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Radical Ion Probes. 11. Reaction of 1,1-Dimethyl-5,7-di-*t*-butylspiro[2.5]octa-4,7-dien-6-one with 5-Hexenyl Magnesium Bromide

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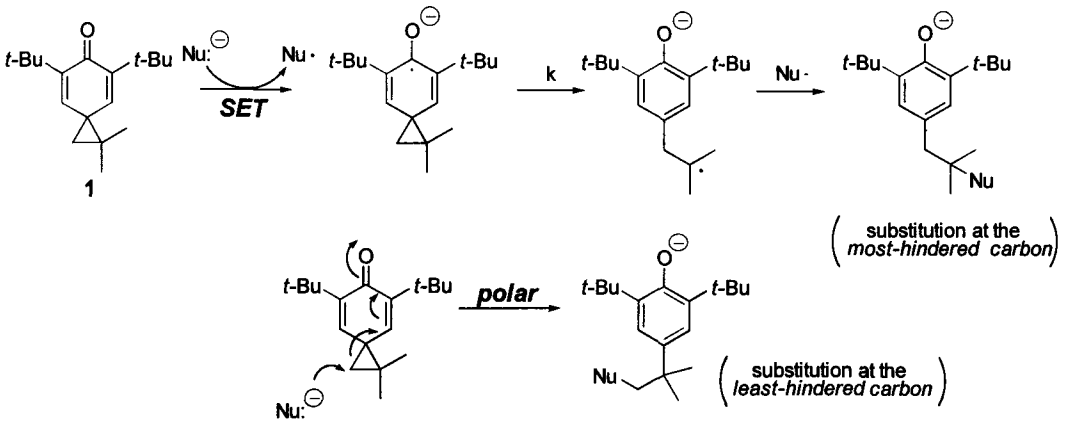
Abstract: In an ongoing effort to establish 1,1-dimethyl-5,7-di-*t*-butylspiro[2.5]octa-4,7-dien-6-one (1) as a mechanistic probe for the detection of single electron transfer (SET), the reaction of 1 with 5-hexenyl magnesium bromide was examined in the hopes of observing cyclization of any intermediate 5-hexenyl radicals to cyclopentylcarbinyl radicals. A polar process dominated the reaction, but in the less prevalent SET process, *the 5-hexenyl → cyclopentylcarbinyl rearrangement was extensive, indicative* of freely diffusing paramagnetic intermediates.

INTRODUCTION

There has been an ongoing effort[1] within this research group to develop and establish 1,1-dimethyl-5,7-di-*t*-butylspiro[2.5]octa-4,7-dien-6-one (**1**) as a mechanistic probe for single electron transfer (SET) in reactions of nucleophiles with conjugated carbonyls. This molecule functions as a rearrangement probe wherein the regiochemistry of spirocyclic ring opening is indicative of either a polar or SET process (Scheme 1). If a single electron transfer process occurs then the resultant ketyl anion radical rapidly ($k > 10^7\ s^{-1}$)[1a,c] rearranges, preferentially to the tertiary distonic radical. Radical coupling then leads to apparent nucleophilic substitution at the more-hindered carbon. On the other hand, if the reaction proceeds through a polar conjugate addition process, substitution at the less-hindered carbon occurs. The term "regiodifferentiation" has been coined by this group to describe the action of such a probe.



Scheme 1. "Regiodifferention" of SET vs. Polar Pathways

The mechanism of the reaction of conjugated carbonyl compounds with Grignard reagents has been extensively studied over the past 35 years. Although the finer mechanistic points are still under significant debate, it is now well established that SET does or at least can play a significant role in this reaction.[2] For this reason, Grignard reagents were chosen as likely candidates with which to test the title compound as an SET probe. Preliminary studies with methyl magnesium bromide have already been reported and are summarized in Scheme 2 below.[1d,3]

Both regiochemistries of addition were observed, with more-hindered product **2** dominating, as anticipated for a SET process. Three non-addition products are also found. Alkene **6** can arise from either

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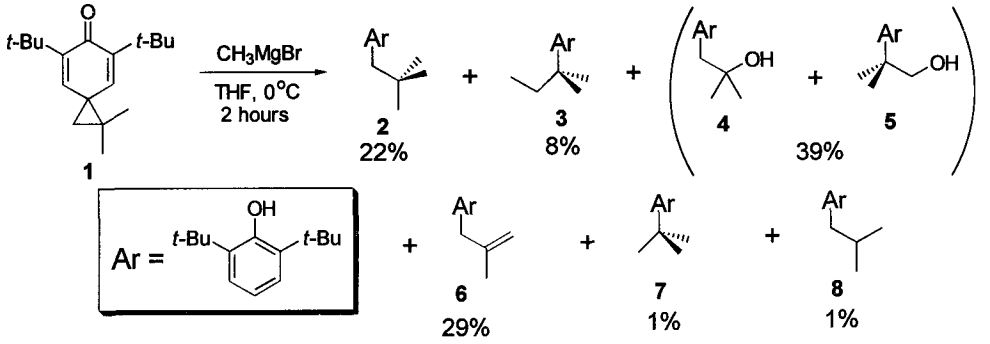
radical disproportionation or from a competing polar elimination (E_2) process. Products **7** and **8** are the disproportionation partners to **6**, but can also occur *via* hydrogen atom abstraction from solvent. Since products **7** and **8** are present in very small amounts relative to product **6**, an E_2 process likely accounts for most of the alkene **6** produced. Products **4** and **5** arise from hydrolysis of unreacted starting material under the mildly acidic workup conditions, and have generally been reported simply as unreacted starting material.

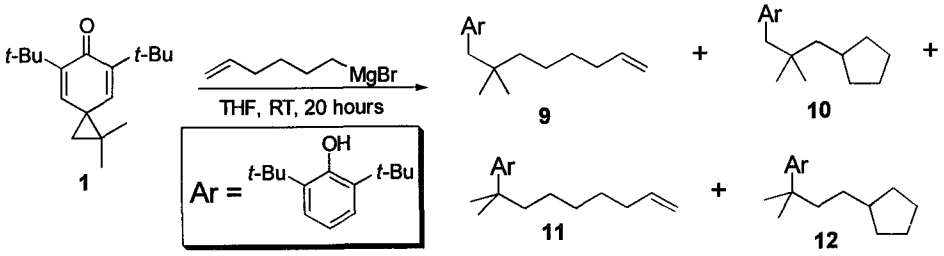


Scheme 2. Methyl Grignard Reaction

Thus, encouraged by these results indicating dominant SET and the ability of **1** to detect such processes, further confirmation was sought. The 5-hexenyl → cyclopentylcarbinyl rearrangement has been extensively studied and occurs (essentially irreversibly)[4] with a rate constant on the order of 10^5 s^{-1} at room temperature.[5] Thus it was hoped that independent evidence for alkyl radical intermediates in the reaction of a Grignard reagent with the title compound could be obtained by using 5-hexenyl magnesium bromide.

Results and Discussion

The reaction of the title compound with 5-hexenyl magnesium bromide yielded four addition products, (**9-12**, Scheme 3), as well as the three non-addition products (**6-8**), and unreacted starting material.



Scheme 3. Addition Products of 5-Hexenyl Magnesium Bromide Reaction.

The addition products were easily separated from the other products by Kugelrohr distillation under vacuum, but the individual addition products proved inseparable by distillation, preparative HPLC, and preparative thin layer chromatography. The peaks were resolvable by gas chromatography, but preparative GC was not feasible. Thus structural assignments were made by a combination of techniques. GC-MS indicated a mass-to-charge ratio of $m/z = 344$ for all four species, confirming that they were the addition products. Further analysis of the mass spectral fragmentations allowed discernment between most and least

hindered products (*m/z* = 247 corresponding to 3° benzylic fragment present in the less-substituted products, *m/z* = 219 corresponding to 1° benzylic fragment present in the more-substituted product. **11,12** → $ArC(CH_3)_2^+$ *m/z* = 247; **9,10** → $ArCH_2^+$ *m/z* = 219). It was further possible to differentiate the 5-hexenyl moiety from the cyclopentylcarbinyl moiety by bromination of the terminal olefin. This allowed total, elucidation of the product structures. Further confirmation was available via GC, GC-MS, and ^1H NMR analysis of a mixture of from an independent reaction of the title compound (**1**) with cyclopentylcarbinyl magnesium bromide. Product yields for five runs are summarized in Table 1.

Table 1. Reaction of **1** with 5-Hexenyl Magnesium Bromide, Product Yields

[1], M*	t, hrs	**9**	**10**	**11**	**12**	**SM****	**6**	**7**	**8**
0.150	44	6%	6%	59%	1%	9%	15%	1%	2%
0.122	20	6%	9%	26%	2%	18%	24%	1%	14%
0.066	44	5%	4%	43%	1%	21%	22%	2%	2%
0.027	44	2%	4%	32%	1%	35%	23%	1%	2%
0.017	45	0.6%	0.5%	5.3%	0.1%	57%	35%	0.3	0.9%

* [**1**] *reported, but this is also equal to the initial concentration of the Grignard reagent, as equimolar quantities were used.*
** "SM" *indicates unreacted starting material, quantitated as hydrolysis products 4 and 5.*

For unexplained reasons, a polar process clearly dominated. The major product was the polar addition product wherein the unrearranged 5-hexenyl moiety is attached to the less-hindered carbon (**11**). A slower but competitive SET process also appears to be occurring, as moderate amounts of the two more-hindered products (**9** and **10**) were formed in roughly equal amounts. Thus, the enhanced yield of cyclization observed in **9/10** (*vs.* **11/12**) demonstrates that when SET is occurring, the 5-hexenyl → cyclopentylcarbinyl rearrangement occurs at a competitive rate. Very small amounts of the cyclopentylcarbinyl moiety at the less-hindered carbon were also observed (**12**). However this could be accounted for either by the much slower anionic rearrangement of 5-hexenyl anion to cyclopentylcarbinyl anion,[6] or by the partial cyclization of the 5-hexenyl moiety during the course of Grignard reagent formation.[7] To study this phenomenon, parallel experiments using the same Grignard solution at the same dilution in the absence of **1** were performed at the same time, for the same duration, and at the same temperature as each of the above experimental runs. These parallel runs were quenched alongside the experimental runs and 1-hexene and methylcyclopentane were quantitated *via* GC to assess the amount of "parallel cyclization" (*i.e.*, the amount of rearrangement of the hexenyl moiety not resulting from a SET pathway in the product forming step.) In all cases this amount of "parallel cyclization" was roughly equivalent to the extent of cyclization at the least-hindered carbon. Thus in the polar process no enhancement of cyclization is observed, whereas in the SET process a very dramatic increase in cyclization is observed (Table 2).

Table 2. Reaction of **1** with 5-Hexenyl Magnesium Bromide, Selectivity and Rearrangement Data

[1], M*	t, hrs	most- to least-hindered ratio	Extent of parallel anionic cyclization	extent of cyclization in less-hindered products	extent of cyclization in more- hindered products
0.150	44	0.2 : 1	< 1%	2.3%	52%
0.122	20	0.5 : 1	~ 10%	7.1%	60%
0.066	44	0.2 : 1	< 1%	2.3%	48%
0.027	44	0.2 : 1	< 1%	2.5%	65%
0.017	45	0.2 : 1	2.1%	2.6%	49%

* [**1**] *reported, but this is also equal to the initial concentration of the Grignard reagent, as equimolar quantities were used.*

One final point is also worthy of note. In addition to the parallel quench experiments described, a small portion of Grignard was quenched and evaluated prior to the experimental runs. This "initial extent of cyclization" was in all cases very close to the total extent of "parallel cyclization" so the majority of the non-product determining 5-hexenyl rearrangement appears to occur during Grignard formation and not *via* an anionic pathway during the course of the parallel experiments.

Conclusions

The reaction of **1** with 5-hexenyl magnesium bromide occurs *via* competing polar and SET pathways. For the polar pathway, substitution occurs at the least-hindered carbon, and little rearrangement of the 5-hexenyl moiety is observed; the small amount of cyclization observed arises during formation of the Grignard reagent, rather than from the intermediacy of a neutral free radical. For the SET pathway, however, substitution occurs at the most-hindered carbon (because of ring opening of $\mathbf{1}^{\bullet-}$ to the more stable 3° distonic radical anion), and extensive cyclization of the of the 5-hexenyl radical is observed. Because the 5-hexenyl → cyclopentylcarbinyl radical rearrangement is known to occur in the microsecond time regime,[5] and solvent cage lifetimes are only on the order of picoseconds,[8] this result provides direct evidence for freely diffusing paramagnetic intermediates in the case where SET is occurring. Thus these experiments provide excellent support for the arguments of Walling[9] that SET-addition reactions between Grignard reagents and conjugated carbonyl-containing compounds involves freely diffusing radicals.

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