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STUDIES IN THE IMIDAZOLE SERIES. 100.* SYNTHESIS OF DERIVATIVES OF IMIDAZO[1,2-*a*]PYRIMIDINE FROM 2-AMINOPYRIMIDINES, METHYL ARYL KETONES, AND HALOGENS

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We have synthesized imidazo[1,2-a]pyrimidine derivatives by reaction of 2-aminopyrimidines with methyl aryl ketones and halogens (bromine, iodine). Using bromine leads to formation of 6-bromo- and 3,6-dibromo-substituted 2-arylimidazo[1,2-a]pyrimidines.

Keywords: imidazopyrimidines, aminopyrimidines, halogens, imidazole, methyl aryl ketones, cyclization.

A disadvantage of the method for synthesis of imidazo[1,2-*a*]pyrimidine derivatives by reaction of 2-aminopyrimidines with α-bromo ketones [2-6] is the inconvenience of working with α-bromo ketones, many of which are lacrimators and in addition are unstable when stored.

Continuing the work in [7] on synthesis of imidazo[1,2-*c*]pyrimidine derivatives from 4-aminopyrimidines, ketones, and halogens, we have extended this method to synthesis of imidazo[1,2-*a*]pyrimidine derivatives and have studied the reaction of 2-aminopyrimidine and some of its C-substituted derivatives with methyl aryl ketones and halogens (bromine and iodine). This reaction proceeds easily in organic solvents (chloroform, ethanol, DMF) at 60-100°C in the presence of sodium carbonate or bicarbonate, required for binding the hydrogen halide liberated during the reaction.

The first step of the process is halogenation of the ketones at the methyl group with formation of the corresponding phenacyl bromides (iodides). The latter attack the ring nitrogen atom of the pyrimidine ring with formation of intermediate 2-imino-1-phenacyl-1,2-dihydropyrimidines. Dehydration of these labile compounds leads to an energetically stable derivative of the heteroaromatic system imidazo[1,2-*a*]pyrimidine [8]. By reaction of 2-aminopyrimidine, its 5-chloro- and 5-bromo-substituted derivatives with equimolar amounts of ketones (acetophenone, *p*-nitroacetophenone) and halogens (bromine or iodine), we synthesized 2-arylimidazo[1,2-*a*]-pyrimidines (**1a-c**).

* For communication 99, see [1].

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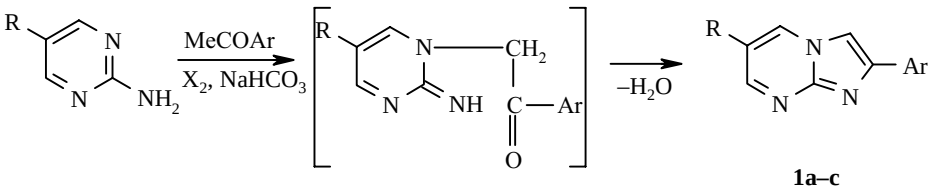
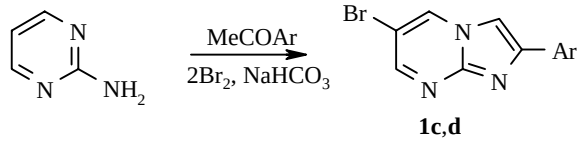


1a–c

1a Ar = $C_6H_4NO_2$-*p*, R = H; **1b** Ar = Ph, R = Cl; **1c** Ar = Ph, R = Br, X = Br, I

Using 2 moles of bromine per mole of the starting 2-aminopyrimidine and methyl aryl ketone and brominating the 2-arylimidazopyrimidines formed at the 6 position of the bicycle lead to 2-aryl-6-bromoimidazo[1,2-*a*]pyrimidines **1c,d**. The structure of these compounds is confirmed in the example of 6-bromo-2-phenylimidazo[1,2-*a*]pyrimidine (**1c**), obtained by an alternative synthesis from 2-amino-5-bromopyrimidine, acetophenone, and bromine.

The preparative method for obtaining 6-bromo-substituted 2-arylimidazo[1,2-*a*]pyrimidines is quite convenient, since it does not require inaccessible 2-amino-5-bromopyrimidine and its C-substituted derivatives.

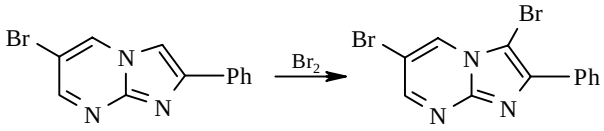


1c,**d**

1c Ar = Ph; **d** Ar = $C_6H_4NO_2$-*p*

Using 3 moles of bromine per mole of the starting 2-aminopyrimidine and methyl aryl ketone leads to further bromination of the intermediate 2-aryl-6-bromoimidazopyrimidines at the 3 position of the bicycle. From 2-aminopyrimidine, acetophenone, and bromine, we synthesized 3,6-dibromo-2-phenylimidazo[1,2-*a*]pyrimidine (**1e**), the structure of which is confirmed by alternative syntheses from 2-amino-5-bromopyrimidine, acetophenone, and bromine (2 moles) and bromination of 6-bromo-2-phenylimidazo[1,2-*a*]pyrimidine **1c** with bromine (1 mole).

In the ^{1}H NMR spectrum of compound **1e**, there is no signal from the proton in the 3 position of the imidazopyrimidine bicycle.



1c **1e**

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent for crystallization)	Yield, %
		C	H	N	Br (Cl)		
1a	$C_{12}H_8N_4O_2$	60.0 / 60.0	3.2 / 3.3	22.9 / 23.3		350 (DMF–water, 1:1)	71-80
1b	$C_{12}H_8ClN_3$	63.1 / 62.8	3.4 / 3.5	18.1 / 18.3	(15.3 / 15.4)	279-281 (ethanol)	52
1c	$C_{12}H_8BrN_3$	52.4 / 52.6	2.9 / 2.9	15.2 / 15.3	28.9 / 29.2	276-277* (ethanol)	30-45
1d	$C_{12}H_7BrN_4O_2$	44.8 / 45.1	2.4 / 2.2	17.5 / 17.6	25.2 / 25.0	350 (DMF–water, 1:1)	70
1e	$C_{12}H_7Br_2N_3$	40.4 / 40.8	2.2 / 2.0	12.0 / 11.9	45.1 / 45.3	191-192 (ethanol)	27-30

* According to the data in [3], mp 279°C.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in KBr disks. The purity of the compounds obtained was determined by TLC on Silufol UV-254 plates, visualization with iodine vapors or in UV light.

Imidazo[1,2-*a*]pyrimidines (1a-e). A. *p*-Nitroacetophenone (1.65 g, 0.01 mol), a solution of iodine (2.54 g, 0.01 mol) in chloroform (20 ml), and anhydrous finely ground sodium bicarbonate (2-2.5 g) were added to a solution of 2-aminopyrimidine (0.95 g, 0.01 mol) in chloroform (20 ml). The mixture was boiled for 4 h, the solvent was driven off under vacuum, water (50-60 ml) was added to the residue, the precipitate was filtered off and washed with water and then alcohol and then dried. Yield of compound **1a** 1.7 g (71%).

B. Bromine (1.6 g, 0.01 mol) was added to a solution of *p*-nitroacetophenone (1.65 g, 0.01 mol) in ethanol (20 ml). The mixture was heated at 50-60°C and stirred until the solution became colorless. Then sodium bicarbonate or carbonate (2-2.5 g) was added in small portions and stirred until evolution of CO_2 stopped, after which 2-aminopyrimidine (0.95 g, 0.01 mol) was added. The reaction mass was boiled for 2 h and treated as described in experiment A. Yield of compound **1a** 1.9 g (80%). A mixed sample of the products obtained by methods A and B did not depress the melting point. The IR spectra of the samples were identical.

Compounds **1b,c** were similarly obtained from 2-amino-5-chloro- and 2-amino-5-bromopyrimidines, except that the reaction was carried out in DMF (2.5 h at 96-98°C). Yield of compound **1c**, 45%.

C. Acetophenone (1.2 g, 0.01 mol), bromine (3.2 g, 0.02 mol), and sodium carbonate (4.5 g) were added to a solution of 2-aminopyrimidine (0.95 g, 0.01 mol) in anhydrous ethanol (20 ml). The mixture was stirred for 20-30 min at 55-60°C, then boiled for 3 h; the solvent was distilled off under vacuum, the residue was treated as described in experiment A. Yield of compound **1c** 0.82 g (30%). A mixed sample with the product obtained according to method B did not depress the melting point. The IR spectra of the samples were identical.

Compounds **1d** were obtained similarly except that the reaction was carried out in DMF (3 h at 96-98°C).

D. Bromine (3.2 g, 0.02 mol) was added to a solution of acetophenone (2.4 g, 0.02 mol) in a mixture of ethanol (30 ml) and DMF (10 ml). The mixture was heated at 50-60°C until it became colorless; then 2-aminopyrimidine (1.9 g, 0.02 mol), bromine (3.2 g, 0.02 mol), and sodium bicarbonate (3.4 g, 0.04 mol) were added and the mixture was boiled for 2 h and then cooled down to 40-50°C. Bromine (3.2 g, 0.02 mol) was added over a period of 10 min. The reaction mass was stirred for 10-15 min at the same temperature, ethanol was distilled off under vacuum, and water (30 ml) and a few drops of a 40% sodium hydroxide solution were added until it tested alkaline. The oil separated after decantation of the aqueous solution and trituration with ethanol was crystallized. The precipitate was washed with water and dried. Yield of compound **1e** 1.9 g (27%).

E. Bromine (0.8 g, 0.005 mol) was added to a solution of acetophenone (0.6 g, 0.005 mol) in a mixture of ethanol (15 ml) and DMF (5 ml). The mixture was heated for 10-15 min at 55-60°C until the solution became colorless, then sodium bicarbonate (2.5 g) and 2-amino-5-bromopyrimidine (0.87 g, 0.005 mol) were added. The reaction mass was boiled for 2 h and cooled down to 40-50°C. Then bromine (0.8 g, 0.005 mol) was added and it was held at this temperature and stirred for 10-15 min. Then the reaction mass was treated as described in experiment D. Yield of compound **1e** 0.52 g (30%). A mixed sample with the compound obtained according to method D did not depress the melting point.

F. A solution of bromine (1.6 g, 0.01 mol) in DMF (5 ml) was added gradually with stirring to a solution of 6-bromo-2-phenylimidazo[1,2-*a*]pyrimidine **1c** (2.74 g, 0.01 mol) in DMF (27 ml). The reaction mixture was stirred for 30 min at 20-22°C, DMF was driven off under vacuum, and water and a sodium hydroxide solution were added to the residue until it tested alkaline. An oily precipitate began to crystallize shortly afterward. It was filtered off, washed with water, and dried. Yield of compound **1e** 1.72 g (50%). A mixed sample with the products obtained by methods D and E did not depress the melting point. The IR and NMR spectra of the samples were identical.

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