SYNTHESIS OF IMIDAZO[1,2-c]PYRIMIDINE DERIVATIVES FROM 4-AMINOPYRIMIDINES, METHYL KETONES, AND HALOGENS

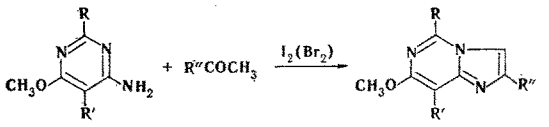
G. K. Rogul'chenko, I. A. Mazur, and P. M. Kochergin

UDC 547.859

Imidazo[1,2-c]pyrimidine derivatives were synthesized from C-substituted 4-aminopyrimidines by the King method. The corresponding 8-bromoimidazo[1,2-c]pyrimidines are formed by reaction of 4-aminopyrimidines without substituents in the 5 position with methyl ketones and bromine in a ratio of 1:1:2.

The well-known King method for the synthesis of imidazo[1,2-a]pyridines [1] has not been used for the preparation of imidazo[1,2-c]pyrimidines. We have studied the reaction of several 4-amino-6-methoxypyrimidines (Ia-d) with methyl ketones (IIa-d) and halogens (iodine and bromine).

2-Arylimidazo[1,2-c]pyrimidines (IIIa-c, Table 1) are actually formed from Ia-c and methyl aryl ketones IIa,b and iodine. If bromine is used in place of iodine, in the case of Ia,b the pyrimidine ring is primarly brominated in the 5 position to give products Ic,d. In the case of a twofold excess of bromine, the corresponding 8-bromoimidazo[1,2-c]pyrimidines (IIId-i) are formed. The structures of the imidazo-[1,2-c]pyrimidines (III) were confirmed by alternative syntheses [2-4].



I-II a-d III a-i

Ia R=R′=H; b R=OCH_3, R′=H; c R=H, R′=Br; d R=OCH_3, R′=Br. IIa R″=p-$NO_2C_6H_4$; b R″=C_6H_5; c R″=CH_3; d R″=p-BrC_6H_4. IIIa R=R′=H, R″=p-$NO_2C_6H_4$; b R=OCH_3, R′=H, R″=C_6H_5; c R=OCH_3, R′=H, R″=p-$NO_2C_6H_4$; d R=H, R′=Br, R″=C_6H_5; e R=H, R′=Br, R″=p-$NO_2C_6H_4$; f R=OCH_3, R′=Br, R″=CH_3; g R=OCH_3, R′=Br, R″=C_6H_5; h R=OCH_3, R′=Br, R″=p-BrC_6H_4; i R=OCH_3, R′=Br, R″=p-$NO_2C_6H_4$

EXPERIMENTAL

2-Arylimidazo[1,2-c]pyrimidines (IIIa-c). A) A 0.01-mole sample of methyl ketone II, 1.68 g (0.02 mole) of sodium bicarbonate, and a solution of 2.54 g (0.01 mole) of iodine in 20 ml of ethanol were added to a solution of 0.01 mole of amine Ia-b in 20 ml of ethanol, after which the mixture was refluxed for 4-6 h. The ethanol was then evaporated, 20 ml of water was added to the residue, and the resulting precipitate was removed by filtration and washed with water to give IIIa-c.

B) A 0.01-mole sample of the appropriate α-bromoketone was added to a solution of 0.01 mole of Ia,b in 30 ml of ethanol, and the mixture was refluxed for 1 h. A 0.015-mole sample of sodium hydrocarbonate was then added, and the mixture was heated for another 3 h. It was then cooled and diluted with 50 ml of water, and the resulting precipitate was removed by filtration, washed with water, and dried.

Imidazo[1,2-c]pyrimidines (IIId-i). A) A 0.01-mole sample of methyl ketone II, 0.01 mole of bromine, and 0.02 mole of sodium bicarbonate were added to a solution of 0.01 mole of amines Ic,d in 20 ml of meth-

Zaporozhe Medical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 93-94, January, 1975. Original article submitted January 31, 1974.

anol (ethanol) and the mixture was heated for 2-3 h. It was then cooled and diluted with 50 ml of water. The resulting precipitate was removed by filtration, washed with water, and dried to give IIId-i.

B) A 0.02-mole sample of bromine, 0.01 mole of methyl ketone, and 0.04 mole of sodium bicarbonate were added to a solution of 0.01 mole of amines Ia,b in 20 ml of methanol (ethanol), and the mixture was refluxed for 3-4 h. The products were isolated as in experiment A.

C) A 0.011-mole sample of α-bromoketone was added to a solution of 0.01 mole of Ic,d in 30 ml of ethanol, 0.015 mole of sodium bicarbonate was then added, and heating was continued for another 3 h. The reaction mixture was then worked up as in experiment A.

Compounds III were purified for analysis by recrystallization from dimethylformamide (a,c), butanol (b,h), dioxane (d), ethanol (f,i), methanol (e), or 50% ethanol (g).

TABLE 1. Imidazo[1,2-c]pyrimidines III

Compound	R	R′	R″	mp, °C (dec.)	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Br	N	C	H	Br	N	
a	H	H	*p*-$NO_2C_6H_4$	270—273	$C_{13}H_{10}N_4O_3$	58,0	3,7	—	20,5	57,8	3,7	—	20,7	73*
b	OCH_3	H	C_6H_5	201—203	$C_{14}H_{13}N_3O_2$	65,8	5,1	—	16,5	65,5	4,9	—	16,5	48
c	OCH_3	H	*p*-$NO_2C_6H_4$	210—213	$C_{14}H_{12}N_4O_4$	56,1	4,4	—	18,6	56,0	4,0	—	18,6	85
d	H	Br	C_6H_5	231—233	$C_{13}H_{10}BrN_3O \cdot H_2O$	47,8	4,3	22,4	12,3	47,7	4,0	22,6	11,9	65—70
e	H	Br	*p*-$NO_2C_6H_4$	260—262	$C_{13}H_9BrN_4O_3$	44,5	2,6	22,9	15,8	44,6	2,6	22,9	16,0	53—86
f	OCH_3	Br	CH_3	240—241	$C_9H_{10}BrN_3O_2$	40,0	3,8	29,5	15,8	39,7	3,7	29,4	15,4	34—67
g	OCH_3	Br	C_6H_5	212—215	$C_{14}H_{12}BrN_3O_2 \cdot H_2O$	47,8	4,3	22,1	12,3	47,8	4,0	22,6	11,9	49—51
h	OCH_3	Br	*p*-BrC_6H_4	283—285	$C_{14}H_{11}Br_2N_3O_2$	40,1	3,0	—	9,8	40,7	2,7	—	10,1	51—94
i	OCH_3	Br	*p*-$NO_2C_6H_4$	162—164	$C_{14}H_{11}BrN_4O_4$	43,8	2,9	—	14,9	44,3	2,9	—	14,8	74—45

* The yields of IIIa-c are those obtained by method A, whereas the yields of IIId-i are those obtained by methods A and B.

LITERATURE CITED

1. L. C. King, J. Amer. Chem. Soc., 66, 894 (1944).
2. E. Ochiai and M. Ianai, J. Pharm. Soc. Japan, 59, 97 (1939); Chem. Abstr., 33, 3791 (1939).
3. P. M. Kochergin and B. M. Petreikova, Chemistry of Pyrimidines and Condensed Systems That Include a Pyrimidine Ring. Summaries of Papers Presented at the All-Union Colloquium [in Russian], Novosibirsk (1969), p. 45.
4. G. K. Rogul'chenko, I. A. Mazur, and P. M. Kochergin, Modern Problems of Pharmaceutical Science and Practice [in Russian], Kiev (1972), p. 370.