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ULTRASONICALLY ACCELERATED CYCLOADDITION – REARRANGEMENT OF ENOL ETHERS

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Summary: Cycloaddition-rearrangement reactions of methyl cyclohexenyl ethers with p-bromobenzenesulfonyl azide in neat homogeneous admixture are substanially accelerated by low-wattage ultrasound. Using ultrasound approximately the same yields of rearranged products are obtained in less time at lower temperature than observed at ambient sonic frequencies and elevated temperature. A previously unreported product structural type has also been found.

Sonication as a tool for the acceleration of organic reactions has grown in importance in recent years.^{1,2} For the most part the kinds of reactions which have been shown to be succeptible to the effects of ultrasound are heterogeneous processes. Thus Barbier reactions, Reformatsky reactions, Simmons-Smith reactions and other transformations initiated by reaction at a metal surface all display rate accelerations and increased yields of products when carried out with ultrasonic mediation.³ Continuous cleaning of metal surfaces by ultrasonically induced cavitation in the liquid phases of these reactions few examples other than nucleophilic displacements, and hydrolyses were reported before 1988.²

High *local* temperatures and pressures are known to be produced in the cavitation process. Recently several reports have appeared that demonstrate the effect of these phenomena on homogeneous reactions. Temperature effects have been suggested to be responsible for the high yields and short reaction times realized in tin hydride promoted reactions carried out at low *bulk phase* temperatures.⁴ In contrast, high pressures developed by sonication have been viewed as responsible for the excellent yields obtained in Diels-Alder reactions which are only poorly successful at normal pressures.^{5, 6, 7, 8}

The cycloaddition rearrangement reaction of arylsulfonyl azides with enols ethers has been the subject of several investigations. First studied by Wohl⁹ the reaction was shown by Dauben and co-workers^{10, 11} to be readily accelerated by high pressure (15 kbar); indeed, substrates which were entirely unreactive at ambient conditions underwent facile reaction under the stress of elevated pressure. From this laboratory there was reported¹² a study of the utility of the reaction for the conversion of aryl methyl ethers to cyclopentenyl carboximidates and esters with the finding that the process is both chemo– and, to a lesser extent, stereoselective. We wish to report now that the sulfonyl azide - enol ether rearrangement is also significantly accelerated by the use of ultrasound under homogeneous conditions and that homogeneous reactions which proceed poorly or slowly under normal conditions of temperature and pressure occur readily with ultrasonic promotion. In addition we report a previously undetected type of product from these azide additions.

In Table 1 are listed examples of results of addition – rearrangement from the reaction of pbromobenzenesulfonyl azide with representative 1,4-cyclohexadiene and cyclohexene substrates under the influence of low wattage ultrasound.¹³ The reactions afford moderate to high yields of the corresponding cyclopentenyl or cyclopentyl products using lower temperatures and, for the most part, shorter reaction times than required in the absence of sonification. For example, substrates 1 and 2 (Entries 1 and 2) afford greater than 80%



yields of product 3 with ultrasonic acceleration at ambient temperature. Comparable yields are obtained otherwise only at temperatures of 62° to 75° and twice the reaction time in each case. For the case of the more hindered substrate 4 (Entry 3) sonication promotes the production of 5 in one-third of the time required for its formation at 65° and in significantly higher yield.

The results shown in entries 4 and 6 of Table I illustrate some of the similarities and differences between running these reactions under ambient conditions, at elevated pressure and under the influence of ultrasound. Neither of the substrates, 6 or 7, affords a significant percentage of product at elevated temperature and ambient

pressure in the absence of ultrasound.¹⁴ In both cases extensive decomposition of the starting material and/or product occurs. Under conditions of higher pressure, ca. 10 kbar, good to excellent yields (95% and 85% respectively) of the rearranged products, 8 and 9, are obtained but we were only able to carry out these reactions on an approximately 0.25 mM scale. In contrast, the ultrasonically promoted process occurs at ambient temperature and affords good yields of easily purified products 8 and 9 on a more than ten-fold greater scale employing up to 4 mM of substrate.¹⁵

As seen previously with ultrasonically promoted reactions the presence or absence of solvent can be critical to the success of the process.⁵ In general we find that maximum yields and minimum reaction times are obtained in the absence of solvent. Thus, with the exception of 7 and 10 for which comparisons were not made, every substrate shown in Table I undergoes cycloaddition-rearrangement more rapidly in neat homogeneous mixture than in solvent. In addition, viscosity appears to play a role in the rates of these reactions.² Acetates 11 and 12, Table II, both give higher yields in shorter times than the corresponding alcohols 13 and 14. In the case of each acetate the solution of the azide in the substrate was substantially more fluid than the viscous but homogeneous mixtures of the corresponding alcohols and the azide.



A suprising difference in the composition of the products was also observed between acetate 12 and al-

cohol 14. Both substrates afford the corresponding rearrangement products, 15 and 16 respectively, but alcohol 14 also yields a significant percentage of the diastereoisomeric sulfonamides 17.¹⁵ This product may result from the formation of an intermediate aziridine 18 when the initial cycloaddition product, 19, opens to a betaine 20 and

subsequently looses nitrogen. *Reversal* of the expected and normally observed regiochemistry of the addition step with subsequent formation of the aziridine would also account for product 17. With the possible exception of the formation of a minor product from the reaction of ethyl vinyl ether and tosyl azide¹⁶ to our knowledge neither of these routes have previously been reported for the addition of azides to enol ethers.¹⁷ Why one or the other should be observed with alcohol 14 and not with the corresponding acetate, 12, is not clear. However, that such products

are common in the cycloaddition - rearrangement of *acyclic* and some *heterocyclic* enol ethers will be illustrated in a subsequent communication.



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- (13) In a typical procedure a mixture of the enol ether (1 eq) and the *p*-bromobenzenesulfonyl azide (1 2 eq) under nitrogen in a flame-dried flask (containing anhydrous acetonitrile in cases where solvent was employed) was subjected to sonication in an American Scientific model ME 4.6 ultrasonic cleaner. After a few minutes in the ultrasonic bath the heterogeneous mixture of reactants, when the reaction was carried out with neat substrates, became homogeneous and evolution of nitrogen was observed. The bath temperature was maintained at 35°C. Progress of the reaction was qualitatively monitored for the disappearance of the enol ether and the appearance of a second UV-active component (tlc, SiO₂, eluting with 90% hexanes in ethyl acetate). After the reaction reached completion the products was isolated and purified by column chromatography (SiO₂, 90% hexanes in ethyl acetate).
- (14) In previous work on the effect of ultrasound on 1,3-cycloaddition reactions shorter reaction times but no difference in yields due to sonication were observed: see Borthakur, D. R.; Sandhu, J. S. J. Chem. Soc., Chem. Commun. 1988, 1444.
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