ORGANIC LETTERS

2000
Vol. 2, No. 15
2303−2306

Formation of Grignard Reagents from Aryl Halides: Effective Radical Probes Hint at a Nonparticipation of Dianions in the Mechanism

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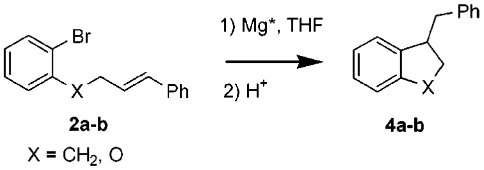
Received May 17, 2000

ABSTRACT

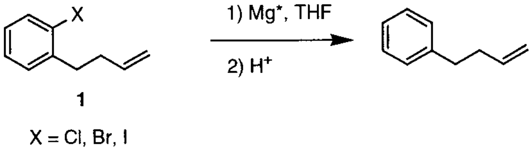


We have prepared highly efficient radical probes 2a–b involving the hex-5-enyl rearrangement. The reaction of 2a–b with active magnesium leads to the cyclized products 4a–b, providing a direct evidence of radical intermediates during the formation of aryl Grignard reagents. The variations of yields for cyclized products 4a–b as a function of structural modifications in 2a–b suggest that the intervention of dianions is not necessary to explain the observed results.

Since the discovery of Grignard reagents, several mechanistic studies have aimed at deciphering the succession of elementary molecular events between substrates plus reagents and products.[1] In the case of alkyl halides, the presence of radical intermediates was clearly established from the CIDNP effect,[2] intra- and intermolecular trapping,[3] although uncertainty remains about their exclusive participation versus a competition polar-SET process.[4] With aryl halides the situation is less clear. The participation of radical intermediates was only suggested from the formation of dimerization products and the quenching of intermediates by the solvent.[5] We report in this paper the definitive evidence of radical intermediates using fast intramolecular radical probes.

In a recent paper,[6] we described the behavior of 2-(3-butenyl)phenyl halides **1** with active Mg* in THF. Despite the fast radical cyclization ($k_{\text{cycl}} = 5.3 \times 10^8$ s^{-1}, 30 °C),[7] only the uncyclized Grignard reagent was formed (Scheme 1). In contrast, using hex-5-enyl alkyl halides ($k_{\text{cycl}} = 10^5$ s^{-1}), about 10% of radicals were trapped.[8] A question therefore arises: are any radical intermediates involved in Grignard formation from aryl halides?

Scheme 1



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[1] (a) Garst, J. F.; Ungváry, F. In *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, 2000; Chapter 7, pp 185−275. (b) van Klink, G. P. M. Doctoral thesis, Free University, Amsterdam, 1998. (c) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286−293. (d) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95−97.

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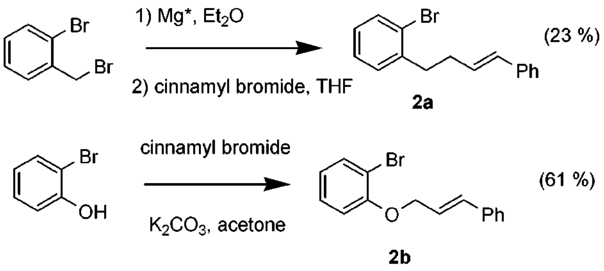
10.1021/ol006071k CCC: $19.00

Garst independently attacked this problem with metallic Mg.[9] In agreement with our results, he observed from **1** in THF 98% of uncylized Grignard reagent and less than 1.5% of cyclized product. In Et_2O, up to 25% of cyclized Grignard reagent was formed. According to his D-model calculation, which rationalizes quite satisfactorily the experimental results observed with alkyl halides, 78% of cyclized Grignard reagent should have been found in THF. Garst discards the possibility of adsorbed radicals at the Mg surface, as well as a very fast geminate reaction between the radical and an active site. He proposed that within this D-model, if aryl radicals exist, their lifetime could be about 10^{-11} s or less, "a possible but unlikely value". He concludes that even if aromatic σ radicals could be formed, a major dianionic pathway takes place. Therefore Garst proposed that the main difference between alkyl and aryl halide is the possibility for the second to reach the dianion stage,[10] whereas the first one is known to undergo a highly dissociative electron transfer.[11] This author pointed out that radical isomerization (including racemization) during Grignard formation varies, for a given halide, in the order alkyl > cyclopropyl > vinyl > aryl. Less radical isomerization would correspond with an increasing participation of the dianionic pathway.[9] Garst noticed that this trend is consistent with the partial knowledge presently accumulated about the relative stabilities of RX radical anions in the series alkyl, cyclopropyl, vinyl, aryl. One may note, however, that electrochemical experiments[12] suggest very short lifetime for the radical anion of aryl halides bearing the type of substituent (alkyl) present in the presently studied radical clocks. Exceptionally strong salt effects[10,13] would have to be invoked to extend these very short lifetimes.

To trap efficiently aryl radicals with short lifetimes, we decided to effect structural changes in the radical probes, aiming at an increase of the cyclization rate of **1**.

The incorporation of a group stabilizing the rearranged radical (like a phenyl group) should accelerate at least 10-fold the cyclization rate.[14] Another possibility consists of replacing the benzylic methylene group by an oxygen atom. This structural change increases the cyclization rate by 1 order of magnitude.[15] Scheme 2 outlines the synthesis of radical probes **2a** and **2b**.

Scheme 2



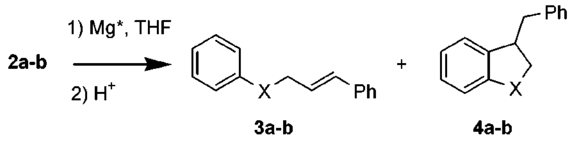
Our results with metal vapor synthesized Mg*[16] are summarized in Table 1. Radical probes **2a** and **2b** lead to the formation of cyclized products **4a** and **4b** (Scheme 3). Each experiment was performed twice, and reproducible yields of products **3a−b** and **4a−b** were obtained.

Table 1. Reaction of Radical Probes **2a** and **2b** with Active Mg* in THF ([RX] = 0.03−0.04 M)

entry	RX	Mg*/RX	*T*	reactn time	yield (%)[a]	RMgX (%)[b]	rel yield (%)[c] **3**	rel yield (%)[c] **4**
1	**2a**	4.7	rt	1 h	95	91	87	13
2	**2b**	1.3	−80 °C	1 h	61[d]	41[e]	41 (45)	59 (55)
3	**2b**	1.3	rt	30 min	92	72[e]	26 (38)	74 (62)

[a] Yields including phenols for reaction of **2b**. Estimated from NMR and GC analysis using anthracene as internal standard. [b] Titration with 1,10-phenanthroline using 1-BuOH/xylene as titrant.[18] [c] Determined by NMR or GC analysis. See the text for the corrected yield given in parentheses. [d] The conversion was 70% according to NMR. [e] Probably underestimated.

Scheme 3



Products **3a−b** and **4a−b**, described in the literature,[17] were identified from GC−MS and NMR analysis of the crude product. Authentic samples of **4a−b** were prepared by reacting **2a−b** with Bu_3SnH in toluene. The presence of

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(14) (a) Curran, D. P. *Synthesis* **1988**, 417−439. (b) The rate of intramolecular cyclization of the 5-decyn-1-yl radical is approximately 40 times slower than the cyclization of the 6-phenyl-5-hexyn-1-yl. Peters, D. G. In *Organic Electrochemistry*; Lund, H.; Baizer, M. M., Eds.; M. Dekker: New York, 1991; Chapter 8, p 372. (c) Newcomb, M.; Choi, S.-Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225−1231.

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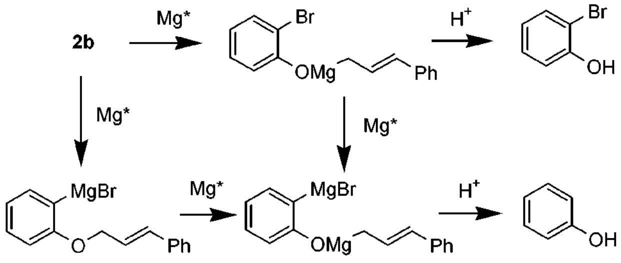
Grignard reagents was established using titration with *o*-phenanthroline.[18] Quantitative GC analyses were based on the effective carbon number concept[19] and injections of model mixtures.

The amount of trapped radicals increases with the cyclization rate of radical probes. Bartak et al. have shown that the *o*-(3-butenyl)phenyl carbanion cyclizes at room temperature.[20] In contrast, previous results suggest that the Grignard reagent formed from *o*-(3-butenyl)phenyl halides do not cyclize.[6,9] We have checked the stability of the Grignard reagent formed from **2a**. The ratio **3a**/**4a** is identical for reaction times of 1 or 24 h. Grignard reactions of indanylmethyl bromide and iodide did not yield products of ring opening in THF or Et_2O.[9] So the same behavior is expected for indanylbenzyl halide, and an equilibrium between cyclized and linear Grignard reagents is unlikely. At −78 °C the *o*-(3-butenyl)phenyl carbanion does not cyclize, in contrast with the corresponding radical.[20] We have, on our side, prepared by reaction of **2b** with BuLi, the lithium anion of **2b**. This anion did not yield **4b** after 1 h at −80 °C. In contrast, reaction of **2b** with Mg* at −80 °C (Table 1, entry 2) shows the participation of radicals during the Grignard formation.

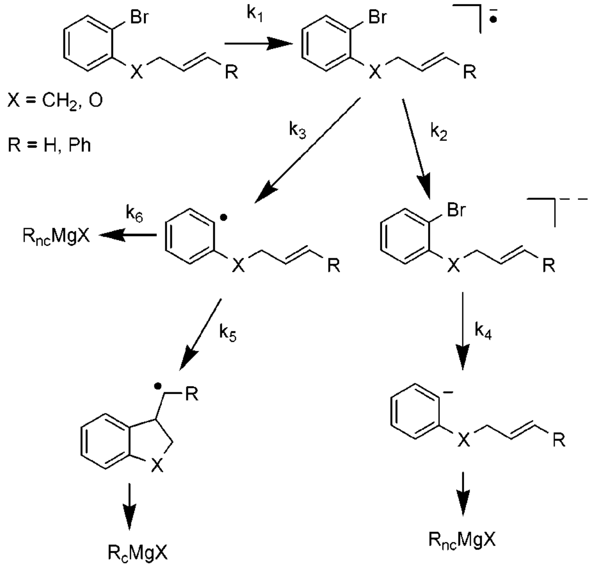
Reaction of 1-phenyl-3-phenoxyprop-1-ene with Mg leads to 3-phenylprop-2-enylmagnesium phenoxide[21] and follow-up byproducts after the quenching. Phenol and bromophenol form about 15% of the reaction mixture (Scheme 4) when **2b** is reacted with Mg* (from GC analysis and co-injection). A corrected yield of **3b** and **4b** is given in Table 1 assuming that all of the formed phenol comes from the Grignard product precursor of **3b**.

Scheme 4



Scheme 5 puts in perspective the dianion mechanism with respect to the radical one. In the dianion mechanism the amount of cyclized product depends on the relative values of k_2 and k_3. In the radical mechanism this amount would be regulated by the relative values of k_5 and k_6.

Scheme 5



The discussion of the set of experimental results seeks to answer the following question: could the structural modifications brought about in the radical probe modify the k_2, k_3 or the k_5, k_6 couple in a direction consistent with the observed facts? Replacing the CH_2 in **2a** by an oxygen should increase k_5 about 10-fold[15] (Scheme 5); the overall increase would be even greater when a phenyl substitutes the exo double bond. Such an increase converges with experimental results (Table 1). This structural modification is, however, not totally discriminating for the radical versus dianion model. Indeed the presence of an alkoxy substituent on the halide radical anion is expected to decrease k_2 and increase k_3,[22] also in agreement with the experimental data in Table 1.

On the other hand, the substitution of the exo double bond by a phenyl group should increase the rate of cyclization k_5 at least 10-fold,[14] in agreement with the greater amount of cyclized RMgX observed for **2a**. Introduction of a phenyl group in substrates **2a** and **2b** could create new sites of reduction. So the first SET could occur at the phenyl conjugated site, as in the reduction of 1-halo-1-methyl-2,2-diphenylcyclopropane with alkali naphthalenide.[10] These could induce more likely a dianion intermediate, therefore favoring the linear Grignard reagent. The opposite is observed (Table 1).

The most probable explanation for our results is that the formed aryl radicals have a very short lifetime and that our radical probes **2a** and **2b** are efficient enough to trap them.

There are several alternatives to the radical anion−dianion hypothesis. Some situate the crossroad of selectivity cyclized-

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(22) Electrochemical experiments suggest that the rate of cleavage of unsubstituted bromobenzene radical anion is already higher than 10^{10} s^{-1} in CH_3CN (counterion NEt_4^+); see: Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Hall, F.; Savéant, J.-M. *J. Am. Chem. Soc.* **1980**, *102*, 3806−3813.

uncyclized at the level of the radical itself. The elementary steps competing with the formed radical cyclization could be (a) reduction of the radical to a carbanion according to Bickelhaupt's proposition,[23] (b) reaction of the radical with •MgX (either in solution or still at the magnesium solid surface), and (c) reaction with Mg^0 (bulk metallic magnesium).[24]

At this point our results do not seem to support the radical anion−dianion hypothesis (Garst, or Walborsky's A-models[25]) but do not allow us to distinguish between the precited possibilities. Further work is in progress to solve this problem.

Supporting Information Available: Experimental procedures for preparation of new compounds **2a−b** including ^{1}H and ^{13}C NMR data and elemental analysis. General procedure for preparation of Grignard reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

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[25] See ref 9, pp 61−66.