Explorations of the Heteroatom Directed Photoarylation Reaction.
A Review of the Photoinitiated Intramolecular Cycloaddition Reactions
of Ylide Systems

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The photoinitiated intramolecular ylide-olefin addition has been developed as an approach for the construction of
one ring and two chiral centers, two rings and three chiral centers or three rings and six chiral centers in a single
experimental operation from relatively simple starting materials. These investigations have uncovered several
interesting and unusual reactions, which are sensitive to controls such as wavelength, temperature and solvent.

key words: Photochemistry, ylide, cycloaddition, photoarylation

INTRODUCTION

The photochemical six-electron heterocyclization reaction
(1→3) reportedly proceeds via trans-fused ylide intermediates 2
[1]. Extensive studies have been carried out to elucidate the
mechanism for this reaction. There is now substantial evidence,
both chemical and spectroscopic, which supports the inter-
mediacy of the ylide system 2 [2-4]. Surprisingly, very little
attention has been focused on the reactions of these ylides.

RESULTS AND DISCUSSION

We initially chose to investigate intramolecular addition
reactions involving the ylide species 5 generated on pho-
cyclization of enone system 4 [5-7]. Preliminary investigations
were carried out with the naphthyl vinyl sulfide 10 [8,9]. The
preparation of 10 is representative of the methods used in the
synthesis of photoprecursors.

Irradiation of 10 in toluene (2×10⁻³ M) at temperatures
ranging from -70°C to 25°C provided the photocyclized
product 11 in 81% isolated yield [8,10]. Conversely, high
temperature photolysis of a solution of 10 in toluene (3×10⁻³
M, 110°C) for 3.5 h resulted in formation of the addition
product 12 which was obtained as a mixture of diastereoisomers
(79% isolated yield). We note that ring closure in the naphthyl
vinyl sulfide 10 occurs only toward the 1-position of the
naphthalene system. Control experiments demonstrate that both
light and heat are required to effect the formation of 12. Thus,
after heating a solution of 10 in toluene at reflux temperature
for 6 h in the dark, only starting material was recovered.
Likewise, 11 was stable toward refluxing toluene and under
the reaction conditions (heat and light) used for formation of
12. None of the anticipated [3+2] adduct 13 was observed in
any of these reactions.

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The photochemistry of phenyl vinyl sulfide 14 was also explored. However, the conversion (14 → 15) requires a higher reaction temperature (4×10^{−3} M, mesitylene, 160°C) than the corresponding addition reaction 10 → 12. Furthermore a significant amount of photocyclized “untrapped” product 16 was observed in the reaction mixture (31%). Again control experiments demonstrated that both heat and light are required to effect the transformation of 14 to 15.

Incorporation of activating groups in the side chain markedly influences the facility and outcome of the intramolecular addition reaction [11-13]. Derivatives bearing an ethyl butenoate side chain were readily prepared from the corresponding acetal 9b by i) phenolate or thiolate promoted epoxide opening ii) acetal hydrolysis and iii) Wittig olefination. Pyrex filtered irradiation of a solution of 17 in toluene (10^{−3} M) at room temperature provided predominantly intramolecular addition product 18 (84% isolated yield). Formation of 18 can even be observed at -70°C (~60% isolated yield).

Two additional products were isolated from the room temperature photolysis of 17. Formation of 19 is consistent with an intramolecular hydrogen shift from an intermediate thiocarbonyl ylide [2]. It has been reported by Schultz that ring closure products such as 3e result from conrotatory ring closure to provide a trans-fused ylide 2c followed by suprafacial hydrogen shift to yield the trans-fused dihydrothiophene. If this is indeed the case the observed cis-fused stereochemistry of dihydrothiophene can be rationalized on the basis of facile enolization of the initially formed trans dihydrothiophene. Other work in our laboratory supports this hypothesis. [2b] Compound 20 results from a photoinitiated intramolecular [2+2] cycloaddition of the dihydrothiophene 19 [14-16]. Thus irradiation of pure 19 in toluene with a Pyrex-Hanovia light source results in clean conversion to adduct 20 (major product) accompanied by the product of allylic rearrangement 21 [17]. Prolonged irradiation of 20 results in complete conversion to rearranged product 21. Both structures 20 and 21 have been confirmed by X-ray crystallographic analysis. Notably if the photolysis of 17 is carried out in methanol compound 19 is obtained almost exclusively. Thus it is possible to direct the course of the photoreaction to favor intramolecular addition product 18, ring closed product 19, [2+2] product 20 or [2+2]-allylic rearrangement product 21.

Consistent with earlier work, the intramolecular addition reaction is less favorable for systems which incorporate a phenyl group as the aromatic component. Thus photolysis of 22 must be carried out at elevated temperatures (160°C) before any appreciable intramolecular addition product 24 is observed.

Replacement of sulfur with oxygen effects a dramatic change in reactivity. Photolysis of aryl vinyl ether 25 in toluene (3×10^{−3} M) for 1 h at room temperature afforded the intramolecular addition product 26 (38%) along with photocyclized product 27 (54%). Notably, formation of the oxygen containing system 26 occurs at room temperature compared to 110°C for the sulfur analog. Furthermore high temperature photolysis of 25 provided a new product 28 resulting from [3+2] ylide alkene cycloaddition [11-12].

Naphthyl vinyl ether 29 bearing an ethyl butenoate side-chain (10^{−3} M, toluene) undergoes facile photoinitiated intramolecular [3+2] ylide alkene cycloaddition to give 30. This reaction proceeds in high yield and can be carried out at -78°C.
The influence of solvent on the photolysis of 29 is particularly dramatic. Thus photolysis of 29 in toluene/methanol did not give any of the usual [3+2] adduct 30. Rather formation of 31 (45%), 32 (24%) and 33 (23%) was observed. As with the sulfur analog 20, compound 33 results from ylide protonation to give the cis-fused dihydrofuran 32 followed by intramolecular [2+2] cycloaddition [15-16].

In summary product distribution in the tandem photocyclization-intramolecular ylide alkene cyclization is sensitive to temperature, solvent, electronic and structural features. Thus it is possible to direct formation of one ring and two chiral centers, two rings and three chiral centers or three rings and six chiral centers from a single starting material. Secondary photoprocesses which proceed in good yield and with excellent stereocontrol allow for formation of three rings and six chiral centers.

Preliminary studies in our laboratory demonstrate that aryl vinyl amines also function well in the photoinitiated ylide alkene cycloaddition reaction. Thus compound 34 provides 35 upon irradiation in toluene.

Tandem Photocyclization-Intramolecular Addition Reactions of Aryl Vinyl Sulfide. The Mechanism of Proton Shift

As noted earlier aryl vinyl sulfides 10 and 17 give rise to intramolecular addition products 12 and 18 respectively upon irradiation through Pyrex. Formation of these products requires photoarylation, carbon-carbon bond formation with the side chain and the addition of a hydrogen to the terminus of the side chain alkene. In an attempt to understand the mechanistic pathways underlying formation of these and other similar cycloaddition products a series of mechanistic studies were carried out [18].
In order to ascertain if the hydrogen addition involved an intermolecular process such as abstraction from the solvent, the photolysis was conducted in toluene-$d_8$. Irradiation of 10 with a Pyrex filtered light source at 110°C gave 12 with no observable deuterium incorporation. Likewise, irradiation of a solution of 17 in toluene-$d_8$ (room temperature) gave 18 which was free of deuterium. Thus hydrogen abstraction does not appear to involve the solvent. Dilution experiments were also carried out within the concentration range employed in our normal photolysis conditions to determine if hydrogen abstraction is an inter- or intramolecular process. The concentration profile for the photolysis of 17 showed that the formation of intramolecular addition product 18 is independent of the concentration of the starting material and supports an intramolecular hydrogen abstraction process.

One plausible intramolecular mechanism involves an initial formation of hydrogen shift product 11 followed by enolization to give 11a. Subsequent ene-like reaction produces 12. However, when 11 was prepared independently and subjected to the reaction conditions, only unchanged starting material was recovered.

In view of the substantial evidence, both chemical and spectroscopic, that supports the intermediacy of an ylide system in the photochemical six-electron heterocyclization reaction ($\text{1} \rightarrow \text{3}$) \cite{2-4} we considered hydrogen transfer pathways that could proceed via these intermediates.

One possible mechanism for production of the intramolecular addition products 12 (and by similar mechanism 18) involves initial formation of trans-fused ylide 36, which can undergo an intramolecular ene-like reaction to provide 37 followed by an inter- or intramolecular enolate protonation to give 12. In this case the hydrogen transfer occurs from the C* center to the alkene terminus. Accordingly two experiments were carried out to test the viability of this process. In the first involving compound 38, the two hydrogens on C* which would be expected to transfer were replaced by methyl groups. However, the presence of these methyl groups did not prevent the formation of hydrogen transfer product 39. In the second experiment, deuterium labeled substrate 40 was prepared in an attempt to follow the course of the hydrogen transfer. However, the irradiation of hexadeuterated precursor 40 furnished product 41 in which all of the deuterium remained at the same positions as in the starting material. Consequently a mechanism involving hydrogen transfer from C* was ruled out.

Next we considered the possible involvement of a cis-fused ylide. Orbital symmetry considerations favor a conrotatory cyclization of the aryl vinyl sulfide systems to provide trans-fused thiocarbonyl ylides. Formation of cis-fused ylide from excited state starting material is forbidden by the Woodward-Hoffmann rules. However, studies carried out by Schultz and Herkstroester \cite{2a} as well as in our own laboratory \cite{2b} show that two transients are formed on laser flash photolysis of the aryl vinyl sulfide systems. Both exhibit properties characteristic of thiocarbonyl ylides and thus it is possible that both cis and trans-fused ylide are produced.

Ring closure of 10 to provide cis-fused ylide 42 can give rise to 12 via an ene-like pathway shown.

In order to test this hypothesis deutero derivative 43 was prepared and subjected to the usual reaction conditions. Formation of 44 from 43 is consistent with a mechanism involving a cis-fused ylide (e.g. 42). Although these results are contrary to the anticipated formation of a trans-fused ylide, they are supported in part by the observed formation of two ylide species in spectroscopic studies carried out by Shultz’s group and our own.
Two factors account for the high reactivity of the naphthalene photoprecursors. i) Frontier Molecular Orbital (FMO) theory predicts that dipolar cycloadditions of thiocarbonyl ylides and carbonyl ylides are controlled by the HOMO (1,3-dipole) - LUMO (dipolarophile) interaction [6]. Thus factors which raise the HOMO of the dipole, such as conjugating and electron donating substituents, and/or lower the LUMO of the dipolarophile, such as electron withdrawing groups, will favor [3+2] cycloaddition. ii) Ylides derived from naphthalene systems benefit from extended conjugation and preservation of aromatic character. Thus they may have longer lifetimes than ylides derived from phenyl substituted systems in which aromaticity is lost. Consequently, electron rich aromatic systems or bicyclic heteroaromatic systems (similar to naphthalene electronically) should perform well in the photoinitiated intramolecular ylide alkene [3+2] cycloaddition.

Compounds 46 and 47 were prepared from 3-ethoxy -cyclohexenone by the usual procedure [12] to evaluate the impact of electron rich 1,3-dipole systems on the intramolecular [3+2] cycloaddition. Photolysis of 46 at 110°C provided a mixture of regioisomers 48-51 resulting from ylide alkene addition (49), hydrogen migration (50, 51) and intramolecular [3+2] ylide-alkene cycloaddition (48). Support for the formation of 48 is given by the following conversions. Treatment of 48 with N-bromosuccinimide in methanol provides the bromoketal 52. Axial addition of Br to the enol ether is expected to provide product with the stereochemistry shown. Acid hydrolysis of 52 (p-TsOH, THF, H2O) provides bromo ketone 53. Similarly, 52 is converted to a mixture of 53 and 54 on standing in CDCl3.

Photolysis of 47 at 110°C in toluene provides hydrogen shift product 55, intramolecular addition product 56, and a third product assigned by NMR analysis as 57. Presumably, 57 forms via photocyclization and intramolecular [3+2] cycloaddition to the intermediate carbonyl ylide 58 and subsequent hydrolysis of the resulting enol ether 59 by adventitious water to provide 57. Notably 57 was not detected in the crude NMR spectrum.

Photoprecursors which incorporate bicyclic heteroaromatic components were also examined. Thus 60, 63, and 66 were prepared by coupling the commercially available hydroxyl substituted aromatic component with cyclohexane epoxide 9b and subsequent elaboration of the side chain as described previously. Photolysis of 60 in toluene at room temperature provided [3+2] adduct 61 accompanied by hydrogen shift product 62. Irradiation of 63 at 110°C yielded both [3+2] adduct 64 and intramolecular addition product 65. Similarly photolysis of 66 (r.t. in toluene) yielded [3+2] adduct 67 and intramolecular addition product 68. Products 61, 62, 64 and 65 provide spectral
data comparable to compounds for which structures have been confirmed by single crystal X-ray analysis. Assignments for 67 and 68 were confirmed by single crystal X-ray analysis.

Compounds 71 and 74 were prepared via standard procedures for the synthesis of 75 and 78.

Irradiation of both 75 and 78 proceeded as expected to provide [3+2] adducts 76 and 74 respectively.
Tandem Photocyclization Intramolecular Addition Reactions of Aryl Vinyl Ethers, Sulfides and Amines. Addition of the Photochemically Generated Ylide Systems to Heterodipolarophiles

In continuation of our studies [18] on the Heteroatom Directed Photoarylation we examined intramolecular addition reactions of photochemically generated ylide systems to pendant heterodipolarophiles. Photoprecursors bearing an aldehyde functional group 81, 82, 86, 88, 90, 91 and 96 in the side chain were prepared from 9b via phenolate, thiolate or aryl amine promoted epoxide opening followed by acetal hydrolysis. Compounds 99a,b and 103 which bear a methyl ketone side chain were prepared by a similar procedure from 9c via 8c. Compound 8c is available from 7 via methyl ketal Grignard addition followed by acid catalyzed hydrolysis and elimination.

Each of these systems were evaluated as substrates for the photoreaction and all provided products consistent with photoarylation and subsequent ylide-dipolarophile addition. It is of interest to examine the kinds of products formed as well the stereoselectivity as a function of structural features in the starting material.

Photolysis of aryl vinyl ether 81 provided regioisomeric products 83 (63%) and 84 (25%) resulting from initial ring closure to the 2- or 6-position of the aromatic system followed by stereospecific addition to the side chain aldehyde. In like manner, photolysis of 82 provided 85 as a single diastereoisomer (87%). The observed stereoselectivity in the side chain addition of these aryl vinyl ether systems appears to be general when the heterodipolarophile is an aldehyde. The resulting product is typically a single stereoisomer (or in some cases the major isomer) in which the resulting alcohol is positioned toward the aromatic system. These results have been confirmed by single crystal X-ray analysis for 83, 84 and 85.

In a similar fashion aryl vinyl ether 86 provided product 87 in which the major isomer 87a was confirmed by single crystal X-ray and had the stereochemistry shown. Notably the yield for 87a,b was lower than is typical for these reactions (35%) and has not been optimized. Our experience with aryl vinyl amine systems shows a similar stereocentral preference. Thus 88 provided exclusively 89 in 81% yield as confirmed by X-ray analysis.

The photolyses of napthyl vinyl sulfides and napthyl vinyl ethers provide an interesting contrast in behavior. Thus photolysis of napthyl vinyl ether 90 provides the novel ketal 93 in 75% yield. The formation of 93 is consistent with a photo-induced six electron conrotary cyclization to give a trans-fused ylide intermediate 92 that undergoes subsequent intramolecular [3+2] dipolar cycloaddition to the side chain aldehyde. Acid catalyzed hydrolysis of 93 provides the diol 94. In contrast, photolysis of aryl vinyl sulfide 91 provides 95a,b as a 1:1 mixture of isomers. In summary, the addition reactions of pendant aldehydes on napthyl vinyl sulfide and napthyl vinyl ether systems parallels that of the corresponding alkene substituted systems in which napthyl vinyl sulfides provide ene-like products and napthyl vinyl ethers provide [3+2] adducts. Interestingly compound 96 also provided products which have spectral data consistent with the structures 97 and 98.

Finally we examined the intramolecular addition reactions of systems bearing a methyl ketone in the side chain. Surprisingly aryl vinyl sulfide 99a provided a single product 100 while aryl vinyl ether 99b gave rise to two products 101 and 102 in nearly a 1:1 ratio. The stereoselectivity observed with the
naphthyl vinyl sulfide system is noteworthy and has also been observed with the corresponding phenyl vinyl sulfide \(103\) which provides two products. The major product \(104\) has the specific geometry shown as confirmed by X-ray while the second is of undetermined geometry.

**Photochemistry of Aryl Vinyl Sulfides and Aryl Vinyl Ethers: Evidence for the Formation of Thiocarbonyl and Carbonyl Ylides**

Studies concerning intramolecular addition reactions of ylide systems such as \(2\), demonstrate that product distribution is influenced by reaction temperature, substrate structure and wavelength of irradiation. It was of interest therefore, to examine the properties of the ylide intermediates which are involved in these transformations. Laser flash photolysis techniques were employed to characterize the ylides and to probe the reactivities of excited state intermediates.

Four systems were selected for study. Aryl vinyl sulfide \(105a\) and aryl vinyl ether \(105b\) incorporate simple chromophores, and previous studies have shown that they efficiently provide products \(107\) and \(108\), respectively, upon photolysis. Aryl vinyl sulfide \(17\) and aryl vinyl ether \(29\) incorporate more complicated functionality and, again, have been shown previously to give rise to products resulting from intramolecular ylide alkene addition. Laser flash photolysis data had been reported previously for \(105b\) \([2a,3b]\). However, until this study there had been no reports on transients derived from \(105a, 17\), or \(29\) \([2b]\).

**One Laser Flash Photolysis of Aryl Vinyl Sulfides**

Laser flash photolysis of the sulfur-containing compound \(105a\) in nitrogen-saturated benzene yielded a long-lived transient with broad absorption maxima in the 600-800 nm region and a second, weaker band with \(\lambda_{\text{max}} = 450\) nm (Figure 1, Table 1). These absorptions are assigned to a thiocarbonyl ylide produced...
by cyclization of the naphthalene and vinyl moieties. A trans ring-fusion as shown in 106a is inferred from an expected conrotatory cyclization [19] and has been demonstrated for related dipole systems via ylide trapping experiments [4,12]. However, the possibility of cis-fused system 109a has not been ruled out.

Several spectroscopic and kinetic characteristics lead to the identification of the transient as a thiocarbonyl ylide: (i) the

Table 1. Lifetimes (µs) of Carbonyl and Thiocarbonyl Ylides

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Compound 105a</th>
<th></th>
<th>Compound 105b</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>750 nm</td>
<td>600 nm</td>
<td>830 nm</td>
<td>630 nm</td>
</tr>
<tr>
<td>C6H6</td>
<td>60</td>
<td>260</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>CH3OH</td>
<td>1.6</td>
<td>1.6</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td></td>
<td>Compound 17</td>
<td></td>
<td>Compound 29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>750 nm</td>
<td>600 nm</td>
<td>830 nm</td>
<td>630 nm</td>
</tr>
<tr>
<td>C6H6</td>
<td>52</td>
<td>280</td>
<td>10</td>
<td>8.3</td>
</tr>
<tr>
<td>CH3OH</td>
<td>0.46</td>
<td>0.63</td>
<td>&lt;0.1</td>
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</table>

Lifetimes (µs) of carbonyl and thiocarbonyl ylides produced on photolysis of the indicated starting materials in benzene and methanol. Lifetimes were measured at two different absorption wavelengths within the ylide absorption band.
absorption spectrum closely resembles that of the corresponding carbonyl ylide reported by Wolff [3b], several structurally related thiocarbonyl ylides described by Herkstroeter and Schultz [2a], and a variety of carbene-derived sulfur and oxygen ylides [20]: (ii) the observed lifetime is typical of carbonyl and thiocarbonyl ylides in solution—for example, both Wolff and Schultz reported lifetimes on the millisecond time scale; (iii) the addition of MeOH, a known quencher of zwitterionic species via proton transfer, significantly decreased the observed lifetime (thus, the decay rate constant increased by 1 order of magnitude when photolysis was carried out in 50:50 MeOH : benzene).

Kinetic analysis of decay lifetimes at various wavelengths within the long wavelength absorption band revealed that, while first-order behavior was observed, the lifetimes calculated were dramatically dependent on the monitoring wavelength within the band. For example, at 600 nm, the lifetime was 260 μs versus 60 μs at 750 nm. Schultz also found two first-order decays within the long wavelength absorption envelope of several similar thiocarbonyl ylides [2a]. In those systems the lifetimes differed by as much as 2 orders of magnitude depending on the absorption wavelength monitored. Similar spectroscopic and kinetic behavior was observed for 17.

One Laser Flash Photolysis of Aryl Vinyl Ethers

Intermediates derived from aryl vinyl ethers 105b and 29 exhibited behavior different from those produced from the aryl vinyl thioethers. Photolysis of 105b yielded two major transient absorption bands (λmax 750, 440 nm) exhibiting dramatically different lifetimes and a third minor absorption band (λmax 460 nm) that decays at roughly the same rate as the long-lived major band at 750 nm (see Figures 1 and 2). The long-lived species absorbing at 750 nm was identified as the ylide and correlates well with data reported by Wolff. [3b] The second band (λmax 440 nm) was produced concurrently with the laser pulse and exhibits fast and slow decaying components. The short-lived component decayed by first order kinetics with τ=200 ns. Figure 2 displays the resolvable growth of the ylide absorption at 750 nm and the corresponding decay of the 440 nm band. The similarity in kinetics for growth of the 750 nm species and the concomitant decay of the short-lived 440 nm transient was not observed in the sulfur series of compounds. We tentatively assign the major (short-lived) component of the low wavelength band to a localized naphthalene triplet-triplet absorption. Support for this assignment is given by the transient behavior in the presence of oxygen. In air-saturated solutions, the decay rate of the short-lived 440 nm absorption and the growth rate of the long wavelength band were significantly enhanced (behavior also noted by Wolff) [3b]. Phosphorescence measurements carried out at low temperatures in methycyclohexane glasses yielded spectra that were nearly identical in shape and wavelength position to that of naphthalene itself (E0 = 60.7 kcal/mol for 105b versus 60.9 kcal/mol for naphthalene) [21]. Additional triplet quenching experiments were attempted using 1,3-cyclohexadiene as a quencher. However, permanent chemical reaction led to complex transient behavior.

A transient absorption spectrum obtained following decay of the short-lived species (1 μs after the laser pulse) exhibits a peak at λmax 750 nm and a minor absorption band at λmax 460 nm. Both bands display similar decay kinetics and are attributed to absorption by the ground state ylide. The ylide absorption at 460 nm is responsible for the slow decay observed at 440 nm. Like the corresponding aryl vinyl thioether systems, kinetic analysis of 105b points to two ylide bands within the same long wavelength absorption envelope. However, there is a much smaller difference in their lifetimes (52 μs at 830 nm versus 64 μs at 630 nm) than in the corresponding thioether systems (60 μs at 750 nm versus 260 μs at 600 nm). Similar behavior was noted for aryl vinyl ether 29. Decay rates measured for each of the aryl vinyl ether-derived ylides were faster than for the corresponding thioethers. Thus, the ylides produced from 105b decayed faster than those from 105a and 29 faster than 17. Reaction with added MeOH was also more efficient for the ether-derived ylides. While the lifetimes of the sulfur ylides for 105a and 17 decreased to 1.6 μs in neat MeOH, the ylide lifetimes for the oxygen systems 105b and 29 in MeOH were less than 100 ns.

(iii) Multiplicity of the Ylide Precursors

Kinetic analysis suggests that the transformation of aryl vinyl sulfides and aryl vinyl ethers to ylide systems occurs via states with different multiplicity. As noted earlier, photolysis of 105b yielded two major transient absorption bands exhibiting dramatically different lifetimes. Growth kinetics for the long wavelength band correlate well with the decay kinetics of the

Figure 2. Transient decay obtained at 440 nm (square symbols) and 750 nm (round symbols) following 308 nm photolysis of compound 105b in nitrogen-saturated benzene.
440 nm band, which we have assigned to a localized
naphthalene triplet-triplet absorption. Ylides derived from 29
exhibit similar kinetic behavior. Thus, for these aryl vinyl
ethers, ylide formation is clearly via the triplet manifold.

On the other hand, ylides derived from 105a and 17 were
produced concurrently with the laser pulse. This observation,
coupled with the lack of an observable naphthalene triplet
absorption, suggests involvement of a short-lived singlet state
in ylide formation. This result is consistent with data reported
by Schultz in which the majority of aryl vinyl sulfide systems
examined provided ylides via the singlet manifold. However,
Schultz also reports that substrates that incorporate the vinyl
substituent in a ring, precluding free rotation in the excited
state, react through a combination of singlet and triplet state
manifolds. In addition, Schultz was able to show ylide formation
following triplet sensitization of several naphthyl vinyl sulfides
[2a,4].

The lack of observation of a triplet absorption does not
preclude a triplet route, since it is possible that reaction from the
triplet is faster than the time resolution of our instrumentation.
In fact, phosphorescence measurements indicate that the triplet
states of 105a and 17 are formed following excitation although
apparently in low yield. However, since the triplet energies of
the naphthalene groups in the sulfur and oxygen compounds
differ only slightly, it is difficult to rationalize a large difference
in triplet reactivity on the basis of energy arguments alone.
Alternatively, production of the triplet may be less efficient in
the sulfur compounds than in the oxygen analogs reflecting a
greater contribution to ylide formation from the short-lived
singlet.

(iv) Ylide Lifetimes

It is reasonable to expect a difference in lifetimes for ylides
derived from systems 105 versus those derived from 17 and
29. Ylides derived from either 105a or 105b are expected to
exhibit decay kinetics which reflect the efficiency of the
intramolecular hydrogen shift whereas ylides derived from 17
and 29 can decay by either intramolecular hydrogen shift or
an intramolecular ylide-alkene addition process. Indeed, ylide
lifetimes for 29 are considerably shorter than for 105b.
Compound 29 provides exclusively compound 30. The structure
of 30 is consistent with intramolecular six-electron conrotatory
cyclization occurring from 29 to provide ylide 45a and
subsequent intramolecular [3+2] dipolar cyclization to the side
chain olefin. Conversely, sulfur-containing systems show little
difference in ylide lifetime regardless of the available modes
for decay. Compound 17 provides three products, 18-20. Both
19 and 20 occur as products of intramolecular hydrogen shift.
Compound 19, which is formed initially, is converted to 20
by a secondary photoprocess involving intramolecular [2+2]
cycloaddition. The mechanism for formation of compound 18
is not certain. However, other work indicates that it may involve
an intramolecular ylide olefin addition process. Furthermore,
neither 19 nor 20 is involved in the formation of 18 [13].

Considering the additional pathways that are available to 17 it
is surprising that the lifetimes for the ylides derived from 105a
and 17 are so similar. The reason for this similarity is unclear
at this time.

Laser and Lamp Product Studies

Product studies were carried out to correlate preparative-
scale photochemistry with our time-resolved data. Pyrex-
filtered Hg lamp irradiation of 105a in benzene provided
exclusively cis-fused product 108a at concentrations ranging
from 10⁻³ to 10⁻⁴ M. Interestingly, analysis of mixtures produced
by 308 nm laser irradiation of 105a showed evidence of both
cis- and trans-fused products 108a and 107a. The ratio of
108a to 107a increased with increasing number of laser pulses.
Previous studies support initial formation of trans-fused ylide
intermediates that undergo suprafacial hydrogen migration to
provide trans-fused dihydrofuran and dihydrothiophene systems.
These are readily converted to the corresponding cis-fused
isomers with mild base treatment.

Photolysis of aryl vinyl ether 105b provided mixtures of cis
and trans products in both the laser and lamp studies. Pyrex-
filtered Hg lamp irradiation of 105b in benzene provided a
mixture of cis-fused and trans-fused products that varied with
the concentration. Thus, photolysis of 105b at 3.5×10⁻⁴ M
gave a mixture of 108b to 107b in a ratio of 3.6:1. Photolysis
of 105b at 9×10⁻⁴ M, however, provided 108b and 107b in a
ratio of 6.4:1. Finally, photolysis of 105b in methanol provided
exclusively cis-fused product 108b.

The observation of exclusively cis-fused products in the
preparative-scale work and mixtures of cis- and trans-fused in the
laser photolysis mixtures of 105a supports a mechanism
involving photoenolization of the initial cycloadducts. In order to
confirm this, the following experiment was carried out. A sample of 105a was irradiated in benzene with 1500 pulses from
the 308 nm laser source. Product analysis by NMR
showed the presence of both 107a and 108a. The sample was
then resubjected to photolysis, this time under preparative-
scale conditions (25 min, Pyrex-filtered Hg lamp irradiation).
Product analysis of the resulting mixture by NMR showed
only cis-fused product 108a. Thus, disparity in cis-trans product
ratios that were observed between the preparative-scale and
time-resolved work can be rationalized in terms of photoenolization of the initially formed trans-fused products [22].

Two Laser Photolysis

Theoretical studies predict that carbonyl ylides may undergo
fragmentation following photoexcitation [23,24], and numerous
experimental examples exist that support this prediction [25].
Direct time-resolved evidence for ylide photochemistry was
obtained by two-laser flash photolysis of the carbonyl ylide
formed by addition of fluorenylidene with acetone [26]. In
this case, 590 nm irradiation resulted in efficient bleaching of
the ylide absorption, indicating the occurrence of photochemistry.
Interestingly, it was found that ylide photolysis merely
accelerated the thermal decay process, i.e., ring closure to form the oxirane. Given the reported photoreactivity of carbonyl ylides, we have carried out two-laser studies on each of the sulfur and oxygen systems. Figure 3 shows the one- and two-laser decays of ylide 105a. It is clear that the second laser pulse (640 nm dye laser) causes extensive, irreversible depletion of the ylide absorption. In fact, this behavior was observed for each of the four ylides studied. This result is interesting in view of Schultz and Herkstroeter’s observation [2a] that the transients produced from 2-naphthyl-1-indenyl sulfide decay with a rate that is independent of the monitoring light intensity. However, we note that the intensity of the second laser used in this two-laser experiment was much higher than the monitoring lamp in Schultz and Herkstroeter’s study and, therefore, would be expected to greatly enhance any photochemical reactions of the ylide. Transient absorption spectra obtained following the second laser pulse failed to show any new transient absorptions. For this reason, two-laser product-oriented studies were carried out in which samples of 105a were subjected to several hundred pairs of laser pulses. The samples were concentrated and analyzed by NMR. However, preliminary results indicate that no products other than those observed following one-laser irradiation were formed (dihydrothiophenes). Although a full discussion of the results is beyond the scope of this article we report here that structure 113b has been confirmed by X-ray analysis.

An area of concern for us was the impact of lengthening the pendant dipolarophile which then provides an opportunity for an intramolecular [2+2] cycloaddition rather than the photoarylation leading to ylide products. Accordingly, the following systems were evaluated to assess the viability of using five atom dipolarophilic side chains in the Photoinitiated Intramolecular Ylide-Alkene Cycloaddition Reaction. As shown, the [2+2] cycloaddition effectively competes with photoarylation in the photolysis of phenyl vinyl ether system 114. However, this can be shifted to favor products of photoarylation by changing the aryl substituent to a naphthalene as in 117. In fact the [2+2] reaction can be completely suppressed as in the case with aryl vinyl sulfide 121.

Further Development of the Photoinitiated Intramolecular Ylide Alkene Cycloaddition Reaction

In an effort to explore the scope of this method for application to natural products synthesis we have initiated studies in a number of areas and report some of our results here. An early concern had been the opportunity for competing photoprocesses. Indeed we have already observed secondary [2+2] photoreactions which occur on photolysis of 17 and 29.

The ease of formation of [2+2] adducts in the forgoing reactions led us to explore the chemistry of naphthalene systems 110-111 which are readily available from the corresponding naphthol, naphthalenethiol or aminonaphthalene. Direct irradiation through Pyrex provided products which had spectral data consistent with formation of [2+2] adducts [15-16]. Although a full discussion of the results is beyond the scope of this article we report here that structure 113b has been confirmed by X-ray analysis.
We also considered that relocation of the pendant dipolarophile may allow access to [3+2] products similar in structure to those previously studied without the complications of competing [2+2] cycloadditions (e.g. 123 → 124). In this regard we have had some success. Thus although phenyl vinyl ether 123 gives rise to exclusively [2+2] product 125, naphthyl vinyl ether 126 provides the product of photoarylation and subsequent intramolecular [3+2] cycloaddition 127. These results are encouraging and suggest that the photophysical parameters of the photosubstrates can be adjusted to favor photoarylation over [2+2] cycloaddition.

Recently we examined methods for the removal of oxygen from [3+2] products such as 30. Treatment of 30 with 2.0 equivalents of BF₃·Et₂O in methanol provides lactone 128. On the other hand, treatment with 1.2 equivalents of BF₃·Et₂O in water provides a rearrangement product which has spectral data consistent with product 129. Thus far however, we cannot rule out formation of 130. Both can be rationalized as occurring from a common intermediate 132.

With respect to an asymmetric variant of the photoarylation, we have only cursory data. Bellus however, has demonstrated the successful utilization of chiral auxiliaries in the photocyclization of aryl vinyl amines for enantioselective synthesis of S-(-)-indoline carboxylic acid 133 [27]. A chiral auxiliary was used to influence the stereochemical outcome of the C-C bond formation in 134 and thus dictate the stereochemistry of intramolecular hydrogen transfer which is known to proceed by a suprafacial migration. In an interesting twist of this reaction he was able to employ 133 as the chiral auxiliary and thus obviate the necessity for separation of auxiliary and product at
the end of the synthesis.

\[ \text{Structure of compounds} \]

Summary

In closing the heteroatom directed photoarylation pioneered by Arthur G. Schultz has proven to be a rich area of study and promises to provide new and efficient methods for construction of exceedingly complex multicyclic systems in just a few experimental operations. Much has been learned in the course of this study. However, there is much more to be gained by a more thorough understanding of the photophysical and structural features that govern the mechanistic pathways involved in these reactions.

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10. Photochemical experiments were conducted using a 450-watt Canrad-Hanovia medium pressure quartz mercury-vapor lamp. The lamp was placed in a water-cooled Pyrex immersion well. Reaction solutions were saturated with argon prior to irradiation. For high and low temperature runs a vacuum-jacketed quartz immersion well was employed with a Pyrex sleeve filter. The immersion well was placed in a large scale (~200 mL) reactor. Heating was carried out with a silicon oil bath and cooling was achieved with a Neslab ULT-80DD low-temperature circulating bath.


14. We originally reported (Dittami, J. P. et al. (1990) Tet. Lett. 3821) that photolysis of A gave small amounts of compound B resulting from [3+2] cycloaddition of the side chain olefin with an intermediate thioaryl ylide. This assignment was made on the basis of $^1$H and $^{13}$C NMR data. The correct structure C, however, was later determined by single crystal X-ray analysis.


18. The results presented here represent preliminary work carried out in our laboratory and to date have not been published in full experimental detail.


22. A dark reaction was performed in order to eliminate the possibility that the isomerization was occurring via a surface-catalyzed reaction rather than via the enolization reaction suggested here. No evidence was found for a surface reaction.


