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THE *p*-(DIMETHYLAMINO)BENZALDEHYDE MODIFICATION OF HANTZSCH REACTION: SYNTHESIS OF 6-(1H-BENZIMIDAZOL-2-YL)PYRIDO[2,3-*d*]PYRIMIDINO-2,4(1H, 3H)-DIONES

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The reaction between p-(dimethylamino)benzaldehyde and 2-acylmethyl-1H-benzimidazoles and 6-amino-1,3-dimethylpyrimidino-2,4(1H,3H)-dione has given previously unknown 5-unsubstituted 6-(1H-benzimidazol-2-yl)pyrido[2,3-d]pyrimidino-2,4(1H,3H)-diones. The reaction occurs on boiling in acetic and acid and includes the formation of 1,4-dihydropyridine-bearing compounds in accordance with the Hantzsch reaction scheme and aromatization as a result of cleavage of N,N-dimethylaniline.

Keywords: aldehydes, benzimidazoles, pyrido[2,3-*d*]pyrimidines, pyrimidines, pyrazoles, aromatization, Hantzsch reaction, selectivity.

Substituted pyridines are frequently made by Hantzsch reaction in various modifications [1, 2]. We have found that the reaction between *p*-(dimethylamino)benzaldehyde (**1**), dimedone, and ammonium acetate on boiling in acetic acid is accompanied by the formation of an aromatic pyridine ring without the use of an oxidizing agent: the reaction occurs through the combination of acridine with the 1,4-dihydropyridine fragment containing the 4-(dimethylamino)phenyl substituent in the γ-position, and ends with the aromatization by the splitting off of N,N-dimethylaniline [3]. There are attractive prospects for using this as a new approach to synthesis of compounds containing γ-unsubstituted pyridine rings, but the situation is not entirely clear. We have examined this on the reactions in a three-component system: the aldehyde **1**, the 2-acylmethyl-1H-benzimidazoles **2a-h**, and 6-amino-1,3-dimethylpyrimidino-2,4(1H,3H)-dione (**3**). The reaction of compound **3** with various 1,3-dielectrophils has recently been used extensively in the synthesis of pyrido[2,3]*d*]pyrimidines [4-18], but the reactions with compounds **1** and **2** has not been examined before.

We found that boiling reagents **1-3** in acetic acid did not end with the formation of typical compounds in the 1,4-dihydropyridine series **4a-h**. The reaction was accompanied by aromatization, which probably occurs *via* the C-protonated forms **5a-h**, which readily split off N,N-dimethylaniline, and these to 5-unsubstituted 6-(1H-benzimidazol-2-yl)pyrido[2,3-*d*]pyrimidino-2,4(1H,3H)-diones **6a-h**. The reaction goes to completion in 2 h. The products are readily isolated by diluting the reaction mixtures with water. The yields are 78-93%.

The process occurs highly selectively under relatively mild conditions and is of fairly general character. It is not complicated by substantial side-reactions such as disproportionation, oxidation, or dehydrogenization of the 1,4-dihydropyridine compounds **4**, or the interaction of the aldehyde **1** with products from the nucleophile reaction centers in them. Correspondingly, the substituent R in position 7 of the pyridopyrimidines **6** may vary

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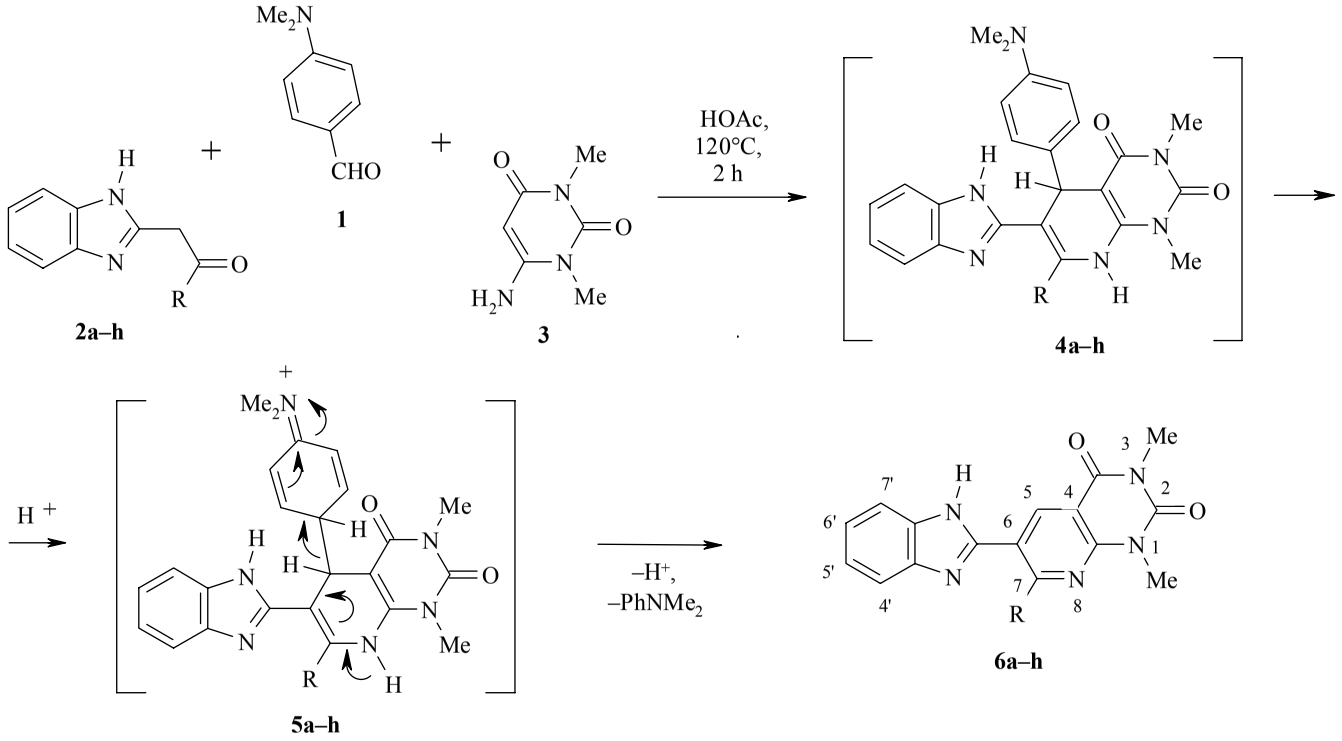

2, 4–6 **a** R = Me, **b** R = Ph, **c** R = 4-$MeOC_6H_4$, **d** R = 3,4,5-$(MeO)_3C_6H_2$, **e** R = 4-BrC_6H_4, **f** R = 3-$O_2NC_6H_4$, **g** R = 4-$O_2NC_6H_4$, **h** R = 2-furyl

TABLE 1. Characteristics of Synthesized Compounds **6a-h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
6a	$C_{17}H_{15}N_5O_2$	63.29 / 63.54	4.88 / 4.71	21.58 / 21.79	248.5-250	93
6b	$C_{22}H_{17}N_5O_2$	68.73 / 68.92	4.55 / 4.47	18.16 / 18.27	303-304.5	78
6c	$C_{23}H_{19}N_5O_3$	66.69 / 66.82	4.78 / 4.63	16.77 / 16.94	337-338.5	85
6d	$C_{25}H_{23}N_5O_5$	63.18 / 63.42	5.02 / 4.90	14.55 / 14.79	272-273.5	79
6e	$C_{22}H_{16}BrN_5O_2$	57.07 / 57.16	3.55 / 3.49	15.13 / 15.15	>350	85
6f	$C_{22}H_{16}N_6O_4$	61.49 / 61.68	3.84 / 3.76	19.41 / 19.62	304-305.5	85
6g	$C_{22}H_{16}N_6O_4$	61.53 / 61.68	3.89 / 3.76	19.44 / 19.62	>350	82
6h	$C_{20}H_{15}N_5O_3$	64.18 / 64.34	3.94 / 4.05	18.57 / 18.76	306-307.5	83

from alkyl to various aryl species, including the furan type. The yield trend in the series **6a-h** indicates that the reaction is only slightly dependent on the nature of the substituent R (when one corrects for the losses on isolation arising from differences in solubility).

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

Compound	δ, ppm (*J*, Hz)
6a	2.98 (3H, s, 7-CH_3); 3.31 (3H, s, 1-CH_3); 3.58 (3H, s, 3-CH_3); 7.22-7.23 (2H, m, H-5',6'); 7.53-7.55 (1H, m, H-7'); 7.67-7.68 (1H, m, H-4'); 8.72 (1H, s, H-5); 12.90 (1H, s, NH*)
6b	3.36 (3H, s, 1-CH_3); 3.65 (3H, s, 3-CH_3); 7.15-7.22 (2H, m, H-5',6'); 7.29 (2H, t, *J* = 7.5, C_6H_5: H-3,5); 7.35 (1H, t, *J* = 7.5, C_6H_5: H-4); 7.38 (1H, d, *J* = 7.8, H-7'); 7.44 (1H, d, *J* = 7.5, C_6H_5: H-4); 7.60 (1H, d, *J* = 7.5, H-4'); 8.61 (1H, s, H-5); 12.59 (1H, s, NH)
6c	3.34 (3H, s, 1-CH_3); 3.62 (3H, s, 3-CH_3); 3.69 (3H, s, CH_3O); 6.78 (2H, d, *J* = 8.4, C_6H_4O: H-3,5); 7.18-7.21 (2H, m, H-5',6'); 7.34 (2H, d, *J* = 9.0, C_6H_4O: H-2,6); 7.50 (2H, m, H-4',7'); 8.53 (1H, s, H-5); 12.68 (1H, s, NH)
6d	3.36 (3H, s, 1-CH_3); 3.41 (6H, s, 3,5-CH_3O); 3.63 (3H, s, 3-CH_3); 3.68 (3H, s, 4-CH_3O); 6.73 (2H, s, C_6H_2); 7.21-7.23 (2H, m, H-5',6'); 7.45 (1H, m, H-7'); 7.64 (1H, m, H-4'); 8.55 (1H, s, H-5); 12.62 (1H, s, NH)
6e	3.35 (3H, s, 1-CH_3); 3.63 (3H, s, 3-CH_3); 7.19-7.21 (2H, m, H-5',6'); 7.33 (2H, d, *J* = 8.4, C_6H_4Br: H-3,5); 7.42-7.48 (3H, m, H-7' + C_6H_4Br: H-3,5); 7.59 (1H, m, H-4'); 8.63 (1H, s, H-5); 12.72 (1H, s, NH)
6f	3.34 (3H, s, 1-CH_3); 3.61 (3H, s, 3-CH_3); 7.16-7.18 (2H, m, H-5',6'); 7.36 (1H, d, *J* = 7.8, H-7'); 7.46-7.50 (2H, m, H-4' + 3-$O_2NC_6H_4$: H-5); 7.65 (1H, d, *J* = 8.4, 3-$O_2NC_6H_4$: H-6); 8.11 (1H, d, *J* = 8.4, 3-$O_2NC_6H_4$: H-4); 8.21 (1H, s, 3-$O_2NC_6H_4$: H-2); 8.72 (1H, s, H-5); 12.89 (1H, s, NH)
6g	3.34 (3H, s, 1-CH_3); 3.61 (3H, s, 3-CH_3); 7.16-7.18 (2H, m, H-5',6'); 7.59 and 7.05 (2×2H, two d, *J* = 9.0, 4-$O_2NC_6H_4$); 8.74 (1H, s, H-5); 12.96 (1H, s, NH)
6h	3.33 (3H, s, 1-CH_3); 3.67 (3H, s, 3-CH_3); 6.60-6.62 (1H, m, furyl: H-4); 6.84 (1H, d, *J* = 3.3, furyl: H-3); 7.21-7.29 (2H, m, H-5',6'); 7.54 (1H, d, *J* = 8.1, H-7'); 7.71 (1H, d, *J* = 7.2, H-4'); 7.77 (1H, d, *J* = 0.9, furyl: H-5); 8.46 (1H, s, H-5); 12.82 (1H, s, NH)

* Undergoes deuterium exchange.

Attempts to replace the aldehyde **1** by formaldehyde, paraformaldehyde, or urotropine in the three-component reaction, including with the addition of nitrobenzene as oxidizing agent, have been unsuccessful: such reactions show little selectivity and it has proved impossible to isolate compounds of type **6** or their precursors of 1,4-dihydropyridine structure.

The compositions and structures of the synthesized pyrido[2,3-*d*]pyridines are confirmed by elemental analysis (Table 1) and by the ^{1}H NMR spectra (Table 2).

The structures of compounds **6a-h** are of the same type, since the signals from the protons in the fragments appearing in each of them occur in narrow ranges in the chemical shifts, and they vary quite regularly with the nature of substituent R. In particular, the H-5 singlet signal (corresponding to the γ-position in the pyridine ring) appears clearly in weak fields at 8.46-8.74 mp, and it shifts towards the weak-field side as we pass from electron-donor substituents R to electron-acceptor ones.

We thus confirm the practical usefulness of the *p*-dimethylaminobenzaldehyde modification of the reaction in the synthesis of previously unknown 5-unsubstituted 6-(1H-benzimidazol-2-yl)pyrido[2,3-*d*]-pyrimidino-2,4(1H,3H)-diones, but it is likely that the topic is not completely exhausted by this particular example.

EXPERIMENTAL

The reactions were monitored and the purity of the synthesized compounds was verified by TLC on Silufol UV-254 plates in the benzene-ethanol solvent system, 9:1, development in UV light. The ^{1}H NMR spectra were recorded with a Varian VXR-300 spectrometer (300 MHz) in DMSO-d_6, standard TMS. All the compounds were dried for 5 h at 145°C before elemental analysis and spectral test.

6-(1H-benzimidazol-2-yl)-1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (6a). A mixture of aldehyde **1** (0.149 g, 1 mmol), 2-acetonylbenzimidazole (**2a**) (0.174 g, 1 mmol), and compound **3** (0.155 g, 1 mmol) was mixed with 2 ml of glacial acetic acid and kept at 120°C for 2 h. Water was added by drops with stirring to the boiling solution until the reaction mixture became thick. After cooling, the precipitate was filtered off and washed with a mixture of 2-propanol and water, 1:1. Yield 0.297 g. The product was recrystallized from a 2:1 pyridine–water mixture.

Similarly, compounds **6b-h** were made from compounds **1**, **2b-h**, and **3**. Compounds **6c-e** were recrystallized from a 2:1 dimethylformamide–water mixture.

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