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ORGANOLITHIUM AND ORGANOSODIUM COMPOUNDS OF N-SUBSTITUTED 2-ALKYLBENZIMIDAZOLES

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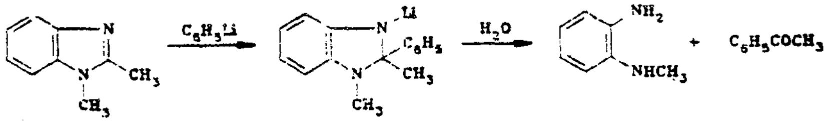
Organolithium and organosodium compounds of 1,2-dimethyl-, 1-methyl-2-ethyl-, 1-methyl-2-propyl-, and 1-phenyl-2-methylbenzimidazole, containing the metal in the alkyl group at position $C_{(2)}$, were obtained by metallation. It was found that metallation can be complicated by the addition of the metalling reagent at the C=N bond of the heterocycle. It was shown that the obtained organometallic compounds can be used for the synthesis of various derivatives of benzimidazole.

It is known that 2-alkylbenzimidazoles are converted into 1-lithio-2-lithioalkylbenzimidazoles by the action of butyllithium [1]. In the present work we describe the metallation of N-substituted 2-alkylbenzimidazoles and some transformations of the obtained organometallic compounds.

Using butyl- and phenyllithium as metallating reagents, we established that the organolithium compounds of N-substituted 2-alkylbenzimidazoles are formed with very low yields at the metallation temperature used for 2-alkylbenzimidazoles (~0°C), except in the case of 2-lithiomethyl-1-phenylbenzimidazole. Calculation of the energies of deprotonation ($\Delta E = E_{HetCH_2} - E_{HetCH_3}$) of 1,2-dimethyl- and 1-phenyl-2-methylbenzimidazole by the CNDO/2 method [2] showed that the latter is a stronger CH acid. The difference in the deprotonation energies of these compounds is 0.12 eV.* With such a difference, calculated by the CNDO/2 method, the rate constants for deuteroexchange of the methyl derivatives of the azoles, which characterize the kinetic CH acidity, may differ by more than an order of magnitude [3].

After hydrolysis of the products from the reaction of phenyllithium with 1,2-dimethylbenzimidazole in the hydrolysis product we found acetophenone and N-methyl-o-phenylenediamine, which are clearly formed according to the following scheme:



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*The calculation was performed with the standard bond lengths. A planar model was used for the carbanion.

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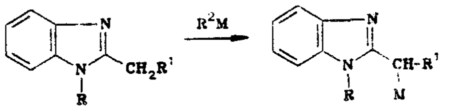
TABLE 1. Results from the Synthesis of the Organolithium and Organosodium Compounds of N-Substituted 2-Alkylbenzimidazoles

Initial compound	Metalling reagent	T_{proc} °C	Obtained organo-metallic compound	Yield* %	Initial compound	Metalling reagent	T_{proc} °C	Obtained organo-metallic compound	Yield,* %
Ia	C_4H_9Li	0	IIa	3	Ib	$C_{10}H_8^{\dot{-}}Na^+$	0	IId	80
Ia	C_4H_9Li	−78	IIa	56	Ic	C_4H_9Li	0	IIe	2
Ia	C_6H_5Li	0	IIa	2	Ic	C_4H_9Li	−78	IIe	8
Ia	C_6H_5Li	−78	IIa	47	Ic	$C_{10}H_8^{\dot{-}}Li^+$	0	IIe	91
Ia	$C_{10}H_8^{\dot{-}}Li^+$	0	IIa	96	Ic	$C_{10}H_8^{\dot{-}}Na^+$	0	IIf	82
Ia	$C_{10}H_8^{\dot{-}}Na^+$	0	IIb	95	Id	C_4H_9Li	0	IIg	38
Ib	C_4H_9Li	0	IIc	4	Id	C_4H_9Li	−78	IIg	73
Ib	C_4H_9Li	−78	IIc	5	Id	C_6H_5Li	0	IIg	79
Ib	C_6H_5Li	0	IIc	3	Id	C_6H_5Li	−78	IIg	90
Ib	C_6H_5Li	−78	IIc	48	Id	$C_{10}H_8^{\dot{-}}Li^+$	0	IIg	39
Ib	$C_{10}H_8^{\dot{-}}Li^+$	0	IIc	94	Id	$C_{10}H_8^{\dot{-}}Na^+$	0	IIh	57

*The yields of the carbinols (III) are given.

Thus, during the metallation of the N-substituted 2-alkylbenzimidazole addition of the metallating reagent to the heterocyclic ring takes place in addition to substitution of the hydrogen atom in the $C_{(2)}$- alkyl group by the metal. The ratio of the rates of metallation and addition of the metallating reagent to the cyclic C=N bond, on which the final result depends, can be affected not only by the CH acidity but also by other factors. Thus, for example, decrease in the temperature of the process to -78°C led to a considerable increase in the yields of some organolithium compounds of N-substituted 2-alkylbenzimidazoles. In all probability, this results from the fact that in these cases the rates of addition of the metallating reagents to the C=N bond decrease more quickly with decrease in temperature than the rates of metallation. If butyl- and phenyllithium are replaced by lithionaphthalene, metallation becomes practically the only process for 1,2-dimethyl-, 1-methyl-2-ethyl-, and 1-methyl-2-propylbenzimidazole. Good results were obtained during the metallation of 1,2-dialkylbenzimidazoles with sodionaphthalene. It is not impossible, however, that the mechanism of the metallation of N-substituted 2-alkylbenzimidazoles with normal metallating reagents and with the adducts of naphthalene with alkali metals differs. (In any case the reaction can take place through the intermediate formation of the radical-anions of the substrate.)

The above-mentioned methods were used to synthesize the following organolithium and organosodium compounds of N-substituted 2-alkylbenzimidazoles:

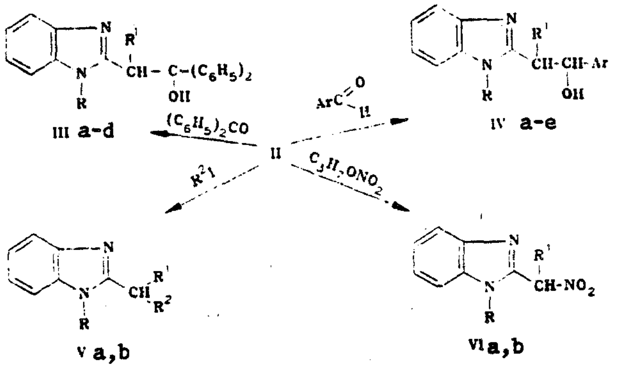


I a-d II a-h

I a-c $R=CH_3$, d $R=C_6H_5$; a, d $R^1=H$, b $R^1=CH_3$, c $R^1=C_2H_5$; II a-f $R=CH_3$, g, h $R=C_6H_5$; a, b, g, h $R^1=H$, c, d $R^1=CH_3$, e, f $R^1=C_2H_5$; a, c, e, g $M=Li$; b, d, f, h $M=Na$; $R^2M=C_4H_9Li$, C_6H_5Li, $C_{10}H_8^{\dot{-}}Li^+$, $C_{10}H_8^{\dot{-}}Na^+$, NH_2Na

The transformations of compounds (II) given below confirm their structure and also illustrate the possibilities for the synthesis of benzimidazole derivatives from them.

1-Methyl-2-(2,2-diphenyl-2-hydroxyethyl)benzimidazole (IIIa) was also obtained from 1-methyl-2-chloromethyl-benzimidazole and dilithiobenzophenone. In the PMR spectrum of 1-methyl-2-(1-methyl-2,2-diphenyl-2-hydroxyethyl)benzimidazole (IIIb) in chloroform there are signals in the regions of 1.15 (d, C-CH_3), 1.95 (s, OH), 3.52 (s, N—CH_3), 4.06 (q, C—H) 6.6-7.6 ppm (m, aromatic protons), which correspond to the assigned structure. The IR spectra of 1-methyl-2-nitromethyl- and 1-phenyl-2-nitromethylbenzimidazoles (VIa, b), which contain absorption bands at 1010, 1060, 1160 ($C=NO_2H$), 3225, 3310 cm^{-1} (OH) respectively, indicate that these compounds exist in the aci-nitro forms. The IR spectra of (IVa, Va) and of authentic samples were identical.



III a-c $R=CH_3$, d $R=C_6H_5$; a,d $R^1=H$, b $R^1=CH_3$, c $R^1=C_2H_5$; IV a-e $R=CH_3$, a, b $R^1=H$, c, d, $R^1=CH_3$, e, $R^1=C_2H_5$; a, c, $Ar=C_6H_5$, b, d, e $Ar=CH_3OC_6H_4$; V a, b $R=CH_3$, $R^1=H$; a $R^2=CH_3$, b $R^2=C_2H_5$; VI a $R=CH_3$, b $R=C_6H_5$; a, b $R^1=H$

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil on a UR-20 instrument. The PMR spectrum was obtained on a Tesla BS-487C spectrometer at 80 MHz with HMDS as internal standard. The N-substituted 2-alkylbenzimidazoles were obtained by the methods in [4-7].

Action of Phenyllithium on 1,2-Dimethylbenzimidazole. To phenyllithium, obtained from 0.9 g (130 mmole) of lithium and 10.2 g (65 mmole) of bromobenzene in 20 ml of ether, we added a solution of 4 g (27 mmole) of 1,2-dimethylbenzimidazole in 20 ml of absolute toluene. The mixture was stirred at 20-25°C for 4 h. We then added 20 ml of water, separated the organic layer, and distilled the ether and toluene. The remaining oil was boiled for 1 h with 30 ml of 5% hydrochloric acid. The mixture was cooled and treated with 25 ml of ether. After distillation of the ether from the organic layer the residue was dissolved in 3 ml of alcohol, and an alcohol solution of 2,4-dinitrophenylhydrazine was added to the solution. The melting point of the separated crystals was 238-239°C, which corresponds to acetophenone 2,4-dinitrophenylhydrazone. The obtained substance did not give a melting point depression with an authentic sample. N-Methyl-o-phenylenediamine, present in the hydrochloric acid solution, was converted by the action of formic acid into 1-methylbenzimidazole, which was identified as the picrate; mp 246-247°C (from water) [8].

Metallation of N-Substituted 2-Alkylbenzimidazoles with Butyl- and Phenyllithium. To butyl- or phenyllithium, obtained from 0.3 g (43.4 mmole) of lithium and 21.7 mmole of butyl bromide or bromobenzene in 15 ml of ether, at 0°C or -78°C we added over 20 min a solution of 10 mmole of the N-substituted 2-alkylbenzimidazole in 10 ml of THF. The reaction was continued for 1 h. To determine the yields of the organolithium compounds we treated them with a solution of 4.19 g (23 mmole) of benzophenone in 10 ml of THF. The temperature was brought to 25°C, and the mixture was kept for 2 h. At the end of the reaction we added 15 ml of water. The organic layer was separated and shaken with 20 ml of 15% hydrochloric acid. Compounds (III) were precipitated from the hydrochloric acid extract with a 10% solution of ammonia, filtered, washed with 10 ml of water, and dried. The results are given in Table 1.

Metallation of N-Substituted 2-Alkylbenzimidazoles with Lithio- and Sodionaphthalene. To lithio- or sodionaphthalene, obtained from 28 mmole of lithium or sodium and 3.6 g (28 mmole) of naphthalene in 20 ml of THF, over 20 min at 0°C we added 14 mmole of the N-substituted 2-alkylbenzimidazole in 10 ml of THF. The reaction was continued for a further 15 min. We then added 5.47 g (30 mmole) of benzophenone in 10 ml of THF. The temperature was brought to 25°C, and after 2 h the mixture was treated with 10 ml of water. The THF was distilled, and the residue was shaken with 20 ml of ether and 20 ml of 15% hydrochloric acid. Compounds (III) were isolated from the hydrochloric acid extract by the method described above (Table 1).

1-Methyl-2-(2,2-diphenyl-2-hydroxyethyl)benzimidazole (IIIa). A solution of 2.5 g (13.8 mmole) of benzophenone in 10 ml of THF was added at 0°C to lithionapthalene [from 0.2 g (28.8 mmole) of lithium and 3.7 g (28.8 mmole) of naphthalene] in 25 ml of THF. To the obtained dilithiobenzophenone we then added over 15 min 2.5 g (13.8 mmole) of 1-methyl-2-

TABLE 2. Characteristics of Compounds (III, IV)

Compound	mp,* °C	Found, %			Molecular formula	Calc., %			Yield,† %
		C	H	N		C	H	N	
IIIa	194—195	80,4	6,4	8,8	$C_{22}H_{20}N_2O$	80,5	6,1	8,5	—
IIIb	168—169	80,7	6,4	8,1	$C_{23}H_{22}N_2O$	80,7	6,5	8,2	—
IIIc	162—163	80,8	6,8	8,0	$C_{24}H_{24}N_2O$	80,9	6,8	7,9	—
IIId	193—194	83,4	5,7	7,4	$C_{27}H_{22}N_2O$	83,0	5,7	7,2	—
IVa	181—182	76,2	6,6	11,3	$C_{16}H_{16}N_2O$	76,2	6,4	11,1	64
IVb	182—183	72,0	6,6	9,6	$C_{17}H_{18}N_2O_2$	72,3	6,4	9,9	52
IVc	176—177	76,8	7,1	10,6	$C_{17}H_{18}N_2O$	76,6	6,8	10,5	66
IVd	149—150	73,2	7,0	9,5	$C_{18}H_{20}N_2O_2$	73,0	6,8	9,5	89
IVe	174—175	73,8	7,2	9,2	$C_{19}H_{22}N_2O_2$	73,5	7,1	9,0	93

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*Compounds (IIIa, c, IVa-c) were recrystallized from alcohol, (IIIb,d) from benzene, and (IVd, e) from ethyl acetate.

†The yields of compounds (IIIa-d) are given in Table 1.

chloromethylbenzimidazole in 15 ml of THF. After the treatment of the reaction mixture described above we obtained 2.2 g (49%) of (IIIa); mp 192-193°C (from benzene). A mixed melting test with compound (IIIa) obtained by the previous method did not give a melting point depression. The IR spectra of the two samples were identical.

1-Methyl-2-(2-aryl-2-hydroxyalkyl)benzimidazoles (IV). To a solution of the organolithium or organosodium compound (II) (from 10 mmole of the N-substituted 2-alkylbenzimidazole, 20 mmole of the alkali metal, and 20 mmole of napthalene) in 23 ml of THF at 0°C we added 25 mmole of the aromatic aldehyde in 10 ml of THF. The mixture was stirred for 1 h 30 min, and compounds (IV) were isolated by the method described for the carbinols (III). The benzimidazoles (IVa,c) were obtained from the organolithium compounds (IIa,c). The benzimidazoles (IVb,d,e) were obtained from the organosodium compounds (IIb,d,f) (Table 2).

1-Methyl-2-ethylbenzimidazole (Va). To 1-methyl-2-sodiomethylbenzimidazole [from 1.46 g (10 mmole) of 1,2-dimethylbenzimidazole] in 23 ml of THF we added 3.14 g (22 mmole) of methyl iodide. The mixture was stirred at -15°C for 1 h 30 min and at 50°C for 30 min. We than added 10 ml of water, separated the organic layer, and treated it with 20 ml of 15% hydrochloric acid. The hydrochloric acid extract was washed with ether and neutralized to pH 7-8 with 25% ammonia. The crystals were filtered off, and dried. The yield was 1.1 g (69%); mp 55°C (from aqueous alcohol). Published data [5]: mp 55°C.

1-Methyl-2-propylbenzimidazole (Vb). The compound was synthesized similarly. From 1.46 g (10 mmole) of 1,2-dimethylbenzimidazole and 3.43 g (22 mmole) of ethyl iodide we obtained 1.0 g (58%) of (Vb); mp 58-59°C (from petroleum ether). Published data [6]: mp 59°C.

1-Methyl-2-nitromethylbenzimidazole (VIa). To a suspension of sodium amide [obtained from 1.57 g (65 mmole) of sodium in 100 ml of liquid ammonia] we added 3.65 g (25 mmole) of 1,2-dimethylbenzimidazole. The mixture was stirred for 30 min, 8.4 g (80 mmole) of propyl nitrate was added drop by drop, the mixture was stirred for a further 30 min, and 100 ml of absolute ether was added in one portion. After evaporation of the ammonia the sodium salt of (VIa) was filtered off and washed with cold absolute alcohol (4 × 10 ml). The 1-methyl-2-nitromethylbenzimidazole was isolated by acidification of the aqueous solution of the salt (VIa) to pH 6-7 with acetic acid. The yield was 1.6 g (33%); mp 147°C (yellowish prisms from alcohol). Found %: C 56.1; H 4.8; N 22.1. $C_9H_9N_3O_2$. Calculated %: C 56.5; H 4.7; N 22.0.

1-Phenyl-2-nitromethylbenzimidazole (VIb). The compound was obtained similarly to (VIa) with a 34% yield; mp 126-127°C (from alcohol). Found %: C 66.1; H 4.4; N 16.7. $C_{14}H_{11}N_3O_2$. Calculated %: C 66.4; H 4.3; N 16.6.

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CHEMISTRY OF 2-HETARYLBENZIMIDAZOLES.

7.* TRANSFORMATIONS OF TRANS-1-METHYL-2-[β-(2'-FURYL)VINYL] BENZIMIDAZOLE

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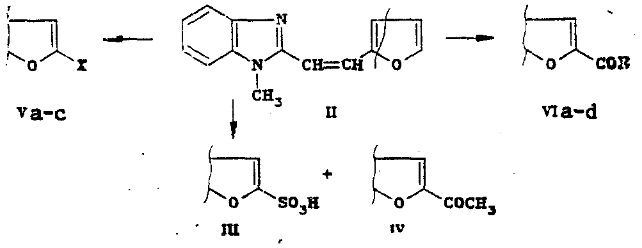
Electrophilic substitution reactions in the furylvinylbenzimidazole series were studied. In nitration, sulfonation, bromination, acylation, formylation, and hydroxymethylation reactions, the substituent enters at the α-position of the furan ring. The presence of a vinylene group reduces the influence of the benzimidazole fragment on the furan ring, and therefore the reactions in the latter proceed considerably more rapidly and under milder conditions than in the case of furylbenzimidazole. Calculated data are given for the π-electronic density on the carbon atoms of furyl-vinylbenzimidazole, obtained by the CNDO method.

The nitration and acetylation of the furan ring in 1-alkyl-2-[β-(2'-furyl)-vinyl] benzimidazole have already been studied in [2].

It was of interest to examine the behavior of 1-methyl-2-[β-(2'-furyl)-vinyl] benzimidazole (II) in other electrophilic substitution reactions, and to compare the reactivity of the furan ring linked directly or through a vinylene group to the benzimidazole radical. For this purpose, we carried out several reactions, as shown in the following scheme:



V a X=Br, b X=CH_2OH, c X=NO_2; VI a R=H, b R=C_2H_5, c R=$CH_2C_6H_5$, d R=C_6H_5

The sulfonation of 1-methyl-2-(2'-furyl)benzimidazole (I) was previously carried out by the action of concentrated sulfuric and polyphosphoric acids at 120°C [3]. Under these conditions, compound II undergoes a complete resinification. We therefore carried out its sulfonation

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*For Communication 6, see [1].

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