Mechanistic Studies on the Reaction of Nitro- and Nitrosoarenes with Vinyl Grignard Reagents

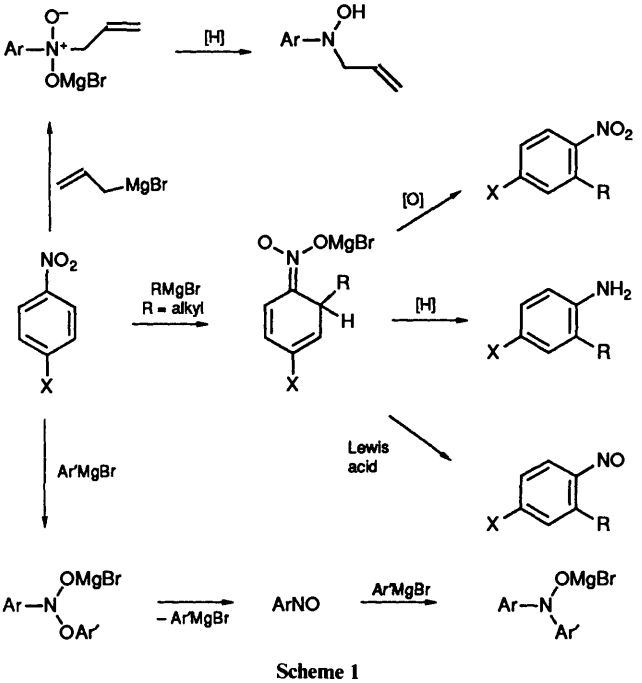
Marcella Bosco,[a] Renato Dalpozzo,[a] Giuseppe Bartoli,*[b] Gianni Palmieri[b] and Marino Petrini[b]

[a] *Dipartimento di Chimica Organica 'A. Mangini,' viale Risorgimento 4,I-40136 Bologna, Italy*
[b] *Dipartimento di Scienze Chimiche, via S. Agostino 1, I-62032 Camerino (Mc), Italy*

The reaction of *ortho*-substituted nitrobenzenes with 3 mol vinylmagnesium halides gives mainly 7-substituted indoles together with minor amounts of the aniline from complete reduction of the nitroarene. Under the same experimental conditions, *para*-substituted nitrobenzenes essentially lead to the corresponding anilines, with indoles being recovered in very low yield. Nitrosoarenes react with 2 mol Grignard reagent to give almost the same product distribution. An accurate analysis of the stoichiometry of the reaction established that in the first stage of the reaction nitroarenes are attacked at the oxygen atoms and are reduced to nitrosoarenes *via* enolate elimination. The nitroso derivative can undergo a 1,2-addition to give an *N*-aryl-*N*-vinylhydroxylamino magnesium salt. Hydrolysis of this intermediate affords hydroxylamine and the carbonyl derivative corresponding to the vinyl Grignard reagent, as proved by the reaction of nitroarenes with 2 mol Grignard reagent. In the presence of an excess of vinyl magnesium halide, a complete reduction to vinylaniline derivatives, which hydrolyse to aniline, occurs. The effect of the bulkiness of the substituent both in the nitroarene and in the Grignard reagent, the orientation of alkylation and the relative reaction rates of indole and aniline formation suggest that indoles arise *via* a completely different route: *i.e.* an inverse 1,2-addition to the N=O double bond. The *N*-aryl-*O*-vinylhydroxylamino magnesium salt intermediate can undergo a [3,3]-sigmatropic rearrangement followed by a rapid ring closure. The third mole of Grignard reagent acts as a base on this bicyclic intermediate, re-aromatizing the six-membered ring. Elimination of water ultimately leads to the indole.

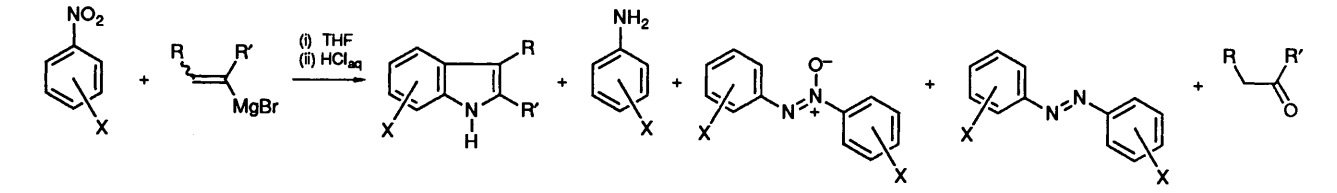
Although the reactivity of aromatic nitro compounds with strong nucleophilic bases, such as Grignard or lithium reagents, has been widely studied in the past few years,[1-7] some aspects have still remained obscure owing to the complex interactions that can occur in the first stage of the reaction (Scheme 1). For example, alkyl Grignard reagents give prevalently conjugate addition to the nitroarenic system;[3] while allyl[5] and allenyl Grignards[7] lead to a product of 1,2-addition to the nitro group. In most cases a source of complication arises from the impossibility of direct characterization of the products formed in the initial stage of the reaction, since they decompose in the medium or during attempts to trap or isolate them. However, it is possible to convert unstable intermediates into stable derivatives by *in situ* treatment with a specific reagent. For example, the unstable nitronate adducts from conjugate addition can be easily turned into ring-alkylated aromatic nitro, amino or nitroso compounds by treatment with an oxidizing agent[8] a reducing agent[9] or a Lewis acid,[10] respectively. The 1,2-addition product can be converted into an *N*-allyl-*N*-arylhydroxylamine[5] or an *N*-(prop-2-ynyl)-*N*-arylhydroxylamine[7] by *in situ* treatment with $LiAlH_4$ and Pd/C. Finally, a further complication is the formation in some cases (alkyl reagents) of redox products such as nitroarene radical anions.[6] High temperatures, polar solvents, lithium derivatives, hindered nitroarenes or reagents[11] and high electron-accepting nitroarenes (*e.g. p*-dinitrobenzene)[12] enhance this reaction.

More complex and hitherto not well documented is the reactivity of arylmagnesium derivatives. Buck and Köbrich suggested[1] that the reaction proceeds *via* addition to the nitro group oxygen atoms, followed by immediate elimination of phenoxide to give the nitrosoarene. This compound rapidly reacts with Ar'MgX, leading to *N*,*N*-diarylhydroxylamino magnesium salt as the final product. Although nitrosoarenes were never isolated from the reaction mixture, the authors reported indirect convincing evidence supporting this mechanism.



Scheme 1

In a recent communication[13] we reported that 7-substituted indoles can be recovered in good yields from the reaction of *ortho*-substituted nitrobenzenes with 3 mol vinylmagnesium bromide, followed by quenching with aqueous ammonium chloride. Unexpectedly, *para* derivatives gave very low yields of the corresponding indole, the major product being the aniline



1
a; X = 2-Me
b; X = 2-Br
c; X = 2-F
d; X = 2-Cl
e; X = 4-Me
f; X = 4-Br
g; X = 4-Cl

2
a; R = R′ = H
b; R = Ph; R′ = H
c; R = Me; R′ = H
d; R = H; R′ = Me

3
aa; X = 7-Me; R = R′ = H
ba; X = 7-Br; R = R′ = H
ca; X = 7-F; R = R′ = H
da; X = 7-Cl; R = R′ = H
ac; X = 7-Me; R = Me; R′ = H
ad; X = 7-Me; R = H; R′ = Me
db; X = 7-Cl; R = Ph; R′ = H
dc; X = 7-Cl; R = Me; R′ = H
ea; X = 5-Me; R = R′ = H
fa; X = 5-Br; R = R′ = H
ga; X = 5-Cl; R = R′ = H
gc; X = 5-Cl; R = Me; R′ = H

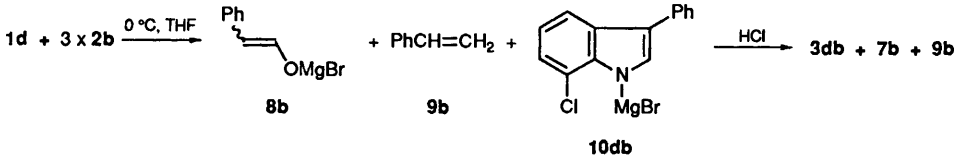
4
a; X = 2-Me
b; X = 2-Br
c; X = 2-F
d; X = 2-Cl
e; X = 4-Me
f; X = 4-Br
g; X = 4-Cl

5
a; X = 2-Me
b; X = 2-Br
c; X = 2-F
d; X = 2-Cl
e; X = 4-Me
f; X = 4-Br
g; X = 4-Cl

6
a; X = 2-Me
b; X = 2-Br
c; X = 2-F
d; X = 2-Cl
e; X = 4-Me
f; X = 4-Br
g; X = 4-Cl

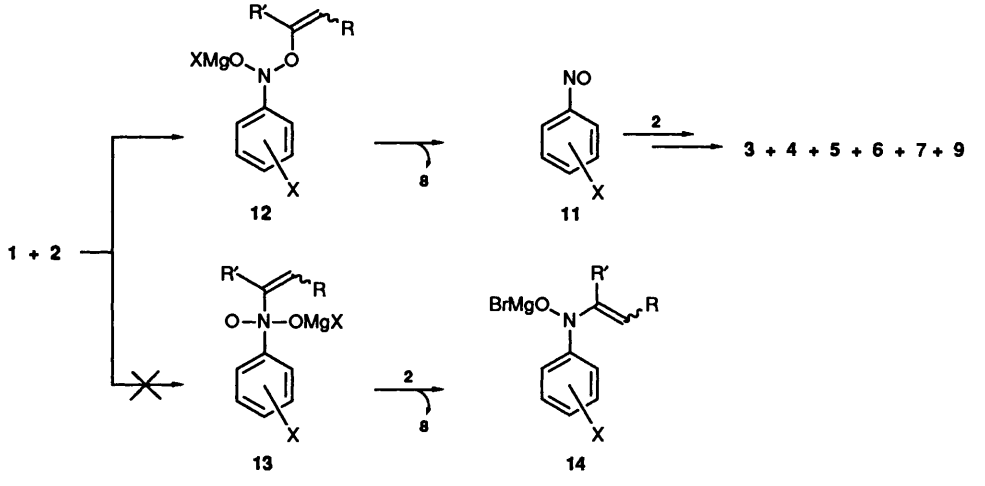
7
a; R = R′ = H
b; R = Ph; R′ = H
c; R = Me; R′ = H
d; R = H; R′ = Me

Scheme 2



8b **9b** **10db**

Scheme 3



12 **11** **13** **14**

Scheme 4

arising from complete reduction of the starting nitrobenzene. In this paper, a preliminary mechanistic investigation on the reaction pathway and on intermediates involved in it will be presented.

Results and Discussion

Reaction of ortho-*Substituted Nitro- and Nitrosoarenes.*—The reaction between (propen-1-yl)magnesium bromide (**2c**, 3 equiv.) and 2-chloronitrobenzene (**1d**, 1 equiv.) at 0 °C gave 7-chloro-3-methylindole (**3dc**, 38%) and 2-chloroaniline (**4d**, 11%) (Table 1, entry 9) together with traces of 2,2′-dichloroazoxybenzene (**5d**), 2,2′-dichloroazobenzene (**6d**) and propionaldehyde (**7a**) as detected by GC–MS analysis (Scheme 2).*

Since the water solubility and the volatility of propionaldehyde made its quantitative determination very difficult, the reaction of ω-styrylmagnesium bromide **2b** with **1d** was carried out under the same experimental conditions. Styrene **9b** (1 mol) and phenylacetaldehyde **7b** (1 mol) per mole of indole were detected[13] (Scheme 3). The equivalent of alkene could have been formed either during the reaction or on the quenching of excess Grignard reagent. Deuterium labelling experiments showed only traces of deuteriated styrene, and the pouring of the reaction mixture onto crushed dry ice gave only traces of cinnamic acid. These findings demonstrate that the alkene **9** must have been formed during the reaction course.

On the other hand, aldehyde **7** obviously arose from quenching of the corresponding enolate **8**. The formation of **8** suggests that, in the first stage of the reaction, nitroarenes should be reduced to nitrosoarenes by 1 mol vinyl Grignard reagent (Scheme 4). In order to confirm this, the reaction of 2-chloronitrosobenzene **11d** with Grignard reagent **2c** (2 mol) at 0 °C was carried out. As expected, 32% of indole **3dc** was recovered together with 18% of 2,2′-dichloroazoxybenzene **5d**, 6% of 2,2′-dichloroazobenzene **6d** and 3% of 2-chloroaniline **4d**

* Although the reaction of vinylmagnesium bromide with **1d** resulted in some 2-oxoindole being recovered,[13] formation of its derivatives was never observed.

Table 1 Product distribution and relative yields from the reaction of substituted nitrosobenzene **1** and vinylmagnesium bromides **2**

Entry	Reactants	1:2 Ratio	Reaction T/°C	Reaction t/min	Yields (%)[a] Indole **3**	Aniline **4**	Nitro **1**	Azoxy **5**	Azo **6**	Carbonyl **7**
1	**1a, 2a**	1:3	−40	20	67[b] (**aa**)	5 (**a**)	–	trace (**a**)	trace (**a**)	[c] (**a**)
2	**1b, 2a**	1:3	−40	20	62[b] (**ba**)	7 (**b**)	–	trace (**b**)	trace (**b**)	[c] (**a**)
3	**1c, 2a**	1:3	−40	20	42[b] (**ca**)	9 (**c**)	–	trace (**c**)	trace (**c**)	[c] (**a**)
4	**1d, 2a**	1:3	−40	20	63[b] (**da**)	7 (**d**)	–	trace (**d**)	trace (**d**)	[c] (**a**)
5	**1a, 2b**	1:3	0	10	47 (**ab**)	7 (**a**)	–	trace (**a**)	trace (**a**)	61 (**b**)
6	**1d, 2b**	1:3	−40	60	44[b,d] (**db**)	9[d] (**d**)	–	trace[d] (**d**)	trace[d] (**d**)	62[d] (**b**)
7	**1d, 2b**	1:3	0	10	47 (**db**)	8 (**d**)	–	trace (**d**)	trace (**d**)	63 (**b**)
8	**1a, 2c**	1:3	0	10	35 (**ac**)	11 (**a**)	–	trace (**a**)	trace (**a**)	[c] (**c**)
9	**1d, 3c**	1:3	0	10	38 (**dc**)	11 (**d**)	–	trace (**d**)	trace (**d**)	[c] (**c**)
10	**1d, 2c**	1:3	−40	60	42 (**dc**)	8 (**d**)	–	trace (**d**)	trace (**d**)	[c] (**c**)
11	**1d, 2c**	1:2	0	10	26[e] (**dc**)	3[f,g] (**d**)	18 (**d**)	trace (**d**)	trace (**d**)	[c] (**c**)
12	**1a, 2d**	1:3	0	10	76 (**ad**)	trace (**a**)	–	trace (**a**)	trace (**a**)	[c] (**d**)
13	**1e, 2a**	1:3	−40	20	16 (**ea**)	40 (**e**)	–	trace (**e**)	trace (**e**)	[c] (**a**)
14	**1f, 2a**	1:3	−40	20	12[b] (**fa**)	42 (**f**)	–	trace (**f**)	trace (**f**)	[c] (**a**)
15	**1g, 2a**	1:3	−40	20	17[b] (**ga**)	35 (**g**)	–	trace (**g**)	trace (**g**)	[c] (**a**)
16	**1g, 2c**	1:2	0	10	8[h] (**gc**)	9[i,j] (**g**)	19 (**g**)	trace (**g**)	trace (**g**)	[c] (**c**)
17	**1g, 2c**	1:3	0	10	11 (**gc**)	39 (**g**)	–	trace (**g**)	trace (**g**)	[c] (**c**)
18*	**1d, 2c**	1:1	0	–	18[d,k] (**dc**)	–	72[d] (**d**)	–	–	[c] (**c**)
19*	**1g, 2c**	1:1	0	–	5[d] (**gc**)	trace[d,l] (**g**)	64[d] (**g**)	trace[d] (**g**)	trace[d] (**g**)	[c] (**c**)

* Reactions performed in a continuous flow fashion (see Experimental).

[a] Yields in pure isolated product. All reactions showed 20–35% yield of material with obscure IR and NMR spectra but with elemental analyses in agreement with vinylanilines. [d] Data from ref. 13. [c] The presence of acetaldehyde **7a**, propionaldehyde **7c** and acetones **7d** was detected by GC–MS analysis. However, a quantitative determination was not possible owing to their volatility and water solubility. [d] GC yields. [e] Taking into account the recovered starting material, the conversion of indole is 32%. [f] Together with 4% *N*-(2-chlorophenyl)-hydroxylamine. [g] Taking into account the recovered starting material, the conversion of aniline plus hydroxylamine is 8.5%. [h] Taking into account the recovered starting material, the conversion of indole is 10%. [i] Together with 21% of *N*-(4-chlorophenyl)hydroxylamine. [j] Taking into account the recovered starting material, the conversion of aniline plus hydroxylamine is 37%. [k] Together with 4% of 2-chloronitrosobenzene and traces of *N*-(2-chlorophenyl)hydroxylamine. [l] Together with 8% of 4-chloronitrosobenzene and 12% of *N*-(4-chlorophenyl)hydroxylamine.

Table 2 Product distributions and relative yields from the reaction of substituted nitrosobenzenes **11** and propenylmagnesium bromide **2c,d** in 1:2 molar ratio in THF at 0 °C

Entry	Reactants	Solvent	Ratio **2**:**11**	Method[a]	Yields (%) Indole **3**	Aniline **4**	Azo **6**	Azoxy **5**
1	**11d, 2c**	THF	2:1	A	32 (**dc**)	3 (**d**)	6 (**d**)	18 (**d**)
2	**11g, 2c**	THF	2:1	A	13 (**gc**)	43 (**g**)	16 (**g**)	7 (**g**)
3	**11a, 2d**	THF	2:1	A	37 (**ad**)	3 (**a**)	5 (**a**)	17 (**a**)
4	**11a, 2d**	THF	2:1	B	54 (**ad**)	4 (**a**)	7 (**a**)	6 (**a**)
5	**11a, 2d**	Et_2O	2:1	B	56 (**ad**)	3 (**a**)	11 (**a**)	–
6	**11a, 2d**	THF	1:1	B	33 (**ad**)	–	–	23 (**a**)

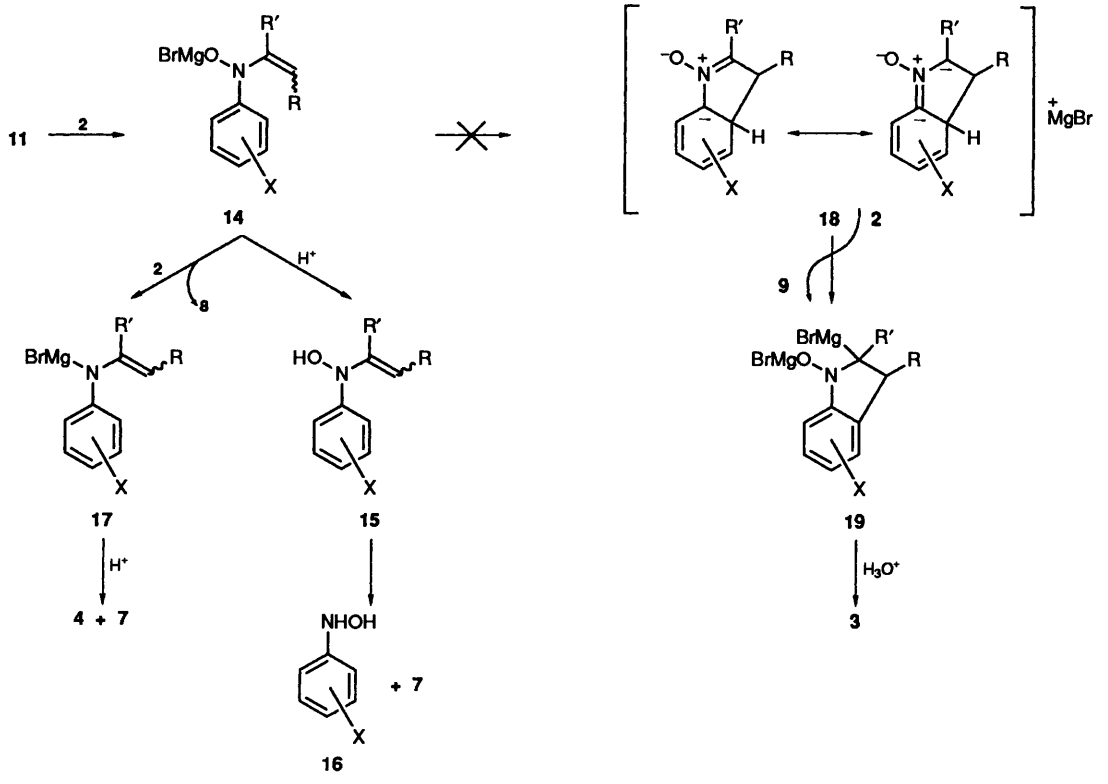
[a] Method A: by dropping the Grignard reagent solution into the cooled substrate solution. Method B: by dropping the substrate solution into the cooled Grignard reagent solution.

(Table 2, entry 1). The formation of **5d** and **6d** will be discussed later in this paper.

Direct evidence of nitrosoarene involvement was obtained by the use of a 'continuous flow' apparatus and GC–MS analysis. In fact, allowing 2-chloronitrobenzene **1d** to react with (propen-1-yl)magnesium bromide **2c** (1 mol), 72% of unreacted **1d**, 18% of indole **3dc**, 4% of chloronitrosobenzene **11d** and traces of *N*-(2-chlorophenyl)hydroxylamine were detected by means of these techniques (Table 1, entry 18). This product distribution confirms that nitrosoarene is the first intermediate of the reaction and that it is much more reactive than the nitro compound, since relevant amounts of indole are also formed with a deficiency of Grignard reagent. As mentioned above, such an hypothesis was earlier made by Buck [1] to explain the mechanism of the reaction of aryl Grignard reagents and nitroarenes. Nitrosoarenes **11** should be originated by attack of the carbanionic moiety of the vinyl Grignard reagent at the oxygen atoms, followed by immediate elimination of enolate from the *O*-alkylated derivative **12**. The alternative hypothesis of a 1,2-addition to the nitro group is less convincing since we found that the homologous allyl-substituted nitrogen tetrahedral intermediates of **13** are stable in solutions and do not undergo reduction by the excess Grignard reagent [5] (Scheme 4).

Reaction of para-*Substituted Nitro- and Nitrosoarenes.*—The reaction of 4-chloronitrobenzene **1g** and of (propen-1-yl)-magnesium bromide **2c** (3 mol) leads to 16% 5-chloro-3-methylindole **3gc**, 39% 4-chloroaniline **4g** (Table 1, entry 17) and traces of 4,4′-dichloroazoxybenzene **5g** and 4,4′-dichloroazobenzene **6g**.

The presence of propionaldehyde among the reaction products was revealed by a GC–MS analysis. Although an exact yield determination of this compound was impossible, its amount appeared larger than in the corresponding reaction of *ortho* derivatives. Aldehyde formation could suggest that nitroso derivatives are involved in this reaction as well. In fact, the reaction of 4-chloronitrosobenzene **11g** and (propen-1-yl)magnesium bromide **2c** (2 mol) leads to 13% indole **3gc** and 43% aniline **4g** together with 7% 4,4′-dichloroazoxybenzene **5g** and 16% 4,4′-dichloroazobenzene **6g** (Table 2, entry 2). Azo and



Scheme 5

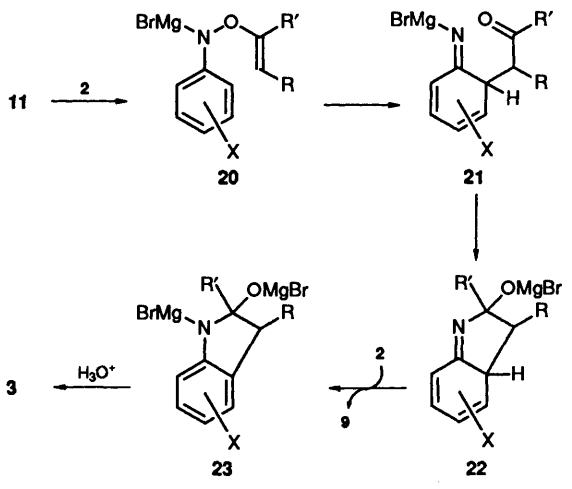
azoxy derivatives are formed *via* the same route as in the reaction of *ortho*-substituted derivatives. The reaction between nitroarene and Grignard reagent in a 1:1 molar ratio run in a continuous flow apparatus affords chloronitrosobenzene **11g** (8%), indole **3gc** (5%), unreacted nitroarene **1g** (64%), *N*-(4-chlorophenyl)hydroxylamine (12%) and traces of aniline **4g** (Table 1, entry 19). These results demonstrate that initially both *para*- and *ortho*-substituted nitrobenzenes give nitroso derivatives.

Mechanism of Formation of Aniline and/or Indole.—First we wish to analyse the mechanism by which the aniline is formed. A 1,2-addition may be hypothesized to occur on the nitroso derivative **11** leading to an *N*,*N*-disubstituted hydroxylamino magnesium salt **14** (Scheme 5), which can be easily reduced by Grignard reagents[14] to the magnesium vinylamide **17**. In acidic media, hydrolysis of **17** affords aniline **4** and aldehyde **7**. The reduction can be controlled by using a deficiency of Grignard reagent. In fact, when the reaction is carried out with 2 mol vinyl magnesium halide, hydroxylamine **16** is mainly obtained (Table 1, entries 11 and 16). Attempts to trap intermediates **14** and **17** failed. Quenching of the reaction in neutral conditions followed by immediate separation afforded products which rapidly decomposed to a vitreous polymeric material. Performing the hydrolysis for longer reaction times led to hydroxylamine being extensively recovered. However, hydrolysis was never quantitative and variable amounts of polymers, ranging from 20–35% of the reaction yields, were always observed.

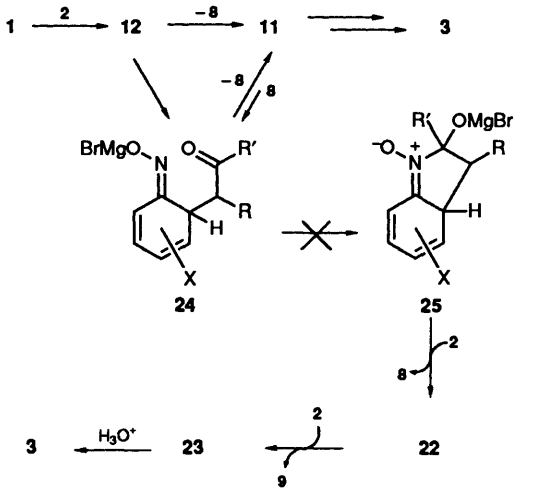
There is considerable evidence in sharp contrast with the hypothesis that indole arises from cyclization of the metallated hydroxylamine **14**. This route does not account for the strong dependence of indole formation on the steric effects exerted on the nitrogen atom by substituents on the aromatic ring or on the Grignard reagent. In fact, while indoles are always obtained in comparable yields from *para* derivatives (Table 1, entries 13, 14, 15 and 17), yields of recovered indoles from *ortho*-substituted nitrobenzenes increase with the bulkiness of either the substituent (Cl instead of F: Table 1, entries 3 and 4) or the Grignard reagent (propen-2-yl instead of vinyl or propen-1-yl: Table 1, entries 1, 8 and 12). Furthermore, cyclization of **14** should occur *via* its α-metallated nitrone form, but these intermediates are reported to be unable to give ring closure[15] with formation of a bicyclic dihydro derivative such as **18**.* A rapid proton transfer from an intermediate to the Grignard reagent must occur to fulfil the stoichiometry of the reaction (Scheme 5, **18** ⟶ **19**). Grignard reagents are reported to metallate only sufficiently acidic hydrogens (pK_a *ca.* <25).[16] Even if an aromatization process is involved, the junction hydrogen very probably does not reach this acidity: although it is allylic, it is near to a carbon atom carrying a partial negative charge.

Finally, the unaffected relative indole amounts obtained when **14** is subtracted from cyclization by reduction is the chief evidence contrasting with this mechanistic hypothesis. In fact, in the reaction with 2 mol Grignard reagent, the conversion into indole is comparable with that of the reaction with 3 mol (32% *vs.* 28% and 10% *vs.* 11% with *ortho*- and *para*-derivatives, respectively: Table 1, entries 9, 11, 16 and 17). On the other hand, the conversion into hydroxylamine plus amine in the former reaction is comparable with the sole amine formation in the latter (8.5% *vs.* 11% and 37% *vs.* 39% with *ortho*- and *para*-derivatives, respectively). In addition, reduction of **14** is much slower than indole formation, as demonstrated by the fact that whilst hydroxylamines could be isolated, it was impossible to detect any intermediate in the indole formation process. As a consequence, in the presence of the required third mole of Grignard reagent, the cyclization of **14** should be preferred to its reduction and the exclusive formation of **3** should be observed.

* A nucleophilic attack at an aromatic ring should be dependent on electronic effects; however, the analysis of the data reported in Table 1 shows that such effects do not influence the product distribution.



Scheme 6



Scheme 7

In conclusion, indole should be originated by a completely different and parallel reaction pathway than that leading to the hydroxylamine salt **14**.

Since the methyl groups of propen-2-yl- and of (propen-1-yl)magnesium bromide were found in the 2- and 3-position, respectively, of the final indole, an attack of the Grignard reagent at the ring position of the nitroso intermediate **11**[17] followed by cyclization to indole in the fashion of the indole synthesis from *ortho*-nitrostyrenes[18] can be ruled out. In fact, in this hypothesis the anionic carbon should occupy the 3- rather than the 2-position of the indole nucleus. Rearrangement of the alkyl substituents are not conceivable under the reaction conditions employed, since they require strongly acidic media and high temperatures to occur.[19] The only logical hypothesis to explain the indole formation remains an inverse 1,2-addition to the N=O double bond followed by a 1-oxa-1'-aza[3,3] sigmatropic rearrangement of the *N*-aryl-*O*-vinylhydroxylamino magnesium salt **20** (Scheme 6).

It is not surprising that such a rearrangement can occur at 0 °C. In fact, theoretical calculations estimate it to be exothermic *ca.* 90 kcal mol^{-1}.*[20] Furthermore, the formation of ring-alkylated products from reaction of *N*-alkyl-*N*-aryl-hydroxylamines with α,β-acetylenic esters and amines in basic medium at 0 °C was explained in terms of sigmatropic rearrangement of a probable intermediate analogous to **20**.[21] Moreover, in our reaction the presence of a relevant amount of negative charge on the nitrogen atom (>N$^-$MgBr$^+$) should enhance the rearrangement. Finally, the sigmatropic rearrangement of the Fischer indole synthesis itself was found to occur at room temperature.[22]

Our attempts to directly characterize the intermediate **21** failed, very probably because of an immediate cyclization step to give **22**. The proton in the junction of compound **22** is much more acidic than a vinyl proton since it is both allylic and in the α-position to a C=N double bond. As a consequence, as soon as **22** is formed it reacts with 1 mol Grignard reagent in an acid–base fashion. This mechanism is in agreement both with the stoichiometry and the orientation of alkylation (the anionic carbon occupies the 2-position of the indole nucleus at the end of the reaction). Finally, this pathway very readily explains the strong dependence of indole formation on steric effects. In fact, the presence of bulky substituents both in the *ortho* position and in the Grignard reagent hinders the nitrogen atom and addresses the attack of the vinyl group to the less-hindered oxygen atom. If this mechanism is operative, the formation of a tetrahedral nitrogen intermediate **13** (Scheme 4) followed by reduction to the hydroxylamino derivative **14** can be completely ruled out, since indole cannot be formed *via* this pathway.

An *O*-alkylation[23] both in nitro- and nitrosoarenes is no surprise if the present results are arranged in the general mechanistic discussion of the initial interaction between Grignard reagents and strong electron acceptors such as nitro and nitroso compounds. In previous work[3,4,6] we suggested that the addition of alkylmagnesium halides to nitroarenes should occur *via* single-electron transfer (SET), or at least a continuous spectrum from polar to SET pathways should exist. If the first interaction between phenyl or vinyl Grignard reagents and the nitro group is an SET process, a nitroarene radical anion and a vinyl radical must be formed. The collapse of the two radical species in the solvent cage might easily occur at the oxygen atom rather than the reactive positions of the ring owing to the electrophilic character of aryl and vinyl radicals.[24] On the other hand, nucleophilic radicals prefer the ring positions. Finally, the higher electron-accepting power of nitrosoarenes compared with nitroarenes[25] makes an analogous behaviour of the former compounds reasonable to imagine. Moreover, since a collapse of radical species is much more sensitive to steric hindrance than are polar reactions,[26] an electron-transfer interpretation of the mechanism can easily explain the different collapse occurring with *ortho*- and *para*-substituted compounds.

A further point must now be discussed. The sigmatropic rearrangement was speculated to occur in the intermediate **20**. However, the occurrence of a rearrangement in intermediate **12** cannot be excluded *a priori*, since this pathway too fulfils the reaction stoichiometry (Scheme 7). The closure of the five-membered ring in intermediate **24** seems to be less probable than cyclization of **21** owing to the less nucleophilic power of the nitrogen of an oxime relative to that of an imine ion. As a consequence, this reaction cannot compete with the formation of enolate **8** and nitrosoarene **11**. Lithium and magnesium enolates are inert towards nitro-[26] and nitrosoarenes[27] since the equilibrium of the reaction is completely shifted towards reagents.

Formation of Azo and Azoxy Derivatives.—As mentioned above, relevant amounts of azo **6** and azoxy **5** derivatives are recovered in the reaction of nitrosoarenes with vinylmagnesium halides. Nitroso derivatives can exist in a mixture of monomeric and dimeric forms.[28] This equilibrium is shifted to the dimer

* 1 cal = 4.184 J.

when bulky substituents occupy the *ortho* position.[29] Since the dimer may be expected to undergo reduction to azoxy rather than addition,[1] the formation of azoxy derivatives **5** may arise from this process. Conversely, in the reaction of nitro derivatives the steady concentration of nitroso is too low to give dimers, and therefore it is not surprising to find a formation of only traces of azoxy derivatives. However, the amount of **5** and **6** depends both on the polarity of the medium and on the reaction conditions. Low-polarity solvents disfavour azoxy and azo formation (Table 2, entries 4 and 5). Moreover, when appreciable amounts of nitroso derivative **11** are present in the reaction medium [*i.e.* when Grignard reagent is dropped into the nitroso derivative solution (method A): Table 2, entry 3], yields of azo and azoxy compounds are much higher than when a reversed addition is accomplished (method B: Table 2, entry 4). In tandem with increasing amounts of azo and azoxy compounds, aniline and indole are recovered in lower yields. These findings suggest the alternative hypothesis of an electron transfer process from hydroxylamino salts **20** and **14** or from metallated indoles **23** to nitrosoarene. Finally, the excess of Grignard reagent can then reduce **5** to azo compounds. This was independently verified by allowing 1 mol of the azoxy compound **5a** to react with 1 mol of Grignard reagent **2a**: after 1 h **6a** was quantitatively recovered.

In conclusion, these studies allow us to draw a general pathway for the reaction of nitro- and nitrosoarenes with vinyl Grignard reagents and to single out the factor influencing the product distribution. Moreover, these results may be synthetically useful and prompt the search for appropriate modifications in order to obtain indoles as the main products. Finally, a further chapter of the reactivity of nitroarenes and Grignard reagents has now been cleared up.

Experimental

^{1}H NMR spectra were recorded with a Varian EM360L instrument. Chemical shifts are given in ppm from Me_4Si in $CDCl_3$ solutions. IR spectra were recorded with a Perkin-Elmer 983 spectrometer. Mass spectra were recorded with a VG 7070 spectrometer or with an HP-59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and an HP-5970 mass detector. M.p.s are uncorrected and were determined with a Büchi apparatus. THF was dried by refluxing over sodium wire until the blue colour of benzophenone ketyl persisted; it was then distilled into a dry receiver under a nitrogen atmosphere. Commercial nitro and nitroso compounds (Aldrich) were recrystallized before use. Chloronitrosobenzenes were synthesized according to literature methods.[30] All coupling constant values *J* are given in Hz.

Reaction of Nitroarenes **1** *with Vinylmagnesium Bromides* **2**.—To a stirred THF solution (30 cm^3) of nitroarene **1** (5 mmol), was added a solution of **2** (16 mmol) at 0 °C or at −40 °C under a nitrogen atmosphere. Stirring was continued for some minutes (see Table 1), after which the reaction was quenched by addition of 10% aqueous hydrogen chloride or a saturated aqueous solution of ammonium chloride. Extraction with diethyl ether was performed immediately or after 15 min. The organic layer, dried over Na_2SO_4, was concentrated and submitted to flash-chromatography on a silica gel column (hexane–diethyl ether, 9:1). Yields are reported in Table 1.

Toluidines **4a** and **4e**, chloroanilines **4d** and **4g**, phenylacetaldehyde **7b**, styrene **9b** and 5-methylindole **3ea** were identified by comparison with the commercial products.

2,7-*Dimethylindole* **3ad**. M.p. 35–36 °C (lit.,[31] 35–37 °C); identified by comparison of its physical data with literature values.[32]

3,7-*Dimethylindole* **3ac**. M.p. 55–56 °C (lit.,[31] 56 °C); identified by comparison of its physical data with literature values.[33]

5-*Chloro*-3-*methylindole* **3gc**. M.p. 114–115 °C (lit.,[34] 114–116 °C); identified by comparison of its physical data with literature values.[34]

7-*Methyl*-3-*phenylindole* **3ab**. M.p. 76–78 °C (Found: C, 86.90; H, 6.35; N, 6.75. $C_{15}H_{13}N$ requires C, 86.92; H, 6.32; N, 6.76%); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3 H, Me), 6.97–7.85 (m, 9 H) and 8.00 (bs, 1 H, NH); *m/z* 207 (M^+), 178, 118, 107, 105, 77 and 51; ν_{max}(film)/cm^{-1} 3427 (NH).

7-*Chloro*-3-*methylindole* **3dc**. M.p. 145–146 °C (Found: C, 65.30; H, 4.85; N, 8.45. C_9H_8NCl requires C, 65.27; H, 4.87; N, 8.46%); ^{1}H NMR ($CDCl_3$) δ 2.33 (d, 3 H, Me, *J* 1), 6.92 (m, 1 H, 2-H), 6.97–7.28 (m, 2 H), 7.45 (dd, 1 H, 4-H, J_o 7, J_p 2) and 7.97 (bs, 1 H, NH); *m/z* 165/167 (M^+), 164/166, 128/130, 101 and 65, 51; ν_{max}(CCl_4)/cm^{-1} 3484 (NH).

Reaction in a 2:1 *ratio*. Nitroarenes **1d** and **1g** (5 mmol) were allowed to react with **2c** (10 mmol) under the reaction conditions reported in Table 1. After work-up as above, the distribution of products obtained was as reported in Table 1.

Deuterium labelling experiments. The reaction mixture arising from **2b** (3 mmol) and **1d** (1 mmol) was quenched with a 5% solution of AcOD in deuterium oxide. The mixture was extracted with diethyl ether, dried (Na_2SO_4) and submitted to a GC–MS quantitative analysis which revealed *ca.* 1 mmol of styrene per mole of indole with traces of deuterium incorporation (calculated on the 104:105 amu ratio in the MS spectrum with respect to a pure sample). The amount of styrene reported above does not include that present in the starting Grignard reagent, which was calculated from a GC–MS quantitative analysis of a sample of the starting solution poured onto crushed dry ice.

Quenching with carbon dioxide. The reaction mixture arising from **2b** (3 mmol) and **1a** (1 mmol) was poured onto crushed dry ice. The mixture was extracted with diethyl ether and washed with a saturated solution of sodium carbonate. The aqueous layer was acidified and after filtration *ca.* 0.1 mmol of cinnamic acid was recovered (identified by comparison with the commercial product).

Reaction in a 1:1 *ratio*. The THF solutions of 2-chloronitrobenzene and (propen-1-yl)magnesium bromide were syringed into a Y-tube flushed with nitrogen over a 10 min period. As soon as the reactants came into contact the mixture was allowed to drop into an aqueous ammonium chloride solution. A sample was analysed by GC–MS and the following product distribution was detected: 2-chloronitrosobenzene (4%), 2-chloronitrobenzene (72%), 7-chloro-3-methylindole (18%) and a trace of *N*-(2-chlorophenyl)hydroxylamine. All products were identified by comparison of their retention times and mass spectra with those of authentic samples.

The same procedure was employed for the reaction of 4-chloronitrobenzene and (propen-1-yl)magnesium bromide. A sample was submitted to GC–MS analysis and the following product distribution found: 4-chloronitrosobenzene (8%), 4-chloronitrobenzene (64%), 5-chloro-3-methylindole (5%), 2-chloroaniline (trace) and *N*-(4-chlorophenyl)hydroxylamine (12%).

Reaction of Nitrosobenzenes **11** *with Vinylmagnesium Bromides* **2c** *and* **2d**.—*Method A*. The reaction was carried out under the same experimental conditions described for nitroarenes, using a nitroso to Grignard ratio of 1:2.2. The reaction mixture was eluted with hexane to give components in the following order: azo derivative **6**, azoxy derivative **5**, indole **3**. Azo and azoxy derivatives were recognized by comparison (TLC, mixed m.p.s, mass spectrum, retention time) with samples prepared according to the literature.[35] Yields are reported in Table 2.

Method B. To a stirred THF solution of the appropriate vinylmagnesium bromide (11 mmol) was added, at 0 °C under a nitrogen atmosphere, a THF solution (30 cm^3) of the nitro compound (5 mmol). Stirring was continued for 5 min and then the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with diethyl ether. The organic layer, dried over Na_2SO_4, was concentrated and submitted to flash-chromatography on a silica gel column (hexane as eluent). Yields are reported in Table 2.

Reaction of 2,2′-*Azoxytoluene* **5a** *with* **2a**.—To a stirred THF solution of **5a** (5 mmol) was added, at 0 °C under a nitrogen atmosphere, a THF solution of **2a** (5 mmol). Stirring was continued for 60 min and then the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with diethyl ether. The organic layer, dried over Na_2SO_4, was concentrated and recrystallized from hexane quantitatively to give 2,2′-azotoluene **6a**.

Acknowledgements

The Italian CNR (Progetto Finalizzato Chimica Fine 2) is acknowledged for financial support.

References

1 P. Buck and G. Köbrich, *Tetrahedron Lett.*, 1967, 1563.
2 Y. Yost, H. R. Gutman and C. C. Muscoplat, *J. Chem. Soc. C*, 1971, 2120.
3 G. Bartoli, *Acc. Chem. Res.*, 1984, **17**, 109.
4 G. Bartoli, M. Bosco, G. Cantagalli, R. Dalpozzo and F. Ciminale, *J. Chem. Soc., Perkin Trans. 2*, 1985, 773.
5 (*a*) G. Bartoli, M. Bosco, R. Dalpozzo and E. Marcantoni, *Tetrahedron Lett.*, 1988, **29**, 2251; (*b*) L. Barboni, G. Bartoli, E. Marcantoni, M. Petrini and R. Dalpozzo, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2133.
6 G. Bartoli, M. Bosco, R. Dalpozzo and L. Grossi. *Polar versus Electron Transfer Pathway in the Reaction of Alkyl Grignard Reagents with Mononitroarenes. Factors Affecting Product Distribution*, in *Paramagnetic Organometallic Species in Activation, Selectivity, Catalysis*, ed. M. Chanon, M. Julliard and J. C. Poite, Kluwer Academic Publishers, Dordrecht, 1989, 489.
7 G. Bartoli, G. Palmieri, M. Petrini, M. Bosco and R. Dalpozzo, *Gazz. Chim. Ital.*, 1990, **120**, 247.
8 (*a*) F. Kienzle, *Helv. Chim. Acta*, 1978, **37**, 449; (*b*) G. Bartoli, G. Baccolini and M. Bosco, *J. Org. Chem.*, 1980, **45**, 522; (*c*) N. Armillotta, G. Bartoli, M. Bosco and R. Dalpozzo, *Synthesis*, 1982, 836.
9 (*a*) G. Bartoli, A. Medici, G. Rosini and D. Tavernari, *Synthesis*, 1978, 436; (*b*) G. Bartoli, M. Bosco, R. Dalpozzo and M. Petrini, *Tetrahedron*, 1987, **43**, 4221.
10 G. Bartoli, R. Leardini, A. Medici and G. Rosini, *J. Chem. Soc., Perkin Trans. 1*, 1978, 692.
11 R. D. Guthrie, C. Hartmann, R. Neill and D. E. Nutter, *J. Org. Chem.*, 1987, **52**, 736.
12 G. Bartoli, R. Dalpozzo and L. Grossi, *J. Chem. Soc., Perkin Trans. 2*, 1989, 573.
13 G. Bartoli, G. Palmieri, M. Bosco and R. Dalpozzo, *Tetrahedron Lett*, 1989, **30**, 2129.
14 G. Tennant, in *Comprehensive Organic Chemistry*, ed. D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 2, p. 506.
15 J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.
16 W. E. Lindsell, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, Pergamon Press, New York, 1982, ch. 4, p. 163.
17 (*a*) R. Okazaki, Y. Inagaki and N. Inamoto, *J. Chem. Soc., Chem. Commun.*, 1974, 414; (*b*) Y. Inagaki, R. Okazaki and N. Inamoto, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 621.
18 (*a*) C. Crotti, S. Cenini, B. Rindone, S. Tollari and F. Demartin, *J. Chem. Soc., Chem. Commun.*, 1986, 784; (*b*) J. I. G. Cadogan, *Quart. Rev.*, 1968, **22**, 222.
19 M. Nazaki, *Bull. Chem. Soc. Jpn.*, 1960, **33**, 461.
20 J. B. Hendrickson, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 47.
21 (*a*) C. H. Cummins and R. M. Coates, *J. Org. Chem.*, 1983, **48**, 2070; (*b*) R. M. Coates, W. F. Burgoyne, Jr., C. W. Hutchins and S. L. Bender, *Chem. Biol. Hydroxamic Acids, (Proc. Int. Symp.), 1st 1981*, 1982, 14 (*Chem. Abstr.*, 1983, **99**, 52 772); (*c*) R. M. Coates and C. W. Hutchins, *J. Org. Chem.*, 1979, **44**, 4742; (*d*) R. M. Coates and I. Md. Said, *J. Am. Chem. Soc.*, 1977, **99**, 2355.
22 G. Baccolini, R. Dalpozzo and E. Errani, *Tetrahedron*, 1987, **43**, 2755.
23 (*a*) A. K. Hoffmann, A. M. Feldman and E. Gelbum, *J. Am. Chem. Soc.*, 1964, **84**, 646; (*b*) K. Reuter and W. P. Neumann, *Tetrahedron Lett.*, 1978, 5235.
24 D. C. Nonhebel, J. M. Tedder and J. C. Walton, *Radicals*, Cambridge University Press, 1979.
25 E. G. Janzen, *Acc. Chem. Res.*, 1969, **2**, 279.
26 T. V. RajanBabu, G. S. Reddy and T. Fukunaga, *J. Am. Chem. Soc.*, 1985, **107**, 5473.
27 G. Bartoli and R. Dalpozzo, unpublished results.
28 (*a*) C. N. R. Rao and K. R. Bhaskar, in *The Chemistry of the Nitro and Nitroso Groups*, part 1, ed. H. Feuer, Interscience, New York, 1968, ch. 3; (*b*) J. H. Boyer, in *The Chemistry of the Nitro and Nitroso Groups*, part 1, ed. H. Feuer, Interscience, New York, 1968, ch. 5.
29 (*a*) R. H. Holmes, *J. Org. Chem.*, 1964, **29**, 3076; (*b*) K. Nakamoto and R. E. Rundle, *J. Am. Chem. Soc.*, 1956, **70**, 1113.
30 R. E. Lutz and M. R. Lytton, *J. Org. Chem.*, 1938, **3**, 68.
31 *Dictionary of Organic Compounds*, Eyre and Spottiswood, London, 1965, vol. 2, p. 1184.
32 M. G. Reinecke, H. W. Johnson Jr. and J. F. Sebastian, *J. Am. Chem. Soc.*, 1969, **91**, 3817.
33 G. S. Bajwa and R. K. Brown, *Can. J. Chem.*, 1969, **47**, 785.
34 I. Fleming and M. Woolias, *J. Chem. Soc., Perkin Trans. 1*, 1979, 829.
35 L. Zechmeister and P. Rom, *Chem. Ber.*, 1926, **59**, 871; M. Busch and K. Schultz, *Chem. Ber.*, 1929, **62**, 1458; L. T. Smith and R. E. Lyons, *J. Am. Chem. Soc.*, 1926, **48**, 3165.

Paper 0/04686H
Received 18*th October* 1990
Accepted 7*th November* 1990