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Received July 9, 1979

2-Methoxy and 2-cyanoquinoline *N*-oxide, when treated with phenylmagnesium bromide, undergo a nucleophilic *ip*so-attack at C-2, yielding, by elimination of methoxymagnesium bromide or cyanomagnesium bromide, the corresponding 2-phenylquinoline *N*-oxides, which react with the excess of Grignard reagents forming 2,2-diphenylquinoline 1-oxyls. Even when the methoxy and cyano groups are in position 4, the attack by the Grignard reagent takes place at C-2 giving 2-phenylquinolines and 2-phenylquinoline *N*-oxides by elimination of hydroxymagnesium bromide and bromomagnesium hydride, respectively; the formation of 2,2-diphenylquinoline 1-oxyls in these reactions is discussed.

J. Heterocyclic Chem., **17**, 293 (1980).

Several years ago studying the reaction between 2-methoxyquinoline *N*-oxide and phenyl magnesium bromide one of us observed the substitution of the methoxy group and the formation of 2-phenylquinoline, with 2-phenylquinoline *N*-oxide proposed as the reaction intermediate (1). More recently we demonstrated that 2-phenylquinoline *N*-oxides react with Grignard reagents to give stable nitroxide radicals of the 1,2-dihydro-2,2-diphenylquinoline 1-oxyls type (2) in good yields.

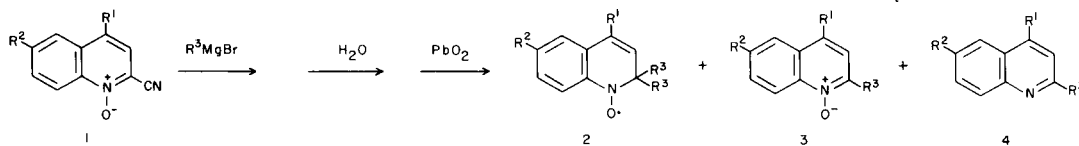
In the present paper we report the synthesis of nitroxide radicals **2** starting from 2-cyano- and 2-methoxyquinoline *N*-oxides **1** and **5**, and arylmagnesium bromide, confirming the intermediate formation of 2-arylquinoline *N*-oxides **3**. Furthermore we report on the reaction, already studied by others (3), between phenylmagnesium bromide and quinoline *N*-oxides **6** that are unsubstituted at C-2, which leads to the unexpected 2,2-diphenyl-substituted nitroxide radicals **7**. The interest of these reactions lies in the fact, hitherto, synthesis of stable nitroxide radicals was linked

to the availability of 2-arylsubstituted quinoline *N*-oxides (2) or the oxidation of 1,2-dihydro-2,2-diphenyl (or dialkyl) quinoline (4).

Results.

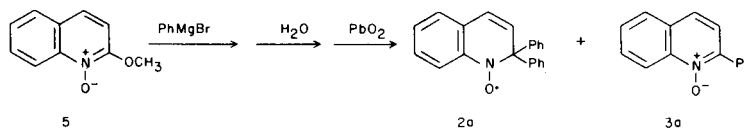
Quinoline *N*-oxides **1a-c**, **5**, **6a-c** and **8**, and arylmagnesium bromide were reacted in tetrahydrofuran at room temperature under a nitrogen atmosphere, using a ratio of *N*-oxide to Grignard reagent of 1:3 and a reaction time of 3 hours. 2-Cyanoquinoline *N*-oxide **1a** was allowed to react with phenyl-, *p*-tolyl- and *p*-anisylmagnesium bromide; in all three cases the main products were 2,2-diarylnitroxide radicals **2a-c** and the 2-arylsubstituted quinoline *N*-oxides **3a-c**; only in the case of **1a** was the deoxygenated product **4** also isolated (Table 1). 2-Cyanoquinoline *N*-oxide **1b** with phenylmagnesium bromide gave the nitroxide radical **2d** in 100% yields, whereas *N*-oxide **1c** led to results very similar to those obtained in the reaction of **1a** with phenylmagnesium bromide (Table 1, Scheme 1).

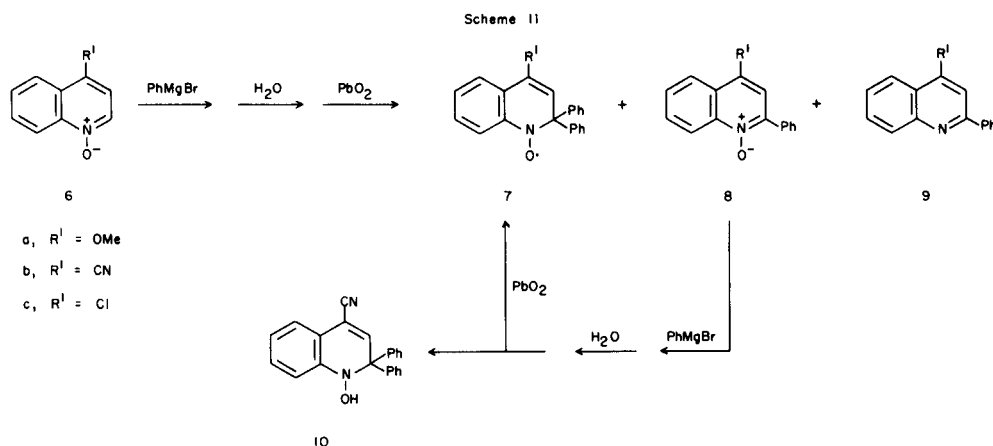
Scheme 1



- a, R¹ = R² = H
 b, R¹ = Me, R² = H
 c, R¹ = H, R² = OMe

- a, R¹ = R² = H, R³ = Ph
 b, R¹ = R² = H, R³ = C₆H₄-Me-*p*
 c, R¹ = R² = H, R³ = C₆H₄-OMe-*p*
 d, R¹ = Me, R² = H, R³ = Ph
 e, R¹ = H, R² = OMe, R³ = Ph





Quinoline *N*-oxides **6a-c** that are unsubstituted at C-2 with phenylmagnesium bromide led mainly to 2-phenyl substituted *N*-oxides **8a-c**, nitroxide radicals **7a-c** in lesser yields, and 2-phenylquinoline **9a-c**, in 3 hours (Table 1); whereas under reflux for 7 hours the reaction gave 2-phenylquinoline **9a-c** almost quantitatively (Scheme 2). Finally, 2-phenylquinoline *N*-oxides **8a-c** with phenylmagnesium bromide gave nitroxide radicals **7a-c** in

quantitative yields (Table 1, Scheme 2). All reactions, after hydrolysis in aq. 10% ammonium chloride, were oxidized with lead dioxide, as the initially formed reaction products are not nitroxide radicals, but rather the corresponding hydroxylamines, which undergo easy oxidation to nitroxides in solution in air. This treatment simplifies the separation of the reaction products by excluding hydroxylamine autoxidation (Schemes 1 and 2). In the reaction of **8b** and phenylmagnesium bromide, hydroxylamine **10** was isolated by omitting the lead-dioxide treatment (Scheme 2). Nitroxide radicals **2b-d** and **7a-c**, which are described

in this paper and for which the analytical data are reported in Table 2, show esr signals similar to those previously described (2) and their hyperfine coupling constants are reported in Table 3.

Discussion.

In the reaction with the Grignard reagent, the 2-cyanoquinoline reacts at the cyano group producing substituted imines, which are readily hydrolyzed to the ketones (5); 2-cyanoquinoline *N*-oxides (**1a-c**) react at the *N*-oxide function by eliminating the cyano group. The calculation of the π charge density of the quinolines and the corresponding *N*-oxides (6) shows that the most positive carbon is C-2, and this is more positive in the quinolines than in the corresponding *N*-oxides. Therefore the differing behavior of 2-cyanoquinoline *N*-oxide in the reaction with phenylmagnesium bromide can probably be attributed to the coordination between the *N*-oxide group and the magnesium atom of the Grignard reagent, which, through a non-planar five-membered cyclic transition

Table 1
Reactions of Quinoline *N*-Oxides **1**, **5**, **6** and **8** with Grignard Reagents (a)

Compound	Grignard reagent	Products (% yield)		
1a	PhMgBr	2a (48)	3a (43)	4a (9)
1a	<i>p</i> -Me-C ₆ H ₄ MgBr	2b (85)	3b (15)	—
1a	<i>p</i> -MeO-C ₆ H ₄ MgBr	2c (90)	3c (10)	—
1b	PhMgBr	2d (100)	—	—
1c	"	2e (60)	3e (40)	—
5	"	2a (20)	3a (80)	—
6a	"	7a (6)	8a (90)	9a (4)
6b	"	7b (5)	8b (75)	9b (20)
6c	"	7c (5)	8c (85)	9c (10)
8a	"	7a (100)	—	—
8b	"	7b (100)	—	—
8c	"	7c (100)	—	—

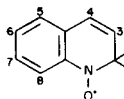
(a) In all reactions, the quinoline *N*-oxide: Grignard reagent ratio was 1:3, and the reaction time was 3 hours; only in the cases of **8a-c** was the quinoline *N*-oxide: Grignard reagent ratio 1:2 and the reaction time 2 hours.

Table 2
Analytical and Ir Data of Compounds 2b-c, 3b, 3c, 7a-c and 10

Compound	M.p. (°C)	Formula	C	% Found (a)			Ir max (cm ⁻¹)
				H	N		
2b	131 (b)	C ₂₂ H ₂₀ NO	84.11 (84.65)	6.20 (6.17)	4.17 (4.29)	1622 (e)	
2c	109 (b)	C ₂₂ H ₂₀ NO ₂	77.14 (77.07)	5.77 (5.62)	3.81 (3.91)	1610 (e)	
2d	160 (c)	C ₂₂ H ₁₈ NO	84.43 (84.58)	5.85 (5.81)	4.43 (4.48)	1650 (e)	
3b	130 (c)	C ₁₆ H ₁₂ NO	81.72 (81.67)	5.65 (5.57)	6.22 (5.95)	—	
3c	109 (c)	C ₁₆ H ₁₂ NO ₂	76.63 (76.47)	5.42 (5.21)	5.59 (5.58)	—	
7a	155 (c)	C ₂₂ H ₁₈ NO ₂	80.18 (80.47)	5.56 (5.52)	4.47 (4.26)	1650 (e)	
7b	195 (c)	C ₂₂ H ₁₆ N ₂ O	81.78 (81.71)	4.72 (4.67)	8.81 (8.66)	1630 (e) 2220 (f)	
7c	120 (c)	C ₂₁ H ₁₅ NOCl	75.98 (75.79)	4.60 (4.54)	4.41 (4.31)	1638 (e)	
10	172 (d)	C ₂₂ H ₁₆ N ₂ O	81.12 (81.46)	4.96 (4.97)	8.47 (8.63)	1610-1620 2240 (e)-3400 (g)	

(a) Required values in parentheses. (b) From petroleum ether. (c) Ethanol. (d) Benzene-petroleum ether. (e) $\text{Ph}-\text{N}-\overset{\cdot}{\text{C}}-\text{Ph}$. (f) C=N. (g) >N-OH.

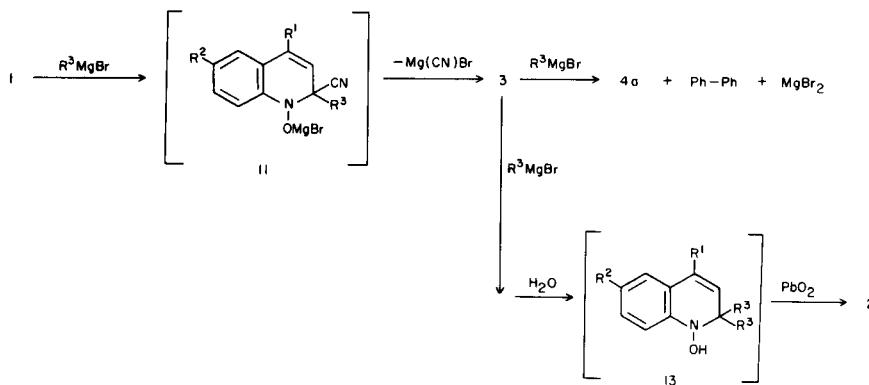
Table 3
Hfccc (in Gauss) of Nitroxide Radicals 2a-e and 7a-c (a)



Radical	a^{N}	$a^{\text{H-3}}$	$a^{\text{H-4}}$	$a^{\text{H-5,7}}$	$a^{\text{H-6,8}}$
2a	10.17	1.42	0.55	1.07-1.07	3.20-3.20
2b	10.15	1.40	0.52	1.10-1.10	3.10-3.10
2c	10.12	1.58	0.58	1.01-1.01	3.20-3.20
2d	10.15	—	—	—	3.22-3.22
2e (b)	10.78	1.42	0.55	1.05-1.05	3.26
7a	10.30	1.05	—	1.05-1.05	3.15-3.15
7b	10.00	1.30	—	1.15-1.15	3.21-3.21
7c	10.00	1.30	—	1.10-1.10	3.20-3.20

(a) Esr spectra were recorded in chloroform solution, (b) See reference 2.

Scheme III



state, attacks the C-2 carbon of the quinoline ring, leading to intermediate **11** (Scheme 3). As the cyanide anion is a good leaving-group, we think that intermediate **11** undergoes spontaneous elimination of cyanomagnesium bromide, probably assisted by the ^+MgBr -group, leading to the more stable *N*-oxides **3**. The substitution of the cyano group at C-2, by the Grignard reagent, can be considered a general peculiarity of *N*-oxide derivatives; in fact, 2-cyano- Δ^1 -pyrroline 1-oxide with methylmagnesium bromide leads to 2-methyl- Δ^1 -pyrroline 1-oxide (7,8), which further reacts with methylmagnesium bromide to give the corresponding nitroxide radical (9). As the reaction is performed with an excess of Grignard reagent, the *N*-oxides **3** (Scheme 3), which are formed in the reaction medium, react with excess Grignard reagent to give hydroxylamines **13**, which are oxidized by lead dioxide to the corresponding nitroxide radicals **2**, for the reason stated in the results section. We think that the reaction between 2-methoxyquinoline *N*-oxide **5** and phenylmagnesium bromide can be explained by a mechanism similar to that shown in Scheme 3, which was discussed above for 2-cyanoquinoline *N*-oxides. The 2-phenylquinoline **4a** isolated in the reaction of **1a** with phenylmagnesium bromide is probably due to a reduction process; in fact, in the reactions between 2-phenylquinoline *N*-oxide and the Grignard reagent, previously studied (2), it was demonstrated that the reducing power of the Grignard reagent is as high as its electron donating power (10).

Quinoline *N*-oxides **6a-c** that are unsubstituted at carbon C-2 give with phenylmagnesium bromide the 2-phenyl substituted quinolines and quinoline *N*-oxides in agreement with the reactions previously described (3) for quinoline *N*-oxides **6a** and **6c**.

The surprising results for these reactions are: i) the cyano group of compound **6b** is not involved in the reac-

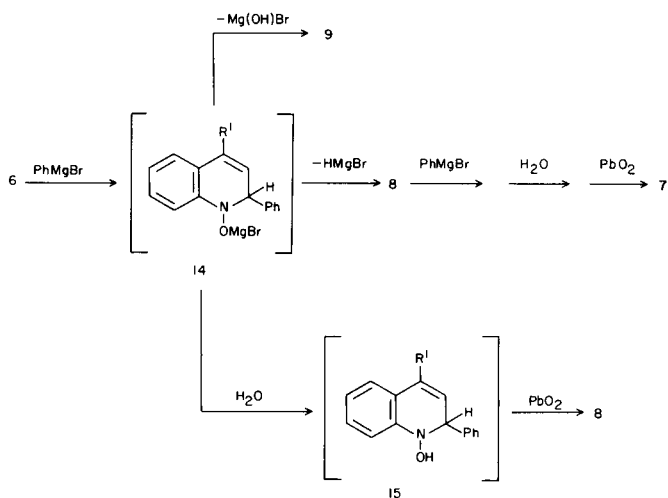
tion with the Grignard reagent, as was observed for the 4-cyanoquinoline (11); ii) nitroxide radicals 2,2-diphenyl substituted **7a-c** are formed.

The reason why the cyano group is not involved in the reaction between *N*-oxide **6b** and phenylmagnesium bromide may be that the nucleophilic attack takes place more readily at the *N*-oxide function than at the cyano group. As to the formation of radicals **7a-c**, we believe that the first step of the reaction between **6a-c** and phenylmagnesium bromide leads to the intermediate **14** (Scheme 4), which partly loses hydroxymagnesium bromide giving 2-phenylquinolines **9** and partly eliminates bromomagnesium hydride leading, in the reaction medium, to 2-phenylquinoline *N*-oxides **8**, which react with the excess of Grignard reagent giving nitroxide radicals **7**. In fact, when 2-phenylquinoline *N*-oxides **8a-c** are allowed to react with phenylmagnesium bromide, they give nitroxide radicals **7** in quantitative yields (Table 1). These last data do not seem to be in agreement with the large amount of 2-phenylquinoline *N*-oxides **8a-c** isolated in the reaction of **6a-c** and phenylmagnesium bromide. The explanation of this evident discrepancy could be the slowness of bromomagnesium hydride elimination, so that the small amount of **8**, which originates during the reaction, controls the formation of nitroxide radicals **7**, whereas the large quantity of 2-phenylquinoline *N*-oxides **8a-c** recovered at the end of the reaction (Table 1), results from the hydrolysis of intermediate **14**, which, at first, leads to hydroxylamine **15** (Scheme 4), and then to 2-phenylquinoline *N*-oxide **8** by oxidation with lead dioxide (12).

It seems from the data discussed above that the elimination of hydroxymagnesium bromide is very slow; in fact, repeating the reaction under reflux for 7 hours, the 2-phenylquinolines **9** are obtained in quantitative yields. Under these conditions we expected a larger amount of the deoxygenated product **9**, but also a greater quantity of nitroxide radical **7**, which, however, did not form at all. The same reaction, when carried out at room temperature over 24 hours, gave the same results as obtained in 3 hours, and the same as when the reaction was performed with a large excess (1:6) of Grignard reagent. All these attempts were made with a view to improving the yield of nitroxide radical **7** and studying more closely the elimination of bromomagnesium hydride, which we propose as an explanation of the formation of 2-phenylquinoline *N*-oxides **8** in the reaction medium, and which other authors (13) proposed in the reaction of the *o*-substitution on azobenzene by Grignard reagent (14).

EXPERIMENTAL

The melting points are uncorrected; the ir spectra were recorded in nujol on a Perkin-Elmer 257 instrument; the esr spectra were recorded on a Varian E4 spectrometer. Compounds **1a** (15), **1b** (16), **1c** (17), **2a** (2),



3d (11), **3e** (2), **4a** (18), **5** (1), **6a** (1), **6b** (15), **6c** (3), **8a** (3), **8c** (3), **9a** (3) and **9c** (3) were prepared as described in the literature. The Grignard reagents were prepared according to the usual methods in nitrogen atmosphere and in tetrahydrofuran.

2-Phenyl-4-cyanoquinoline (19) **9b**.

Compounds **9b** and **8b** already described in the literature, have been prepared by these new methods. Thionyl chloride (2.5 g.) was added to a solution of 2.0 g. of 2-phenylquinoline-4-carboxamide in 30 ml. of dimethylformamide at 0° with stirring; the addition of thionyl chloride was done at such a rate that the temperature remained below 3°. After 12 hours, the reaction mixture was poured into 100 ml. of water; the precipitate, separated by filtration in vacuum, gave compound **9c** in 90% yields, m.p. 140° from ethanol.

2-Phenyl-4-cyanoquinoline 1-Oxide (20) **8b**.

2-Phenyl-4-cyanoquinoline (2.8 g.), acetic acid (20 ml.) and 36% w/w hydrogen peroxide (2.8 ml.) were refluxed for 3 hours. After the addition of another 2.8 ml. of hydrogen peroxide the reflux was continued for 1.5 hours. Compound **8b**, precipitated by cooling, was separated by filtration, m.p. 152° [lit. 149° (20)] 85% yield.

Reaction with Grignard Reagents.

The Grignard reagent (15 mmoles) in 20 ml. of tetrahydrofuran was added to a solution of quinoline *N*-oxide (5 mmoles) in 60 ml. of tetrahydrofuran, at room temperature and with stirring in nitrogen atmosphere. After 3 hours the reaction mixture was poured into 10% aqueous ammonium chloride (100 ml.) and extracted with chloroform. The organic layer was separated and dried over sodium sulphate and evaporated to dryness. The residue was taken up with 50 ml. of benzene and treated with lead dioxide (3 g.) with stirring. After 2 hours the mixture was filtered and the filtrate was chromatographed on a silica column, first eluting with benzene and then with benzene-acetone (9:1), the compounds reported in Table 1 were isolated and identified by comparison with authentic samples obtained by an independent synthesis or with their analytical and spectroscopic data (Table 3). In the reaction between **8b** and phenylmagnesium bromide, omitting the lead dioxide treatment, compound **10** (Scheme 2) was isolated by crystallization from ether-petroleum ether of the residue obtained from the chloroform solution.

2-(*p*-Methyl)phenylquinoline 1-Oxide **3b** and 2-(*p*-Methoxy)phenylquinoline 1-Oxide **3c**.

Compounds **3b** and **3c** were prepared in quantitative yields starting from quinoline *N*-oxide and *p*-methyl- or *p*-methoxyphenylmagnesium bromide, as described above, with a reaction time of 15 minutes. Analytical and physical data are reported in Table 3.

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