Tretyakov, and J. Elguero, Synthesis and Properties of Acetylenic Derivatives of Pyrazoles, *Adv. Heterocycl. Chem.*, 2002, **82**, 1.
3. T. Sakamoto, Y. Kondo, and M. Yamanaka, *Heterocycles*, 1988, **27**, 2225.
4. E. V. Tretyakov, D. W. Knight, and S. F. Vasilevsky, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3721.
5. S. F. Vasilevsky, E. V. Mshvidobadze, and J. Elguero, *J. Heterocycl. Chem.*, 2002, **39**, in press.
6. F. J. Urban, B. G. Anderson, S. L. Orrill, and P. J. Daniels, *Organic Process Research & Development*, 2001, **5**, 575.
7. T. Sakamoto, A. Numata, H. Saitoh, and Y. Kondo, *Chem. Pharm. Bull.*, 1999, **47**, 1740.
8. T. Sakamoto, A. Numata, and Y. Kondo, *Chem. Pharm. Bull.*, 2000, **48**, 669.
9. M. S. Shvartsberg, S. F. Vasilevsky, T. V. Anisimova, and V. A. Gerasimov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 1342.
10. S. F. Vasilevsky, A. V. Pozdnyakov, and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1367.
11. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *The Tautomerism of Heterocycles*, Academic Press, New York, 1976.
12. S. F. Vasilevsky and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 1071.