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Sulfur Ylides via Decarboxylation of Carboxymethylsulfonium Betaines: A Novel and Mild Protocol for the Preparation of Oxiranes

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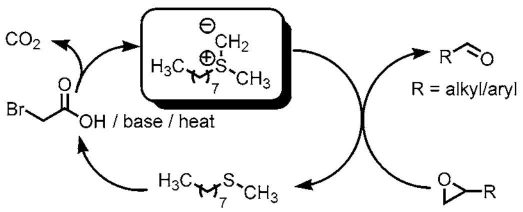
ABSTRACT



A novel protocol for the generation of sulfur ylides is described. The overall process involves thermal decarboxylation of a carboxymethylsulfonium betaine to give a sulfur ylide that, in the presence of an aldehyde, affords the corresponding terminal oxirane. Yields were found to correlate with the electron deficiency of the aryl aldehyde. In situ generation of betaine in the presence of an aldehyde successfully afforded the desired oxirane in moderate yield, thus demonstrating the feasibility of a catalytic process.

The construction of oxiranes represents an extremely useful synthetic transformation for the introduction of functionality into organic molecules.[1] Of the two common disconnections (Figure 1), the sulfur ylide approach offers potential advantages in terms of atom efficiency and facility for stereocontrol.[2] In addition to epoxide formation, sulfur ylides can be used to prepare a wide range of synthetically valuable compounds such as aziridines[3] and cyclopropanes[4,5] via methylidene transfer to the appropriate π acceptors such as suitably activated imines and conjugated olefins.[6]

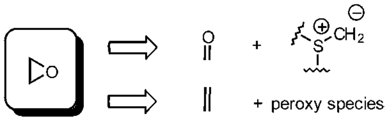


Figure 1. Strategic disconnections in oxirane formation.

A number of methods are available for the generation of sulfur ylides.[7,8] The classic method involves a stepwise

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(1) (a) Rao, A. S. In *Comprehensive Organic Synthesis: Oxidation*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Chapter 3.1. (b) Plesnicar, B. In *Oxidation in Organic Chemistry*; Trahanovski, W. S., Ed.; Academic Press: New York, 1978; Chapter III.

(2) (a) Aggarwal, V. K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. II, pp 679−693. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.

(3) For the use of sulfonium and sulfoxonium ylides in aziridination chemistry, see: (a) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635. (b) Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Lin, L. *J. Org. Chem.* **1998**, *63*, 4338. (c) García-Ruano, J. L.; Fernandez, I.; Prado Catalina, M.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.

(4) For general discussions on the use of sulfur ylides in cyclopropanation chemistry, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998; Chapter 7. (b) *Nitrogen Oxygen and Sulfur Ylides in Synthesis: A Practical Approach*; Clark, J. S., Ed.; Oxford Press: Oxford, 2002.

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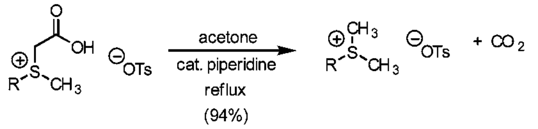
sequence of (1) alkylation of a dialkyl sulfide to form a sulfonium salt and (2) treatment of the sulfonium salt with strong base to form the ylide. Aggarwal and co-workers have demonstrated and refined an ingenious catalytic asymmetric approach to homochiral epoxides and aziridines based on the generation of *S*-ylides via reaction of chiral sulfides with rhodium metallocarbenes.[9] Through this approach, a range of substituted epoxides can be generated in high yield and with excellent control of both absolute and relative stereochemistry.[10] The same author has also demonstrated a similar catalytic cycle using Simmons−Smith reagents (Et_2Zn/$ClCH_2I$) as *S*-ylide precursors.[11] In yet another approach, Tanzawa and co-workers reported the generation of *S*-benzylsulfonium ylides via fluoride-mediated desilylation of trimethylsilylmethylbenzyl sulfonium precursors under essentially nonbasic conditions.[12] The generation of sulfur ylides under mild conditions has been shown to be particularly beneficial in situations where base-sensitive aldehydes are employed.[13]

In our search for alternative mild protocols for *S*-ylide generation that might be capable of sustaining catalytic methylidene tranfers, we were intrigued by the possibility of the decarboxylation of carboxymethyl-substituted sulfonium salts. Our initial search of the literature revealed a key paper by Burness,[14] who described the decarboxylation of carboxymethyldodecylmethyl sulfonium tosylate in refluxing acetone using catalytic piperidine (Scheme 1). This reaction furnished the corresponding dimethyl-dodecylsulfonium tosylate in 94% yield. It occurred to us that this process involves the intermediacy of a sulfur ylide.

Scheme 1[a]



[a] R = *n*-alkyl (C_7H_{15}−$C_{16}H_{33}$ and −$(CH_2)_n$−).

We now wish to report a new protocol for the generation of sulfur ylides based on the decarboxylation of carboxymethylsulfonium betaines under aprotic conditions (Scheme 2), as well as their trapping with aldehydes to form epoxides.[15]

The key betaine reagent **2** was readily prepared from the corresponding thetin bromide **1** according to the known method of Ratts and Yao.[16] The choice of the relatively lipophilic betaine **2** was driven by its high level of solubility in most commonly used organic solvents of medium to even low polarity.

Handling the carboxymethylsulfonium betaines was found to be problematic at temperatures higher than 40°C or when dissolved in nonpolar aprotic media.[17] However, when (1) kept in solution using either methanol and/or water or (2) stored in crystalline form in the refrigerator, betaine **2** can be stored for months without appreciable decomposition. Significantly, use of solvents such as chloroform revealed a half-life of approximately 5 h at room temperature, whereas when placed in nitrobenzene, gas evolution (CO_2) was observed immediately at room temperature.

It was anticipated that the rate of decarboxylation and therefore the efficiency of methylidene transfer would be strongly solvent dependent.[17] For example, highly polar and protic solvents would likely provide good solvation for the charged betaine relative to the transition state and thereby raise the effective activation barrier for decarboxylation. At the other extreme, nonpolar aprotic solvents would be expected to facilitate decarboxylation by providing minimal solvation, althougth the extent of bond breaking in the transition state will also be an important factor.

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(5) For the use of sulfur mediators in cyclopropanation chemistry, see: (a) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267. (b) Solladié-Cavallo, A.; Diep-Vohuule, A.; Isarno, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1689. (c) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **1997**, *62*, 2337.

(6) For a general discussion on the construction of three-membered rings using ylides, see: Dai, L.-X.; Hou, X.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, *71*, 369 and references therein.

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(9) (a) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747. (b) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni; M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *41*, 1430. (c) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004.

(10) (a) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Studley, J.; Jones, R. V. H.; Fieldhouse, R. In *Current Trends in Organic Synthesis*; Scolastico, C., Nicotra, F., Eds.; Academic Press: New York, 1999; pp 191−199. (b) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. In *Selective Reactions of Metal-Activated Molecules*; Werner, H., Schreier, P., Eds.; Vieweg: Gottingen, Germany, 1998; pp 13−24.

(11) (a) Aggarwal, V. K.; Coogan, M. P.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Eur. J. Org. Chem.* **2002**, 319. (b) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587.

(12) Tanzawa, T.; Shiria, N.; Sato, Y.; Hatano, K.; Kurono, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2845.

(13) Aggarwal, V. K.; Abdel-Rahman, H.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron Lett.* **1995**, *36*, 1731.

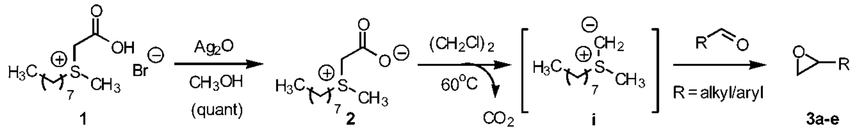
(14) Burness, D. *J. Org. Chem.* **1959**, *24*, 849.

(15) **Representative Reaction Procedure.** An oven-dried round-bottomed flask was equipped with a stir bar, septum, and drying tube. To this system was added aldehyde (1.0 equiv) and 1,2-dichloroethane (0.1 M, 3.0 mL). The system was externally heated to 60 °C (sand bath) at which time a solution of betaine (2.0 equiv) in 1,2-dichloroethane (0.1 M, 4.0 mL) was added via syringe pump over a period of 1.0 h. The reaction mixture was allowed to stir for an additional period of 2.0 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and immediately purified by silica gel chromatography using a gradient eluent system of hexanes and EtOAc (3 column equiv per solvent combination) to afford analytically pure oxirane [hexanes/EtOAc, 100:0, 64:1, 32:1, 16:1, 10 × 30 mm SiO_2, 10 mL fractions].

(16) Ratts, K. W.; Yao, A. N. *J. Org. Chem.* **1966**, *31*, 1185.

(17) We are currently looking into a more detailed study on the decarboxylative process in terms of solvent dielectric strength. See: Grate, J.; McGill, R.; Andrew, H. *J. Am. Chem. Soc.* **1993**, *115*, 8577. Adams, J.; Hoffman, L.; Trost, B. M. *J. Org. Chem.* **1970**, *35*, 1600.

Scheme 2



Using 4-nitrobenzaldehyde and carboxymethylsulfonium betaine **2** in dichloroethane as our benchmark, we began optimization studies focusing on stoichiometry and temperature. Results from these studies were then used as a basis for exploring the scope of this reaction in terms of substrate generality and also to explore the feasibility of an in situ protocol based on the use of commercially readily available materials (sulfides, halocarboxylic acids, etc).

Starting with a ratio of aldehyde to betaine of 1:1, we studied a total of five temperatures in order to test the efficiency of methylene transfer. Because appreciable decomposition was first observed at 40 °C, this temperature was used as a starting point and increasing intervals of 10 °C were used for each subsequent run ending at a temperature of 80 °C. Reaction progress was expressed as a ratio of aldehyde to oxirane (by GC area). The optimal temperature was 60 °C, yielding a ratio of 16:84 aldehyde to oxirane. It is important to note that all reactions were clean as judged by GC with aldehyde (recovered), oxirane (isolated), and sulfide the only significant components.

In terms of stoichiometry, a 1:2 ratio of aldehyde to betaine was optimal and gave the best conversions to oxirane. However, background decomposition of the betaine does lead to inefficiency in methylene transfer and presumably affords byproducts that are relatively nonvolatile. Using a 1:2 ratio of aldehyde to betaine and a reaction temperature of 60 °C, crude GC analysis showed complete consumption of the aldehyde, resulting in an 84% isolated yield of oxirane. Aldehyde to betaine ratios of 1:1 and 2:1 resulted in incomplete consumption of the aldehyde. With these results at hand, a study on substrate generality was carried out and is presented below.

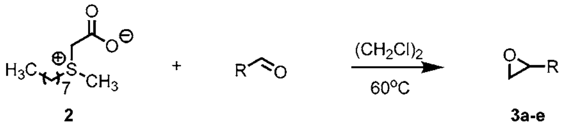
Table 1 reveals some interesting trends. Overall, electron-deficient aryl aldehydes (entries 1−4) were superior to aliphatic and electron-rich aryl aldehydes (entries 5 and 6) and benzophenone (entry 7). Several attempts varying reaction conditions with these and other carbonyl derivatives were made that consistently resulted in very low yields of the desired oxirane. With each substrate that did not afford the desired oxirane, the starting carbonyl derivative was isolated and recovered in >95%, thus confirming the poor efficiency of methylene transfer.

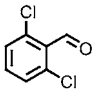
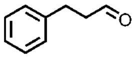
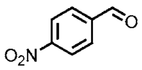
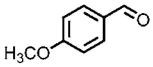
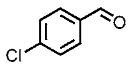
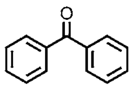
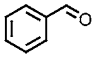
The absence of oxirane products in entries 6 and 7 is worthy of comment. Benzophenone epoxidation with dimethylsulfonium methylide has been achieved in excellent yields using protocols based on dimsylsodium[7a] (84%) and KOH[7d] (78%). Both procedures operate at or close to room temperature. In the present case, however, epoxidations are carried out at 60 °C, a temperature necessary to achieve acceptable rates of decarboxylation/ylide formation. Further, unstabilized sulfur ylides are known to have short half-lives in solution, typically on the order of a few minutes even at room temperature.[7a,8b,c] Therefore, under our experimental conditions, we propose that benzophenone is unable to compete with rapid decomposition of the ylide. Likely decomposition pathways for methylides include disproportionation, protonation, and elimination.[7a,8b,c] Efforts toward isolating byproducts formed in systems that did not have good to moderate levels of conversion to oxirane were both unsuccessful and deemed secondary.

One final study involved the in situ generation of both sulfonium bromide **1** and sulfonium betaine **2**. Reaction of methyl octyl sulfide with bromoacetic acid in the presence of both 4-nitrobenzaldehyde and silver(I) carbonate on Celite (approximately 2 equiv) in a hot solution of 1,2-dichloroethane (0.1 M, 60 °C) afforded the desired oxirane (40% conversion) and some unreacted aldehyde. The product was identified by GC and its structure confirmed by NMR. This single result demonstrated not only the feasibility of in situ preparation of sulfur ylide using commercial reagents but also the possibility of performing these reactions using only a catalytic quantity of sulfide.

In view of the very short half-lives expected for unstabilized sulfur ylides at temperatures approaching 60 °C and in order to improve the efficiency of the betaine decarbox-

Table 1. Carboxymethylsulfonium Betaine-Promoted Oxirane Formation



entry	carbonyl derivative	**3**, %[a]	entry	carbonyl derivative	**3**, %[a]
1, **a**		85	5, **e**		45
2, **b**		84	6		–[b]
3, **c**		62	7		–[b]
4, **d**		55			

[a] Isolated yields of chromatographically homogeneous spectroscopically pure products are reported. [b] Desired oxirane not isolated; carbonyl derivative recovered in >95%.

ylation process and minimize side reactions during epoxidation, part of our research is geared to finding inherently less stable betaines that decarboxylate at lower temperatures. To do this, we have prepared some aryl-substituted betaines, and we will report results using these fourth-generation compounds in due course.

In summary, a novel approach has been developed that permits the transformation of aldehyde functionality to oxirane in good yield using carboxymethylsulfonium betaine **2** as a promoter. The latter is a stable crystalline compound that decarboxylates on heating in solvent to give ylid and CO_2 ("ylide in a bottle"). Ylide generation and trapping of aldehyde to give oxirane occurs under mild and metal-free conditions. Electron-deficient aryl aldehydes provided the highest conversion to the desired oxirane. The basis of a process involving in situ generation of betaine and *S*-ylide has also been demonstrated using 4-nitrobenzaldehyde as a carbonyl acceptor. Our continued research in this area will explore (1) solvation effects on betaine decarboxylation, (2) the use of chiral nonracemic sulfur templates, (3) the development of ultralabile betaines, and (4) the extension of this methodology to aziridines via use of activated imines.

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Supporting Information Available: Synthetic and experimental procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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