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A new route to pyrazolo[3,4-*c*] and [4,3-*c*]pyridinones via heterocyclization of *vic*-substituted hydroxamic acids of acetylenylpyrazoles

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Abstract—We report in this paper the synthesis of 6-substituted pyrazolo[4,3-*c*]pyridin-4-ones, 6-substituted 5-hydroxypyrazolo[4,3-*c*]pyridin-6-ones, 5-substituted pyrazolo[3,4-*c*]pyridin-7-ones and 5-substituted 6-hydroxypyrazolo[3,4-*c*]pyridin-7-ones by heterocyclization of *vic*-acetylenylpyrazol-hydroxamic acids under the influence of copper(I) salt in dimethylformamide or with organic bases in butanol or methanol.

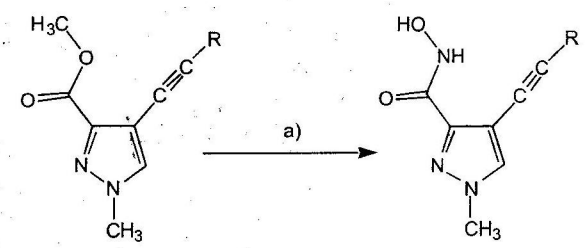
1. Introduction

Pyrazolopyridines, due to their analogy with purines have been the subject of many studies[1,2] particularly in what concerns their pharmacological properties, the five isomers, [3,4-*b*], [3,4-*c*], [4,3-*c*], [4,3-*b*] and [1,5-*a*], displaying high biological activity.[3] We have already published two papers[4,5] and one review[6] on these fused systems, for example, on the more common pyrazolo[3,4-*c*]pyridines[4–6] and on the less frequent pyrazolo[4,3-*c*]pyridines[5] (for a recent report on this last ring system see Ref. 3). In one of them[4] we reported that the heterocyclization of 4-acetylenylpyrazole-5-hydroxamic acids under influence of copper(I) salt in dimethylformamide or with organic bases in butanol or methanol leads to 5-substituted pyrazolo[3,4-*c*]pyridin-7-ones and 5-substituted 6-hydroxy-pyrazolo[3,4-*c*]pyridin-7-ones.

It is known that the electrophilicity of a triple bond and the nucleophilicity of a functional group depend on their position in the pyrazole ring. In fact, we showed earlier that the direction of cycloisomerization of *vic*-functionalized acetylenylpyrazoles depends on the mutual arrangement of acetylenic and the other functional group.[1,7] These facts prompted us to carry out a systematic investigation of the cyclization of *vic*-substituted hydroxamic acids of acetylenylpyrazoles. In the present article we report the study of cyclization of (4-acetylenylpyrazolyl-3)- and (3-acetylenyl-pyrazolyl-4)hydroxamic acids.

2. Results and discussion

Heating the methyl esters of 1-methyl-4-phenylethynyl- (**1a**) and 1-methyl-4-(phenoxymethyl-ethynyl)pyrazole-3 (**1b**) carboxylic acids with an excess of hydroxylamine in boiling methanol leads to the corresponding 4-acetylenic derivatives of pyrazole-3 hydroxamic acids **2a** (95%) and **2b** (87%) (see Scheme 1 and Section 3).



1a,b **2a,b**

R = C_6H_5 (**a**), $CH_2OC_6H_5$ (**b**)

Scheme 1. (a) NH_2OH/MeOH. R = C_6H_5 (**a**), $CH_2OC_6H_5$ (**b**).

Keywords: Pyrazolopyridines; Cross-coupling; Hydroxamic acids; Hetarylacetylenes; Heterocyclization.

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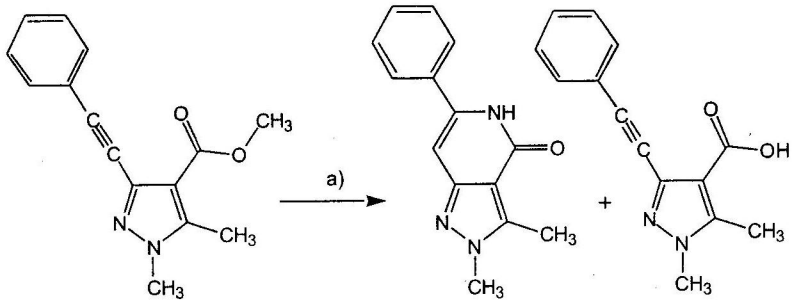
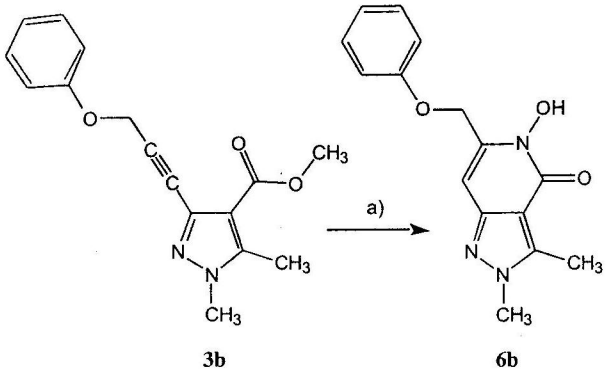


Scheme 2. (a) NH_2OH/MeOH, 12 h.

Isolation of the intermediate hydroxamic acid by interaction of the isomeric methyl esters of 1-methyl-4-(phenoxymethylethynyl)pyrazole-5 carboxylic acids with an excess of hydroxylamine in the same reaction conditions[4] was not possible and only the product of cyclization, namely the *N*-hydroxylactame was obtained. This fact confirms the necessity to study the reactivity of all the isomeric positions of acetylenylpyrazoles.

Another result was obtained in the attempt to prepare hydroxamic acids by interaction of the methyl esters of 1,5-dimethyl-3-phenylethynylpyrazole-4-carboxylic acid (**3a**)[5] with hydroxylamine in boiling methanol (Scheme 2). We observed the formation of the product of cyclization, that is, 6-phenylpyrazolo[4,3-*c*]pyridin-4-one (**4a**, 44%), as well as the product of hydrolysis of the starting ester, i.e. 1,5-dimethyl-3-phenylethynylpyrazole-4 carboxylic acid (**5**, 27%). Physical and spectral data of **5** are in agreement with literature ones.[8]

The phenoxymethylethynyl derivative **3b**[6] leads directly only to 5-hydroxy-2,3-dimethyl-6-phenoxymethyl-2,5-dihydropyrazolo[4,3-*c*]pyridin-4-one (**6b**, 50%, Scheme 3), without isolation of the hydroxamic acid intermediate.



Scheme 3. (a) NH_2OH/MeOH.

The different behavior of 4- and 3-acetylenylpyrazoles (isolation of hydroxamic acids **2a,b** and formation of pyrazolo[4,3-*c*]pyridines **4a**, **6b**) is related to the reduced electrophilicity of the ethynyl group in 4 position and the higher nucleophilicity of the 5 position of the pyrazole ring.

Isolation of the hydroxamic acids in the case of **2a** and **2b** allowed us to study the behavior of phenylethynyl (**2a**) and phenoxymethylethynyl (**2b**) derivatives both in neutral and basic conditions of heterocyclization (Scheme 4).

We have showed that heterocyclization of hydroxamic acids could be carried out in the presence of a weaker organic base (Et_3N instead of KOH, as in Schemes 2 and 3). Thus, the cycloisomerization of hydroxamic acids **2a** and **2b** occurs at reflux of **2a** and **2b** in presence of Et_3N in butanol and leads to the formation of the corresponding *N*-hydroxylactames **7a** (12 h) and **7b** (3 h) (76 and 54%) derived from the pyrazolo[3,4-*c*]pyridine skeleton.

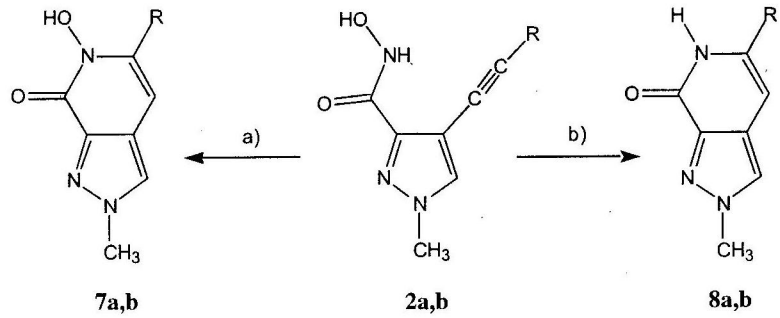
The reaction performed in neutral conditions using CuCl in boiling DMF, as well as in basic conditions, leads to the 6-membered aminolactames **8a** and **8b** (57 and 40%), the *N*-oxygen atom being unexpectedly lost in the final product.

We propose (see Scheme 5) that pyrazolo[3,4-*c*]pyridines **8a** and **8b** are formed via tautomeric equilibrium followed by thermal deoxygenation of tautomer **I**, by analogy to the loss of the oxygen atom that takes place for *N*-oxides of 2-imidazoline derivatives.[9] Thus, as follows from the above data, the cyclization of acetylenic derivatives of pyrazolylhydroxamic acids both in basic and neutral conditions leads to 4-substituted pyrazolo[4,3-*c*]pyridin-6-one and 5-substituted pyrazolo[3,4-*c*]pyridin-3-one.

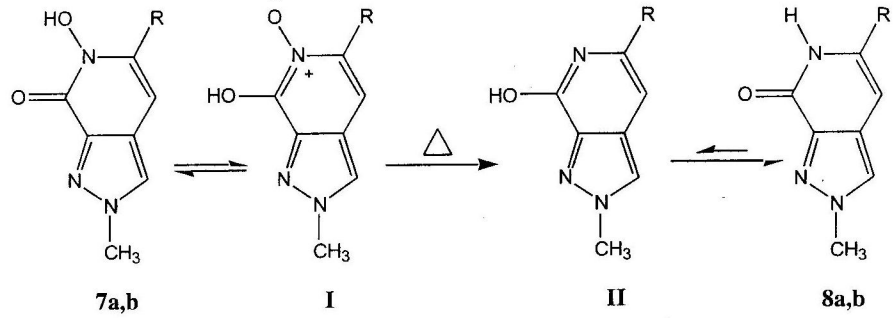
3. Experimental

3.1. General

Melting points were determined with a Kofler apparatus. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). The R_f values were measured on aluminium backed TLC plates of silica gel Silufol UV-254 with the indicated eluent. NMR spectra were recorded on a 'Bruker Avance 300' spectrometer at 25 °C. ^{1}H NMR chemical shifts (δ in ppm) were given from internal $CHCl_3$ (7.26) or DMSO-d_6 (2.5) standards. Coupling constants (J in Hz) were accurate to ± 0.2 Hz for ^{1}H. Mass spectra (HRMS) at 70 eV using electron impact mode were performed on a Finnigan SSQ-710. The IR-spectra were recorded in KBr pellets on a 'Bruker IFS 66' instrument. Sodium, hydroxylamine hydrochloride, Et_3N, CuCl



Scheme 4. (a) Et_3N/butanol; (b) CuCl/DMF/Argon. R=C_6H_5 (**a**), $CH_2OC_6H_5$ (**b**).



Scheme 5.

('Aldrich') were commercially available reactants. All the organic solvents were of analytical quality.

3.1.1. 1-Methyl-4-(phenylethynyl)pyrazolo-3-hydroxamic acid (2a). 1.21 g (53.0 mmol) of Na was added to 30 mL of absolute methanol and then 1.76 g (24.0 mmol) of hydroxylamine hydrochloride in 20 mL of absolute methanol were added. The sodium chloride precipitate was filtered off. To the prepared solution of free hydroxylamine was added 2.2 g (9.10 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid (**1**). The reaction mixture was refluxed 10 min (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH=5–6). Precipitate **2a** was filtered off and crystallized from water (2.10 g, 95%), mp 133–134 °C; ν/cm^{-1} (KBr): 2223 (C≡C), 3446 (NH), 1663 (C=O), 3368 (OH); δ^1H (DMSO-d_6) 2.15s (1H, OH); 3.93s (3H, NCH_3); 7.58s [1H, H(5)], 7.31–7.53 m (5H, ArH); 8.54s (1H, NH). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 64.72; H, 4.59; N, 17.42. Found: C, 64.79; H, 4.60; N, 17.36.

3.1.2. 1-Methyl-4-(phenoxymethylethynyl)pyrazolo-3-hydroxamic acid (2b). 1.40 g (61.0 mmol) of Na was added to 30 mL of absolute methanol and then 2.10 g (29.0 mmol) of hydroxylamine hydrochloride in 20 mL of absolute methanol were added. The sodium chloride precipitate was filtered off. To the prepared solution of free hydroxylamine was added 2.63 g (9.7 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid **1**. The reaction mixture was boiled 10 min (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH=5–6). Precipitate **2** was filtered off and crystallized from water (2.30 g, 87.5%), mp 99–100 °C; ν/cm^{-1} (KBr): 2244 (C≡C), 3399 (NH), 1657 (C=O), 3364 (OH); δ^1H (DMSO-d_6) 1.52s (1H, OH); 3.89s (3H, NCH_3); 4.94s (2H, CH_2); 7.53s [1H, H(5)], 6.95–7.36 m (5H, ArH); 9.18s (1H, NH). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.89; N, 15.49. Found: C, 62.13; H, 4.75; N, 15.25.

3.1.3. 2,3-Dimethyl-6-phenyl-2,5-dihydropyrazolo[4,3-*c*] pyridin-4-one (4a). 1.07 g (46.5 mmol) of Na was added to 20 mL of absolute methanol and then 1.56 g (22.6 mmol) of hydroxylamine hydrochloride in 20 mL of absolute methanol. The sodium chloride precipitate was filtered off. To prepared solution of free hydroxylamine was added 1.95 g (7.60 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid **3a**. The reaction mixture was boiled 12 h (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH=5–6). Precipitate **4a** was filtered off and crystallized from EtOH (0.68 g, 43.9%), mp 252–253 °C; ν/cm^{-1} (KBr): 1651 (C=O), 3432 (NH); δ^1H ($CDCl_3$) 2.64 [s, 3H, CH_3 (3)]; 3.87 (s, 3H, NCH_3); 6.29 [s, 1H, H(7)]; 7.36–7.54 (m, 5H, Ph); 8.3 (s, 1H, NH); MS (70 eV) *m/z*: 239 $[M]^+$ (100); 43 (8); 56 (14); 77 (10); 171 (7); 224 (9); 238 (51); 240 (17). M_w: found *m/z* 239.10801 $[M]^+$, $C_{14}H_{13}N_3O$; calcd: M= 239.10586.

3.1.4. 5-Hydroxy-2,3-dimethyl-6-phenoxymethyl-2,5-dihydropyrazolo[4,3-*c*]pyridin-4-one (6b). 1.22 g (53.0 mmol) of Na were added to 25 mL of absolute methanol and then 1.76 g (24.0 mmol) of hydroxylamine hydrochloride in 25 mL of absolute methanol. To a prepared

solution of free hydroxylamine was added 2.23 g (7.82 mmol) of the methyl ester of ethynylpyrazolecarboxylic acid (**3b**). The reaction mixture was refluxed 7 h (TLC control). Methanol was distilled off in vacuum, the residue was dissolved in water and acetic acid added (pH= 5–6). Precipitate **6b** was filtered off and crystallized from water (1.32 g, 59.2%), mp 200.5–202 °C; ν/cm^{-1} (KBr): 1665 (C=O), 3434 (OH); δ^1H (DMSO-d_6) 2.64 [s, 3H, CH_3 (3)]; 3.86 (s, 3H, NCH_3); 6.44 [s, 1H, H(7)]; 5.07 (s, 2H, CH_2); 6.98–7.35 (m, 5H, Ph); 2.1 (s, 1H, OH); MS (70 eV) *m/z*: 285 $[M]^+$ (28); 43 (17); 56 (31); 65 (13); 77 (13); 146 (15); 149 (51); 162 (61); 176 (61); 192 (100). $C_{15}H_{15}N_3O_3$, M_w: found *m/z* 285.11146 $[M]^+$; calcd: 285.11133. Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.29; N, 14.73. Found: C, 62.89; H, 5.21; N, 14.47.

3.1.5. 6-Hydroxy-2-methyl-5-phenyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (7a). 0.50 g (2.10 mmol) of the hydroxamic acid of acetylenylpyrazole **2a** and 5 mL of triethylamine in 10 mL butanol were refluxed 12 h (TLC control). The solvent was distilled off in vacuum, the product **7a** was recrystallized from ethanol. (0.38 g, 76%), mp 228–230 °C; ν_{max}/cm^{-1} (KBr) 3410 (OH), 1659 (C=O); δ^1H ($CDCl_3$) 2.0s (1H, OH); 4.18s (3H, N-CH_3); 6.47s (1H, 4-H); 7.3–7.5 m (5H, ArH); 7.65s [1H, H(3)]; $\delta^{13}C$ ($CDCl_3$) 40.32 (NCH_3); 94.01 [C(4)]; 116.09 [C(3′)]; 124.03–128.65 ($Ph^{o,m,p}$); 132.68 [C(7)]; 135.80 (Ph^i); 143.62 [C(7′)]; 147.77 [C(5)]; 175.47 (CO). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.44; H, 4.66; N, 17.35.

3.1.6. 6-Hydroxy-2-methyl-5-phenoxymethyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (7b). 0.5 g (1.90 mmol) of the hydroxamic acid of acetylenylpyrazole (**2b**) and 5 mL of triethylamine in 10 mL butanol were refluxed 3 h (TLC control). The solvent was distilled off in vacuum, the product **7b** was recrystallized. (0.27 g, 54%), mp 201–202 °C [EtOH/H_2O (5:3)]; ν_{max}/cm^{-1} (KBr) 3440 (OH), 1660 (C=O); δ^1H ($CDCl_3$) 2.7s (1H, OH); 4.08s (3H, NCH_3); 5.16s (2H, CH_2); 6.54s (1H, H(4)]; 6.9–7.2 m (5H, ArH); 7.56s [1H, H(3)]. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.80; N, 15.49. Found: C, 61.79; H, 4.75; N, 15.33.

3.1.7. 2-Methyl-5-phenyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (8a). 0.3 g (1.2 mmol) of hydroxamic acid **2a**, 0.13 g (1.30 mmol) CuCl in 4 mL of dimethylformamide were refluxed 3 h under an atmosphere of argon (TLC control). The reaction mixture was cooled and poured into chloroform and then was washed with aqueous ammonia. Chloroform solution was dried with Na_2SO_4 and filtered through alumina (3×1.5 cm^2), the solvent was evaporated under reduced pressure. The product **8a** was recrystallized from ethanol, yield 0.17 g, 57%, mp 313–315 °C (lit.: mp. 314–315 °C[10]).

3.1.8. 2-Methyl-5-phenoxymethyl-2,6-dihydropyrazolo[3,4-*c*]pyridin-7-one (8b). 1.0 g (3.70 mmol) of hydroxamic acid **2c**, 0.20 g (2.00 mmol) CuCl in 12 mL of dimethylformamide were refluxed 30 min in an atmosphere of argon (TLC control). The reaction mixture was cooled and poured into chloroform and then was washed with aqueous ammonia. Chloroform solution was dried with Na_2SO_4 and filtered through alumina (3×1.5 cm^2), the solvent was evaporated under reduced pressure. The product **8b** was recrystallized from ethanol, yield 0.35 g, 40%, mp 236.5–237.5 °C; ν/cm^{-1} (KBr): 3428 (NH), 1647 (C=O); δ^1H ($CDCl_3$) 3.91s (3H, NCH_3); 4.76s (2H, CH_2); 6.43s [1H, H(4)]; 6.9–7.4 m (5H, ArH); 7.49s [1H, H(3)]; 10.1s (1H, NH). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.86; H, 5.13; N, 16.46. Found: C, 66.13; H, 4.96; N, 16.47.

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