JOC Article

Contrasting Responses of Pyrido[2,1-*a*]isoindol-6-ones and Their Sultam Counterparts to Photochemical Activation

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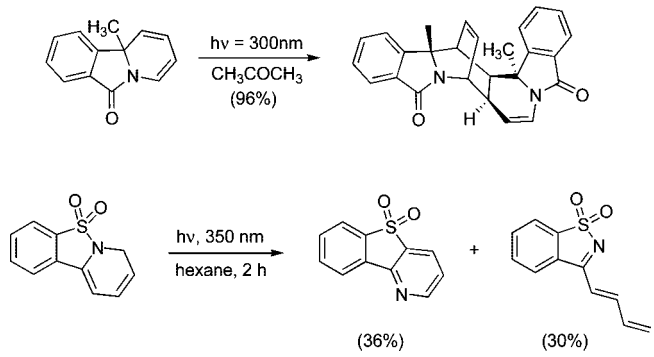
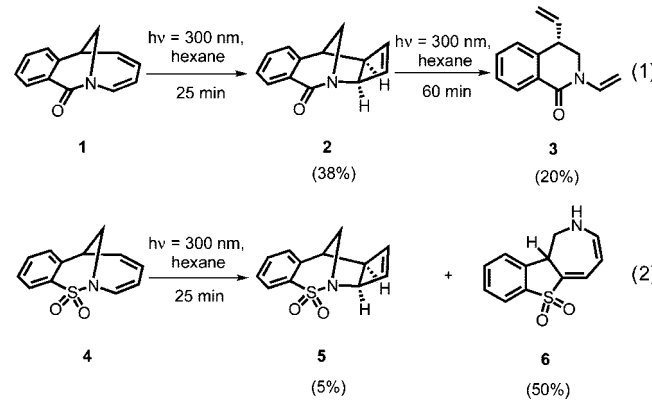


A ring-closing metathesis-based strategy has allowed access to an unreported pair of pyridoisoindolones and their previously unknown sultam counterparts. The synthetic routing takes advantage of the ready availability of *N*-allylphthalimide and *N*-allylsaccharin and proceeds via the proper incorporation of small side chains into the heterocyclic ring. Positionally selective introduction of the conjugated diene functionality was realized efficiently. Detailed study of the excited-state chemistry of **7** and **8** showed both lactams to be subject to [4 + 2] dimerization under acetone-sensitized conditions. Different regioselectivities are involved, with the response of **8** being far more efficient than that exhibited by **7**. No dimers could be isolated from the photolyzates of **9** and **10** under any conditions. While the latter sultam undergoes extensive polymerization, **9** is transformed via direct irradiation at 350 nm into **46** and **47** via [1,3]-sigmatropy involving the S−N bond and heterocyclic ring cleavage, respectively.

Introduction

Lactams and sultams having a cyclic conjugated diene chromophore as an integral structural component are known to exhibit interesting reaction profiles when subjected to photoactivation.[1,2] Thus, **1** and **4** experience in common stereocontrolled disrotatory ring closure to some degree.[3] However, they differ notably in the competing isomerizations that lead via retro-[2 + 2]-cycloaddition to **3** (eq 1) and [1,5]-sigmatropic rearrangement to **6** (eq 2), respectively.



In the present investigation, attention has been directed to the synthesis and photochemistry of a pair of representative members of each of two previously unknown classes of heterocycle. The two representative pyrido[2,1-*a*]isoindol-6-ones **7** and **8**[4] and an equal number of 9-thia-8a-azafluorene 9,9-dioxides, viz. **9** and **10**, have been specifically targeted,

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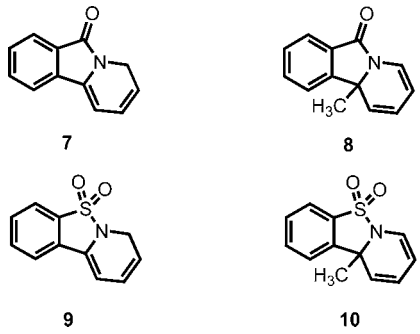
thereby setting the stage for detailed probing of their individual response to excitation with light.



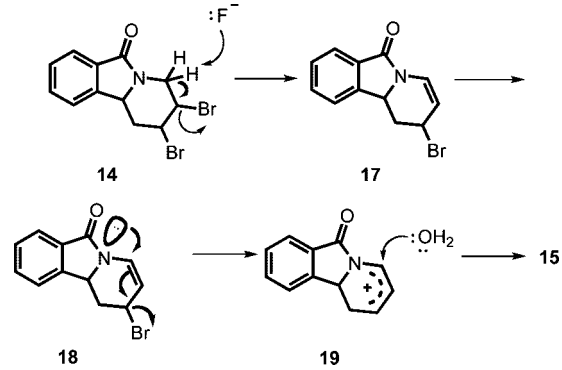
7 **8** **9** **10**

Results and Discussion

Preparation of 4*H*- and 10b*H*-Pyrido[2,1-*a*]isoindol-6-ones. The initial strategy applied to the acquisition of **7** began with the exposure of readily available *N*-allylphthalimide (**11**)[5] in sequence to lithium triethylborohydride, acetic anhydride, and allyltrimethylsilane/bismuth triflate[6] (Scheme 1). The resultant diene lactam **12** underwent ring-closing metathesis[7] uneventfully to generate tricyclic intermediate **13** in high yield. The dibromination of **13** led to **14**, whose projected role it was to serve as progenitor to the diene upon two-fold dehydrobromination. However, the targeted **7** was not observed, a single isomer of allylic alcohol **15** being formed instead. Dibromide **14** proved to be quite reactive toward $Bu_4N^+F^-$ in THF at 25 °C,[3] conditions that led within 15 min to the crystalline carbinolamine,[15] whose three-dimensional structure was established by X-ray analysis.

This unexpected transformation may well materialize by virtue of a significant level of activation provided by the proximal amide nitrogen that directs well-defined proton abstraction, as shown in Scheme 2. The generation of allylic bromide **17** in this manner is likely conducive to the formation of iminium ion **19**,[8] which resulted from electron donation away from the nitrogen atom. Trapping of this intermediate by nucleophilic attack of water would expectedly occur with high levels of regio- and stereocontrol.

SCHEME 2



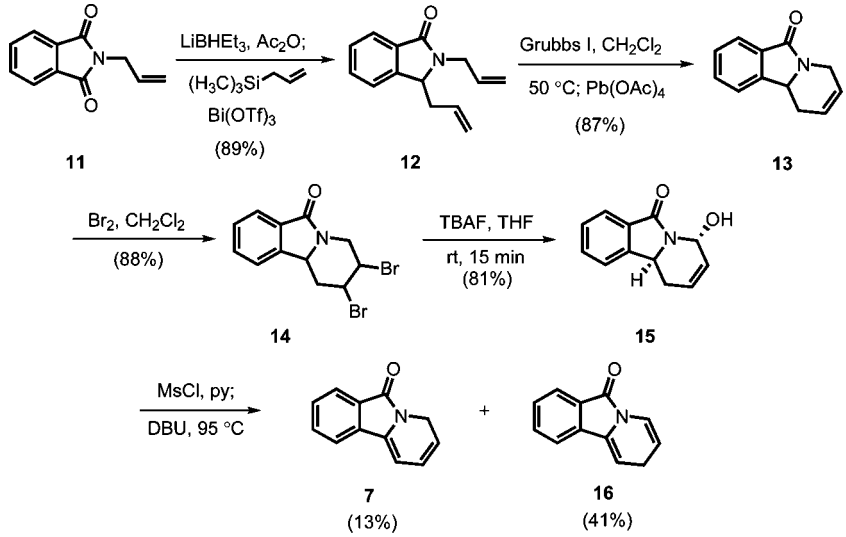
14 **17** **18** **19**

A striking consequence of this chemical event is the suitability of **15** to subsequent dehydration. This transformation was best accomplished by treatment with methanesulfonyl chloride in pyridine, followed by direct heating of the corresponding sulfonate ester with DBU at 95 °C for an extended time period. The 1:3 mixture of **7** and **16**[9] that results is believed to be diagnostic of the operation of [1,5]-hydrogen shifting in order to attain a more extended level of π-conjugation with the benzene ring.

The bonding-specific arrangement in these dienes can be better appreciated by initially pursuing the installation of an angular OMOM substituent as in **23**. The main strength of this strategy resides in the benzylic nature of the C−O bond, the heterolysis of which is thereby facilitated. Additionally, conversion to the more thermodynamically favored **7** (see Table 1) operates directly.

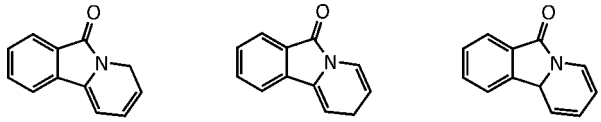
A clear route to **23** began with the coupling of propargylmagnesium bromide to *N*-allylphthalimide (Scheme 3). This organometallic reagent is distinctively reactive,[10] such that 1,2-carbonyl addition proceeds efficiently in ether at −10 °C without ensuing C−N bond cleavage and ring opening. It will be recognized that compound **20** is in a higher oxidation state than required. However, the presence of a triple bond allows the subsequent hydroxyl group protection to proceed with minimal

SCHEME 1



11 **12** **13** **14** **15** **7** (13%) **16** (41%)

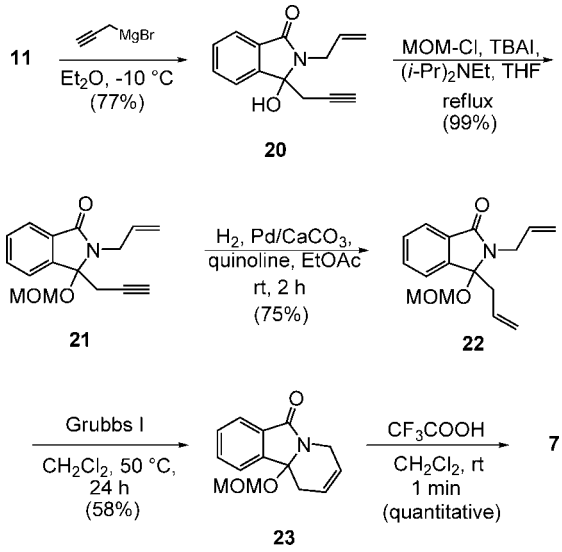
TABLE 1. Relative Energies in kcal/mol



7	16	16a

calculation method	7	16	16a
MMFF94s	0	11.04	18.06
B3LYP/631G*	0.82	0	9.10
B3LYP/6311+G**	0.61	0	7.59

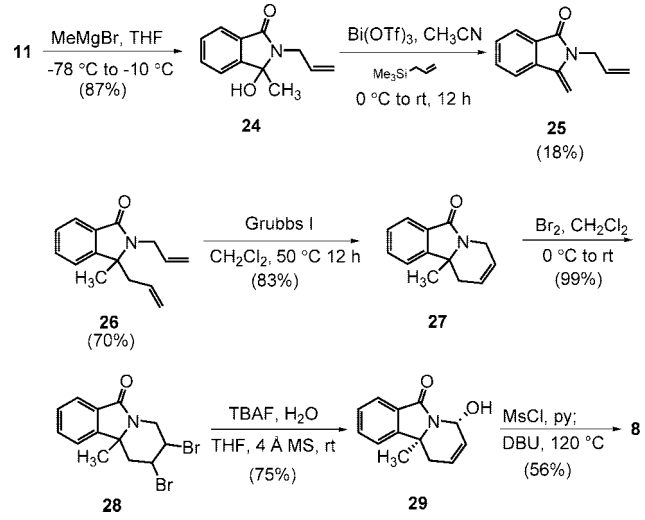
SCHEME 3



complication from spontaneous dehydration. The desired intermediate **22** could be generated without event under Lindlar conditions and subjected directly to ring-closing metathesis in a manner paralleling that deployed earlier in the case of **12**. The final step, which utilizes trifluoroacetic acid in CH_2Cl_2 at rt, proceeds to completion within a minute to deliver **7** quantitatively.

In order to reposition the conjugated chromophore in these networks, attention was directed to proper installation of an angular methyl group. This tactic was expected to deter the operation of undesired sigmatropic migration during the final dehydration step. As shown in Scheme 4, the addition of methylmagnesium bromide to **11** at low temperature initiated a series of steps comparable to that detailed previously in the conversion of **12** to **15**. With the exception of modest levels of

SCHEME 4



dehydration leading from **24** to **25**,[11] the reactivity exhibited during the five-stage acquisition of **29** proved closely parallel. The relative configuration assigned to **29** is derived principally from mechanistic analogy, closely comparable ^1H and ^{13}C NMR spectra, and response to dehydration. As anticipated, compound **8** proved to be intrinsically stable to the dehydration conditions employed.

Access to the 9-Thia-8a-azafluorene 9,9-Dioxides. From the foregoing results, it could not be safely assumed that the replacement of a carbonyl with a sulfonyl group would have an entirely comparable effect on the closed carbinol/open ketone equilibrium. To gain insight into this matter, effort was initially directed to reduction of the known allyl saccharin **30**[12] with Super-Hydride in CH_2Cl_2 at −60 °C (Scheme 5).

Direct ensuing acetylation delivered the overreduction products **31** and **32** in the approximate ratio of 1:2. Apparently, there exists a relationship between the reducing power and chelation capability of the hydride reagent, as the alternative use of Dibal-H smoothly transformed **30** into the intact amino alcohol. To achieve the isolation of **33**, it was necessary first to quench the reaction mixture and subsequently to perform direct acetylation of the crude product. Irrespective of the actual cause underlying the isolation of **33**, no further complications were manifested during the subsequent allylation, ring-closing metathesis, and bromination steps that led to **36**.

The task of effecting the two-fold dehydrobromination of **36** proved complicated. Since an equivalent to acyliminium ion intervention was less likely to facilitate this process,[13] it seemed advisable to abandon the use of relatively mild conditions in favor of more powerful options. To this end, recourse was made to the combination of TBAF in DMSO at 50 °C.[14] The operationally useful nature of this reagent combination was demonstrated by its reproducible efficiency and the wholesale migration of its conjugated diene unit into conjugation with the benzene ring as in **9**.

The melding of these observations alongside those associated with the generation of lactam **8** prompted exploration of the

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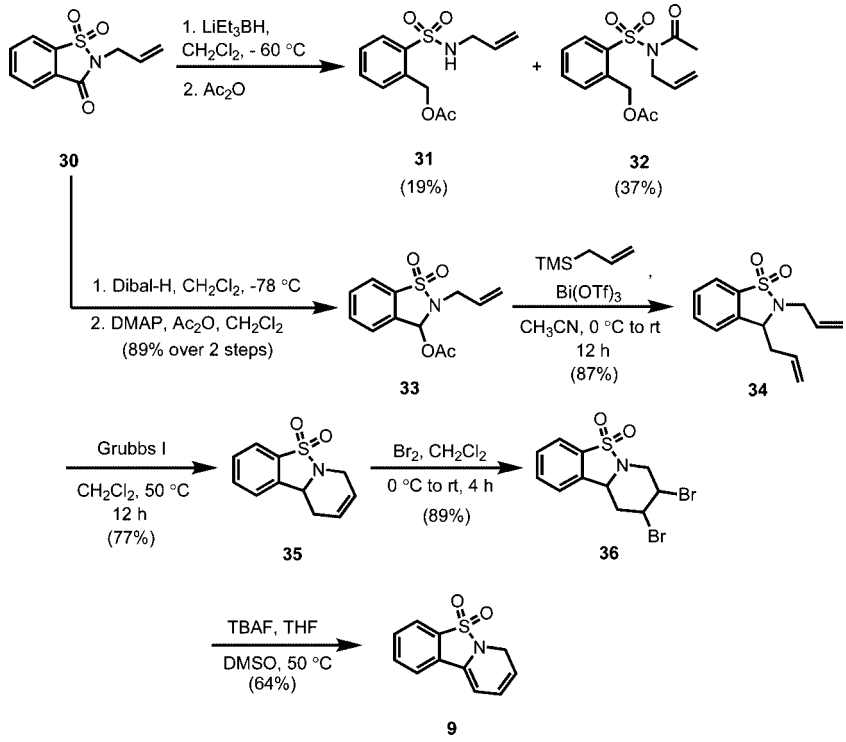
SCHEME 5



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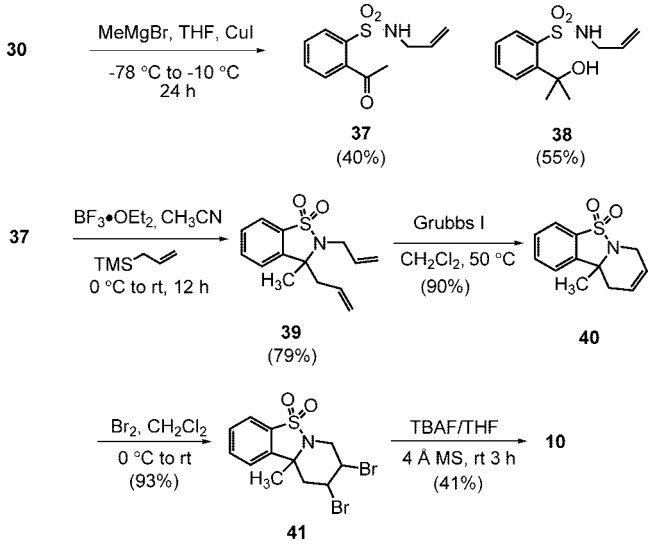
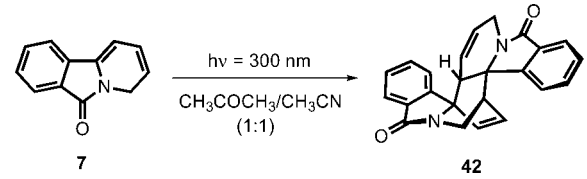


consequences of adding methylmagnesium bromide to **30** at low temperature (Scheme 6). Of the variety of conditions that were explored, none produced ketone **37** at a level exceeding 40%. Evidently, its consumption in second-stage reaction with CH_3MgBr operates at a level competitive with the initial addition to **30**. Eventually, we settled upon the chromatographic separation of **37** from **38**. When purified, **37** was subjected to the action of boron trifluoride etherate and allyltrimethylsilane in acetonitrile. Direct conversion to **39** took place. The utilization of 2 equiv of Lewis acid proved most efficacious, in line with ready ionization of the carbinolamine following the initial cyclization that reconstitutes the heterocyclic ring. The considerable advantage offered by this transformation provided the undergirding necessary to reach sultam **10** without incident.

SCHEME 7



Photochemical Studies. The launching point for this phase of the investigation was the unsaturated lactam **7**. The chromophore presenting this minimally substituted pyrodoisoindolone was expected to lend itself to several photochemical responses. Indeed, **7** exhibits a substantive sensitivity to light, giving rise within short time frames to a very broad array of products (TLC analysis) under a wide range of conditions. These included, but are not limited to, direct irradiation at several wavelengths and triplet sensitization in a number of solvent systems.

Ultimately, we settled on the use of a reaction medium consisting of a 1:1 ratio of acetonitrile and acetone with a 300 nm light source through quartz at 20 °C in a Rayonet reactor. By means of preparative thin layer chromatography on silica gel, it proved possible to isolate in pure form a component of the gross mixture in 2% yield (Scheme 7).

No other product was isolable in quantities allowing full characterization. Compound **42** was identified as a dimer on the strength of spectroscopic data, most particularly its ^1H NMR spectrum in conjunction with several 2D techniques which included COSY, HMQC, and NOE experiments in $CDCl_3$ or C_6D_6 as solvents. The atom connectivity in **42**, a colorless waxy substance, is shown in Figure 1. The distinctive chemical shift differences exhibited by the two sets of benzene ring protons hold interest. A possible root cause of this phenomenon may be the high level of strain inherent to this structure, one consequence of which is to alter the overlap of one amide group

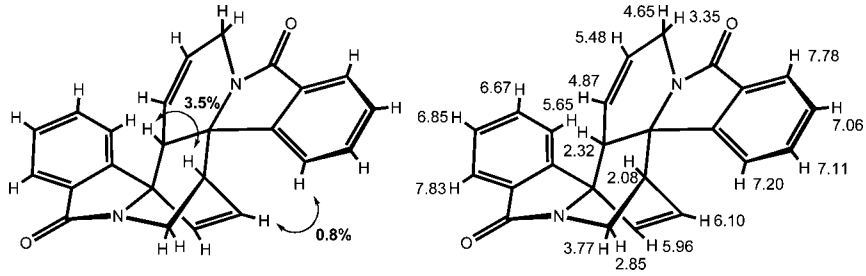
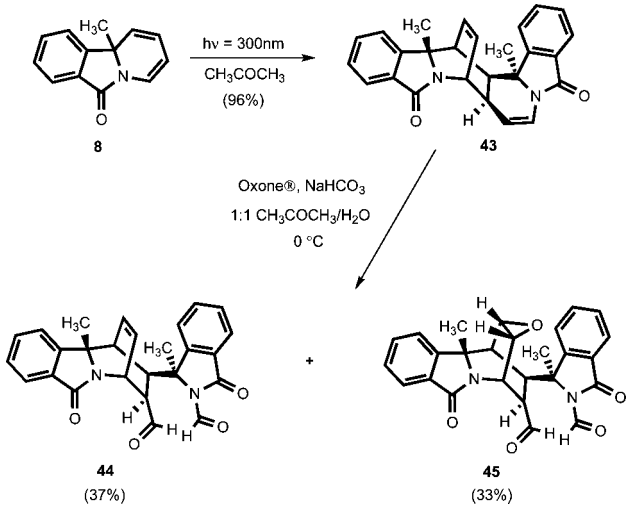
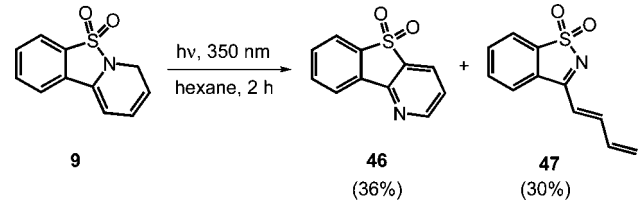


FIGURE 1. Atom connectivity in **42**.

SCHEME 8



SCHEME 9



with the attached aromatic ring. The resulting disruption of full conjugation lessens the electron-withdrawing effect. This state of affairs also manifests itself in the ^{13}C NMR spectrum where one amide carbonyl appears at 167.4 ppm and the second at 165.6 ppm. These data also attest to the absence of symmetry in this photoproduct.

In contrast, the excited-state chemistry of **8** in which the 1,2-diene system is no longer conjugated to the benzene ring proved to be essentially unidirectional in delivering **43** very efficiently (acetone, 300 nm, 96% yield).[15] However, the efficiency of this process suffered when lactam **8** was subjected to direct irradiation in hexanes. Prolonged exposure under these conditions led to the wholesale decomposition of **43**.

This product (**8**) was shown to exhibit spectral properties consistent with its assignment as an unsymmetrical dimer. Principal supportive evidence was gained by high-resolution mass spectral analysis ($[M + Na]^+$ calcd 417.1579, obsd 417.1582) and ^1H NMR data recorded at 500 MHz. The latter confirmed the existence of a single enamide functionality and an isolated olefinic site, neither of which were styrenyl in nature (COSY measurements). Additional supportive evidence for the structural assignment as **43** was gained by way of a chemical interconversion. Specifically, reaction of the glassy photoproduct with dimethyl dioxirane in aqueous acetone at 0 °C led to the smooth formation of **44** (37%) and **45** (33%), both of which are highly crystalline solids amenable to X-ray crystallographic analysis[15] (Scheme 8).

The proclivity of **7** and **8** to undergo photodimerization provided considerable inducement for the close inspection of the photolyzates derived from sultams **9** and **10**. As conditions for evaluating their photochemical behavior were being researched, note was taken of the fact that triplet sensitization invariably resulted in extensive degradation and/or polymerization. In contrast, the irradiation of **9** in hexane solution with a 350 nm lamp source provided predominantly a two-component mixture that proved amenable to chromatographic separation. The less polar product, isolated in 35% yield, was identified as the previously described[16] benzo[4,5]thieno[3,2-*b*]pyridine 5,5-dioxide (**46**) (Scheme 9). The origin of **46** likely stems from sequential operation of a [1,3]-sigmatropic shift after S−N bond cleavage, followed by aromatization to generate the thienopyridine core.

The ^1H NMR spectrum of the more polar **47** featured an array of olefinic proton signals suggestive of the presence of an olefinic chain housing a central trans double bond. Corroborative proof of the formation of **47**, presumably initiated via homolysis of the weaker C−N bond in **9**, was also derived from X-ray crystallographic analysis. The near-identical extent to which the pathways giving rise to **46** and **47** operate reflects the closely competitive nature of these processes.

In contrast, the ability of methyl homologue **10** to deliver well-defined photoproducts under a host of experimental variables could not be harnessed. The results showed **10** to be notably prone to photopolymerization. For all experiments, the responsiveness of **10** to activation by light proved not to be controllable.

Overview

Several possible mechanisms can be envisioned to rationalize the photochemical reactivity of **7**−**10**. It appears almost certain that triplet state photoproducts are first formed when acetone serves as the reaction medium either neat or as mixed 1:1 with acetonitrile. During the ensuing dimerization, cycloadducts are formed by exo $\pi_2 + \pi_4$ bonding, although in diverse fashion. When **7** is involved, the benzene rings are oriented anti. For **8**, the orbital overlap is reversed, but also favoring an anti approach

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of the two reactants. No [4 + 4] product(s) is (are) observed, and no endo approach of the dienophile component proved operational.

Worthy of serious consideration is the efficiency with which **43** is formed and the exceptional susceptibility of its enamide double bond to oxidative cleavage. These transformations are most probably due to the enhanced level of π-electron density resident in this site of unsaturation. The results of the studies conducted so far in this area have led to the unmasking of several novel photochemical reactions involving the chromophores resident in **7**−**10**. These excited-state processes, evidently quite varied, demonstrate the wealth of information that can be made available from the examination of structurally related systems.

Experimental Section

Photodimerization of 7. Diene **7** (100 mg, 0.55 mmol) was dissolved in a 1:1 mixture of acetone/acetonitrile (400 mL), placed in a quartz flask, and deoxygenated with argon for 30 min. The solution was then irradiated at 300 nm for 45 min and concentrated to leave an orange gum, which was quickly purified on silica gel (elution with 10:1 to 1:1 dichloromethane/ethyl acetate). The latter fractions were combined and repurified by preparative TLC (silica gel, elution with dichloromethane/ethyl acetate, 2:1) to give **42** as a colorless waxy solid (4 mg, 2%): IR (thin film, cm^{-1}) 1694, 1682; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81−7.34 (m, 3H), 7.63 (t, J = 6.0 Hz, 1H), 7.57 (t, J = 6.0 Hz, 1H), 7.37 (t, J = 6.0 Hz, 1H), 7.13 (t, J = 6.0 Hz, 1H), 7.07 (t, J = 6.0 Hz, 1H), 5.67−5.64 (m, 1H), 4.57 (dd, J = 14.0, 4.4 Hz, 1H), 4.07 (dd, J = 6.0, 1.6 Hz, 1H), 3.37 (d, J = 14.0 Hz, 1H), 3.25−3.20 (m, 1H), 3.17 (d, J = 8.8 Hz, 1H), 3.13 (br s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 167.2, 164.8, 148.7, 142.9, 138.1, 134.5, 133.2, 132.6, 131.8, 130.8, 129.1, 128.9, 128.2, 125.9, 124.3, 122.9 (2C), 121.5, 68.9 (2C), 39.7, 38.7, 38.3, 37.3; HRMS ES $[M + Na]^+$ calcd 389.1266, obsd 389.1263.

The NMR data are also reported in benzene (solvent used for the COSY and NOESY experiments): ^1H NMR (400 MHz, C_6D_6) δ 7.83 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.21−7.19 (m, 1H), 7.12−7.10 (m, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.10 (t, J = 7.6 Hz, 1H), 5.96 (dd, J = 7.6, 1.2 Hz, 1H), 5.65 (d, J = 7.6 Hz, 1H), 5.48 (dd, J = 10.0, 8.4 Hz, 1H), 4.89−4.85 (m, 1H), 4.65 (dd, J = 17.6, 8.4 Hz, 1H), 3.77 (dd, J = 11.2, 2.4 Hz, 1H), 3.35 (d, J = 17.2 Hz, 1H), 2.85 (d, J = 17.2 Hz, 1H), 2.32 (br s, 1H), 2.08 (br s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 167.4, 165.6, 148.8, 142.9, 136.7, 135.0, 133.8, 133.5, 131.1, 130.8, 129.3, 129.0 (2C), 124.8, 124.0, 123.9, 123.8, 121.2, 69.0, 68.9, 39.5, 39.1, 39.0, 37.3.

Photodimerization of 8. A solution of **8** (50 mg, 0.25 mmol) in 255 mL of acetone was deoxygenated with argon for 30 min in a quartz reaction vessel and irradiated in a Rayonet reactor with a bank of 300 nm lamps for a period of 3 h. The solvent was evaporated, and the residue was purified directly on silica gel (ethyl acetate) to yield 48 mg (96%) of **43** as an off-white, sticky gum: IR (thin film, cm^{-1}) 1693, 1682, 1407, 1360; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.67−7.64 (m, 2H), 7.54−7.49 (m, 2H), 7.26 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 7.5 hz, 1H), 6.35−6.32 (m, 1H), 5.91 (t, J = 7.5 Hz, 1H), 5.25 (dd, J = 8.0, 3.5 Hz, 1H), 4.90−4.87 (m, 1H), 3.20−3.17 (m, 1H), 2.52 (d, J = 6.5 Hz, 1H), 1.80 (d, J = 8.5 Hz, 1H), 1.18 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 163.4, 152.5, 149.3, 133.2, 132.8, 132.2, 131.1, 131.0, 130.2, 128.7, 128.8, 124.8, 124.6, 122.6, 121.3, 120.7, 113.5, 68.8, 62.3, 52.5, 41.6, 40.6, 38.5, 27.8, 27.1; HRMS $[M + Na]^+$ calcd 417.1579, obsd 417.1582.

Oxidation of 43 with Dimethyl Dioxirane. A cold (0 °C) solution of **43** (35 mg, 0.093 mmol) in 1:1 acetone/water (1 mL) was admixed with $NaHCO_3$ (78 mg, 0.93 mmol). Oxone (288 mg, 0.469 mmol) was introduced portionwise over 20 min, and stirring was maintained for an equal length of time. The reaction mixture was filtered through a pad of Celite, concentrated, and purified over silica gel (elution with 4:1 hexane/ethyl acetate) to provide **44** as a colorless, crystalline solid (15 mg, 37%), mp 214−216 °C: IR (thin film, cm^{-1}) 1740, 1698, 1300; ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.24 (d, J = 5.5 Hz, 1H), 7.89 (dd, J = 17.0, 7.5 Hz, 1H), 7.73−7.66 (m, 2H), 7.59−7.54 (m, 4H), 7.44 (d, J = 7.5 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 6.44 (td, J = 6.5, 1.0 Hz, 1H), 4.83−4.80 (m, 1H), 3.64 (d, J = 6.0 Hz, 1H), 3.17−3.13 (m, 1H), 3.01 (d, J = 9.5 Hz, 1H), 1.60 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 173.9, 167.4, 160.3, 151.9, 149.2, 135.5, 134.5, 133.1, 133.0, 129.9, 129.7, 129.3, 129.0, 125.9, 125.3, 123.1, 120.8, 70.2, 66.6, 57.6, 51.2, 43.5, 40.3, 29.7, 27.8, 26.6; HRMS $[M + Na]^+$ calcd 449.1477, obsd 449.1461.

Continued elution led to the isolation of **45** as a colorless crystalline solid (15 mg, 33%), mp 259−260 °C: IR (thin film, cm^{-1}) 1738, 1697, 1300; ^1H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.87 (s, 1H), 7.94 (dd, J = 11.5, 7.5 Hz, 2H), 7.76 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 5.22 (t, J = 4.5 Hz, 1H), 3.91 (t, J = 5.0 Hz, 1H), 3.57 (t, J = 4.5 Hz, 1H), 3.29 (d, J = 5.0 Hz, 1H), 2.80 (d, J = 11.0 Hz, 1H), 2.59 (dd, J = 10.5, 4.5 Hz, 1H), 1.73 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 174.2, 167.9, 160.3, 151.3, 150.6, 134.9, 133.4, 129.6, 129.5, 127.9, 126.0, 125.4, 123.2, 120.6, 68.2, 66.5, 56.3, 53.8, 50.4, 49.5, 41.2, 36.9, 29.7, 28.2, 27.4; HRMS $[M + Na]^+$ calcd 465.1426, obsd 465.1420.

Benzo[4,5]thieno[3,2-*b*]pyridine 5,5-Dioxide (46). Diene **9** (50 mg, 0.23 mmol) was dissolved in 1 mL of dichloromethane and added to 228 mL of hexane. This solution was then deoxygenated for 1 h with argon and irradiated at 350 nm in a quartz reaction vessel. After 2 h, the reaction mixture was concentrated and purified directly over silica gel (elution with 10:1 dichloromethane/ethyl acetate) to yield **46** as an off-white solid (18 mg, 36%), mp 222−223 °C (lit[16b,c] mp 221−222 °C): ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, J = 4.5 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.45 (dd, J = 7.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 150.6, 139.1, 134.3, 132.8, 132.3, 132.2, 129.9, 124.0, 122.6, 121.8.

3-Buta-1,3-dienylbenzo[*d*]isothiazole 1,1-Dioxide (47): Isolated as a colorless crystalline solid (14 mg, 30%); mp 220 °C dec; IR (thin film, cm^{-1}) 1519, 1323, 1169; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96−7.64 (m, 1H), 7.89 (dd, J = 15.0, 11.5 Hz, 1H), 7.79−7.72 (m, 3H), 6.79 (d, J = 15.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 147.7, 140.6, 135.2, 133.6, 133.5, 129.5, 123.7, 122.8, 118.1; HRMS $[M + Na]^+$ calcd 242.0252, obsd 242.0258.

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Supporting Information Available: Experimental details for the preparation of **7**−**10**, ^1H and ^{13}C NMR spectra for all new compounds reported herein, and X-ray crystallographic data for **15**, **44**, **45**, and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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