STUDIES ON THE COHALOGENATION OF LIMONENE WITH *N*-HALOSUCCINIMIDES AND *N*-HALOSACCHARINS IN WATER. A CHEMO- AND STEREOSELETIVE PREPARATION OF (1*S*, 2*R*, 4*R*)-1,2-EPOXYLIMONENE

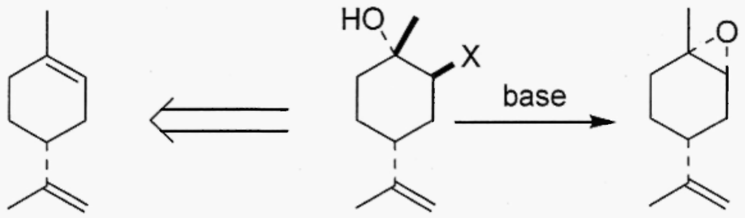
Marcio C.S. de Mattos* and Rafael Berrelho Bernini
Instituto de Química, Departamento de Química Orgânica, Universidade Federal do Rio de Janeiro, Caixa Postal 68545, 21945-970, Rio de Janeiro, Brazil.
E-mail: mmattos@iq.ufrj.br

Abstract: Cohalogenation of (*R*)-limonene with *N*-halosuccinimides and *N*-halosaccharins followed by base treatment (Na_2CO_3 / EtOH / H_2O) of the resulting halohydrins produced stereoselectively (1*S*, 2*R*, 4*R*)-1,2-epoxylimonene (*trans*-1,2-epoxylimonene). The best results were obtained with *N*-bromosuccinimide (54 % total yield).

Introduction

(1*S*, 2*R*, 4*R*)-1,2-Epoxylimonene (*trans*-1,2-epoxylimonene, **1**) is a useful intermediate in the synthesis of natural products (1) and widely spread in essential oils of limes (2). It is obtained as a *ca.* 1:1 mixture with the *cis*-isomer by direct oxidation of (*R*)-limonene (**2**) with diverse oxidants (3). Although these two isomers can be separated by preparative gas chromatography (4) or by careful spinning-band distillation (5), it is a difficult and slow task. More practical methodologies involve selective chemical destruction of the *cis*-epoxide in the mixture of *cis*- and *trans*-1,2-epoxylimonene (6) or oxirane ring opening of both epoxides to produce a diasteromeric mixture followed by separation and chemical regeneration of the *trans*-epoxide **1** (3).

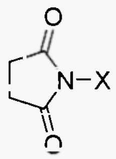
The chlorohydrin **3a** is prepared by HCl addition to the mixture of *cis/trans*-1,2-epoxylimonene followed by derivatization and separation of the two diastereoisomeric chlorohydrins (7). The bromohydrin **3b** is formed stereosselectively in the cobromination of limonene with *N*-bromoacetamide (7) or NBS (8). On the other hand, the reaction of limonene with I_2 / $Cu(OAc)_2{\bullet}H_2O$ in aqueous dioxane produced stereospecifically the iodohydrin **3c** (9). Halohydrins **3** produced *trans*-1,2-epoxylimonene when treated with aqueous bases (8 – 10) Scheme-1.



2 **3** **a** X = Cl
b X = Br
c X = I
1

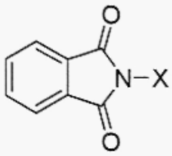
Scheme 1

The cohalogenation of alkenes (halogenation in the presence of a nucleophilic solvent) provides valuable, vicinal halo-functionalized compounds for diverse organic transformations (11). Continuing our interest in both cohalogenation reactions (12) and in the chemistry of limonene (13), we communicate here our results on the cohalogenation of limonene with diverse *N*-haloimides (NXS) e *N*-halosaccharins (NXSac) in aqueous media. The halohydrins were subsequently converted into epoxides.



NXS

X = Cl (NCS)
Br (NBS)
I (NIS)



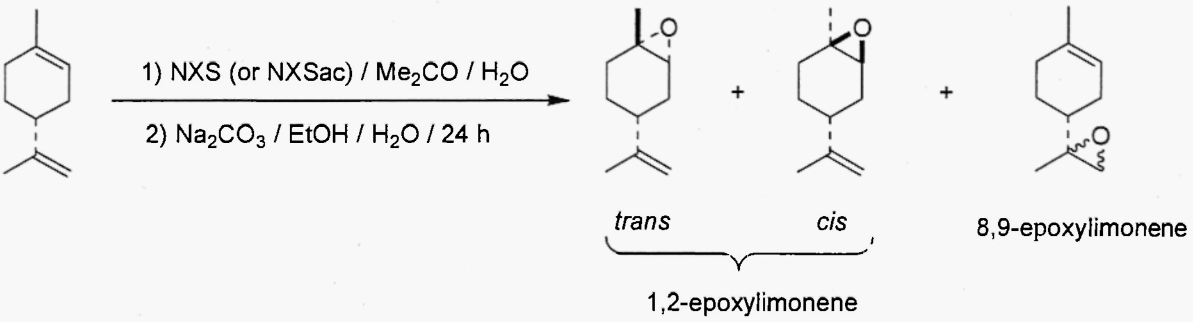
NXSac

X = Cl (NCSac)
Br (NBSac)
I (NISac)

Results

The cohalogenation of limonene was performed by the reaction with 1 mol equiv. of NXS (or NXSac) in aqueous acetone at room temperature (14). After the end of the reaction (15), the solvent was evaporated under reduced pressure and the haloidrins were reacted with excess Na_2CO_3 in aqueous etanol for 24 h. The crude products were analyzed by HRGC by co-injection with authentic samples (9, 16) and the results are summarized in Scheme-2 and Table-1.

As expected (17), the NXSac were more reactive than the corresponding NXS and the reactivity decreased in order I > Br > Cl. In contrast to other results (17, 18), the reaction of limonene with NBSac was disappointing and NBS presented high chemo- and stereosectivity for the *trans*-1,2-epoxide. On the other hand, the reaction with NISac was the only case were 8,9-epoxylimonene predominated. In the cases of the reaction of limonene with NCS and NCSac, HRGC-MS analysis showed several by-products arising from radical chlorination of the substrate.



Scheme-2

Table-1 : Results obtained according with Scheme-2.

Reagent	t[a]	Limonene recovered (%)	Total yield (%)[b]	Epoxides	
				trans / cis	1,2 / 8,9
NCS	120 h	24	22	3.7	5.1
NBS	2.5 h	25	54	22.9	14.6
NIS	15 min	19	35	4.4	1.4
NCSac	< 1 min	17	20	5.1	22.0
NBSac	< 1 min	28	2.5	2.2	3.1
NISac	< 1 min	15	25	7.1	0.6

[a]Consumption of reagent. [b]Chromatographic yield (internal standard: octadecane).

Conclusions

Cohalogenation of limonene with *N*-halosuccinimides and *N*-halosaccharins followed by base treatment of the resulting halohydrins produced stereoselectively *trans*-1,2-epoxylimonene. The best results were obtained with *N*-bromosuccinimide (54 % total yield).

Acknowledgments

M.C.S.M. thanks CNPq for financial support and R.B.B. thanks PIBIC/UFRJ for a fellowship.

References

1. (a) X. Chen, L. Gottlieb and J.G. Millar, *Synthesis* 269 (2000). (b) R. Baker, M. Borges, N.G. Cook and R.H. Herbert, *J. Chem. Soc., Chem. Commun.* 414 (1987).
2. P. Dugo, A. Cotroneo, I. Bonaccorsi and L. Mondello, *Flavour Fragrance J.* **13**, 93 (1998).
3. A.F. Thomas and Y. Bessiere, *Nat. Prod. Rep.* **6**, 291 (1989).
4. J.C. Leffingwell and E.E. Royals, *Tetrahedron Lett.* 2829 (1965).
5. A. Kergomard and H. Veschambre, C. R. Hebd. Seances, *Acad. Sci. Ser C* **279**, 155 (1974).
6. A.G. dos Santos, F.L. Castro and J. Jones Jr., *Synth. Commun.* **26**, 2651 (1996).
7. R. Wilde and J.-M. Teulon, *Bull. Soc. Chim. Fr.* 758 (1970).
8. K.N. Gurudutt, S. Rao and P. Srinivas, *Flavour Fragrance J.* **7**, 343 (1992).
9. A.M. Sanseverino, F.M. da Silva, J. Jones Jr. and M.C.S. de Mattos, *J. Braz. Chem. Soc.* **11**, 381 (2000).
10. M. Wengert, A.M. Sanseverino and M.C.S. de Mattos, *J. Braz. Chem. Soc.* **13**, 700 (2002).
11. (a) F.M. da Silva, J. Jones Jr. and M.C.S. de Mattos, *Curr. Org. Synth.* **2**, 393 (2005). (b) A.M. Sanseverino, F.M. da Silva, J. Jones Jr. and M.C.S. de Mattos, *Quim. Nova* **24**, 637 (2001). (c) J. Rodriguez and J.-P. Dulcère, *Synthesis* 1177 (1993).
12. R.A.S. Villegas, J.L. do Espírito Santo Jr., A.M. Sanseverino, M.C.S. de Mattos, M.R.M.P. de Aguiar and A.W.S. Guarino, *Synth. Commun.* **35**, 1627 (2005) and references cited therein.

13. M.C.S. de Mattos and A.M. Sanseverino, *Phosphorus, Sulfur, Silicon and Rel. Elem.* **179**, 1203 (2004) and references cited therein.

14. NXSac were prepared as early described. NCSac and NBSac: S.P.L. de Souza, J.F.M. da Silva and M.C.S. de Mattos, *Synth. Commun.* **33**, 935 (2003). NISac: D. Dolenc, *Synlett* 544 (2000).

15. Determined when an aliquot did not produce a color change in a wet iodide-starch test paper [in analogy to G.F. Mendonça, A.M. Sanseverino and M.C.S. de Mattos, *Synthesis* 45 (2003)].

16. Q.A.R. Almeida and J. Jones Jr., *Synth. Commun.* **35**, 1285 (2005).

17. S.P.L. de Souza, J.F.M. da Silva and M.C.S. de Mattos, *Heterocycl. Commun.* 9, 31 (2003).

18. S.P.L. de Souza, J.F.M. da Silva and M.C.S. de Mattos, *J. Braz. Chem. Soc.* **14**, 832 (2003).

Received on February 28, 2006.