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N,N-DIMETHYLANILINE AS A SOLVENT FOR INTRAMOLECULAR DIELS ALDER REACTIONS.

IMPROVED YIELDS AND CHANGES IN STEREOISOMER RATIOS

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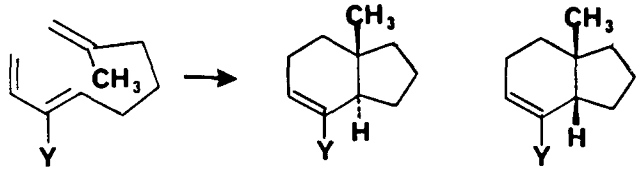
Summary. N,N-Dimethylaniline was found to be a superior solvent for intramolecular Diels Alder closures of 1,3,8-nonatrienes to trans-hydrindenes.

The intramolecular Diels Alder reaction has been the subject of intense study by numerous groups during the last decade.[1] These reactions are generally carried out in hydrocarbon solvents,[2] with or without the addition of Lewis acids. It appears that the effects of solvent on the yield of an intramolecular Diels Alder reaction and on the ratio of products have been described only once.[3,4]

As part of our studies on the intramolecular cycloadditions of the 1,3,8-nonatrienes,[5] we have investigated the closure of the substituted trienes *1*[6] in hydrocarbon solvents and in N,N-dimethylaniline. Use of the latter solvent leads to improved yields and also increases the ratio of *trans: cis* hydrindene products (*2*:*3*).

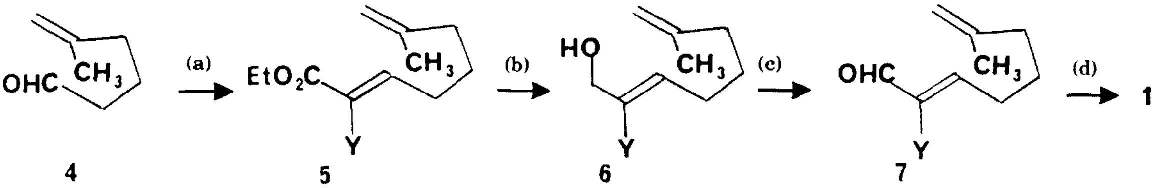


1 **2** **3**

a Y = H **c** Y = Br

b Y = CH_3 **d** Y = $CH_2SC_6H_5$

Nonatrienes *1* were prepared from aldehyde *4* by one of the four-step sequences depicted in Scheme 1.[7]



(*a*) $(C_6H_5)_3P = CYCO_2Et$: for Y = Br, see Boeckman, R. K., Jr., Ko, S. S., *J. Am. Chem. Soc.*, *1980*, *102*, 7146; for Y = $CH_2SC_6H_5$, see Semmelhack, M. F., Tomesch, J. C., Czarny, M., Boettger, S., *J. Org. Chem.*, *1978*, *43*, 1259. The (E)- and (Z)-isomers of *5* were separated by chromatography. (*b*) Dibal, 25° (*c*) PCC for Y = H, CH_3, Br; PDC for Y = $CH_2SC_6H_5$. (*d*) $(C_6H_5)_3P=CH_2$.

Scheme I

The cycloaddition reactions were performed at 200–220° in hydrocarbon solvents containing 2,5-di-t-butylhydroquinone (DTBH) or methylene blue in sealed tubes or in N,N-dimethylaniline (DMA) containing DTBH under nitrogen. Product ratios (Table I) were determined by analysis of the high resolution (250 MHz) nmr spectra of the chromatographed product mixtures. For each isomeric pair, the higher field methyl singlet was assigned to the *trans* hydrindene.[8]

TABLE I. Product Ratios and Yields

Substrate	Products	*2:3* (Yield) Solvent: C_6H_6 or $C_6H_5CH_3$ (a)	*2:3* (Yield) Solvent: DMA
1a Y=H	2a + 3a	0.33 (b)	0.70 (61%)
1b Y=CH_3	2b + 3b	0.67 (50%)	3.6 (80%)
1c Y=Br	2c + 3c	0.70 (b)	1.0 (70%)
1d Y=$CH_2SC_6H_5$	2d + 3d	0.50 (55%)	1.7 (78%)

(a) Substrates *1a – c*, were cyclized in benzene; *1d* was cyclized in toluene. (b) Yield less than 20% .

Inspection of the data reveals that, for each closure, a higher yield of hydrindene products was obtained from the reaction in which dimethylaniline served as solvent. Furthermore, in each closure the ratio of *trans:cis* fused product increased when dimethylaniline was used.

On the basis of the limited available data it is not possible to assign the origins of these effects. However, the suggestions that the use of high-viscosity solvents results in the acceleration of intramolecular (cycloaddition) reactions[3,9] and improved yields[3] are intriguing in the context of this study.

Although the $\Delta\Delta G^{\ddagger}$ required to effect the observed changes in product ratios would generally be considered small,[10] the changes in yield of cycloaddition products and also in the amount of each isomer in the product mixture must be considered significant. Additional investigations designed to determine the generality of this and related solvent effects seems warrented; furthermore, in the absence of a general theory, routine solvent studies may lead to useful improvements in intramolecular cycloaddition reactions which are of interest for the purposes of synthesis.

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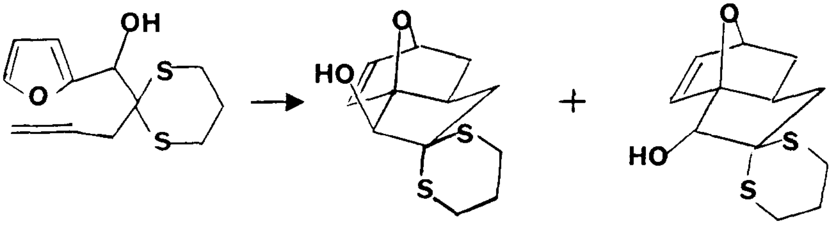
References

1. (a) Ciganek, E., *Organic Reactions, 1984, 32*, pp 1-374.
   (b) Fallis, A. G., *Can J. Chem., 1984, 62*, pp 183-234.

2. Inspection of the tables in reference 1a reveals a small number of reports of experiments carried out in alcohol solvents, alcohol water mixtures, chlorocarbons, acetonitrile, DMF, and pyridine.

3. In 1982, Sternbach and Rossana reported that the closure of substituted furan i gave a mixture of the two possible *exo* cycloaddition products, *ii* and *iii*, stereoisomeric at the carbon bearing the hydroxyl group. The yield of the product mixture as well as the ratio of stereoisomers *ii* and *iii* was found to be solvent dependent.



i ii iii

See Sternbach, D.D., Rossana, D. M., *Tetrahedron Lett., 1982, 23*, 303.

4. At this time, there is no evidence that hydrophobicity is effective in accelerating intramolecular closures. In at least some systems where the diene is furan, intramolecular closure is actually retarded in water but accelerated in water containing β-cyclodextrin: Sternbach, D. D., Rossana, D. M., *J. Am. Chem. Soc.*, *1982*, *104*, 5853.

5. Parker, K. A., Iqbal, T., *J. Org. Chem.*, *1982*, *47*, 337.

6. The cyclization of *1b* in toluene has been reported by Mao to give a mixture of *2b* and *3b* and a double bond-isomerized product; however the results of this experiment are inconsistent with our own in which no double bond-isomerized product was detected. Furthermore the presence of *3b* in Mao's product mixture was not supported by his nmr data which included no methyl singlet at $\delta < 0.9$ ppm. See Mao, D. T., Ph.D. Thesis, Indiana University, 1980.

7. Each new compound was characterized by ir and nmr spectroscopy. Structures *5a-d*, *6c* and *6d*, *7a-d* and *1a*, *1b*, and *1d* were characterized by high resolution mass spectrometry (molecular ion); bromotriene *1c* decomposed on standing and was not submitted to HRMS. Aldehyde *4* and alcohols *6a* and *6b* are known compounds: for *4*, see Wilson, R. M., Rekers, J. W., Packard, A. B., Elder, R. C., *J. Am. Chem. Soc.*, *1980*, *102*, 1633; for *6a*, see Bianchini, J. P., Waegell, B., Gaydou, E. M., Rzehak, H., Keim, W., *J. Mol. Catal.*, *1981*, *10*, 247; for *6b*, see Moiseenkov, A. M., Czeskis, B. A., Semenovsky, A. V., *Tetrahedron Lett.*, *1980*, 853.

8. This designation is analogous to the well-known correlation for 14α- and 14β-$\Delta^{8,9}$-steroids: see Bhacca, N. S., Williams, D. H., *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field.* San Francisco, Holden Day, 1964, Table 2-3 (pp 19-24). For each stereoisomeric hydrindene pair except *2a* *3a* it was possible to assign the vinyl proton signals by comparison of the integral values for these peaks with these for the angular methyl groups. The signals observed and their assignments were:

   2a 0.71 (CH_3); *3a* 0.97 (CH_3);
   2b 0.70 (CH_3), 5.20 (vinyl H); *3b* 0.95 (CH_3), 5.30 (vinyl H);
   2c 0.81 (CH_3), 5.88 (vinyl H); *3c* 1.03 (CH_3), 5.97 (vinyl H);
   2d 0.70 (CH_3), 5.36 (vinyl H); *3d* 0.90 (CH_3), 5.48 (vinyl H).

9. (a) Firestone, R. A., Saffar, S. G., *J. Org. Chem.*, *1983*, *48*, 4783.
   (b) Firestone, R. A., Vitale, M. A., *J. Org. Chem.*, *1981*, *46*, 2160.

10. In the conversion *1b* → *2b* + *3b*, the change in $\Delta\Delta G^{\ddagger}$ when benzene is replaced with DMA is 1.6 kcal. Other changes in $\Delta\Delta G^{\ddagger}$ are smaller.

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