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Photochemical Route to the Synthesis of Thiolane 1-Oxides

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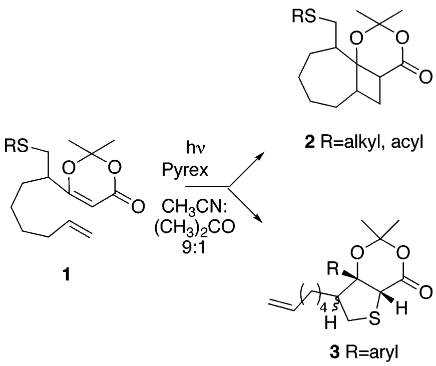
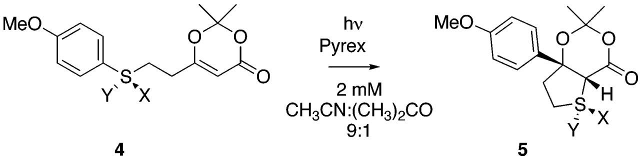
During the course of our studies on a second-generation synthesis of ingenol,[2,3] we have described the intramolecular photocycloaddition of dioxenone **1** (R = *i*-Bu) to give photoadduct **2** (R = *i*-Bu) in 31% yield.[4] We report herein that the outcome of the photocycloaddition of **1** depends critically on the nature of the sulfur R group. In the case of aromatic sulfides, irradiation of **1** (R = *p*-MeOPh) leads not to the formation of the expected [2 + 2] photocycloaddition products corresponding to **2** (R = *p*-MeOPh), but instead to the formation of highly substituted thiolanes, such as **3** (R = *p*-MeOPh).[5] We also present preliminary results on the manipulation of these thiolane photoproducts.

Scheme 1



The lack of participation of the 5-hexenyl moiety in the photocycloaddition of **1** led us to examine the reactivity of the simplified sulfide **4a**,[6] which we anticipated would generate analogous thiolane structures. In the event, irradiation of **4a** led to the formation of thiolane **5a** in 53% yield. We next examined the role of the oxidation state of sulfur on this novel photochemically induced rearrangement. We were delighted to find that irradiation of the sulfoxide **4b** led to the formation of **5b** as a 1.2:1 mixture of epimeric sulfoxides in 98% yield as confirmed by X-ray crystallographic analysis. The reaction of sulfone **4c** proceeded to give the corresponding sulfone product **5c** in lower yield (22%).

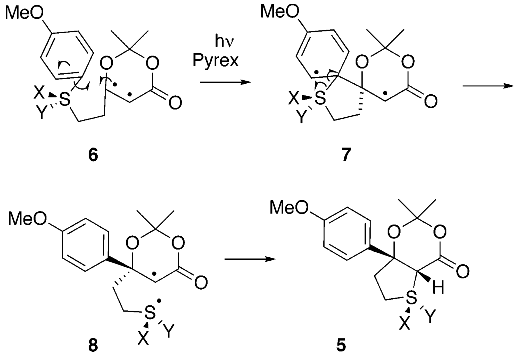
Table 1. Survey of the Sulfur Oxidation State



rxn	4	X	Y	time	5	yield (%)
1	**4a**	--	--	1 h	**5a**	53
2	**4b**	O	--	15 min	**5b**	98 (1.2:1 β:α)
3	**4c**	O	O	15 min	**5c**	22

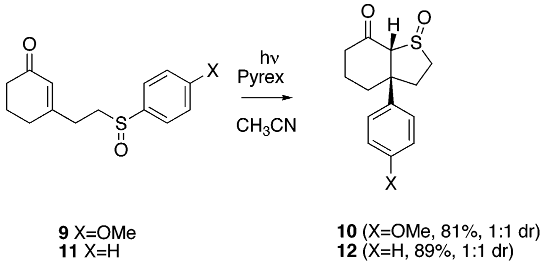
The formation of **5** is consistent with the mechanistic proposal shown in Scheme 2. Addition of the β radical of the dioxenone triplet **6** to the *ipso* carbon of the aromatic ring leads to the formation of **7**, which can undergo fragmentation with concomitant rearomatization to generate **8**, leading to the observed product **5** upon radical recombination. Both sensitization and quenching experiments are consistent with the reaction proceeding through a triplet state. Without acetone, the reaction does not occur, and the addition of piperylene suppresses it. This mechanistic scheme is also consistent with the high yield obtained on irradiation of sulfoxide **4b** since the sulfinyl group is known to be an excellent radical stabilizing group as indicated in **8** (X = O; Y = --).[7]

Scheme 2



We next extended these studies to the examination of the enone chromophore, as shown in **9**[8] (Scheme 3). Irradiation of **9** leads to thiolane 1-oxide **10** (obtained as a ca. 1:1 mixture of epimeric sulfoxides) in 81% yield, attesting to the scope of this novel photochemical transformation. We note that the rearrangement also occurs using substrate **11**, which lacks the electron-donating group on the aromatic ring, to provide **12** in comparable yield (89%). That the enone photocycloaddition reaction proceeds through the triplet state is supported by analogous quenching experiments with piperylene. Sensitization is not required in the enone case, but the reaction also proceeds in the presence of acetone.

Scheme 3



In an effort to further extend the utility of this process, we have examined the effect of different heteroatom substitution on the aromatic ring of **9**, as outlined in Scheme 4. Irradiation of **13** leads to the formation of hemiketal **14** in excellent yield, which undergoes

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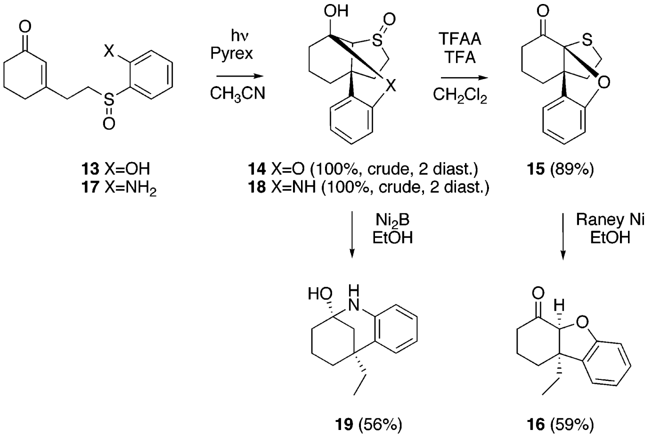
Scheme 4

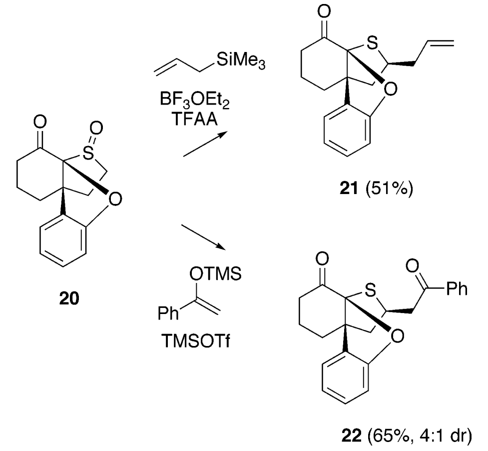


Pummerer rearrangement to give tetracyclic thiolane **15**. Desulfurization of **15** with Raney nickel leads to the efficient formation of the angularly substituted reduced dibenzofuran **16**.

We have also examined the photochemical rearrangement of the analogous *ortho*-amino substrate **17**, irradiation of which leads to the formation of **18** as a mixture of sulfoxide epimers in quantitative yield. In contrast to the facile Pummerer rearrangement of **14**, we found that **18** did not undergo the analogous rearrangement reaction. Removal of sulfur without rearrangement was then examined. Desulfurization of **18** using Raney nickel afforded hemiaminal **19** in 31% yield. The modest yield for the formation of **19** is consistent with the work of Simpkins[9] and prompted us to examine alternative desulfurization protocols. Exposure of **18** to nickel boride led to the formation of the desulfurized hemiaminal **19** in 56% yield.

To underscore the versatility of the thiolane products that result from this photochemical−Pummerer cascade, we have incorporated a second Pummerer reaction into this sequence. Oxidation of **15** provides the Pummerer substrate **20**. Addition of allyltrimethylsilane to sulfoxide **20** under Pummerer conditions (BF_3-Et_2O; TFAA) furnishes the highly functionalized thiolane system **21** (Scheme 5). Other carbon nucleophiles can also be employed, that is, addition of the trimethylsilyl enol ether of acetophenone to **20** in the presence of trimethylsilyl triflate generated **22**. The stereoselectivities observed in the formation of both **21** and **22** are consistent with addition of both nucleophiles from the convex face of the thiohydrindane (6/5) ring system.

Scheme 5



These studies describe a novel photochemically mediated transformation that affords a general route for the construction of thiolane heterocycles. These preliminary results establish the versatility of this ring system for the generation of diverse structural types. Further applications of this methodology in synthesis are currently underway, and our results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for **1**, **3**−**5**, and **9**−**22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recipient of the Novartis Graduate Fellowship in Organic Chemistry, 2004−2005.
(2) For the first synthesis of ingenol, see: Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726−9728.
(3) For more recent total syntheses of ingenol, see: (a) Tanino, K.; Onuki, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498−1500. (b) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc*. **2004**, *126*, 16300−16301.
(4) A preliminary report on our second-generation approach to the synthesis of ingenol has appeared: Winkler, J. D.; Lee, E. C. Y.; Nevels, L. I. *Org. Lett.* **2005**, *7*, 1489−1491.
(5) For examples of the photochemistry of enone aryl sulfides, see: Dittami, J. P.; Ramanathan, H.; Breining, S. *Tetrahedron Lett.* **1989**, *30*, 795−798. Dittami, J. P.; Nie, X. Y.; Nie, H.; Ramanathan, H.; Buntel, C.; Rigatti, S.; Bordner, J.; Decosta, D. L.; Willard, P. *J. Org. Chem.* **1992**, *57*, 1151−1158. Dittami, J. P.; Luo, Y.; Moss, D.; McGimpse, W. G. *J. Org. Chem.* **1996**, *61*, 6256−6260.
(6) Sulfide **4a** was prepared by conjugate addition of 4-methoxythiophenol to 2,2-dimethyl-6-vinyl-[1,3]dioxen-4-one, which is available via dioxenone formation from 3-oxo-pent-4-enoic acid *tert*-butyl ester using TFAA, TFA, Ac_2O, and acetone.
(7) Guo, Y.; Jenks, W. S. *J. Org. Chem*. **1995**, *60*, 5480−5486. Guo, Y.; Jenks, W. S. *J. Org. Chem.* **1997**, *62*, 857−864. Vos, B. W.; Jenks, W. S. *J. Am. Chem. Soc.* **2002**, *124*, 2544−2547. Wagner, P. J.; Sedon, J. H.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579−2580.
(8) Sulfoxide **9** was prepared by conjugate addition of 4-methoxythiophenol to 3-vinylcyclohex-2-enone followed by oxidation of the sulfide with *m*-CPBA.
(9) Armer, R.; Begley, M. J.; Cox, P. J.; Persad, A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3105−3112.

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