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Synthesis of Polyazaheterocycles by Michael Addition of CH Acids to α,β-Unsaturated Nitriles. Synthesis of Pyrido[1,2-a]benzimidazole and Pyrimido[5′,4′:5,6]pyrido[1,2-a]benzimidazole Derivatives

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Abstract. Addition of 1H-benzimidazole-2-carbonitrile (**1**) to arylidenemalononitrile (**2**) gave 1-amino-3-aryl pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**3**), 2-aryl-benzimidazole (**4**) and 1H-benzimidazole-2-acetonitrile,α-(arylmethylene) (**5**). Compounds (**3**) reacted with formamide yielding 4-amino-5-aryl pyrimido[5′,4′:5,6]pyrido[1,2-a]benzimidazole (**6**).

The chemistry of pyrido[1,2-a]benzimidazole has been of increasing interest, since some of its derivatives have found application as chemoterapeutics [1]. On the other hand, various benzimidazoles themselves can act as tuberculostatic agents [2].

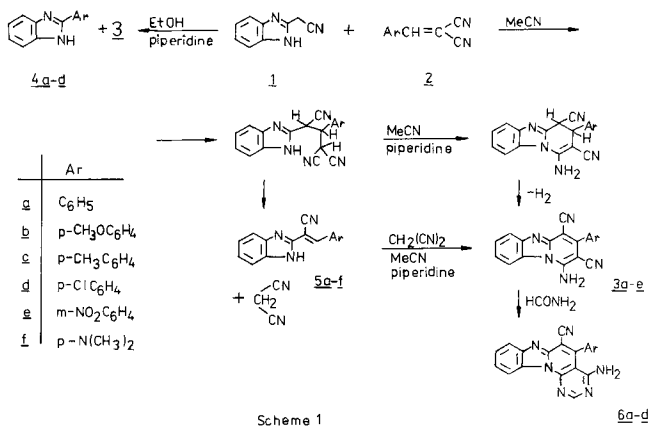
One of the routes for pyrido[1,2-a]benzimidazole skeleton synthesis is based on the condensation of 1H-benzimidazole-2-acetonitrile **1** with 1,3-dicarbonyl compounds. Ried et al. [3]. reported the synthesis of 1,3-dimethyl-pyrido[1,2-a]benzimidazole-4-carbonitrile using **1** and 2,4-pentandione. Kappe et al. [4, 5] claimed that the reaction of β-keto esters e.g. ethyl acetoacetate, ethyl benzoylacetate or 2-ethyl cyclopentanonecarboxylate in the presence of ammonium acetate gave 1-oxo-pyrido[1,2-a]benzimidazole-4-carbonitrile derivatives.

Continuing our study on the reaction of α,β-unsaturated nitriles with compounds containing active methylene groups [6, 7] we turned our attention on **1**. Although compound **1** may act as bifunctional nucleophile, bearing nucleophilic center at the methylene carbon atom as well as at one of nitrogen atom of imidazole ring, various reactions showed that the methylene group is the stronger activated one, e.g. the acylation with arylisothiocyanate occurs at this position [8].

In this paper we report a one step synthesis of 1-amino-3-aryl-pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile involving the reaction of **1** with substituted benzylidenemalononitriles **2a – e**. Various substituted benzylidenemalononitriles were used to determine the influence of the substituents on yields and the type of obtained products.

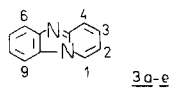
The reaction of **1** with **2a – e** performed in boiling ethanolic solution in the presence of piperidine furnished a mixture of the desired pyrido[1,2-a]benzimidazole derivatives **3a – e** in yields ranging from 15 % to 46 % and already reported 2-aryl-benzimidazoles **4a – e** [9, 10] (Scheme 1).

To increase the yield of compounds **3** and to avoid the formation of undesired products, we carried out the reaction of **1** with **2** in acetonitrile with catalytic amounts of piperidine. These reactions led almost exclusively to compounds **3** in moderate to very good yields. The structure of obtained compounds **3a – e** were established on the basis of analytical and i.r, ^{1}H n.m.r. and m.s. spectral data. Compounds **3a – e** are stable yellow crystalline products, with high m.p.s. and poor solubility in common organic solvents (Table 1).

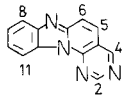


Scheme 1

Table 1 Physical properties and spectral data of compounds obtained



3a-e



6a-d

No	Yield (%)	m.p. (° C) solvent	i.r. (cm^{-1})	^1H NMR (δ ppm)	MS (m/z %)
3a	81[a] 15[b]	355 – 360 decomp. DMF-H_2O sublim.	2208 C≡N 2224 3240 NH_2 3320 3430	7.27 – 7.83 m 8H arom. 8.55 d 1H C9 8.64 s 2H NH_2	308.8 100
3b	83[a] 21[b]	332 – 337 decomp. BuOH sublim.	2218 C≡N 3110 NH_2 3330 3420	3.82 s 3H OCH_3 7.05 – 7.84 m 7H arom. 8.50 d 1H C9 8.58 s 2H NH_2	338.9 100
3c	94[a] 46[b]	325 – 330 decomp. dioxane sublim.	2200 C≡N 3216 NH_2 3320 3430	2.46 s 3H CH_3 7.38 – 7.94 m 7 H arom. 8.65 d 1H C9 8.73 s 2H NH_2	323 20
3d	64[a] 32[b]	340 – 350 decomp. dioxane sublim.	2200 C≡N 3200 NH_2 3310 3440	7.46 – 7.95 m 7H arom. 8.65 d 1H C9 8.81 s 2H NH_2	344 100
3e	37[a]	360 – 370 DMF	2216 C≡N 3390 NH_2 3480	7.38 – 8.65 m 8H arom. 8.83 s 2H NH_2	354 100
6a	92	350 – 354 decomp. DMF sublim.	2230 C≡N 3290 NH_2 3440	7.50 – 9.35 m 9H arom. 9.16 s 1H C2	335.6 100
6b	93	360 – 365 decomp. DMF	2224 C≡N 3290 NH_2 3450	4.05 s 3H OCH_3 7.20 – 9.50 m 8H arom. 9.25 s 1H C2	366.0 100
6c	93	350 – 355 decomp. DMF sublim.	2220 C≡N 3290 NH_2 3440	2.62 s 3H CH_3 7.40 – 9.45 m 8H arom. 9.18 s 1H C2	349.6 100
6d	83	350 – 353 decomp. DMF	2225 C≡N 3290 NH_2 3450	7.40 – 9.35 m 8H arom. 9.16 s 1H C2	370.3 100

The reaction of **1** with **2** leading to **3** ist assumed to proceed as shown in Scheme 1, and involves Michael addition. The resulting adduct may undergo cyclization in situ by nucleophilic attack of the nitrogen atom of imidazole ring at the cyano group to form the six membered ring which, on aromatization gives **3**. The Michael adduct may also split into malononitrile and 1H-benzimidazole-2-acetonitrile, α-(arylmethylene) **5**, [10, 11]. This course of reaction was observed when **1** and **2a – e** reacted in acetonitrile without piperidine (Scheme 1). We have noticed that the way of transformation of the preliminary formed Michael adduct is strongly influenced by reaction medium as well as by the substituent in aryl moiety. Reaction of **1** with **2e** containing m-NO_2- group led exclusively to **3e** whereas reaction of **1** with **2f** containing p-$(CH_3)_2N$-group afforded under the investigated conditions compound **5f** in quantitative yield (82 – 90 %). The reac-

tion course of **1** with **2** leading to **3** or/and **5** is similar to recently reported reactions of cyanomethyl derivatives of thiazole [12, 13] and pyrazole [14] with α,β-unsaturated nitriles.

Hammad et al. [15] have recently reported the synthesis of some pyrido[1,2-a]benzimidazoles, which seen to be isomeric with these prepared by us. The difference concerns the position of aryl and amino groups attached to the pyridine moiety of the molecule. The reported synthesis involved the reaction of **5** with malononitrile[1]. To compare the compounds **3**, with those reported by Hammad, we repeated the reaction of **5a – b** with malononitrile in the presence of piperidine (Scheme 1). The products obtained in these reactions were in all respects identical with samples **3a,b** prepared by addition of **1** to **2a,b**. Thus the structure of compounds obtained by Hammad is identical with the structure established by us.

Compounds **3** behave as typical o-amino nitriles. They reacted readily with formamide yielding pyrimidine derivative **6** in excellent yield (Scheme 1). Some of compounds **6** showed strong green-yellow fluorescence in organic solvents.

Experimental

Melting points were determined with a Boëtius apparatus and are corrected. The i.r. spectra were obtained on a IR-80 (Carl-Zeiss, Jena) spectrometer in nujol mulls. The ^{1}H n.m.r. spectra were recorded on a Tesla BS-567 A (100 MHz) spectrometer using DMSO-d_6 as solvent and Me_4Si as internal standard. The position of protons of NH_2 group in compounds **3** were established by deuteration. The spectra of **6** were measured in CF_3COOD. The m.s. spectra were taken on LKB-9000S and Jeol IMS-D100 instruments. Elemental analyses were performed on a Perkin Elmer Analyser Type 240.

Starting materials 1H-benzmidazole-2-acetonitrile **1** [16] and arylidenemalononitriles (**2a – f**) [17] were prepared according to literature procedures.

1-Amino-3-aryl-pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (3a – e)

a) Reaction **1** *with* **2** *in acetonitrile*

A mixture of **1** (0.78 g, 5 mmol) and corresponding benzylidenemalononitrile **2** (0.94 g, 6 mmol, **2a**) was refluxed for 4 h in 40 ml of acetonitrile with few drops of piperidine. After cooling the precipitate was filtered off. Evaporation of acetonitrile under reduced pressure gave oily residue, which by treating with methylene chloride gave an additional portion of product **3**. Compounds were crystallized from solvents given in Table 1. Some samples for analyses were purified by sublimation.

[1] In the abstract of ref. [15] instead of $R'CH_2CN$ there is $R'C_2CN$ ($R' = CN$).

b) Reaction of **1** *with* **2** *in ethanol*

The mixture of **1** (1.57 g, 10 mmol) and **2** (1.69 g, 11 mmol, **2a**) was refluxed for 4 h in ethanol with catalytic amounts of piperidine. The precipitated solid of **3** was filtered off. The ethanolic solution was evaporated and the residue was treated with 10 ml of methylene chloride. The precipitate was filtered off and then treated with boiling ethanol. Insoluble in ethanol the product (**3**) was separated. Evaporation and cooling of ethanolic solution afforded compound **4** in yield 40 – 60 %.

c) Reaction of **5** *with malononitrile*

The mixture of **5** (0.51 g, 2 mmol **5a**) and of malononitrile (0.13 g, 2 mmol) was refluxed for 3 h in 15 ml of acetonitrile with few drops of piperidine. The solvent was evaporated under reduced pressure, and the semisolid product was treated with 10 ml of ethanol, filtered off and crystallized. Average yield 17 %. The identity of products **3** obtained by methods a, b and c was confirmed by comparison of m.p.s and i.r. spectra.

1-H Benzimidazole-2-acetonitrile, α-(arylmethylene) (5)

A solution of **1** (0.78 g, 5 mmol) and **2** (0.92 g, 6 mmol, **2a**) in 40 ml of acetonitrile was refluxed for 4 h. After cooling the precipitate was filtered off and crystallized from ethanol. The chemical and physical properties of obtained compounds **5a – f** were consistent with those reported in ref. [11].

4-Amino-5-aryl-pyrimido[5′,4′:5,6]pyrido[1,2-a]benzimidazole (6a – d)

1 g of **3** was refluxed in 20 ml of freshly distilled formamide for 2 h. After cooling the precipitate was filtered off and crystallized from DMF.

Table 2 Analytical data of compounds **3a – e** and **6a – d**

No	Molecular formula (molecular weight)	Analyses Calcd/Found % C	H	N
3a	$C_{19}H_{11}N_5$ (309.32)	73.77 73.56	3.58 3.50	22.64 22.05
3b	$C_{20}H_{13}N_5O$ (339.34)	70.78 70.55	3.86 3.89	20.64 20.69
3c	$C_{20}H_{13}N_5$ (323.34)	74.29 73.99	4.05 4.10	21.66 21.61
3d	$C_{19}H_{10}ClN_5$ (343.77)	66.68 66.15	2.93 2.90	20.37 20.38
3e	$C_{19}H_{10}N_6O_2$ (354.32)	64.40 64.16	2.84 2.75	23.72 24.24
6a	$C_{20}H_{12}N_6$ (336.34)	71.41 71.08	3.59 3.51	24.99 24.97
6b	$C_{21}H_{14}N_6O$ (366.37)	68.84 68.54	3.85 3.90	22.94 22.90
6c	$C_{21}H_{14}N_6$ (350.37)	71.98 71.90	4.03 4.03	23.99 23.73
6d	$C_{20}H_{11}ClN_6$ (370.79)	64.78 64.48	2.99 2.97	22.67 22.73

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