Cross-condensation of derivatives of cyanoacetic acid and carbonyl compounds
2.* One-pot synthesis of substituted 2-amino-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans in ethanol and ionic liquid [bmim][PF_6]

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The three-component reaction of 4-hydroxy-6-methylpyran-2(2*H*)-one with cyanoacetic acid derivatives and carbonyl compounds in EtOH or in the ionic liquid, *viz.*, 1-butyl-3-methylimidazolinium hexafluorophosphate ([bmim][PF_6]), affords substituted 2-amino-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans. The yield of substituted pyrano[4,3-*b*]pyrans in [bmim][PF_6] is by 10—14% higher than that in EtOH.

Key words: malononitrile, carbonyl compounds, 2-amino-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans, isatin, 4-hydroxy-6-methylpyran-2(2*H*)-one, spiropiperidinoisoquinoline, ionic liquids.

Methods for synthesis of substituted 2-amino-4*H*-pyrans are being intensely developed because of their practical use as drugs, pesticides, and starting substances in syntheses of blood anticoagulants, antidepressants, immunomodulators, calcium antagonists, and other biologically active compounds.[2]

Earlier,[2—5] these compounds were synthesized in two steps: unsaturated nitriles or unsaturated carbonyl compounds were synthesized in the first step, and then they were used in the reaction with 1,3-dicarbonyl compounds or cyanoacetic acid derivatives. The one-pot method of synthesis based on the three-component condensation of carbonyl compounds (aldehydes, ketones) and CH acids (1,3-dicarbonyl compounds, substituted pyrazolin-5-ones, benzoannelated 3-oxo-2*H*-pyrroles, 3-oxo-2*H*-thiophenes, and others) with cyanoacetic acid derivatives (cyanoacetic esters, malononitrile) is widely used in the recent time.[1,2,6—15]

Continuing our studies of multicomponent reactions of carbonyl compounds with cyanoacetic acid derivatives,[2,6—17] we studied the reactions of 4-hydroxy-6-methylpyran-2(2*H*)-one with cyanoacetic acid derivatives in EtOH or in the ionic liquid, *viz.*, 1-butyl-3-methylimidazolinium hexafluorophosphate ([bmim][PF_6]). We have previously found[18,19] that the use of [bmim][PF_6] as the solvent in multicomponent reactions involving CH acids increases the yield of cyclopropanes, pyrazolopyrans, and thiopyrans. The ionic liquid can be used several times in the reaction. Aromatic aldehydes, some of which contain group-components of many biologically active substances, aliphatic aldehydes, and heterocyclic ketones were chosen as carbonyl compounds. Unlike the authors of the cited publication[4] on the reaction of arylmethylenemalononitriles with pyranone only, we studied the multicomponent reaction and enlarged considerably the scope of the starting reagents and reaction media.

The reactions of pyranone **1** with cyanoacetic acid derivatives **2** and aromatic aldehydes **3** on short refluxing in EtOH in the presence of Et_3N as the catalyst (Scheme 1, method *A*) are established to afford substituted 2-amino-4-aryl-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans **4**.

Unlike the reaction in EtOH (method *A*), the reactions of pyranone **1** and malononitrile **2a** with aldehydes **3c,e,i** containing electron-withdrawing groups in [bmim][PF_6] occur without addition of the main catalyst (method *C*). It is likely that the role of the catalyst is played by the ionic liquid itself. Using the procedure of ionic liquid saturation (the reaction is conducted three times in the same [bmim][PF_6] sample), we succeeded to increase the yield of the target compounds by 10—14% compared to similar transformations in EtOH. When the reactions of pyranone **1**, malononitrile **2a**, and aldehydes **3b,g** containing electron-releasing substituents and the reactions of pyranone **1**, cyanoacetic ester **2b**, and aldehyde **3d** containing the electron-withdrawing substituent are carried out in the ionic liquid, the main catalyst Et_3N should be added additionally (method *C*). Probably, this is related to different reactivities of intermediates **5** formed by the Knoevenagel reaction from aldehydes **3** and cyanoacetic acid derivatives **2**. Unsaturated nitriles **5** containing electron-releasing substituents or one ester group

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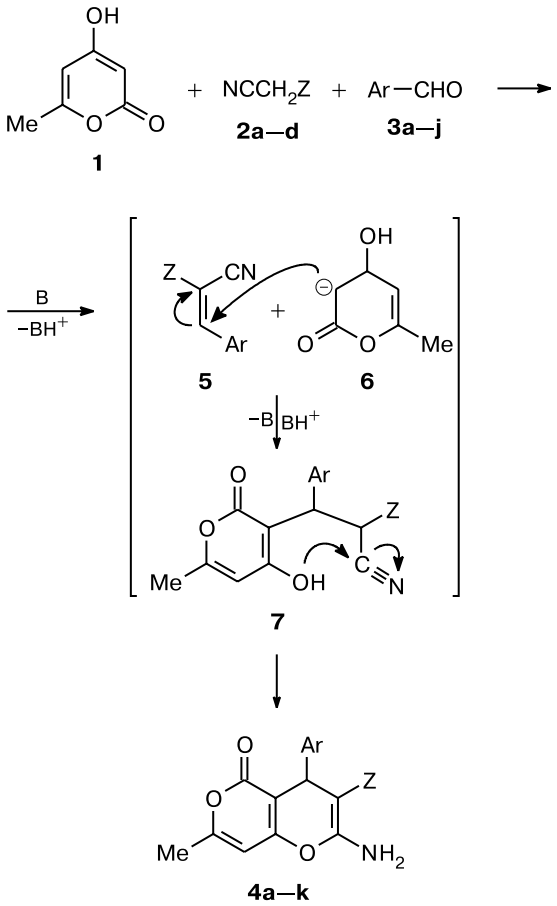
Scheme 1



B = Et_3N, [bmim][PF_6]

2: Z = CN (**a**); COOEt (**b**); $COO(CH_2)_2OMe$ (**c**); $COOCHMe_2$ (**d**)

3, 4	Ar	**3, 4**	Ar
a	2-F,5-$MeOC_6H_3$	**f, k**	4-$CF_3C_6H_4$
b	3-MeO,4-$Pr^nOC_6H_3$	**g**	3-MeO,4-$Pr^iOC_6H_3$
c	4-$MeOOCC_6H_4$	**h**	2,4,5-$(MeO)_3C_6H_2$
d	2-FC_6H_4	**i**	3,4-$F_2C_6H_3$
e	2,4-$F_2C_6H_3$	**j**	4-$CF_3SC_6H_4$

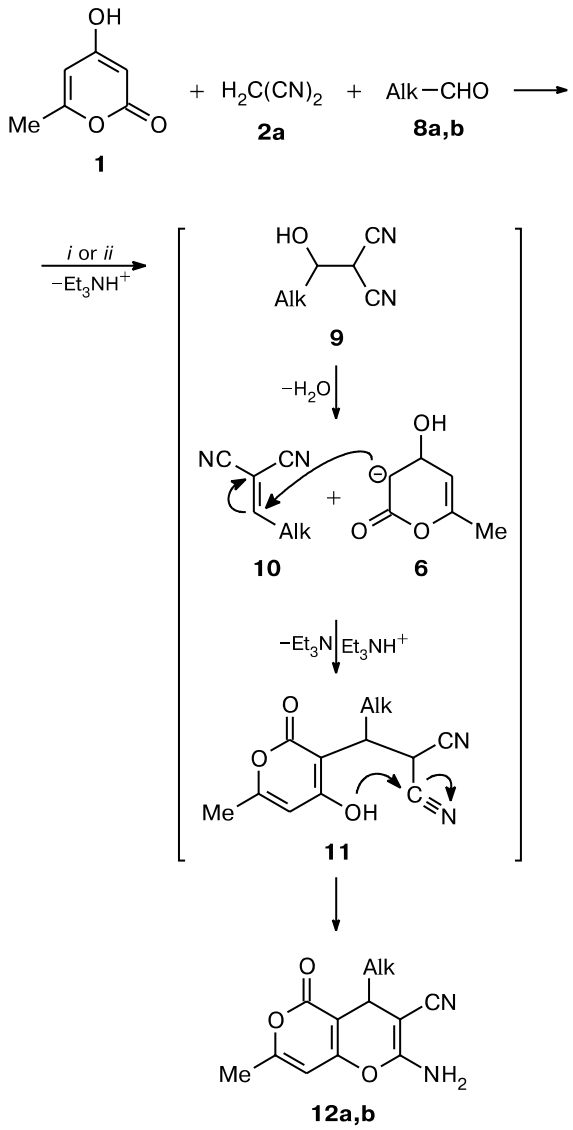
4: Z = CN (**a—c,e,g—j**); COOEt (**d**); $COO(CH_2)_2OMe$ (**f**); $COOCHMe_2$ (**k**)

Reagents and conditions: (***A***) EtOH, Et_3N, Δ or (***B***) [bmim][PF_6], Et_3N, 80—90 °C, or (***C***) [bmim][PF_6], 80—90 °C.

(Z = COOR) are less electrophilic than arylmethylenemalononitriles (Z = CN) containing electron-withdrawing substituents in the benzene ring. Therefore, Et_3N should be added for the formation of Michael adducts **7** and their intramolecular ring closure to form pyrano[4,3-*b*]pyrans **4**. The Knoevenagel reaction affording unsaturated nitriles **5** should also be easier when malononitrile **2a** is used and aldehydes **3** contain electron-withdrawing substituents.

The yield of pyrano[4,3-*b*]pyrans **12a,b** also increases (by 11—12%) when EtOH is replaced by [bmim][PF_6] in the reaction of pyranone **1**, malononitrile **2a**, and aliphatic aldehydes **8**. In this case, the addition of Et_3N as the catalyst is needed for the reaction to occur. The favorable effect of [bmim][PF_6] is probably related to the different rates of water elimination from intermediate aldol **9** in the ionic liquid and in EtOH (Scheme 2).

Scheme 2

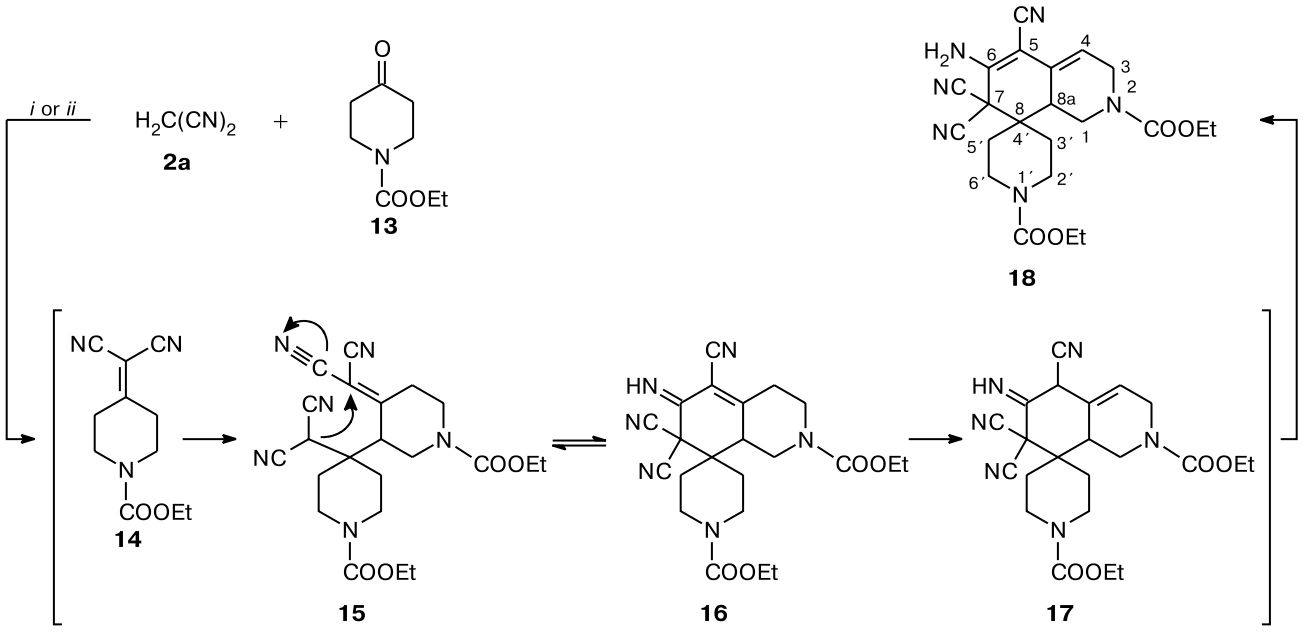


8, 12: Alk = $CHMe_2$ (**a**); CH_2CHMe_2 (**b**)

Reagents and conditions: *i*) EtOH, Et_3N, Δ; *ii*) [bmim][PF_6], Et_3N, 70 °C.

Our results agree well with the data in the publications,[20,21] which show that the aldol condensation in ionic liquids increases the reaction rate and yield of the con-

Scheme 3



Reagents and conditions: *i*) EtOH, Et_3N, Δ; *ii*) [bmim][PF_6], Et_3N, 70 °C.

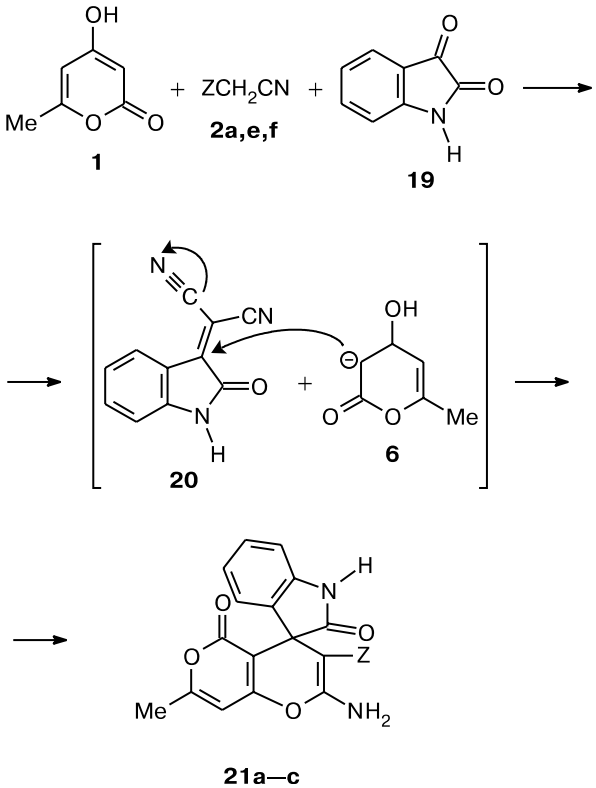
densation products. The further transformations of nitriles **10** *via* the scheme presented afford substituted 4-alkylpyrano[4,3-*b*]pyrans **12**.

When we attempted to conduct the three-component condensation of pyranone **1**, malononitrile **2a**, and piperidin-4-one (**13**), the reaction proceeded *via* the different route, regardless of the type of the solvent used, and afforded spiroheterocycle **18**. Evidently, pyranone **1** is not involved in the reaction (Scheme 3).

Probably, the reaction proceeds through the formation of unsaturated nitrile **14**, which does not react with pyranone **1** but is dimerized to form Michael adduct **15**. The Thorpe—Ziegler ring closure of the latter affords isoquinoline **16**, whose further tautomeric transformations to intermediate **17** and spiroheterocycle **18** complete the reaction. In fact, we obtained compound **18** from malononitrile **2a** and ketone **13** in EtOH in the presence of Et_3N. We earlier observed the similar dimerization with the formation of spiropiperidinoisoquinoline in the reaction of *N*-methylpiperidin-4-one with malononitrile.[1] This reaction is probably related to the enhanced CH acidity of intermediate **14** compared to pyranone **1**.

This assumption is favored by the following fact. When isatin **19** containing no β-CH acidic moiety is introduced into the system, spiro[indoline-3,4′-pyrano[4,3-*b*]pyranes] **21** are formed instead of dimerization products. The yields of spiroheterocycles **21a—c** in the reactions in EtOH and in the ionic liquid are comparable and achieve 92—97% (Scheme 4).

Scheme 4



Z = CN (**2a, 21a**); COOMe (**2e**, **21b**); COOBn (**2f**, **21c**)

Reagents and conditions: *i*) EtOH, Et_3N, Δ or *ii*) [bmim][PF_6], Et_3N, 70 °C.

The resulting pyrans **4**, **12**, and **21** are solid colorless powders, which are stable in air and well soluble in acetone, DMF, or DMSO. The structures of these compounds were confirmed by the data of elemental analysis, IR spectroscopy, and ^{1}H NMR spectroscopy (Tables 1 and 2). The IR spectra of pyrans **4**, **12**, and **21** exhibit the characteristic absorption bands of the enaminonitrile or enaminocarbonyl moieties at δ_{NH_2} 1663—1688, ν_{NH_2} 3140—3994, ν_{CN} 2192—2206, or ν_{COOR} 1692—1696 cm^{-1}. An analogous pattern was observed in the IR spectra of the previously synthesized 4*H*-pyrans containing similar moieties.[1,7,9—12] A distinctive feature of the IR spectra of pyrano[4,3-*b*]pyrans **4**, **12**, and **21** is the absorption band of the cyclic ester group at ν 1702—1718 cm^{-1}. In addition, the IR spectra of spiroheterocycles **21** contain the absorption band of the amide group with the endocyclic nitrogen atom of the isatin moiety at ν_{CON} 1728—1730 cm^{-1}. In addition to signals of the aromatic and CH_3 groups, the ^{1}H NMR spectra of pyrans **4** contain characteristic signals of protons of the C(4)H and NH_2 groups as singlets at 4.23—4.74 and 6.89—7.64 ppm, respectively. The spectra of spiroheterocycles **21** contain no signals of the C(4)H group but exhibit signals of protons of the isatin moiety. The signal of a proton of the C(4)H groups in pyrans **12a,b** appears as a doublet at 3.17 ppm or a triplet at 3.22 ppm with the spin-spin coupling constants J = 2.7 and 2.8 Hz, respectively.

We can conclude that the cross-condensation reactions studied are based on the method of simultaneous

Table 1. Physicochemical characteristics of substituted 2-amino-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans **4**, **12**, and **21**

Compound	M.p./°C	Yield (%) EtOH/[bmim][PF_6]*	Found / Calculated (%)			Molecular formula
			C	H	N	
4a	226—228	89	62.30 62.20	4.11 3.99	8.43 8.53	$C_{17}H_{13}FN_2O_4$
4b	215—216	68/78	65.10 65.21	5.53 5.47	7.49 7.60	$C_{20}H_{20}N_2O_5$
4c	245—246	87/98	63.85 63.90	4.29 4.17	8.19 8.29	$C_{18}H_{14}N_2O_5$
4d	205—206	62/76	62.67 62.60	4.55 4.67	4.14 4.06	$C_{18}H_{16}FO_5$
4e	217—218	80/91	60.51 60.76	3.07 3.19	8.64 8.86	$C_{16}H_{10}F_2N_2O_3$
4f	141—142	78	56.25 56.47	4.12 4.27	3.02 3.29	$C_{20}H_{18}F_3NO_6$
4g	181—182	76/87	65.07 65.21	5.18 5.47	7.36 7.60	$C_{20}H_{20}N_2O_5$
4h	251—253 (decomp.)	86	61.47 61.62	4.73 4.90	7.29 7.56	$C_{19}H_{18}N_2O_6$
4i	198—199	79/89	60.32 60.76	3.26 3.19	8.97 8.86	$C_{16}H_{10}F_2N_2O_3$
4j	238—239	92	53.85 53.69	2.84 2.92	7.45 7.37	$C_{17}H_{11}F_3N_2O_3S$
4k	150—151	77	58.37 58.68	4.22 4.43	3.14 3.42	$C_{20}H_{18}F_3NO_5$
12a	225—226	57/69	63.16 63.40	5.51 5.73	11.14 11.38	$C_{13}H_{14}N_2O_3$
12b	193—194	62/73	64.85 64.60	6.47 6.20	10.95 10.76	$C_{14}H_{16}N_2O_3$
21a	>300	76/75	63.18 63.55	3.14 3.45	12.83 13.08	$C_{17}H_{11}N_3O_4$
21b	258—260 (decomp.)	57	60.85 61.02	3.63 3.98	7.64 7.91	$C_{18}H_{14}N_2O_6$
21c	189—190	61	66.68 66.97	4.03 4.22	6.32 6.51	$C_{24}H_{18}N_2O_6$

* The average yields of compounds after three experiments in the same portion of the ionic liquid are presented for [bmim][PF_6] (see Experimental).

Table 2. Spectral characteristics of substituted 2-amino-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans **4**, **12**, and **21**

Compound	IR, ν/cm^{-1}				^{1}H NMR (300 MHz, DMSO-d$_6$), δ (*J*/Hz)					
	δNH$_2$	NH$_2$	C=N	C=O	CH$_3$ (s, 3 H)	C(8)H (s, 1 H)	C(4)H (s, 1 H)	NH$_2$ (s, 2 H)	Z	Ar, Alk, NH
4a	1669	3208, 3316, 3388	2196	1708	2.22	6.26	4.48	7.16	—	3.70 (s, 3H, Me); 6.79 (s, 1 H, C(6)H, Ar); 6.83 (d, 1 H, C(4)H, Ar, *J* = 7.9); 7.05 (d, 1 H, C(3)H, Ar, *J* = 7.9)
4b	1663	3201, 3307, 3390	2198	1703	2.23	6.13	4.23	6.89	—	1.03 (t, 3 H, Me, *J* = 8.4); 1.71—1.79 (m, 2 H, CH$_2$); 3.29 (s, 3 H, OMe); 3.90 (q, 2 H, CH$_2$O, *J* = 8.8); 6.65 (s, 1 H, C(2′)H, Ar); 6.78 (d, 1 H, C(5′)H, Ar, *J* = 7.7); 6.85 (d, 1 H, C(6′)H, Ar, *J* = 7.7)
4c	1672	3216, 3296, 3360	2192	1688, 1708	2.24	6.28	4.38	7.23	—	3.84 (s, 3 H, OMe); 7.34 (d, 2 H, C(2′)H, C(6′)H, Ar, *J* = 8.2); 7.91 (d, 2 H, C(3′)H, C(5′)H, Ar, *J* = 8.2)
4d	1688	3300, 3428	—	1696, 1702	2.23	6.16	4.74	7.55	1.09 (t, 3 H, Me, *J* = 8.4); 3.97 (q, 2 H, CH$_2$, *J* = 8.4)	6.93—7.24 (m, 4 H, C$_6$H$_4$)
4e	1675	3207, 3322 3400	2197	1710	2.22	6.18	4.32	6.95	—	7.04—7.28 (m, 3 H, C$_6$H$_3$)
4f	1683	3295, 3367	—	1692, 1718	2.21	6.20	4.65	7.64	3.21 (s, 3 H, OMe); 3.32—3.44 (m, 2 H, CH$_2$); 3.96—4.11 (m, 2 H, CH$_2$O)	7.41 (d, 2 H, C(2′)H, C(6′)H, Ar, *J* = 8.5); 7.51 (d, 2 H, C(3′)H, C(5′)H, Ar, *J* = 8.5)
4g		1665	3205, 3318, 3396	2195	1708	2.21	6.21	4.24	6.99	1.22, 1.25 (both d, 3 H each, Me, *J* = 0.73); 3.73 (s, 3 H, OMe); 4.46 (m, 1 H, CHO); 6.65 (d, 1 H, C(5′)H, Ar, *J* = 7.9); 6.80 (s, 1 H, C(2′)H, Ar); 6.87 (d, 1 H, C(6′)H, Ar, *J* = 7.9)
4h	1668	3185, 3310, 3458	2198	1705	2.23	6.18	4.38	6.70	—	3.70, 3.75, 3.80 (all s, 3 H each, OMe); 6.58 (s, 1 H, C(3′)H, Ar); 6.86 (s, 1 H, C(6′)H, Ar)
4i	1664	3196, 3328, 3992	2193	1705	2.24	6.17	4.33	6.97	—	7.04—7.28 (m, 3 H, C$_6$H$_3$)
4j	1668	3205, 3317, 3994	2195	1710	2.22	6.26	4.38	7.24	—	7.37 (d, 2 H, C(3′)H, C(5′)H, Ar, *J* = 7.2); 7.68 (d, 2 H, C(2′)H, C(6′)H, Ar, *J* = 7.2)
4k	1682	3308, 3407	—	1717, 1695	2.24	6.22	4.58	7.68	0.87, 1.20 (both d, 3 H each, Me, *J* = 5.9); 4.58 (m, 1 H, CHO)	7.39 (d, 2 H, C(2′)H, C(6′)H, Ar, *J* = 8.4); 7.51 (d, 2 H, C(3′)H, C(5′)H, Ar, *J* = 8.4)

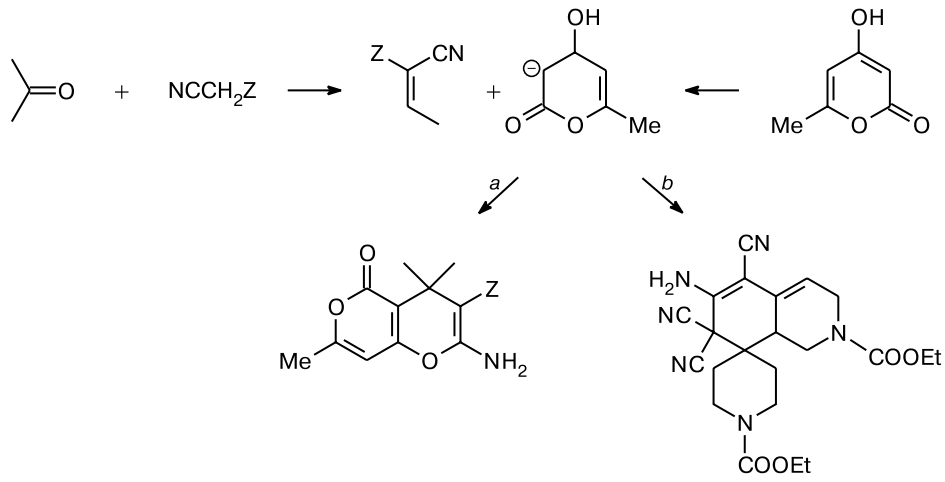
(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}				^{1}H NMR (300 MHz, DMSO-d$_6$), δ (*J*/Hz)					
	δNH$_2$	NH$_2$	C=N	C=O	CH$_3$ (s, 3 H)	C(8)H (s, 1 H)	C(4)H (s, 1 H)	NH$_2$ (s, 2 H)	Z	Ar, Alk, NH
12a	1665	3203, 3325, 3984	2206	1708	2.23	6.18	3.17 (d, 1 H, *J* = 2.7)	7.08	—	0.68, 0.97 (both d, 3 H each, Me, *J* = 6.71); 1.94 (m, 1 H, C<u>H</u>Me)
12b	1667	3208, 3337, 3985	2203	1705	2.22	6.17	3.22 (t, 1 H, *J* = 2.8)	7.06	—	0.82, 0.93 (both d, 3 H each, Me, *J* = 6.5); 1.40 (m, 2 H, CH$_2$); 1.77 (m, 1 H, C<u>H</u>Me)
21a	1680	3140,* 3300 3352	2196	1708, 1732	2.22	6.30	—	7.23	—	6.80—7.22 (m, 4 H, isatin); 10.41 (s, 1 H, NH)
21b	1686	3288,* 3436	—	1720, 1728	2.21	6.22	—	7.87	3.30 (s, 3 H, O<u>Me</u>)	6.68—7.11 (m, 4 H, isatin): 10.10 (s, 1 H, NH)
21c	1680	3312,* 3444	—	1720, 1729	2.20	6.25	—	9.97	4.84 (s, 2 H, CH)	6.56—7.24 (m, 9 H, isatin, Ph); 10.20 (s, 1 H, NH)

* Overlapped with the absorption band of NH of the isatin moiety.

Scheme 5



double generation of a nucleophile (pyranone anion) and an electrophile (unsaturated nitrile) in the reaction medium. The interaction of intermediates at the "reaction crossing" can afford pyranopyrans (Scheme 5, route *a*) or isoquinoline (route *b*).

Experimental

Melting points were determined on the Köffler heating stage. IR spectra were recorded on Specord M-80 and Perkin—Elmer 577 instruments in KBr pellets (1/200). ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz) in DMSO-d$_6$. Chemical shifts are presented relatively to Me$_4$Si in the δ scale in ppm. The proposed assignments of signals in ^{1}H NMR spectra are the authors´ opinion and based on various analogies. Elemental analysis was conducted on a Perkin—Elmer C,H,N-Analyzer instrument. The course of reactions and individual character of the compounds synthesized were monitored by thin layer chromatography on Silufol UV-254 plates using hexane—acetone (5 : 3) mixtures as eluants. Spots were detected by iodine vapor.

General procedure of synthesis of 2-amino-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyrans (4, 12, 21). ***A.*** A mixture of carbonyl compound **3**, **8**, or **19** (10 mmol), the corresponding cyanoacetic acid derivative **2** (11 mmol), and 4-hydroxy-6-methylpyran-2(2*H*)-one **1** (1.39 g, 11 mmol) was stirred with heating in 95% EtOH (20 mL) until the reactants were dissolved, and Et$_3$N (0.5 mL, 0.5 mmol) was added. The reaction mixture was refluxed for 5—10 min and left for crystallization. The precipitate formed was filtered off and washed with 95% EtOH and hexane.

B. Triethylamine (0.33 mL, 2.3 mmol) was added to a mixture of equimolar amounts of pyranone **1** (0.25 g, 2 mmol),

carbonyl compound **3**, **8**, or **19**, and the corresponding cyanoacetic acid derivative **2** in [bmim][PF_6] (10 mL). The reaction mixture was stirred at 80—90 °C for 10 min and cooled to 20 °C, and then stirring was continued for 4—5 h. The precipitate formed was filtered off and washed successively with ethanol and hexane. Pyranopyrans **4**, **12**, and **21** were obtained after recrystallization from ethanol.

C. To synthesize compounds **4c,e,i**, the reaction in [bmim][PF_6] was carried out without Et_3N.

The ionic liquid can be used in the same reaction three times without regeneration. After several reaction cycles, the ionic liquid can easily be purified by washing with water followed by evacuation. Thus regenerated [bmim][PF_6] can be used in further transformations without decreasing the yield of the final products.

6-Amino-5,7,7-tricyano-2,1′-bis(ethoxycarbonyl)spiro-[3,7,8,8a-tetrahydro-1*H*-isoquinoline-8,4′-piperidine] (18). ***A.*** Triethylamine (0.33 mL, 2.3 mmol) was added to a mixture of equimolar amounts of pyranone **1** (0.25 g, 2 mmol), ketone **13** (0.34 g, 2 mmol), and malononitrile **2a** (0.13 g, 2 mmol) in [bmim][PF_6] or 95% EtOH (10 mL). The reaction mixture was stirred at ~70 °C for 10 min and cooled to 20 °C, and then stirring was continued for 4—5 h. The precipitate formed was filtered off and successively washed with 95% EtOH and hexane. After recrystallization from 95% EtOH, spiro compound **18** was obtained in 62% yield (0.27 g), m.p. 86—187 °C. Found (%): C, 60.02; H, 5.86; N, 19.35. $C_{22}H_{26}N_6O_4$. Calculated (%): C, 60.26; H, 5.98; N 19.17. IR, ν/cm^{-1}: 1672 (δNH_2),1692 (CO), 2220 (CN), 3204, 3332, 3352 (NH_2). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.14—1.26 (m, 7 H, $(CH_3)_2$, C(8a)H); 1.53—1.65 (m, 1 H, C(5′)H_{eq}); 1.70—1.79 (m, 1 H, C(5′)H_{ax}); 2.10—2.21 (m, 2 H, C(3′)H_{ax}, C(3′)H_{eq}); 2.55—2.62 (m, 1 H, C(6′)H_{eq}); 3.01—3.11 (m, 1 H, C(6′)H_{ax}); 3.19—3.24 (m, 1 H, C(2′)H_{eq}); 3.58—3.79 (m, 2 H, C(2′)H_{ax}, C(1)H_e); 3.89 (m, 1 H, C(1)H_{ax}); 4.06 (m, 4 H, $(CH_2O)_2$); 4.30 (m, 2 H, C(3)H_2); 5.78 (s, 1 H, C(4)H); 7.46 (s, 2 H, NH_2).

B. A mixture of equimolar amounts of ketone **13** (0.34 g, 2 mmol) and malononitrile **2a** (0.13 g, 2 mmol) was stirred with heating in 95% EtOH (20 mL) until the reactants dissolved, and Et_3N (0.32 mL, 2.3 mmol) was added. The reaction mixture was refluxed for 5—10 min and left for crystallization. The precipitate formed was filtered off and washed with 95% EtOH and hexane. Compound **18** was obtained in 78% yield (0.34 g).

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