Tetrahedron Vol. 36, pp. 1843 to 1846

0040-4020/80/0615-1843/$02.00/0

C-NITROSO COMPOUNDS—XXXV

REACTION OF ORGANOMETALLIC COMPOUNDS WITH 1-CHLORO-1-NITROSO-2,2,6,6-TETRAMETHYLCYCLOHEXANE

C. Schenk and Th. J. de Boer*
Laboratory for Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129,
1018 WS Amsterdam, The Netherlands

(*Received in UK* 10 *September* 1979)

Abstract—Reaction of Grignard reagents and organolithium compounds (RM) with the congested 1-chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane **1** leads to the formation of significant amounts of the reduction product 2,2,6,6-tetramethylcyclohexanone oxime **3** (61–90%) together with the corresponding oxime O–R ether **4** (0–11%). Attack on nitrogen is unimportant as shown by very low yields of nitrone. Formation of the products is rationalised with a pathway involving transfer of an electron from RM to **1**. This leads—after separation of MCl—to a radical pair consisting of R$^\cdot$ and the relatively stable iminoxy radical **2** (Schemes 1 and 2). Combination of these radicals explains formation of oxime ether **4** and nitrone **5**, while reaction of iminoxy radical **2** with excess of RM can give oxime **3**. Reactive radicals R$^\cdot$ (i.e. Me, Ph, and to a minor extent *n*-Bu) are furthermore capable of abstracting hydrogen from the solvent (diethyl ether, toluene, or cumene), and the solvent derived radicals can also combine with **2** on oxygen, under formation of oxime ether (26% of **6a**). The corresponding benzyl- and cumyl ethers **6b** and **6c** are only formed in trace amounts because dimerisation of benzyl radicals (7%) and cumyl radicals (22%) is favoured.

In a previous investigation[1] on reactions of Grignard reagents RMgX with α-chloronitrosoadamantane (AdClNO) we have found that the methyl and phenyl Grignard reagents give significant amounts of α,α-adamantylidene-N-R nitrones (59 and 87%, respectively), while other Grignard reagents (i.e. n-butyl, t-butyl, neopentyl, benzyl) give adamantanone oxime as the major product (up to 60%). We have rationalised these results by the tentative assumption that not only "normal" 1,2-addition of RMgX to the nitroso group takes place with ultimate formation of nitrone (by loss of chlorine from the initially formed N-α-chloroalkylhydroxylamine), but also a reduction process involving single electron transfer (SET) from the organometallic compound to the nitroso compound, ultimately leading to the formation of adamantanone oxime (Ad = NOH) and oxime ether (Ad = NOR). The electron donating power and consequently the importance of the SET processes varies with the nature of RMgX, thus explaining the widely varying product distributions with different Grignard reagents.

In order to establish the influence of steric effects on product formation, we have now investigated reactions of the highly congested 1-chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane **1** with a series of Grignard reagents, and also with some alkyllithium compounds.

RESULTS AND DISCUSSION

Reactions of 1 *with Grignard reagents*

Upon reaction of the brightly blue coloured nitroso compound **1** with a series of Grignard reagents RMgX a rapid decolouration is observed, and after aqueous work-up products can be obtained in yields as summarised in Table 1. The results clearly indicate that formation of oxime **3** is strongly favoured with all Grignard reagents (61–90%), and that nitrone yields are very low, if not zero. This is even observed in the reactions of the methyl and phenyl Grignard reagents, which are known to give high yields of nitrone and small amounts of oxime and oxime ether with unhindered α-chloronitroso compounds.[1,2]

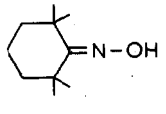
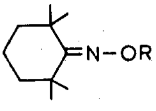
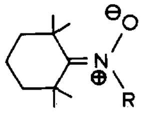
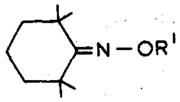
It has been suggested that transfer of an electron from an organometallic compound to a substrate may be an outer sphere process, that does not necessarily require intimate approach of the interacting species.[3,4] Such a process is expected to be much less hampered by steric hindrance than polar 1,2-addition. Experimentally this effect has been observed in reactions of Grignard reagents with aromatic ketones, where the reductive reaction pathway (SET) becomes strongly favoured by bulky groups around the carbonyl function.[4–6]

In the present case, formation of nitrone via polar 1,2-addition of the Grignard reagent to the nitroso group of **1** is indeed completely hindered by the flanking Me substituents. Steric requirements being less severe for electron transfer, this becomes virtually the exclusive process with all Grignard reagents. As pointed out earlier,[1] such an electron transfer leads to radicals R$^\cdot$, and the relatively stable 2,2,6,6-tetramethylcyclohexanone iminoxy radicals **2** (see Scheme 1). This radical pair is responsible for the formation of the final products (see Scheme 2). Obviously, steric hindrance also influences the distribution of products obtainable from the radical pair. Combination of radicals R$^\cdot$ with the iminoxy radical, that may lead to considerable amounts of nitrone **5** in the absence of steric effects (combination at nitrogen),† will now lead predominantly to oxime ether **4** (combination at oxygen).[7] Because ether formation is not entirely unhindered either, the combination reaction will be relatively slow, and many iminoxy radicals **2** can therefore escape from the cage and form oxime by accepting an electron from the Grignard reagent.[8]

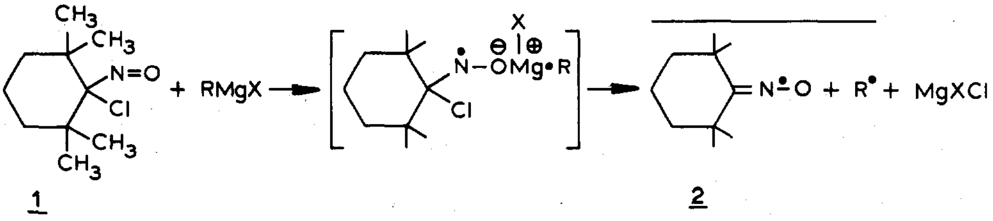
---

†We suggest that the trace amounts of the *N*-methyl nitrone **5** ($R = Me_3$) are formed through combination of iminoxy radical **2** with the relatively small methyl radical (see Ref. 8). However, we cannot altogether exclude its formation by polar 1,2-addition, or via trapping of Me radicals by **1**.[1]

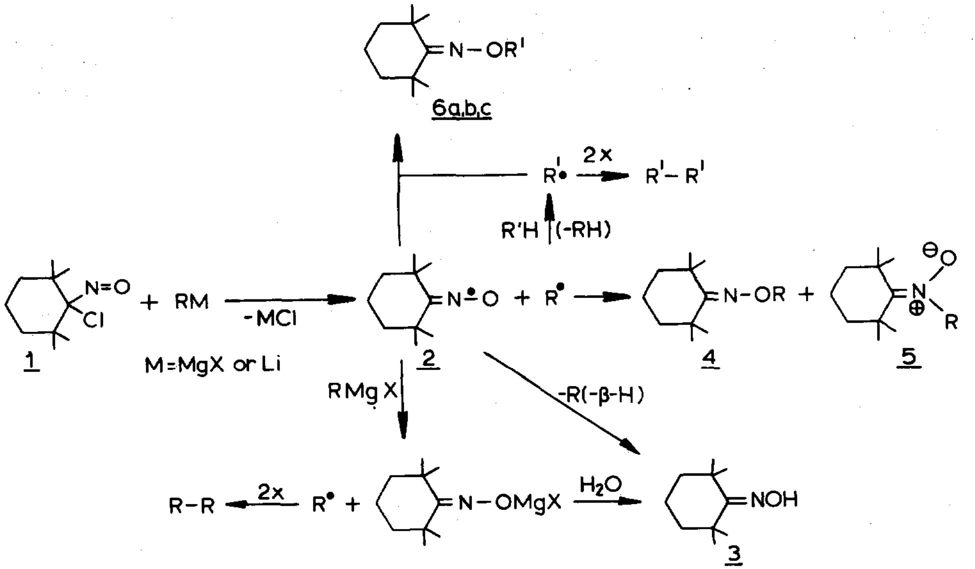
Table 1. Yields[a] of products obtained from reactions of 1-chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane 1 with Grignard reagents RMgX[b] in various solvents R'H

R	Solvent R'H				
		3	4	5	6
CH_3	$(C_2H_5)_2O$	69	—	1-2	25
CH_3	C_6H_6	80	—	1-2	—
CH_3[c]	$C_6H_5CH_3$	82	—	1-2	trace
CH_3[d]	$C_6H_5C(CH_3)_2H$	85	—	1-2	3
n-C_4H_9[e]	$(C_2H_5)_2O$	80	9	—	1-2
$(CH_3)_3C$	$(C_2H_5)_2O$	85	11	—	—
$C_6H_5CH_2$[f]	$(C_2H_5)_2O$	90	5	—	—
C_6H_5	$(C_2H_5)_2O$	61	4	—	26

[a] Yields (%) have been determined by weight of isolated materials, and are based upon 1.
[b] X is bromide except when R = CH_3, where it is iodide.
[c] 7% (based upon 1) of dibenzyl (R'R') was found in this reaction.
[d] 22% of dicumyl (R'R') is also formed.
[e] n-Butyl chloride is not formed in this reaction (see Ref. 1).
[f] Furthermore, 66% of dibenzyl (RR) was analysed. Benzyl chloride is not present in the reaction mixture (see Ref. 1).

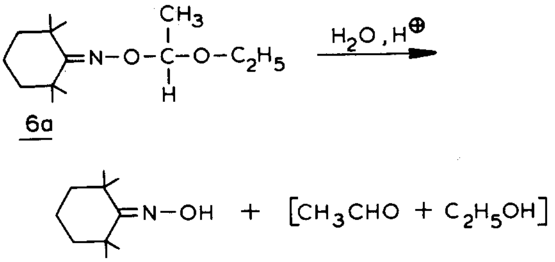


Scheme 1.



Scheme 2.

It should be noted that in reactions of 1 with the n-Bu and t-Bu Grignard reagents oxime may, in principle, also be formed by disproportionation of a radical pair, as separately shown in Scheme 2. Free radicals R˙ are not only capable of reacting with the relatively stable iminoxy radical 2 to give nitrone and oxime ether, as has been established unambiguously for free R˙ and di-t-butyliminoxy radicals,[8] but can also recombine. This is particularly important with the benzyl Grignard reagent: dibenzyl (RR) is found in 66% yield. The relatively reactive Me and Ph radicals, and to a minor extent n-Bu radicals are, better than benzyl, capable of stripping hydrogen from the solvent (diethyl ether), to give the relatively stable α-ethoxy-ethyl radical. Just like di-t-butyliminoxy radicals combine with this radical on oxygen,[8] this is also true for the structurally related iminoxy radical **2**, and yields up to 25% can be obtained of 1-ethoxy-1-iminoxy ethane **6a**, an acetal-like oxime ether. The structure of **6a** is supported by its facile hydrolysis to oxime **3** with dilute hydrochloric acid.

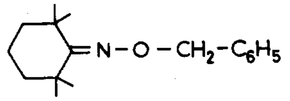


6a

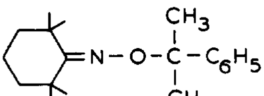
3

*Reactions of **1** with Grignard reagents in hydrocarbon solution*

In an attempt to determine the mechanism of the reaction of organometallic compounds with organic halides, Bryce-Smith[9] carried out some of the reactions in isopropylbenzene. Isolation of dicumyl (i.e. 2,3-dimethyl-2,3-diphenylbutane) was interpreted in terms of intermediate radicals which abstracted hydrogen from the solvent, followed by dimerisation of cumyl radicals. Bearing this in mind, reactions of methylmagnesium iodide with nitroso compound **1** were performed in isopropylbenzene, and for comparison also in toluene and benzene (R'H). The results of these reactions show that several products were obtained derived from cumyl and benzyl (not phenyl) radicals (see Table 1). These radicals do not dimerise exclusively (to R'R'), but can also combine with the relatively stable iminoxy radical **2** on oxygen, to give trace amounts of the oxime ethers **6b** and **6c**. That reactions in hydrocarbon solvents occur essentially as in ethereal solvents may be concluded from the formation of high yields of oxime **3** (80–85%), and trace amounts of nitrone **5**.



6b



6c

*Reactions of **1** with organolithium compounds*

From nitroso compound **1** in diethyl ether solution and two alkyllithium compounds, the same products have been obtained in essentially the same yields as with the corresponding Grignard reagents (Table 2). The similarity in the product distribution suggests a similarity in the reaction mechanism as well (see Scheme 2). In this connection it is of interest to note that during the reactions of **1** with the organolithium compounds, significant concentrations of iminoxy radical **2** could be detected in the mixture by the ESR technique.

Table 2. Yields (%) of products obtained from 1 and alkyllithium compounds RLi

R	3	4	5	6a
n-C_4H_9	82	10	—	trace
t-C_4H_9	82	14	—	—

EXPERIMENTAL

IR spectra were recorded on a Unicam SP200 or a Perkin-Elmer 257 spectrophotometer. ^1H NMR spectra were obtained with Varian A60 and HA100 instruments, using TMS as an internal standard ($\delta = 0$). Mass spectra were taken on a Varian MAT 711 mass spectrometer.

Compound **1** has been prepared by a previously described method.[10] Diethyl ether was purified according to Vogel.[11] Benzene and toluene were distilled from CaH_2 prior to use. Cumene was purified by shaking commercial material (Fluka AG) with portions of conc H_2SO_4 until the acid remained practically colourless, washing, drying, and then distilling it over CAH_2. Grignard reagents were prepared by known methods[12,13] with Grignard grade Mg turnings (E. Merck). Organolithium compounds were purchased from Fluka AG, and reactions with **1** were performed as with Grignard reagents.

Reaction procedure in diethyl ether solution

Generally, 0.5–1.0 M solns of the Grignard reagents RMgX were used, and 0.1 M solns of the nitroso compound (5 mmol), both in diethyl ether. After addition of the Grignard reagent and aqueous work-up according to the previously described procedure,[1] the product mixture was separated by chromatography over silica gel, using chloroform as the eluent. This furnished the products summarised in Table 1. An impure sample of a nitrone could only be obtained from the mixture of MeMgJ and **1**. It was isolated as a viscous colourless oil (10–15 mg) after elution with MeOH of the upper layer of the silica gel column. Hydrolysis readily afforded 2,2,6,6-tetramethylcyclohexanone. The similarity of the IR ($CHCl_3$) data (1243 (m), 1154 (m) and 1050 (s) cm^{-1}) with those of α,α-di-t-butyl-N-methyl nitrone[8] and the presence in the NMR ($CDCl_3$) spectrum of a separate and typical $CH_3N^{\oplus}$ singlet ($\delta = 3.84$), support the structuree of the N-methyl nitrone **5**.

Reaction procedure in hydrocarbon solution

The Me Grignard reagents were prepared from Mg and MeI in an anhydrous nitrogen atmosphere, using a minimum amount of diethyl ether as solvent (*ca* 3 ml for 40 mmol of Mg). This afforded upon intense heat development a gray slurry of the Grignard reagent, which was subsequently diluted with hydrocarbon R'H at room temp. By this procedure, 1.6 M reagents were obtained with a molar ratio R'H : ether of 7.5 : 1 with benzene, 6.5 : 1 with toluene, and 5 : 1 with cumene. These were added to 0.5 M solns of **1** in R'H. Hydrolytic work-up, evaporation of excess of R'H at diminished pressure, and chromatography, gave the products (see Table 1). From the reaction carried out in toluene, chromatography gave a colourless oil (75 mg), while oxime eluted later as a separate fraction. The oil contained dibenzyl and a trace of the oxime O-benzyl ether **6b**, as shown by glc (3 m, ϕ 10 mm, 20% SE 30/chromosorb S, 45–60 mesh, 150°) and comparison with authentic samples. The reaction carried out in cumene also gave first a colourless oil with chromatography, and three components were shown to be present. Separation by glc (140°) afforded subsequently 0.156 mmol of oxime ether **6c** as a colourless oil, 1.13 mmol of dicumyl as a white solid, and 65 mg of an unknown compound as a colourless oil. The identity of **6c** follows unambiguously from spectral data. IR ($CHCl_3$): 1600 (w), 1490 (m), 1380 (m), 1364 (m) and 1010 (s) cm^{-1}. NMR ($CDCl_3$): δ 1.10 (s, $(CH_3)_2)$; 1.38 (s, $(CH_3)_2)$, 1.54 (m, $(CH_2)_3)$, 1.64 (s, $(Me_2)CO)$, 7.35 (m, Ar). Consistent with the proposed structure is furthermore the mass spectrum (70 eV), that is very similar to that of other oxime ethers. The major fragmentation is a C–O bond fission:

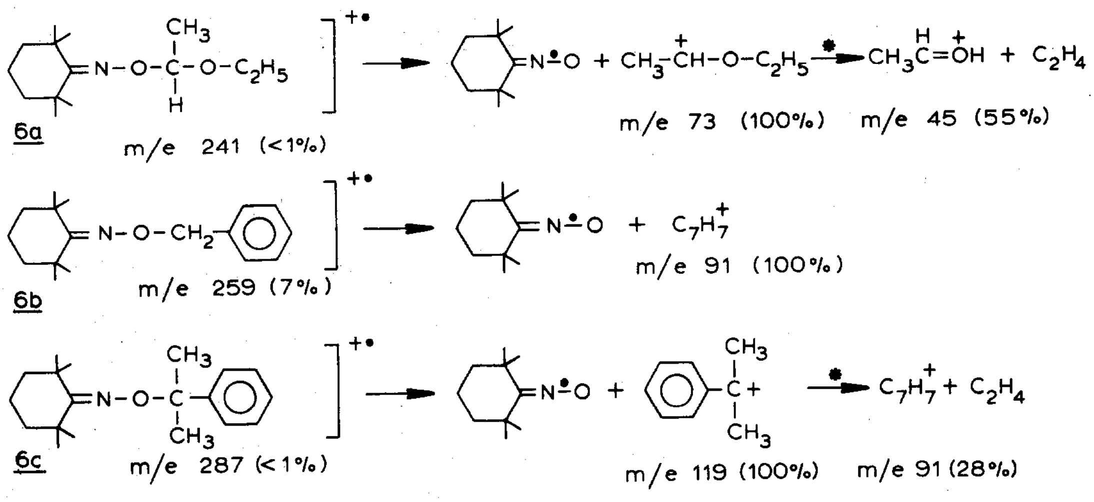
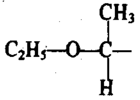


Table 3. Spectroscopic and analytical data of 2,2,6,6-tetramethylcyclohexanone oxime ethers **4** and **6a**

R–	IR (CHCl$_3$); cm^{-1}	NMR (CDCl$_3$); δ in ppm	Element analysis
n-C_4H_9–	1394, 1370, 1090–910	0.80 (t, CH_3, J = 6.5), 1.14 (s, $(CH_3)_2$), 1.24 (s, $(CH_3)_2$), 1.30–1.75 (m, CH_2, 10H), 3.93 (t, CH_2–O, J = 6)	$C_{14}H_{27}NO$ Calcd: C 74.66; H 12.00; N 6.22 Found: C 74.72; H 11.99; N 6.24
t-C_4H_9–	1385, 1361, 944	1.10 (s, $(CH_3)_2$), 1.17 (s, $(CH_3)_2$), 1.18 (s, $(CH_3)_3$), 1.46 (m, $(CH_2)_3$)	$C_{14}H_{27}NO$ Calcd: C 74.66; H 12.00; N 6.22 Found: C 74.73; H 12.16; N 6.27
$C_6H_5CH_2$–	1376, 1355, 1005, 910	1.10 (s, $(CH_3)_2$), 1.21 (s, $(CH_3)_2$), 1.47 (m, $(CH_2)_3$), 4.91 (s, CH_2–O), 7.22 (m, Ar)	$C_{17}H_{25}NO$ Calcd: C 78.76; H 9.65; N 5.40 Found: C 78.60; H 9.42; N 5.28
C_6H_5–	1390, 1370, 912	1.28 (s, $(CH_3)_2$), 1.38 (s, $(CH_3)_2$), 1.58 (m, $(CH_2)_3$), 7.18 (m, Ar)	$C_{16}H_{23}NO$ Calcd: C 78.32; H 9.45; N 5.71 Found: C 78.24; H 9.36; N 5.62
 $C_2H_5{-}O{-}\overset{CH_3}{\underset{H}{C}}{-}$	1384, 1365, 1150–1070, 950–910	1.07 (t, $C\underline{H}_3$–CH_2O, $J_{AX_3} = J_{BX_3} = 7$), 1.09 (s, $(CH_3)_2$), 1.20 (s, CH_3), 1.24 (s, CH_3), 1.25 (d, $C\underline{H}_3$–CHO, J = 5.5), 1.47 (m, $(CH_2)_3$), 3.43 (m, CH_3–$C\underline{H}_2O$, $J_{AX_3} = 7$, $J_{AB} = 10$, 1H), 3.71 (m, CH_3–CH_2O, $J_{BX_3} = 7$, $J_{AB} = 10$, 1H), 5.03 (q, CH_3–$C\underline{H}O$, J = 5.5)	$C_{14}H_{27}NO_2$ Calcd: C 69.71; H 11.20; N 5.81 Found: C 69.80, H 11.15; N 5.95

REFERENCES

[1] C. Schenk, M. L. Beekes and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas* submitted for publication.

[2] C. Schenk, M. L. Beekes, J. A. M. van der Drift and Th. J. de Boer, *Ibid.* submitted for publication.

[3] W. A. Nugent, F. Bertini and J. K. Kochi, *J. Am. Chem. Soc.* **96**, 4945 (1974).

[4] T. Holm and I. Crossland, *Acta Chem. Scand.* **25**, 59 (1971).

[5] M. Ōkubo, *Bull. Chem. Soc. Jap.* **48**, 1057, 1327, 2057 (1975).

[6] I. G. Lopp, J. D. Buhler and E. C. Ashby, *J. Am. Chem. Soc.* **97**, 4966 (1975).

[7] J. A. Villarreal and E. J. Grubbs, *J. Org. Chem.* **43**, 1896 (1978).

[8] C. Schenk and Th. J. de Boer, *Tetrahedron* **35**, 2119 (1979).

[9] D. Bryce-Smith, *J. Chem. Soc.* 1603 (1956).

[10] A. H. M. Kayen, K. de Boer and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas* **96**, 1 (1977).

[11] A. I. Vogel, *A Textbook of Practical Organic Chemistry*, p. 165. Longmans Green, London (1970).

[12] M. S. Kharash and O. Reinmuth, *Grignard Reactions of Non-metallic Substances*. Prentice-Hall, New York (1954).

[13] K. Nützel in Houben-Weyl, *Methoden der Organischen Chemie*. Vol. XIII/2a, pp. 47–529. Thieme Verlag, Stuttgart (1973).