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Deoxygenation of 1,4-Epoxides by Grignard Reagents

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Abstract: Freshly prepared Grignard reagents in refluxing THF smoothly deoxygenate benzo-fused 1,4-dihydro-1,4-epoxides to afford the corresponding naphthalenes and anthracenes in good yields.
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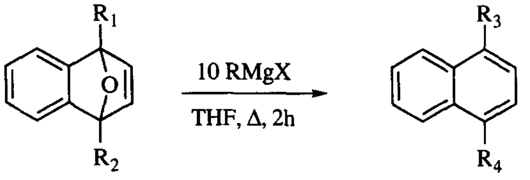
We report here that 1,4-dihydro-1,4-epoxyacenes are smoothly deoxygenated[1] in the presence of 10 equivalents of commercially available Grignard reagents in refluxing THF (Scheme 1). This method expands the library of conventional methods[2] by offering a milder alternative.



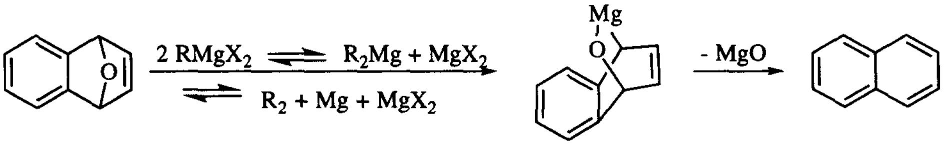
1, 4: $R_1, R_2, R_3, R_4 = H$

2, 5: $R_1, R_3 = H$; $R_2, R_4 = Me$

3, 6: $R_1, R_2, R_3, R_4 = Me$

Scheme 1

In this Letter, we also provide evidence for the mechanism of this unexpected transformation, which we believe may be driven by the formation of the Wurtz[3] coupling product from the Grignard reagent. This shifts the Schlenk[4] equilibrium towards a highly activated Mg° / MgX_2 Rieke-like[5] complex which we believe results in insertion[5,6] into the C-O bond of the epoxide, and subsequent loss of MgO with concomitant aromatization (Scheme 2). This mode of activity is different from that of Grignard reagents with 1,2-epoxides[7] or with non-benzo-fused 1,4-endoxides[8].



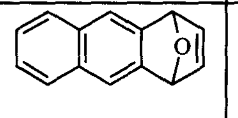
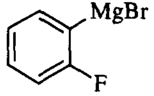
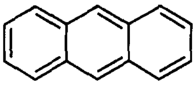
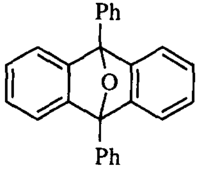
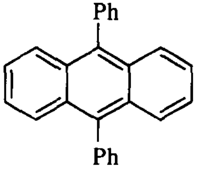
Scheme 2

Our initial investigation stemmed from attempts to repeat the known reaction[9] of *o*-bromofluorobenzene, magnesium and furans, which yield 1,4-dihydro-1,4-epoxynaphthalenes through a benzyne intermediate. Previous reactions run in our laboratory had resulted in only modest yields of 1,4-dihydro-1,4-

epoxynaphthalenes. In an effort to raise the yield, excess Mg was employed to ensure insertion into the C-Br bond.

It was subsequently evident from both the NMR and GC/MS spectra of the crude reaction product that naphthalene had been produced under these reaction conditions. Apparently, we failed to observe this fact previously because distillation and rigorous drying of the epoxide had volatilized the naphthalene! Optimization of reaction conditions and isolation of the aromatic products served to further establish the applicability of this transformation, as shown in Table 1. Steric limitations were examined by varying both the substituents on the endoxide and the nature of the Grignard reagent.

Table 1

ENTRY	SUBSTRATE	GRIGNARD	PRODUCT	YIELD
1	**1**	10 eq. PhMgBr	**4**	100% [b]
2	**1**	10 eq. *i*PrMgBr	**4**	59% [a]
3	**1**	10 eq. *t*BuMgBr	**4**	40% [a]
4	**2**	10 eq. PhMgBr	**5**	75% [a]
5	**2**	10 eq. *i*PrMgBr	**5**	60% [b]
6	**2**	8 eq. *t*BuMgBr	**5**	65% [b]
7	**3**	10 eq. *i*PrMgBr	**6**	73% [a]
8	 **7**	 1 eq. **8**	 **9**	9% [a]
9	**7**	10 eq. *i*PrMgBr	**9**	42% [a]
10	 **10**	10 eq. *i*PrMgBr	 **11**	52% [a]

[a] Isolated yield. [b] Yield determined by GC/MS.

Initially, we believed that benzyne might be responsible for this extrusion by direct attack on the oxygen. This was disproved by generation of benzyne from anthranilic acid[10] in the presence of epoxynaphthalene, which failed to produce any naphthalene. To investigate whether the initally formed Grignard reagent might be responsible for this transformation, we refluxed a variety of Grignard reagents in the presence of different endoxides in THF. When using 2 to 5 equivalents of a Grignard reagent, incomplete reaction was observed. Ten equivalents (and in one case 8) of the Grignard drove the reaction to completion (Table 2). These experiments showed that the Grignard reagent was the species responsible for this extrusion, but the mechanism remained unclear.

Early in our investigations, we attempted reactions of epoxynaphthalene with elemental Mg and/or Mg halides, but no reaction was observed, even after several days of reflux. This result was deceptive - the Mg° or Mg salts simply were insufficiently active to afford any of the transformed product.

Table 2

ENTRY	SUBSTRATE	GRIGNARD	PRODUCT	YIELD
1	**1**	1 eq. PhMgBr	**N.R.**	---
2	**1**	2 eq. **8**	**4**	27% [b]
3	**1**	10 eq. **8**	**4**	79% [a]

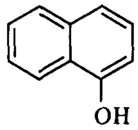
[a] Isolated yield. [b] Yield determined by GC/MS.

It was postulated that a small amount of the naphthalene formed may have been acting as an electron transfer agent[11] to accelerate the reaction. This was disproved by refluxing epoxynapthalene in the presence of a catalytic amount of 2,3-dimethylnaphthalene and Mg. No formation of naphthalene could be detected from this experiment. However, we were able to extrude oxygen with 2 equivalents of SmI_2,[12] yielding naphthalene in 78% isolated yield.

In one experiment biphenyl was detected in the reaction of epoxynapthalene with 10 equivalents of PhMgBr and this provided some insight into the mechanism. Re-investigation of reactions with other Grignard reagents indicated Wurtz products as significant by-products which were lost during product purification, or undetectable by our initial methods of analysis (TLC, GC/MS). Additionally, we found traces of 2-fluorobiphenyl and 2-bromobiphenyl in the GC/MS spectra of the initial experiment. This could only have resulted from benzyne attack on the Grignard reagent, giving R-Mg-R followed by reductive elimination of R-R, thus generating elemental (Rieke-like) Mg°. Interestingly, only highly reactive Mg has been known to insert into C-F bonds[5]. Only this insertion could lead to the production of 2-bromobiphenyl. Attempts to repeat this work by generation of Grignard reagents with Rieke[5] Mg° were not successful, and this remains puzzling.

Thus, under these conditions, we believe that a highly activated mixture of Mg° and Mg halides is formed, which may be responsible for both insertion into the C-O bond of the endoxide and loss of MgO with aromatization at refluxing THF temperatures. The loss of metal oxides is a precedented route of oxygen extrusion in heteroaryne furan reactions[13]. Thermal oxygen extrusions[14] have only been seen at much higher temperatures. No evidence has been found for the generation of a substituted naphthol under our conditions in refluxing THF. However, as shown in Table 3, we have found that MeMgBr in one case gives substituted naphthol, **12**, in addition to the aromatic product. In the case of the more sterically hindered dimethyl epoxynaphthalene, no reaction was observed at 45°C. We believe aromatization to be the driving force behind this transformation. The MeMgBr examples serve to expose the boundaries of the reaction conditions necessary for this unexpected reaction of benzo-fused endoxides with excess Grignard reagents.

Table 3

ENTRY	SUBSTRATE	GRIGNARD	PRODUCT	YIELD
1	**1**	10 eq. MeMgBr	**4 + 1**	40% , 60% [a]
2	**1**	10 eq. MeMgBr	 **4** + **12**	77% , 22% [b]
3	**2**	10 eq. MeMgBr	**5**	73% [c]
4	**3**	10 eq. MeMgBr	NR	b

[a] THF/Et_2O, 45 °C, 2 h., by GC/MS. [b] THF/Et_2O, 45 °C, 18 h., by GC/MS. [c] Isolated yield.

References and Notes:

1. Typical reaction conditions: The substrate (1 mmol or less) was charged to a flame dried, N_2 flushed 25 mL 3 neck flask, and dissolved in THF with magnetic stirring. This solution was brought to reflux, at which time 10 equivalents of the Grignard reagent were added dropwise. In most cases the reaction was complete within 2 hours. The reaction was quenched with aqueous ammonium chloride, the product extracted into ethyl acetate, dried over sodium sulfate, filtered, concentrated and purified by flash chromatography.
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