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On the [2,3] Sigmatropic Rearrangement of Allylic Nitro Compounds

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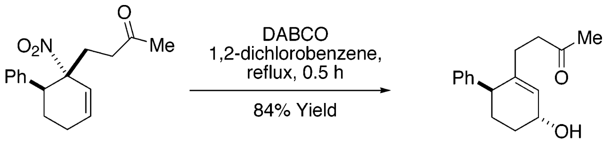
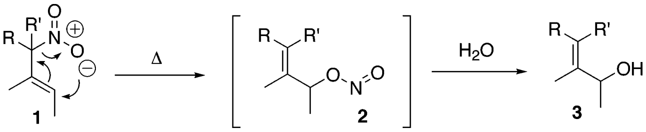
ABSTRACT



Allylic nitro compounds undergo relatively clean [2,3] sigmatropic rearrangement upon heating in refluxing 1,2-dichlorobenzene in the presence of DABCO to give the corresponding allylic alcohols via the intermediate allylic nitrite.

Some years ago, we described the thermal conversion of allylic nitro compounds **1** into the rearranged allylic alcohols **3**.[1] The reaction most probably proceeds through a [2,3] sigmatropic rearrangement of the nitro group into the corresponding nitrite **2**, which then undergoes rapid hydrolysis to give allylic alcohol **3**, as shown in Scheme 1. This transformation would thus be related to the Mislow−Evans−Braverman rearrangement of allylic sulfoxides and selenoxides,[2] as well as the rearrangement allylic iodoxyl derivatives and the Meisenheimer rearrangement of allylic tertiary amine oxides.[3]

Scheme 1. Thermal Rearrangement of an Allylic Nitro Group



Despite its apparent simplicity and synthetic potential, this new transformation of allylic nitro derivatives has not attracted much attention from the synthetic community.[4] One of the reasons is the generally modest yield of allylic alcohols. In the most favorable case of tertiary allylic nitro compounds, the yield hovers around 50−60%, rarely reaching or exceeding 70%. It is even lower in the case of secondary derivatives. Primary allylic nitro compounds are not useful substrates since the temperature needed to induce the transformation is much too high, and only extensive decomposition is observed.

Initially, we thought that the problem was due to the formation of nitrous acid by the three possible pathways indicated in Scheme 2: (a) by hydrolysis of the intermediate nitrite **2**; (b) by the known syn elimination of the nitro group from starting material **1** leading to dienes;[5] and (c) by syn elimination of the nitrite from **2** also leading to a diene. Indeed, we had found variable quantities of dienes as side products in some of the reactions. A further complication, arising from partial homolytic decomposition of the nitrite intermediate to give alkoxy radical **5** at the high temperatures

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[1] Boivin, J.; El Kaim, L.; Kervagoret, J.; Zard, S. Z *J. Chem. Soc., Chem. Commun.* **1989**, 1006.

[2] For a review, see: Brückner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 873.

[3] (a) Johnstone, R. A. W. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; John Wiley & Sons: New York, 1969; Vol. 2, pp 249−266. (b) von Schickh, O.; Apel, G.; Padeken, H. G.; Scharz, H. H.; Segnitz, A. In *Houben-Weyl-Müller: Methoden der Organischen Chemie*; Thieme: Stuttgart, 1971, Vol. X/1. (c) Davies, S. G.; Fox, J. F.; Jones, S.; Price, A. J.; Sanz, M. A.; Sellers, T. G. R.; Smith, A. D.; Teixeira, F. C. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 1757 and references cited therein.

[4] For applications, see: (a) Barlaam, B.; Boivin, J.; El Kaim, L.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 623. (b) Boivin, J.; Barlaam, B.; El Kaim, L.; Elton-Farr, S.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 1675. (c) Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Chem. Commun.* **1999**, 2009.

[5] Chow, Y. L. In *The Chemistry of Amino, Nitro, and Nitroso Compounds and their Derivatives*; Patai, S., Ed.; Wiley-Interscience: Hoboken, NJ, 1982; Suppl. F, Vol. 1, p 181.

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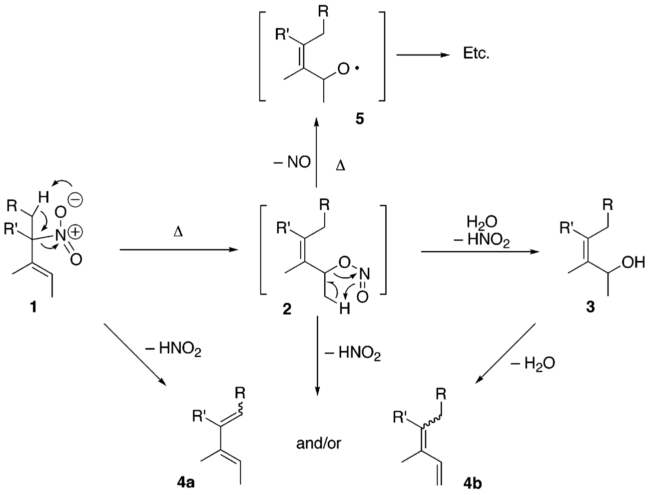
(>150 °C) required for the rearrangement, was also a possibility (Scheme 2).[6]

Scheme 2. Side Reactions



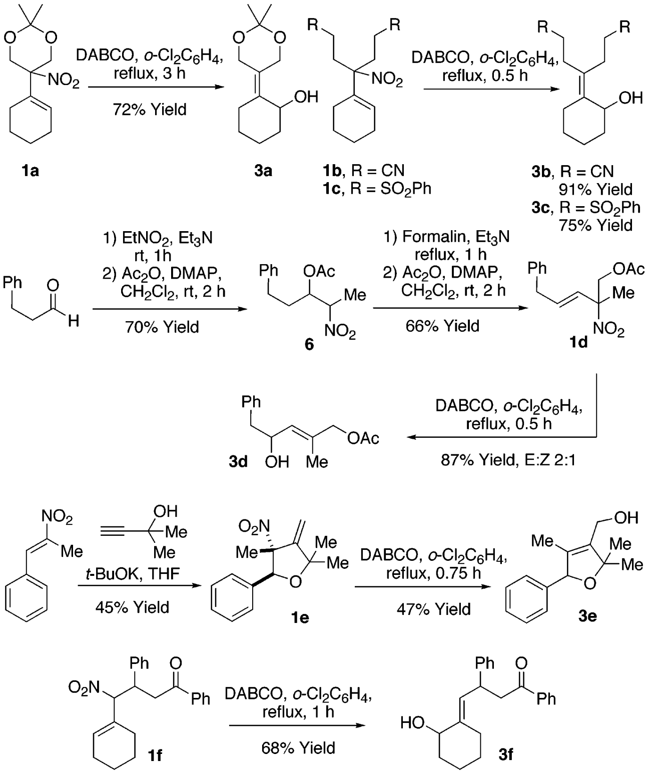
Attempts at improving the yield by addition of scavengers for nitrous acid or additives that could react cleanly with the nitrite were unfortunately not successful.[1] The formation of dienes could also arise by acid-catalyzed elimination of water from the allylic alcohol or by acid-catalyzed elimination of nitrous acid from the intermediate nitrite. The silica surface of the glass flask could become sufficiently acidic at the high reaction temperature to cause these undesired eliminations. Indeed, addition of glass wool to the reaction medium increased significantly the amount of dienes in the crude reaction mixtures.

To counteract the deleterious acidity of the silica on the reaction outcome, we explored the effect of added base. Various bases were screened, but no significant increase in the yield of the allylic alcohol was observed in most cases. In particular, we had high hopes for *N*,*N*-dimethylaniline, which could act both as a weak base and as a scavenger for nitrous acid and nitrogen oxides in general. Unfortunately, our hopes did not materialize in practice. Some improvement was found using proton sponge, but by far the best results were obtained with DABCO. Indeed, as the following examples will demonstrate, thermolysis in the presence of DABCO of secondary and tertiary allylic nitro compounds becomes a synthetically very useful process.

We had found that derivative **1a**, obtained by a double Henry reaction of 1-nitromethylcycloxenene with formaldehyde followed by protection as the isopropylidene ketal, rearranged into alcohol **3a** in 53% yield in the absence of DABCO.[1] When we repeated the experiment in the presence of 1.5 equiv of DABCO, the yield jumped to 72%. The yield was even higher with substrates **1b** and **1c**, which gave the allylic alcohols **3b** and **3c** in 91 and 75% yields, respectively.

Significant improvement was also observed in the case of the open-chain derivative **1d**, a substrate readily prepared from hydrocinnamaldehyde by the sequence shown in Scheme 3. The yield was 67%[7] in the absence of DABCO but increased to 87% in its presence. The most spectacular improvement was observed with nitro-olefin **1e**. This substrate can be prepared in one step from 1-methyl-1-nitrostyrene[8] and was reported to rearrange into allylic alcohol **3e** in only 13% yield.[4c] In the presence of DABCO, the yield of **3e** was 47%, representing a nearly 4-fold increase.

Scheme 3. Examples of the Thermal Rearrangement



The beneficial effect of DABCO was also observed in the case of secondary nitro derivative **1f**. This compound was prepared as essentially one diastereoisomer by Michael addition of 1-nitromethylcyclohexene to chalcone and could be rearranged into **3f** in 68% yield. In the absence of DABCO, the yield dropped to 42%. Interestingly, alcohol **3f** was obtained as a single diastereoisomer (vide infra), the relative stereochemistry of which was not determined.

The examples outlined in Scheme 4 further illustrate the scope. These transformations start from commercially available 1-nitrocyclohexene, a compound exhibiting a remarkably versatile chemistry.[9] Thus, Henry addition to formaldehyde[10]

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(6) Pyrolyses of simple nitrites are reported to proceed by way of alkoxyl radicals: Batt, L. In *The Chemistry of Amino, Nitroso and Nitro Compounds*; Pataï, S., Ed.; Wiley: New York, 1982; Suppl. F, Chapter 12, p 417.

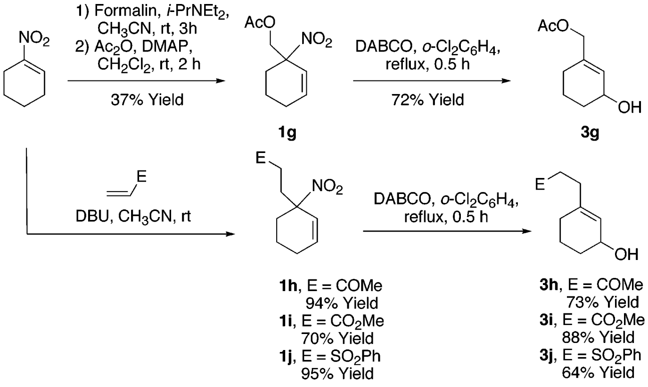
(7) Barlaam, B. Thèse de Doctorat en Sciences, Université Paris-Sud, Orsay, France, 1992.

(8) Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *J. Chem. Commun.* **1997**, 1831.

(9) (a) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294. (b) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.

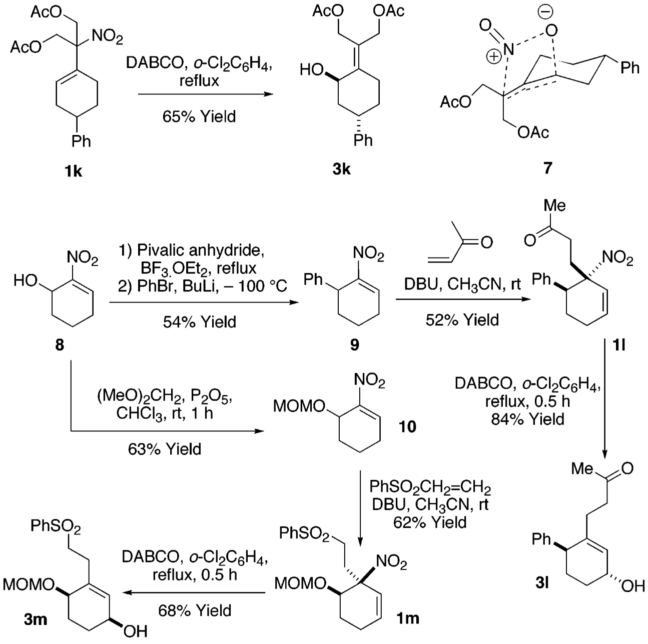
(10) Ono, N.; Namamoto, I.; Kamimura, A.; Kaji, A.; Tamura, R. *Synthesis* **1987**, 258.

Scheme 4. Allylic Alcohols from 1-Nitrocyclohexene



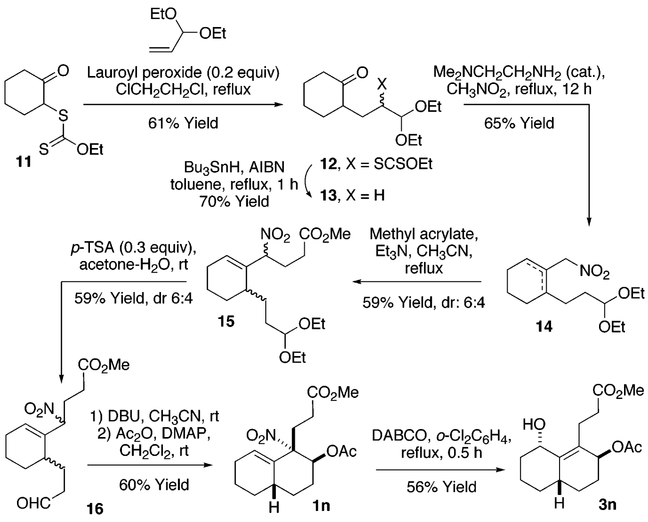
and acetylation furnished allylic nitro derivative **1g**, which upon heating in *o*-dichlorobenzene gave rise to the expected allylic alcohol **3g** in 72% yield. Alternatively, Michael addition to methyl vinyl ketone, methyl acrylate, and phenyl vinyl sulfone provided precursors **1h**, **1i**, and **1j** in generally good yield. Thermolysis in *o*-dichlorobenzene furnished the corresponding allylic alcohols **3h**, **3i**, and **3j** in 73, 88, and 64% yields, respectively. Many of these compounds would be tedious to make by traditional approaches. That the rearrangement of the nitro group is indeed a suprafacial process in the presence of DABCO was confirmed by the transformation of **1k** into **3k** in 65% yield. Only the trans isomer is formed, and this can be easily rationalized by the transition structure **7**, where the bulky phenyl group occupies the expected equatorial position. In order for adequate orbital overlap to take place, the incipient C−O bond has to form from the axial position, leading to the observed isomer. A phenyl group also acted as a stereochemical marker in the more complex structure **1l**. This substrate was prepared from nitroolefin **9**, itself made from glutaraldehyde and nitromethane by a short sequence devised by Seebach and coworkers.[11] The Michael addition to methyl vinyl ketone proceeded in high yield and took place from the same side as the phenyl group as determined by NMR (NOESY). Thermolysis in the presence of DABCO in the usual manner gave allylic alcohol **3l** as the sole isomer in 84% yield, confirming once again the suprafacial nature of the rearrangement. In the same fashion, allylic nitro derivative **1m** rearranged to give **3m**, also as a single isomer. Interestingly, in contrast to the case of **1l**, the conjugate addition leading to **1m** occurred from the side opposite to the −OMOM group. Because of the reversibility of the Michael addition, both reactions are presumably under thermodynamic control and result in the formation of the more stable diastereoisomer.

Scheme 5. Stereochemical Aspects of the Rearrangement



The synthetic utility of this rearrangement was further confirmed by combining the rich chemistry of the nitro group[12] with an intermolecular radical addition mediated by xanthates.[13] As depicted in Scheme 6, lauroyl peroxide-induced addition of xanthate **11** to the diethyl acetal of acrolein gave adduct **12** in 61% yield. The xanthate group was reductively removed in 70% yield with tributylstannane and the resulting ketone **13** subjected to condensation with nitromethane. This Knoevenagel-type reaction, induced by a catalytic amount of *N*,*N*-dimethylethylenediamine, provided nitroolefin **14** in 65% yield. We had, many years ago, demonstrated the efficiency of ethylenediamine and its congeners as “organo-catalysts” for accomplishing difficult

Scheme 6. Stereoselective Synthesis of a Bicyclic Structure



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(11) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861.

(12) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (d) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1.

(13) For a review, see: Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672; *Angew. Chem.* **1997**, *109*, 724.

condensations of nitromethane with hindered ketones.[14] In the present case, the condensation leads to a 3:2 mixture of isomeric nitro derivatives, the major being the kinetic, deconjugated isomer with the least substituted olefin. However, both gave the same Michael addition product **15** in 59% yield (82% based on recovered starting material) as a 6:4 mixture of diastereomers. The addition to methyl acrylate had to be performed using triethylamine, since the more basic DBU caused extensive formation of the double Michael adduct.

The stage was now set to construct the second ring. Hydrolysis of the acetal group was accomplished with *p*-toluenesulfonic acid in wet THF to give the intermediate aldehyde **16** in 59% yield, still as a 6:4 mixture of diastereoisomers. Exposure of the mixture to DBU in methanol induced diastereoselective ring-closure into bicyclic derivative **1n** in 60% yield after acetylation. Clearly, the reversibility of the intramolecular Henry reaction ensures the formation of the most stable isomer, whose relative stereochemistry was determined by NMR (NOESY). Finally, thermolysis in refluxing *o*-dichlorobenzene in the presence of DABCO provided the expected allylic alcohol **3n** in 56% yield as the sole isomer, as would be expected from a suprafacial process.

In summary, we now have in hand a practical, flexible route to even complex allylic alcohols. The precursors are readily prepared by exploiting the remarkable ability of the nitro group to mediate C−C bond formation under very mild conditions, through the Henry and Michael reactions. Allylic alcohols are direct precursors of enones, and the corresponding acetates or carbonates serve as substrates in numerous transition-metal-catalyzed transformations.

Acknowledgment. We wish to thank Ecole Polytechnique for a Bourse Monge (to C.A.-A.).

Supporting Information Available: Experimental procedures and detailed analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1982**, 551; *Bull. Chim. Soc. Fr.* **1983**, 61. For further examples of this procedure, see: Tamura, R.; Sato, M.; Oda, D. *J. Org. Chem.* **1986**, *53*, 4368.