

An Unexpected Two-Group Migration Involving a Sulfonynamide to Nitrile Rearrangement. Mechanistic Studies of a *Thermal* N $\rightarrow$ C Tosyl Rearrangement

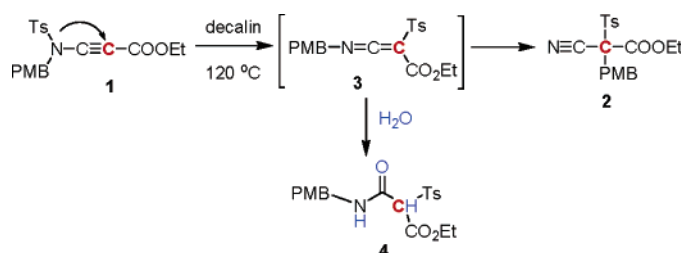
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ABSTRACT



We report the discovery of the first double-barreled thermal rearrangement of a sulfonynamide and a methoxybenzyl to a nitrile and the first rearrangement of an SO₂ group from sulfonynamide to ketimine. The rearrangement occurs under surprisingly mild conditions (onset at 100 °C in the melt).

Sulfonynamides have been studied for at least 100 years.¹ They are robust compounds that are known to be one of the most stable nitrogen protecting groups.² Cleavage of the S(O₂)-N bond requires extremely harsh conditions such as strong acid or base, as well as dissolving metal reduction.^{3,4} To the best of our knowledge, there is no reported example of an ArS-(O₂)-N bond breakage under mild, *thermal*, and neutral conditions.⁵

In our effort to develop a novel benzyne precursor,⁶ we have synthesized the ynamide **1**.^{7,8} Unexpectedly, in refluxing

toluene, **1** underwent a clean, truly deep-seated rearrangement to furnish sulfone **2** (Scheme 1 and Figure 1).⁸ To the best of our knowledge this rearrangement is unprecedented in organic chemistry since both the *p*-toluenesulfonyl (Ts) and *p*-methoxybenzyl (PMB) groups have migrated from the nitrogen atom onto a neighboring carbon at the β -position.⁹ We sought to elucidate the mechanism of this novel rearrangement in detail, and here we report our preliminary results.¹⁰

The rearrangement proceeds cleanly (isolated yield, 92%) in both neat (melt) and solutions (toluene, 1,2-dichlorobenzene, *o*-xylene, decalin) at 100–120 °C.¹¹ The rearrangement

(1) (a) *Sulfur in Organic and Inorganic Chemistry*; Senning, A., Ed.; Marcel Dekker: New York, 1971–1982; Vols. 1 and 4. (b) *The Chemistry of Sulfonic Acids, Esters and their Derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991.

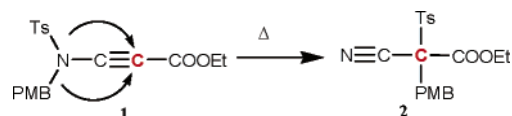
(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Ed.; John Wiley & Sons: New York 1999.

(3) Iley, J. In *The Chemistry of Sulfonic Acids, Esters and their Derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991; Chapter 12, pp 447–485.

(4) Searles, S., Jr.; Nukina, S. *Chem. Rev.* **1959**, 59, 1077–1103.

(5) For base-catalyzed 1,3-shift of the Ts group, see ref 3. For photochemical rearrangement, see: Elghamry, I.; Döpp, D.; Henkel, G. *Synthesis* **2001**, 1223–1227.

Scheme 1



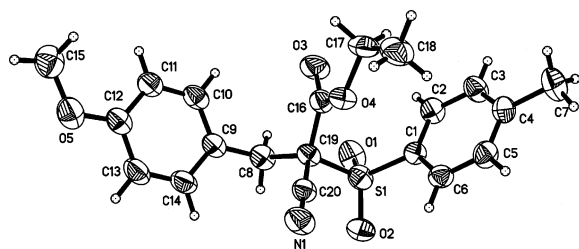


Figure 1. ORTEP drawing of product 2.

was conveniently followed by variable temperature ^1H NMR.⁸ In the nonpolar nonaromatic solvent¹² decalin, the rearrangement occurred via a detectable intermediate (3), Scheme 2. Rearrangement from the reactant 1 to an intermediate 3 was found to be first-order in reactant ($k_1(1 \rightarrow 3) = 5.69 \times 10^{-5} \text{ s}^{-1}$). The concentration of this intermediate accumulated up to about 29%, followed by a decrease as the reaction progressed (Figure 2). The reaction

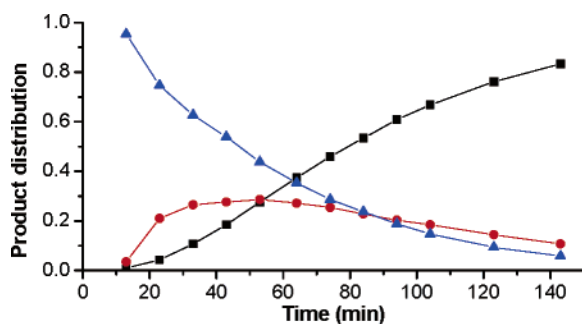
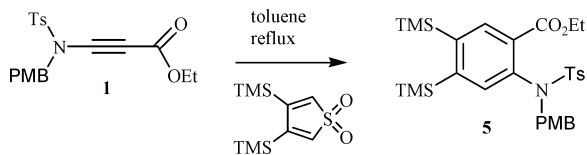


Figure 2. Rearrangement in decalin- d_{18} at 394 K: (▲) reactant 1, (●) intermediate 3, (■) product 2.

leading from the intermediate 3 to product 2 was again a first-order process. The intermediate was found to be stable at room temperature under inert atmosphere; however, it reacts readily with water during purification on a preparative TLC plate to afford amide 4 (Scheme 2). The structure of 4

(6) Duong, H. M.; Bendikov, M.; Steiger, D.; Zhang, Q.; Sonmez, G.; Yamada, J.; Wudl, F. *Org. Lett.* **2003**, 5, 4433–4436.

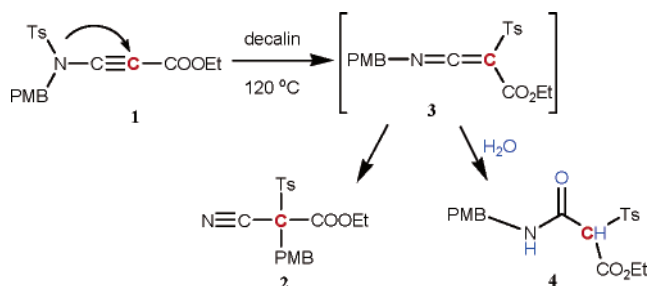
(7) Our original idea was to synthesize compound 5 by following reaction:



(8) For details see Supporting Information.

(9) We note that a relatively strained tertiary nitrile is produced. For hydrogen and silyl group rearrangement, see: Chiang, Y.; Grant, A. S.; Guo, H.-X.; Kresge, A. J.; Paine, S. W. *J. Org. Chem.* **1997**, 62, 5363. Gornowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1971**, 93, 1571. Ketenimine to nitrile rearrangement: Lee, K.-W.; Horowitz, N.; Ware, J.; Singer, L. A. *J. Am. Chem. Soc.* **1977**, 99, 2622. Neuman, R. C., Jr.; Sylwester, A. P. *J. Org. Chem.* **1983**, 48, 2285.

Scheme 2



was confirmed by X-ray analysis (Figure 3).¹³ The tosyl group is the first to migrate onto the former alkynyl carbon (labeled in red in Scheme 2) while the *p*-methoxybenzyl group remains attached to the nitrogen atom. From the crystal structure of amide 4, a keteneimine structure was inferred as intermediate 3. The observed ^1H and ^{13}C NMR signals of the reaction mixture are consistent with that inference for 3. This rearrangement required the breaking of an $\text{ArS}(\text{O}_2)\text{-N}$ bond under neutral conditions, which is unprecedented in organic chemistry. Thus, we discovered the **first thermal uncatalyzed tosyl rearrangement from sulfonamide to sulfone**.

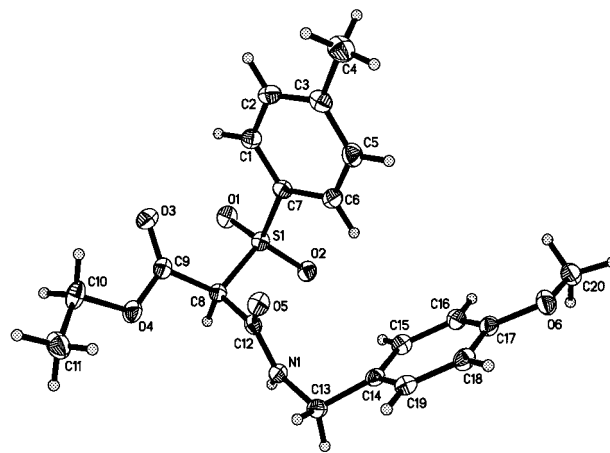


Figure 3. X-ray structure of 4 resulting from hydration of the intermediate 3.

Interestingly, in 1,2-dichlorobenzene (ODCB- d_4) and *o*-xylene, the reaction was found to be second-order in reactant with a nearly perfect straight fit in the Arrhenius plot ($R^2 =$

(10) Preliminary results with several related sulfonamides are presented in Supporting Information.

(11) In other high boiling solvents (hexachlorobutadiene and nitrobenzene) that were investigated, the rearranged product was also detected but in a less pure conversion.

(12) No dependence could be found between reaction rate and solvent polarity, suggesting no ionic species as intermediate or rate-determining transition state.

(13) An intermediate was detected (although in a smaller amount, the concentration accumulated up to about 5%) when the reaction was performed in hexachlorobutadiene and as neat.

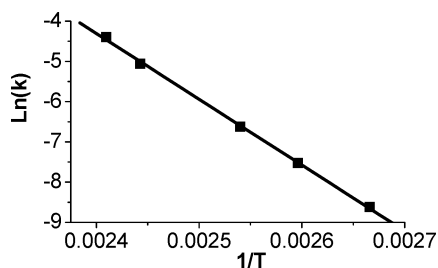


Figure 4. Arrhenius plot of the rearrangement of **1** established by ^1H NMR (ODCB- d_4), $R^2 = 0.999$.

0.999, $T = 375\text{--}415\text{ K}$, Figure 4. The second-order rate constant was determined to be $1.41 \times 10^{-3}\text{ M}^{-1}\text{ s}^{-1}$ at 394 K, with an activation energy of 32.4 kcal/mol. Despite data acquisition at multiple temperatures, no intermediate was detected during the course of the rearrangement. In aromatic solvents the reaction is second-order, indicating that the mechanism is different from the nonaromatic solvent studied (decalin), where the rearrangement is first-order in reactant.¹⁴

The rearrangement occurred much faster when **1** was heated neat, compared to solution. According to differential scanning calorimetry (DSC), **1** melts around 89 °C, followed by a very exothermic process (ca. 34 kcal/mol, Figure 5). Undoubtedly the exothermic process is due to the energy released as a result of the rearrangement.

To further understand this unusual transmogrification, we have used quantum mechanical calculations.⁸ Since this rearrangement involves the breaking of an S–N bond without the assistance of acid or base, the question that arises is what is the S–N bond energy? Unfortunately, to the best of our knowledge, there are no experimental or theoretical data on the value of the $\text{SO}_2\text{--N}$ bond energy in $\text{RSO}_2\text{--NR}_2$ systems

(14) Surprisingly, the activation energy was positive (+8 eu) in this bimolecular rearrangement. A possible speculation might be a rearrangement that gives an intermediate **3**, which is reversibly trapped in more polar solvents by a second molecule of starting material (zwitterionic [2 + 2] reaction), giving a second intermediate that falls apart to product plus reactant. Thus, the PMB group might either rearrange directly from linear ketoimine in nonpolar solvents and lead to ketoimine intermediate, or the PMB rearrangement might be assisted by [2 + 2] reaction in more polar solvent (which may not necessarily lead to a cyclobutene but might just begin to form a new C–C bond, by coordination, that leads to bending of the ketoimine, concomitantly assisting the PMB rearrangement). Hence, the activation barrier for the latter case is lowered and no ketoimine intermediate is observed. We note that this suggestion will require further investigation.

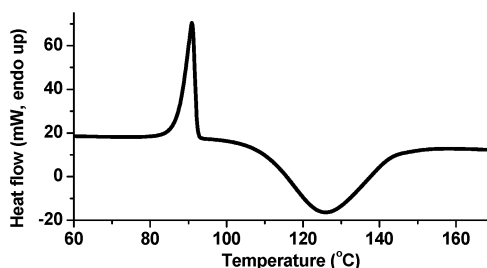
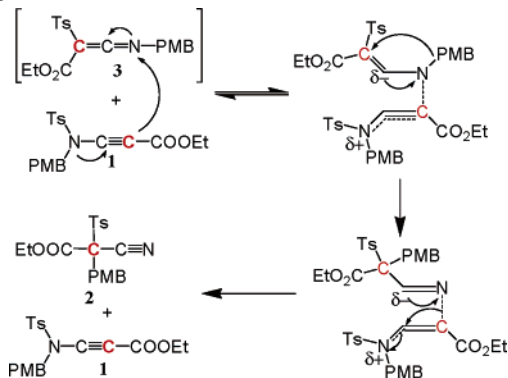


Figure 5. Dynamic DSC of **1**. Scan rate is 10 °C/min.

(where R = alkyl or aryl). Compared to high level ab initio theory, density functional theory is known to overestimate electron–electron repulsions in the S–N bond,¹⁵ which led to significant overestimation of the $\text{SO}_2\text{--N}$ bond length. The calculated S–N bond energy of $\text{Me}_2\text{N--SO}_2\text{Me}$ is 71.8 kcal/mol at the G2 level, whereas it is only 47.4 kcal/mol at B3LYP/6-31G*+ZPVE.^{16,17} Apparently the tosyl group rearrangement is facilitated by strong resonance stabilization of the transition state, i.e., scission of the S–N bond in **1** requires 16.5 kcal/mol less energy than in $\text{Me}_2\text{N--SO}_2\text{Me}$ (at B3LYP/6-31G*+ZPVE). Since a G2 level calculation predicts an S–N bond energy of 71.8 kcal/mol for $\text{Me}_2\text{N--SO}_2\text{Me}$, we believe that the dissociation of the same bond in **1** in the gas phase requires only ca. 55 kcal/mol.¹⁷ At the B3LYP/6-31G*+ZPVE level, the intermediate **3** and product **2** are more stable than the reactant **1** by 24.2 and 35.3 kcal/mol, respectively, while G2 corrected^{8,18} energies are 16.8 and 34.4 kcal/mol, respectively. The latter value is in good agreement with the DSC experiment. Thus, both steps of the rearrangement are thermodynamically favored.

To conclude, we have discovered the first uncatalyzed thermal sulfonamide to sulfone rearrangement and the first rearrangement of an arylsulfonyl group from a sulfonamide to keteneimine.

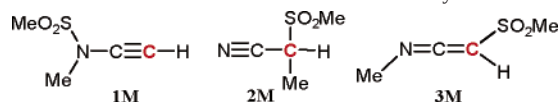
Acknowledgment. We are grateful to Dr. S. I. Khan for X-ray crystallographic analysis, Prof. Ohyun Kwon (UCLA) and Prof. William J. Leigh (McMaster University) for helpful discussions, and Dr. R. E. Taylor for help with NMR measurements (Department of Chemistry and Biochemistry,

(15) Bharatam, P. V.; Gupta, A.; Kaur, D. *Tetrahedron* **2002**, *58*, 1759–1764.

(16) Similarly, B3LYP/6-31G*+ZPVE predicts the S–N bond energy of $\text{Me}_2\text{N--SMe}$ to be 47.0 kcal/mol, whereas G2 theory predicts 61.1 kcal/mol.

(17) We note that our calculations are for heterolytic bond cleavage in gas phase. In contrast, in solution, we expect the dissociation energy to be lower as a result of solvation of the intermediate. We do not suggest that the reaction proceeds via complete S–N bond cleavage in the TS. However, we believe that reduced S–N bond energy in **1** or in $\text{Me}_2\text{N--SO}_2\text{Me}$ contributes to the low temperature of the rearrangement in Scheme 1.

(18) The large size of these molecules forbids studying them at the ab initio level of theory, so we used B3LYP/6-31G*+ZPVE for **1**, **2**, and **3** with corrections from examination of model compounds **1M**, **2M**, and **3M** at both G2 and B3LYP/6-31G*+ZPVE levels of theory.



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Supporting Information Available: Experimental details for the synthesis of **1–4** and their characterization (NMR,

IR, MS, elemental analysis); a kinetic study of **1**; X-ray data and CIF files for **1**, **2**, and **4**; and DFT calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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