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Reactions with 2-Aminobenzimidazole: Synthesis of Several New Pyrimido[1,2-*a*]benzimidazole Derivatives

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Several new pyrimido[1,2-*a*]benzimidazole derivatives were synthesized by reacting 2-aminobenzimidazole with α, β-unsaturated nitriles and benzoylacetonitrile derivatives. The structures of the products were established on the basis of elemental analyses, IR and ^{1}H-NMR spectral data.

Umsetzungen mit 2-Aminobenzimidazol: Synthese einiger neuer Pyrimido[1,2-a]benzimidazol-Derivate

Mehrere neue Pyrimido[1,2-a]benzimidazole Derivate wurden durch Reaktionen von 2-Aminobenzimidazol mit α, β-ungesättigten Nitrilen und Benzoylacetonitril-Derivaten synthetisiert. Die Strukturen der neuen Derivate wurden anhand der Elementaranalyse, der IR- und ^{1}H-NMR-Spectren identifiziert.

The incorporation of an imidazole nucleus, a biologically accepted pharmacophore, in the benzimidazole nucleus has made it a versatile heterocycle possessing a wide spectrum of biological activities. In addition, a large variety of substituted 2-aminobenzimidazoles have been found to possess *in vivo* and *in vitro* growth inhibitory activity against various strains of bacteria, fungi and viruses. Moreover, several 1- and 1,3-disubstituted benzimidazoles and pyrimido[1,2-a]benzimidazoles are known to exhibit CNS depressant, anti-inflammatory, antithyroid and cardiovascular activities[1]. The above mentioned biological and medicinal activities of benzimidazoles and related compounds prompted our interest for the synthesis of several new derivatives of these ring systems. The reactions of 2-aminobenzimidazole **(1)** with α, β-unsaturated nitriles and benzoylacetonitrile derivatives **(2)** seemed to us to be a sole, easy and facile route for the synthesis of these derivatives.

Thus, **1** reacted base catalyzed with the α, β-disubstituted acrylonitriles **2a–e** to yield products which can be formulated as the 2-aminopyrimido[1,2-a]benzimidazoles **4a–e**. The formation of **4a–e** is assumed to proceed via the non-isolable Michael adducts **3** which consequently cyclised by the addition to the cyano function to yield **4a–e**. Their structures were confirmed by elemental analyses and spectral data (cf. Experimental Part). Moreover, isomeric forms for **4a–e** (the 4-amino-analoges) were ruled out on the basis of the products obtained by the reaction of **1** with the ylidene derivative **2f** and **2g** as follows.

Thus, in contrast to its behaviour towards **2a–e**, **1** reacted with the acrylonitrile **2f** under identical conditions to the isolable *Michael* adduct **5**. Structure **5** was confirmed by its correct elemental analysis and its spectral data. Thus, its IR spectrum revealed the presence of NH_2, saturated CH, CN and ester C=O groups. The ^{1}H-NMR of **5** revealed a triplet at (δ ppm) 1.3 (CH_3) and a quartet at 3.8 (CH_2) of the ethoxy group beside signals due to NH_2, CH and aromatic protons (cf. Tables 1 and 2). Moreover, a

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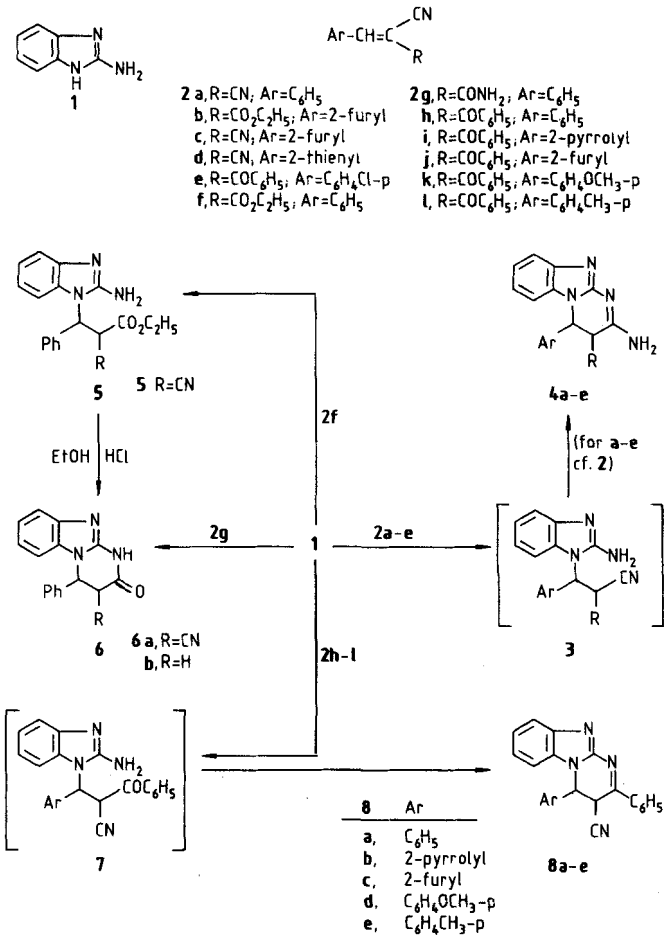

further proof of structure **5** was achieved by its cyclisation to the pyrimido[1,2-a]benzimidazole **6a** (data see Tables 1 and 2).

1 reacted with **2g** to the pyrimido[1,2-a]benzimidazole **6b** probably via the formation of the corresponding Michael adduct which then cyclises via loss of NH_3 followed by hydrolysis and decarboxylation to give **6b** whose structure was confirmed on the basis of elementary analysis and spectroscopic backgrounds (cf. Experimental Part).

1 reacted with **2h–l** to the 3,4-dihydropyrimido[1,2-a]benzimidazoles **8a–e**, respectively. The formation of **8a–e** is assumed to proceed via the formation of the non-isolable Michael adducts **7** which were cyclised via the loss of water to afford **8a–e** (see Tables 1 and 2).

Experimental Part

MP. uncorr.-IR (KBr): Pye Unicam SP-1100 spectrophotometer. – ^{1}H-NMR: Varian EM-360 MHz. TMS int. stand. (DMSO-D_6); chemical shifts: δ (ppm). – Microanalyses: microanalytical centre at Cairo University. – Compounds **2a–h, k** were prepared following. lit.[2-7].

Preparation of **2i–j**

0.1 mol benzoylacetonitrile in 100 ml EtOH and 1 ml piperidine was stirred with 0.1 mol of either pyrrole 2-carboxaldehyde or furfural for 15 min then diluted with water. The solid product was collected and crystallized from EtOH to give **2i, j,** respectively (cf. Tables 1 and 2).

Tab. 1: Characterization data of 2i, j, 4a–e, 5, 6a, b and 8a–e

Comp.	Solv.	M.P. (°C)	Yield (%)	Mol. Form.	Analysis % Calcd./Found C	H	N
2i	EtOH	155	85	$C_{14}H_{10}N_2O$ (222.2)	75.7 75.7	4.53 4.71	12.6 12.8
2j*	EtOH	110	92	$C_{14}H_9NO_2$ (223.2)	75.3 75.5	4.06 4.12	6.2 6.4
4a	DMF	220	75	$C_{17}H_{13}N_5$ (287.3)	71.0 70.8	4.56 4.64	24.3 24.5
4b	DMF	> 300	82	$C_{17}H_{16}N_4O_3$ (324.3)	63.0 63.1	4.97 5.14	17.2 17.2
4c	DMF	> 350	80	$C_{15}H_{11}N_5O$ (277.3)	65.0 64.8	3.99 4.14	25.2 25.4
4d**	EtOH	190	92	$C_{15}H_{11}N_5S$ (293.3)	61.4 61.2	3.77 3.70	23.8 24.0
4e***	EtOH	295	90	$C_{23}H_{17}ClN_4O$ (400.9)	68.9 69.1	4.27 4.46	14.0 14.0
5	DMF	270	68	$C_{19}H_{18}N_4O_2$ (334.4)	68.2 68.2	5.42 5.34	16.7 16.6
6a	DMF	320	70	$C_{17}H_{12}N_4O$ (288.3)	70.8 70.6	4.19 4.02	19.4 19.5
6b	AcOH	225	65	$C_{16}H_{13}N_3O$ (263.3)	73.0 72.7	4.97 4.81	16.0 15.7
8a	DMF	330	90	$C_{23}H_{16}N_4$ (348.4)	79.3 79.1	4.62 4.83	16.1 16.0
8b	EtOH	130	80	$C_{21}H_{15}N_5$ (337.4)	74.7 74.6	4.48 4.64	20.7 20.8
8c	AcOH	> 300	83	$C_{21}H_{14}N_4O$ (338.4)	74.5 74.7	4.17 4.23	16.5 16.7
8d	AcOH	300	95	$C_{24}H_{18}N_4O$ (378.4)	76.1 76.1	4.79 5.01	14.8 15.0
8e	AcOH	280	90	$C_{24}H_{18}N_4$ (362.4)	79.5 79.3	5.00 5.12	15.4 15.3

* Compound **2j**, lit.[7] m.p. 108–109°.
** Compound **4d**, % S; Calcd. (Found): 10.9 (11.1).
*** Compound **4e**, % Cl; Calcd. (Found): 8.8 (8.9).

Tab. 2: IR and ^{1}H-NMR data of **2i**, **4a–e**, **5**, **6a**, b and **8a–e**

Comp.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
2i	3350 (NH); 2210 (CN); 1680 (C=O) and 1600 (C=C).	6.8 (dd, 1H, pyrrole H-4); 7.3 (d, 1H, pyrrole H-3); 7.4–7.6 (m, 5H, Ar'H); 7.7 (dd, 1H, pyrrole H-5); 7.9 (s, br, 1H, NH) and 8.3 (s, 1H, CH).
4a	3300, 3220 (NH_2); 2220 (CN); 1640 (C=N) and 1600 (C=C).	5.3 (s, br, 2H, NH_2); 6.7 (d, 1H, CH); 7.0–7.5 (m, 9H, Ar'H) and 7.8 (d, 1H, CH).
4b	3320, 3180 (NH_2); 1730 (C=O); 1620 (C=N) and 1600 (C=C).	1.3 (t, 3H, $\underline{CH_3}$); 3.8 (q, 2H, $\underline{CH_2}CH_3$); 5.4 (s, br, 2H, NH_2); 6.5 (q, 1H, furan H-3); 6.7 (d, 1H, CH); 7.3 (q, 1H, furan H-4); 7.4–7.8 (m, 4H, Ar'H); 7.8 (d, 1H, CH) and 7.9 (q, 1H, furan H-5).
4c	3300, 3150 (NH_2); 2200 (CN); 1630 (C=N) and 1600 (C=C).	5.3 (s, br, 2H, NH_2); 6.5 (q, 1H, furan H-3); 6.7 (d, 1H, CH); 7.3 (q, 1H, furan H-4); 7.4–7.6 (m, 4H, Ar'H); 7.8 (d, 1H, CH) and 7.9 (q, 1H, furan H-5).
4d	3280, 3150 (NH_2); 2200 (CN); 1640 (C=N) and 1600 (C=C).	5.4 (s, br, 2H, NH_2); 6.5 (d, 1H, CH); 7.1 (q, 1H, thiophene H-3); 7.5 (dd, 1H, thiophene H-4); 7.6–7.7 (m, 4H, Ar'H); 7.8 (d, 1H, CH) and 7.9 (dd, 1H, thiophene H-5).
4e	3300, 3100 (NH_2); 1660 (C=O); 1620 (C=N) and 1600 (C=C).	5.5 (s, br, 2H, NH_2); 6.6 (d, 1H, CH); 7.1–7.5 (m, 13H, Ar'H) and 7.9 (d, 1H, CH).
5	3300, 3100 (NH_2); 2220 (CN); 1720 (C=O); 1625 (C=N) and 1600 (C=C).	1.3 (t 3H, $CH_2\underline{CH_3}$); 3.8 (1, 2H, $\underline{CH_2}CH_3$); 6.2 (d, 1H, CH); 6.5 (s, br, 2H, NH_2); 7.0–8.0 (m, 9H, Ar'H) and 8.8 (d, 1H, CH).
6a	3340 (NH); 2250 (CN); 1680 (C=O); 1630 (C=N) and 1600 (C=C).	6.6 (d, 1H, CH); 6.9 (d, 1H, CH); 7.3–7.7 (m, 9H, Ar'H) and 8.7 (s, br, 1H, NH).
6b	3350 (NH); 1690 (C=O); 1630 (C=N) and 1600 (C=C).	5.9 (d, 2H, CH_2); 6.2 (t, 1H, CH); 7.0–7.8 (m, 9H, Ar'H) and 8.8 (s, br, 1H, NH).
8a	2200 (CN); 1640 (C=N) and 1600 (C=C).	2.8 (d, 1H, CH); 3.1 (d, 1H, CH) and 7.3–8.0 (m, 14H, Ar'H).
8b	3500 (NH); 2200 (CN); 1630 (C=N) and 1600 (C=C).	2.8 (d, 1H, CH); 3.0 (d, 1H, CH); 6.1 (d, 1H, pyrrole H-3); 6.3 (q, 1H, pyrrole H-4); 6.6 (d, 1H, pyrrole H-5) and 7.3–7.9 (m, 10H, Ar'H and NH).
8c	2250 (CN); 1630 (C=N) and 1600 (C=C).	2.9 (d, 1H, CH); 3.2 (d, 1H, CH); 6.3 (q, 1H, furan H-3); 6.8 (q, 1H, furan H-4) and 7.3–8.0 (m, 10H, Ar'H and furan H-5).

Comp.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
8d	2200 (CN); 1640 (C=N) and 1600 (C=C).	2.7 (d, 1H, CH); 3.0 (d, 1H, CH); 3.8 (s, 3H, OCH_3) and 7.2–7.8 (m, 13H, Ar'H).
8e	2190 (CN); 1620 (C=N) and 1600 (C=C).	2.3 (s, 3H, CH_3); 2.7 (d, 1H, CH); 3.1 (d, 1H, CH) and 7.0–7.6 (m, 13H, Ar'H).

Reactions of **2a–l** *with* **1**: *General procedure*

0.01 mol **2a–e** in 30 ml EtOH containing 1 ml piperidine was heated with 0.01 mol **1** under reflux for 3–4 h. The solid product obtained after cooling was crystallized from the proper solvent to give **4a–e**, **5**, **6b** and **8a–e**, respectively (cf. Tables 1 and 2).

Preparation of **6a**

0.5 g **5** in 20 ml EtOH was heated with 5 ml HCl under reflux for 3 h. The solvent was evaporated i. vac. and the remaining solid was triturated with EtOH and crystallized from DMF to give **6a** (cf. Tables 1 and 2).

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