REACTIONS OF N-SUBSTITUTED DIAZOLES AND THEIR HALO DERIVATIVES WITH NAPHTHYLLITHIUM AND NAPHTHYLSODIUM

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1-Methylimidazole and halo derivatives of some 1-substituted imidazoles and pyrazoles react with naphthyllithium(sodium) to give organolithium(sodium) compounds. 1-Benzyl-3,5-dimethylpyrazole undergoes debenzylation on reaction with naphthyllithium.

On the basis of the concept of the mechanism of metallation [1, 2], one might have supposed that diazoles, which are metallated by active organometallic compounds, would also be metallated by naphthyllithium and naphthylsodium.

We have found that 2-lithio-1-methylimidazole is formed in the reaction of 1-methylimidazole (I) with naphthyllithium, but the reaction proceeds more slowly than with butyllithium. 1-Phenylimidazole, which is metallated by butyllithium [3] and phenylsodium [4], is not converted to an organometallic compound on reaction with naphthyllithium and naphthylsodium. 1-Benzyl-3,5-dimethylpyrazole reacts with naphthyllithium to give 1-lithio-3,5-dimethylpyrazole, but gives 1-(α-lithiobenzyl)-3,5-dimethylpyrazole on reaction with butyllithium.

The metallation of the diazoles can be represented by the following scheme:

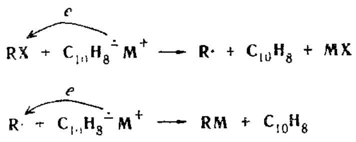
$$\mathrm{RH + R'M(C_{10}H_8^{\dot{-}}M^+) \longrightarrow RH^{\dot{-}}M^+ + R'\cdot(C_{10}H_8)}$$

$$\mathrm{RH^{\dot{-}}M^+ + R'\cdot(C_{10}H_8^{\dot{-}}M^+) \longrightarrow RM + R'H(C_{10}H_9M)}$$

R = heteryl R′ = alkyl, aryl M = Li, Na

If it is assumed that the rate-determining step in this process is detachment of hydrogen atoms from the anion radicals of the diazoles by radical particles, realization of the indicated step should be hindered when naphthyllithium and naphthylsodium are used as the reagents because of delocalization of the density of the unpaired electron in the $C_{10}H_8^{\dot{-}}$ anion radical. When the rate-determining step is not realized, other processes may occur in place of metallation. Thus our results do not contradict the above-presented scheme for the metallation of diazoles.

Halodiazoles exchange halogen atoms (chlorine and bromine) for the alkali metal readily rapidly on reaction with naphthyllithium and naphthylsodium.* Two one-electron transfers evidently occur in this case, and the halogen is split out as the anion.



$$\mathrm{RX + C_{10}H_8^{\dot{-}}M^+ \longrightarrow R\cdot + C_{10}H_8 + MX}$$

$$\mathrm{R\cdot + C_{10}H_8^{\dot{-}}M^+ \longrightarrow RM + C_{10}H_8}$$

R = heteryl X = Cl, Br; M = Li, Na

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*Alkyllithiums and aryllithiums react poorly with chloro derivatives, and bromo and iodo derivatives therefore are usually employed in order to obtain organolithio compounds via exchange reaction RX + R'Li ⇄ RLi + R'X (X = halogen).

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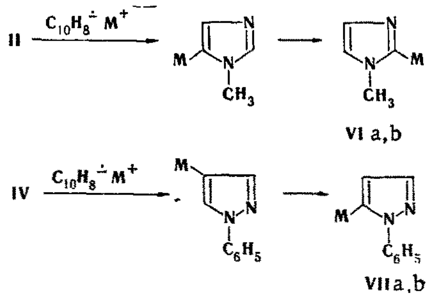
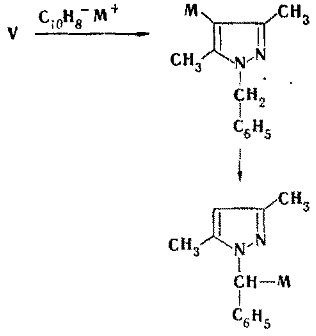
5-Chloro-1-methylimidazole (II), 5-chloro-3-methyl-1-phenylpyrazole (III), 4-bromo-1-phenylpyrazole (IV), and 4-bromo-1-benzyl-3,5-dimethylpyrazole (V) were subjected to reaction with naphthyllithium(sodium). The organometallic compounds formed from II, IV, and V isomerized during the reaction.



VI–VIII a M = Li; b M = Na



VIII b

In order to determine the yields of 2-lithio(sodio)-1-methylimidazole (VIa,b), 5-lithio(sodio)-1-phenyl- (VIIa,b), 5-lithio(sodio)-3-methyl-1-phenyl- (IXa,b), and 1-[α-lithio(sodio)benzyl]-3,5-dimethylpyrazoles (VIIIa,b) we converted them to the corresponding alcohols (Xa-d, Table 1) by reaction with benzophenone.

The structures of VIa,b, VIIa,b, and IXa,b were proved by conversion of them to, respectively, diphenyl(1-methyl-2-imidazolyl)carbinol (Xa) and 1-phenyl- and 3-methyl-1-phenylpyrazole-5-carboxylic acids. The structure of VIIIa,b was confirmed by the PMR spectrum of the 1-(1,2,2-triphenyl-2-hydroxyethyl)-3,5-dimethylpyrazole (Xd) obtained from them. The assignment of the signals was made on the basis of a comparison of the spectrum of this compound with the spectra of 1-benzyl-3,5-dimethyl- and 4-bromo-1-benzyl-3,5-dimethylpyrazoles.

EXPERIMENTAL

The PMR spectra were recorded with a Telsa BS 487 C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard and $CDCl_3$ as the solvent.

1-Methyl-, 1-Phenyl-, and 5-Chloro-1-methylimidazoles and 4-Bromo-1-phenylpyrazole. These compounds were obtained by the methods in [5-8].

5-Chloro-3-methyl-1-phenylpyrazole. This compound was synthesized by the reaction of phosphorus oxychloride with 3-methyl-1-phenyl-5-pyrazolone by the method described for the preparation of 5-chloro-3-methylpyrazole [9]. The yield of product with bp 205-210° (65 mm) was 65%. Found: C 62.4; H 4.7; Cl 18.2; N 14.6%. $C_{10}H_9ClN_2$. Calculated: C 62.3; H 4.7; Cl 18.4; N 14.5%.

1-Benzyl-3,5-dimethylpyrazole. A mixture of 30 g (0.31 mole) of 3,5-dimethylpyrazole and 44.3 g (0.35 mole) of benzylchloride was heated at 170-180° for 4 h. It was then cooled, and 250 ml of water heated to 50-60° and 40 ml of concentrated hydrochloric acid were added. The mixture was then treated with benzene, and the aqueous layer was separated and made alkaline with 10% ammonium hydroxide. The liberated base was extracted with ether, the

TABLE 1. Synthesis of Lithio- and Sodiodiazoles

No. of compound	Organometallic product	mp of Xa–d, °C	Empirical formula	Found, %			Calc., %			Yield, %*
				C	H	N	C	H	N	
I	2-Lithio-1-methylimidazole	185—186[2]	$C_{17}H_{16}N_2O$	77,1	6,0	10,8	77,2	6,1	10,6	87
II	2-Lithio (sodio)-1-methylimidazole	186—187[2]†	$C_{17}H_{16}N_2O$	77,0	6,0	10,7	77,2	6,1	10,6	88 (73)
III	5-Lithio (sodio)-3-methyl-1-phenylpyrazole	154—155[3] ‡	$C_{23}H_{20}N_2O$	81,1	5,7	8.2	81,1	5,9	8.2	45 (51)
IV	5-Lithio (sodio)-1-phenylpyrazole	148—149[3]‡	$C_{22}H_{18}N_2O$	80,7	5.6	8,6	80,9	5,6	8,6	43 (38)
V	1-[α-Lithio (sodio) benzyl]-3,5-dimethylpyrazole	180—181[3]‡	$C_{25}H_{24}N_2O$	81,4	6,4	7,9	81,5	6,6	7,6	74 (66)

*The yields of alcohols Xa-d obtained from the organosodium compounds are presented in parentheses.

†From alcohol.

††From benzene.

ether solution was dried with sodium sulfate, the ether was removed by distillation, and the residue was vacuum distilled to give 54 g (93%) of a product with bp 172-178° (12 mm). Found: C 77.1; H 7.7; N 15.2%. $C_{12}H_{14}N_2$. Calculated: C 77.4; H 7.6; N 15.0%. PMR spectrum, δ, ppm: 2.10, 2.21 (3-CH_3 and 5-CH_3), 5.19 (N-CH_2), 5.81 (4-H), and 6.9-7.6 (C_6H_5).

4-Bromo-1-benzyl-3,5-dimethylpyrazole. This compound, with bp 210-214° (10 mm), was obtained in 81% yield by the method in [8]. Found: C 54.4, H 5.1; Br 29.9; N 10.7%. $C_{12}H_{13}BrN_2$. Calculated: C 54.4; H 5.0; Br 30.1; N 10.6%. PMR spectrum, δ, ppm: 2.04, 2.15 (3-CH_3 and 5-CH_3), 5.13 (N-CH_2), and 6.9-7.3 (C_6H_5).

Metallation of 1-Methylimidazole with Naphthyllithium and Butyllithium. 1) A mixture of 0.3 g (43.2 mg/atom) of finely ground lithium, 5.5 g (42.9 mmole) of naphthalene, and 30 ml of tetrahydrofuran (THF) was stirred at 20-25° in an argon atmosphere for 3 h, and the resulting solution of naphthyllithium was then cooled to –15°, and a solution of 1-methylimidazole in 5 ml of THF was added to it in the course of 10 min. After 1 h, 5.4 g (29.6 mmole) of benzophenone in 10 ml of THF was added gradually, and the temperature of the mixture was raised to 20-25°. After two days, 10 ml of water was added, the bulk of the THF was removed by distillation, and the residue was treated with 15 ml of 15% hydrochloric acid and 20 ml of ether. The hydrochloric acid extract was separated and made alkaline with 10% ammonium hydroxide. The liberated diphenyl(1-methyl-2-imidazolyl)carbinol (Xa) was removed by filtration and purified by recrystallization from alcohol to give 2.1 g (40%) of product. The product was identical to a genuine sample obtained by the method in [4]. The yield of 2-lithio-1-methylimidazole was raised to 87 and 82%, respectively, when the reaction time was increased to 3 h or when the temperature was raised to 20°.

2) 2-Lithio-1-methylimidazole was formed in 81% yield (with respect to Xa) after 1 h at –15° in the metallation of 1.6 g (19.5 mmole) of 1-methylimidazole with butyllithium [from 0.6 g (86.4 mg-atom) of lithium and 5.9 g (43.1 mmole) of butyl bromide in 35 ml of ether].

Action of Naphthyllithium and Naphthylsodium on 1-Phenylimidazole. The reaction was carried out as described above for 1-methylimidazole. A resin from which individual substances could not be isolated was formed after successive treatment of the reaction mixture with benzophenone and hydrochloric acid. Replacement of naphthyllithium by naphthylsodium, obtained in the same way as naphthyllithium, gave the same results.

3,5-Dimethylpyrazole. A solution of 5 g (26.8 mmole) of 1-benzyl-3,5-dimethylpyrazole in 5 ml of THF was added to a solution of naphthyllithium [from 11 g (85.8 mole) of naphthalene and 0.6 g (86.4 mg-atom) of lithium in 60 ml of THF], and after 2 h the mixture was treated with water. The usual workup gave 2 g (78%) of 3,5-dimethylpyrazole with mp 107-108° (from water) [10]. The IR spectra of this product and of a genuine sample were identical. No melting-point depression was observed for a mixture of the product and genuine sample.

Metallation of 1-Benzyl-3,5-dimethylpyrazole with Butyllithium. A solution of 1.9 g (10.2 mmole) of 1-benzyl-3,5-dimethylpyrazole in 10 ml of ether was added in the course of 20 min at 0° to butyllithium [from 0.4 g (57.6 mg-atom) of lithium and 4 g (29.1 mmole) of butyl bromide in 20 ml of ether]. After 2 h, a solution of 5.3 g (29.1 mmole) of benzophenone in 20 ml of ether was added, the temperature was raised to room temperature, and the mixture was held at room temperature for 2 h. Treatment of the mixture with 20 ml of water and workup of the aqueous mixture gave 2.7 g (72%) of 1-(1,2,2-triphenyl-2-hydroxyethyl)-3,5-dimethylpyrazole with mp 180-181° (from benzene). Found: C 81.3; H 6.6; N 7.8%. $C_{25}H_{24}N_2O$. Calculated: C 81.5; H 6.6; N 7.6%.

Synthesis of Organolithium and Organosodium Compounds of Diazoles from Halodiazoles. A solution of 12 mmoles of halodiazole in 10 ml of THF was poured in the course of 15 min into a cooled (to −15°) and vigorously stirred solution of naphthyllithium or naphthylsodium obtained from 43.2 mg-atom of alkali metal and 5.5 g (42.9 mmole) of naphthalene in 30 ml of THF, after which the mixture was held at this temperature for 15 min. In the case of 4-bromo-1-phenylpyrazole, the reaction was carried out at −35°. A solution of 3.9 g (21.4 mmole) of benzophenone in 10 ml of THF was added in the course of 20 min to the resulting organometallic compound, and the temperature of the mixture was raised to room temperature. After 2 h, the mixture was worked up as described above to isolate alcohols Xa-d. The IR spectra of alcohols Xa and Xd obtained from organometallic compounds VIa,b and VIIIa,b were identical to the IR spectra of diphenyl (1-methyl-2-imidazolyl)carbinol and 1-(1,2,2-triphenyl-2-hydroxyethyl)-3,5-dimethylpyrazole synthesized via the methods described above. No melting point depressions were observed for mixtures of the products and authentic samples. PMR spectrum of Xd, δ, ppm: 2.05, 2.13 (3-CH_3 and 5-CH_3), 5.65 (N–CH), 5.91 (4-H), and 6.8-7.6 (C_6H_5 group).

3-Methyl-1-phenylpyrazole-5-carboxylic Acid. This compound, with mp 181-182° (from water) (mp 178.5-179.5° [12]), was obtained by dry-ice carbonization of IXa,b. Found: C 65.2; H 4.9; N 14.1%. $C_{11}H_{10}N_2O_2$. Calculated: C 65.3; H 5.0; N 13.9%.

1-Phenylpyrazole-5-carboxylic Acid. This compound, with mp 182-183° (from water) [12], was formed by carbonization of VIIa,b. Found: C 63.9; H 4.5; N 15.0%. $C_{10}H_8N_2O_2$. Calculated: C 63.8; H 4.3; N 14.9%. The IR spectra of the product and an authentic sample were identical. No melting-point depression was observed for a mixture of the product and a genuine sample.

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