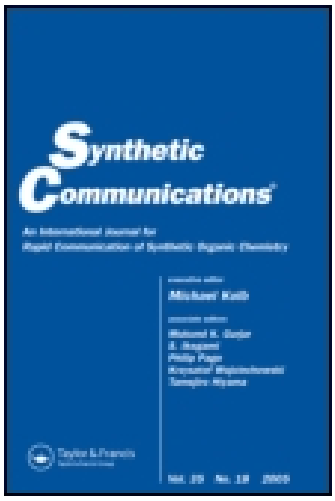

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Published online: 17 Aug 2006.

To cite this article: S. Fadel , Y. Hajbi , E. M. Rakib , M. Khouili , M. D. Pujol & G. Guillaumet (2004) Condensation of 2-Pyrone with 3-Aminopyrazolone. A Novel Synthesis of Pyrazolo[3,4-b]pyridines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:12, 2195-2204, DOI: 10.1081/SCC-120038500

To link to this article: http://dx.doi.org/10.1081/SCC-120038500

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 12, pp. 2195–2204, 2004

Condensation of 2-Pyrone with 3-Aminopyrazolone. A Novel Synthesis of Pyrazolo[3,4-*b*]pyridines

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ABSTRACT

A simple route to the preparation of new heterocyclic systems: pyrazolo [3,4-*b*]pyridines from the easily available 2-pyrone and 3-aminopyrazolone. The structure of the compounds and the mechanism of their formation are reported.

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DOI: 10.1081/SCC-120038500 0039-7911 (Print); 1532-2432 (Online)

Key Words: Decarboxylation; Esterification; *n*-Butanol; Pyrones; Pyrazolo[3,4-*b*]pyridines.

INTRODUCTION

Pyrazolo[3,4-*b*]pyridines are considered as very interesting compounds and have received considerable attention as result of their biological activity and structural relationship to indoles. A number of pyrazolo[3,4-*b*]pyridines are under intensive development by research groups throughout the world. Several compounds display interesting anxiolytic activity,[1,2] are potential biologically active compounds as new inhibitors of xantine oxidases,[3] or for treatment of erectile dysfunction.[4] Moreover, other pyrazolo[3,4-*b*] pyridines have proved to be active against Gram positive and Gram negative bacteria,[5] as cholesterol formation-inhibiting compounds,[6] or are promising for the treatment of cataracts associated with diabetis.[7]

RESULTS AND DISCUSSION

Pyrazolo[3,4-*b*]pyridines have been prepared generally by cyclization reactions starting from different heterocyclic reagent.[8–12] As a continuation of our work on the synthesis of pyridine analogs which have potential pharmacological properties; we investigated the condensation of 2-pyrone with 5-aminopyrazolone. The pyrone derivatives are versatile and increasingly used in a variety of organic syntheses, in particular in the synthesis of new types of heterocyclic compounds. The pyrones are electrophilic and highly reactive toward binucleophiles; their reactivity has been reported in the literature.[13–19] We have found that the reaction of 2-pyrone with 5-aminopyrazolone constitutes a facile method for the synthesis of several novel pyrazolo[3,4-*b*]pyridines. Thus, it has been found that condensation of 3-aminopyrazolone **1** with pyrone **2** in refluxing *n*-butanol affords the mixture of two isomeric pyrazolo[3,4-*b*]pyridines **3** and **4** (Sch. 1).

The products **3** and **4** were separated by silica gel chromatography and their structures were assigned by 2D NMR-experiments (HMQC and HMBC). The carbon at 157.0 ppm is assignable as the C-7a, and this carbon shows a cross-peak with the CH_2 at 3.62 ppm. Whereas the methyl group at 2.25 ppm gives a cross-peak to carbon signal at 158.9 ppm corresponding to C-7a. The absence of CH_2 signal due to the methylene protons of the pyrazole **1** in ^{1}H NMR spectrum of the compounds **3** and **4**, shows that cyclization is carried out on C-4 carbon of the pyrazole ring.

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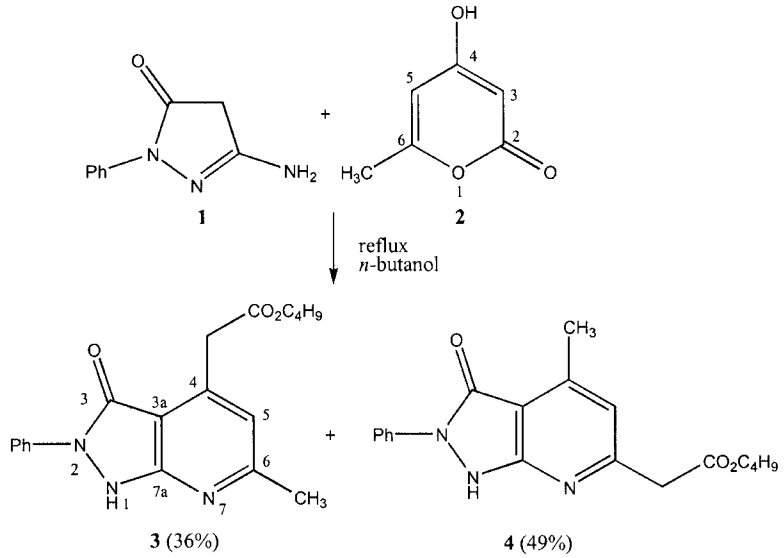


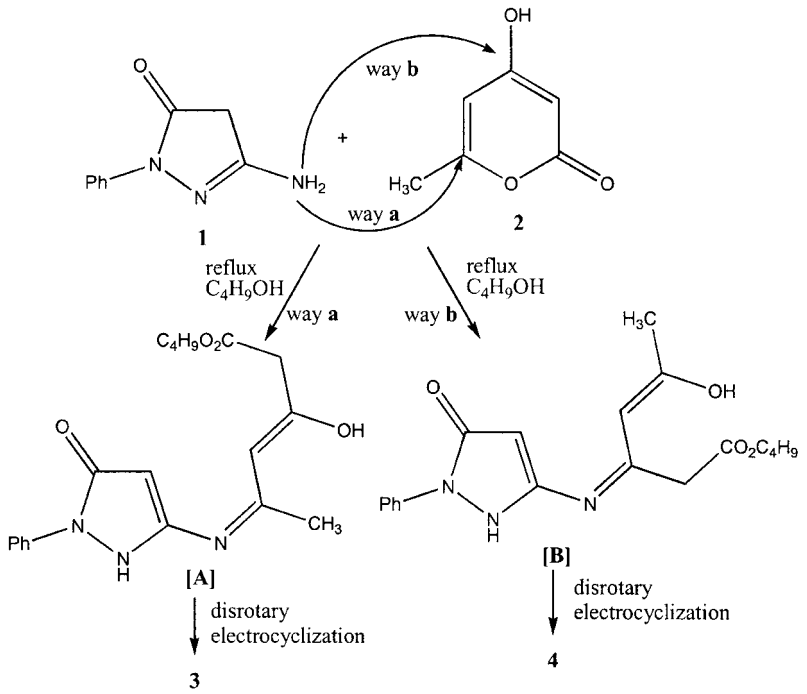
Scheme 1.

The synthesis of the compounds **3** and **4** can be explained by the following mechanism: initial competitive attack of the amino group on C-6 and C-4 of pyrone **2** followed by the opening of the pyranic cycle and formation of the intermediates **[A]** and **[B]**. Butanol (weak nucleophile) plays an important role in this mechanism. These intermediates thus formed undergo an disrotary electrocyclization 6eπ leading after aromatization of the pyridine cycle to the pyrazolo[3,4-*b*]pyridines **3** and **4** (Sch. 2).

In a classical experiment, 3-aminopyrazolone **1** reacted with pyrone **2** under reflux in *n*-butanol in the presence of catalytic amount of *p*-toluenesulfonic acid, giving two different compounds: pyrazolo[3,4-*b*]pyridines **3** and **5** (Sch. 3).

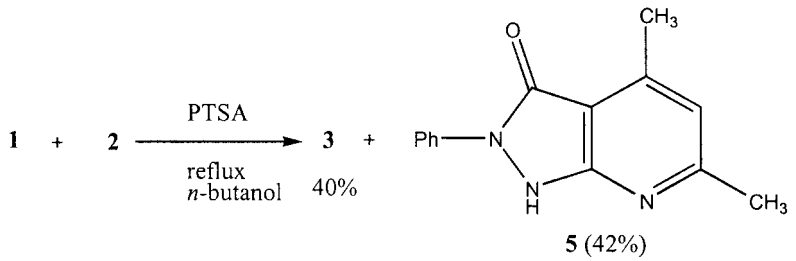
The ^{1}H NMR spectrum of the product **5** revealed two singlets at 2.24 and 2.72 ppm corresponding to the methyl groups, and the peak at 6.54 ppm assignable to CH group of pyridine ring.

The catalytic amount of PTSA is very important in this reaction; the initial attack of the amino group takes place on the C-6 of the pyrone **2** giving the intermediate **[A′]**. The compound obtained cyclizes in two different pathways: decarboxylation or esterification and then intramolecular electrocyclization affording compounds **3** and **5** (Sch. 4). In the presence of PTSA the attack was regioselectively at C-6 of the pyrone.



Scheme 2.

In order to investigate the scope of this reaction, we studied the condensation of the pyrone **2** with the 3-aminopyrazolone in acetic acid. Under these conditions, two products were isolated: product **5** identified in the reaction with backward flow of *n*-butanol with PTSA and the pyrazolo[3,4-*b*]pyridine **6**. The formation of **6** suggests the attack of the amino group at C-4 of the pyrone **2** (Sch. 5).



Scheme 3.

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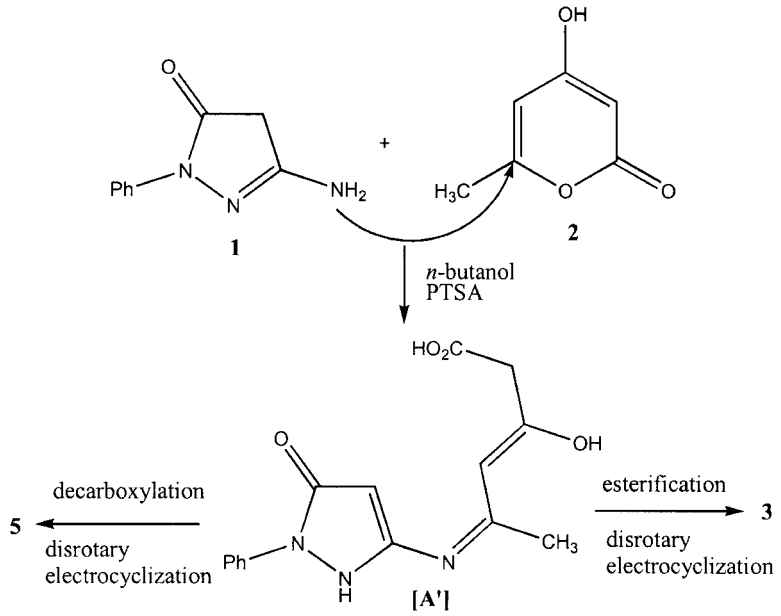
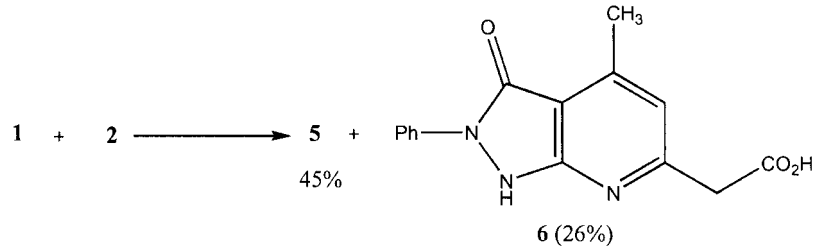


Scheme 4.

When the acetic acid is used as a solvent, the aminopyrazolone attacks directly the carbon on position 4 of pyrone. The intermediate **[B′]** evolves according to two ways leading after aromatization to the pyrazolopyridines **5** and **6** (Sch. 6).

In conclusion, we found that the condensation of pyrone with 3-amino-pyrazolone is dependent on the reaction conditions. Whereas in presence of *n*-butanol condensation is initiated at the C-6 and C-4 carbons of pyrone **2**, in *n*-butanol with PTSA the aminopyrazolone attacks directly the carbon at position 6 of pyrone, and in acetic acid, it is the C-4 position, which is attacked, in the first step.



Scheme 5.

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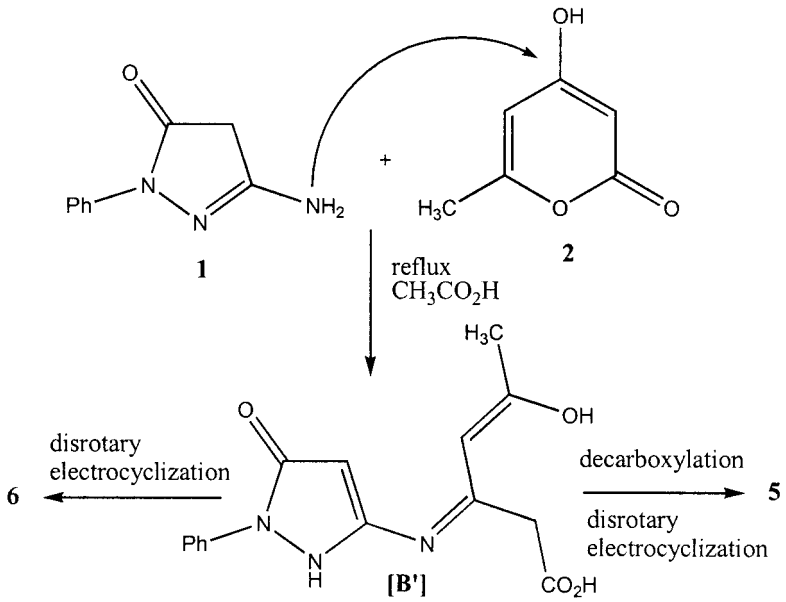

Scheme 6.

EXPERIMENTAL

General Instrumentation

Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 577 spectrometer using KBr disks, only noteworthy IR absorptions are listed (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 and 300 spectrometer and δ values are expressed in ppm; J values are given in Hz. HMQC and HMBC data were recorded at 400 Hz (Varian-Unity 400). Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra were recorded on a Varian MAT 112 spectrometer MS. Elemental analysis data were taken on a Perkin–Elmer 240C elemental analytical instrument. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). TLC was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm) and the spots located with UV light. All solvents were dried or purified by standard methods. All reagents were used as purchased from commercial sources.

Commercial chemicals: 3-aminopyrazolone **1** and 2-pyrone **2** were used without purification.

Synthesis of pyrazolo[3,4-*b*]pyridines 3 and 4. 4-Hydroxy-6-methyl-pyran-2-one (1.26 g, 10 mmol) was added to a solution of 3-aminopyrazolone (5 mmol) in 50 mL of *n*-butanol. The reaction mixture was refluxed for 48 hr. After evaporation of solvent, the residue was then purified over silica gel column chromatography using a 60 : 40 mixture of hexane and ethyl acetate as eluent.

2-(6-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl) acetic acid butylester (3). Yield 36%, orange solid. M.p. 129–131°C; IR: 1620, 1730 (CO), 3010 (NH); ^{1}H NMR ($CDCl_3$): δ 0.89 (t, $J = 7.4$ Hz, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 2.74 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.06 (t, $J = 6.6$ Hz, 2H, CH_2O), 6.86 (s, 1H, H-5), 7.26 (m, 1H, CH), 7.45 (m, 2H, CH), 7.86 (dd, $J = 0.8$, 8.4 Hz, 2H, CH), 14.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 17.3 (CH_3), 19.0 (CH_2), 30.4 (CH_2), 42.9 (CH_2), 65.2 (CH_2O), 109.5 (C-4), 119.5 (CH-5), 119.7, 125.3, 129.0 (5CH), 137.1 (C-1′), 150.8 (C-6), 156.7 (C-3a), 157.0 (C-7a), 159.6 (CON), 169.4 (CO); MS (EI): m/z 339 (M^+). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.34; H, 6.20; N, 12.44.

2-(4-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl) acetic acid butylester (4). Yield 49%, orange solid. M.p. 114–116°C; IR: 1670, 1740 (CO), 2960 (NH); ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, $J = 7.2$ Hz, CH_3), 1.36 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.15 (t, $J = 6.6$ Hz, 2H, CH_2O), 6.74 (s, 1H, H-5), 7.24 (m, 1H, CH), 7.42 (m, 2H, CH), 7.88 (dd, $J = 0.8$, 8.2 Hz, 2H, CH), 14.02 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 19.1 (CH_2), 23.1 (CH_3), 30.5 (CH_2), 35.5 (CH_2), 65.3 (CH_2O), 108.3 (C-4), 117.9 (CH-5), 120.0 (2CH), 125.4 (CH), 129.0 (2CH), 137.5 (C-1′), 146.4 (C-6), 155.2 (C-3a), 158.9 (C-7a), 159.7 (CON), 169.8 (CO); MS (EI): m/z 339 (M^+). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.18; H, 6.28; N, 12.40.

Synthesis of pyrazolo[3,4-*b*]pyridines 3 and 5. To a solution of 4-hydroxy-6-methylpyran-2-one (1.26 g, 10 mmol) and 3-aminopyrazolone **2** (5 mmol) in 40 mL of *n*-butanol was added *p*-toluenesulfonic acid (0.5 mg). The reaction mixture was refluxed for 48 hr. After evaporation of solvent, the residue was then purified over silica gel column chromatography using a 60 : 40 mixture of hexane and ethyl acetate as eluent. Under these conditions the compound **3** was obtained in 40% yield.

4,6-Dimethyl-2-phenyl-1,2-dihydro-pyrazolo[3,4-*b*]pyridin-3-one (5). Yield 42%, orange solid. M.p. 199–201°C; IR: 1660 (CO), 3040 (NH); ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 6.54 (s, 1H, H-5), 7.20 (m, 1H, CH), 7.42 (m, 2H, CH), 7.94 (dd, $J = 1.6$, 7.8 Hz, 2H, CH), 13.81 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.6 (CH_3), 20.9 (CH_3),

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108.6 (C-4), 111.8 (CH-5), 118.5 (2CH), 123.8 (1CH), 128.6 (2CH), 139.3 (C-1′), 150.1 (C-6), 153.5 (C-3a), 155.0 (C-7a), 159.1 (CON); MS (EI): m/z 239 (M^+). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.36; H, 5.44; N, 17.50.

Synthesis of pyrazolo[3,4-*b*]pyridine 5 and 6. A mixture of 4-hydroxy-6-methylpyran-2-one (126 g, 10 mmol) and 3-aminopyrazolone (5 mmol) in acetic acid (40 mL) was heated under reflux for 30 hr. After evaporation of the solvent, the residue was then purified over silica gel column chromatography using a 30 : 70 mixture of hexane and ethyl acetate as eluent.

Under these conditions the compound **5** was obtained in 45% yield.

2-(4-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl) acetic acid (6). Yield 26%, white solid. M.p. 175–177°C; IR: 1690 (CO), 3040 (NH); ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 7.17 (m, 1H, CH), 7.33 (s, 1H, H-5), 7.37 (m, 2H, CH), 7.80 (dd, $J = 1.4$, 7.6 Hz, 2H, CH), 9.38 (s, 1H, OH), 13.90 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 25.0 (CH_3), 42.5 (CH_2), 111.6 (C-4), 120.0 (2CH), 122.6 (CH-5), 126.2 (1CH), 130.8 (2CH), 141.3 (C-1′), 151.6 (C-6), 155.2 (C-3a), 157.1 (C-7a), 160.1 (CON), 178.2 (CO); MS (EI): m/z 283 (M^+). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.66; H, 4.61; N, 14.79.

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Received in Poland December 9, 2003

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