ORGANIC LETTERS

2002
Vol. 4, No. 3
423−425

One-Step Synthesis of Substituted 6-Amino-5-cyanospiro-4-(piperidine-4′)-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyrans

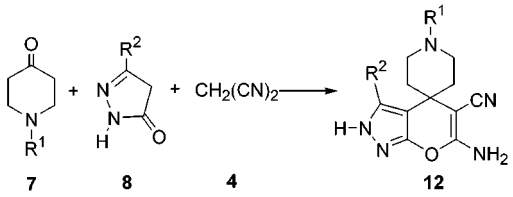
Anatoliy M. Shestopalov,[†,‡] Yuliya M. Emeliyanova,[†] Aleksandr A. Shestopalov,[†] Lyudmila A. Rodinovskaya,[†,‡] Zukhra I. Niazimbetova,[‡] and Dennis H. Evans*[,‡]

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russia, and Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

dhevans@udel.edu

Received November 26, 2001

ABSTRACT



Three-component condensation of 4-piperidinones (7), 5-pyrazolones (8), and malononitrile (4) proceeds chemically and electrochemically and is a convenient one-step means of synthesis of substituted 6-amino-5-cyanospiro-4-(piperidine-4′)-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyrans (12). The electrochemical reactions proceed under milder conditions and with yields 12–15% greater than those of the reactions catalyzed by chemical bases.

Substituted 6-amino-4*H*-pyrazolo[3,4-*b*]pyrans have been synthesized with the aim of identifying new physiologically active compounds.[1−4] The first representative of this class of compounds was obtained by the reaction of 3-methyl-1-phenylpyrazolin-5-one with tetracyanoethylene.[1] Various 6-amino-5-cyano-4-aryl-4*H*-pyrazolo[3,4-*b*]pyrans (**6**) were synthesized by reaction of arylidenemalononitriles (**1**) with 3-methylpyrazolin-5-ones (**2**), or by condensation of 4-arylidenepyrazolin-5-ones (**3**), with malononitrile (**4**).[2−4]

A simpler approach toward the synthesis of **6** was developed by Sharanin and co-workers which consisted of a three-component condensation of aromatic aldehyde (**5**), malononitrile (**4**), and substituted pyrazolin-5-ones (**2**) in ethanol using triethylamine as a catalyst[4] (Scheme 1).

In this Letter we describe a three-component condensation in which substituted piperidin-4-ones have been used in place of aromatic aldehydes to synthesize a new spiro heterocyclic system. We report that the base-catalyzed reaction of substituted piperidin-4-ones (**7**), pyrazol-5-ones (**8**), and malononitrile (**4**) proceeds in ethanol at 20 °C with the formation of substituted 6-amino-5-cyanospiro-4-(piperidine-4′)-2*H*,4*H*-dihydropyrazolopyrans, **12** (method A, experimental procedure footnote[8]).

This process is autocatalytic when the nitrogen atom of the piperidinone has an alkyl substituent causing the basicity of the piperidin-4-one to be high enough so that this reactant catalyzes the reaction (preparation of **12a**,**b**). However, a base catalyst, for instance Et_3N, is necessary for the reaction when the substituents are $C(O)CH_3$ or $COOC_2H_5$ instead of alkyl (preparation of **12c**−**e**, Table 1).

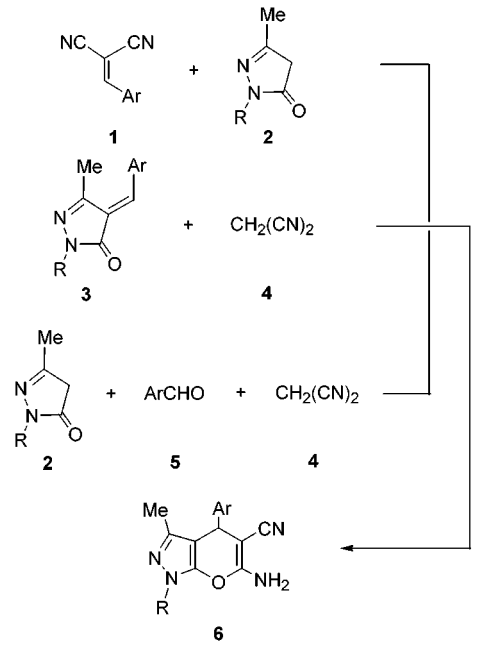
In earlier work it was found to be possible to replace chemical bases with an electrogenerated base (EGB) to promote base-catalyzed reactions.[5] In many instances, an

[†] Russian Academy of Sciences.
[‡] University of Delaware.

(1) Junek, H.; Aigner, H. *Chem. Ber.* **1973**, *106*, 914−921.
(2) Tacconi, G.; Gatti, G.; Desimoni, G. *J. Prakt. Chem.* **1980**, *322*, 831−834.
(3) Sharanina, L. G.; Marshtupa, V. P.; Sharanin, Yu. A. *Khim. Geterosikl. Soedin.* **1980**, *10*, 1420.
(4) Sharanin, Yu. A.; Sharanina, L. G., Puzanova, V. V. *Zh. Org. Khim.* **1983**, *19*, 2609−2615.

10.1021/ol0102747 CCC: $22.00 © 2002 American Chemical Society
Published on Web 01/12/2002

Scheme 1



Ar = C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 2-FC_6H_4
R = H, C_6H_5

electrogenerated base resulted in higher yields and differing stereoselectivities compared to catalysis by chemical bases. Many of these reactions were promoted by the EGB, superoxide, formed by cathodic reduction of oxygen from air dissolved in the electrolysis solution. However, in the present case it was found that the presence of oxygen was deleterious to the reaction so the electrolyses were conducted with nitrogen purging of the solution. Under these conditions (method B, experimental procedure footnote[8]), it was found that the three-component condensation was quite successful in the preparation of **12** (Table 1). We presume that the EGB in the present case is the anion of malonitrile, formed along with dihydrogen by the reduction of malonitrile at the platinum cathode.[6] As the reaction is catalytic, the currents used were rather small and the total charge passed was correspondingly small, only 0.03−0.05 Faradays per mole of the starting materials. The total reaction time (2−3 h) was much shorter than that required for the chemical method. It should be noted that the electrochemical process is more

(5) (a) Niyazymbetov, M. E.; Evans, D. H. *J. Org. Chem.* **1993**, *58*, 779−783. (b) Laikhter, A. L.; Niyazymbetov, M. E.; Evans, D. H.; Samet, A. V.; Semenov, V. V. *Tetrahedron Lett.* **1993**, *34*, 4465−4468. (c) Niyazymbetov, M. E.; Laikhter, A. L.; Semenov, V. V.; Evans, D. H. *Tetrahedron Lett.* **1994**, *35*, 3037−3040. (d) Niyazymbetov, M. E.; Evans, D. H. *Denki Kagaku* **1994**, *62*, 1139−1143. (e) Samet, A. V.; Niyazymbetov, M. E.; Semenov, V. V.; Laikhter, A. L.; Evans, D. H. *J. Org. Chem.* **1996**, *61*, 8786−8791. (f) Suba, C.; Niyazymbetov, M. E.; Evans, D. H. *Electrochim. Acta* **1997**, *42*, 2247−2255. (g) Niazimbetova, Z.; Treimer, S. E.; Evans, D. H.; Guzei, I.; Rheingold, A. L. *J. Electrochem. Soc.* **1998**, *145*, 2768−2774. (h) Niazimbetova, Z. I.; Evans, D. H.; Guzei, I. A.; Incarvito, C. D.; Rheingold, A. L. *J. Electrochem. Soc.* **1999**, *146*, 1492−1495. (i) Shestopalov, A. M.; Niazimbetova, Z. I.; Evans, D. H.; Niyazymbetov, M. E. *Heterocycles* **1999**, *51*, 1101−1107.

(6) Treimer, S. E.; Evans, D. H. *J. Electroanal. Chem.* **1998**, *455*, 19−28.

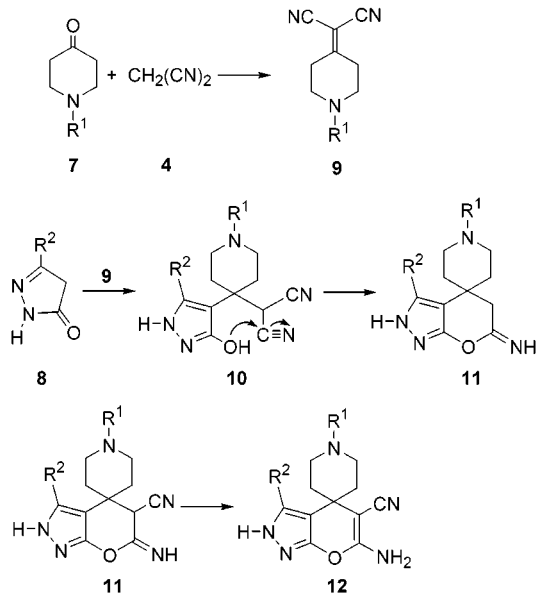
Table 1. Method and Yields of Substituted Pyrazolo[3,4-*b*]pyrans **12a**−**e**

	yield, %		electrolysis conditions	
sample	method A	method B	current, mA	charge, C
12a	82			
12b	84			
12c	78	90	3.8	38
12d	65	79	6.2	43
12e	64	79	4.8	39

regioselective; the products of the reaction are analytically pure and do not require recrystallization. The yield of final products **12** obtained electrochemically is ca. 12−15% higher than that in the chemical method for the three cases investigated (Table 1). No attempt was made to optimize the electrolysis conditions; those reported in Table 1 are based on past experience and monitoring of the progress of the reaction by thin layer chromatography.

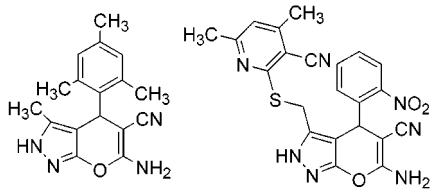
A similar high regioselectivity was observed earlier in the electrochemical synthesis of 2-amino-4-aryl-3-cyano-6-methyl-5-ethoxycarbonyl-4*H*-pyrans.[5i] Probably this regioselectivity resulted from adherence to a specific reaction sequence. Electrogeneration of the anion of malononitrile leads to the initial formation of unsaturated nitrile **9**, which in turn reacts with the pyrazolin-5-one to give Michael adduct **10**. Subsequent intramolecular cyclization and tautomeric transformation of intermediate **11** leads to the formation of the desired product **12** (Scheme 2).

Scheme 2

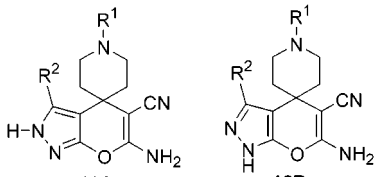


12a $R^1 = R^2 = CH_3$
12b $R^1 = CH_3$; $R^2 = CH_3OCH_2$
12c $R^1 = CH_3CO$; $R^2 = CH_3OCH_2$
12d $R^1 = CH_3CO$; $R^2 = CH_3CH_2CH_2$
12e $R^1 = COOCH_2CH_3$; $R^2 = CH_3OCH_2$

The structures of the compounds that were prepared were confirmed by IR and NMR and by comparison with the known structures of 6-amino-4-aryl-3-alkyl-5-cyano-2*H*,4*H*-pyrazolo[3,4-*b*]pyrans **13** and **14** that have been determined by IR and NMR data and by X-ray crystallography.[7] On the basis of these data, we propose that the compounds **12** exist in the tautomeric form **12A** as opposed to **12B**.



13 **14**



12A **12B**

OL0102747

(7) Tsyganov, D. V.; Yakybov, A. P.; Krayushkin, M. M.; Shestopalov, A. M.; Nesterov, V. N. 7th Blue Danube Symposium on Heterocyclic Chemistry, June 7−10, 1998, p 145.

(8) **Typical Experimental Procedures. Method A (chemical base):** A mixture of 10 mmol of the corresponding 4-piperidineone (**7**), 10 mmol of malononitrile, 10 mmol of the pyrazoline (**8**), and 0.5 mL of Et_3N (no Et_3N in the cases with 1-methyl-4-piperidinone) was stirred in 25 mL of absolute ethanol at ca. 20 °C for 12 h. The precipitate was filtered off, washed with ethanol and hexane, and then recrystallized from acetonitrile to give **12**. **Method B (electrogenerated base):** The procedure was very similar to that reported in ref 5i. The cell for the electrolysis was an 80-mL glass beaker with a polyethylene cover into which was fitted the anode compartment which was surrounded by a cylindrically shaped platinum gauze cathode (ca. 20 cm^2). The anode compartment was a polyethylene tube about 2 cm in diameter into which the magnesium anode (6-mm diameter rod) was fitted through a pierced septum. About 30 holes (5 mm) were drilled through the side of the tube that was wrapped with three layers of tracing paper to serve as separator between the anode and cathode compartments. The catholyte was 40 mL of 0.10 M Bu_4NBr in acetonitrile containing 0.01 mol each of **4**, **7**, and **8**. The anode compartment held about 20 mL of electrolyte. The electrolyses were carried out under controlled current conditions (Table 1) in vigorously stirred solutions. The solutions were purged with dry nitrogen to remove dissolved oxygen. After passing the specified amount of charge (Table 1), the solvent was removed from the catholyte with a rotary evaporator. The residue was taken up in ethanol (ca. 20 mL), and the product was precipitated by addition of 5−10 mL of water. The precipitate was filtered off and washed with water, ethanol, and hexanes to give pure powders of **12a**−**e**. No purification was required. **Spectral Characteristics and Properties of 12a**−**e.** ^{1}H NMR spectra were obtained with Bruker AM 300 (Moscow) and Bruker AM 250 (Delaware) spectrometers. **6-Amino-5-cyano-3,1′-dimethylspiro-4-(piperidine-4′)-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyran (12a):** mp 153−155 °C. IR, ν/cm^{-1} (KBr): 1658 (δNH_2, NH); 2193 (C≡N); 3075, 3243, 3395 (NH_2). ^{1}H NMR, δ (DMSO-d_6): 11.97 (s, 1H, NH); 6.49 (s, 2H, NH_2); 2.81 (m, 2H, $C^{2'}H_2$); 2.62 (m, 2H, $C^{6'}H_2$); 2.26 (s, 6H, $(CH_3)_2$); 2.10 (m, 2H, $C^{3'}H_2$); 1.77 (m, 2H, $C^{5'}H_2$). Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 59.83; H, 6.27; N, 26.54. **6-Amino-5-cyano-3-methoxymethylspiro-4-(1′-methylpiperidine-4′)-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyran (12b):** mp 155−157 °C. IR, ν/cm^{-1} (KBr): 1658 (δNH_2, NH); 2190 (C≡N); 3124, 3240, 3386 (NH_2). ^{1}H NMR, δ (DMSO-d_6): 12.36 (s, 1H, NH); 6.44 (s, 2H, NH_2); 4.47 (s, 2H, CH_2); 3.35 (s, 3H, CH_3); 2.83 (m, 2H, $C^{2'}H_2$); 2.62 (m, 2H, $C^{6'}H_2$); 2.30 (s, 3H, CH_3); 2.11 (m, 2H, $C^{3'}H_2$); 1.78 (m, 2H, $C^{5'}H_2$). $C_{14}H_{19}N_5O_2$. Anal. Calcd: C, 58.12; H, 6.81; N, 24.20. Found: C, 57.86; H, 6.52; N, 23.72. **6-Aminospiro-4-(1′-acetylpiperidine-4′)-5-cyano-3-methoxymethyl-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyran (12c):** mp 176−177 °C. IR, ν/cm^{-1} (KBr): 1642 (δNH_2, NH); 1672 (C═O); 2196 (C≡N); 3200, 3317, 3392 (NH_2). ^{1}H NMR, δ (DMSO-d_6): 12.56 (s, 1H, NH); 6.87 (s, 2H, NH_2); 4.36 (s, 2H, CH_2); 4.22 (m, 1H, $C^{2'}H_a$); 3.86 (m, 1H, $C^{2'}H_e$); 3.73 (m, 1H, $C^{6'}H_a$); 3.42 (m, 1H, $C^{6'}H_e$); 3.18 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 1.80−2.04 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$). $C_{15}H_{19}N_5O_3$. Anal. Calcd: C, 56.77; H, 6.03; N, 22.07. Found: C, 56.42; H, 5.74; N, 21.68. **6-Amino-spiro-4-(1′-acetylpiperidine-4′)-5-cyano-3-propyl-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyran (12d):** mp 199−200 °C. IR, ν/cm^{-1} (KBr): 1638 (δNH_2, NH); 1668 (C═O); 2192 (C≡N); 3196, 3312, 3385 (NH_2). ^{1}H NMR, δ (DMSO-d_6): 12.15 (s, 1H, NH); 6.81 (s, 2H, NH_2); 4.21 (m, 1H, $C^{2'}H_a$); 3.73 (m, 2H, $C^{2'}H_e$, $C^{6'}H_a$); 3.39 (m, 1H, $C^{6'}H_e$); 2.02 (s, 3H, CH_3); 1.97 (t, 2H, CH_2); 1.87 (m, 2H, CH_2); 1.80−1.82 (m, 4H, $C^{3'}H_2$, $C^{5'}H_2$); 0.88 (t, 3H, CH_3, J^3 = 7.04 Hz). $C_{16}H_{21}N_5O_2$. Calcd: C, 60.94; H, 6.71; N, 22.20. Found: C, 60.65; H, 6.43; N, 21.84. **6-Amino-5-cyano-3-methoxymethylspiro-4-(1′-ethoxycarbonylpiperidine-4′)-2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyran (12e):** mp 157−160 °C. IR, ν/cm^{-1} (KBr): 1640 (δNH_2, NH); 1684 (C═O); 2197 (C≡N); 3204, 3316, 3390 (NH_2). ^{1}H NMR, δ (DMSO-d_6): 12.40 (s, 1H, NH); 6.62 (s, 2H, NH_2); 4.38 (s, 2H, CH_2); 4.08 (q, 2H, CH_2, J^3=7.02 Hz); 3.88 (m, 2H, $C^{2'}H_2$); 3.62 (m, 2H, $C^{6'}H_2$); 3.28 (s, 3H, CH_3); 2.07 (m, 2H, $C^{3'}H_2$); 1.74 (m, 2H, $C^{5'}H_2$); 1.24 (t, 3H, CH_3, J^3 = 7.02 Hz). $C_{16}H_{21}N_5O_4$. Calcd: C, 55.32; H, 6.09; N, 20.16. Found: C, 55.07; H, 5.82; N, 19.68.