

Modulation of Carbene Spin State Population through Precursor Photophysics

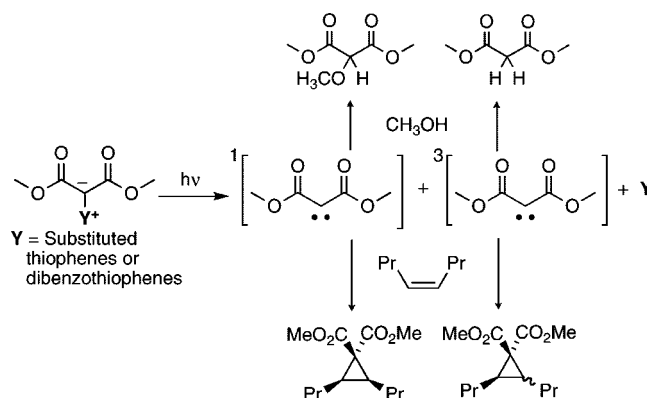
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Received December 19, 2008

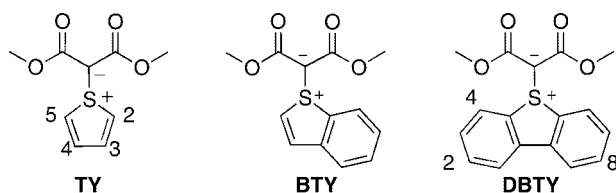
ABSTRACT



Dicarbomethoxycarbene can be generated by photolysis of S–C sulfonium ylides derived from thiophene. By manipulating the thiophene (leaving group) portion of the ylide, the initial spin distribution of the carbenes can be strongly influenced. With certain carbene traps, product distributions from dicarbomethoxycarbene depend on the initial spin state distribution in which the carbene is generated and this is used as a means to report on the initial spin state distributions. This approach should be general for other carbenes generated from analogous precursors.

We recently reported that photolysis of thiophene-based sulfonium ylides **TY**, **BTY**, and **DBTY** results in formation of dicarbomethoxycarbene, **1**.¹

Photolysis of these compounds in methanol resulted in different ratios of the formal OH insertion product **2**, interpreted as the product of the singlet carbene (**1**), and dimethyl malonate (**3**), interpreted as the product of **3****1** (Scheme 1). The ratio of **2**:**3** varied from a high of about 14 for **BTY** to a low of about 1.4 for **DBTY**.



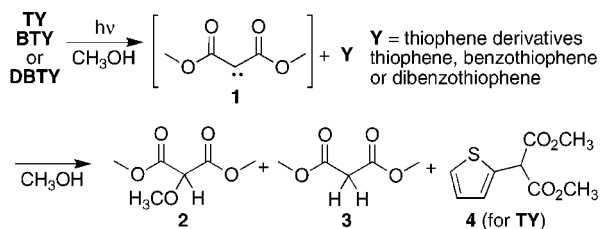
It is notable that, for these carbene precursors, the chromophore is centered on the thiophene, rather than on the carbene. It was posited that the variation in **2**:**3** was due to the intimate photophysics of each chromophore and the relative initial populations of **1****1** and **3****1** that are generated. Indeed, the generation of both singlet and triplet benzoylnitrene from the closely related *N*-benzoyl dibenzothiophene sulfilimine was recently documented.²

This supposition requires that trapping of the carbene is faster than, or at least competitive with, intersystem crossing by the carbene. Jones and co-workers showed that direct and sensitized photolysis of methyl dizaomalonate gave differing stereochemical outcomes for cyclopropanation,³ so the notion

(1) Stoffregen, S. A.; Heying, M.; Jenks, W. S. *J. Am. Chem. Soc.* **2007**, *129*, 15746–15747.

(2) Desikan, V.; Liu, Y.; Toscano, J. P.; Jenks, W. S. *J. Org. Chem.* **2007**, *72*, 6848–6859.

Scheme 1. Photolysis of Thiophene Ylides in Methanol^a



^a A 22% yield of **4** was obtained from photolysis of **TY**.

of intersystem crossing (ISC) being slower than or comparable in rate to reactions of the carbene was not without precedent. It also must be the case that the triplet energy of the precursor is at least as high as the S–C BDE required to produce the thiophene derivative and the triplet carbene. Using data from a previous computational investigation⁴ the S–C BDE in **TY** can be estimated at approximately 44 kcal/mol, surely lower than the triplet energy of the ylide. Similarly, an estimate of approximately 60 kcal/mol can be obtained for **DBTY**, which is similar to or a few kcal/mol lower than our best estimate of the triplet energy of that ylide, based on dibenzothiophene sulfoxide.⁵

In this letter, we show that the initial spin distribution of dicarbomethoxycarbene can be manipulated over a wide range by adjusting the structure of the thiophene portion of the sulfonium ylide precursor. This allows the decoupling of the spin state of the carbene from *its* structure, instead relying on the photophysics of the leaving group, where the critical chromophore of the precursor resides. A heavy-atom strategy seemed particularly plausible, given previous results in which heavy atom substitution on dibenzothiophene-S-oxide had modestly increased the quantum yield of photochemical deoxygenation.⁶

A series of substituted analogs of **TY** and **DBTY** were prepared and photolyzed in methanol. The rate of reaction between **1** and neat methanol should approach 10^{10} s^{-1} .⁷ While the rate of intersystem crossing from **1** to **3** is not known, it is not likely to be competitive with such a reaction velocity. However, the rate of reaction by hydrogen abstraction by **3** is likely to be ~ 3 orders of magnitude slower.⁸

The ratio of **2/3** was determined at low conversion (ca. 10%) by GC and was within experimental error of values

obtained at full conversion, as determined by NMR integration.⁹ Enough repetitions were done for the new compounds to determine reasonable standard deviations of the yields (Table 1). The fractions of products attributable to singlet insertion, that is, **2**, are also given.¹⁰

Table 1. Yields of OH Insertion and Hydrogen Abstraction on Photolysis of Sulfonium Ylides in Methanol

precursor ^a	yield 2 (%) ^b	yield 3 (%) ^b	2/(2 + 3)
TY ^c	52	5	0.91
2,5-dichloro TY	94.2 ± 1.3	4.8 ± 0.6	0.95
2-bromo TY	94.7 ± 4.3	5.9 ± 1.1	0.94
2,4-dibromo TY	86.5 ± 2.5	9.4 ± 1.4	0.90
3,4-dibromo TY	86.2 ± 2.1	12.0 ± 2.1	0.88
2-iodo TY	49.3 ± 1.4	27.6 ± 1.3	0.64
DBTY ^c	54	39	0.58
4-bromo DBTY	50.3	44.6	0.53
2,8-dibromo DBTY	51.5	48.0	0.52
³ BP + DBTY ^d	9	57	0.14
6	28	65	0.30
7	3.7	80	0.044

^a See illustration of parent compounds for ring numbering. ^b Yields at full conversion. Error limits for yields of **2** and **3** are standard deviations. ^c Reference 1. Compound **4** also formed from **TY**. ^d **DBTY** sensitized by irradiation of benzophenone.

Two compounds merit specific discussion. 2,4-Dibromo**TY** decomposed even in the dark over the course of tens of hours. On standing in methanol in the dark for two days, only 2,4-dibromothiophene and dimethyl methoxymalonate (**2**) were observed.

Photolysis of 2-iodo**TY** produced not only the expected products but also thiophene. However, closely monitored photolyses showed that thiophene was a secondary photolysis product of 2-iodothiophene. Thus, the distribution of **2** and **3** derives only from photolysis of 2-iodo**TY** and not from a mixture of that and **TY** itself.

It is apparent from the error limits that **TY**,¹⁰ 2,5-dichloro**TY**, and 2-bromo**TY** produce essentially the same fraction of singlet product with methanol. The dibrominated derivatives of **TY** did produce a larger fraction of triplet product **3**, as did 2-iodo**TY**. Similarly, the brominated analogs of **DBTY** gave larger fractions of **3** than the unsubstituted analog. Benzophenone-sensitized **DBTY** gave more **3** than direct photolysis of any of the bromo- or iodo-compounds (57%) and considerably less **2**, but the mass balance is not as good.

Photochemical cleavage of a selenophene ylide was also investigated, based on the precedent of sulfoxide (or selenoxide) deoxygenation. Substitution of selenium for sulfur enhances the efficiency of photochemical deoxygenation of dibenzoselenophene-Se-oxide vs dibenzothiophene-S-oxide

(9) Overlap of ¹H signals made integration difficult at low to moderate conversion.

(10) The reaction of **1** with thiophene to form **4** is probably a singlet reaction and therefore artificially lowers the yield of **2** (and its fraction) when **TY** is the precursor. The analog of **4** was not found in any other case.

(3) (a) Jones, M., Jr.; Ando, W.; Hendrick, M. E.; Kulczycki, A., Jr.; Howley, P. M.; Hummel, K. F.; Malament, D. S. *J. Am. Chem. Soc.* **1972**, *94*, 7469–79. (b) Jones, M., Jr.; Ando, W.; Kulczycki, A., Jr. *Tetrahedron Lett.* **1967**, *139*, 1–6.

(4) Stoffregen, S. A.; McCulla, R. D.; Wilson, R.; Cercone, S.; Miller, J.; Jenks, W. S. *J. Org. Chem.* **2007**, *72*, 8235–8242. A group additivity approach must be used to approximate the BDE for **TY** or **DBTY**.

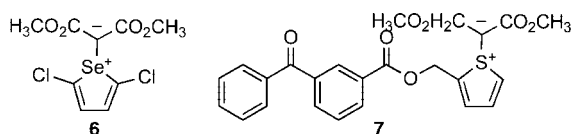
(5) Jenks, W. S.; Lee, W.; Shutters, D. *J. Phys. Chem.* **1994**, *98*, 2282–2289.

(6) Nag, M.; Jenks, W. S. *J. Org. Chem.* **2004**, *69*, 8177–8182.

(7) Wang, J.-L.; Toscano, J. P.; Platz, M. S.; Nikolaev, V.; Popik, V. *J. Am. Chem. Soc.* **1995**, *117*, 5477–5483.

(8) See, for example, Luszyk, J.; Kanabus-Kaminska, J. M. Representative Kinetic Behavior of Selected Reaction Intermediates: Free Radicals. In *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. 2, pp 177–209.

by an order of magnitude,¹¹ although it is not clear whether the enhanced quantum yield is due to the weaker Se–O bond or the heavy atom effect.



The parent malonic selenophene ylide was known to be insufficiently stable at room temperature for these experiments.¹² However, malonic ylide of 2,5-dichloroselenophene **6** was straightforward to handle.¹³ Photolysis of **6** in methanol led to a very high proportion of the triplet product, greater than any other compound that was not sensitized (Table 1).

Control experiments, in which all of the substituted thiophene ylides, dibenzothiophene ylides and **6** were heated in a septum-sealed tube in methanol in an oven at 80 degrees until all the material was decomposed, resulted in formation of only **2**, to the exclusion of **3**. This implies that the population of ¹**1** is quantitatively trapped before ISC. However the benzophenone-sensitized results at least suggest that some ³**1** to ¹**1** ISC occurs on the time scale of the slower hydrogen abstraction reaction of the triplet carbene. Given this result, and the low mass balance, compound **7** was also prepared,¹⁴ with the idea that internal triplet sensitization should be quantitative and that irradiation could be carried out so that nearly all the light was absorbed by the benzophenone moiety. The mass balance after photolysis was considerably improved, compared to the bimolecular sensitization case. As shown, the fraction of singlet product was 4.4%. We take this as an implication that there is a slight leakage of ³**1** to ¹**1** ISC that competes with hydrogen abstraction.

A second classic probe for spin multiplicity is the stereochemistry observed on cyclopropanation. Singlet carbenes (and related species) are expected to react with alkenes with retention of stereochemistry, while triplet carbenes give cyclopropanes of mixed stereochemistry. Thus, starting from a *cis* alkene, the appearance of the *trans* cyclopropane is diagnostic of triplet reactivity.

Direct irradiation of methyl diazomalonate is known to give approximately 90% retention of stereochemistry with *cis*-4-methyl-2-pentene, whereas the opposite ratio was obtained on sensitization with benzophenone.³ However, it was concluded that, at high alkene concentrations, some of the loss of stereochemistry on direct irradiation was due to reaction between the excited diazo compound and the alkene,

bypassing the carbene completely. We do not have any evidence for similar reactivity of the sulfonium ylides.¹

Here, thermolysis of **TY** and **DBTY** was carried out in 10% *cis*-4-octene in acetonitrile as a control for 100% singlet generation,¹⁵ and nearly quantitative yields of *cis*-**5** were accompanied by only trace quantities of the *trans* adduct. This established that the “singlet carbene limit” is nearly quantitative *cis*-**5**, which can be compared to the results for other conditions in Table 2.

Table 2. Yields of *cis*- and *trans*-Cyclopropanes from Photolysis of Sulfonium Ylides in 10% *cis*-4-octene in Acetonitrile

precursor	yield <i>cis</i> - 5 ^a	yield <i>trans</i> - 5	% singlet ^b
TY ^d	95	5	88
2,5-dichloro TY	95.2	3.7	91
2-bromo TY	93.5	3.2	92
2,4-dibromo TY	89.5	8.3	80
3,4-dibromo TY	86.8	8.6	78
2-iodo TY	70.2	20.4	46
DBTY ^d	60	40	4.3
4-bromo DBTY	62.1	35.4	13
2,8-dibromo DBTY	61.5	36.8	10
7	58.3 ± 0.3	41.7 ± 0.5	0 ^c

^a Yields determined at complete conversion using GC. ^b Determined from (*cis*-**5** – 1.40 • *trans*-**5**)/(*cis*-**5** + *trans*-**5**), and assumes no intersystem crossing. See text. ^c Used as the standard to establish a lower limit of singlet chemistry. ^d Relative yields.

Using direct photolysis of methyl diazomalonate, Platz and co-workers obtained rate constants near $3 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ for the reaction of *cis*-alkenes with **1** in concentration ranges of up to a few M,⁷ similar to the concentration used here, near 1 M. They make no mention of curvature in their quenching plots, which indicates a single kinetic species. This implies that either intersystem crossing of **1** is very fast (subnanosecond) or that very little triplet carbene was generated in their experiments. We find the latter interpretation to be more consistent with current results, and believe that quantitative trapping of ¹**1** on the time scale of a few ns by ~1 M alkene to be very plausible.

In contrast, the all-³**1** product limit in 1 M *cis*-4-octene should be a mixture of the *cis* and *trans* cyclopropanes. It was established using compound **7**. Multiple photolyses were carried out in order to establish a standard deviation for reproducibility, which was approximately 1% of the reported yields. A ratio of *cis* to *trans* **5** of 1.40 was obtained.

Obviously, this is not the equilibrium ratio of the two cyclopropanes. Two interpretations are possible: (1) ISC of ³**1** to ¹**1** competes with its capture by the octene; (2) the

(15) Thermolysis was at 80 °C in a sealed tube, using the same initial concentration and solvent mixture as for the photolyses.

(11) McCulla, R. D.; Jenks, W. S. *J. Am. Chem. Soc.* **2004**, *126*, 16058–16065.

(12) Bien, S.; Gronowitz, S.; Hoernfeldt, A. B. *Chem. Scr.* **1984**, *24*, 253–254.

(13) Compound **6** was prepared by coupling of dimethyl diazomalonate in the usual fashion to 2,5-dichloroselenophene. Gronowitz, S.; Frejd, T. *Acta Chem. Scand. B* **1976**, *B30*, 439–449.

(14) Compound **7** was prepared by esterification of 3-benzoylbenzoic acid with commercially available thienylmethanol, followed by coupling of the diazomalonate in the usual fashion.

biradical formed on addition of $^3\mathbf{1}$ to the olefin does not equilibrate completely before its closure. We do not have the data to distinguish between these possibilities with any certainty, but we can recognize this as the maximum fraction of *trans*-**5** obtainable.

Accordingly, the present ylides were photolyzed in the same solvent mixture of 10% *cis*-4-octene in acetonitrile. The results are given in Table 2. If it is assumed that only $^3\mathbf{1}$ is generated on photolysis of **7**, and both the singlet and triplet carbenes are quantitatively trapped by the olefin before ISC, then the 58.3:41.7 (1.40) ratio of cyclopropane stereoisomers can be taken to reflect the limit achieved from reaction of only $^3\mathbf{1}$. Given that $^1\mathbf{1}$ results only in the *cis* isomer, then the fraction of singlet chemistry in cyclopropanation can be determined from the observed yields of *cis* and *trans* cyclopropane **5** for a given precursor. These numbers, given in Table 2, are only an upper limit on the initial yield of $^1\mathbf{1}$, because we cannot establish that $^3\mathbf{1}$ is quantitatively trapped.

The results in Tables 1 and 2 deserve comparison. The parallelism between the methanol and olefin photolysis results is striking, with 2,5-dichloro**TY** and 2,5-dibromo**TY** giving nearly identical *cis/trans* ratios, followed descending stereospecificity for the rest of the entries. However, in contrast to the alkene results, the methanol chemistry clearly shows that some singlet chemistry occurs even on quantitative generation of $^3\mathbf{1}$, so the exact estimates of singlet chemistry cannot align quantitatively.

The obvious trend, regardless of the precision of the estimate of the fraction of singlet carbene, is that heavy atom substitution on the thiophene or dibenzothiophene chromophore leads to greater fractions of triplet chemistry. This confirms the original proposal¹ that the variation from thiophene to benzothiophene to dibenzothiophene was itself due to variations in the photophysics of the precursor. As expected, there is little effect with Cl substitution. It is clear that the 3- and 4-positions are better than 2- and 5-positions for increasing the triplet yield from the thiophene based ylides from the bromo compounds, though we did not try to duplicate this effect with iodo substituents. This is, in part, because the most efficient manner for generating triplet

carbene would obviously be compound **7**, whose preparation is very straightforward as well.

As a final remark, it is worth pointing out that the photodissociation of these ylides to form carbenes has proven to be considerably more flexible, with respect to the thiophene derivative, than the corresponding generation of O atoms from sulfoxides.^{6,11,16} Photochemical generation of nitrenes from sulfilimines appears to be, reasonably, an intermediate case.^{2,17} While a causal relationship has yet to be established, a good correlation exists between this and estimates of the relevant bond dissociation energies which are weakest for the sulfonium ylides.¹⁸ We believe this approach to carbene generation using one or more of the sulfonium ylides should be general for preparation of any carbene whose corresponding *S,C* ylide is synthetically accessible.

Acknowledgment. We acknowledge the National Science Foundation (CHE 0213375) for partial support of this research.

Supporting Information Available: Detailed procedures and product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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