O1).[47] The connection of the three subunits is accomplished by interaction of the "formaldehyde oxygen" with the available lateral coordination site of the adjacent bent metallocene moiety.[15] In comparison to the Zr–O linkage in the metallacyclic three-membered rings, only slightly longer bond distances have been found for this connection (e.g., Zr1–O1: 2.178 Å).

Compound **28** is a quite remarkable substrate, not only because it appears to represent the first (η^2-formaldehyde) complex characterized by X-ray diffraction that has been obtained by the carbonylation of a transition-metal hydride[47] but also because it cleaves all three CO-derived $-CH_2-$ groups upon thermolysis (200 °C) to form the known ($Cp_2Zr{=}O$) trimer **29**.[48]

Conclusions

It seems that bis(η-cyclopentadienyl)zirconium(IV) alkyl and hydride complexes are informative model substrates for studies directed toward an understanding of metal-induced reduction and coupling processes of the carbon monoxide molecule. In the +4 oxidation state the involved group 4 transition-metal carbonyl complexes lack a considerable backbonding contribution of the M–CO linkage, making d^0 zirconocene carbonyl complexes very unstable and reactive. After initial CO coordination, subsequent stabilizing reactions therefore take place at very low temperature. On the other hand, the pronounced binding affinity for oxygen centers from reagents as well as ligands already coordinated to the metallocene moiety provides a considerable additional stabilization for a number of possible reactive intermediates. These factors together have allowed the observation of otherwise undisclosed kinetically controlled pathways in carbonylation reaction sequences under very mild reaction conditions.

(η^2-Aldehyde)zirconocene complexes are of a special importance as intermediates for the reductive coupling of carbon monoxide at the bent metallocene unit. The occurrence of free formaldehyde in metal-catalyzed transformations of CO/H_2 mixtures is highly questionable in view of its unfavorable thermodynamics.[2,44] However, pathways for reductive coupling of the CO molecule through a CH_2O intermediate side-on coordinated to a metal surface is quite possible from the studies on our zirconocene model system.

There is strong evidence that hydrocarbon products in heterogeneously catalyzed Fischer–Tropsch processes are obtained from reactions of methylene groups on a metal surface.[49] The fact that all three carbon monoxide derived methylene groups are cleaved upon thermolysis of the (η^2-formaldehyde)zirconocene complex **28** to form the "metal oxide" **29** emphasizes the similarity of our model system with a real Fischer–Tropsch process. Though the fate of the methylene groups "lost" in the model system has not been established at present, this observation may constitute an important basis for future studies directed toward an understanding of the factors controlling Fischer–Tropsch type processes on a well-defined molecular level.

It is a great pleasure to acknowledge the many contributions of my co-workers Frank Rosenfeldt and Kurt Kropp, the invaluable advice, stimulation, and encouragement of Professors Wolfgang Roth and Roald Hoffmann, and generous financial support of the Deutsche Forschungsgemeinschaft.

(47) To my knowledge, X-ray structures of only three other η^2-formaldehyde transition-metal complexes had been reported at the time this Account was written. They have all been prepared by reactions of suitable metal complex precursors with formaldehyde solutions (C–O bond lengths of the CH_2O ligand are given in parentheses): (a) $Os(\eta^2\text{-}CH_2O)(CO)_2(PPh_3)_2$, (1.59 Å): Brown, K. L.; Clark, G. R.; Headford, C. E. L.; Marsden, K.; Roper, W. R. *J. Am. Chem. Soc.* **1979**, *101*, 503. (b) $Fe(\eta^2\text{-}CH_2O)(CO)_2[P(OCH_3)_3]_2$, (1.32 Å): Berke, H.; Huttner, G.; Weiler, G.; Zsolnai, L. *J. Organomet. Chem.* **1981**, *219*, 353 (c) $Cp_2V(\eta^2\text{-}CH_2O)$, (1.353 Å): Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Am. Chem. Soc.* **1982**, *104*, 2019.

(48) Average Zr–O bond length: 1.959 Å; Zr–O–Zr angle (mean value): 142.5° for **29**. Fachinetti, G.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Am. Chem. Soc.* **1979**, *101*, 1767.

(49) Brady, R. C., III; Pettit, R. *J. Chem. Soc.* **1980**, *102*, 6181.

Conjugate Addition of Alkyl-Grignard Reagents to Mononitroarenes

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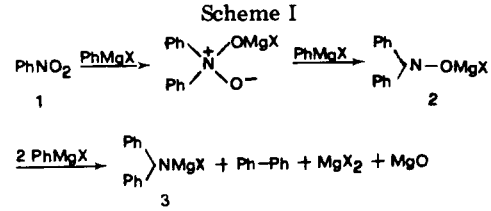
Until a few years ago some fundamental aspects of the reaction between mononitroarenes and Grignard reagents were unknown or misinterpreted; only the reactions with arylmagnesium halides had been examined in detail. Gilman and McCracken,[1] and later on Kursanov and Solodkov,[2] had explained the formation

Scheme I



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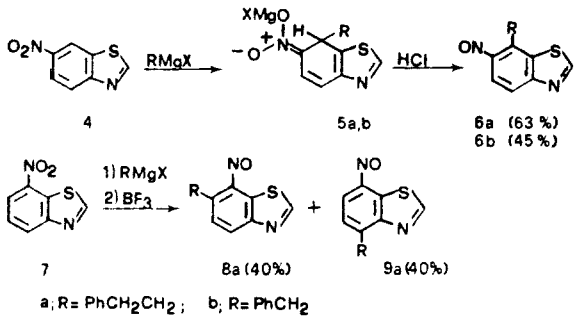
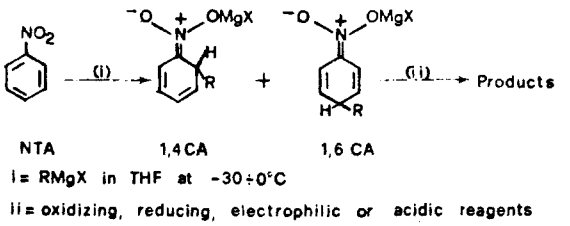
Scheme II



Scheme III



of diphenylamine, phenol, and biphenyl from the reaction of PhMgBr with nitrobenzene (1) in terms of 1,2-addition of PhMgBr to the nitro group, followed by complete reduction to diphenylamino derivative **3** via the hydroxylamino intermediate **2**. The general guidelines of this mechanism had been later confirmed by Yost,[3] who succeeded in isolating hydroxylamino derivatives in appreciable yields. Much less attention has been paid to the reactivity of mononitroarenes with alkyl-Grignard reagents. Only scant reports appeared during the first two decades of this century, which showed nitroso, azoxy, and azo compounds in addition to primary and secondary arylamines, to be among the reaction products.[4]

Although Severin[5] had reported in 1963 that RMgX can add to polynitrobenzenes in conjugate fashion, the reactivity of mononitroarenes had not been reinvestigated. The view that alkyl-Grignard reagents, like aryl ones, have only a reducing and *N*-alkylating action on the nitro group had been long accepted,[6] the reactivity of polynitrobenzenes having been considered to be abnormal.[7]

In 1976 we reported the first example[8] of a conjugate addition of alkyl-Grignard reagents to a mononitroarenic system. We obtained, in fact, large amounts of products **6** from reaction of $PhCH_2CH_2MgX$ and $PhCH_2MgX$ with 6-nitrobenzothiazole (**4**) (see Scheme II). These preliminary results appeared to open a simple route to the alkylation of aromatic nitro compounds, which was of remarkable interest in view of the fact that the few available methods had serious limitations.[9] With this in mind, the reactivity of alkyl-Grignard reagents has been investigated with a large number of systems. Our findings have led to the conclusion that conjugate addition is the normal reactivity fashion exhibited by alkylmagnesium halides toward mononitroarenes.

General Features

The reaction between a generic nitroarene (NTA) and an alkylmagnesium halide proceeds through two separate stages: (i) formation of nitronate compounds 1,4-CA and/or 1,6-CA from 1,4- and/or 1,6-conjugate addition, respectively, of RMgX to NTA system, (ii) decomposition of nitronate compounds 1,4-CA and 1,6-CA to final products (see Scheme III). Nitronic derivatives are relatively unstable,[10] and, consequently, nitronate compounds 1,4-CA and 1,6-CA must be quickly converted into stable compounds. The possibility of isolating them in their nitronic forms is confined to special cases[11] (see Scheme V). It should be noted that the success of the reaction depends on both the extent of conjugate addition and on the possibility of controlling decomposition of the nitronate intermediates. For example, the fact that the expected 5-butyl-6-nitrosoquinoline was recovered only in 5% yield upon addition of BF_3 to the reaction mixture of 6-nitroquinoline and BuMgBr in THF[12] could suggest at first sight failure of this system to undergo conjugate addition. However, the high yields in 6-chloro-5-butylquinoline, obtained afterward upon addition of sodium hypochlorite to the same reaction mixture,[13] indicated that the previous unsuccessful results were due to failure of decomposing the nitronate adduct to nitrosoquinoline. Various experimental procedures have been optimized in order to offer convenient methods of wide applicability. They include oxidation[14,15] and reduction[16] methods, reactions with electrophiles,[13] and acidic treatments.[12,17] Owing to the complexity of these results, they will be discussed in detail later.

Nitronate adduct formation requires, in principle, a 1:1 RMgX/substrate molar ratio. However, we have observed that some unreacted material is left, in most instances,[15] when equimolar amounts or slight excess of RMgX are used even if prolonged reactions times are employed. This causes considerable difficulties in the purification of the reaction products. In our experiments, we have generally used a 2:1 RMgX/substrate molar ratio in order to ensure completeness of the reaction in short times (a few minutes are required in most instances for substrate concentrations of 5×10^{-1} M at temperatures ranging from −30 to 0 °C). Under

(1) H. Gilman and R. McCracken, *J. Am. Chem. Soc.*, **49**, 1052 (1927).
(2) D. N. Kursanov and P. A. Solodkov, *Zh. Obshch. Khim., Ser A*, **5**, 1487 (1935); *Chem. Abstr.*, **30**, 2181 (1936).
(3) Y. Yost, H. R. Gutmann, and C. C. Muscoplat, *J. Chem. Soc. C*, 2120 (1971).
(4) R. H. Pickard and J. Kenyon, *Proc. Chem. Soc.*, **23**, 153 (1907); H. Hepworth, *J. Chem. Soc.*, 1004 (1920); B. Oddo, *Chem. Zentralbl.*, **2**, 1113 (1904).
(5) T. Severin and R. Schinitz, *Chem. Ber.*, **96**, 3081 (1963); T. Severin and M. Adam, *ibid.*, **97**, 106 (1964).
(6) H. S. Kharash, and O. Reimnuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York, 1954, p 384; P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969); K. Nutzel in "Methoden der Organischen Chemie", Houben-Weyl, 4th ed., E. Muller, Ed., Stuttgart, 1973, Vol. 13, p 47.
(7) Y. Inagari, R. Okazari, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **48**, 3727 (1975).
(8) G. Bartoli and G. Rosini, *Synthesis*, 270 (1976).
(9) V. J. Traynelis and J. Y. McSweeney, *J. Org. Chem.*, **31**, 243 (1966); G. A. Russel and S. A. Weiner, *ibid.*, **31**, 248 (1966).
(10) A. T. Nielsen, in "The Chemistry of Nitro and Nitroso Groups", H. Feuer, ed., Interscience, New York, 1969, p 349.
(11) G. Bartoli, M. Bosco, and C. A. Boicelli, *Synthesis*, 570 (1981).
(12) G. Bartoli, R. Leardini, A. Medici, and G. Rosini, *J. Chem. Soc., Perkin Trans. 1*, 692 (1978).
(13) G. Bartoli and M. Bosco, *Synthesis*, 616 (1980).
(14) F. Kienzle, *Helv. Chim. Acta*, **37**, 449 (1978).
(15) G. Bartoli, M. Bosco, and G. Baccolini, *J. Org. Chem.*, **45**, 522 (1980).
(16) G. Bartoli, A. Medici, G. Rosini, and D. Tavernari, *Synthesis*, 436 (1978).
(17) G. Bartoli, M. Bosco, A. Melandri, and A. C. Boicelli, *J. Org. Chem.*, **44**, 2087 (1979).

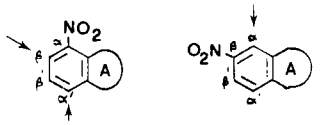


Figure 1.

the aforementioned conditions, formation of unwanted byproducts could occur owing to the reducing effect of the RMgX excess on the nitronate function.[16] However, this can be completely avoided by bringing out an immediate decomposition of the nitronate intermediate, since the reduction process on the nitronate function is very slow unless catalyzed by cuprous iodide (CuI).[16]

Orientation of Alkylation

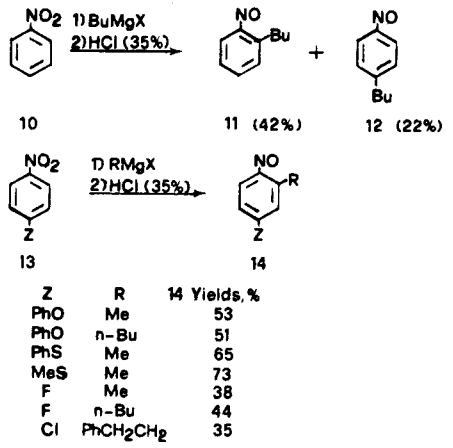
Orientation of alkylation mainly depends on the structure of aromatic substrate (i.e., mono-, bi-, or polycyclic) and on the presence of substituents in reactive positions.

Orientation in Unsubstituted Mononitroarenes. Nitrobenzene (**10**) undergoes attack by the entering alkyl group at ortho and para positions, the ortho/para alkylation ratio being as predicted by the statistical factor (~2:1).[17] For example, acidic treatment of the reaction mixture of **10** with BuMgBr gives 42% and 22% of nitroso derivatives **11** and **12**, respectively (see Scheme IV). In a bicyclic system, such as benzothiazole (see Scheme II), the orientation depends upon the position occupied by the nitro group; in fact, the 7-nitro isomer **7** gives 4- and 6-alkyl-7-nitroso derivatives in comparable yields,[18] whereas the 6-nitro isomer **4** gives almost exclusively the 7-alkyl derivative **6**.[18] Since analogous results have been obtained from a large variety of bicyclic substrates, the following orientation rules apply to aromatic bicyclic systems. If the four positions of the benzene ring, condensed with a generic aromatic nucleus A, are denoted α, α', β, and β' as in Figure 1, alkylation occurs at both the β- and the α'-ones to a comparable extent when the nitro group is linked to an α-position. Exclusive alkylation at the adjacent α-position takes place, however, in a β-substituted nitro derivative.

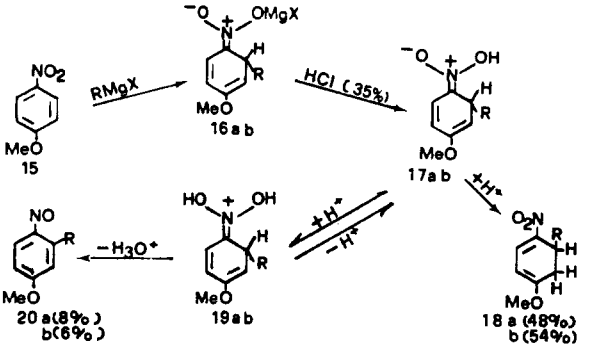
Among polycyclic systems, only 9-nitroanthracene has been investigated.[19] This substrate has been found to undergo alkylation at the 10-position (see Scheme X).

Orientation in Substituted Compounds. In systems having heterosubstituents in reactive positions, ipso attack readily occurs when the substituent occupies the only reactive position. A typical example, illustrated in Scheme V, is offered by 1-methoxy-2-nitronaphthalene (**21**) (a β-nitro-substituted bicyclic system), which is alkylated exclusively at the C-1 carbon.[17] Conversely, with a number of *p*-Z-substituted nitrobenzenes (Z = OMe, OAr, SMe, SPh, Cl, F), almost exclusive alkylation at unsubstituted ortho carbons is observed (see Scheme IV).[17] The higher reactivity of unsubstituted positions is confirmed by the results obtained with other aromatic systems such as methoxy-substituted 1-nitronaphthalenes:[20,21] the 4-methoxy

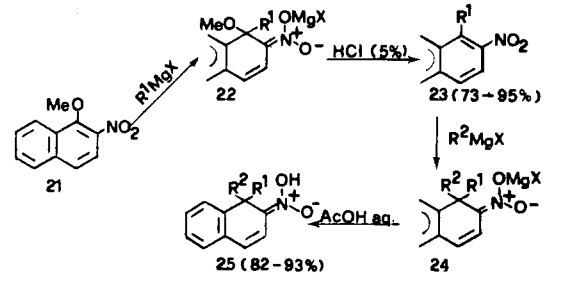
Scheme IV



Z	R	14 Yields, %
PhO	Me	53
PhO	n-Bu	51
PhS	Me	65
MeS	Me	73
F	Me	38
F	n-Bu	44
Cl	$PhCH_2CH_2$	35



Scheme V



R^1 = Me, $PhCH_2CH_2$, $PhCH_2$

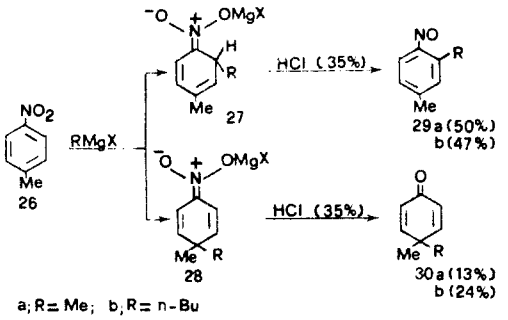
R^2 = Me, $PhCH_2CH_2$, $PhCH_2$, $n\text{-}C_8H_{17}$

derivative **31** undergoes alkylation almost exclusively at the 2-position (see Scheme VII), while the 2-methoxy derivative **50** is alkylated preferentially at the 4-position (see Scheme XII). In all cases, methoxy-substitution product does not exceed 5%.[20]

Different from what is observed with heterosubstituents, carbon carrying a methyl group shows a reactivity comparable to that of the unsubstituted one. In fact, 4-methyl-1-nitrobenzene (**26**) gives both 1,4-addition and 1,6-addition product, **27** and **28**, respectively, in ~2:1 ratio, according to statistical factor[22] (see Scheme VI). On this basis, it is not surprising that exhaustive alkylation at C-1 of 1-R^1-2-nitronaphthalene (**23**) can be carried out in high yields[11] (see Scheme V). Another significant example is provided by the two-step synthesis[19] of 10-R^1-10-R^2-anthracen-9-ones (**47**) from 9-nitroanthracene (**45**) (see Scheme X).

(18) G. Bartoli, R. Leardini, M. Lelli, and G. Rosini, *J. Chem. Soc., Perkin Trans. 1*, 884 (1977).
(19) N. Armillotta, G. Bartoli, M. Bosco, and R. Dalpozzo, *Synthesis*, 836 (1982).
(20) G. Bartoli, M. Bosco, and G. Baccolini, *J. Org. Chem.*, **45**, 2649 (1980).
(21) G. Bartoli, M. Bosco, F. Ciminale, and R. Dalpozzo, *J. Org. Chem.*, **47**, 5227 (1982).
(22) G. Bartoli, M. Bosco, and G. Pezzi, *J. Org. Chem.*, **43**, 2932 (1978).

Scheme VI



a; R = Me; b, R = n-Bu

Decomposition of Nitronate Adducts

Conversion of nitronate adducts to stable compounds in high yields makes the conjugate addition of RMgX to nitroarenes a reaction of synthetic value. With this in mind, the reactivity of cyclohexadiene nitronic systems toward Lewis acids, protonating, halogenating, oxidizing, and reducing agents has been investigated.

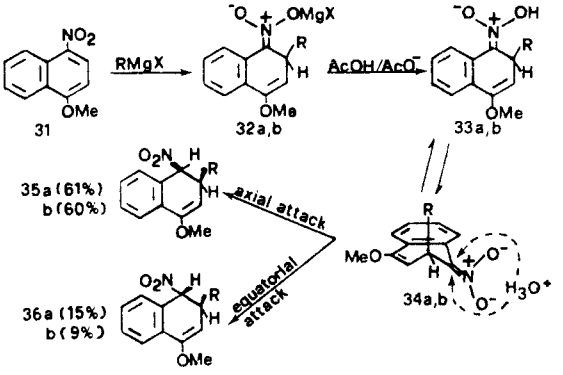
Acidic Treatments. When treated with acids, nitronate adducts can follow different decomposition pathways, depending on the nature of the substituent linked to the aromatic carbon undergoing alkylation. (i) If the carbon carries a good leaving group, the acidic medium promotes the explusion of the leaving group as anion.[17] For instance, 1-methoxy-2-nitronaphthalene (**21**) leads ultimately to the formation of demethoxyalkylation product **23** (see Scheme V). (ii) When the substituent is not a good leaving group, conversion of nitronic to carbonylic function occurs (Nef reaction[23]). A typical example is provided by the decomposition of **28** (Scheme VI) to cyclic ketone **30** upon addition of HCl. (iii) Nitronate adducts arising from alkylation at unsubstituted positions are generally decomposed by Lewis acids (HCl or BF_3) to yield aromatic alkyl nitroso compounds. This reactivity is characteristic for a cyclohexadiene nitronate compound, the driving force of such reaction being the readily feasible aromatization of the system.

As illustrated in Scheme IV in the case of the formation of product **20** from nitronate **16**, the reaction pathway can be accounted for by an acid-promoted elimination of water from nitronic acid **17**, which is immediately formed when **16** is added to a strong acidic medium. This reaction has been shown to be of wide applicability as demonstrated by the satisfactory results obtained from a large variety of aromatic substrates. Examples include benzoxazole, indole, benzothiophene, and naphthalene systems,[12] besides those reported in Schemes II and IV.

Electron-attracting or weakly electron-donating substituents do not change this reactivity pattern, whereas strong electron donors such as methoxy bring about a different decomposition pathway[17] (see Scheme IV). In fact, nitronic acid **17** gives mainly its tautomer **18** and only small amounts of the expected nitroso derivative **20**. This peculiar reactivity can be explained in terms of an usual *aci*-nitro tautomerization promoted by prototropic attack at the β-carbon of the vinyl ether function in nitronic acid **17**. It is clear, therefore, that in the absence of strong electron donors in the 4-position, protonation at C-3 competes unfavorably with protonation at the oxygen of nitronic function. Thus,

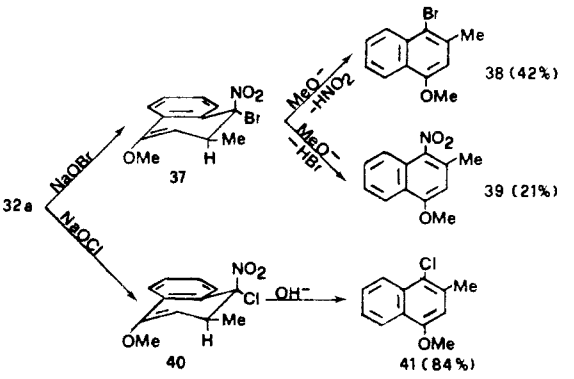
(23) J. V. Nef, *Justus Liebigs Ann. Chem.*, 280, 264 (1894).

Scheme VII



a, R = Me ; b, R = $PhCH_2$

Scheme VIII



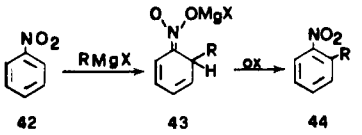
in other *p*-Z-substituted nitrobenzenes (**13**) (Z = OPh, SMe, SPh, F, Cl), the usual decomposition to nitroso derivatives **14** can be observed[17] almost exclusively.

C-Protonation and C-Halogenation at Nitronate Function. Nitronate compounds are readily converted to their nitro forms upon neutralization of their basic solutions.[10] The possibility of obtaining long-lived nitronic acids is confined to situations in which C-protonation at nitronic function is sterically hindered by large alkyl substituents as in 1,1-dialkyl-1,2-dihydronaphthalene-2-nitronic acids[11] (**25**) (see Scheme V). Compounds **25**, in fact, are stable for several days at 0 °C, with the exception of the 1,1-dimethyl derivative, which rapidly tautomerizes into its nitro form.

C-Protonation has been studied in 1,4-addition nitronate compounds, such as **32** (see Scheme VII), in view of a number of interesting stereochemical phenomena.[20] Compound **32**, when treated with AcOH–AcOK buffer, gives rise to preferential formation of less stable cis isomer **35**. In this system the stereoselectivity is clearly induced by steric control exerted by the alkyl substituent at the 2-position on the prototropic attack direction in a transition state that closely resembles reactants. In nonplanar cyclohexadiene nitronate **34**, in fact, the alkyl substituent must preferentially assume an axial conformation so as to minimize its steric interaction with the oxygens of the nitronate function. Such arrangement causes the protonating species to enter preferentially from the less hindered axial direction. The observed increase in kinetic preference for the cis compound on going from methyl to the bulkier benzyl group strongly supports this interpretation.

Substitution of a halogenating agent for a protonating species gives rise to interesting synthetic applications.

Scheme IX



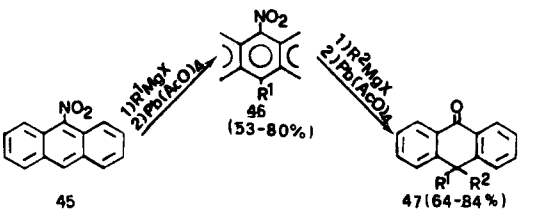
Treatment of compound **32a** with alkaline sodium hypobromite solution at 0 °C immediately leads to the almost exclusive formation of the dihydro isomer **37**, in which bromine and the methyl group are in a trans configuration[24] (see Scheme VIII). The higher stereoselectivity observed in this instance with respect to C-protonation, is clearly due to larger bulkiness of the brominating agent. Compound **37**, when treated with MeO^- in MeOH under conditions favoring an E_2-type elimination of vicinal groups,[25] undergoes a preferential HNO_2 loss, leading mainly to product **38**, accompanied by minor amounts of dehydrobromination product **39**. A synchronous elimination will easily occur in nonplanar system **37** between the trans diaxial groups (NO_2 and H), the estimated dihedral angle (>164°) being close to the ideal value of 180° for an antiperiplanar elimination. The cis groups (Br and H) will clearly eliminate with greater difficulty, for their dihedral angle does not fulfill the ideal geometry (0°) for syn elimination. This fact would bring about remarkable strain in the transition state when the bulky substituents (nitro and methyl group) are expected to have almost eclipsed configuration. Moreover, a preferential axial arrangement in **37** is strongly suggested by the low $J_{H\text{-}3,H\text{-}4}$ value (3.3 Hz), found in its ^1H NMR spectra. On the other hand, the difference in the heterolytic bond breaking energies between C–Br and C–NO_2 linkages can balance, in part, the strong tendency for an antiperiplanar elimination.

The observed **38**/**39** ratio of 2:1, therefore, must be interpreted as an average result of these counteracting factors. In fact, substituting bromine by chlorine (a group of lesser leaving ability than bromine), HNO_2 elimination becomes strongly predominant; only product **41** is obtained upon addition of alkaline hypochlorite solution to **32a**. In this case, the intermediate **40** was not isolated and its decomposition was carried out in the same reaction medium in which it had been formed. A large variety of chloroalkylarenes has been synthesized in good yields from the corresponding nitro derivatives.[13] In addition to the reaction reported in Scheme VIII, other significant examples are represented by the formation of 6-chloro-5-methylquinoline (73%) from 6-nitroquinoline and 6-chloro-7-benzylbenzothiazole (53%) from 6-nitrobenzothiazole.

Oxidation of Nitronate Adducts to Alkylnitroarenes. The conversion of generic nitronate adduct **43** (see Scheme IX) to the corresponding aromatic nitro derivative **44** requires an equivalent of an oxidizing agent. This reaction was first carried out on a number of benzene and naphthalene derivatives by adding dicyanodichloro-*p*-benzoquinone (DDQ) in THF to a freshly prepared solution of nitronate adduct at 0 °C.[14]

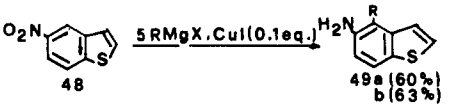
(24) G. Bartoli, M. Bosco, E. Foresti, and G. Pradella, *J. Org. Chem.*, **46**, 3109 (1981).
(25) N. A. Lebel, "Advances in Alicyclic Chemistry", Academic Press, New York, 1971, Vol. 3, p 195.

Scheme X



R^1= Me, $PhCH_2CH_2$, n-C_6H_{13}, c-C_6H_{11}.
R^2= Me, $PhCH_2CH_2$, n-C_6H_{13}.

Scheme XI



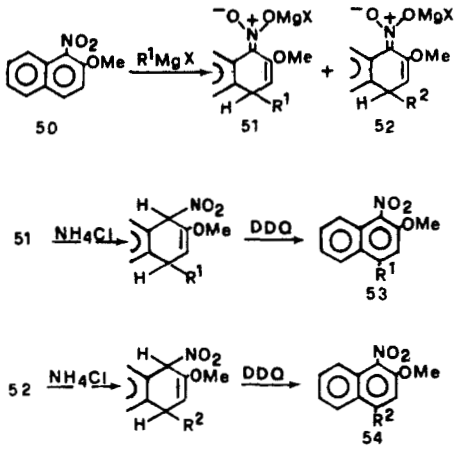
a: R= n-C_4H_9; b R= $PhCH_2CH_2$.

Furthermore, if the nitronate compounds are prepared by using an excess of RMgX, the incompatibility of DDQ with the presence of RMgX in the reaction medium can be avoided by performing the oxidation with a two-step procedure. This method consists of isolating the nitronic intermediates in their nitro forms, followed by their quantitative oxidation with DDQ in refluxing dry benzene[17] or THF.[21] An example of this alternative procedure is reported in Scheme XII.

However, DDQ is a very expensive reagent and its use should be confined to situations in which the presence in the molecule of other oxidable functional groups such as a C=C double bond requires a chemioselective oxidant[21] (see Scheme XII). We have, therefore, developed two methods that offer the following advantages: (i) one-pot procedures employing cheap oxidant, (ii) preparation of nitronate adducts achieved by using RMgX excess. The first method consists of treating **43** with $KMnO_4$ in alkaline acetone–water solution at 0 °C, the excess of RMgX being immediately decomposed in the protic medium.[15] The second method utilizes $Pb(CH_3COO)_4$ in CH_2Cl_2 solution containing 3% of CH_3COOH, having provided in advance for decomposition of RMgX excess by adding a few drops of glacial acetic acid to THF nitronate solution.[19] The wide applicability of the $KMnO_4$ method is evidenced by the satisfactory results obtained with a large variety of aromatic substrates, including substituted and unsubstituted benzene and naphthalene systems as well as other bicyclic systems such as indole, benzothiazole, benzothiophene, etc. The $Pb(CH_3COO)_4$ method, on the other hand, represents an effective alternative for polycyclic systems (see Scheme X).

One-Pot Synthesis of Aromatic Alkylamines. The one-pot conversion of nitroarenes into alkylated arylamines has represented a further challenge to the synthetic utility of reaction of aromatic mononitro compounds with RMgX. This aim has been accomplished by reacting nitroarenes with a fivefold excess of RMgX at −10 °C for a few minutes and then at room temperature for several hours in the presence of catalytic amounts of CuI[16] (see Scheme XI). The use of the catalyst is essential, since uncatalyzed reactions proceed extremely slowly (3–4 days) and lead to a large amount of tars as well as of N-alkylated products. Besides the example reported in Scheme XI, this procedure has proved successful also with benzothiazole

Scheme XII



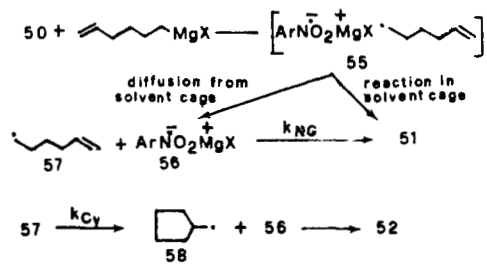
R^1 = 5-hexenyl, R^2 = cyclopentylmethyl.

and naphthalene systems.[16]

Preliminary Mechanistic Results on the Interaction between RMgX and Nitroarenic Substrates

A preliminary study concerning the nature of interaction between Grignard reagents and nitroarenic systems[21] was undertaken in order to establish whether these reactions proceed through a polar mechanism or rather, as already recognized for related reactions of RMgX with aromatic ketones,[26,27] through a single-electron-transfer (SET) pathway. For this purpose we incorporated a radical probe in the alkyl group of the Grignard reagent. The 5-hexenyl group was chosen in view of the fact that 5-hexenyl radicals are known to undergo rapid cyclization ($k \sim 10^5$ s^{-1} at room temperature) to cyclopentylmethyl radical.[28] As a consequence, the C-alkylation product containing cyclopentylmethyl group is likely to be formed if the reaction proceeds with radical character. 5-Hexenylmagnesium bromide was, therefore, allowed to react with 2-methoxy-1-nitronaphthalene (**50**) at room temperature in THF and the resulting nitronate adducts **51** and **52** oxidized with DDQ to alkylnitronaphthalene **53** and **54**, respectively, through a two-step procedure (see Scheme XII). From this reaction **53** and **54** were obtained in a 64:36 ratio, respectively (overall yields 78%). These results show that at least 36% 1,6-conjugate addition proceeds through a SET pathway. However, it seems reasonable to assume that an analogous mechanism might take place also in the formation of uncyclized product. A single electron transfer might occur from R^1MgX to **50** to give a radical pair (**55**) (see Scheme XIII). The 5-hexenyl radical thus produced could migrate from the region in which it is formed (near the nitro group) to the para position of the nitroarene radical anion and then collapse at this position in a geminate recombination[29] or escape from solvent cage. Geminate recombination is likely to give exclusively uncyclized product **51**. In fact, if the lifetime of the radical pair is controlled by diffusion coefficient of usual magnitude,[30] the cage reactions should be complete

Scheme XIII



within 10^{-9} s and, therefore, cyclization ($k_{cy} = 10^5$ s^{-1}) cannot compete with geminate recombination or cage escape. Thus, cyclization is likely to occur only in radicals that have escaped their geminate partners.

Free-radical **57**, in fact, can collapse with **56** in a nongeminate recombination to give uncyclized product **51** or cyclize to **58** before recombining with **56** to give cyclized product **52**. The **51**/**52** ratio, originated by nongeminate recombination, is governed by the following equation: $d[51]/d[52] = k_{NG}[56]/k_{cy}$, where k_{NG} is the second-order rate constant of nongeminate recombination between **56** and **57**. k_{NG} has been estimated to be 10^8 M^{-1} s^{-1} for coupling between ketyls and 5-hexenyl radicals,[31] and a close value can be reasonably assumed to hold for the nitro radical anion **56**. On this basis, a steady concentration of [**56**] $< 10^{-3}$ M is sufficient to allow most radicals escape geminate recombination to cyclize before recombining with **56**.

Further evidence for a SET pathway in the reaction of **50** with RMgX is given by recent results.[32] From competitive reactions of **50** with various RMgX the following reactivity order was found: *i*-PrMgBr > $PhCH_2MgBr \simeq$ EtMgBr > MeMgBr, in line with their donating power, as established by oxidation potential data.[33] In addition, it must be noted that in reactions proceeding through a polar mechanism, such as 1,2-addition to acetone, a reversed reactivity order has been usually observed.[34]

Finally, we feel that the evidence for a SET mechanism occurring with substrate **50** can be assumed to be indicative of wide generality. Among nitroarenes, in fact, the ability of **50** to undergo electron transfer is very poor because of the presence, in the ortho position, of a strong electron donor such as MeO, which decreases the reduction potential of the system. Further work is needed to fully clarify all the phenomena involved in such reactions.

Concluding Remarks

When in the course of our studies on the reactivity of benzothiazole system, we found the first example of ring alkylation of an alkyl RMgX on mononitroarene, we wondered whether this unexpected reactivity could be due to a particular effect of the thiazole condensed ring or could be of wide generality. Our results obtained with a large variety of substrates (including mono-, bi- and polycyclic systems) clearly demonstrate that conjugate addition represents the usual reactivity exhibited by an alkyl RMgX toward a mononitroarenic system.

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In addition, heterocondensed rings such as thiazole, oxazole, thiophene, pyrrole, and pyridine, and substituents such as F, Cl, OMe, OPh, SMe, and SPh are fully consistent with such a trend. Another relevant challenge was the investigation of the synthetic potential of this new kind of reactivity. We think that the aim has been fully reached since a number of general methods for the syntheses of aromatic alkyl compounds containing different nitrogen functional groups (NO_2, NO, or NH_2) or a chlorine group have been devised. The synthetic utility of these reactions is also evidenced by specific methods involving the synthesis of unknown, 1,1-dialkyl-1,2-dihydronaphthalene-2-nitronic acids or difficulty available 10,10-dialkylanthracen-9-ones from commercial 1-methoxy-2-nitronaphthalene and 9-nitroanthracene, respectively.

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Proton Transfer from Intramolecularly Hydrogen Bonded Acids

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Proton transfers are important because of their widespread occurrence as elementary steps in many reactions. In acid- and base-catalyzed and enzyme-catalyzed reactions, proton transfer between oxygen and nitrogen atoms in the catalyst and substrate is often a key step in the mechanism.

In enzymic reactions, in particular, proton transfer often occurs between groups that are involved in intramolecular hydrogen bonds. For example, in the charge relay mechanism of action of serine proteases a proton is delivered from serine to aspartate through an intervening histidine residue that is held in position by intramolecular hydrogen bonds.[1] Protons are transferred simultaneously from serine to histidine and from histidine to aspartate along these intramolecular hydrogen bonds.

Mechanistic proposals such as this are more complicated than any mechanisms that have been found for proton transfer in chemical systems. If these processes are to be understood, it is important to provide information from studies of more simple model systems.

Fortunately the kinetics of proton transfer between most oxygen and nitrogen acids is particularly straightforward since the reactions are usually diffusion controlled.[2] In one direction the rate coefficient has the diffusion limited value (10^9–10^{10} dm^3 mol^{-1} s^{-1}) and in the other direction the rate coefficient therefore differs from the diffusion-controlled limit by a factor equal to the value of the equilibrium constant of the reaction.

However, when the acidic proton in an oxygen or nitrogen acid is involved in an intramolecular hydrogen bond, as in many of the examples in enzymic reactions, the situation is more complicated. The rate of proton removal by external base is much reduced and the kinetic behavior varies considerably from one system to another. Until recently,[3] no definite information was available to explain these results and there was some controversy[4] about the mechanism of proton removal from acids of this type.

Two possible mechanisms had been suggested.[2,5] One possibility[2] is a two-step process involving a rapid equilibrium between hydrogen-bonded and non-hydrogen-bonded forms of the acid with proton transfer occurring from the more reactive open form present in low concentration. An alternative mechanism[5] consists of a single-step attack by base on the hydrogen-bonded proton through a transition state in which the hydrogen bond is partially broken. The difference between these mechanisms is quite subtle.

Some of our work in recent years has been directed toward understanding the reasons for slow proton removal from intramolecular hydrogen bonds. Significant progess has been made. Firm mechanistic conclusions have been reached and quite dramatic and unexpected effects have been observed in some cases. For example, an aromatic amine has been found that binds a proton so tightly that the amine is protonated even in 1 mol dm^{-3} aqueous sodium hydroxide. Under extremely basic conditions when proton removal is favorable, deprotonation occurs very slowly and a conventional spectrophotometer can be used to follow the reaction, in sharp contrast to the diffusion-controlled rates ob-

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