



Radical intermediates in the Zn-promoted Barbier-type alkylation of diphenyl diselenide in aqueous medium

José Ayron Lira dos Anjos^{a,*}, Lothar Wilhelm Bieber^b

^a Centro Acadêmico do Agreste, Universidade Federal de Pernambuco, Caruaru PE 55002-970, Brazil

^b Departamento de Química Fundamental, Universidade Federal de Pernambuco, Recife PE 50670-901, Brazil

ARTICLE INFO

Article history:

Received 25 July 2012

Revised 13 September 2012

Accepted 14 September 2012

Available online 23 September 2012

Keywords:

Barbier reaction

Radical clocks

Diphenyl diselenide

Aqueous medium

ABSTRACT

The zinc promoted Barbier-type reaction of alkyl halides and diphenyl diselenide in aqueous medium leads to high yields of mixed selenides even in acidic medium. Especially the efficient formation of *t*-butylphenylselenide cannot be explained by nucleophilic substitution and raises the question of an alternative reaction mechanism. Three suitable halide precursors of 'radical clocks' of increasing rate of unimolecular rearrangement were used in order to evidence possible radical intermediates. Only the fastest one, halomethyl cyclopropane led to linear, rearranged, mixed selenides in amounts increasing from the chloride to bromide and iodide as leaving group. The results indicate a nucleophilic substitution as the most important mechanism in the formation of mixed selenides competing with an alternative, radical based process. The latter becomes exclusive in the case of tertiary alkyl halides.

© 2012 Elsevier Ltd. All rights reserved.

Introduction

Barbier-type reactions in aqueous medium have attracted growing interest in recent years.¹ The metal-promoted one-pot addition of allylic,² benzylic³ and propargylic halides⁴ to carbonyl compounds has shown comparable or even better results than traditional methods using Li or Mg reagents under anhydrous conditions. Saturated halides⁵ and α -haloesters⁶ have also been reacted successfully. On the other hand, different electrophilic substrates such as carboxylic esters and anhydrides,⁷ nitriles,⁸ oximes,⁹ imines,¹⁰ and iminium ions¹¹ have shown interesting reactivities. Even nitrobenzene¹² and diphenyl diselenide,⁵ rather unusual electrophiles in organometallic reactions, have been alkylated in preparative yields in protic or aqueous medium. Especially the zinc promoted preparation of alkyl phenyl selenides⁵ has proved its general scope and usefulness for almost all types of organic halides. The success of this extremely simple and 'green' procedure even under neutral or weakly acidic conditions for most primary and secondary halides and the surprising formation of *t*-alkyl phenylselenides motivated the present mechanistic study.

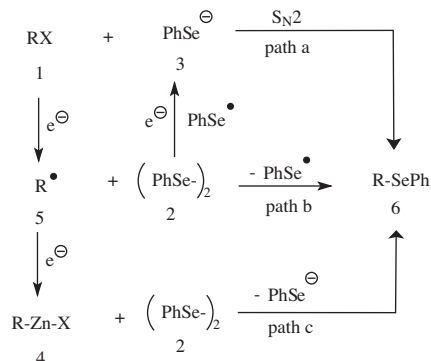
As can be seen in Scheme 1, the simultaneous action of metallic zinc on two reducible reagents, halide (**1**) and diphenyl diselenide (**2**), opens at least three main pathways to the final product.

Path **a** represents an S_N2 reaction between **1** and phenylselenide anion **3** produced by reduction of diselenide **2**. On the other extreme, the halide **1** is reduced by two electrons to an organozinc

intermediate which acts as a nucleophile on **2** (path **c**). The intermediate pathway **b** starts with a single electron transfer to **1** generating the radical **5** which effects a homolytic substitution on **2** giving the mixed selenides **6**.

The possible participation of path **a** was first investigated by comparison of the typical 'in situ' Barbier-type procedure with a metal free S_N2 reaction where sodium borohydride reduces selectively **2**. Four different halides, iodoethane **7**, **2-iodobutane 8**, 2-bromo- and 2-iodo-2-methylpropane **9** (**a,b**) were used as representative primary, secondary and tertiary halides.

In both procedures **2** was dissolved in acetonitrile and an aqueous solution of different alkalinity was added at room temperature: pH 14 (KOH), pH 7 (phosphate buffer) and pH 4 (NaH_2PO_4). In procedure A, the halide was added under stirring



Scheme 1.

* Corresponding author.

E-mail address: ayronanjos@gmail.com (J.A.L. dos Anjos).

followed immediately by excess zinc in one portion. In procedure B, an excess of sodium borohydride was added first decolorizing the yellow reaction mixture to selenol or selenolate in a few minutes of stirring, and then the halide was introduced at once.

Results and discussion

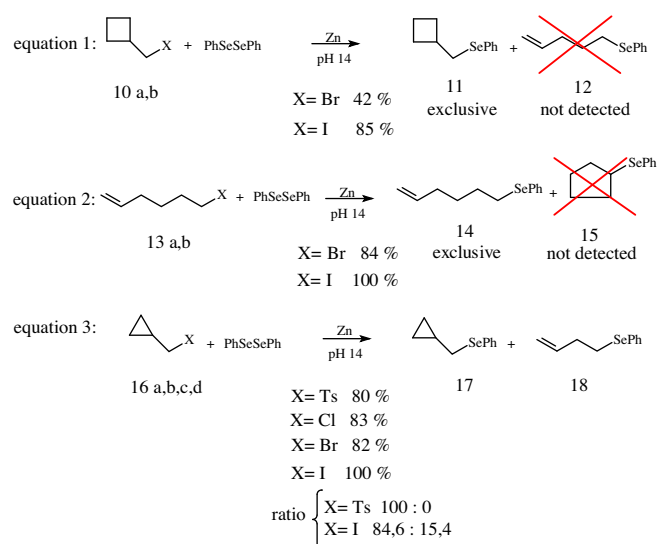
At pH 14, ethyl iodide gave identical high yields by both procedures (Table 1, entry 1). Under neutral conditions, procedure B (S_N2) produced still quantitative transformation, whereas Barbier-type conditions reduced the yield to half (Table 1, entry 2). In acidic medium both procedures had very low efficiency (Table 1, entry 3). At all three pH values, procedure B gave equal or better results than procedure A, indicating that nucleophilic substitution is the most important pathway in the absence of zinc. Similar trends were observed for 2-iodobutane **8** (Table 1, entries 4 and 5) except at pH 4 where procedure A produced a surprising yield of 62% (Table 1, entry 6). Even less expected was a 31% yield with *t*-butyl bromide **9a** in procedure A which could be increased to 100% when only 0.025 mmol of diselenide were used (10-fold excess of halide) (Table 1, entries 7 and 8). By contrast, procedure B gave a very modest yield of 9% in the normal stoichiometry and complete failure to produce products in high excess of **1**. Very similar results were observed when *t*-butyl iodide **9b** was used under the same conditions (Table 1, entries 9 and 10). The very low yields or the complete failure in procedure B is in good agreement with the general failure of tertiary halides in nucleophilic displacement reactions.

By contrast, the results obtained with procedure A are incompatible with an S_N2 mechanism because the better leaving group iodide gives lower yields (Table 1, entries 7 and 9) and decrease of the concentration of **1**, the precursor of the possible nucleophile, increases the yield of **6**. Also an S_N1 mechanism, the only generally accepted for tertiary halides and independent of the nucleophile concentration, cannot explain the unusual high yield produced exclusively by procedure A.

In view of the incompatibility of pathway **a** in Scheme 1 at least with the behaviour of the tertiary halides, the pathways **b** and **c** were considered. Both alternatives have in common the radical intermediate R \cdot produced by a single electron transfer to the

halide. Radical intermediates produced by halides on metal surfaces have been evidenced directly by EPR spectroscopy in anhydrous medium.¹³ However the observation of electronic resonance would be an excellent proof for radicals in any reaction not only in the formation of **6**.

Another indirect method for the study of radical reactions is the use of suitable precursors of radicals designed to undergo rapid, unimolecular rearrangements to a more stable radical. There is a great number of such 'radical clocks' of known rearrangement rates which allow deducing the reaction rate of the radical consuming step by analysis of the isomer ratio in the final product.¹⁴ We used halide precursors of three of these 'radical clocks' of different rate constants in the aqueous Barbier-type reaction with diphenyl diselenide.



The first halides investigated were bromo- and iodomethyl cyclobutane **10** (**a**, **b**) (equation 1). In basic solution the iodo compound **10b** gave yields comparable to ethyl iodide, whereas **10a** was significantly less reactive (equation 1). In all cases, the cyclic, unrearranged selenide **11** was the only product as evidenced by GC/MS and NMR-analysis, no trace of the linear product **12** could be detected.

6-Bromo and 6-iodo-1-hexene (**13a, b**) showed good reactivity even in acidic medium and nearly quantitative transformation under basic conditions (equation 2). Once more, the unrearranged, linear selenide **14** was the only product observed in all reactions excluding completely the formation of **15**. These results allow two alternative conclusions: either there is no radical intermediate or its rearrangement is much slower than the coupling reaction.

In a last attempt, three halomethylcyclopropanes (**16a–c**) were examined. The possible radical derived from these precursors is expected to rearrange to the homoallylic radical at a rate 4 and 2 orders more rapid than those derived from **10** and **13**, respectively. This system, finally, produced small quantities of the rearranged, linear product **18** for all three halides, ranging from 15,4% for X=I to 0.3% for X=Cl (equation 3; Table 2, entries 1–3).

Table 1
Reaction of diphenyl diselenide and organic halide in acetonitrile/aqueous solution using the procedures A and B

Entry	RX	pH	Yield (%)		Special conditions
			A ^a	B ^b	
1	EtI	14	93	93	—
2	EtI	7	44	100	—
3	EtI	4	15	22	—
4	<i>s</i> -But-I	14	64	80	—
5	<i>s</i> -But-I	7	45	62	—
6	<i>s</i> -But-I	4	62	53	—
7	<i>t</i> -But-Br	14	31	9	—
8	<i>t</i> -But-Br	14	100	0	0.025 mmol (PhSe-)₂
9	<i>t</i> -But-I	14	21	9	—
10	<i>t</i> -But-I	14	100	0	0.025 mmol (PhSe-)₂

^a To 1 mL of an aqueous solution of pH indicated in Table 1, was first added, under vigorous stirring, a solution of 0.125 mmol of diphenyl diselenide (2) and 0,5 mmol of organic halide (1) in 0.5 mL of acetonitrile, and then was added in one pot dust zinc. After 5 min the reaction mixture was hydrolyzed by 10 mL of HCl 2 M and extracted with 1 mL of a solution of CCl₄/anisole.

^b To 0.25 mL of a solution of 0.125 mmol of **2** in acetonitrile was first added, under vigorous stirring, 0.5 mmol of sodium borohydride and then was added 1 mL of an aqueous solution of pH indicated in Table 1. After a few minutes of stirring, when the yellow reaction mixture became colourless a solution of 0.5 mmol of **1** in 0.25 mL of acetonitrile was introduced. After 5 min the reaction mixture was hydrolyzed by 10 mL of HCl 2 M and extracted with 1 mL of a solution of CCl₄/anisole.

Table 2
Reaction of cyclopropylmethyl reagents with diphenyl diselenide using the procedure A in acetonitrile/alkaline aqueous solution

Entry	RX = 16	pH	Yield (%) 17 + 18	Ratio 17:18
1	Cl-CH ₂ -cPr	14	83	99,7:0,3
2	Br-CH ₂ -cPr	14	82	98,8:1,2
3	I-CH ₂ -cPr	14	100	84,6:15,4
4	Ts-CH ₂ -cPr	14	80	100:0

These results show unambiguously that radical intermediates are involved at least in part in the reaction of alkyl halides with diphenyl diselenide promoted by zinc in aqueous basic medium.

The rearrangement increases with the polarizability of the leaving groups as can be expected for a single electron transfer process and the electron affinity also supports this interpretation. Further confirmation brought a control experiment with the corresponding tosylate **16d**, a leaving group with no electron acceptor properties, which led to exclusive formation of the cyclic, unrearranged product **17** in high yield (Table 2, entry 4).

Conclusion

Summarizing all the experiments described here we can conclude that most primary and secondary halides showed a behaviour very similar to an S_N2 mechanism (Scheme 1 path a).

In contrast, tertiary butyl halides gave surprisingly high yields of mixed selenides, incompatible with an S_N2 or S_N1 mechanism. An alternative mechanism via alkyl radicals (Scheme 1, path b) seems to be responsible for the totality of the formation of *t*-butyl-phenyl selenide and for part of the product derived from **16**, especially when iodide was the leaving group.

Substantial contribution of an organozinc intermediate **4** (Scheme 1, path c) can be rejected, because the formation of such organometallic species is known to proceed under partial (**10** and **13**) or complete (**16**) rearrangement at room temperature.¹⁵ Future investigations will be directed to a more detailed elucidation of this new mechanism examining the experimental conditions which influence the rearrangement.

Acknowledgments

We gratefully acknowledge the support from CNPq and FACEPE.

References and notes

1. (a) Blomberg, C. *The Barbier Reaction and Related One-Step Process*; Springer-Verlag: Berlin, 1993; (b) Li, C.-J. *Tetrahedron* **1996**, 52, 5643; (c) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: NY, 1997.
2. Jaworsky, W. J. *Russ. Phys.-Chem. Soc.* **1908**, 40, 702. *Chem. Zetralblatt* **1908**, II, 1412.
3. Ila, H.; Junjappa, H.; Barun, O. J. *Organomet. Chem.* **2001**, 624, 34.
4. (a) Bieber, L. W.; Silva, M. F.; Costa, R. C.; Silva, L. O. S. *Tetrahedron Lett.* **1998**, 39, 3655; (b) Bieber, L. W.; Storch, E. C.; Malvestiti, I.; Silva, M. F. *Tetrahedron* **1998**, 39, 9393.
5. Bieber, L. W.; de Sá, A. C. P.; Menezes, P. H.; Gonçalves, S. M. C. *Tetrahedron Lett.* **2001**, 42, 4597.
6. Bieber, L. W.; Malvestiti, I.; Storch, E. C. *J. Org. Chem.* **1997**, 62, 9061.
7. Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* **1989**, 30, 1581.
8. Estevam, I. H. S.; Bieber, L. W.; Silva, M. F. *Tetrahedron Lett.* **2003**, 44, 7601.
9. Kopylovich, M. N.; Haukka, M.; Kirillov, A. M.; Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem.-Eur. J.* **2006**, 13, 786.
10. Ortega, M.; Rodríguez, M. A.; Campos, P. J. *Tetrahedron* **2004**, 60, 6475.
11. (a) Estevam, I. H. S.; Bieber, L. W. *Tetrahedron Lett.* **2003**, 44, 667; (b) Silva, R. A.; Estevam, I. H. S.; Bieber, L. W. *Tetrahedron Lett.* **2007**, 48, 7680.
12. Bieber, L. W.; Costa, R. C.; Silva, M. F. *Tetrahedron Lett.* **2000**, 41, 4827.
13. (a) Ingold, K. U.; Griller, D. *Acc. Chem. Res.* **1980**, 13, 317; (b) Newcomb, M. *Tetrahedron* **1993**, 49, 1151.
14. (a) Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 173; (b) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970; (c) Chatgialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, 103, 7739; (d) Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, 52, 3509; (e) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, 36, 3509; (f) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, 111, 275.
15. Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, 121, 4155.