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Experimental and theoretical evidences of 2-aza-Cope rearrangement of nitrones

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Dedicated to professor Miguel Yus on occassion of his 60th birthday

Abstract—Both the intramolecular cycloaddition of diastereomeric homochiral *N*-alkenyl nitrones and the corresponding theoretical calculations using DFT and ab initio methods provided evidences of a thermal [3,3] sigmatropic rearrangement of the nitrones with a complete chirality transfer.

The aza-Cope rearrangement is a well-known [3,3] sigmatropic process which can take place with a variety of substrates containing a nitrogen atom in their structure.[1] Depending on the position of the nitrogen the rearrangement is identified as a *n*-aza-Cope process (*n* = 1, 2 or 3),[2] the 3-aza-Cope reaction being the more studied.[3] The 2-aza-Cope rearrangement has been reported mainly taking place with iminium salts.[4] The synthetic utility of the reaction has been widely demonstrated.[4,5] In the case of nitrones, the possibility of a 2-aza-Cope rearrangement has only been suggested (see Scheme 1).[6]

Although in one instance it was possible to isolate a rearranged nitrone as a side-product,[7] the actual intermediate was an iminium salt formed in situ. Up to now it has not been demonstrated the existence of a 2-aza-Cope rearrangement with nitrones. In this communication, we report, for the first time, experimental evidences of a 2-aza-Cope rearrangement of nitrones based on the use of homochiral compounds. Also, a theoretical study of the process has allowed to locate the corresponding transition structure for the [3,3] sigmatropic rearrangement agreeing with the experimental findings.

Readily available homoallylhydroxylamines 1[8] are useful building blocks for the construction of a variety of nitrogen-containing compounds.[9] In the course of our research directed to the synthesis of enantiomerically pure nitrogen-containing products[10] we envisaged compounds 1 as suitable starting materials for the preparation of 6-substituted 4-hydroxy pipecolic acids.[11] The key step of the approach consisted of the intramolecular cycloaddition of *N*-alkenyl nitrone 2, obtained from the corresponding hydroxylamine 1a by MnO_2-mediated oxidation.[12] The (*Z*)-configuration of nitrone 2 was assigned by 1D NOE experiments and unequivocally established by X-ray crystallography. Heating nitrone 2 in a sealed tube at 100 °C in toluene for 72 h afforded a mixture of compounds 4, 5 and 6 in a 75:5:20 ratio, respectively.[13] The configuration of all cycloadducts was unequivocally assigned by NMR including COSY, ROESY, and HSQC 2D experiments, and in the case of major adduct 4 an X-ray analysis confirmed its *exo/exo* configuration.

Whereas the obtention of compounds 4 and 5 from nitrone 2 was expected according to the stereochemical
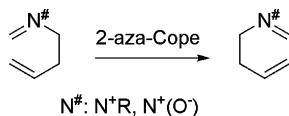
2-aza-Cope

N#: N+R, N+(O-)

Scheme 1.

outcome of the reaction, compound **6** only can be obtained if a [3,3] sigmatropic rearrangement of nitrone **2** took place and nitrone **3** is formed in situ. The intramolecular cycloaddition of nitrone **3** should lead to compounds **4** (also accessible from **2**) and **6**. A similar result had been observed by Hoffmann and Endesfelder[6] but it could not be demonstrated because starting from a racemic compound, the same results could have been obtained from a *E/Z* isomerization of the nitrone.[14] In our case, the stereogenic center present in the dioxolane ring allows to discard the *E/Z* isomerization, since a different diastereomer should have been obtained (see Scheme 2).

Indeed, the same result was obtained starting from diastereomeric hydroxylamine **1b**, which after oxidation and intramolecular cycloaddition led to a 82:5:13 mixture of cycloadducts.[15] From this mixture cycloadduct **9**, formed via the 2-aza-Cope rearrangement, was identified and its absolute configuration unequivocally assigned by X-ray crystallography.

From the obtained results with the two diastereomeric series it is also suggested that the reaction proceeds with thermodynamic control. In order to verify this point isolated cycloadducts and mixtures of them were subjected to the intramolecular cycloaddition conditions. No traces of other isomers neither changes in the ratio (when mixtures were used) were observed, thus confirming the irreversibility of the process. Therefore, the stereochemical outcome of the reaction is controlled by the interconversion of nitrones **2** and **3**, which should account with a complete chirality transfer as it consists of a [3,3] sigmatropic rearrangement. Wuts and Jung[7] observed the only reported case of a 2-aza-Cope rearrangement of a nitrone, as a side reaction and upon treatment of an alkenyl nitrone with 1.0 equiv of

TMSOTf to convert it into an iminium salt more suitable for the rearrangement.[4] All attempts (thermal or in the presence of a variety of Lewis acids) of obtaining nitrone **3** from **2** failed. Then we undertook the alternative synthesis of nitrone **3** from D-glyceraldehyde **10**[16] and the racemic homoallyl hydroxylamine **11**[6] (Scheme 3). Unfortunately, the diastereomeric nitrones **3** and **12** were inseparable under chromatographic conditions and only enriched mixtures could be obtained. Nevertheless, the use of these mixtures allowed us to confirm the interconversion of nitrones **2** and **3**. Thus, subjecting mixtures of nitrones **3** and **12** to the intramolecular cycloaddition conditions, identical results to those obtained from **2** and the corresponding nitrone obtained from **1b** were obtained. These results confirm not only the interconversion of **2** and **3** but also a similar activation energy for both the intramolecular cycloaddition reactions and the 2-aza-Cope rearrangement.

In order to verify the last statement we also carried out a theoretical study using DFT and ab initio methods.
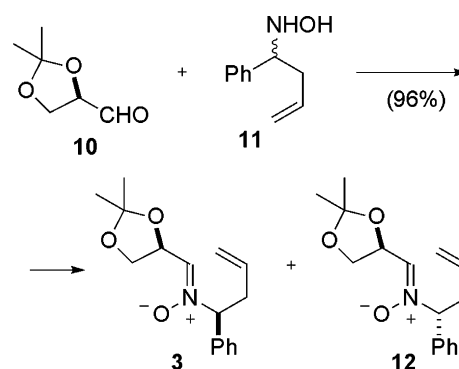
Scheme 3. Reagents and conditions: MgSO$_4$, CH$_2$Cl$_2$.
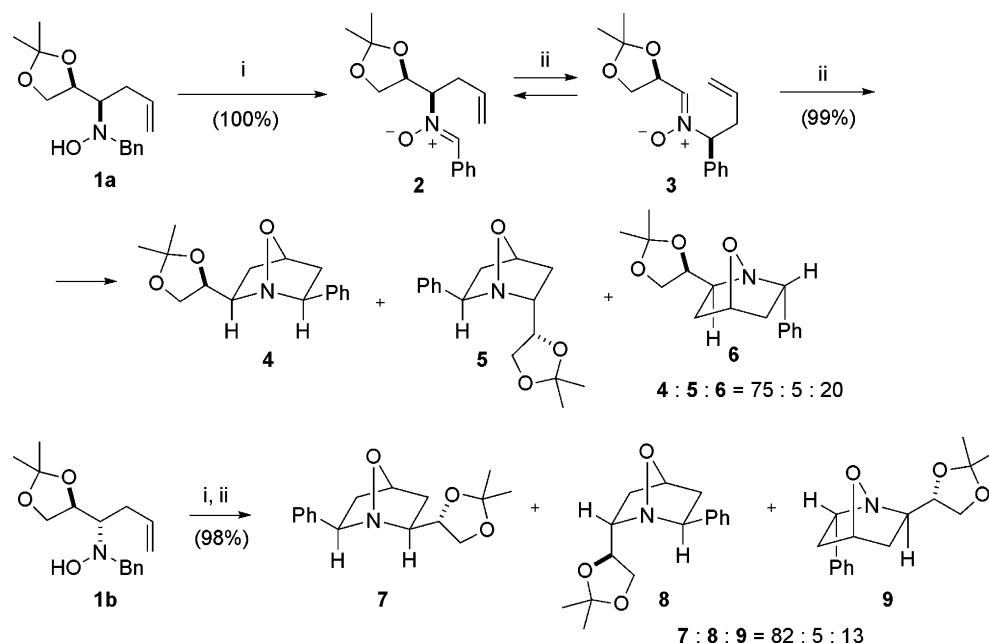
Scheme 2. Reagents and conditions: (i) MnO$_2$, CH$_2$Cl$_2$, 0 °C, 8 h. (ii) Toluene, 100 °C, 72 h.

Thus, all transition structures for the intramolecular cycloadditions were located. The intramolecular cyclo-addition of C-phenyl nitrone **IM_01N** leads to two diastereomeric TSs (**TS1A** and **TS1B**), corresponding to the only possible *endo* approach of the double bond to both faces of the nitrone. The calculated activation energies show that the most stable transition structure is **TS1A** leading to *exo/exo* adduct **IM_B01**. Similarly, the values obtained for the corresponding C-methyl nitrone **IM_02N** indicated that the most stable TS is **TS2A** also leading to *exo/exo* adduct **IM_B01**, which shown to be the most stable. The energy differences observed between the different TSs (Fig. 1) are in close agreement with the observed experimental results.

While the energy barriers found for the cycloaddition processes are in agreement with the irreversibility of those reactions, the values found for the 2-aza-Cope rearrangement support the reversibility of the processes. The observed energy barriers between nitrones **IM_01N** and **IM_02N** through **AC_TS** indicated that the process is reversible and competitive with the corresponding intramolecular cycloadditions. According to these data it is expected that when enough energy is achieved for promoting the 2-aza-Cope rearrangement, the intramolecular cycloaddition is also favored, in agreement with the previously discussed experimental results. The *E/Z* isomerization between nitrones has been discarded on the basis of previous kinetic investigations.[17] Although it has been reported that *E/Z* isomerization of nitrones might be competitive with the cycloaddition[14a,18] studies on twisting about the C=N bond on different compounds showed rather high energy barriers for such a transformation.[19] In the case of nitrones these values are around 33.6 kcal/mol.[17] The transition structure located for the 2-aza-Cope rearrangement **AC_TS** is gathered in Figure 2. In general terms, the geometry is in agreement with a concerted process and displayed a [3,3] sigmatropic rearrangement character. The observed
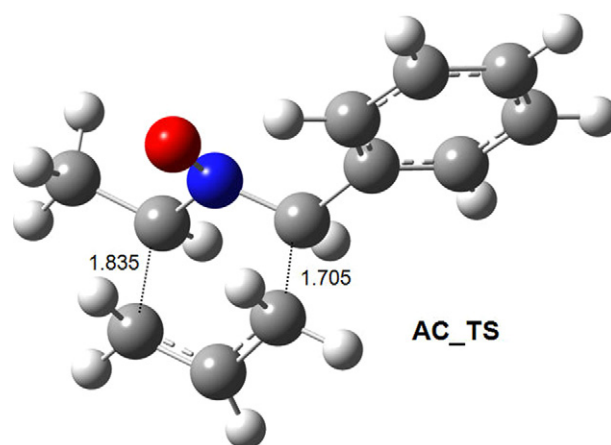
Figure 2. Transition structure (B3LYP/6-31G*) for the 2-aza-Cope rearrangement of nitrones 2 and 3 (the dioxolane ring has been replaced by a methyl group). Forming bond lengths given in angstrong.

energy barrier for the 2-aza-Cope rearrangement of nitrones is rather lower than those found for other thermal aza-Cope rearrangements[20] but similar to 2-aza-Cope rearrangements of iminium salts.[4b]

In conclusion, experimental evidences of a 2-aza-Cope rearrangement of nitrones have been found by carrying out intramolecular cycloadditions with homochiral compounds, the *E/Z* isomerization of the starting nitrones being discarded. The interconversion of nitrones through the [3,3] sigmatropic process needs an activation energy near to that required for the intramolecular dipolar cycloaddition. These results are also well-predicted by theoretical calculations which allowed to characterize for the first time the transition structure corresponding to the 2-aza-Cope rearrangement of nitrones. Indeed, the results of the calculations predict the competitive formation of the observed cycloadducts
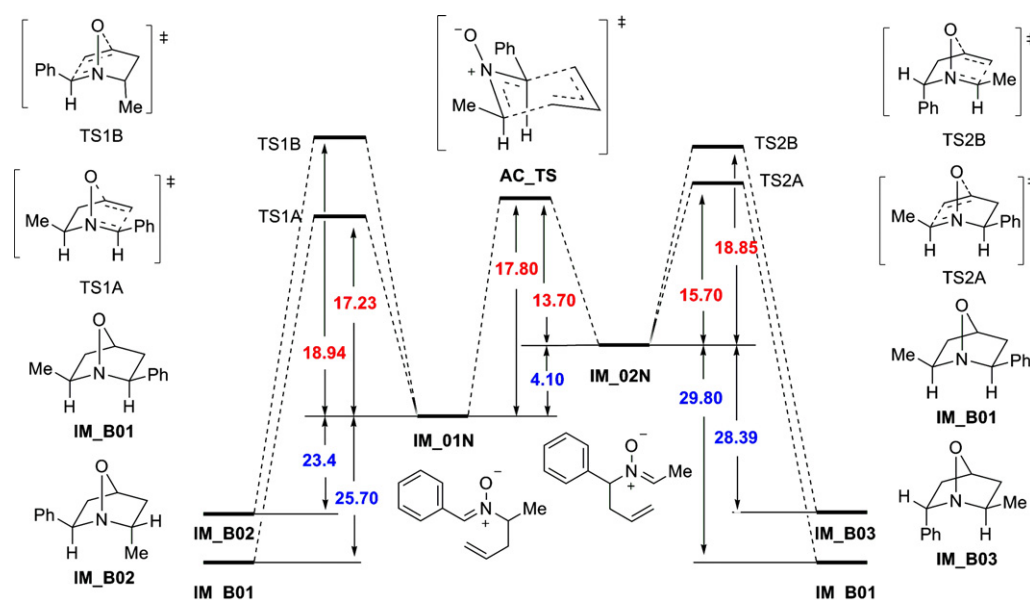
Figure 1. Energy diagram for 1,3-DC and 2-aza-Cope rearrangement. Relative energies (MP2/6-31G*//B3LYP/6-31G*) are given in kcal/mol.

as they are formed through the [3,3] sigmatropic rearrangement.

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13. Data for **4**: R_f (hexane/EtOAc, 4:1) = 0.38. White solid; mp: 98–99 °C. $[\alpha]_D^{20}$ −34 (*c* 0.41, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ 7.40–7.33 (m, 2H), 7.32–7.27 (m, 2H), 7.22–7.14 (m, 1H), 4.95 (t, 1H, J = 4.8), 4.26 (q, 1H, J = 6.9), 4.01 (dd, 1H, J = 8.1, 6.9), 3.93 (dd, 1H, J = 8.3, 4.8), 3.72 (dd, 1H, J = 8.1, 6.9), 3.18 (td, 1H, J = 7.6, 4.8), 2.15 (dd, 1H, J = 11.8, 8.3), 2.05–1.94 (m, 1H), 1.75 (dd, 1H, J = 11.8, 8.0), 1.68–1.57 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H). Data for **5**: R_f (hexane/EtOAc, 4:1) = 0.30. White solid; mp: 148–149 °C. $[\alpha]_D^{20}$ +31 (*c* 0.07, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 7.47–7.42 (m, 2H), 7.37–7.33 (m, 2H), 7.27–7.21 (m, 1H), 5.05–5.00 (m, 1H), 4.61 (t, 1H, J = 6.5), 4.28 (dt, 1H, J = 8.5, 6.9), 4.14 (dd, 1H, J = 8.0, 6.3), 3.77 (t, 1H, J = 7.6), 3.58 (ddd, 1H, J = 10.0, 8.5, 6.3), 2.19–2.08 (m, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.26 (dd, 1H, J = 11.2, 6.3). Data for **6**: R_f (hexane/EtOAc, 4:1) = 0.33. White solid; mp: 96–97 °C. $[\alpha]_D^{20}$ −34 (*c* 0.23, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ 7.47–7.29 (m, 5 H), 5.03 (t, 1H, J = 5.0), 4.75 (dd, 1H, J = 10.2, 6.4), 4.13 (ddd, 1H, J = 8.0, 6.5, 5.7), 3.97 (dd, 1H, J = 8.5, 6.5), 3.64 (dd, 1H, J = 8.5, 5.7), 3.17 (td, 1H, J = 8.0, 5.5), 2.47–2.34 (m, 1H), 1.75 (dd, 1H, J = 11.6, 6.4), 1.62 (dd, 1H, J = 11.2, 8.0), 1.58–1.49 (m, 1H), 1.33 (s, 3H), 1.26 (s, 3H).
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15. Data for **7**: R_f (hexane/EtOAc, 4:1) = 0.54. White solid; mp: 76–77 °C. $[\alpha]_D^{20}$ +54 (*c* 1.28, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ 7.29–7.25 (m, 2H), 7.24–7.21 (m, 2H), 7.17–7.10 (m, 1H), 5.01 (t, 1H, J = 4.9), 4.20 (dd, 1H, J = 8.6, 5.9), 4.08–3.80 (m, 3H), 3.00 (td, 1H, J = 8.5, 4.0), 2.11 (dd, 1H, J = 11.5, 8.4), 2.04–1.96 (m, 2H), 1.76 (dd, 1H, J = 11.8, 7.8), 1.35 (s, 3H), 1.25 (s, 3H). Data for **8**: R_f (hexane/EtOAc, 4:1) = 0.45. White solid; mp: 140–141 °C. $[\alpha]_D^{20}$ −51 (*c* 0.09, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ 7.45–7.38 (m, 2H), 7.37–7.29 (m, 2H), 7.28–7.19 (m, 1H), 5.01 (t, 1H, J = 5.2), 4.54 (dd, 1H, J = 8.3, 4.6), 4.43 (ddd, 1H, J = 8.2, 6.5, 3.6), 4.16 (dd, 1H, J = 8.2, 6.5), 3.66 (t, 1H, J = 8.2), 3.50 (ddd, 1H, J = 9.7, 5.9, 3.6), 2.20 (dd, 1H, J = 11.2, 8.3), 2.16–2.00 (m, 2H), 1.69 (dd, 1H, J = 10.9, 5.9), 1.47 (s, 3H), 1.42 (s, 3H). Data for **9**: R_f (hexane/EtOAc, 4:1) = 0.50. White solid; mp: 80–81 °C. $[\alpha]_D^{20}$ +83 (*c* 0.11, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ 7.46–7.30 (m, 5H), 5.08 (t, 1H, J = 5.1), 4.68 (dd, 1H, J = 10.1, 6.5), 4.14 (dd, 1H, J = 8.3, 6.1), 3.95 (dt, 1H, J = 9.0, 6.1), 3.56 (dd, 1H, J = 8.3, 6.1), 2.91 (ddd, 1H, J = 8.6, 8.2, 4.7), 2.40–2.26 (m, 1H), 2.01–1.90 (m, 1H), 1.82 (dd, 1H, J = 11.9, 6.5), 1.76 (dd, 1H, J = 11.8, 8.0), 1.29 (s, 3H), 1.25 (s, 3H).
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