Synthesis of Novel 3-Carboethoxy-6-methyl-4-oxo-4*H*-pyrimido[1′,2′:5,6]-[1,3,5]triazino[1,2-*a*]benzimidazoles [1]

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Reaction of 4-amino-2-methylbenzimidazo[1,2-*a*][1,3,5]triazines **2** with diethyl ethoxymethylenemalonate afforded 3-carboethoxy-6-methyl-4-oxo-4*H*-pyrimido[1′,2′:5,6][1,3,5]triazino[1,2-*a*]benzimidazoles **3**, a new ring system.

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Derivatives of benzimidazoles [2], 1,3,5-triazines [3] and pyrimidines [4] occupy a conspicuous place in the domain of heterocyclic chemistry in view of their broad spectrum biological activity exhibited by these compounds as drugs. Sometimes the fusion of heterocyclic nuclei resulting in polyheterocyclic compounds enhances the biological profile many fold more than its parent nucleus. In our program in the novel fused pyrimidines, we recently described the synthesis of some 2-substituted 6-carboethoxy-5-oxo-5*H*-1,3,4-oxodiozolo[4,5-*a*]pyrimidines [5] and 3-carboethoxy-4,11-dihydro-11-alkyl/phenyl-4-oxopyrimido-[1,2-*b*][1,2,4]benzothiadiazine-6,6-dioxides [6]. These find-

Scheme

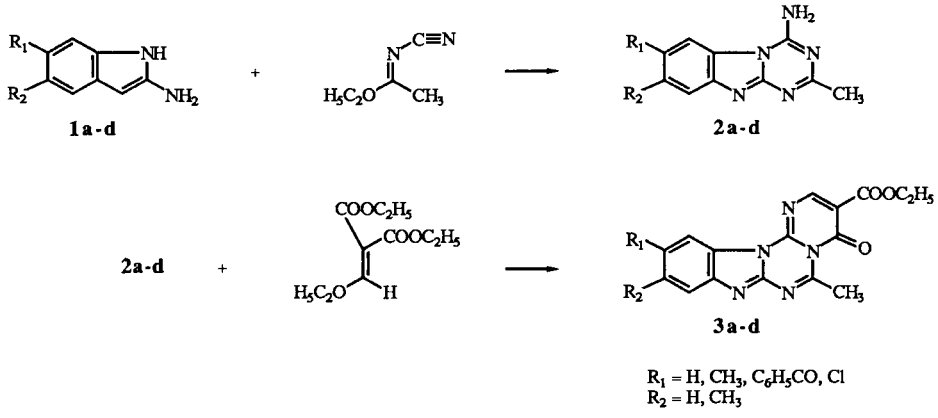

Table 1

No.	R_1	R_2	mp °C	Yield (%)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	M^+ (m/e)
2a	H	H	293-295 [a]	74	$C_{10}H_9N_5$				199
2b	CH_3	CH_3	278-279	80	$C_{12}H_{13}N_5$	63.42 63.19	5.76 5.80	30.82 31.10	227
2c	C_6H_5CO	H	191-193	79	$C_{17}H_{13}N_5O$	67.32 67.08	4.32 4.40	23.09 23.19	303
2d	Cl	H	256-259	65	$C_{10}H_8ClN_5$	51.41 51.52	3.45 3.50	29.97 29.78	233
3a	H	H	205-206	78	$C_{16}H_{13}N_5O_3$	59.44 59.80	4.05 4.00	21.66 21.70	323
3b	CH_3	CH_3	185-188	80	$C_{18}H_{17}N_5O_3$	61.53 61.60	4.88 4.81	19.93 20.00	351
3c	C_6H_5CO	H	241-244	79	$C_{23}H_{17}N_5O_4$	64.63 64.50	4.01 4.09	16.39 16.44	427
3d	Cl	H	227-229	68	$C_{16}H_{12}ClN_5O_3$	53.72 53.90	3.38 3.41	19.57 19.45	357

[a] Lit [7] mp 293-295.

ings prompted us to make efforts to develop a synthetic route leading to pyrimido[1',2':5,6][1,3,5]triazino[1,2-*a*]-benzimidazoles, a novel ring system which possess pyrimidine, triazine and benzimidazole moieties in a single molecule.

Ethyl *N*-cyanoacetimidate has been shown to interact with 2-aminobenzimidazole (**1a**) to give 4-amino-2-methylbenzimidazole[1,2-*a*][1,3,5]triazine (**2a**) [7]. In the present work, compounds **2b-d** (Table 1) were synthesized for the first time by the reaction of 2-amino-5,6-substituted benzimidazoles **1b-d** with ethyl *N*-cyanoacetimidate in 65-80% yields employing the literature procedure [7].

Diethyl ethoxymethylenemalonate (EMME) as a synthon [8] has attracted considerable interest on account of its versatility as a reagent in the development of various heterocyclic systems [9-11]. We report herein a facile synthesis of compounds **3a-d** (Table 1), an entirely new class of tetracyclic ring system in 68-80% yields by condensing **2a-d** and EMME in refluxing dimethylformamide for 6 hours in a single step (Scheme). Ethyl *N*-cyanoacetimidate was made as reported [12].

The characterisation of **2b-d** and **3a-d** is based on elemental analyses and spectroscopic data.

EXPERIMENTAL

Melting points were determined on Buchi 510 apparatus and are uncorrected. Infrared (ir) spectra were recorded with a Perkin Elmer 221 spectrophotometer. The ^{1}H nmr spectra have been obtained with a Varian FT-80A spectrometer using TMS as an internal standard. Mass spectra were recorded on VG micromass 70-70H mass spectrometer at 70 eV.

Typical Reaction Procedure.

4-Amino-2,7,8-trimethylbenzimidazo[1,2-*a*][1,3,5]triazine (**2b**).

A mixture of 2-amino-5,6-dimethylbenzimidazole (1.61 g, 0.01 mole), ethyl *N*-cyanoacetimidate (2.24 g, 0.02 mole) and dimethoxyethane (20 ml) was refluxed for 1 hour with stirring. After cooling, the precipitate was filtered and recrystallised from dimethylformamide to give **2b**; ir (potassium bromide): 3130, 1650 and 1540 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.7 (s, 2H, 6- and 9-H), 6.7 (broad, 2H, NH_2, deuterium oxide-exchangeable), 2.6 (s, 3H, 2-CH_3), 2.5 (s, 6H, 7- and 8-CH_3).

3-Carboethoxy-6,10,11-trimethyl-4-oxo-4*H*-pyrimido[1',2':5,6]-[1,3,5]triazino[1,2-*a*]benzimidazole (**3b**).

A solution of 4-amino-2,7,8-trimethylbenzimidazo[1,2-*a*][1,3,5]-triazine (2.27 g, 0.01 mole) and diethyl ethoxymethylenemalonate (2.16 g, 0.01 mole) in dimethyl formamide (40 ml) was refluxed for 6 hours with stirring and was concentrated under reduced pressure. The concentrated solution was poured into ice cold water. The residue formed was filtered, washed with water and recrystallised from ethanol to give **3b**; ir (potassium bromide): 1700, 1640 and 1580 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.0 (s, 1H, 2-H), 7.8 (s, 2H, 9- and 12-H), 4.4 (q, 2H, CH_2, J = 7 Hz), 2.6 (s, 3H, 6-CH_3), 2.5 (s, 6H, 10- and 11-CH_3), 1.4 (t, 3H, CH_2CH_3, J = 7 Hz).

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