SYNTHESIS OF HALOGENOAZOLES

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On reaction with halogens, organolithium and organomagnesium derivatives of azoles are converted into halogenoazoles. Halogen derivatives of N-substituted imidazoles, benzimidazoles, and indazoles have been studied.

We have previously [1] established that on reaction with iodine 2-diethoxymethyl-5-lithiofuran is converted into 2-diethoxymethyl-5-iodofuran. Continuing this work, we have synthesized halogenoazoles by the same method.

Organolithium derivatives of N-substituted imidazoles, benzimidazoles, and indazoles were obtained by the metallation reaction. Under the action of butyl- and phenyllithiums, 1-phenyl- and 1-methoxymethylbenzimidazoles give low yields of the 2-lithio derivatives, and therefore the corresponding organomagnesium compounds were used. In the preparation of the organomagnesium derivatives of 1-phenyl- and 1-methoxymethylbenzimidazoles the metallating agent selected was dibutylmagnesium, which, unlike alkylmagnesium halides [2], is capable of readily metallating N-substituted benzimidazoles in ether. Because of the instability of the unsymmetrical organomagnesium compounds [3] the reaction led to the formation of bis(1-phenylbenzimidazol-2-yl)magnesium and bis(1-methoxymethylbenzimidazol-2-yl)magnesium. This method also permits halogen to be introduced into halogen derivatives of azoles if the metallation of the latter is not complicated by other processes such as the Wurtz–Fittig reaction. The results of the synthesis of the halogenoazoles are given in Table 1.

Table 2 gives the PMR spectra of 1-methylimidazole (X), 1-methylbenzimidazole (XI), 2-methylindazole (XII), and compounds (I, IV, and VIII). The spectra of (I) and (IV) lack the signal of 2-H, and the spectrum of (VIII) the signal of 3-H.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS 487 C spectrometer with a working frequency of 80 MHz using TMS as the internal standard and $CDCl_3$ as the solvent.

1-Methylimidazole [4], 1-phenylimidazole [5], 5-chloro-1-methylimidazole [6], 1-methylbenzimidazole [7], 1-methoxymethylbenzimidazole [8], 1-phenylbenzimidazole [9], and 2-methyl- and 2-ethylimidazoles [10] were obtained by methods described in the literature, as indicated.

2-Iodo-1-methylimidazole (I). In an atmosphere of nitrogen at 0°C, 4.5 g (0.033 mole) of butyl bromide in 8 ml of ether was added over 45 min to 0.45 g (0.065 g-atom) of comminuted lithium in 15 ml of ether. The mixture was stirred for another 15 min, and then, at −15°C a solution of 1.5 g (0.018 mole) of 1-methylimidazole in 10 ml of ether was added over 40 min. After 1 h, the mixture was cooled to −78°C and a solution of 6 g (0.024 mole) of iodine in 60 ml of ether was added. The temperature was brought up to that of the room, and then 10 ml of water, 5 ml of saturated sodium sulfite solution, and 20 ml of 20% hydrochloric acid were added. The hydrochloric acid extract was made alkaline with 20% caustic soda solution, and the base was extracted with chloroform. The chloroform solution was dried with sodium sulfate, and the solvent was distilled off. Compound (I) was purified by recrystallization from petroleum ether.

2-Iodo-1-phenylimidazole (II) and 5-chloro-2-iodo-1-methylimidazole (III) were obtained similarly.

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TABLE 1. $RM + X_2 = RX + MX$

RX	RM	X_2	mp of RX, °C	Solvent for crystallization
I	2-Lithio-1-methylimidazole	I_2	88—89	Petroleum ether
II	2-Lithio-1-phenylimidazole	I_2	102—103	Benzene – hexane
III	5-Chloro-2-lithio-1-methyl-imidazole	I_2	104—105	Petroleum ether
IV	2-Lithio-1-methylbenzimidazole	Br_2	101—102	Petroleum ether
V	2-Lithio-1-methylbenzimidazole	I_2	114—115	Hexane
VI	Bis(1-methoxymethylbenzimid-azol-2-yl)magnesium	Br_2	67—68	Heptane
VII	Bis(1-phenylbenzimidazol-2-yl)magnesium	I_2	155—156	Ethanol
VIII	3-Lithio-2-methylindazole	I_2	150—151	Benzene – petroleum ether
IX	2-Ethyl-3-lithioindazole	I_2	86—87	Benzene – petroleum ether

RX	Empirical formula of RX	Found, %				Calc., %				Yield, %
		C	H	halog.	N	C	H	halog.	N	
I	$C_4H_5IN_2$	23,4	2,5	61,3	13,3	23,1	2,4	61,0	13,5	69
II	$C_9H_7IN_2$	40,4	2,5	47,0	10,5	40,0	2,6	47,0	10,4	72
III	$C_4H_4ClIN_2$	20,0	1,6	66,3	11,5	19,8	1,7	67,0	11,6	54
IV	$C_8H_7BrN_2$	45,8	3,3	37,5	13,6	45,5	3,4	37,8	13,3	46
V	$C_8H_7IN_2$	37,6	2,6	48,8	11,2	37,2	2,7	49,2	10,9	52
VI	$C_9H_9BrN_2O$	44,8	4,0	33,2	11,7	44,8	3,8	33,1	11,6	56
VII	$C_{13}H_9IN_2$	49,2	2,6	39,7	8,5	48,8	2,8	39,6	8,7	62
VIII	$C_8H_7IN_2$	37,6	3,1	49,6	10,6	37,2	2,7	49,2	10,9	50
IX	$C_9H_9IN_2$	39,6	3,5	46,2	10,2	39,7	3,3	46,6	10,4	39

TABLE 2. PMR Spectra of N-Substituted Azoles and Their Halogen Derivatives*

Compound	Chemical shifts of the protons, δ, ppm			
	2-H	3-H	4-H and 5-H	$N-CH_3$
X	7,35	—	6,82; 6,96	3,57
I	—	—	7,00	3,57
XI	7,66	—	—	3,58
IV	—	—	—	3,60
XII	—	7,62	—	3,95
VIII	—	—	—	4,19

*2-H; 3-H; 4-H; and 5-H are the protons of the five-membered heterocyclic ring.

2-Iodo-1-methylbenzimidazole (V). At −78°C, 3.3 g (0.025 mole) of 1-methylbenzimidazole in 30 ml of toluene was added over 30 min to the butyllithium obtained from 0.5 g (0.072 g-atom) of lithium and 5 g (0.036 mole) of butyl bromide in 30 ml of ether. After 1 h, 6.4 g (0.025 mole) of iodine in 65 ml of ether was added. The temperature was raised to 20-25°C, the unchanged iodine was eliminated with 6 ml of a saturated solution of sodium sulfite, and the compound (V) was isolated as described previously [11].

2-Bromo-1-methylbenzimidazole (IV). The synthesis was performed as in the preceding case except that the solution of iodine was replaced by a solution of the corresponding amount of bromine in 30 ml of dioxane.

2-Bromo-1-methoxymethylbenzimidazole (VI). To the butylmagnesium bromide obtained from 1.3 g (0.054 g-atom) of magnesium and 7.4 g (0.054 mole) of butyl bromide in 50 ml of ether was added 10 ml of dioxane. To the dibutylmagnesium so formed was added a solution of 3.24 g (0.02 mole) of 1-methoxymethylbenzimidazole in 5 ml of ether, the mixture was boiled for 1 h, and then 5.7 g (0.036 mole) of bromine in 20 ml of dioxane was added. After 10 min, 10 ml of a saturated solution of sodium sulfite and 30 ml of water were added, and then the aqueous dioxane layer was separated off and treated with ether. Compound (VI) was isolated from the combined ethereal solutions in the same way as (V).

2-Iodo-1-phenylbenzimidazole (VII). The method of synthesis was similar to the preceding case. Bis(1-phenylbenzimidazol-2-yl)magnesium was obtained from 1.94 g (0.01 mole) of 1-phenylbenzimidazole and was treated with 4.4 g (0.017 mole) of iodine.

3-Iodo-2-methylindazole (VIII). 3-Lithio-2-methylindazole was obtained from 1.32 g (0.01 mole) of 2-methylindazole [12] and was treated with 3.1 g (0.012 mole) of iodine in 30 ml of ether. The unchanged iodine was eliminated with 3 ml of a saturated solution of sodium sulfite, the organic layer was separated off and washed with water, and the solvent was distilled off. The residue was dissolved in 10 ml of 20% hydrochloric acid, and the solution was boiled with activated carbon and filtered, the filtrate was diluted with an equal volume of water, and the (VIII) was precipitated with a 20% solution of ammonia.

3-Iodo-2-ethylindazole (IX) was synthesized in the same way.

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