NEW DEVELOPMENTS OF THE WHARTON TRANSPOSITION

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<u>Abstract</u>: The synthetically useful Wharton transposition can be improved by using a more adequate procedure in the critical step of the intermediate α -epoxyhydrazone cleavage. Either for stable hydrazones or unstable ones, the yield of the transposed allylic alcohol is increased by treatment under anhydrous conditions with highly basic reagents (KDA in the former case, NEt₂ in the latter).

Introduction

The reductive opening of α , β -epoxyhydrazones, obtained in two steps from α , β -enones, results in the formation of allylic alcohols in which the oxygen functionality has undergone a 1,3 shift as shown in Scheme 1. This original and direct method was first described by Wharton and Bohlen in 1961¹, then by Huang-Minlon and Chung-Tungshun². In the original papers, the number of examples is small, with applications limited to the case of some steroids.





As methods to achieve such a 1,3-transposition are not numerous³, the Wharton procedure has a significant synthetic potential. However, reports of its utilisation are not frequent⁴, possibly because literature does not provide a generally acceptable procedure or guidelines to find easily optimal conditions. The yields can greatly vary from low to excellent, according to parameters (e.g. structure, stereoelectronic effects, procedure) whose influence is not clearly understood⁵.

Undesired side reactions can occur (Scheme 2) : pyrazoles $\underline{3}$ result from the evolution of epoxyhydrazones such as $\underline{1}^6$, and an unexpected cyclisation takes place from $\underline{4a}^7$.

The mechanism of this cyclisation involves a free radical intermediate formed spontaneously from an unstable diazene (see below)⁸. The quasi failure of the Wharton transposition to yield the α -damascols (Z,E mixture) <u>6a</u> seemed to make unpractical a very short synthetic scheme of the valuable damascone family⁹ from the cheap and easily available ionones. The necessary reexamination of the general experimental conditions was then undertaken.



Results and discussion

Besides the epoxides of α - and B-ionones <u>5a</u> and <u>5b</u> we investigated the Wharton transposition of several α -epoxy carbonyl compounds known to give poor results under the classical conditions. The epoxides of citral <u>10</u>¹¹, (-)-myrtenal <u>13</u>^{10b} and (-)-carvone <u>17</u>^{10b} were chosen. The generally accepted course of the reaction^{6b} is represented as follows.



There is a strong similarity to the Wolff-Kishner carbonyl reduction¹². Step 2 (III+ IV) is here irreversible, due to the epoxide ring opening. In contrast, the hydrazone-diazene prototropy in the Wolff-Kishner reaction is slow and reversible. The cleavage of the C-N bond in the diazene IV^{13} , can be initiated either by a homolytic hydrogen abstraction by several agents, possibly oxygen¹⁴, or by proton abstraction, to give, after loss of nitrogen in each case, a vinylic radical or anion. From the work of Stork⁸, the homolytic process leads to the undesired compound <u>7</u>. It should then be possible to favour the desired ionic process by the use of highly basic conditions. This necessitates to run the reaction in anhydrous solutions, and as a consequence, to prepare the α -epoxyhydrazone in an initial separate step. These ideal conditions cannot always be fulfilled as epoxyhydrazones are frequently unstable. A solution would be to form the hydrazone under anhydrous conditions¹⁵, which enhance the basicity of the eagent taken in excess (pK of hydrazine : 8.1) or of an auxiliary base (pK of e.g. NEt₃ : 0.6). A series of α , β -enones was easily transformed to the corresponding α -epoxyketones (II) y standard methods¹⁶. Two different cases should be considered separately, according to the tability of the α -epoxyhydrazones.

- Stable epoxyhydrazones

reatment of epoxides 5a and 5b in dichloromethane with hydrazine hydrate (2 mol. equiv.) ives the corresponding epoxyhydrazones in high yields. These compounds can be stored after rying and evaporation of the solvent, in pentane or tetrahydrofuran (THF) solutions at -20°C ithout appreciable decomposition (checked after 1 month). NMR and IR spectra confirm the atisfactory purity of the epoxyhydrazones, which are allowed to react at low temperature -100 to -80°C) with a strong base. n-Butyl-lithium, lithium diisopropylamide (LDA), its otassium equivalent (KDA)¹⁷, and potassium t-butoxide were tested but the first two reagents roved to be less satisfactory (lower yields). As soon as the base is added the reaction ccurs and nitrogen is rapidly evolved. The expected allylic alcohols are obtained in good ields as shown in Table 1, and the undesired bicyclic compound <u>7</u> is virtually absent under nese conditions.

Epoxyhydrazone	Base ^a	Product	Yield % ^b	Lit. yield
X	t Bu OK	ОН	76	20 ^c
<u>5a</u>	KDA	<u><u><u>6a</u></u></u>	68	
	t Bu OK	→ → →	71	
<u><u>5</u></u>	KDA	<u><u><u>6</u></u></u>	67	

Table 1 _ Wharton transposition of st	table epoxynygrazone:
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See experimental part. ^bIsolated yields of purified material. ^CSee Ref.7.

- Unstable epoxyhydrazones

is case is more difficult as the decomposition begins frequently before the formation of the oxyhydrazone is completed. A possible solution to this problem consists in replacing the oxyhydrazone by a stable derivative, such as an epoxysemicarbazone. A favourable example is und with the transposition of citral to linalool, as indicated in Scheme 4.



While the classical reaction of $\underline{10}$ to $\underline{12}$ is described with a 35% yield¹¹, our procedure improves this yield up to 47%. Other examples tested proved to be disappointing and the use of semicarbazones was not further explored. The other approach consisting in the preparation of the epoxyhydrazones under virtually anhydrous conditions was then examined.

Commercial anhydrous hydrazine proved to give no synthetic advantage and to be experimentally inconvenient. It appeared much preferable to prepare it in situ from its salts by reaction with triethylamine in acetonitrile, as shown below :

$$H_2 N = NH_3 X^{-} + NEt_3 = H_2 N = NH_2 + Et_3 NH^{+} X^{-} X^{-} = CI, SO_4 H^{-}$$

This slow heterogeneous reaction can be greatly accelerated by sonication of the mixture in an ultrasonic cleaning bath. As triethylamine is more basic than hydrazine, the equilibrium is shifted to the right. Addition of the epoxyketone to this mixture yields the epoxyhydrazone which transposes immediately as shown by the nitrogen evolution. An alternative procedure consisting in running the reaction in a single step from the hydrazinium salt gives no yield advantage. Two remarks can be made : the water molecule formed in the condensation is probably trapped by the triethylammonium salt which acts as an in situ drying agent, and a possible catalytic role of triethylamine in the formation of the hydrazone can also be envisaged¹⁸. Table 2 summarizes up the results obtained from various epoxyketones. In most cases, subtantial yield improvements are observed in comparison with the usual Wharton procedure,

giving thus substance to our predictive interpretation. From a stereochemical point of view our results are in accordance with the findings of Klein and Ohloff^{10b}. From the epoxides of α - and β -ionones <u>5a</u> and <u>5b</u> the transposition at low temperature yields mostly (Z)- α - and β -damascols <u>6a</u> and <u>6b</u> as established by IR and NMR

spectra^{7,19}. This result indicates that the stereochemical outcome at low temperature should be determined during the ring opening of the epoxide via intramolecular chelation of the cation (Li⁺ or K⁺) by the epoxide oxygen and the hydrazone nitrogen atoms.



Dreiding models show that the chelated transition state for the epoxide opening leading to $(E)-\underline{6a}$ is more strained than that which affords $(Z)-\underline{6a}$.



Table 2 _ Wharton transposition of unstable epoxyhydrazones

^aSee experimental., ^bIsolated yields of purified material. ^C4-isopropyl-1-methyl-cyclohexanol is also isolated. ^dSee Ref. 11. ^eSee Ref. 10b. ¹See Ref. 1.

3 - Oxidation of the secondary allylic alcohol

The 1,3-carbonyl transposition to α ,B-enones is completed by oxidation of the allylic alcohols. Instead of the capricious manganese dioxide²⁰ known to give poor yields from 2-damascol <u>6a</u>⁷ we preferred to use the hypervalent iodine compound <u>21</u>²¹ (Periodinane^R). Satisfactory results are shown in Table 3.



(+)-Pinocarvone <u>22</u> and (+)-carvone <u>23</u> are optically pure, and α -damascone <u>8a</u> is accompanied by traces of α -ionone <u>4a</u>. With β -damascol <u>6b</u>, manganese dioxide proved to be superior to reagent <u>21</u>, and better yields of <u>8b</u> were obtained¹⁹.

The 1,3-transposition of a carbonyl functionality in a \mathfrak{a} -enone is thus efficiently completed.

Allylic alcohol	Product	yield ^b	1,3-carbonyl transposition overall yield
<u>- l</u> ; он (+)- <u>14</u>	(+)- <u>22</u>	71	41
OH <u><u><u>6a</u></u></u>		83 [°]	50
		c,d 30,64	25 [°]
ОН (-)- <u>18</u>		92	55
ОН 20	<u>24</u>	62 ^f	31

Table 3 - Oxidation of the secondary allylic alcohols

^aSee experimental part. ^bIsolated yields of purified material. $^{c}Z/E=9/1$. ^dWith MnO₂. ^eThis low figure is due to a low epoxidation yield of ß-ionone (56%)²². $^{c}Z/E=2/3$.

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Experimental part

Thin layer chromatography (TLC) was performed on Merck silica gel on aluminium, and visualisation was effected with molybdophosphoric acid in ethanol. Merck (70-230 mesh) silica gel and (60-100 mesh) Florisil were employed for column chromatography. A Perkin-Elmer 397 spectrometer was used to record IR spectra (as neat liquid films). Brücker WP 80 or AM 300 Fourier transform spectrometers were employed for the NMR spectra, using tetramethylsilane (TMS) as the internal standard in CDCl₃ solutions. ¹³C-NMR peak assignments were made from off-resonance and NOE experiments. Mass spectra were obtained on a MS 30AEI mass spectrometer (70 eV. electron impact). Optical rotations were measured with a Perkin Elmer polarimeter Model 141. Combustion analyses were effected by the Service Central d'Analyse du CNRS, Lyon. Sonications were effected at 15°C in a Sonoclean SHE 2500 ultrasound cleaning bath.

Preparation of epoxyketones and epoxyaldehydes

Epoxides of α -ionone⁷, citral¹¹, (-)-myrtenal^{10b}, (-)-carvone^{3a}, isophorone²³, and 1-acetyl-1-cyclohexene were prepared with 30% aqueous H₂O₂ in the presence of 6N aqueous NaOH, following the standard procedure²³.

NaOH, following the standard procedure . 1-Acetyl-1-cyclohexene oxide 19 (yield : 80 %) : b.p. 86-87 (12 torr). IR (neat) : 3050, 2940, 2860, 1710, 1435, 1355, 1240, 1175, 1140, 860, 840 and 740 cm⁻¹. H-NMR (80 MHz) : 3.30 (m, 1H), 2.04 (s, 3H), 2.6-1.7 (m, 8H). ¹³C-NMR (80 MHz) : 208.23, 62.90, 56.65, 24.23, 23.12, 22.03, 19.26, 18.74. MS M⁺ : 140. Anal. Calcd. for C₈ $H_{12}O_2$: C : 68.54 % ; H : 8.63 %. Found : C : 68.49 %, H : 8.91 %.

Preparation of stable epoxyhydrazones

 α -Ionone epoxide 5a (5 mmoles) and hydrazine monohydrate (98 %)(10 mmoles) in CH₂Cl₂ (10 ml) was cooled to 0°C. One drop of AcOH was added and the mixture was magnetically stirred at 0°C during 48 hours. The organic layer was washed with water and dried (Na SO.). Solvent evaporation under vacuum afforded the crude epoxyhydrazone in quantitative yield,⁴ as an oil. IR (neat) : 3400, 1620, 1450, 1365 and 890 cm⁻¹. H-NMR (80 MHz) : 5.48 (m, 1H), 5.22 (m, 2H), 3.38 (d, 1H, J=2.2 Hz), 2.77 (dd, 1H, J=8.7 Hz, J=2.2 Hz), 1.98-1.14 (m, 5H), 1.70 (m, 3H), 1.53 (s, 3H) 1.09 (s, 3H), 0.92 (s, 3H).

The epoxyhydrazone of ß-ionone $\frac{5b}{50}$ was obtained quantitatively by the same procedure. IR (neat) : 3380, 1620, 1450, 1365, 895, 880 and 865 cm⁻¹. H-NMR (80 MHz) : 5.29 (m, 2H), 3.44 (m, 1H), 3.33 (d, 1H, J=2.3 Hz), 1.89-1.24 (m, 6H), 1.63 (m, 3H), 1.58 (s, 3H) 1.18 (s, 3H), 1.07 (s, 3H).

Preparation of citral epoxysemicarbazone²⁴ :oil, ¹H-NMR (80 MHz) : 9.95 (m, 1H), 9.60 (d, 1H, J=7 Hz), 5.72 (m, 2H), 5.09 (m, 1H), 3.10 (d.d, 1H, J=8 Hz, J=1.5 Hz), 2.20-1.5 (m, 4H), 1.70 (s, 3H), 1.62 (s, 3H), 1.38 (d, 3H, J=1.5 Hz).

Rearrangement of stable epoxyhydrazones and epoxysemicarbazone

Method A : The epoxyhydrazone (1 mmole) dissolved in a mixture of dry THF and pentane (3:2, 2 ml) under an argon atmosphere was cooled to -100°C (pentane, liquid N₂). To this stirred solution, freshly sublimed t-BuOK (224 mg, 2 mmoles) in 1 ml of THF was added in 0.5 h. A rapid evolution of nitrogen started at once during the addition and for 1 hour after, the temperature was kept below -85° C then 10 ml of ether was added with 0.5 ml of methanol. The organic layer was washed three times (sat. aq. NH₂Cl) dried (Na₂SO₄) and the solvents evaporated. The residue was purified on a Florisil column (eluent : CH₂Cl₂). α -Damascol² and β -damascol⁹ exhibited physical data in accordance to those previously² described.

Method B :

KDA was prepared in dry THF (3 ml) and pentane (1 ml) solution¹⁷ from 1.5 mmoles of freshly sublimed t-BuOK, 1.38 mmoles of diisopropylamine and 0.5 ml of a 2.5M n-BuLi solution. After cooling to -100°C, 0.5 mmole of the epoxyhydrazone or epoxysemicarbazone in 1 ml of THF was added during 0.25 h. Then the same general procedure as above was followed.

Preparation and rearrangement of unstable epoxyhydrazones

Method C : Hydrazine monohydrochloride (2 mmoles) and triethylamine (3 mmoles) in dry acetonitrile (2 ml) were sonicated for 2 h. The α -epoxyketone (0.65 mmole) in 1 ml of acetonitrile was added at O°C. The mixture was stirred at O°C (epoxide of citral) or at room temperature (other cases). Progress of the reaction was followed by TLC (1 h to 48 h). The solvents were evaporated under vacuum and the residue extracted (CH₂Cl₂). The organic layer was washed (sat. aq. NaCl), dried (Na₂SO₄) and the solvent evaporated. The crude allylic alcohol was purified on a Florisil or SiO_2 column (eluent CH₂Cl₂ or hexane-AcOEt : 8-2). Method D :

The a-epoxyketone (1 mmole) was added at 0°C to an excess of anhydrous hydrazine in dry THF The d-eposylectone (1 mmole) was added at 0°C to an excess of annydrous hydrazine in dry ine or acetonitrile. After disappearance of the epoxylectone (TLC), the mixture was treated as in method C. Linalool <u>12</u>, (+)-pinocarveol <u>14</u>^T ($\begin{bmatrix} \alpha \end{bmatrix}_{23}^{23}$ + 52°, c = 0.1, CHCl₃), 1,5,5-trimethylcyclohex-2-ene-1-ol <u>16</u>^{5a,b}, (-)-carveol <u>18</u> ($\begin{bmatrix} \alpha \end{bmatrix}_{23}^{23}$ + 139°, c = 1.2), exhibited physical data in accordance to those previously reported. <u>2-Ethylidene cyclohexanol 20</u>^C (Z/E mixture) b.p. 68-69°C (5 torr) IR (neat) : 3380, 1660, 1440, 980, 915, 880, 840 and 825 cm³. H-NMR (80 MHz) : 5.34 (d.t, 1H, J=1,5 Hz), 4.76 and 4.07 (m, 1H), 2.5-1.1 (m, 12H). ¹³C-NMR (80 MHz) 141.46, 140.30, 116.61, 114.96, 73.41, 64.63, 35.86, 33.63, 31.99, 27.60, 26.65, 25.25, 22.68, 20.24, 12.10. MS M⁺:126.

Oxidation of secondary allylic alcohols

Reagent 21 was obtained from Aldrich, or prepared according to the published procedure 21. 1 mmole of the allylic alcohol and 1.3 mmole of the reagent were stirred in 10 ml of CH_Cl_ at room temperature. At the end of the reaction (TLC), 20 ml of ether were added followed by 10 ml of 1.3 M NaOH. The mixture was stirred for 10 mn, the ethereal layer was separated and

extracted with 10 ml of 1.3 M NaOH then with 10 ml of water.(+)-Pinocarvone^{4,26} ($[a]_{D}^{23}$ + 59°, c=1.7 CHCl₃), (+)-carvone 23, 2-ethylidene cyclohexanone 24^{4a,7,27}, a-damascone 8a and B-damascone 8b^{4a,19,28} exhibited physical data in accordance to those previously described.

¹³C-NMR (300 MHz) : α-Damascone (Z) : 203.8 (C4), 142.1 (C2), 130.7 (C6), 128.5 (C3), 123.1 (C7), 64.5 (C5), 32.4 (C10), 31.27 (C9), 27.9 and 27.5 (C11 and C11'), 23.1 (C8), 22.6 (C12), 15.6 (C1). ß-damascone (Z) : 202.2 (C4), 143.3 (C6), 141.5 (C2), 131.1 (C3), 129.3 (C5), 38.9 (C9), 33.7 (C10), 31.2 (C7), 28.4 (C11 and C11'), 20.5 (C12), 18.9 (C8), 15.6 (C1).



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