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Grignard Reaction of Peroxides Containing Neighboring Nitrogen Atom

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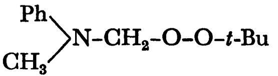
Synopsis. The substituent effect on the reaction of bis(2-aryl-1,2,3,4-tetrahydro-1-isoquinolyl) peroxide with PhMgBr as well as the product obtained on the reaction of 2-*p*-tolyl-1,2,3,4-tetrahydro-1-isoquinolyl *t*-butyl peroxide with PhMgBr were interpreted in terms of the coordination of the neighboring nitrogen atom to Mg atom.

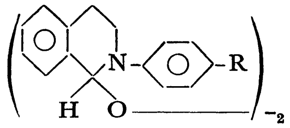
In the previous report on the Grignard reaction of neighboring oxygen- and/or nitrogen-containing peroxides,[1] the effect of coordination of the hetero atoms to the Mg atom was emphasized. However, it was doubted that the high reactivity of the previously studied *N*-methylanilinomethyl *t*-butyl peroxide (**1**) was due to its sterically unhindered and flexible molecular structure but not due to the effect of the neighboring nitrogen atom. This consideration led us to examine the Grignard reaction of peroxides having sterically crowded and rigid structures. The results of the study on the substituent effect of bis (2-aryl-1,2,3,4-tetrahydro-1-isoquinolyl) peroxides (**2**)[2] and the product obtained from 2-*p*-tolyl-1,2,3,4-tetrahydro-1-isoquinolyl *t*-butyl peroxide (**3**)[3] will be reported in this paper. These peroxides were selected from several nitrogen-containing ones reported by Rieche and his coworkers[4] on the basis of the molecular structure appropriate for the present purpose: the peroxides 1) having "neighboring" nitrogen atom and 2) having neither >NH nor –OOH groups were selected.

The reaction of **2a**, **2b**, and **2c** with one and a half molar equivalents of PhMgBr in THF at 10 °C under nitrogen was followed by iodometry. The results thus obtained are shown in Fig. 1 (a), which indicate that the higher electron-density on the nitrogen atom facilitates its coordination to the Mg atom and thus accelerates the decomposition.

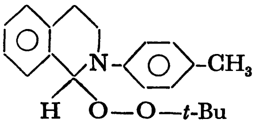


$(Ph)(CH_3)N\text{-}CH_2\text{-}O\text{-}O\text{-}t\text{-}Bu$

(1)



(2a): $R=CH_3$
(2b): $R=H$
(2c): $R=Cl$



(3)

The similar plots obtained from the reaction of **3** are shown in Fig. 1 (b). When 1.30 molar equivalents of PhMgBr were used (Fig. 1 (b)-i), 36.4% of **3** remained even after stirring for 48 h at 15 °C. On the other hand, when 2.50 molar equivalents of the reagent were used (Fig. 1 (b)-ii), almost all (92.7%) of **3** was consumed after 24 h. As shown in Fig. 1 (b)-ii, the high decomposition velocity at the initial stage is clearly distinguished from the low velocity at the later stage. On the basis of the previous discussion given for the similar feature observed in the Grignard reaction of aroyl peroxides,[5] the low velocity at the later stage is ascribable to the aggregation of the unreacted peroxide with the reaction products: the aggregation could retard the attack of the Grignard species.[5]

The crude oily product obtained in a 91% yield after the treatment of **3** with three molar equivalents of PhMgBr for 24 h followed by the usual work-up, crystallizes on standing overnight. Purification by column chromatography (silica gel, petroleum benzine) and recrystallization from petroleum ether afforded colorless crystals, mp 76—77.5 °C. The product gave no ν_{OH} absorption band in its IR spectrum, and a large amount of phenol was detected by GLC after the treatment with dilute hydrochloric acid. The structure (**4**) can be given on the basis of NMR data (CCl_4): δ=6.58—7.15 (13H, m, aromatic), 5.20 (1H, s, >CH), 3.48 (2H, m, >N–CH_2–CH_2–), 2.82 (2H, t, –CH_2–Ar), and 2.09 (3H, s, CH_3–Ar). The chemical shift of the benzylic methine proton appeared in the remarkably lower field may be reasonable, because the methine carbon has both the neighboring oxygen and

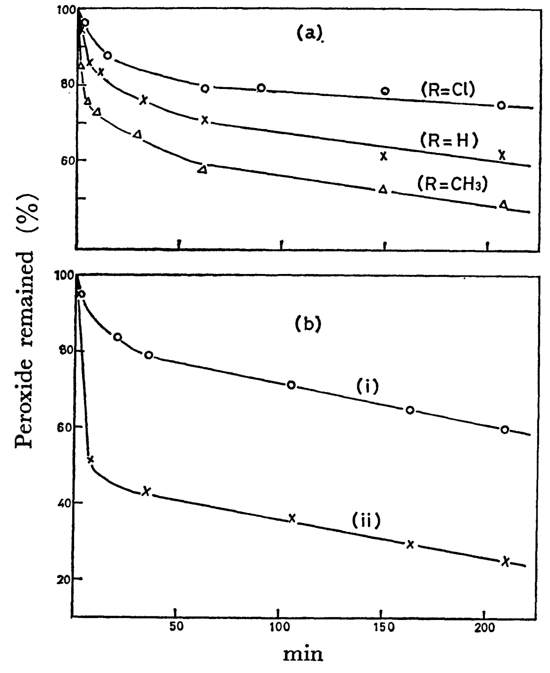
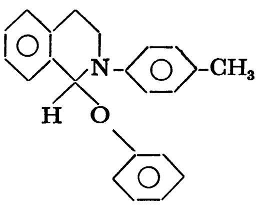


Fig. 1. Decomposition velocity of peroxides **2a**, **2b**, **2c**, and **3** on the reaction with PhMgBr.
(a) Peroxides **2a**, **2b**, **2c**: 0.0023 mol; PhMgBr: 0.0035 mol. At 10 °C; in 50 ml THF.
(b)-i) Peroxide **3**: 0.0064 mol; PhMgBr: 0.00835 mol.
ii) Peroxide **3**: 0.0096 mol; PhMgBr: 0.024 mol. At 15 °C; in 59 ml THF.


(4)

nitrogen atoms. If being stood for a few days, the product **4** decomposed gradually and gave pale yellow polymeric material insoluble in CCl_4 and benzene. Contrary to the products of the reaction of **1**,[1] the phenyl group of the Grignard reagent combines with the α-oxygen atom which is nearer to the nitrogen atom of **3**. This result is explicable if it is considered that the rigid structure of **3** requires the attack by the dimeric or trimeric aggregate of the reagent as illustrated in Fig. 2. The coordination of the nitrogen atom to Mg atom could induce some positive charge on the α-oxygen atom. This effect allows the exclusive attack of the anionic phenyl group of another Grignard molecule. This suggestion is compatible with the discussion given above for the substituent effect on the decomposition velocity.

Though the peroxides **2** and **3** are less reactive than the less crowded **1** which can be decomposed by the equimolar PhMgBr,[1] the results obtained are interpreted in terms of coordination of the neighboring nitrogen atom. In addition, the peroxides **2** and **3** were found to be titrated in the simplest manner by the use of KI and acetic acid.[6] The previously proposed correlation between the reactivity of peroxides toward alkali halides and that toward Grignard reagent[1] is thus confirmed.

Experimental

Materials. The peroxides **2**[2] and **3**[3] were prepared by the reported methods from the corresponding 2-aryl-3,4-dihydroisoquinolinium bromides[7] which were synthesized from isochroman. Tetrahydrofuran was dried over sodium wire, distilled, and stored on sodium wire.

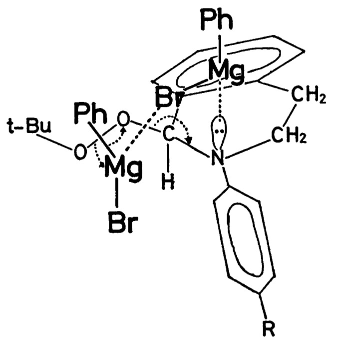


Fig. 2. Illustration of the reaction of peroxide **3** with the dimeric aggregate of PhMgBr.

Procedures. The THF solution (25 ml) of PhMgBr (0.0289 mol) was prepared under nitrogen. The peroxide **3** (0.00965 mol) dissolved in THF (40 ml) was added at once. The mixture was stirred for 24 h, and quenched by saturated aqueous NH_4Cl. The crude product obtained was purified in the manner described in the text.

The plots given in Fig. 1 were obtained by taking out the 1 ml portions of the respective reaction mixtures at definite time intervals followed by iodometric titration by the reported method.[6]

Elemental analysis of **4**: Found: C, 83.92; H, 6.72; N, 4.36; O, 5.02%. Calcd for $C_{22}H_{21}NO$: C, 83.80; H, 6.67; N, 4.44; O, 5.08%.

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