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New Synthesis of Ethyl 6-Amino-4-aryl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates

V. L. Gein, T. M. Zamaraeva, and I. V. Kozulina

Perm State Pharmaceutical Academy, Polevaya ul. 2, Perm, 614000 Russia
e-mail: geinvl48@mail.ru

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Abstract—Ethyl 6-amino-4-aryl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazol-3-carboxylates were synthesized by a reaction of diethyloxalacetate sodium salt with aromatic aldehyde, hydrazine hydrate, and malononitrile in the presence of acetic acid.

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One of the most promising methods of heterocycles synthesis in organic chemistry is multicomponent reactions [1].

A four-component reaction between aromatic aldehydes, malononitrile, acetylenedicarboxylate, and hydrazine hydrate was described as a convenient preparative method for the synthesis of 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates [2]. 2-Amino-4*H*-pyrans and fused heterocycles on their basis attract the interest as a heterocyclic class of organic substances exhibiting a fairly wide range of biologic action [3–5].

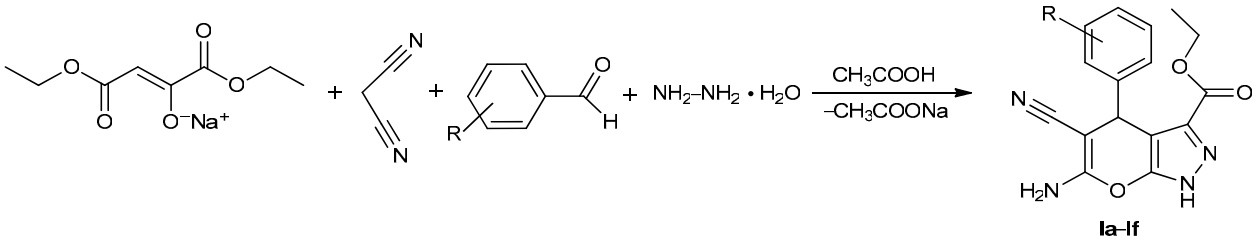
Aiming at the preparation of new fused pyranes we examined the reaction of diethyloxalacetate sodium salt with malononitrile, aromatic aldehyde, and hydrazine hydrate. The reaction proceeds at short boiling of the mixture in ethanol affording ethyl 6-amino-4-aryl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates **Ia–If** (Scheme 1).

Compounds **Ia–If** are colorless crystalline substances soluble in DMF, DMSO, chloroform, ethanol, insoluble in water. IR spectra of compounds **Ia–If** contain the absorption bands of stretching vibrations in the groups COOEt (1720 cm^{-1}), CN (2248–2288 cm^{-1}), NH (3216–3288 cm^{-1}), NH_2 (3320–3550 cm^{-1}), and C=C (1604–1628 cm^{-1}).

The characteristic signals in the ^1H NMR spectra of compounds **Ia–If** alongside the signals of aromatic protons and the groups attached to the aromatic ring are the resonances of the ester group (1.14 and 4.15 ppm), a singlet of the proton H^4 (4.67 ppm), singlets of protons of groups NH_2 (6.80 ppm) and NH (13.45 ppm).

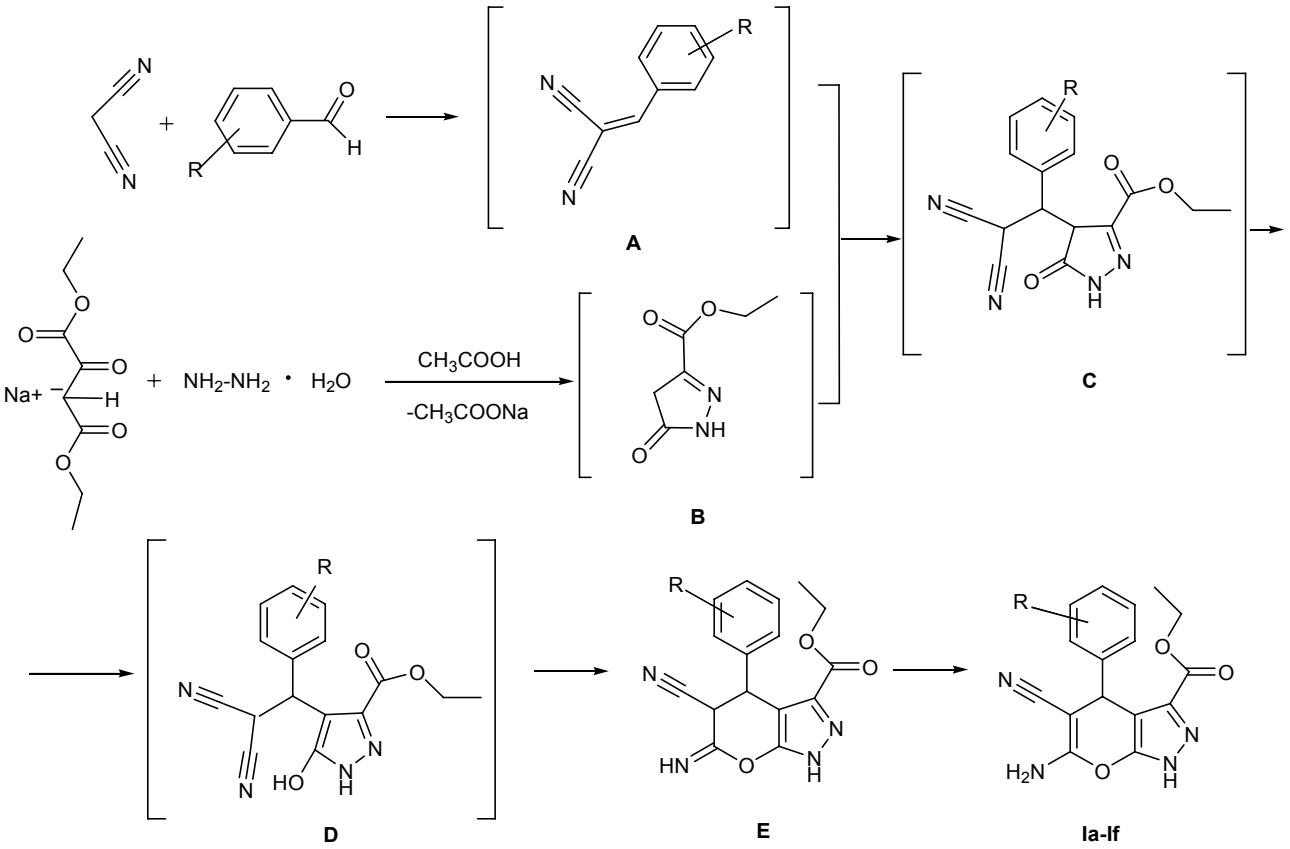
The ^{13}C NMR spectrum of compound **Ib** contains chemical shifts of carbon atoms from the ester group (160.17 ppm), CH_3O (55.00 ppm), CH (38.98 ppm) groups, and also the signals of aromatic carbons (111.4–159.11 ppm).

Scheme 1.



R = H (**a**), 3-MeO (**b**), 4-Cl (**c**), 3-NO_2 (**d**), 3-F (**e**), 4-Pr-*i* (**f**).

Scheme 2.



In the mass spectrum of compound **Ia** the peak of the ion $[M]^+$ (*m/z* 310) is observed and also peaks of fragment ions $[M - C_2H_5OCO - C_6H_5]^+$ (*m/z* 160), $[Ph]^+$ (*m/z* 77) confirming the assumed structure.

Apparently in the first stage two parallel reactions proceed of malononitrile with the aromatic aldehyde and of the diethyloxalacetate sodium salt with hydrazine hydrate in the presence of acetic acid leading to the formation of intermediate arylidenemalonodinitrile **A** and pyrazolone **B** respectively. In the second stage the intermediates **A** and **B** react with each other to provide intermediate **C** whose isomerization into compound **D** followed by a cyclization through a 6-imino derivative **E** gives finally compounds **Ia–If** (Scheme 2).

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 from mulls in mineral oil. ^{1}H NMR spectra were registered on a spectrometer Bruker 500 (operating frequency 500.13 MHz) in DMSO-d_6, internal reference TMS. ^{13}C NMR spectra were taken in DMSO-d_6 on a spectrometer Bruker-300 (operating frequency 75 MHz). The assignment of carbon atoms in CH, CH_2, CH_3 groups and quaternary carbon atoms was carried out applying Dept experiment. Mass spectrum was obtained on a Finnigan MAT INCOS-50 instrument (ionizing electrons energy 70 eV). Elemental analysis was performed on a Perkin Elmer 2400 analyzer. Melting points were measured on a M-565 instrument.

Ethyl 6-amino-4-phenyl-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (Ia). A mixture of 0.66 g (0.01 mol) of malononitrile, 1 mL (0.01 mol) of benzaldehyde in ethanol was boiled for 1 h, then a mixture was added of 2.10 g (0.01 mol) of diethyloxalacetate sodium salt with 0.5 mL (0.01 mol) of hydrazine hydrate in the presence of 2 mL of acetic acid. The reaction mixture was boiled for 0.5 h, and on cooling the precipitate was filtered off and recrystallized from ethanol. Yield 2.51 g (81%), mp 217–219°C (EtOH). IR spectrum, ν, cm^{-1}: 3320–3472 (NH_2), 3240 (NH), 2288 (CN), 1720 (COOEt), 1616 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H,

3-CH$_3$CH$_2$O, *J* 7.12 Hz), 4.08 q (2H, 3-CH$_3$CH$_2$O, *J* 7.12 Hz), 4.67 s (1H, H^4), 6.90 br.s (2H, 6-NH$_2$) 7.06–7.25 m (5H, C$_6$H$_5$), 13.75 s (1H, N^{1}H). Found, %: C 61.84, 62.05; H 4.46, 4.63; N 17.95, 18.16. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.93; H 4.55; N 18.05.

Compounds **Ib–If** were prepared similarly.

Ethyl 6-amino-4-(3-methoxyphenyl)-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (Ib). Yield 2.41 g (71%), mp 205–207°C (EtOH). IR spectrum, ν, cm^{-1}: 3360–3472 (NH$_2$), 3216 (NH), 2288 (CN), 1720 (COOEt), 1628 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.07 t (3H, 3-CH$_3$CH$_2$O, *J* 6.9 Hz), 3.71 s (3H, 3-CH$_3$O), 4.11 q (2H, 3-CH$_3$CH$_2$O, *J* 6.9 Hz), 4.75 s (1H, H^4), 6.65 d (1H, H^6$_{aryl}$, *J* 6.9 Hz), 6.66 s (1H, H^2$_{aryl}$, *J* 6.9 Hz), 6.76 d.d (1H, H^5$_{aryl}$, J 6.9, 2.1 Hz), 7.05 br.s (2H, 6-NH$_2$), 7.21 d (1H, H^4$_{aryl}$, *J* 7.8 Hz), 13.77 c (1H, N^{1}H). ^{13}C NMR spectrum, δ, ppm: 13.80 (3-CH$_3$), 38.98 (4-CH), 55.00 (CH$_3$O), 57.81 (C–C≡N), 60.90 (CH$_2$), 103.55 (C$_{Ar}$), 111.47, 113.68, 119.52 (3C$_{Ar}$), 120.33, 129.11 (2C$_{Ar}$), 129.45 (C$_{Ar}$), 146.55, 155.66, 158.24, 159.11 (4C$_{Ar}$) 160.17 (CO). Found, %: C 59.89, 60.13; H 4.67, 4.83; N 16.34, 16.57. $C_{17}H_{16}N_4O_4$. Calculated, %: C 60.00; H 4.74; N 16.46.

Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (Ic). Yield 2.90 g (84%), mp 224–226°C (EtOH). IR spectrum, ν, cm^{-1}: 3368–3488 (NH$_2$), 3288 (NH), 2248 (CN), 1720 (COOEt), 1608 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, 3-CH$_3$CH$_2$O, *J* 7.4 Hz), 4.16 q (2H, 3-CH$_3$CH$_2$O, *J* 7.4 Hz), 4.70 s (1H, H^4), 6.89 br.s (2H, 6-NH$_2$), 7.07–8.56 m (4H, ClC$_6$H$_4$), 13.51 s (1H, N^{1}H). Found, %: C 55.64, 55.87; H 3.71, 3.90; N 16.16, 16.36. $C_{16}H_{13}ClN_4O_3$. Calculated, %: C 55.74; H 3.80; N 16.25.

Ethyl 6-amino-4-(3-nitrophenyl)-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (Id). Yield 3.16 g (89%), mp 221–223°C (EtOH). IR spectrum, ν, cm^{-1}: 3376–3456 (NH$_2$), 3168 (NH), 2288 (CN), 1720 (COOEt), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, 3-CH$_3$CH$_2$O, *J* 7.4 Hz), 4.09 q (2H, 3-CH$_3$CH$_2$O, *J* 7.4 Hz), 4.92 s (1H, H^4), 7.01 br.s (2H, 6-NH$_2$), 7.48–8.79 m (4H, NO$_2$C$_6$H$_4$), 13.59 s (1H, N^{1}H). Found, %: C 53.97, 54.21; H 3.58, 3.79; N 19.59, 19.84. $C_{16}H_{13}N_5O_5$. Calculated, %: C 54.09; H 3.69; N 19.71.

Ethyl 6-amino-4-(3-fluorophenyl)-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (Ie). Yield 3.01 g (92%), mp 220–222°C (EtOH). IR spectrum, ν, cm^{-1}: 3350–3550 (NH$_2$), 3150 (NH), 2288 (CN), 1720 (COOEt), 1604 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.13 t (3H, 3-CH$_3$CH$_2$O, *J* 6.5 Hz), 4.09 q (2H, 3-CH$_3$CH$_2$O, *J* 6.5 Hz), 4.73 s (1H, H^4), 6.76 br.s (2H, 6-NH$_2$) 6.81–7.27 m (4H, FC$_6$H$_4$), 13.57 s (1H, N^{1}H). Found, %: C 58.43, 58.63; H 3.92, 4.06; N 16.97, 17.19. $C_{16}H_{13}FN_4O_3$. Calculated, %: C 58.54; H 3.99; N 17.07.

Ethyl 6-amino-4-(4-isopropylphenyl)-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylate (If). Yield 2.67 g (76%), mp 222–224°C (EtOH). IR spectrum, ν, cm^{-1}: 3328–3472 (NH$_2$), 3216 (NH), 2288 (CN), 1720 (COOEt), 1612 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.18 d.d [6H, (CH$_3$)$_2$CHC$_6$H$_4$], 1.02 t (3H, 3-CH$_3$CH$_2$O, *J* 7.11 Hz), 2.80 m [1H, (CH$_3$)$_2$CHC$_6$H$_4$], 4.09 q (2H, 3-CH$_3$CH$_2$O, *J* 7.11 Hz), 4.70 s (1H, H^4), 6.83 br.s (2H, 6-NH$_2$), 6.99–7.17 m [4H, C$_6$H$_4$], 13.70 s (1H, N^{1}H). Found, %: C 64.64, 64.89; H 5.66, 5.80; N 15.78, 16.01. $C_{19}H_{20}N_4O_3$. Calculated, %: C 64.76; H 5.72; N 15.90.

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