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AROMATIZATION WITH DEARYLATION ON HANTZSCH CYCLOCONDENSATION OF 4-(DIMETHYLAMINO)BENZALDEHYDE, CYCLOHEXANE-1,3-DIONES, AND SOME 1,3-[N,C]DINUCLEOPHILES

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The Hantzsch three-component cyclization of 4-(dimethylamino)benzaldehyde, cyclohexane-1,3-diones, and some 1,3-[N,C]-dinucleophiles (5-amino-3-methyl-1-phenylpyrazole, 3,5-dimethoxyaniline, and 4-amino-1,3-dimethylpyrimidine-2,6-dione) proceeds in boiling acetic acid with the splitting off N,N-dimethylaniline and the formation of polycondensed heterocyclic sytems with a γ-unsubstituted pyridine ring (pyrazolo[3,4-b]quinoline, acridine, and pyrimido[4,5-b]quinoline).

Keywords: acridines, pyrazolo[3,4-*b*]quinolines, pyrimido[4,5-*b*]quinolines, aromatization, dearylation, Hantzsch reaction.

The Hantzsch pyridine synthesis, including pyridines condensed with other rings, consists of two stages, the formation of the 1,4-dihydropyridine ring and its subsequent oxidation [1-5]. The method has been improved in practical organic chemistry during 125 years and has been changed in principle when obtaining compounds with a γ-unsubstituted pyridine ring, since the classical scheme using formaldehyde gives unsatisfactory results [6].

It was established primarily that formaldehyde may be replaced by other aldehydes. Thus, 1,4-dihydropyridines obtained from some aliphatic aldehydes [6-10], polyfluorobenzaldehydes [11], and 4-(dimethylamino)benzaldehyde (**1**) [12], are aromatized with the splitting off the substituent in the γ-position by the action of certain oxidizing agents, sodium cyanide, and electrophilic reagents.

Secondly, procedures were proposed for conversion of the two-stage synthesis into one stage. For example, 1,4-dihydropyridines obtained from antipyrine-4-carbaldehyde, are aromatized with the splitting off antipyrine even under the conditions of formation (20°C, 18 h), although the initial aldehyde must first be converted into the more reactive chloropyridinium salt [13]. We have found that the aldehyde **1** mentioned above is more convenient for that purpose. On carrying out the reaction involving it in boiling acetic acid (120°C, 2 h), as shown in the synthesis of derivatives of acridine [14], pyrazolo[3,4-*b*]pyridine [15], and

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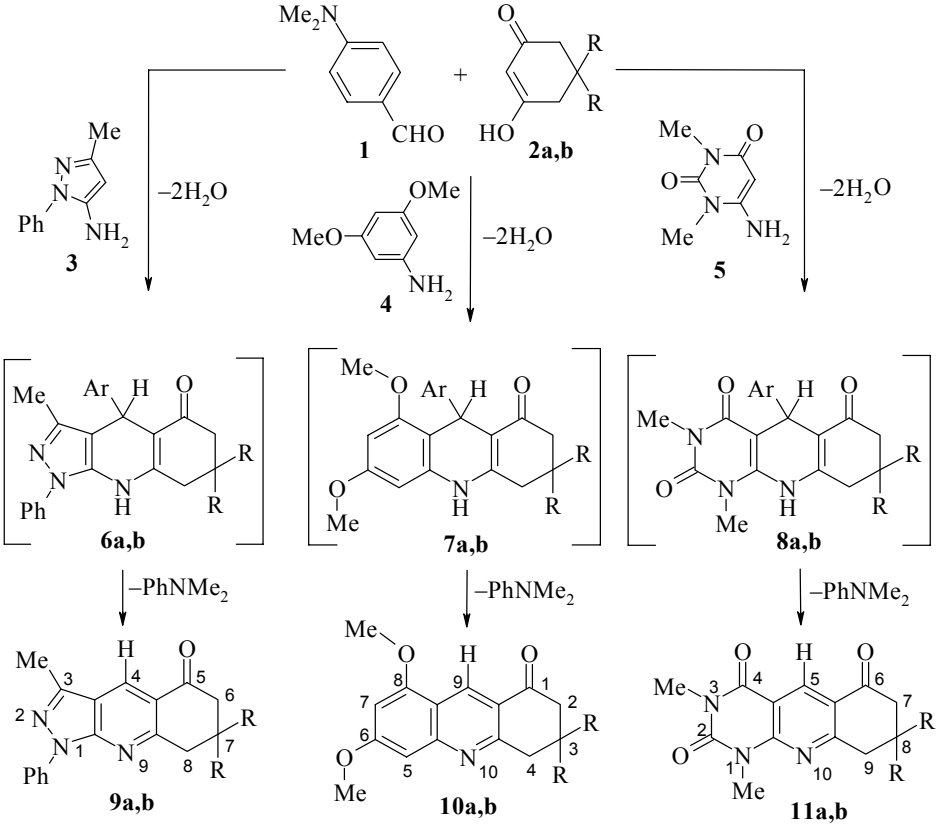
pyrido[2,3-*d*]pyrimidine [16], the formation of a 1,4-dihydropyridine ring and its aromatization are combined in one process, which in spite of the data of [5], proceeds not with retention of the 4-(dimethylamino)phenyl substituent, but with selective spitting off N,N-dimethylaniline.

In the latter synthetic procedure, available, stable, and low toxicity starting materials are used, and the desired products are isolated easily from the reaction mixture, and in high yield. With the aim of broadening the scope of the method the three-component interaction of aldehyde **1**, cyclohexane-1,3-dione **2a,b** and some 1,3-[N,C]dinucleophiles, aminopyrazole **3**, dimethoxyaniline **4**, and aminopyrimidinedione **5** has been studied for the first time in the present work.

We found that the interaction of reactants **1**, **2**, and **3-5** in boiling acetic acid proceeds through 1,4-dihydropyridine-containing compounds of the type of **6-8**, which are aromatized with splitting off dimethylaniline and the formation of derivatives of pyrazolo[3,4-*b*]quinoline **9**, acridine **10**, and pyrimido-[4,5-*b*]quinoline **11** respectively.

Reaction by the given scheme (method A) is complete in 2 h, and the N,N-dimethylaniline formed in it does not interfere in the isolation of the desired products. Products **9** and **11** were isolated in yields of 76-94% on diluting the reaction mixtures with water, and acridines **10** in 75-82% yield after removing the acetic acid and washing.



2, 6–11 a R = H, **b** R = Me; **6–8** Ar = 4-$Me_2NC_6H_4$

The process may stop at the stage of forming compounds containing a 1,4-dihydropyridine ring. In the three-component cyclocondensations involving dimedone **2b** in 2-propanol products **6b** and **7b** are formed and product **8b** is formed in acetic acid at 80°C. On boiling compounds **6b-8b** in acetic acid products **9b-11b** (method B) are also formed. The yields in both stages were high, however the two-stage scheme of synthesis of these compounds has no advantage over the one-stage, since the gain in overall yield is insignificant, and the consumptions of time and materials grow noticeably.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
6b	$C_{27}H_{30}N_4O$	75.31 / 76.03	6.76 / 7.09	13.47 / 13.13	223-225	96
7b	$C_{25}H_{30}N_2O_3$	73.54 / 73.86	7.23 / 7.44	6.72 / 6.89	288-289.5	89
8b	$C_{23}H_{28}N_4O_3$	67.80 / 67.63	6.69 / 6.91	13.88 / 13.72	210-211	77
9a	$C_{17}H_{15}N_3O$	73.48 / 73.63	5.57 / 5.45	15.07 / 15.15	123-124	87 (A)
9b	$C_{19}H_{19}N_3O$	74.64 / 74.73	6.34 / 6.27	13.58 / 13.76	164.5-166 (130 [17])	94 (A), 95 (B)
10a	$C_{15}H_{15}NO_3$	69.88 / 70.02	5.76 / 5.88	5.28 / 5.44	151-152.5	75 (A)
10b	$C_{17}H_{19}NO_3$	71.42 / 71.56	6.57 / 6.71	4.78 / 4.91	154-155.5	82 (A), 85 (B)
11a	$C_{13}H_{13}N_3O_3$	60.08 / 62.23	5.18 / 5.05	16.15 / 16.21	186.5-188	76 (A)
11b	$C_{15}H_{17}N_3O_3$	62.56 / 62.71	5.85 / 5.96	14.53 / 14.62	182-183.5	92 (A), 95 (B)

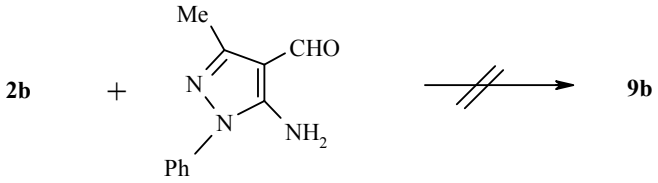
TABLE 2. IR and ^{1}H NMR Spectra of the Synthesized Compounds

Compound	IR spectrum, $\nu_{C=O}$, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
6b	1620	0.95 and 1.02 (3H and 3H, two s, 7-, 7-CH_3); 1.91 (3H, s, 3-CH_3); 1.95 and 2.15 (1H and 1H, two d, *J* = 16, H-8,8); 2.51 (2H, m, H-6,6); 2.82 (6H, s, $N(CH_3)_2$); 4.86 (1H, s, H-4); 6.61 and 7.01 (2H and 2H, two d, *J* = 8.1, C_6H_4); 7.38 (1H, m, H-4 Ph); 7.51 (4H, m, H-2,3,5,6 Ph); 9.33 (1H, s, H-9)
7b	1630	0.90 and 1.00 (3H and 3H, two s, 3-, 3-CH_3); 1.95 and 2.13 (1H and 1H, two d, *J* = 16.0, H-4,4); 2.31 and 2.42 (1H and 1H, two d, *J* = 17.0, H-2,2); 2.75 (6H, s, $N(CH_3)_2$); 3.64 and 3.69 (3H and 3H, two s, 6-, 8-OCH_3); 5.02 (1H, s, H-9); 6.11 and 6.13 (1H and 1H, two d, *J* = 2.0, H-5,7); 6.48 and 6.91 (2H and 2H, two d, *J* = 9.0, C_6H_4); 9.20 (1H, s, H-10)
8b	1655, 1680	0.91 and 1.04 (3H and 3H, two s, 8-, 8-CH_3); 2.02 and 2.20 (1H and 1H, two d, *J* = 16.0, H-9,9); 2.55 and 2.60 (1H and 1H, two d, *J* = 16.0, H-7,7); 2.79 (6H, s, $N(CH_3)_2$); 3.09 (3H, s, 1-CH_3); 3.44 (3H, s, 3-CH_3); 4.75 (1H, s, H-5); 6.54 and 7.01 (2H and 2H, two d, *J* = 8.4, C_6H_4); 8.94 (1H, s, H-10)
9a	1680	2.13 (2H, m, H-7,7); 2.60 (3H, s, CH_3); 2.70 (2H, t, *J* = 6.0, H-8,8); 3.18 (2H, t, *J* = 6.0, H-6,6); 7.34 (1H, t, *J* = 7.5, H-4 Ph); 7.56 (2H, t, *J* = 7.8, H-3,5 Ph); 8.25 (2H, d, *J* = 7.5, H-2,6 Ph); 8.72 (1H, s, H-4)
9b	1700	1.06 (6H, s, 7-, 7-CH_3); 2.61 (2H, s, H-8,8); 2.62 (3H, s, 3-CH_3); 3.12 (2H, s, H-6,6); 7.33 (1H, t, *J* = 7.5, H-4 Ph); 7.56 (2H, t, *J* = 7.8, H-3,5 Ph); 8.28 (2H, d, *J* = 7.5, H-2,6 Ph); 8.73 (1H, s, H-4)
10a	1680	2.11 (2H, m, H-3,3); 2.67 (2H, t, *J* = 6.0, H-4,4); 3.12 (2H, t, *J* = 7.5, H-2,2); 3.91 (3H, s, 6-CH_3); 3.96 (3H, s, 8-CH_3); 6.62 (1H, d, *J* = 2.0, H-7); 6.93 (1H, d, *J* = 2.0, H-5); 8.76 (1H, s, H-9)
10b	1690	1.03 (6H, s, 3-CH_3); 2.58 (2H, s, H-4,4); 3.04 (2H, s, H-2,2); 3.92 (3H, s, 6-OCH_3); 3.97 (3H, s, 8-OCH_3); 6.65 (1H, s, H-7); 6.96 (1H, s, H-5); 8.77 (1H, s, H-9)
11a	1670, 1690, 1710	2.11 (2H, m, H-8,8); 2.66 (2H, t, *J* = 6.5, H-9,9); 3.10 (2H, t, *J* = 6.5, H-7,7); 3.27 (3H, s, 1-CH_3); 3.55 (3H, s, 3-CH_3); 8.56 (1H, s, H-5)
11b	1650, 1670, 1700	1.05 (6H, s, 8-, 8-CH_3); 2.60 (2H, s, H-9,9); 3.06 (2H, s, H-7,7); 3.29 (3H, s, 1-CH_3); 3.58 (3H, s, 3-CH_3); 8.60 (1H, s, H-5)

TABLE 3. Main Bond Lengths (*l*) and Valence Angles (ω) of the Compound **9** Molecule

Bond	*l*, Å	Angle	ω, deg
N(1)–C(1)	1.340(2)	C(5)N(1)C(1)	114.66(13)
N(1)–C(5)	1.336(2)	C(1)N(2)N(3)	110.19(12)
N(2)–C(1)	1.367(2)	N(2)N(3)C(10)	107.15(12)
N(2)–N(3)	1.390(2)	N(3)C(10)C(2)	110.80(13)
C(10)–N(3)	1.312(2)	C(10)C(2)C(1)	107.15(12)
C(10)–C(2)	1.428(2)	C(2)C(1)N(2)	106.89(13)
C(2)–C(1)	1.408(2)		

Note that all the synthesized compounds were previously unknown, although as is evident, they are easily formed from fairly accessible reactants. The data of [17] on the synthesis of compound **9b** on fusing dimedone with aminoformylpyrazole **12** do not correspond to actuality, since its characteristics (melting point and parameters of ^{1}H NMR spectra) are clearly different from those found by us.



The structure of compound **9b** was established by us by the X-ray structural method (Figs. 1 and 2, Table 3). The central heterocyclic fragment N(1)C(1-5) is planar (maximum mean-square deviation of atoms was only 0.007 Å) and the pyrazole ring N(2)N(3)C(1)C(2)C(10) also planar (maximum mean-square deviation 0.003 Å) lies in practically the same plane (corresponding dihedral angle 0.99°). The dihedral angle between the pyrazole ring N(1)N(2)C(1)C(2)C(10) and the phenyl ring C(14)–C(19) was 9.5°. The C(4)–C(9) ring is nonplanar and has a *half-chair* conformation with a flattened fragment C(9)C(4)C(5) (corresponding modified Cremer-Pople parameters [18] are $S = 0.75$, $\psi = 13.00°$, $\theta = 35.88°$).

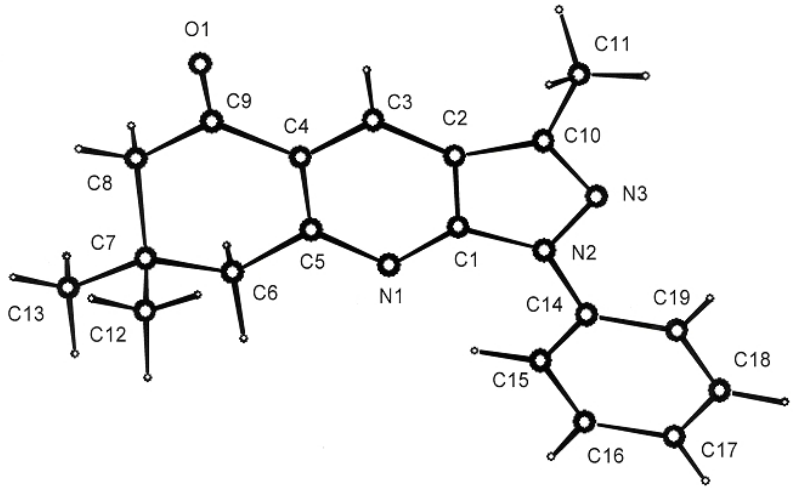


Fig. 1. General shape of the compound **9b** molecule.

The composition and structure of all the compounds were also confirmed by data of elemental analysis (Table 1), IR spectra, and ^{1}H NMR spectra (Table 2). In particular in the ^{1}H NMR spectrum of compound **9b** the chemical shifts of the *gem*-dimethyl grouping (1.06 ppm) and the 3-CH_3 group (2.62 ppm) differ sharply, while according to the data of [17] all three methyl groups are displayed as one nine-proton singlet (2.5 ppm). The diastereotopic CH_3 groups and the protons of the CH_2 group of compounds **6b**, **7b**, and **8b** resonate as in their known analogs of the pyrazolo[3,4-*b*]quinoline type [19].

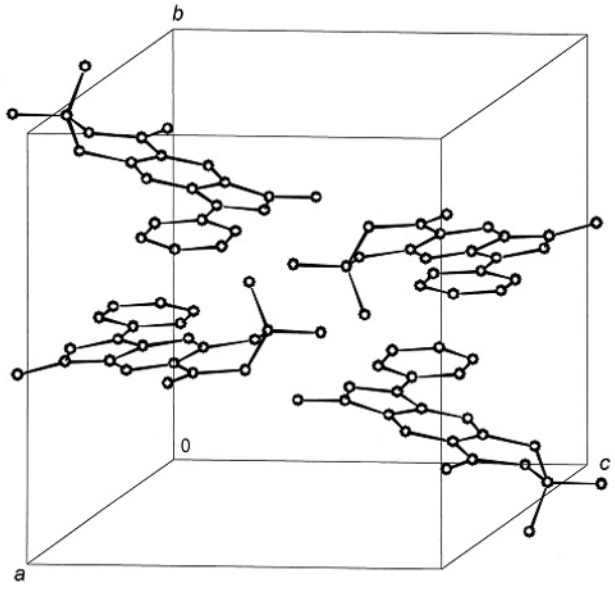


Fig. 2. Fragment of the crystal packing of compound **9b**.

A method of synthesis based on the use of 4-(dimethylamino)benzaldehyde in the Hantzsch reaction has enabled previously unknown partially hydrogenated derivatives of pyrazolo[3,4-*b*]quinolines, acridines, and pyrimido[4,5-*b*]quinolines, containing a γ-unsubstituted pyridine ring to be obtained easily.

EXPERIMENTAL

A check on the progress of reactions and the purity of the compounds synthesized was carried out by TLC on Silufol UV-254 plates in the solvent system benzene–ethanol, 9:1, visualizing in UV light. The IR spectra of compounds were recorded on a UR-20 instrument in KBr disks. The ^{1}H NMR spectra were obtained on a Bruker Avance DRX 500 instrument (500 MHz) in DMSO-d_6, standard was TMS.

X-Ray structural investigation of a monocrystal of size 0.25×0.31×0.43 mm, grown from a solution of compound **9b** in ethanol was carried out at room temperature on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (CuKα radiation, λ = 1.54178 Å, 2θ/ω scanning, $\theta_{max} = 70^o$, sphere segment $-13 \le h \le 12$, $0 \le k \le 15$, $0 \le l \le 13$). Overall 2929 reflections were collected of which 2217 are symmetrically independent (R_{int} = 0.01). Crystals of **9b** were monoclinic, a = 11.238(2), b = 12.584(2), c = 11.787(2) Å, β = 108.88(2)°, V = 1577.15(11) Å^3, M = 305.38, Z = 4, d_{calc} = 1.29 g/cm^3, μ = 6.093 cm^{-1}, F(000) = 649.70, space group $P2_1/n$ (N 15-17). The structure was solved by the direct method and refined by the least squares method (MNK) in a full-matrix anisotropic approximation using the CRYSTALS set of programs [20]. In the refinement 2217 reflections with $I > 3\sigma(I)$ were used (209 parameters refined, number of reflections per parameter 10.6). The hydrogen atoms were placed geometrically and included in the refinement with fixed thermal and positional

parameters. The weight scheme of Chebyshev [21] was used in the refinement with parameters 2.68, 2.93, 2.56, 0.813, and 0.574. The final values of the divergence factors R = 0.041 and R_w = 0.046, *GOOF* = 0.990. The residual electon density from the Fourier difference series was -0.19 and 0.17 e/Å^3. Calculation of absorption in the crystal was carried out with the aid of the azimuthal scanning method of [22]. The complete set of X-ray structural data for compound **9b** has been deposited in the Cambridge structural data bank (CCDC 664295).

4-[4-(Dimethylamino)phenyl]-3,7,7-trimethyl-1-phenyl-1,4,6,7,8,9-hexahydro-5H-pyrazolo[3,4-*b*]-quinolin-5-one (6b). A solution of compounds **1** (2.98 g, 20 mmol), **2b** (2.8 g, 20 mmol), and **3** (3.46 g, 20 mmol) in 2-propanol (7.5 ml) was maintained for 72 h at 15-20°C. The solid which separated was filtered off, washed with 2-propanol, and with hexane. Analytically pure product **6b** (4.1 g) was obtained.

9-[4-(Dimethylamino)phenyl]-6,8-dimethoxy-3,3-dimethyl-3,4,9,10-tetrahydroacridin-1(2H)-one (7b). A mixture of compounds **1** (0.298 g, 2 mmol), **2b** (0.28 g, 2 mmol), and **4** (0.306 g, 2 mmol) in 2-propanol (2 ml) was maintained at 75°C for 30 min. The cooled mass was filtered, the solid washed with 2-propanol, with hexane, and analytically pure product **7b** (0.723 g) was obtained.

5-[4-(Dimethylamino)phenyl]-1,3,8,8-tetramethyl-5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-2,4,6(1H,3H,7H)-trione (8b). A mixture of compounds **1** (1.49 g, 10 mmol), **2b** (1.4 g, 10 mmol), and **5** (1.55 g, 10 mmol) in glacial acetic acid (6 ml) was maintained at 80°C for 4 h. The cooled mass was filtered, the solid washed with 2-propanol, crystallized from pyridine, and product **8b** (2.5 g) was obtained.

3,7,7-Trimethyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-*b*]quinolin-5-one (9b). A. A mixture of compounds **1** (0.596 g, 4 mmol), **2b** (0.56 g, 4 mmol), and **3** (0.692 g, 4 mmol) in glacial acetic acid (4 ml) was maintained for 2 h at 120°C. The boiling reaction mixture was diluted with water (4 ml) with stirring. The cooled mass was filtered, the solid washed with a mixture of 2-propanol–water 1:1, crystallized from a mixture of pyridine–water, 1:1, and product **9b** (1.149 g) was obtained.

Product 9a was obtained analogously from compounds **1**, **2a** (0.56 g, 5 mmol), and compound **3**.

B. A mixture of compound **6b** (1.7 g, 4 mmol) and glacial acetic acid (4 ml) was maintained at 120°C for 2 h. The product was isolated as in method A, and compound **9b** (1.163 g) was obtained, which, according to data of TLC and mp, was identical to a sample obtained by method A.

6,8-Dimethoxy-3,3-dimethyl-3,4-dihydroacridin-1(2H)-one (10b). A. A mixture of compounds **1** (0.596 g, 4 mmol), **2b** (0.7 g, 5 mmol), and **4** (0.765 g, 5 mmol) in glacial acetic acid (4 ml) was maintained at 120°C for 2 h. The acetic acid was evaporated at the vacuum of a water-jet pump. The residue was dissolved with heating in acetone (4 ml). The hot solution was diluted with 20% aqueous ammonia solution (4 ml) and water (4 ml). The cooled mass was filtered, the solid washed with a mixture of 2-propanol–water, 1:2, crystallized from ethanol–water, 2 : 1, and product **10b** (0.934 g) was obtained.

Product 10a was obtained analogously from compounds **1**, **2a**, and **4**.

B. Product **10b** was obtained from compound **7b** by method B given for compound **9b** and isolated as given above for method A.

1,3,8,8-Tetramethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1H,3H,7H)-trione (11b). A. A mixture of compounds **1** (0.596 g, 4 mmol), **2b** (0.56 g, 4 mmol), and **5** (0.620 g, 4 mmol) in glacial acetic acid (4 ml) was maintained at 120°C for 2 h. The boiling reaction mixture was diluted with water (4 ml) with stirring. The cooled mass was filtered, the solid washed with a mixture of 2-propanol–water 1:1, crystallized from 2-propanol, and product **11b** (1.058 g) was obtained.

Product **11a** was obtained analogously from compounds **1**, **2a**, and **5**.

B. Product **11b** was obtained from compound **8b** by method B given for compound **9b**.

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