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p-(DIMETHYLAMINO)BENZALDEHYDE MODIFICATION OF THE HANTZSCH REACTION: SYNTHESIS OF 3-(1H-BENZ-IMIDAZOL-2-YL)-5,7-DIMETHOXY-QUINOLINES

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A three component cyclocondensation of p-(dimethylamino)benzaldehyde with 3,5-dimethoxyaniline and 2-phenacyl-1H-benzimidazoles gives previously unknown 2-aryl-3-(1H-benzimidazol-2-yl)-5,7-dimethoxyquinolines. The Hanztsch type reaction occurs in refluxing acetic acid and is accompanied by aromatization of the 1,4-dihydroquinolines formed through loss of N,N-dimethylaniline.

Keywords: aldehydes, anilines, benzimidazoles, quinolines, aromatization, dearylation, Hantzsch reaction, selectivity.

The Hantzsch synthesis of pyridines usually consists of two stages: a three component cyclocondensation of aldehydes with acetoacetic ester and ammonia (or ammonium acetate) and subsequent oxidation of the 1,4-dihydropyridines formed [1]. Exchange of acetoacetic ester for dimedone similarly gives acridine compounds with an aromatic pyridine ring (including those not containing a substituent at position 10) but the first stage of the reaction involving formaldehyde (or paraformaldehyde) occurs with very low selectivity and in only 41% yield [2]. As we reported earlier [3] the same acridine compound is obtained in 85% yield by replacing formaldehyde by *p*-(dimethylamino)benzaldehyde **1** in the starting three component system. In this case the reaction of the reagents in refluxing acetic acid does not stop at the formation of the corresponding 10-aryl-1,10-dihydroacridine but is accompanied by a previously unknown aromatization *via* fission of N,N-dimethylaniline. Such a modification of the Hantzsch reaction has clear advantages: 1) the aldehyde **1** is available and, in contrast to formaldehyde, stable on storage and readily measured out; 2) the use of an oxidant is not required; 3) the N,N-dimethylaniline formed in the reaction has a high solubility and does not hinder the separation of the product from the reaction mixture; 4) the process is single stage and efficient. In our opinion this variation of the Hantzsch reaction can be efficiently used as a novel and convenient method for preparation of compounds with a γ-unsubstituted pyridine ring which we have also demonstrated in our work on the synthesis of novel quinoline compounds.

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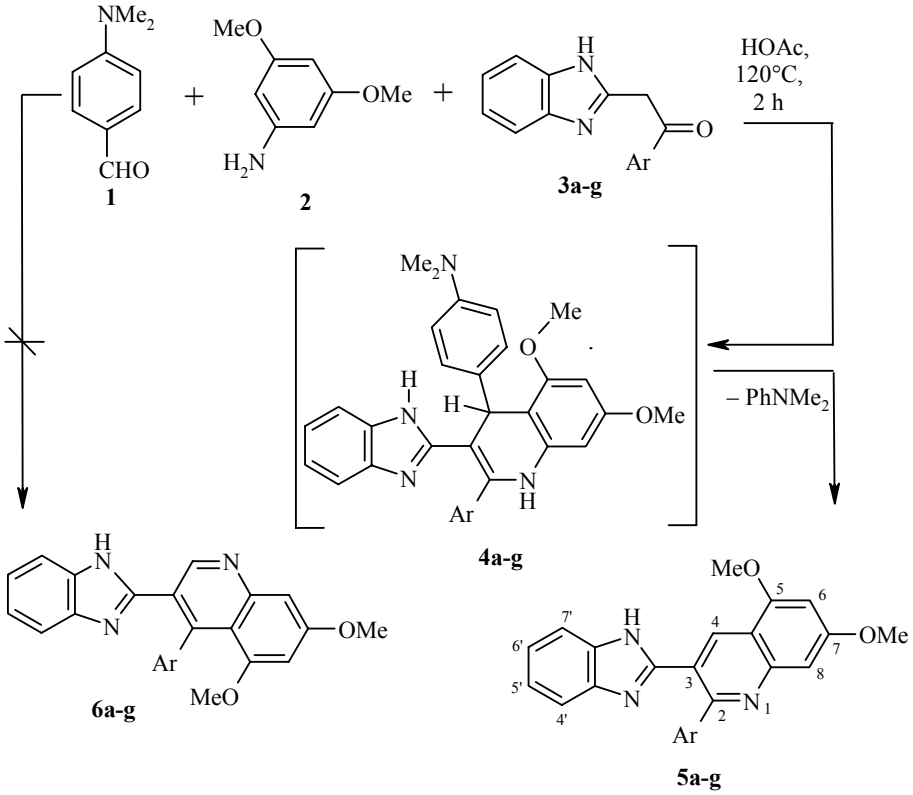
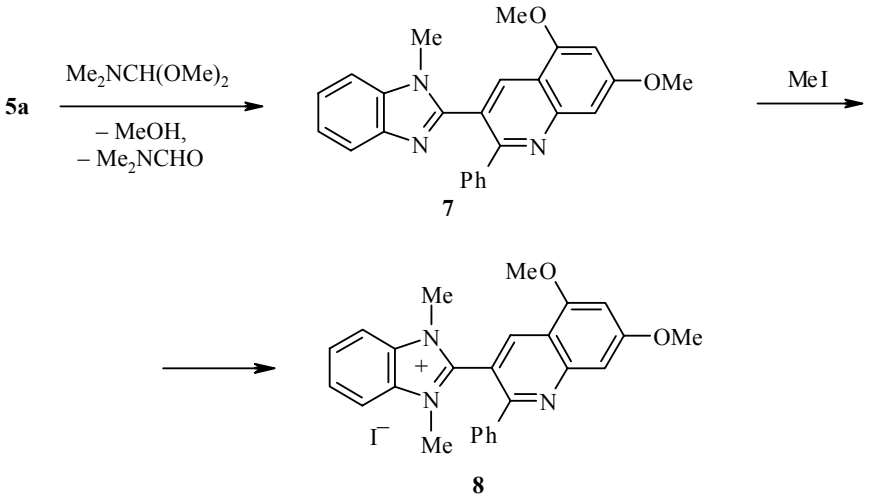
We began with the fact that one of the methods of preparing 1,4-dihydropyridines is based on a three component [1+3+2] cyclocondensation of aldehydes with β-aminocrotonic ester and acetoacetic ester [4]. This method can be extended by varying the nature of the reaction components, in particular was use of 5-aminopyrazoles and dimedone for synthesis of pyrazoloquinolines [5]. For the first time we have used a similar reaction of aldehyde **1** with 3,5-dimethoxyaniline **2** as the 1,3-[N,C]-dinucleophilic component and the 2-phenacyl-1H-benzimidazoles **3a-g** as the methylene carbonyl component. It was found that the three component cyclocondensation of aldehydes, anilines, and methyl ketones to form quinolines (known as the so called Bayer reaction) occurs such that the starting aldehyde introduces its substituent into the 2 position of the target product [6].

We have found that the reactions of the reagents **1-3** occur regioselectively in refluxing acetic acid *via* a Hanztsch reaction. However, they do not stop at the formation of the expected compounds **4a-g** which contain a 1,4-dihydropyridine fragment but undergo subsequent aromatization with fission of N,N-dimethylaniline to give the previously unknown 4-unsubstituted 2-aryl-3-(1H-benzimidazol-2-yl)-5,7-dimethoxyquinolines **5a-g**. The products with an isomeric 2-unsubstituted quinoline structure **6a-g** were not detected (their formation would have been possible if the process occurred *via* a Bayer reaction scheme).



3–6 a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-MeC_6H_4, **d** Ar = 3,4,5-$(MeO)_3C_6H_2$, **e** Ar = 4-BrC_6H_4, **f** Ar = 3-$O_2NC_6H_4$, **g** Ar = 4-$O_2NC_6H_4$

The reaction is not markedly complicated by side processes (e.g. reaction of aldehyde **1** with the target material which have a reactive nucleophilic center) and is complete after 2 h. The products were separated from the reaction mixtures by dilution with water in 72-94% yields.



The structure of compound **5a** was confirmed by methylation at the benzimidazole nitrogen atom and subsequent quaternization of product **7** with methyl iodide to give the salt **8**. In contrast to the remaining synthesized compounds we have been able to grow crystals suitable for X-ray analysis from this salt. The overall view of cation **8** and its basic geometric parameters are given in Figure 1. Both bicyclic systems $N_{(1)}N_{(2)}C_{(1\text{-}7)}$ and $N_{(3)}C_{(8\text{-}16)}$ are planar (the deviation of the atoms from the mean square planes not exceeding 0.007 and 0.026 Å). The dihedral angle between these systems is 65.6º. The benzene ring $C_{(19\text{-}24)}$ is twisted by 39.4º relative to the $N_{(3)}C_{(8\text{-}16)}$ plane. The $N_{(1)}$ and $N_{(2)}$ atoms have a planar trigonal configured bonds (sum of valence angles at these atoms 360.0 and 359.9º). Evidently it is position 4 and not 2 which is unsubstituted in the quinoline ring of cation **8**. This conclusion also extends to compounds **7** and **5a** since the chemical changes occurring in them only alter the immediate surroundings of the nitrogen atoms in the molecules.

The composition and structure of all of the synthesized compounds were confirmed through elemental analysis (Table 1) and from their ^{1}H NMR spectra (Table 2).

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
5a	$C_{24}H_{19}N_3O_2$	75.48 / 75.57	4.89 / 5.02	10.89 / 11.02	300-301.5	88
5b	$C_{25}H_{21}N_3O_3$	72.79 / 72.98	5.01 / 5.14	10.03 / 10.21	319-320.5	75
5c	$C_{25}H_{21}N_3O_2$	75.78 / 75.93	5.44 / 5.35	10.47 / 10.63	311-312.5	87
5d	$C_{27}H_{25}N_3O_5$	68.65 / 68.78	5.25 / 5.34	8.74 / 8.91	233-235	86
5e	$C_{24}H_{18}BrN_3O_2$	62.49 / 62.62	3.81 / 3.94	8.97 / 9.13	287.5-289	92
5f	$C_{24}H_{18}N_4O_4$	67.47 / 67.60	4.18 / 4.25	13.07 / 13.14	272.5-274	72
5g	$C_{24}H_{18}N_4O_4$	67.49 / 67.60	4.15 / 4.25	13.09 / 13.14	276.5-278	94
7	$C_{25}H_{21}N_3O_2$	75.79 / 75.93	5.21 / 5.35	10.48 / 10.63	198.5-200	91
8	$C_{26}H_{24}IN_3O_2$	58.05 / 58.11	4.26 / 4.50	7.69 / 7.82	273-276 (dec.)	81

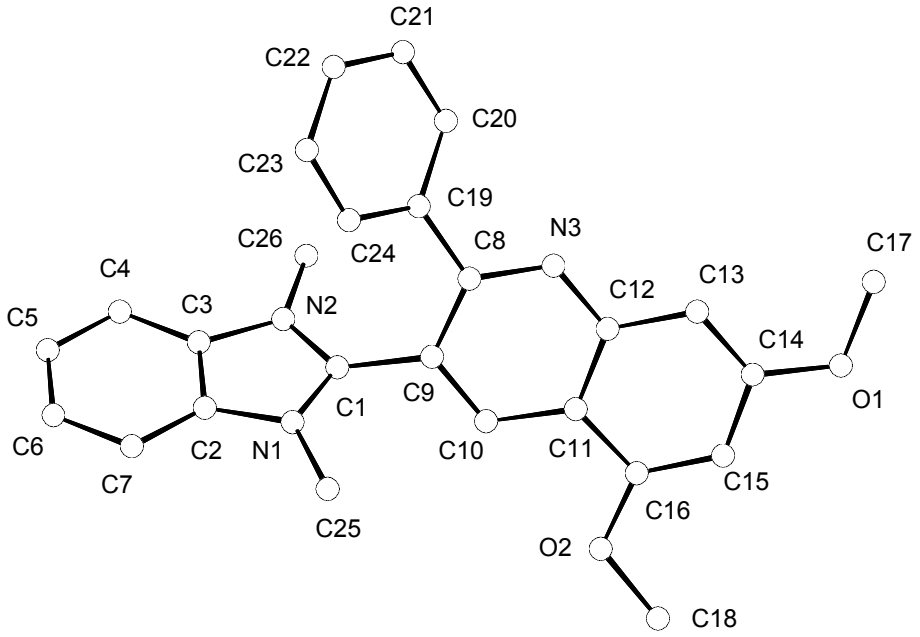


Fig. 1. Overall view of the compound **8** cation. Basic bond lengths (*l*) and valence angles (ω).
l: ($N_{(1)}$–$C_{(1)}$ 1.334(2), $N_{(1)}$–$C_{(2)}$ 1.386(2), $N_{(2)}$–$C_{(1)}$ 1.335(2), $N_{(2)}$–$C_{(3)}$ 1.384(2), $N_{(3)}$–$C_{(8)}$ 1.318(2), $N_{(3)}$–$C_{(12)}$ 1.362(2) Å; ω: $C_{(1)}N_{(1)}C_{(2)}$ 108.4(1), $C_{(1)}N_{(2)}C_{(3)}$ 108.7(1), $C_{(8)}N_{(3)}C_{(12)}$ 119.7(2) deg.

The similarity of structure for compounds **5a-g** follows from the fact that the chemical shifts of identically placed protons in their bicyclic fragments have very small differences whose dependence can be fully related to the change in the nature of the Ar substituent. In particular, the singlet signal for the quinoline ring H-4 appears clearly at 8.64-8.81 ppm, shifted to lower fields with a systematic change from electron-donor to electron-acceptor aryl R substituent.

Hence the limits of the Hantzsch reaction in the synthesis of compounds with an aromatic γ-unsubstituted pyridine ring can be overcome by exchanging formaldehyde for *p*-(dimethyl-amino)benzaldehyde. Such a reaction modification has quite a widespread usage and is particularly suitable for preparing the previously unknown 4-unsubstituted 3-(1H-benzimidazol-2-yl)-5,7-dimethoxyquinolines.

EXPERIMENTAL

Monitoring of the reaction course and purity of the synthesized compounds was carried out by TLC on Silufol UV-254 plates using the solvent system benzene–ethanol (9:1) and revealed using UV light. ^{1}H NMR Spectra for the compounds were recorded on a Varian VXR-300 spectrometer (300 MHz) using DMSO-d_6 solvent and TMS as standard. Before determination of elemental analysis and spectroscopic investigation the compounds were dried for 5 h at 145ºC (crystals of salt **8** were dried at 20-25ºC for X-ray analysis).

X-ray Structural Investigation of Compound 8 Single Crystal which was grown from ethanol and had dimensions 0.30×0.30×0.45 mm was carried out at room temperature on a Bruker Apex II automatic diffractometer (MoKα radiation, λ = 0.71069 Å, θ_{max} = 35º, $-29 \le h \le 33$, $-17 \le k \le 14$, $-35 \le l \le 19$). In all 25,150 reflections were collected (9941 independent reflections, R_{int} = 0.023). Crystals of compound **8** are monoclinic with a = 20.739(2), b = 10.8940(8), c = 22.033(2) Å, β = 91.84(1)º, V = 4975.3(7) Å^3, M = 545.4,

TABLE 2. ^{1}H NMR Spectroscopic Characteristics of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm, (*J*, Hz)
5a	3.97 (3H, s, 5-CH_3O); 4.02 (3H, s, 7-CH_3O); 6.77 (1H, d, *J* = 1.8, H-6); 7.12 (1H, d, *J* = 1.8, H-8); 7.16-7.19 (2H, m, H-5',6'); 7.33 (3H, m, 3H_{Ph}-*m*,-*p*); 7.40 (1H, m, H-7'); 7.46-7.48 (2H, m, 2 H_{Ph}-*o*); 7.61-7.63 (1H, m, H-4'); 8.70 (1H, s, H-4); 12.40 (1H, s, NH*)
5b	3.74 (3H, s, CH_3O_{Ar}); 3.96 (3H, s, 5-CH_3O); 4.00 (3H, s, 7-CH_3O); 6.72 (1H, d, *J* = 1.8, H-6); 6.85 and 7.46 (2 × 2H, two d, *J* = 8.4, 4H_{Ar}); 7.08 (1H, d, *J* = 1.8, H-8); 7.16-7.19 (2H, m, H-5',6'); 7.42 (1H, m, H-7'); 7.61-7.64 (1H, m, H-4'); 8.64 (1H, s, H-4); 12.24 (1H, s, NH)
5c	2.28 (3H, s, CH_3); 3.96 (3H, s, 5-CH_3O); 4.00 (3H, s, 7-CH_3O); 6.74 (1H, d, *J* = 1.8, H-6); 7.09 and 7.39 (2 × 2H, two d, *J* = 8.7, 4H_{Ar}); 7.08 (1H, d, *J* = 1.8, H-8); 7.16-7.19 (2H, m, H-5',6'); 7.41 (1H, m, H-7'); 7.61 (1H, m, H-4'); 8.65 (1H, s, H-4); 12.38 (1H, s, NH)
5d	3.45 (6H, s, 2CH_3O_{Ar}-*m*); 3.65 (3H, s, CH_3O_{Ar}-*p*); 3.98 (3H, s, 5-CH_3O); 4.00 (3H, s, 7-CH_3O); 6.75 (1H, d, *J* = 1.8, H-6); 6.78 (2H, s, 2H_{Ar}); 7.11 (1H, d, *J* = 1.8, H-8); 7.20–7.23 (2H, m, H-5',6'); 7.43-7.46 (1H, m, H-7'); 7.65-7.68 (1H, m, H-4'); 8.64 (1H, s, H-4); 12.45 (1H, s, NH)
5e	3.97 (3H, s, 5-CH_3O); 4.02 (3H, s, 7-CH_3O); 6.78 (1H, d, *J* = 2.1, H-6); 7.12 (1H, d, *J* = 2.1, H-8); 7.17–7.22 (2H, m, H-5',6'); 7.39 and 7.52 (2 × 2H, two d, *J* = 8.7, 4H_{Ar}); 7.43–7.46 (1H, m, H-7'); 7.60-7.63 (1H, m, H-4'); 8.72 (1H, s, H-4); 12.51 (1H, s, NH)
5f	3.97 (3H, s, 5-CH_3O); 4.04 (3H, s, 7-CH_3O); 6.80 (1H, d, *J* = 2.1, H-6); 7.15-7.18 (3H, m, H-8 + H-5',6'); 7.41 (1H, d, *J* = 7.2, H-7'); 7.52-7.56 (2H, m, H-4' + H_{Ar}-5); 7.66 (1H, d, *J* = 7.2, H_{Ar}-6); 8.20 (1H, d, *J* = 7.5, H_{Ar}-4); 8.42 (1H, s, H_{Ar}-2); 8.81 (1H, s, H-4); 12.64 (1H, s, NH)
5g	3.97 (3H, s, 5-CH_3O); 4.04 (3H, s, 7-CH_3O); 6.80 (1H, d, *J* = 2.1, H-6); 7.11 (1H, d, *J* = 2.1, H-8); 7.15-7.23 (2H, m, H-5',6'); 7.44 (1H, d, *J* = 7.2, H-7'); 7.55 (1H, d, *J* = 7.2, H-4'); 7.67 and 8.15 (2 × 2H, two d, *J* = 9.0, 4H_{Ar}); 8.81 (1H, s, H-4); 12.74 (1H, s, NH)
7	3.10 (3H, s, NCH_3); 3.98 (3H, s, 5-CH_3O); 4.00 (3H, s, 7-CH_3O); 6.78 (1H, d, *J* = 1.8, H-6); 7.15 (1H, d, *J* = 1.8, H-8); 7.25-7.37 (5H, m, H-5',6' + 3H_{Ph}-*m*,-*p*); 7.42–7.44 (3H, m, H-7' + 2H_{Ph}-*o*); 7.69–7.72 (1H, m, H-4'); 8.62 (1H, s, H-4)
8	3.70 (6H, s, 2NCH_3); 4.02 (3H, s, 5-CH_3O); 4.03 (3H, s, 7-CH_3O); 6.90 (1H, d, *J* = 1.8, H-6); 7.27 (1H, d, *J* = 1.8, H-8); 7.33 (2H, t, *J* = 7.8, 2H_{Ph}-*m*); 7.40-7.46 (3H, m, 3H_{Ph}-*o*,*p*); 7.71–7.75 (2H, m, H-5',6'); 8.02–8.07 (2H, m, H-4',7'); 9.08 (1H, s, H-4)

* Undergoes deuterium exchange.

Z = 8, d_{calc} = 1.46 g/cm^3, μ = 13.16 cm^{-1}, *F*(000) = 2192, space group *C*2/*c* (N 15). The structure was solved by a direct method and refined by least squares analysis in a full matrix anisotropic approximation using the CRYSTALS program package [7]. 6001 reflections were used in the refinement with $I > 3\sigma(I)$ (294 refinement parameters, number of reflections per parameter 20.4). All of the hydrogen atoms (with the exception of the water solvate molecules) were revealed in electron density difference synthesis and included in the refinement with fixed positions and thermal parameters. The Chebyshev [8] weighting scheme was used in the refinement with the five parameters 1.03, 1.09, 1.07, 0.38, and 0.27. The final divergence factor values were *R* = 0.029 and R_w = 0.031, *GOOF* = 1.086. The residual electron density from Fourier synthesis was 0.53 and 0.83 e/Å^3. The full set of X-ray data for compound **8** has been placed in the Cambridge structural database (CCDC 631876).

3-(1H-Benzimidazol-2-yl)-5,7-dimethoxy-2-phenylquinoline (5a). A mixture of aldehyde **1** (0.164 g, 1.1 mmol), aniline **2** (0.229 g, 1.5 mmol), and 2-phenacyl-1H-benzimidazole **3a** (0.236 g, 1 mmol) in glacial acetic acid (2 ml) was held at 120ºC for 2 h. The refluxing solution was stirred and diluted with water (4 ml). After cooling, the precipitate was filtered off and washed with a mixture of 2-propanol and water (1:1). Yield 0.338 g. The product was recrystallized from a mixture of pyridine and water (4:1).

Compounds 5b-g were prepared similarly from **1**, **2**, and **3b-g**.

5,7-Dimethoxy-3-(1H-1-methylbenzimidazol-2-yl)-2-phenylquinoline (7). A mixture of compound **5a** (0.381 g, 1 mmol), DMF dimethylacetal (1 ml), and anhydrous pyridine (1 ml) was held at 105-110ºC for 6 h. Water (3 ml) was added with stirring. After cooling, the precipitate was filtered off and washed with a mixture of 2-propanol and water (1:1) to give the product in an analytically pure state (0.361 g).

2-(5,7-Dimethoxy-2-phenylquinolin-3-yl)-1,3-dimethyl-3H-benzimidazol-1-ium Iodide (8). A mixture of compound **7** (0.198 g, 0.5 mmol), methyl iodide (1.2 ml, 20 mmol), and anhydrous acetonitrile (2 ml) was heated on a bath at 70-75ºC for 12 h. The reaction mixture was treated with toluene (5 ml), refluxed with stirring, the low boiling components removed, and filtered hot. The precipitate on the filter was washed with refluxing toluene and with diethyl ether after cooling. Crystallization from a mixture of ethanol and water (3:1) gave 0.21 g of the product.

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