Single-step synthesis of substituted 7-aminopyrano[2,3-*d*]pyrimidines

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A single-step method for the synthesis of substituted 7-aminopyrano[2,3-*d*]pyrimidines was developed. The method involves a three-component reaction of barbituric acid or 4,6-dihydroxypyrimidine with aromatic aldehydes and malononitrile in DMF in the presence of *N*-methylmorpholine as a catalyst.

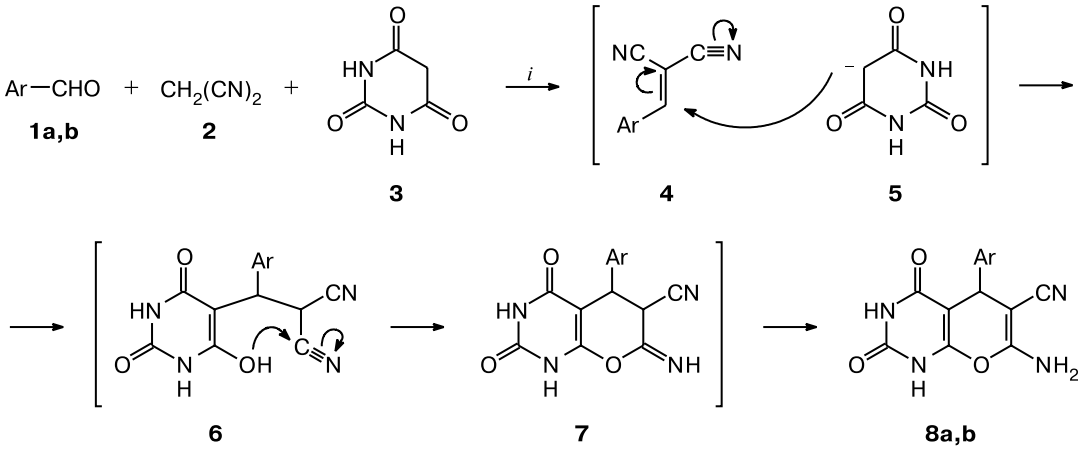
Key words: malononitrile, barbituric acid, 4,6-dihydroxypyrimidine, pyrano[2,3-*d*]pyrimidines.

Substituted 2-amino-4*H*-pyrans are of great practical interest. Some of them have been found to exhibit antibacterial and anticancer activities, while others can potentially be used to cure people of Alzheimer's and Parkinson's diseases and various types of sclerosis.[1,2] Earlier, these compounds were synthesized in two steps: (1) first, arylidenemalononitrile was synthesized from an aldehyde and malononitrile and then its reaction with 1,3-dicarbonyl compound was carried out or (2) first, an α,β-unsaturated carbonyl compound was synthesized from an aldehyde and 1,3-dicarbonyl compound (ethyl acetoacetate or barbituric acid) and then the reaction with malononitrile was carried out.[1,2]

With the aim of developing a single-step method for the synthesis of 2-amino-4*H*-pyrans annelated with the pyrimidine ring, we studied three-component reactions of aldehydes **1**, malononitrile (**2**), and barbituric acid (**3**) (Scheme 1). It was found that these reactions in DMF in the presence of *N*-methylmorpholine at 90—95 °C give earlier reported[3] 7-amino-5-aryl-6-cyano-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidines **8**. Under these conditions, the yields of compounds **8a,b** were 85 and 89%, respectively, which is comparable with the yields of pyrano[2,3-*d*]pyrimidines obtained at the second step of the previously reported reactions from the corresponding arylidenemalononitriles and barbituric acid[3] (87 and 92%) and even exceed them by 12—15% with respect to the total yield after the two steps.

The high regioselectivity of this reaction is probably due to a strict sequence of transformations (see Scheme 1). Apparently, electrophilic olefin **4** (through the Knoevenagel reaction) and nucleophilic barbiturate

Scheme 1



1, 8: Ar = Ph (**a**), 4-ClC_6H_4 (**b**)

Reagents and conditions: *i*. DMF, *N*-methylmorpholine, 15 min, 90—95 °C.

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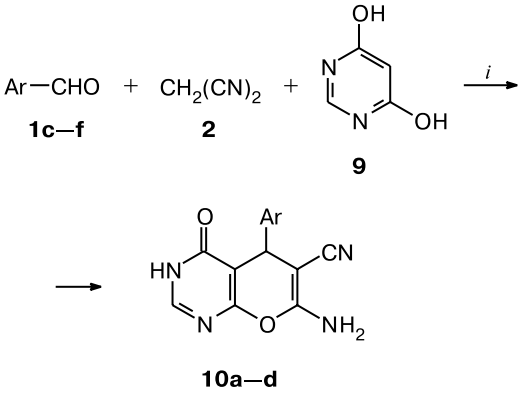
anion **5** are initially generated simultaneously from the starting compounds in the presence of a base. A subsequent Michael reaction of intermediates **4** and **5** yields adduct **6** which undergoes Thorpe—Ziegler intramolecular cyclization into iminopyran **7**. The 1,3-sigmatropic shift results in aminopyrans **8**. The structures of products **8a,b** were confirmed by a comparison of their IR and ^{1}H NMR spectra and melting points with the literature data for these compounds.[3]

We discovered that 4,6-dihydroxypyrimidine (**9**) also enters into this reaction under analogous conditions to give substituted 7-aminopyrano[2,3-*d*]pyrimidines **10a—d** in 88—92% yields (Scheme 2).

Apparently, the reaction between compounds **1**, **2**, and **9** follows Scheme 1, occurring as a sequence of transformations: Knoevenagel reaction → Michael reaction → Thorpe—Ziegler reaction.

Products **10a—d** are high-melting colorless powders. They are insoluble in most organic solvents, which makes it difficult to study their tautomerism. However, by comparing their IR and ^{1}H NMR spectra with relevant data for compounds **8** [3] and 2*H*-pyrano[3,2-*c*]pyridine-2,5-diones[4] or 2*H*-pyrano[2,3-*d*]pyridazine-2,5-diones,[4,5] one can assume that the compounds obtained exist in one tautomeric form, namely, as 7-amino-5-aryl-6-cyano-4-oxo-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidines **10**. The

Scheme 2



Ar = 4-MeOOCC$_6$H$_4$ (**1c**, **10a**), 4-EtOC$_6$H$_4$ (**1d**, **10b**), 2-CF$_3$C$_6$H$_4$ (**1e**, **10c**), 3,4-(MeO)$_2$C$_6$H$_3$ (**1f**, **10d**)

Reagents and conditions: *i*. DMF, *N*-methylmorpholine, 15 min, 90—95 °C.

Table 1. Physicochemical and spectral properties of 7-amino-5-aryl-6-cyano-4-oxo-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidines **10a—d**

Compound	M.p. /°C	Yield (%)	Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}			^{1}H NMR, δ (*J*/Hz)				
			C	H	N		δ(NH$_2$), CONH	NH$_2$	C≡N	H(5) (s, 1 H)	H(2) (s, 1 H)	NH$_2$ (s, 2 H)	NH (s, 1 H)	R
10a	293—295	87	59.48 59.26	3.97 3.73	16.95 17.28	$C_{16}H_{12}N_4O_4$	1638, 1672, 1695, 1710	3198, 3264, 3388, 3404	2196	4.51	8.12	7.14	12.68	3.82 (s, 3 H, Me); 7.34, 7.90 (both d, 2 H each, C$_6$H$_4$, *J* = 7.9)
10b	274—276	92	61.72 61.93	4.37 4.55	17.83 18.05	$C_{16}H_{14}N_4O_3$	1637, 1675, 1689	3190, 3244, 3375, 3402	2195	4.34	8.11	7.08	12.68	1.29 (t, 3 H, Me, *J* = 7.9); 3.98 (q, 2 H, CH$_2$, *J* = 7.9); 6.84, 7.11 (both d, 2 H each, C$_6$H$_4$, *J* = 7.8)
10c	289—291	90	53.72 53.90	2.85 2.71	16.54 16.76	$C_{15}H_9F_3N_4O_2$	1634, 1675, 1687	3175, 3250, 3386, 3400	2198	4.79	8.12	7.11	12.61	7.28 (d, 1 H, C$_6$H$_4$, *J* = 7.3); 7.41 (dd, 1 H, C$_6$H$_4$, *J* = 7.3, *J* = 7.1); 7.58 (dd, 1 H, C$_6$H$_4$, *J* = 7.1, *J* = 6.9); 7.65 (d, 1 H, C$_6$H$_4$, *J* = 6.9)
10d	284—286	91	58.53 58.89	4.12 4.32	17.45 17.17	$C_{16}H_{14}N_4O_4$	1632, 1679, 1689	3178, 3262, 3374, 3408	2195	4.36	8.12	7.10	12.69	3.82 (s, 6 H, 2 Me); 6.65 (d, 1 H, C$_6$H$_3$, *J* = 6.7); 6.80 (s, 1 H, C$_6$H$_3$); 6.87 (d, 1 H, C$_6$H$_3$, *J* = 6.7)

^{1}H NMR spectra of these compounds contain, apart from signals for the aryl, NH_2, and H(5) protons, signals for the H(2) proton as a singlet at δ 8.11—8.12 and the NH proton at δ 12.61—12.69. In the presence of other tautomers, the signals for the OH or N(1)H protons should be shifted upfield to δ 6.5—6.8 because they become shielded with the aryl substituent or the O atom of the pyran ring. This correlates with the literature data[2—5] and the ^{1}H NMR spectra calculated for all possible tautomers of pyranopyrimidines **10**. The IR spectra of compounds **10** show characteristic absorption bands of the conjugated CN group and bands due to the stretching and bending vibrations of the CONH and NH_2 groups (Table 1), which agree with the literature data.[3—5]

Experimental

Melting points were determined on a Kofler unit. IR spectra were recorded on a Perkin—Elmer 577 instrument (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) in DMSO-d_6. Elemental analysis was performed with a Perkin—Elmer C,H,N-analyzer. The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates with hexane—acetone (5 : 3) as the eluent; spots were visualized with the iodine vapor.

7-Amino-5-aryl-6-cyano-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidines 8a,b. A mixture of aldehyde **1a,b** (0.01 mol), malononitrile (**2**) (0.01 mol), barbituric acid (**3**) (0.01 mol), and *N*-methylmorpholine (0.2 mL, 0.002 mol) in 40 mL of freshly distilled DMF was stirred at 90—95 °C for 15 min. The hot solution was filtered through a folded filter, kept at 4 °C for a day, diluted with water (5—6 mL), and acidified with 10% HCl (1 mL). The precipitate that formed was filtered off and washed in succession with hot water, ethanol, and hexane to give spectrally pure compounds **8a,b** (^{1}H NMR data). The IR and ^{1}H NMR spectra of compounds **8a,b** agree with the literature data.[3]

Compound 8a. Yield 85%, m.p. 209—211 °C (*cf.* Ref. 3: m.p. 210—211 °C).

Compound 8b. Yield 89%, m.p. 241—242 °C (*cf.* Ref. 3: m.p. 240—241 °C).

7-Amino-5-aryl-6-cyano-4-oxo-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidines 10a—d were obtained as described for compounds **8** from equimolar amounts of the corresponding aldehydes **1c—f**, malononitrile (**2**), and 4,6-dihydroxypyrimidine (**9**). Physicochemical and spectral data for compounds **10** are given in Table 1.

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