On the reactions of aroylacetonitriles with acetoacetates

V. A. Dorokhov, A. V. Vasilyev, S. V. Baranin, O. V. Afanas´ev, and A. S. Vorushilov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: vador@mail.ioc.ac.ru

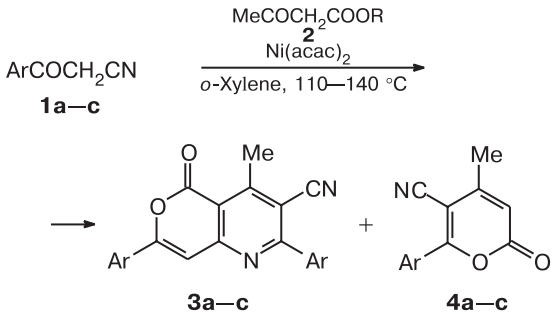
2,7-Diaryl-3-cyano-4-methylpyrano[4,3-*b*]pyridin-5-ones were synthesized by $Ni(acac)_2$-catalyzed condensation of aroylacetonitriles with acetoacetates. The competitive Knoevenagel reaction gave 6-aryl-5-cyano-4-methylpyran-2-ones as by-products. A preparative method for the synthesis of the latter compounds in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst was proposed.

Key words: aroylacetonitriles, acetoacetates, condensation, nickel acetylacetonate, catalysis, the Knoevenagel reaction, 2,7-diaryl-3-cyano-4-methylpyrano[4,3-*b*]pyridin-5-ones, 6-aryl-5-cyano-4-methylpyran-2-ones.

Until recently, no literature data on the reactions of β-oxo nitriles with β-diones were available, although both types of compounds are referred to as traditional and popular organic reagents. Previously,[1] we have shown that benzoylacetonitrile can react with acetoacetate in the presence of $Ni(acac)_2$ as a catalyst. The resulting product was identified from spectroscopic data as 3-cyano-4-methyl-2,7-diphenylpyrano[4,3-*b*]pyridin-5-one.

In the present work, the reactions of aroylacetonitriles with acetoacetates are examined more closely. It was found that heating nitriles **1a—c** with esters **2** in *o*-xylene in the presence of catalytic amounts of $Ni(acac)_2$ gives, along with 3-cyanopyrano[4,3-*b*]pyridin-5-ones **3a—c**, 6-aryl-5-cyano-4-methylpyran-2-ones **4a—c** (Scheme 1).

Scheme 1



Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**); R = Me, Et

The reaction products were easily separated because of higher solubilities of pyranones **4a—c** in most organic solvents (*e.g.*, MeCN).

The yields of pyranopyridinones **3a—c** were higher for a nitrile-to-ester ratio of 3 : 2 (Table 1). For a ratio of 2 : 1, which would seem to be optimum since a molecule of **3** is obviously formed from two molecules of nitrile **1** and one molecule of ester **2**, the condensation was accompanied by partial resinification reducing the yield of bicyclic product **3**. When the ratio between the starting reagents was 1 : 1, the yields of compounds **3a—c** decreased, while the yields of pyranones **4a—c** increased

Table 1. Reaction conditions and the yields of compounds **3a—c** and **4a—c**

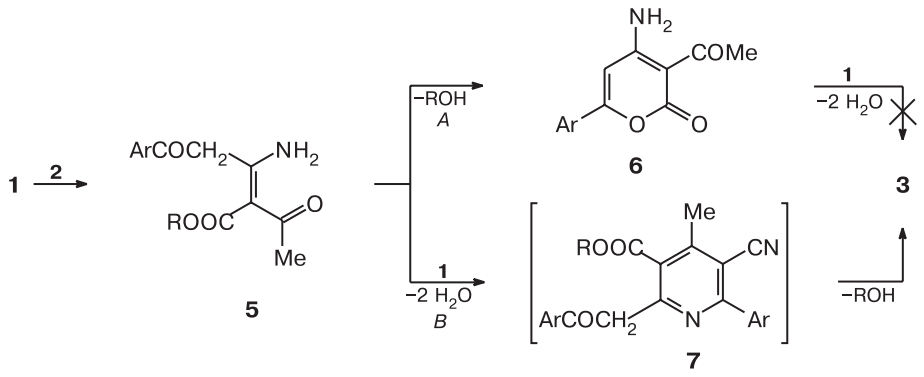
Starting reagents		Ratio of **1** : **2**	Solvent	Heating time/h	Condensation products, yield[a] (%)	
1	**2** R				**3**	**4**
1a	Et	3 : 2	*o*-Xylene	7	**3a**, 50	**4a**, 7
1a	Me	3 : 2	*o*-Xylene	7	**3a**, 36	**4a**, 7
1a	Et	2 : 1	*o*-Xylene	7	**3a**, 30	**4a**, 6
1a	Et	1 : 1	*o*-Xylene	7	**3a**, 25	**4a**, 15
1a	Et	2 : 1	Toluene	8	**3a**, 5	**4a**, 8
1a	Et	1 : 1	Toluene	8	**3a**, 3	**4a**, 19
1a	Et	1 : 1	Benzene[b]	8	—	**4a**, 15
1b	Et	3 : 2	*o*-Xylene	7	**3b**, 28	**4b**, 10
1b	Et	2 : 1	*o*-Xylene	7	**3b**, 22	**4b**, 6
1b	Et	1 : 1	*o*-Xylene	7	**3b**, 13	**4b**, 12
1c	Et	3 : 2	*o*-Xylene	7	**3c**, 16	**4c**, 14
1c	Et	2 : 1	*o*-Xylene	7	**3b**, 9	**4b**, 9

[a] The yields were calculated with respect to the starting nitrile **1**.
[b] Compound **1a** was partially recovered (>15%); on further refluxing for up to 20 h, the yield of product **4a** remains unchanged.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1422—1425, August, 2002.

1066-5285/02/5108-1545 $27.00

Scheme 2



only slightly. At lower reaction temperatures (in boiling toluene or benzene), compounds **3a**—**c** were obtained in low yields; however, the yields of the pyranones did not exceed 15—19% because of slow condensation and gradual resinification of the reaction mixture on heating for more than 7—8 h.

Pyranopyridinones **3a**—**c** are bright yellow crystalline compounds, which are soluble in $CHCl_3$, DMF, and DMSO; they are well crystallized from MeCN and Py. The mass spectra of compounds **3a**—**c** show molecular ion peaks. Their IR spectra contain absorption bands at 2220—2225 cm^{-1} (C≡N) and 1745—1760 cm^{-1} (C=O). Their ^1H NMR spectra (DMSO-d_6) show characteristic singlets at δ 7.21—7.59 (H(8)) and signals at δ 3.01—3.15 (C(4)Me).

Pyranones **4a**—**c** are light yellow crystalline substances, which are well soluble in most organic solvents (except for hexane and Bu^nOH). The mass spectra of compounds **4a**—**c** show molecular ion peaks; their IR spectra contain absorption bands at 2240—2255 cm^{-1} (C≡N) and 1740—1760 cm^{-1} (C=O). Their ^1H NMR spectra show characteristic singlets at δ 6.44—6.47 for the H(3) protons of the pyran ring and singlets at δ 2.34—2.50 (C(4)Me), but they contain no signals for the alkoxycarbonyl R group.

It is known that transition metal acetylacetonates catalyze addition of β-diones with the active methylene group to the C≡N bond of activated nitriles such as trihaloacetonitriles,[2—5] malononitrile,[6,7] and some cyanoheterocycles.[8,9]

Apparently, key intermediates in the synthesis of pyranopyridinones **3** are adducts **5** of esters **2** with nitriles **1** (Scheme 2).

It has originally been assumed[1] that under the condensation conditions presented in Scheme 1, compound **5** undergoes intramolecular cyclization with elimination of ROH to give substituted 3-acetyl-4-aminopyran-2-one **6** (pathway *A*), whose subsequent Friedlander reaction with nitrile **1** yields pyranopyridinones **3**.

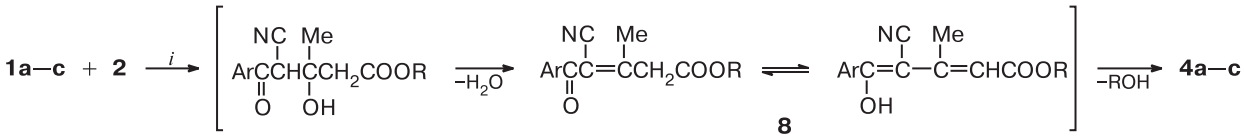
While reacting nitriles **1** with an equimolar amount of an ethyl acetoacetate Ni chelate, compounds **5** [1] and **6** [10] were isolated and identified. However, the reaction of pyranone **6** (Ar = Ph) with nitrile **1a** in boiling *o*-xylene afforded no bicyclic product **3a**. Presumably, aroylacetonitriles **1** react with enaminones **5** (pathway *B*) to give functionalized pyridines **7**, which undergo intramolecular cyclization into pyranopyridines **3**. This hypothesis cannot be verified experimentally because compounds **5** undergo resinification on heating. However, if condensation of adducts **5** with nitriles **1** occurs most probably at the very moment they are formed, pathway *B* seems not to be improbable.

Obviously, methylene-active esters **2** not only add to the C≡N bond of nitriles **1**, but also enter into the Knoevenagel condensation with nitriles **1**, which act themselves as methylene-active components. The intermediate δ-hydroxy acid esters **8** undergo *in situ* cyclization into pyranones **4** (Scheme 3).*

As was noted earlier,[1] aroylacetonitriles **1** do not react with esters **2** in boiling benzene, toluene, or xylene without a catalyst. Therefore, $Ni(acac)_2$ also catalyzes the addition of the methylene-active nitrile to the C=O bond, though the mechanism of its promotion calls for further investigations (we are aware of only one example of the Ni(acac)-catalyzed Knoevenagel reaction,[11] namely, the condensation of acetylacetone with 2-furaldehyde). The synthesis of pyranones **4** in such a way is of no preparative interest (see Table 1). For this reason, we attempted to stimulate the Knoevenagel reaction of compounds **1** with esters **2** by using commonly employed catalysts. In the presence of Et_3N, Py, or piperidine, the reaction mixture undergoes resinification to give unidentified products; the condensation of nitriles **1a**—**c**

* Theoretically, esters **8** can also be converted into pyridines **7** under the action of nitriles **1**. However, we have no sufficient grounds to prefer this pathway to intermediates **7** to the cyclization shown in Scheme 2.

Scheme 3



Reagents and conditions: *i*. $Ni(acac)_2$, *o*-xylene (C_6H_6, MePh), 80—140 °C or DBU, Bu^nOH, Δ.

with ester **2** (R = Et) in boiling Bu^nOH with DBU as a catalyst does afford pyranones **4a—c** in 45—47% yields (see Scheme 3).

Hence, the reactions of aroylacetonitriles with alkyl acetoacetates afford substituted pyrans or pyrano[4,3-*b*]pyridines in 45—50% yields, depending on the catalyst, the temperature, and the ratio of the reagents. The compounds obtained are of interest as potential starting reagents for heterocyclic synthesis. For example, pyranopyridinones **3** can be converted into 2,7-naphthyridine derivatives.[12]

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker WM-250 instrument (250.13 and 62.9 MHz, respectively) with Me_4Si as the internal standard. IR spectra were recorded on a Specord M-80 instrument (in pellets with KBr). Mass spectra were recorded on a Kratos MS-30 spectrometer (EI, 70 eV). All solvents were purified according to the standard procedures. Column chromatography was carried out on Chemapol L 40/100 silica gel.

2,7-Diaryl-3-cyano-4-methylpyrano[4,3-*b*]pyridin-5-ones (3a—c) and **6-aryl-5-cyano-4-methylpyran-2-ones (4a—c) (general procedure).** A mixture of ester **2** (10 mmol) and $Ni(acac)_2$ (1 mmol) in 5 mL of *o*-xylene was heated to 110 °C under dry nitrogen. A solution of a nitrile (**1a—c**, see Table 1) (10—20 mmol) in 35—45 mL of *o*-xylene was added dropwise over 1.5 h. The reaction mixture was heated at 135—140 °C for an additional 5.5 h. The solvent was removed, and the residue was dissolved in 60 mL of $CHCl_3$ and chromatographed on SiO_2 (40/100) in a short column. The chloroform was removed, and the residue was treated with 20 mL of Et_2O and filtered off. The solid substance from the filter was recrystallized from MeCN and dried *in vacuo* to give pyranopyridinones **3a—c**. The mother liquors (in Et_2O and MeCN) were combined, the solvents were removed, and the residue was chromatographed on SiO_2 in AcOEt—hexane (1 : 1, by volume), R_f 0.7—0.8. Evaporation of the solvents gave pyranones **4a—c**.

When the condensation of nitrile **1a** (10—20 mmol) with ester **2** (R = Et, 10 mmol) in the presence of $Ni(acac)_2$ (1 mmol) was carried out in toluene or benzene, the reaction mixture was refluxed with the Dean—Stark trap.

The yields of compounds **3a—c** and **4a—c** are given in Table 1; their physicochemical parameters and spectroscopic data are presented in Tables 2 and 3.

Synthesis of compounds 4a—c from nitriles 1a—c and ester 2 (R = Et) in the presence of DBU

5-Cyano-4-methyl-6-phenylpyran-2-one (4a). A mixture of nitrile **1a** (1.45 g, 10 mmol) and ester **2** (1.30 g, 10 mmol) was heated in 20 mL of Bu^nOH until compound **1a** was completely dissolved. Then DBU (0.15 g, 1 mmol) was added, and the reaction mixture was refluxed for 5 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 in AcOEt—hexane (1 : 1, by volume). The eluent was removed,

Table 2. Melting points, elemental analysis data, and IR and MS spectra of compounds **3a—c** and **4a—c**

Compound	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula	IR, ν/cm^{-1}	MS, *m/z*
		C	H	N	Cl			
3a	237—238 (MeCN)	78.22 / 78.09	4.17 / 4.17	8.10 / 8.28	—	$C_{22}H_{14}N_2O_2$	2225 (C≡N), 1745 (C=O), 1640, 1550	338 $[M]^+$
3b	277—278 (MeCN)	78.41 / 78.67	5.00 / 4.95	7.70 / 7.65	—	$C_{24}H_{18}N_2O_2$	2223 (C≡N), 1756 (C=O), 1630, 1555	366 $[M]^+$
3c	245—246 (MeCN)	64.98 / 64.88	3.08 / 2.97	7.00 / 6.88	17.10 / 17.41	$C_{22}H_{12}Cl_2N_2O_2$	2220 (C≡N), 1760 (C=O), 1635, 1495	405, 407 $[M]^+$
4a	150—151 (AcOEt—hexane)	73.71 / 73.92	4.42 / 4.29	6.66 / 6.63	—	$C_{13}H_9NO_2$	2255 (C≡N), 1760 (C=O), 1620, 1530	211 $[M]^+$
4b	165—166 (AcOEt—hexane)	74.52 / 74.56	5.04 / 4.92	6.35 / 6.22	—	$C_{14}H_{11}NO_2$	2250 (C≡N), 1740 (C=O), 1630, 1560	225 $[M]^+$
4c	178—179 (AcOEt—hexane)	63.72 / 63.56	4.42 / 3.28	5.72 / 5.70	14.56 / 14.43	$C_{13}H_{18}ClNO_2$	2240 (C≡N), 1750, 1740 (C=O), 1630, 1580	245, 247 $[M]^+$

Table 3. ^{1}H NMR spectra (DMSO-d_6) of compounds **3b,c**[a] and **4a—c**

Compound	δ (*J*/Hz)
3b [b]	2.44, 2.46 (both s, 3 H each, 2 4-$\underline{Me}C_6H_4$); 3.15 (s, 3 H, 4-Me); 7.21 (s, 1 H, =CH); 7.32, 7.37 (both d, 2 H each, 4-$MeC_6\underline{H}_4$, *J* = 7.5); 7.82—7.88 (m, 4 H, 4-$MeC_6\underline{H}_4$)
3b	2.41, 2.45 (both s, 3 H each, 2 4-$\underline{Me}C_6H_4$); 3.03 (s, 3 H, 4-Me); 7.35 (s, 1 H, =CH); 7.36—7.91 (m, 8 H, 2 4-$MeC_6\underline{H}_4$)
3c	3.01 (s, 3 H, Me); 7.60 (s, 1 H, =CH); 7.60, 7.70, 7.94, 8.05 (all d, 2 H each, 2 4-ClC_6H_4, *J* = 8.0)
4a [c]	2.34 (s, 3 H, Me); 6.47 (s, 1 H, =CH); 7.63—7.93 (m, 5 H, Ph)
4b	2.33 (s, 3 H, 4-Me); 2.42 (s, 3 H, 4-$\underline{Me}C_6H_4$); 6.44 (s, 1 H, =CH); 7.44, 7.80 (both d, 2 H each, 4-$MeC_6\underline{H}_4$, *J* = 6.0)
4c	2.50 (s, 3 H, 4-Me); 6.47 (s, 1 H, =CH); 7.72, 7.94 (both d, 2 H each, 4-ClC_6H_4, *J* = 9.0)

[a] For the data for compound **3a** see Ref. 1.
[b] The spectrum was recorded in $CDCl_3$.
[c] ^{13}C NMR (DMSO-d_6), δ: 20.7 (Me); 94.0; 112.0; 115.7 (C≡N); 128.8; 129.5; 130.4; 133.2; 154.9; 158.8; 168.4 (CO).

and the solid residue was dried *in vacuo* to give pyranone **4a** (0.95 g, 45%).

5-Cyano-4-methyl-6-(4-methylphenyl)pyran-2-one (4b) was obtained analogously from nitrile **1b** and ester **2** (yield 46%).

6-(4-Chlorophenyl)-5-cyano-4-methylpyran-2-one (4c) was obtained analogously from nitrile **1c** and ester **2** (yield 47%).

The melting points and spectroscopic data of pyranones **4a—c** synthesized from nitriles **1** and ester **2** (R = Et) in the presence of DBU are exactly the same as those presented in Tables 2 and 3 for pyranones **4a—c** obtained with $Ni(acac)_2$ as the catalyst.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 00-03-32751a).

References

1. V. A. Dorokhov, S. V. Baranin, A. Yu. Yagodkin, V. S. Bogdanov, and Z. K. Dem´yanets, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2295 [*Russ. Chem. Bull.*, 1995, **44**, 2201 (Engl. Transl.)].
2. K. Uehara, Y. Ohashi, and M. Tanaka, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1447.
3. A. S. Veronese, C. Talmelli, V. Gandolfi, B. Corain, and M. Basato, *J. Mol. Catal.*, 1986, **34**, 195.
4. V. A. Dorokhov, A. V. Komkov, L. S. Vasil´ev, O. G. Azarevich, and M. F. Gordeev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2639 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 2311 (Engl. Transl.)].
5. V. A. Dorokhov, L. S. Vasil´ev, F. E. Surzhikov, and V. S. Bogdanov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1329 [*Russ. Chem. Bull.*, 1995, **44**, 1283 (Engl. Transl.)].
6. A. S. Veronese, V. Gandolfi, B. Corain, and M. Basato, *J. Mol. Catal.*, 1986, **36**, 339.
7. V. A. Dorokhov, O. G. Azarevich, V. S. Bogdanov, B. I. Ugrak, and L. S. Vasil´ev, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1432 [*Russ. Chem. Bull.*, 1994, **43**, 1356 (Engl. Transl.)].
8. L. S. Vasil´ev, V. S. Bogdanov, E. M. Shashkova, N. K. Khoa, K. L. Cherkasova, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1323 [*Russ. Chem. Bull.*, 1993, **42**, 1266 (Engl. Transl.)]; V. A. Dorokhov, V. S. Bogdanov, L. S. Vasil´ev, and N. K. Khoa, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 710 [*Russ. Chem. Bull.*, 1996, **45**, 671 (Engl. Transl.)].
9. L. S. Vasil´ev, A. B. Sheremetev, N. K. Khoa, Z. K. Dem´yanets, D. E. Dmitriev, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1220 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1280 (Engl. Transl.)].
10. V. A. Dorokhov, A. V. Vasilyev, and S. V. Baranin, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 467 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 503 (Engl. Transl.)].
11. J. H. Nelson, P. N. Howell, G. C. Delullo, G. L. Landen, and R. A. Henry, *J. Org. Chem.*, 1980, **45**, 1246.
12. V. A. Dorokhov, A. Yu. Yagodkin, V. S. Bogdanov, and S. V. Baranin, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1079 [*Russ. Chem. Bull.*, 1997, **46**, 1041 (Engl. Transl.)].

Received March 25, 2002;
in revised form April 24, 2002