# Synthesis of 3-acetyl-4-amino-6-arylpyran-2-ones and ethyl 7-aryl-4,5(1*H*,5*H*)-dioxopyrano[4,3-*b*]pyridine-2-carboxylates

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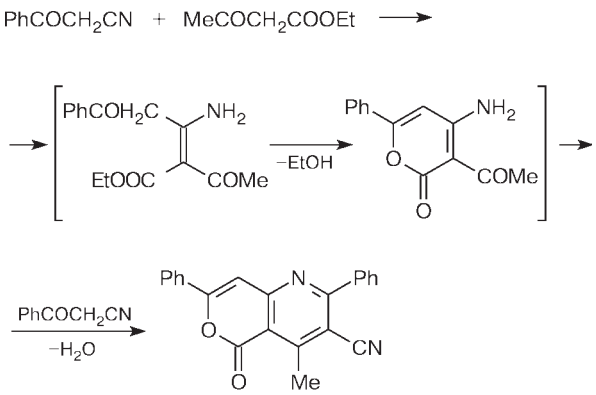
The reactions of aroylacetonitriles with the nickel chelate of ethyl acetoacetate afforded new block heterocyclic reagents, *viz.*, 3-acetyl-4-amino-6-arylpyran-2-ones. The reactions of the latter with diethyl oxalate gave rise to ethyl 7-aryl-4,5(1*H*,5*H*)-dioxopyrano[4,3-*b*]pyridine-2-carboxylates.

**Key words:** aroylacetonitriles, ethyl acetoacetate, nickel chelates, 3-acetyl-4-amino-6-arylpyran-2-ones, ethyl 7-aryl-4,5(1*H*,5*H*)-dioxopyrano[4,3-b]pyridine-2-carboxylates.

Previously, 3-cyano-4-methyl-2,7-diphenylpyrano[4,3-*b*]pyridin-5-one (**1**) has been synthesized[1] by refluxing a mixture of benzoylacetonitrile and ethyl acetoacetate taken in a ratio of 2 : 1 in xylene in the presence of catalytic amounts of $Ni(acac)_2$ (Scheme 1). Compound **1** was used for the construction of the corresponding substituted 1,6- and 2,7-naphthyridines.[2] It was assumed that 3-acetyl-4-amino-6-arylpyran-2-one was one of the key intermediates of condensation. The latter compound has attracted interest as a potential reagent in the heterocyclic synthesis.

**Scheme 1**

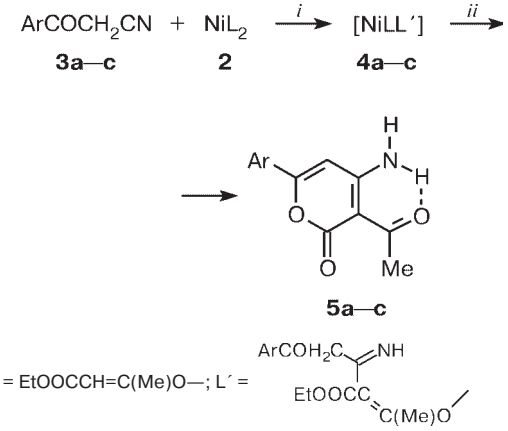



**1**

For azoles and azines containing the vicinal $NH_2$ and Ac substituents, we have developed efficient procedures for annelation of the pyridine or pyrimidine ring and synthesized a series of nitrogen-containing bicyclic systems.[3—8] The aim of the present study was to devise a procedure for the preparation of previously unknown 3-acetyl-4-amino-6-arylpyran-2-ones starting from aroylacetonitriles and ethyl acetoacetate. However, we failed to terminate condensation shown in Scheme 1 at the stage of formation of the corresponding pyranones even in the presence of an excess of ethyl acetoacetate. Attempts to perform the reactions at lower temperatures or in other solvents have not met with success as well.

An approach based on the use of the Ni chelate of ethyl acetoacetate **2** instead of this ester, as such, proved to be more successful. Refluxing of aroylacetonitriles **3a—c** with an equimolar amount of complex **2** afforded adducts **4a—c**, which precipitated as red powders (Scheme 2). Decomposition of the latter compounds by refluxing with

**Scheme 2**




**Reagents and conditions.** *i*. Xylene, Δ. *ii*. AcOH, $CHCl_3$, Δ.

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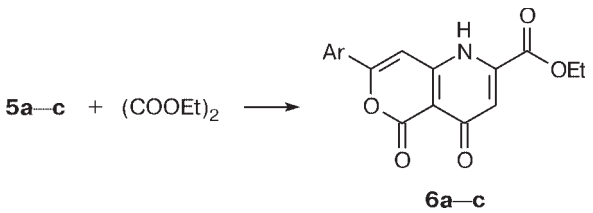
AcOH in $CHCl_3$ produced 3-acetyl-4-amino-6-arylpyran-2-ones in moderate yields.

White crystalline compounds **5a—c** are poorly soluble in most of organic solvents. In their mass spectra, the molecular ion peaks are the most intense. The $^1H$ NMR spectra confirm the presence of the $NH_2$ group and the absence of the OEt fragment. One of singlets of the NH group is observed at low field (at δ ~10.5—10.65 in $CDCl_3$), which is indicative of intramolecular N—H...O hydrogen bonding. The elucidation of the structures of intermediate complexes **4a—c** generated in the synthesis of pyranones **5a—c** was hindered by their very low solubility in organic solvents, which makes purification of the adducts difficult and does not allow us to obtain reproducible results of elemental analysis. In the preliminary communication,[1] we reported that acidification of adduct **4a** under mild conditions (~20 °C) enabled us to isolate ethyl 2-acetyl-3-amino-5-oxo-5-phenylpentene-2-carboxylate (see Scheme 1). However, subsequent attempts to prepare the chelating ligands L´H from complexes **4a—c** were often accompanied by complete or partial cyclization of the latter compounds to give pyranones **5a—c**. This cyclization was substantially accelerated at high temperatures (it is also not inconceivable that EtOH can be eliminated already in the coordination sphere of the Ni atom in adducts of type **4**).*

As mentioned above, pyranones **5a—c** can be considered as convenient block reagents for the synthesis of pyrano[4,3-*b*]pyridine derivatives. We found that heating of compounds **5a—c** with diethyl oxalate in the presence of a solution of EtONa in EtOH followed by treatment with AcOH in EtOH afforded ethyl 7-aryl-4,5(1*H*,5*H*)-dioxopyrano[4,3-*b*]pyridine-2-carboxylates (**6a—c**) in 65—71% yields (Scheme 3).

**Scheme 3**




**6a—c**

Ar = Ph (**a**), 4-$MeC_6H_4$ (**b**), 4-$ClC_6H_4$ (**c**).

**Reagents and conditions:** 1) EtONa, EtOH, Δ;
2) AcOH, EtOH, Δ.

Bicyclic compounds **6a—c** are poorly soluble in organic solvents. Their mass spectra are characterized by the presence of the $[M]^+$ peaks. The $^1H$ NMR spectra have signals of the OEt group and two singlets of CH (δ 6.80—7.40) of the bicyclic system. Like compound **1**,[2] pyrano[4,3-*b*]pyridines of type **6** can apparently be used for transformations into naphthyridines.

* The structures of complexes **4** will be discussed elsewhere after additional investigations.

## Experimental

The NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz for $^1H$ and 62.9 MHz for $^{13}C$); the chemical shifts are given relative to $Me_4Si$. The $^{13}C$ chemical shifts were measured in the mode of $^{13}C—\{^1H\}$ resonance with full proton decoupling. The NMR spectra of compounds **6b**,**c** were recorded at 80 °C because of their low solubility in DMSO-$d_6$. The IR spectra were measured on a Specord M-80 instrument in KBr pellets. The mass spectra were obtained on a Varian MAT CH-6 spectrometer.

All solvents were dried. The nickel complex of ethyl acetoacetate **2** was prepared according to a procedure described previously.[9]

**3-Acetyl-4-amino-6-phenylpyran-2-one (5a).*** A mixture of chelate **2** (3.17 g, 10 mmol) and nitrile **3a** (1.45 g, 10 mmol) in *o*-xylene (15 mL) was refluxed for 4 h. The red precipitate (**4a**) that formed was filtered off, washed with $Et_2O$ (10 mL), and refluxed with glacial AcOH (3 mL) in $CHCl_3$ (15 mL) for 30 min. The resulting solution was treated with water (3×20 mL) and concentrated to dryness. The residue was recrystallized from *o*-xylene. Pyranone **5a** was obtained in a yield of 0.57 g (25%), m.p. 238—239 °C (*o*-xylene). Found (%): C, 67.93; H, 4.84; N, 6.11. $C_{13}H_{11}NO_3$. Calculated (%): C, 68.11; H, 4.89; N, 6.03. MS, *m/z*: 229 $[M]^+$. IR (KBr), ν/cm$^{-1}$: 3140, 3294 br (NH); 1670, 1650, 1600 (C=O, C=C). $^1H$ NMR (DMSO-$d_6$), δ: 10.10 and 8.60 (both s, 1 H each, $NH_2$); 7.50—7.70 (m, 5 H, Ph); 6.70 (s, 1 H, HC=); 2.47 (s, 3 H, Me). $^1H$ NMR ($CDCl_3$), δ: 10.60 and 5.65 (both s, 1 H each, $NH_2$); 7.50—7.85 (m, 5 H, Ph); 6.25 (s, 1 H, HC=); 2.68 (s, 3 H, Me). $^{13}C$ NMR (DMSO-$d_6$), δ: 198.87 (Me<u>C</u>O), 162.02, 161.60, 159.40, 131.50, 130.57, 129.18, 125.61, 97.17, 94.21, 32.25.

**3-Acetyl-4-amino-6-tolylpyran-2-one (5b).** Pyranone **5b** was prepared from chelate **2** (3.17 g, 10 mmol) and nitrile **3b** (1.59 g, 10 mmol) in a yield of 0.66 g (27%) analogously to the synthesis of **5a**, m.p. 240—241 °C (EtOH). Found (%): C, 69.10; H, 5.37; N, 5.90. $C_{14}H_{13}NO_3$. Calculated (%): C, 69.12; H, 5.39; N, 5.76. MS, *m/z*: 243 $[M]^+$. IR (KBr), ν/cm$^{-1}$: 3350 br (NH); 1670, 1652, 1640, 1590 (C=O, C=C). $^1H$ NMR (DMSO-$d_6$), δ: 10.10 and 8.50 (both s, 1 H each, $NH_2$); 7.70 and 7.35 (both d, 2 H each, Ar, $J$ = 7.5 Hz); 6.65 (s, 1 H, HC=); 2.40 and 2.50 (both s, 3 H each, 2 Me). $^1H$ NMR ($CDCl_3$), δ: 10.50 and 5.80 (both s, 1 H each, $NH_2$); 7.70 and 7.25 (both d, 2 H each, Ar, $J$ = 7.5 Hz); 6.21 (s, 1 H, HC=); 2.67 and 2.41 (both s, 3 H each, 2 Me).

**3-Acetyl-4-amino-6-(4-chlorophenyl)pyran-2-one (5c).** Pyranone **5c** was prepared from chelate **2** (3.17 g, 10 mmol) and nitrile **3c** (1.80 g, 10 mmol) in a yield of 0.74 g (28%) as described for **5a**, m.p. 223—224 °C (EtOH). Found (%): C, 59.06; H, 3.80; N, 5.35, Cl, 13.51. $C_{13}H_{10}NO_3Cl$. Calculated (%): C, 59.22; H, 3.82; N, 5.31; Cl, 13.45. MS, *m/z* : 263 $[M]^+$. IR (KBr), ν/cm$^{-1}$: 3300, 3150 br (NH); 1670, 1650, 1600 (C=O, C=C). $^1H$ NMR (DMSO-$d_6$), δ: 10.05 and 8.00 (both s,

* Compound **5a** was synthesized with the participation of A. Yu. Yagodkin.

1 H each, $NH_2$); 7.90 and 7.50 (both d, 2 H each, Ar, $J$ = 7.8 Hz); 6.70 (s, 1 H, HC=); 2.40 (s, 3 H, Me).

**Ethyl 7-phenyl-4,5(1*H*,5*H*)-dioxopyrano[4,3-*b*]pyridine-2-carboxylate (6a).** Pyranone **5a** (0.23 g, 1 mmol) was dissolved in EtOH (5 mL) upon heating. Then a solution of diethyl oxalate (0.44 g, 3 mmol) and EtONa (0.21 g, 3 mmol) in EtOH (5 mL) was added and the mixture was refluxed for 8 min. The precipitate that formed was filtered off, washed with EtOH (5 mL), and refluxed with AcOH (3 mL) in EtOH (15 mL). After cooling, the residue was filtered off, washed with $H_2O$ (2×15 mL) and EtOH (5 mL), and dried *in vacuo*. Ester **6a** was obtained in a yield of 0.22 g (71%), m.p. 245—246 °C (MeCN). Found (%): C, 65.41; H, 4.10; N, 4.38. $C_{17}H_{13}NO_5$. Calculated (%): C, 65.59; H, 4.21; N, 4.50. MS, *m/z*: 311 $[M]^+$. IR (KBr), $\nu/cm^{-1}$: 3440 (NH); 1732, 1648, 1588 (C=O, C=C). $^1$H NMR (DMSO-$d_6$), δ: 7.90 (br.s, 1 H, NH); 7.60—7.90 (m, 5 H, Ph); 7.40 and 7.00 (both s, 1 H each, 2 HC=); 4.40 (q, 2 H, $OCH_2$, $J$ = 6.8 Hz); 1.40 (t, 3 H, Me, $J$ = 6.8 Hz).

**Ethyl 7-tolyl-4,5(1*H*,5*H*)-dioxopyrano[4,3-*b*]pyridine-2-carboxylate (6b).** Ester **6b** was obtained from pyranone **5b** (0.25 g, 1 mmol) in a yield of 0.22 g (68%) analogously to ester **6a**, m.p. 278—279 °C (DMF). Found (%): C, 66.23; H, 4.73; N, 4.37. $C_{18}H_{15}NO_5$. Calculated (%): C, 66.46; H, 4.65; N, 4.31. MS, *m/z*: 325 $[M]^+$. IR (KBr), $\nu/cm^{-1}$: 3440 (NH); 1730, 1640, 1595 (C=O, C=C). $^1$H NMR (DMSO-$d_6$), δ: 7.75 and 7.30 (both d, 2 H each, Ar, $J$ = 7.5 Hz); 7.20 and 6.80 (both s, 1 H each, 2 HC=); 4.40 (q, 4 H, $OCH_2$, $J$ = 6.8 Hz); 2.4 (s, 3 H, $\underline{Me}C_6H_4$); 1.30 (t, 3 H, $\underline{Me}CH_2O$, $J$ = 6.8 Hz).*

**Ethyl 7-(4-chlorophenyl)-4,5(1*H*,5*H*)-dioxopyrano-[4,3-*b*]pyridine-2-carboxylate (6c).** Ester **6c** was prepared from pyranone **5c** (0.27 g, 1 mmol) in a yield of 0.23 g (65 %) analogously to ester **6a**, m.p. 290—291 °C (DMF). Found (%): C, 58.81; H, 3.61; N, 3.99; Cl, 10.16. $C_{17}H_{12}ClNO_5$. Calculated (%): C, 59.06; H, 3.50; N, 4.05; Cl, 10.25. MS, *m/z*: 345 $[M]^+$. IR (KBr), $\nu/cm^{-1}$: 3440 (NH); 1740, 1650, 1590 (C=O, C=C). $^1$H NMR (DMSO-$d_6$), δ: 7.95 and 7.60 (both d, 2 H each, Ar, $J$ = 7.8 Hz); 7.40 and 7.03 (both s, 1 H each, 2 HC=); 4.45 (q, 4 H, $OCH_2$, $J$ = 6.8 Hz); 1.40 (t, 3 H, Me, $J$ = 6.8 Hz).*

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* The signals of NH are not observed due to exchange with water present in the solvent.