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An easy synthesis of benzimidazole N-oxides, and their reactivity with organometallic reagents to give stable nitroxide radicals, are described. 1-Hydroxy-2-phenylbenzimidazole does not react in spite of its tautomeric equilibrium with the N-oxide structure.

In previous works (1-3) we reported on the addition reactions of organometallic reagents on N-oxides (1) leading to the hydroxylamines 2 which are easily oxidized to stable nitroxide radicals 3:

Block 1

In the present paper we report on the analogous reaction of organo metallic compounds with benzimidazole N-oxides which presents some particular features.

Benzimidazole N-oxides 4a and 4b were prepared by catalytic hydrogenation in pyridine of N-phenyl-N-acyl-o-nitroaniline 7a and 7b because the methods used in the literature (4,5) gave poor or zero yields, or were too complex. The same synthetic method, however, starting from 8 failed to prepare benzimidazole 9, for which an equilibrium exists with the tautomeric structure 10 (5). Compound 9 was therefore prepared as reported in the literature (6) (see Experimental).

2-Alkyl(or phenyl)3-phenylbenzimidazole N-oxides 4a and 4b react with organolithium or Grignard reagents to give 2,2-dialkyl(or phenyl)-3-phenyl-2,3-dihydrobenzimidazole-1-oxyls 6a and 6b (Scheme), via the intermediate hydroxylamines 5 which could never be isolated owing to their tendency towards autoxidation.

Nitroxide 6b was isolated in the solid pure state in 63% yield and is stable; on the contrary, the formation of radical 6a was observed in solution, but it could never be isolated. Radical 6a was formed both from 4a with phenyllithium and from 4b with methyllithium. The esr spectrum of 6b is resolved enough to be fully interpreted: it shows the interaction of the unpaired electron with the nitroxide nitrogen (a^N = 10.3 G), with two pairs of hydrogens (a^H = 3.6 and 0.75 G, respectively), and with the N-3 (a^N = 0.6 G). The larger coupling constant values for the two pairs of hydrogens was assigned to the hydrogens bonded to carbons C-5 and C-7 (ortho and para, respectively, to nitroxide nitrogen), and the lesser to the C-4 and C-6 hydrogens (meta to nitrogen) of the benzimidazole ring, on the basis of the analogy with several similar cases (1-3).

The esr spectrum of 6a is not well resolved owing to the further interaction with the hydrogens of the C-2 methyl group, and only the a^N and $a^{Ho,p}$ values could be obtained from the experimental spectrum (10.65 and 3.65 G, respectively). On the other hand, 1-hydroxy-2-phenylbenzimidazole 9 did not react with organo metallic reagents in spite of the presence of the tautomeric structure 10 (5) in the equilibrium mixture (7).

Scheme

4 a: R = Me
  b: R = Ph

7 a: R = Me
  b: R = Ph

6 a: R = Me; R' = Ph
  b: R = R' = Ph

Finally, the reduction of 8 deserves some comment: the catalytic hydrogenation stops at the hydroxylamine stage 11, which in acetic acid solution is easily transformed by autoxidation to the azoxy derivative 12 (8). Reaction of 12 with phenyllithium or phenylmagnesium bromide gave a solution from which an intense and well-resolved esr signal could be registered (Figure 1a). The signal was interpreted and satisfactorily reconstructed (Figure 1b),

Figure 1a.   Esr first-derivative spectrum of the nitroxide **14**: observed spectrum in benzene solution.
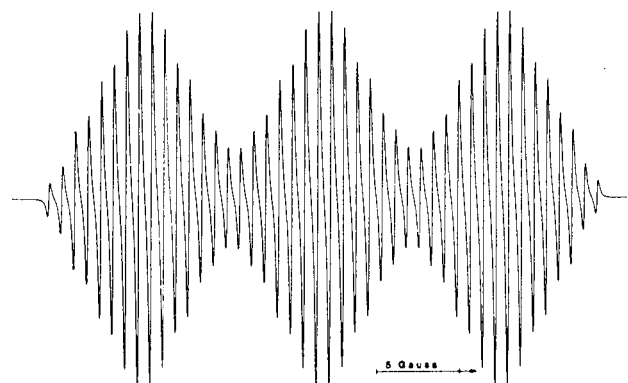

Figure 1b. Calculated spectrum of the nitroxide **14** with Lorentzian line width of 0.23 G.

by means of an automatic calculation program, using the following values for the coupling constants: a^N = 10.64 G; a^H = 3.04 G (2 H); a^H = 1.52 G (2 H); a^N = 0.76 G; a^H = 0.76 G. These values would be in agreement with structure **14**: unfortunately, from the reaction solution we were only able to isolate traces, too low to be analysed, of an unstable product, for which only the mass (besides the esr) spectrum could be registered: an intense peak at 287 was observed (the molecular peak of **14** would be 287), but the isolated product was neither very pure nor very stable. The formation of **14** by reduction and cyclisation of **12**, while surprising, would present some similarity with analogous cases reported in the literature (9); again while compound **10** did not react with phenyl-lithium, as reported above, reduction of **12**, not to mention **8** and **9** gave the cyclisation product **13**.

EXPERIMENTAL

The melting points are uncorrected. The ir spectra were recorded in nujol on a Perkin-Elmer 257 spectrophotometer; the nmr spectra were recorded on a Perkin-Elmer R12 B spectrophotometer using TMS as the internal standard. The esr spectra were recorded on a Varian E 4 apparatus.

N-Acetyl-N-phenyl-o-nitroaniline (**7a**) (4).

o-Nitrodiphenylamine (11.78 g.), acetyl chloride (10 ml.) and zinc chloride (1 g.) in 50 ml. of benzene were refluxed for 3 hours. The reaction solution was evaporated to dryness and the residue was taken up with 30 ml. of boiling ethanol; by cooling 11 g. (78%) of the corresponding N-acetyl derivative **7a** were obtained, m.p. 137° (from ethanol); ir: 1670 cm^{-1} (C=O).

N-Benzoyl-N-phenyl-o-nitroaniline (**7b**).

Starting from the same quantities of o-nitrodiphenylamine and zinc chloride, using 20 ml. of benzoyl chloride, and working as described above, we obtained 10.5 g. (60%) of the benzoyl derivative, m.p. 137° (from ethanol); ir: 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.75; H, 4.48; N, 8.76.

2-Methyl-3-phenylbenzimidazole 1-Oxide (**4a**) (4).

N-Acetyl-N-phenyl-o-nitroaniline (**7a**) (5.2 g.) in 50 ml. of pyridine was hydrogenated on a Parr apparatus in the presence of 5% palladium/carbon (200 mg.), for 2.5 hours. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue, taken up with ethyl acetate, gave 3.4 g. (78%) of the N-oxide derivative **4a**, m.p. 173° (from benzene/ligroin).

2,3-Diphenylbenzimidazole 1-Oxide (**4b**).

Starting from N-benzoyl-N-phenyl-o-nitroaniline (**7b**) (12 g.) in 80 ml. of pyridine and 5% palladium/carbon (300 mg.), and working as described above, were isolated 6.7 g. (62%) of the N-oxide derivative **4b**, m.p. 203° (from benzene/ligroin).

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.95; H, 4.91; N, 9.83.

o-Benzoylaminophenylhydroxylamine (**11**).

o-Nitrobenzoylaniline **8** (2.42 g.) in 50 ml. of pyridine was hydrogenated for 1 hour in the presence of 5% palladium/carbon (150 mg.). The catalyst was filtered off and the filtrate, when evaporated to dryness, gave a yellow orange residue, which was taken up with ethanol and gave 400 mg. of 2,2'-dibenzoylamino-azoxybenzene (**12**) (7), m.p. 194° (from benzene). The filtrated ethanolic solution, evaporated to dryness, gave 1.75 g. of **11**, m.p. 115° (from benzene).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.27. Found: C, 68.65; H, 5.32; N, 12.35.

2,2'-Debenzoylaminoazoxybenzene (**12**).

o-Benzoylaminophenylhydroxylamine **11** (580 mg.) was stirred in 20 ml. of acetic acid for 10 hours and gave the azoxyderivative **12**, quantitatively.

2-Phenylbenzimidazole **13** from the Azoxy Derivative **12**.

Azoxy derivative **12** (1 g.) and iron powder (1 g.) were refluxed in 25 ml. of acetic acid for 1 hour. The reaction mixture was filtered, the filtrate was diluted with water and the solution, neutralized with sodium carbonate, was accurately extracted with benzene. The benzenic layer, dried on sodium sulphate and evaporated to dryness, gave 650 mg. of 2-phenylbenzimidazole (**13**), m.p. 300° (from ethanol) [lit. (6) 294°].

2-Phenylbenzimidazole (**13**) from o-Nitrobenzoylaniline (**8**).

Starting from o-nitrobenzoylaniline (**8**) (2 g.), iron powder (2 g.) and 30 ml. of acetic acid, and working as described above, there was obtained 1.35 g. (78%) of 2-phenylbenzimidazole.

1-Hydroxy-2-phenylbenzimidazole (**9**) (6).

The reaction between o-nitroaniline and benzaldehyde in

toluene was carried out according to the literature (6), and always gave a mixture of 2-phenylbenzimidazole (13) and 1-hydroxy-2-phenylbenzimidazole (9), which were separated by chromatography on a silica gel column using benzene/acetone 9:1 as the eluent: compound 9 was isolated in a 55% yield, m.p. 230° [lit. (6) 220°].

Reaction of 4a and 4b with Organometallic Reagents.

A THF solution of phenylmagnesium bromide obtained from 0.96 g. of magnesium and 2 g. of bromobenzene was added to a solution of 1.5 g. of 2,3-diphenylbenzimidazole 1-oxide (4b) in 25 ml. of THF, at room temperature and under stirring. After 1 hour the reaction solution was poured into water and extracted with chloroform. The chloroform layer was dried over sodium sulphate and evaporated to dryness. The residue, taken up with ethanol, gave 1.2 g. (63%) of nitroxide radical 6b, m.p. 182° (from ethanol).

Anal. Calcd. for $C_{25}H_{19}N_2O$: C, 82.62; H, 5.27; N, 7.71. Found: C, 82.50; H, 5.37; N, 7.82.

The same results were obtained using phenyllithium in 20% excess. When compound 4b was reacted with methylmagnesium iodide or methyllithium the nitroxide radical 6a was detected in the reaction solution *via* esr spectroscopy. The same esr signal as for radical 6a was detected in the reaction solution, when 4a and phenyllithium or phenylmagnesium bromide were reacted as described above for 4b.

Reaction of Compound 12 with Phenyllithium.

Phenyllithium (4 mmoles) was added to the azoxy derivative 12 (1 mmole) in 20 ml. of THF, at room temperature with stirring. After 30 minutes the reaction solution was poured into aqueous 5% ammonium chloride (50 ml.) and extracted with chloroform. The chloroform layer was dried on sodium sulphate and evaporated to dryness; the residue was taken up with benzene and chromatographed on a silica gel preparative tlc; the orange fraction was extracted with chloroform and from this chloroformic solution an intense signal, attributable to the radical 14, was recorded. All attempts to purify this radical by chromatography failed, owing to its easy decomposition.

REFERENCES AND NOTES

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