Tetrahedron Letters,Vol.30,No.17,pp 2213-2216,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

FRAGMENTATION OF ISOPULEGOL BY A RADICAL PROCESS

Michel BULLIARD, Geneviève BALME and Jacques GORE,

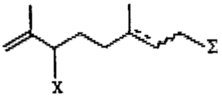
Laboratoire de Chimie Organique I associé au CNRS , Université Claude Bernard
ESCIL - 43 Bd du 11 Novembre 1918, 69622 VILLEURBANNE, France.

Summary. The reaction of isopulegol with sulfuryl chloride leads in certain conditions to a mixture of 8-chloro citronellal and 6-chloro isocitronellal. The radical character of this fragmentation is supported by the result of two reactions known to proceed via an alkoxy radical.

The obtention of linear bifunctional building blocks is of great importance in the synthesis of biologically active molecules bearing a terpenoïd chain. The recent C_{10} + C_{10} synthesis of retinol achieved by OTERA et al. is an example of the use of these building blocks (1).

Among them, halogenated compounds such as 1 and 2 are particularly interesting because of the synthetic flexibility of the carbon-halogen bond. Unfortunately, the allylic chlorination of diverse monoterpenes (geraniol, citronellol, citral, citronellal etc. with free or protected functional groups) leads to variable yields of secondary chlorides 3 and 4 (2) which react with nucleophilic species generaly with high regioselectivity but poor stereoselectivity giving 5 and 6 as an E+Z mixture (E/Z ~ 2.5) (3).

1 (Δ-2) ; 2 (dihydro-2,3)

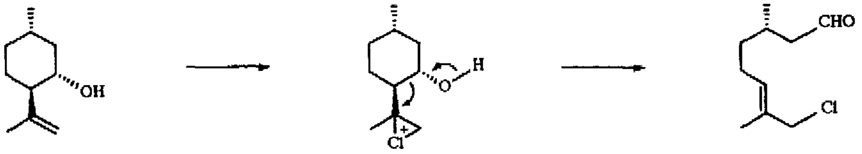


3 (Δ-2) ; 4 (dihydro-2,3)

5 (Δ-2) ; 6 (dihydro-2,3)

X = halogen ; Σ = functional group

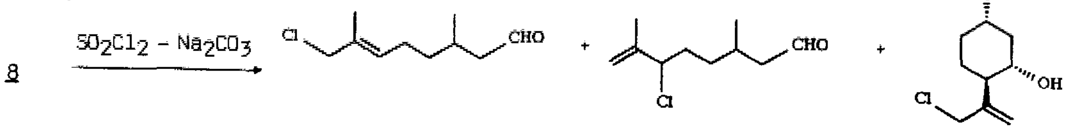
These considerations led us to study the possibility of obtaining the chloro-aldehyde 7 (a compound of type 2) by the fragmentation, via a chloronium ion 9, of isopulegol 8 induced by a chlorinating reagent.



8 9 7

The success of such a transformation 8 → 7 can be anticipated since it was shown very recently that isopulegol epoxide is cleanly transformed to 8-hydroxy citronellal by treatment with aluminium isopropoxide (4,5) ; furthermore, the fragmentation of homoallylic secondary alcohols by chlorine in strained polycyclic sesquiterpenes has been previously described (6).

Several chlorine sources were successively used in order to promote the expected fragmentation. In our hands, by far the best results were obtained using sulfuryl chloride (one molar equivalent) in halogenated solvents and in the presence of sodium (or lithium) carbonate (7). Three chlorinated compounds are formed whose proportions are dependent on the temperature of the reaction : two of them, 7 and 10, come from the expected fragmentation while 11 is the result of an allylic chlorination.



7 10 11

CH_2Cl_2 - 0°C		71%
CCl_4 - 20°C	30%	60%
CH_2Cl_2 - 20°C	31%	63%
CH_2Cl_2 - reflux	60%	30%
Trichloroethylene-reflux	73%	22%

The mixture of the unstable chloro-aldehydes 7 and 10 can be separated from 11 by flash-chromatography after acetalisation ; their relative proportions (7/10 ~ 2) can be then deduced from the ^1H NMR spectrum.

From these results, it appears that the reaction of isopulegol 8 with sulfuryl chloride can be directed preferentially to the fragmentation process, but this occurs with low regioselectivity giving two isomeric chloro-aldehydes. This problem can be circumvented since the reaction of the mixture of the dioxolannes of 7 and 10 by sodium benzene sulfinate in a phase transfer catalysis system (8) takes place specifically on the primary pole giving compounds 12 (45%) preferentially under the E configuration (E/Z~6). This result emphasizes the use of a primary chloride such as 7 for this nucleophilic substitution : the use of a secondary chloride, 6-chloro isogeraniol 13 in the same reaction leads also to the primary sulfone but with a lower stereoselectivity (E/Z~2.5).

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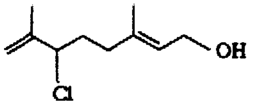

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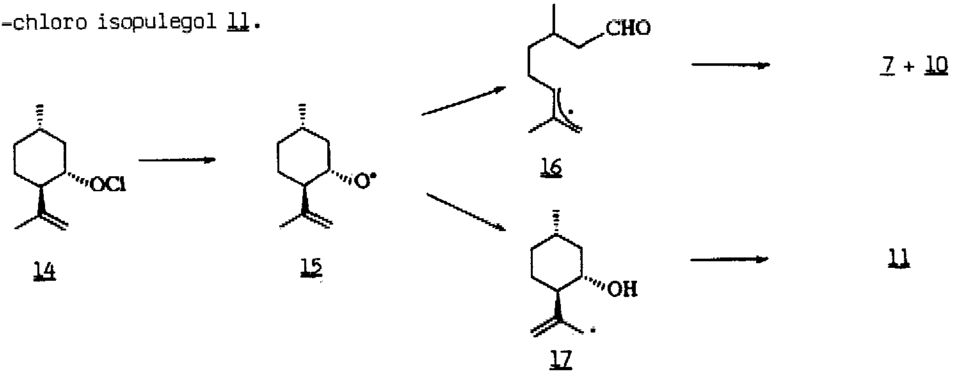
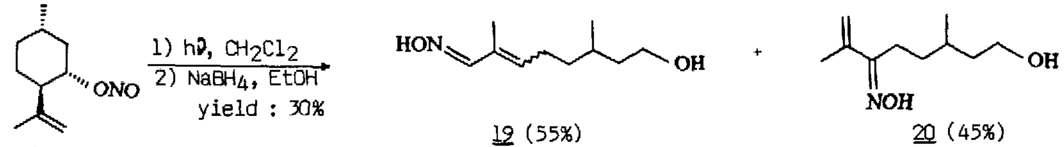
The simultaneous obtention of both chloro-aldehydes rules out an ionic process for the observed fragmentation and reflects probably a radical pathway. One possibility would be that an initially formed hypochlorite 14 could be transformed to the alkoxy radical 15 which can give rise either to the fragmentation or to a 1,5-hydrogen shift leading ultimately via the radical 17 to 9-chloro isopulegol 11.



In order to verify these hypotheses, we ran two reactions known to proceed via an alkoxy radical such as 15.

* the photolysis of isopulegol nitrite 18 (9) in dichloromethane with a high pressure mercury lamp gave only the fragmentated products 19 and 20 (but in low yield) after reduction of the aldehyde group with sodium borohydride to facilitate purification.



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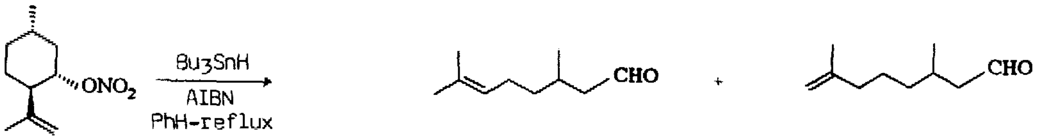
19 (55%)

E/Z = 1.75

20 (45%)

* the treatment of isopulegol nitrate 21, prepared by the conventional way (10), with 2 molar equivalent of tributyltin hydride and 0,3 equivalent of AIBN leads exclusively in a 85% yield to a mixture of citronellal 22 (70%) and isocitronellal 23 (30%).



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Consequently, it appears that the only fate of the secondary alkoxy radical 15 is the fragmentation process leading to its allylic open chain isomer 16 ; in the reaction of isopulegol 8 with sulfuryl chloride, the chloro-alcohol 11 is probably formed by an ionic process. Unfortunately, all attempts to encourage the radical pathway by using initiators ($h\nu$, AIBN, benzoyl peroxide etc...) were completely unsuccessful.

If the fragmentation of tertiary alkoxy radicals is a well documented process (11), it seems unusual for secondary ones (12). The easy fragmentation of 15 is probably mainly the consequence of the allylic stabilization of the obtained radical 16.

Finally, we tried to trap this last radical 16 with carbon species : the reaction of 8 with sulfuryl chloride as well as the reduction of isopulegol nitrate by tributyltin hydride were run in the presence of ten molecular equivalents of ethyl acrylate without noticeable change in the nature of the reaction products, showing that the intermolecular carbon-carbon bond forming from this type of radical is not a favored process under these conditions. However, we were able to observe such an intramolecular process with the same kind of fragmentation : the reaction of the alcohol 24 with sulfuryl chloride in refluxing dichloromethane leads with a 68% yield to a 1/1 mixture of the chloro-ketones 25 and 26 resulting probably from a fragmentation-recyclisation process via the radical 27 (13).

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We are presently studying some applications of the above-described fragmentation of isopulegol 8 as well as synthetic uses of the C_{10} building block 12.

The constant interest and financial support of Rhône-Poulenc Recherche are gratefully acknowledged.

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(Received in France 28 January 1989)