ORGANOSODIUM COMPOUNDS OF N-SUBSTITUTED BENZIMIDAZOLES

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UDC 547.785.5+542.957

1-Alkylbenzimidazoles and 1-benzylbenzimidazole react with phenylsodium to form the corresponding 2-sodio derivatives. 5-Bromo-1-ethylbenzimidazole does not react with phenyl- and amylsodium. The metallation of 1-arylbenzimidazoles with phenylsodium is appreciably complicated by side processes. A path for the preparation of 2-sodio-1-arylbenzimidazoles from 1-arylbenzimidazoles and o-anisylsodium is proposed. Some transformations of the organosodium compounds of N-substituted benzimidazoles were studied.

This paper, which is a continuation of the research in [1], is devoted to the synthesis and study of the transformations of organosodium compounds of N-substituted benzimidazoles.

It is known that N-substituted benzimidazoles are metallated by the action of organolithium compounds and also add either the metallating agent or the 2-lithiobenzimidazole formed to the C =N bond [2-4]. We have found that 1-alkylbenzimidazoles and 1-benzylbenzimidazole react with phenylsodium to form primarily 2-sodio derivatives, while the yield of organosodium compounds of 1-arylbenzimidazoles does not exceed 40% (Table 1).

It was found by means of competitive metallation that 1-arylbenzimidazoles are weaker C −H acids than 1-alkylbenzimidazoles. Treatment of a mixture of 1-phenyl- and 1-methylbenzimidazoles with phenylsodium gives primarily 2-sodio-1-methylbenzimidazole (I). However, the chief reason for the reduced capacity of 1-arylbenzimidazoles for metallation at the 2 position is apparently the weakening of the aromatic character of the benzimidazole ring as a consequence of its conjugation with the N-substituent, by virtue of which addition reactions at the C =N bond, which lead to a benzimidazoline system, become dominant. This assumption is confirmed by the fact that the tendency for replacement of hydrogen by metal increases both in the case of 1-mesitylbenzimidazole in which the angle between the plane of the benzimidazole fragment of the molecule and the plane of the N-substituent is greater than in the other 1-arylbenzimidazoles* presented in Table 1, and when phenylsodium is replaced by a less nucleophilic reagent, o-anisylsodium, for example.

An anomalous property was observed for 5-bromo-1-ethylbenzimidazole: it does not give an organosodium compound even on prolonged action of phenylsodium and amylsodium, although it would seem that bromine, whose −I effect exceeds the +M effect, should promote detachment of a proton from the $C_{(2)}$ atom; nor do reactions with the participation of a bromine atom and the C =N bond occur. It is remarkable that 5-bromo-1-ethylbenzimidazole is inert also in other cases. Thus, in contrast to 1-alkylbenzimidazoles, it does not react with sodium amide and potassium metal [5, 6].

*1-Arylbenzimidazoles are not coplanar as a consequence of overlapping of the radius of the hydrogen atom or of a substituent in the ortho position of the N-aryl group and the radius of the hydrogen atom in the 7 position of the benzimidazole ring. If the N-aryl group contains one ortho substituent, the conformation in which the radii of the hydrogen atoms overlap is energetically more favorable.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1238-1242, September, 1971. Original article submitted June 28, 1970.

TABLE 1. Metallation 1-R-Benzimidazoles with Phenylsodium and o-Anisylsodium

R	Empirical formula of copper salt of the N-substituted benzimidazole-2-carboxylic acid	Found, %			Calc., %			Yield, %*
		C	H	N	C	H	N	
CH_3	$C_{18}H_{14}N_4O_4Cu$	52,0	3,2	13,9	52,2	3,4	13,5	86
C_2H_5	$C_{20}H_{18}N_4O_4Cu$	54,1	3,8	13,0	54,4	4,1	12,7	61
n-C_3H_7	$C_{22}H_{22}N_4O_4Cu$	56,0	4,6	12,1	56,2	4,7	11,9	63
i-C_3H_7	$C_{22}H_{22}N_4O_4Cu$	55,9	4,6	12,2	56,2	4,7	11,9	57
n-C_4H_9	$C_{24}H_{26}N_4O_4Cu$	57,5	5,3	11,0	57,9	5,3	11,3	62
$CH_2C_6H_5$	$C_{30}H_{22}N_4O_4Cu$	64,0	3,5	9,6	63,6	3,9	9,9	70
C_6H_5	$C_{28}H_{18}N_4O_4Cu$	63,1	3,3	10,3	62,5	3,4	10,4	36 (78)
4-$CH_3C_6H_4$	$C_{30}H_{22}N_4O_4Cu$	63,3	3,9	10,2	63,6	3,9	9,9	29 (71)
2-$CH_3C_6H_4$	$C_{30}H_{22}N_4O_4Cu$	63,1	3,8	9,9	63,6	3,9	9,9	40 (65)
2,4,6-$(CH_3)_3C_6H_2$	$C_{34}H_{30}N_4O_4Cu$	66,0	4,7	8,7	65,6	4,9	9,0	47 (58)

* The yields in the metallation of 1-arylbenzimidazoles with o-anisylsodium are given in parentheses.

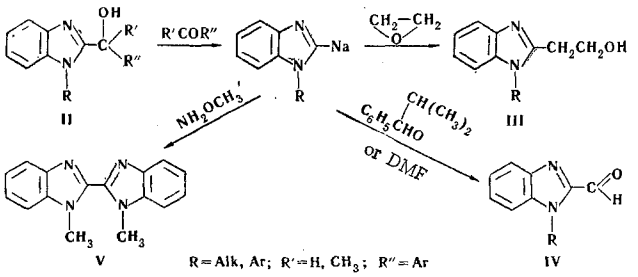
TABLE 2. Compounds Obtained from 2-Na-N-R-Benzimidazoles

Compound	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %*
			C	H	N	C	H	N	
Phenyl(1-methyl-2-benzimidazolyl)carbinol	156—157**	$C_{15}H_{14}N_2O$	75,3	5,7	12,0	75,6	5,9	11,8	67
p-Dimethylaminophenyl-(1-methyl-2-benzimidazolyl)carbinol	153—154	$C_{17}H_{19}N_3O$	73,0	6,5	15,1	72,6	6,8	14,9	58
m-Nitrophenyl(1-methyl-2-benzimidazolyl)-carbinol	150—151	$C_{15}H_{13}N_3O_3$	64,1	4,8	14,5	63,6	4,6	14,8	20
Methylphenyl(1-methyl-2-benzimidazolyl)carb.	190—191	$C_{16}H_{16}N_2O$	76,3	6,1	11,1	76,2	6,4	11,1	48
1-Ethyl-2-formylbenzimidazole	55—56	$C_{10}H_{10}N_2O$	68,6	6,0	15,9	68,9	5,8	16,1	25
p-Diethylaminophenyl(1-propyl-2-benzimidazolyl)carbinol	135—136	$C_{21}H_{27}N_3O$	74,4	8,0	12,8	74,7	8,1	12,5	57
3,4-Dimethoxyphenyl(1-phenyl-2-benzimidazolyl)carbinol	159—160	$C_{22}H_{20}N_2O_3$	73,3	5,5	8,1	73,3	5,6	7,8	72
1-(p-Tolyl)-2-formylbenzimidazole	92—93	$C_{15}H_{12}N_2O$	75,7	5,6	12,1	76,2	5,1	11,9	35

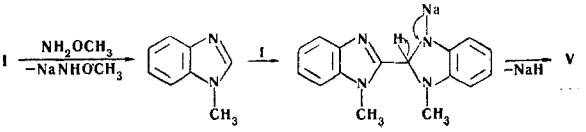
* The yields were calculated for N-substituted benzimidazoles.
† According to [8], mp 158-160°.

To determine the yields of the organosodium compounds of N-substituted benzimidazoles, they were subjected to carbonation, after which the resulting sodium salts of the benzimidazole-2-carboxylic acids were quantitatively converted to insoluble copper salts by treatment with copper sulfate solution.

2-Sodiobenzimidazoles react readily with aldehydes, ketones, ethylene oxide, isopropylformanilide, and dimethylformamide (DMF) to form II-IV:



An attempt to obtain the corresponding 2-amino derivative from 2-sodio-1-methylbenzimidazole (I) and α-methylhydroxylamine did not give the expected result. 1,1'-Dimethyl-2,2'-dibenzimidazolyl (V) was isolated from the reaction products. The reaction to form V can be represented in the following manner:



It is known that the Wurtz-Fittig reaction usually occurs during the action of halogen derivatives of hydrocarbons on arylsodium compounds. By allowing ω-iodophenylacetylene instead of 1-methyl-2-(phenylethynyl)benzimidazole to react with 2-sodio-1-methylbenzimidazole, we obtained 2-iodo-1-methylbenzimidazole. It should be noted that iodine cannot be introduced into the 2-position of the benzimidazole ring by the methods described in the literature for its halogenation.

Our results indicate that the organosodium compounds of N-substituted benzimidazoles can be used for the synthesis of various derivatives of this heterocycle.

EXPERIMENTAL

1-Methyl-, 1-Ethyl-, 1-Propyl-, 1-Isopropyl-, 1-Butyl-, and 5-Bromo-1-ethylbenzimidazoles. These compounds were obtained by the methods in [9, 10].

1-Phenyl- and 1-(p-Tolyl)benzimidazoles. These compounds were synthesized by the methods in [4,11].

1-(o-Tolyl)benzimidazole. Powdered tin [38 g (0.32 g-atom)] was added with heating in the course of 1 h to a mixture of 40 g (0.15 mole) of 2,4-dinitro-2-methyldiphenylamine [12], 100 ml of 15% hydrochloric acid, and 30 ml of 85% formic acid, and the mixture was then refluxed for 12 h. At the end of the reaction, 300 ml of water was added, and the tin was precipitated with finely granulated aluminum and removed. The medium was made strongly alkaline, and the base was extracted with chloroform. The chloroform extract was washed with water and dried with sodium sulfate. The chloroform was removed by distillation, after which 5-amino-1-(o-tolyl)benzimidazole distilled at 230-235° (4 mm). The amine [21 g (0.1 mole)] was dissolved in 100 ml of 15% hydrochloric acid and diazotized at −5° with 7 g (0.1 mole) of sodium nitrite in 20 ml of water. A solution of 42 g (0.4 mole) of potassium hypophosphite in 100 ml of water was added to the diazo compound, and the mixture was allowed to stand at 0° for 24 h and was then treated with 25% ammonium hydroxide. The oil that was liberated was extracted with ether, the extract was dried with potassium carbonate, the ether was removed by distillation, and the residue was distilled to give 7 g (23%) of 1-(o-toyl)benzimidazole with bp 195-200° (10 mm). According to [13], bp 197-198° (14 mm). Found %: C 80.4; H 6.1; N 13.6. $C_{14}H_{12}N_2$. Calculated %: C 80.7; H 5.8; N 13.4.

2,4-Dinitro-2',4',6'-trimethyldiphenylamine. A mixture of 43 g (0.32 mole) of 2,4-dinitrochlorobenzene was heated at 170-200° for 3 h to give 22 g (23%) of a product with mp 178-179° (from alcohol). Found %: N 14.0. $C_{15}H_{15}N_3O_4$. Calculated %: N 13.9.

4-Nitro-2-amino-2',4',6'-trimethyldiphenylamine. Sulfur [2.7 g (0.08 g-atom)] was added to 20 g (0.08 mole) of crystalline sodium sulfide, and 22 g (0.07 mole) of 2,4-dinitro-2,4,6-trimethyldiphenylamine in 90 ml of alcohol was added to the resulting solution. The mixture was held at 50-60° for 2 h, refluxed for 30 min, diluted with 30 ml of water, and cooled. The precipitated dark-red crystals were removed by filtration and recrystallized from benzene to give 16 g (80%) of a product with mp 191-192°. Found %: N 15.7. $C_{15}H_{17}N_3O_2$. Calculated %: N 15.5.

5-Nitro-1-mesitylbenzimidazole. A mixture of 16 g (0.06 mole) of 4-nitro-2-amino-2',4',6'-trimethyldiphenylamine, 50 ml of 85% formic acid, and 1 ml of concentrated hydrochloric acid was refluxed for 4 h. A large amount of the formic acid was removed by distillation, and the residue was treated with 20% sodium hydroxide. The yellow crystals were removed by filtration, washed with water, and recrystallized from aqueous alcohol to give 13 g (78%) of a product with mp 144-145°. Found %: N 14.8. $C_{16}H_{15}N_3O_2$. Calculated %: N 14.9.

5-Amino-1-mesitylbenzimidazole. A mixture of 13 g (0.05 mole) of 5-nitro-1-mesitylbenzimidazole, 100 ml of water, 60 ml of alcohol, 3 ml of hydrochloric acid, and 65 g (1.2 g-atom) of iron powder was refluxed with stirring for 2.5 h. The mixture was neutralized with potassium carbonate and filtered. The

amine was extracted from the precipitate on the filter and from the aqueous solution with chloroform. The combined chloroform extracts were dried with potassium carbonate, and the chloroform was removed by distillation. The residue crystallized to give 10 g (86%) of 5-amino-1-mesitylbenzimidazole with mp 86-87° (from benzene). Found %: N 17.0. $C_{16}H_{17}N_3$. Calculated %: N 16.7.

1-Mesitylbenzimidazole. A solution of 10 g (0.04 mole) of 5-amino-1-mesitylbenzimidazole in 60 ml of 15% hydrochloric acid was diazotized at −5° with 2.8 g (0.04 mole) of sodium nitrite in 10 ml of water. A total of 40 ml of 20% hypophosphorous acid was added to the diazo compound, and the solution was allowed to stand at 0° for 50 h. Treatment of the solution with ammonium hydroxide liberated an oil that distilled at 185-195° (7 mm). The distillate was stirred with 5 ml of ether, the mixture was filtered away from the undissolved material, and the ether was removed by distillation. The residue was distilled again to give 1.9-2.3 g (20-24%) of 1-mesitylbenzimidazole with bp 185-190° (7 mm). Found %: C 81.7; H 6.7; N 12.1. $C_{16}H_{16}N_2$. Calculated %: C 81.3; H 6.8; N 11.9. The picrate had mp 166-167° (from alcohol).

Metallation of 1-Alkyl- and 1-Arylbenzimidazoles with Phenylsodium. Powdered sodium [1.1 g (0.048 g-atom)] in 20 ml of toluene was activated with isoamyl alcohol, and 2.6 g (0.023 mole) of chlorobenzene in 5 ml of toluene was added to it under nitrogen in the course of 30 min at 30-35°. After 1 h, a solution of 0.015 mole of 1-alkyl- or 1-arylbenzimidazole in 10-15 ml of toluene was added to the resulting phenylsodium at −15°. The reaction was carried out at this temperature for 1 h. To determine the yield of 2-sodiobenzimidazole, the reaction mass was carbonated with dry ice. The excess dry ice was removed, and the mixture was shaken with 50 ml of water. The aqueous layer was separated and acidified with acetic acid, and a 5% copper sulfate solution was added until the precipitation of the copper salt of the N-substituted benzimidazole-2-carboxylic acid was complete. The salt was removed by filtration, washed with water and alcohol, and dried (Table 1).

Metallation of 1-Arylbenzimidazoles with o-Anisylsodium. Anisole [10 g (0.093 mole)] was added to phenylsodium obtained from 2 g (0.087 g-atom) of sodium and 4.8 g (0.043 mole) of chlorobenzene in 30 ml of benzene, and the mixture was allowed to stand at 20-25° for 48 h. The o-anisylsodium was cooled to −15°, and 0.01 mole of 1-arylbenzimidazole in 10 ml of benzene was added to it. The metallation reaction was carried out in 1 h. The yield of 2-sodio-1-arylbenzimidazole was determined by the preceding method (Table 1).

Action of Phenylsodium and Amylsodium on 5-Bromo-1-ethylbenzimidazole. 5-Bromo-1-ethylbenzimidazole was subjected to the action of phenylsodium in benzene or amylsodium in hexane for 4 h at −15°. After carbonation, 5-bromo-1-ethylbenzimidazole was isolated almost completely from the organic layer.

Arylbenzimidazolylcarbinols. The carbonyl compound (0.04 mole) dissolved in the minimum amount of toluene or benzene was added to 2-sodio-1-alkyl- or 2-sodio-1-arylbenzimidazole (from 0.03 mole of 1-alkyl- or 1-arylbenzimidazole). The reaction was carried out at −15° for 1.5 h. At the end of the reaction, the unchanged sodium was removed with 10 ml of alcohol, and the mixture was treated twice with 25 ml of 10% hydrochloric acid. The hydrochloric acid extract was made alkaline with 40% sodium hydroxide, and the carbinol was removed by filtration, washed with water, dried, and recrystallized from benzene–petroleum ether (Table 2).

2-(1'-Methyl-2'-benzimidazolyl)ethanol. Ethylene oxide [11 g (0.25 mole)] was bubbled into 2-sodio-1-methylbenzimidazole [from 8.4 g (0.064 mole) of 1-methylbenzimidazole in 150 ml of toluene at −15°], and the mixture was stirred for 1 h, after which 25 ml of alcohol and 50 ml of water were added. The toluene layer was treated with 50 ml of 10% hydrochloric acid, and the acid extract was mixed with the water layer and made alkaline with NaOH. The base was extracted with chloroform, and the extract was dried with potassium carbonate. The chloroform was removed by distillation, and the residue was vacuum distilled to give 4.8 g (43%) of a product with bp 165-167° (7 mm). Found %: C 68.4; H 6.5; N 16.3. $C_{10}H_{12}N_2O$. Calculated %: C 68.2; H 6.9; N 15.9.

1-Methyl-2-formylbenzimidazole. N-Isopropylformanilide [6.5 g (0.04 mole)] was added to 2-sodio-1-methylbenzimidazole obtained from 4.2 g (0.032 mole) of 1-methylbenzimidazole. The reaction mass was stirred at 0° for 2 h, 6 ml of acetic acid and 30 ml of water were added, and the layers were separated. The aqueous layer was neutralized with sodium carbonate, and the oil that was liberated was extracted with chloroform. The toluene layer was combined with the chloroform extract, and the isopropylaniline and solvents were removed by steam distillation. The crude aldehyde was extracted with chloroform, the chloroform was removed by distillation, and the oily residue was treated with 4 ml of 35% sodium bisulfite solu-

tion. After 1 h, the bisulfite compound of 1-methyl-2-formylbenzimidazole was precipitated by the addition of alcohol followed by ether. The bisulfite compound was decomposed with saturated sodium carbonate solution to give 1.9 g (37%) of 1-methyl-2-formylbenzimidazole with mp 118-119° (from water) (mp 110 [14]). Found %: C 67.3; H 5.4; N 17.3. $C_9H_8N_2O$. Calculated %: C 67.5; H 5.0; N 17.5.

1-Ethyl-2-formylbenzimidazole (Table 2) was similarly obtained.

1-Phenyl-2-formylbenzimidazole. Dimethylformamide [5.5 g (0.075 mole)] was added rapidly at −15° to 2-sodio-1-phenylbenzimidazole obtained by the metallation of 2.9 g (0.015 mole) of 1-phenylbenzimidazole with o-anisylsodium, and the mixture was stirred at 0° for 1.5 h. Workup as described above gave 0.9 g (27%) of 1-phenyl-2-formylbenzimidazole with mp 77-78° (from benzene−petroleum ether). Found %: C 75.3; H 4.7; N 12.9. $C_{14}H_{10}N_2O$. Calculated %: C 75.7; H 4.5; N 12.6.

1-(p-Tolyl)-2-formylbenzimidazole (Table 2) was similarly obtained.

Reaction of 2-Sodio-1-methylbenzimidazole with α-Methylhydroxylamine. 2-Sodio-1-methylbenzimidazole from 5 g (0.038 mole) of 1-methylbenzimidazole and 0.9 g (0.019 mole) of α-methylhydroxylamine was stirred at −15° for 30 min and at room temperature for 1 h. Alcohol (10 ml) and 30 ml of water were then added, and the layers were separated. The organic layer yielded 1 g (20%) of 1,1'-dimethyl-2,2'-dibenzimidazolyl with mp 208-209°. Recrystallization from alcohol raised the melting point to 210-211°. This product did not depress the melting point of 1,1'-dimethyl-2,2'-dibenzimidazolyl obtained by the method in [15].

2-Iodo-1-methylbenzimidazole. ω-Iodophenylacetylene [6.6 g (0.029 mole)] was added to 2-sodio-1-methylbenzimidazole [obtained from 3.7 g (0.028 mole) of 1-methylbenzimidazole], and the mixture was stirred at 0° for 30 min. After this, 10 ml of alcohol and 30 ml of 10% hydrochloric acid were added. The liberated base hydrochloride was removed by filtration and introduced into the separated water layer of the filtrate and treated with 25% ammonium hydroxide to give 2.6 g (36%) of 2-iodo-1-methylbenzimidazole with mp 114-115° (from hexane). Found %: C 37.5; H 2.8; N 10.7. $C_8H_7IN_2$. Calculated %: C 37.2; H 2.7; N 10.9.

LITERATURE CITED

1. B. A. Tertov and S. E. Panchenko, Zh. Obshch. Khim., 33, 3671 (1963).
2. R. C. Elderfield and V. B. Meyer, J. Am. Chem. Soc., 76, 1891 (1954).
3. P. W. Alley and D. A. Shirley, J. Org. Chem., 23, 1791 (1958).
4. B. A. Tertov, N. A. Ivankova, and A. M. Simonov, Zh. Obshch. Khim., 32, 2989 (1962).
5. A. M. Simonov, Outline of the Chemistry of Azoles [in Russian], Izd. RGU (1965), p. 59.
6. B. A. Tertov and A. V. Koblik, Khim. Geterotsikl. Soedin., 955 (1967).
7. N. I. Sheverdina and K. A. Kocheshkov, Zh. Obshch. Khim., 8, 1825 (1938); Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 75 (1941).
8. A. F. Wagner, P. E. Wittreich, A. Lusi, and K. Folkers, J. Org. Chem., 27, 3236 (1962).
9. A. F. Pozharskii and A. M. Simonov, Zh. Obshch. Khim., 33, 179 (1963).
10. B. N. Feitelson, P. Mamalis, R. J. Moualim, V. Petrou, O. Stephenson, and B. Sturgeon, J. Chem. Soc., 2389 (1952).
11. B. K. Martsokha, A. F. Pozharskii, and A. M. Simonov, Zh. Obshch. Khim., 34, 1317 (1964).
12. Beilstein, 12, 787 (1929).
13. F. Montanari and P. Passerini, Boll. Sci. Facolta Ind. Bologna, 11, 46 (1953); Chem. Abstr., 48, 6436 (1954).
14. M. T. Le-Bris and H. Wahl, Bull. Soc. Chim. France, 343 (1959).
15. B. A. Tertov, A. V. Koblik, and Yu. V. Kolodyazhnyi, Tet. Lett., 4445 (1968).