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REACTION OF DI-T-BUTYLIMINOXY RADICALS WITH ORGANOMETALLIC COMPOUNDS

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Abstract—Reactions of the title iminoxy radical 1 with Grignard and organolithium reagents RM yield initially di-t-butyl ketoxime 2 (in salt form) together with the radical $R^{\cdot}$. This radical $R^{\cdot}$ can combine with unreacted iminoxy radical on oxygen to give the oxime ether 3. For steric reasons attack on nitrogen is difficult and therefore nitrone 6 is not formed, or in trace amounts only. The even more hindered attack on carbon is never observed, i.e. there is no formation of (intermediary) nitroso compounds. The relatively reactive methyl and phenyl radicals can abstract hydrogen from the solvent (diethyl ether). In this way α-ethoxyethyl radicals are formed, which can combine with the iminoxy radical on oxygen, yielding the acetal-like oxime ether 7.

Reactions of free radicals with organometallic compounds have been well documented.[1-3] During the last decade it has become apparent that many of such reactions involve—often extremely rapid—bimolecular homolytic substitution (S_H2) at the metallic center (eqn (1)).

$$Y^{\cdot} + MR_n \rightarrow YMR_{n-1} + R^{\cdot} \tag{1}$$

In the course of an investigation on reactions of organometallic compounds with nitroso compounds carrying an electronegative (i.e. Cl, Br, NO_2, AcO) substituent in the α-position, it was found that reactions are initiated by electron transfer from the organometallic to the nitroso compound,[4] and that iminoxy radicals are transient intermediates. This has prompted our interest in the interaction between such radicals and organometallics. As a model we have chosen the di-t-butyliminoxy radical 1, which has been prepared and isolated as such by Ingold.[5] In this paper we describe its reactions with various Grignard reagents and organolithium compounds. Despite the steric effects engendered by the bulky iminoxy model, some mechanistic conclusions can be presented.

RESULTS AND DISCUSSION

Reaction of di-t-butyliminoxy radicals with Grignard reagents. The di-t-butyliminoxy radicals 1 were conveniently prepared according to Ingold[5b] from the oxime by oxidation with Ag_2O. When a solution of a Grignard reagent RMgX is added slowly to an ice-cold ethereal solution of iminoxy radicals 1, the characteristic and dominant blue colour of the latter fades rapidly, while a white precipitate is formed in an exothermic reaction. The magnesium salt 2a, furnishing di-t-butyl ketoxime 2 upon hydrolysis, is the major product in all experiments (56–71%), and is accompanied by minor amounts of oxime ether 3 (13–31%). Somewhat surprisingly oxime ether was absent in the reaction of 1 with methylmagnesium iodide (Table 1). Formation of the two products (i.e. oxime and oxime ether) can *a priori* be rationalized with attack of the iminoxy radical at the metal center of the Grignard reagent RMgX (eqn (2)). This leads to the MgX salt of the oxime with simultaneous expulsion of the radical $R^{\cdot}$ (homolytic substitution). In a subsequent step the radical $R^{\cdot}$ can combine with another iminoxy radical 1, producing the oxime ether (eqn (3)). An analogous sequence of reaction steps has been suggested in the literature to explain product formation in reactions of relatively stable oxygen (i.e. nitroxyl[6] and aroxyl[7,8]) and nitrogen (i.e. tetrazinyl[9]) centered radicals with Grignard reagents.†

It is of interest to note that Ingold and Roberts have pointed out, that homolytic reactions which result in the net replacement of one radical by another, do not necessarily proceed by direct substitution.[1] The rate controlling step for the formation of the products may well involve some charge separation or even the transfer of an electron from the organometallic compound to the radical. Furthermore, it has been suggested that initial electron transfer will be favoured over direct substitution if the newly formed bond becomes progressively more ionic. One may expect such an electron transfer in particular with sterically hindered radicals, where bimolecular substitution is thwarted. Since the bonds which magnesium forms with carbon in organomagnesium compounds are usually regarded as being covalent and a new oxygen-metal bond is formed with more ionic character, we are inclined to consider it very likely that the crowded di-t-butyliminoxy radical accepts in first instance an electron from the Grignard reagent (eqn (2)), at least in reactions with organometallic derivatives which have good electron donor properties.[10]

The multident reactivity of iminoxy radicals. ESR spectra of iminoxy radicals are characterized by a large nitrogen splitting of usually more than 30 G, indicating that there is significant spin density on nitrogen in an orbital with considerable s character.[11] Calculations have indicated that in the iminoxy radical derived from dimethylglyoxime the unpaired spin density is almost equally divided between the oxygen and the nitrogen atom.[12] Ingold *et al.* determined spin densities in the di-1-adamantyliminoxy radical, and found that ρ_N is approximately 25%.[13]

Although no spin density on the central C atom of iminoxy radicals has been assumed, radical reactions can occur nevertheless via carbon, as was demonstrated with the formation of C–O dimers -head-to-tail- upon the slow

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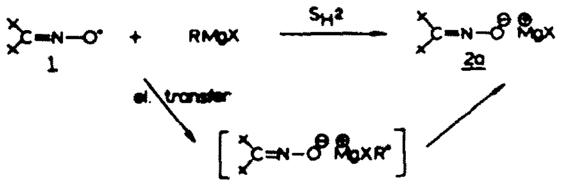
†An alternative S_H2 substitution with attack on carbon and formal expulsion of $MgX^{\cdot}$ has no precedence in the literature.[1-3]



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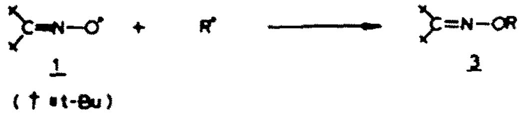
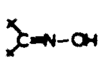
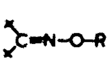
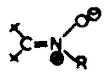
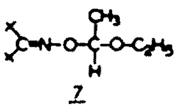


(3)

Table 1. Yields [a] (%) of products from the reaction of $(\text{t-Bu})_2\text{C=N}^{\cdot}\text{O}$ 1 with Grignard reagents RMgX and with organolithium compounds RLi.

RM		 2		 3		 6		 7	
R	M	MgX[b]	Li	MgX[b]	Li	MgX[b]	Li	MgX[b]	Li
CH_3		71	65	—	—	3	2	trace	trace
n-Bu		56	63	25	20	4	2	—	—
t-Bu		58	60	22	18	—	—	—	—
$C_6H_5CH_2$[c]		61	—[d]	31	—[d]	—	—[d]	—	—[d]
C_6H_5		66	54	13	10	—	—	15	15

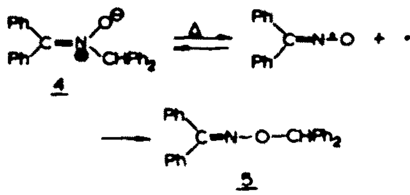
[a] Yields refer to isolated products and are based upon iminoxy radical 1.

[b] X is bromide except when R = CH_3, where it is iodide.

[c] The reaction with benzylmagnesium bromide gave furthermore 13% of dibenzyl.

[d] The reaction with benzyllithium was not performed.

decay of the sterically hindered di-iso-propyl- and di-t-butyliminoxy radicals.[14] The presence of spin density on nitrogen as well as on oxygen may be illustrated with the results obtained by Grubbs *et al.* on the thermal isomerization of α,α-diphenyl-N-benzhydryl nitrone 4 to the isomeric benzophenone O-benzhydryl oxime 5.[15,16] Convincing evidence (ESR, CIDNP, kinetics, nature of by-products) has been presented that the thermolysis proceeds via benzhydryl and diphenyliminoxy radicals. The amounts of mixed nitrone 4 and mixed oxime ether 5 obtained in a cross-over study employing 4 and its analogue deuterated in all para positions, indicate that benzhydryl radical combination at the oxygen atom of the benzophenone iminoxy radical is slightly favoured over combination at the nitrogen atom, whereas reaction at the central carbon atom, to give a tertiary nitroso compound, is presumably too slow to compete.[15a]



The consequence of the multident character of iminoxy radicals in the present case is that radicals R˙, formed upon reaction of di-t-butyliminoxy radicals 1 with Grignard reagents (eqn (2)), do not combine with unreacted 1 exclusively on oxygen to give oxime ether 3, but also on nitrogen to give α, α-di-t-butyl-N-R nitrone 6. Experimentally we find that nitrone 6 is always a minor component (up to 4%) because of severe steric hindrance caused by the two flanking t-Bu groups in the iminoxy radical (see Table 1 and Scheme 1). Thus, only the relatively small primary radicals such as Me and n-Bu seem to be capable of combining at nitrogen, leading to α,α-di-t-butyl-N-methyl and α,α-di-t-butyl-N-n-butyl nitrone respectively. As in the combination of diphenyliminoxy and benzhydryl radicals we have no indications for the third possibility: reaction on carbon.

The isolated nitrones were shown to be stable at room temperature and consequently they cannot be intermediates in the formation of oxime ether 3 (cf. 4→5). We suggest that this is also true for nitrones with R = t-Bu, $C_6H_5CH_2$ and C_6H_5. That these are not found in practice is therefore *not* due to ease of isomerization (to oxime ether), but to steric hindrance.

The N-methyl- and N-n-butyl-nitrones 6 could not be obtained in an analytically pure state, but spectroscopic properties fully support their formation. For instance the IR spectrum of the N-Me derivative shows a major absorption at 1155 cm^{-1}, which is characteristic for aliphatic ketonitrones.[17-19] The nitrone chromophore is responsible for an absorption maximum at 263 nm, in reasonable agreement with its position in electronic spectra of the few other known non-conjugated ketonitrones.[17-21] The easily interpreted NMR spectrum shows for the N-Me group a singlet with a chemical shift ($\delta = 3.86$) typical for its position near an electron deficient nitrogen center.[22] Furthermore, as a consequence of the non-symmetrically substituted C=N double bond the two t-Bu groups appear as two separate singlets (i.e. $\delta = 1.48$ and 1.52).

No systematic study has been made of the importance of radical combination (to RR) and/or disproportionation† under the reaction conditions. In the case of benzylmagnesium bromide we found dibenzyl to the extent of 13%. More reactive species than benzyl, like methyl and phenyl radicals are capable of abstracting hydrogen from the diethyl ether solvent. The resulting relatively stable α-ethoxyethyl radical can combine with the iminoxy radical on oxygen (*not* on nitrogen) to give 1-ethoxy-1-iminoxy ethane 7, an acetal-like oxime ether. Upon treatment with dilute hydrochloric acid, 7 is rapidly converted into di-t-butyl ketoxime (78%), thus supporting the proposed structure, because this facile hydrolysis to oxime is well-known for related systems.[23,24] As was established in a blank experiment, di-t-butyliminoxy radicals 1 are stable in diethyl ether solution under the reaction conditions. This rules out formation of oxime ether 7 via abstraction of hydrogen from the solvent by the iminoxy radical‡.

Reaction of di-t-butyliminoxy radicals with organolithium compounds

Organolithium compounds RLi give with di-t-butyliminoxy radicals 1 the same products in essentially the same yields as the corresponding Grignard reagents (Table 1). It is therefore reasonable to assume a similarity in the mechanism as well,[27] i.e. initial formation of the lithium salt **2b** of di-t-butyl ketoxime and radical R˙, which reacts further to give the other products as visualized in Scheme 1.

EXPERIMENTAL

IR spectra refer to $CHCl_3$ solns and were recorded on a Unicam SP200 or Perkin Elmer 257 spectrophotometer. ^1H NMR spectra were obtained with Varian A60, A60D, HA-100 and XL-100 instruments, using TMS as internal standard. Chemical shifts are given in ppm (δ scale). MS spectra were determined on an AEI MS-902 or a Varian MAT-711 instrument. Analyses by glc were performed on a Varian Aerograph 90P gas chromatograph, using a copper column (10 ft × 1/4 in.) packed with 20% SE 30 on Chromosorb S, 45–60 mesh at 150°.

Di-t-butyliminoxy radicals 1 were prepared in about 85% yield from the parent oxime 2 by oxidation with Ag_2O in benzene, as described earlier by Ingold.[30] Prior to use the radical was purified twice by distillation *in vacuo* by the bulb-to-bulb technique with the receiver in liquid N_2. Grignard reagents were obtained from commercial grade Grignard Mg turnings (E. Merck) and the appropriate organic halide in diethyl ether, using standard procedures.[28,29] The solns were allowed to settle and the reagent was carefully drawn from the clear top portion. Organolithium reagents were commercially available as 2M solns (Fluka AG).

Reaction of 1 with organometallic compounds

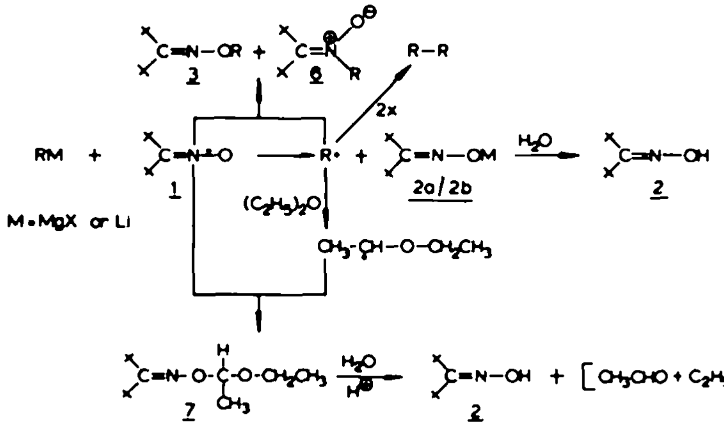
General procedure. A 1–2 M soln of the organometallic compound was added slowly to a 0.10–0.20 M soln of 1 in anhyd diethyl ether at 0° (under helium) until disappearance of the blue colour of the radical. Then the mixture was allowed to warm to room temp. and subsequently stirred for an additional 15 min. After addition of an excess of NH_4Cl aq and separation of the ether layer, the resultant water layer was repeatedly extracted with $CHCl_3$. Removal of the solvents from the combined extracts *in vacuo* after drying over $MgSO_4$, then gave the crude colourless to pale yellow product mixture.

Isolation of oxime ethers. The products were separated by preparative column chromatography on silica gel using $CHCl_3$ as the eluent. Oxime ethers 7 and 3 could be isolated successively as colourless oils, while 2 eluted later as a separate fraction and was obtained as a white solid. The oxime ethers isolated by this procedure all had a correct element composition with the exception of the benzyl derivative, which had to be separated from dibenzyl with glc. The spectroscopic data summarized in Table 2 unequivocally support the proposed structures. Their mass spectra show usually hardly any parent peak; as an example the main fragments in the 70 eV spectrum of 7 are given: M 229 (< 1%), *m/e* 73 ($[CH_3CHOCH_2CH_3]^+$, 100%), *m/e* 57 ($(CH_3)_3C^+$, 28%), *m/e* 45 ($[CH_3CHOH]^+$, 61%).

Isolation of nitrones. As a consequence of their extremely small R_F value the nitrones remained on the column, and could only be obtained (as pale yellow viscous oils) after repeated elution of the upper layer of the silica gel column with dry MeOH, when the other products had been eluted with $CHCl_3$.

α,α-Di-t-butyl-N-methyl nitrone. IR ($CHCl_3$), ν_{max} 3000 (s), 1490 (m), 1395 (m), 1375 (m), 1265 (s) 1155 (s) and 1055 (s) cm^{-1}. UV (CH_3CN), λ_{max} 263 nm. NMR ($CDCl_3$) δ 1.48 (s, $(CH_3)_3C$, 9H), 1.52 (s, $(CH_3)_3C$, (9H), 3.86 (s, CH_3–N, 3H). MS (70 eV), M 171 (17%).

α,α-Di-t-butyl-N-n-butyl nitrone. IR ($CHCl_3$), ν_{max} 3000 (s), 1490 (s), 1395 (w), 1370 (m), 1260 (w), 1155 (m) and 1055 (m) cm^{-1}. UV (CH_3CN), λ_{max} 258 nm. NMR ($CDCl_3$), δ 0.97 (t,



Scheme 1. General scheme for product formation in reactions of di-t-butyliminoxy radical 1 with Grignard and organolithium compounds RM.

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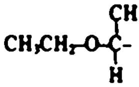
†Di-t-butyl ketoxime 2 can, in principle, also be formed by disproportionation of the radical pair consisting of iminoxy radical 1 and R˙, in case the latter contains β-hydrogens (i.e. R = t-Bu).

‡The O–H bond dissociation energy[25] in di-t-butyl ketoxime 2 is approximately 81 kcal.mole^{-1}. The ease of hydrogen abstraction by iminoxy radical 1 from a suitable donor may be illustrated with its rapid and exothermal reaction with 1,4-cyclohexadiene (D[C–H] = 81 kcal.mole^{-1}),[26] to give stoichiometric amounts of oxime 2 and benzene.

CH_3-CH_2, J = 7, 3H), 1.3 (broad m, CH_2, 2H), 1.49 (s, $(CH_3)_3C$, 9H), 1.53 (s, $(CH_3)_3C$, 9H), 1.97 (broad m, CH_2, 2H), 3.98 (t, CH_2-N, J = 7, 2H). MS (70 eV), M 213 (15%).

Determination of dibenzyl. In a helium atmosphere a soln of benzylmagnesium bromide was prepared from commercial grade Grignard Mg turnings (120 mmol) and benzyl bromide (40 mmol) in 40 ml of dry (Na) diethyl ether, freed from peroxides and deaerated with helium.[30] Excess of Mg metal was employed in order to minimize the amount of unreacted halide. The clear top portion of the Grignard reagent was transferred in a stream of dry helium into a narrow (ϕ 10 mm) calibrated dropping funnel and used for reaction with 1 (3.7 mmol). After completion, an aliquot of the Grignard reagent was hydrolysed simultaneously with the mixture, and after a standard work-up the amount of dibenzyl in both residues was determined by means of glc, using *trans*-stilbene as an internal standard. Formation of 0.47 mmol of dibenzyl could be established by this prodedure.

Table 2. Spectroscopic and analytical data of di-t-butyl ketoxime ethers $(t\text{-}Bu)_2C{=}N\text{-}OR$ 3 and 7

R-	IR ($CHCl_3$); ν_{max} in cm^{-1}	NMR (CCl_4); δ in ppm	Element analysis
n-C_4H_9	1390, 1365(t-Bu) 1090–890 (C–O)	0.94(t, CH_3–CH_2, J = 7, 3H) 1.19(s, $CH_3)_3C$, 9H) 1.30(s, $(CH_3)_3C$, 9H) 1.55(m, CH_2–CH_2, 4H) 3.94(t, CH_2–O, J = 6, 2H)	$C_{13}H_{27}NO$ (213.3) Calc.: C 73.24, H 12.67, N 6.57 Found: C 73.05, H 12.63, N 6.49
t-C_4H_9	1390, 1360(t-Bu) 940 (C–O)	1.21(s, $(CH_3)_3C$, 9H) 1.24(s, $(CH_3)_3C$–O, 9H) 1.31(s, $(CH_3)_3C$, 9H)	$C_{13}H_{27}NO$ (213.3) Calc.: C 73.24, H 12.67, N 6.57 Found: C 73.24, H 12.64, N 6.66
$C_6H_5CH_2$-	1400, 1372(t-Bu) 1018, 1000, 910(C–O)	1.18(s, $(CH_3)_3C$, 9H) 1.31(s, $(CH_3)_3C$, 9H) 5.00(s, CH_2–O, 2H) 7.29(s, C_6H_5, 5H)	$C_{16}H_{25}NO$ (247.3) Calc.: C 77.73, H 10.12, N 5.66 Found: C 77.65, H 10.14, N 5.57
C_6H_5-	1395, 1370(t-Bu) 910 (C–O)	1.52(s, $(CH_3)_3$, 9H) 1.44(s, $(CH_3)_3$, 9H) 7.11(m, C_6H_5, 5H)	$C_{15}H_{23}NO$ (233.3) Calc.: C 77.25, H 9.87, N 6.00 Found: C 77.20, H 10.01, N 5.91
 $CH_3CH_2\text{-}O\text{-}CH(CH_3)\text{-}$	1400, 1374(t-Bu) 1115, 940, 920(C–O)	1.08(t, CH_3–CH_AH_B–O, $J_{AX_3} = J_{BX_3} = 7$, 3H) 1.17(s, $(CH_3)_3C$, 9H) 1.27(d, CH_3CHO_2, J = 5.5, 3H) 1.30(s, $(CH_3)_3C$, 9H) 3.47(double q, CH_3–CH_AH_B–O, J_{AB} = 10, J_{AX_3} = 7, 1H) 3.74(double q, CH_3–CH_AH_B–O, J_{AB} = 10, J_{BX_3} = 7, 1H) 5.09(q, CH_3–CH–O_2, J = 5.5, 1H)	$C_{13}H_{27}NO_2$ (229.3) Calc.: C 68.12, H 11.79, N 6.11 Found: C 68.93, H 12.06, N 6.07

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