Photochemistry of 4-Acylisoxazoles

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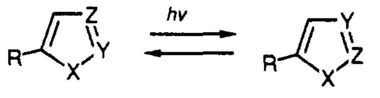
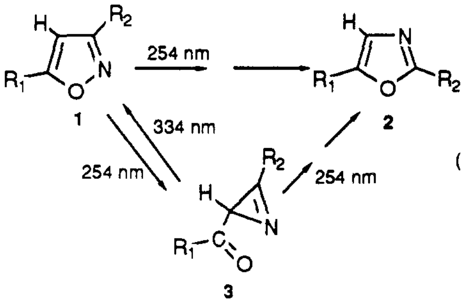
The photochemistry of 4-acylisoxazoles **4**, **5**, **13**, **14**, and **17** was investigated in a effort to clarify literature contradictions and anomalies and to provide a more detailed picture of the nature and number of intermediates involved in photoreactions of these systems. In contrast to a previous report on the photorearrangement of **14**, both oxazoles expected from a 2*H*-azirine intermediate have been observed. Wavelength studies of **5** and the derived 2*H*-azirine **10** revealed evidence for the involvement of at least two distinct product-forming intermediates. The results of quantum yield and laser flash photolysis measurements for ketones **4**, **14**, and **17** have been interpreted in terms of rapid ring openings of ketone triplet states to form diradical-like intermediates coupled with efficient reclosures (70–99%).

Photochemical transformations of heterocyclic ring systems have received considerable attention from both synthetic and mechanistic chemists. Of particular fascination have been the atom transposition reactions (eq 1)



(1)

by which two ring atoms interchange positions. A summary of the different mechanistic pathways by which these changes can occur is outlined in a recent review.[2] In one of the more thoroughly studied systems, Singh and coworkers demonstrated that rearrangements of certain isoxazoles 1 (R_1, R_2 = Ar) to isoxazoles 2 proceed via 2*H*-azirines 3 as shown in the eq 2.[3] These workers also



(2)

demonstrated that 2*H*-azirines could be transformed back to isoxazoles using long-wavelength ultraviolet light. The wavelength dependency was ascribed to selective excitation of the imine vs carbonyl chromophores in the 2*H*-azirine. Excitation into the carbonyl chromophore initiates homolytic cleavage of a C–N bond to form a diradical intermediate that can reclose to give isoxazole. Heterolytic cleavage of a C–C bond from the imine excited state produces a zwitterion that can lead to oxazole.

Although 2*H*-azirines have not been detected in some photorearrangements of isoxazoles, their presence has usually been inferred and this pathway remains the generally accepted one for photorearrangements of isoxazoles to form oxazoles. For example, Schmid et al. proposed that the methyl group scrambling they observed in the photorearrangement of 3-phenyl-4-acetyl-5-methylisoxazole to 2-phenyl-4-acetyl-5-methyloxazole proceeded via formation and partial rotational equilibration of a diradical intermediate prior to 2*H*-azirine formation.[4] Unfortunately, because they neither isolated nor detected the putative 2*H*-azirine, the exact stage at which scrambling occurred is undetermined since scrambling could have occurred during rearrangement of the 2*H*-azirine back to the isoxazole. On the other hand, recent studies by Padwa et al.[5] invoked a mechanism for photoisomerization of isoxazole 14 that did not involve either diradicals or a 2*H*-azirine because of the expectation that these intermediates would ultimately produce a mixture of two oxazoles. Instead, it was proposed that a specific conformer of a rearranged zwitterionic intermediate formed directly from an excited state of 3-phenyl-4-benzoyl-5-methylisoxazole (see below). Rapid collapse of the zwitterion in competition with restricted rotation about partial double bonds could lead to preferential formation of a unique oxazole.[6] Parenthetically, ketone 14 was claimed to be unreactive (under unspecified conditions) by Singh et al.[3a] who cited the result in support of a singlet-state mechanism for their isoxazole to 2*H*-azirine photorearrangements. Ferris and Trimmer[7] provided evidence from low-temperature IR spectroscopy for the transitory formation of a 2*H*-azirine in the rearrangement of a 4,5-tetramethyleneisoxazole to form an oxazole. In a closely related system, these workers found evidence for ketene imine formation on irradiation at low temperature in nonpolar media but isolated oxazole in high yield on irradiation in ethanol at 25 °C. Both products were postulated to arise from a common nitrene-like intermediate, but 2*H*-azirines were not invoked as intermediates in the formation of oxazole.

Our initial interest in the mechanisms of these transformations was stimulated by the theoretical studies of Tanaka et al. who proposed that isoxazole singlet states rearrange *directly* to 2*H*-azirine triplet states by an adiabatic transformation.[8] Although our efforts to substantiate this proposal by intramolecular trapping experiments were unsuccessful, mechanistic questions were raised concerning the number and nature of excited states and intermediates that are involved in these reactions.[9] In this paper we extend our earlier studies to include experiments designed not only to address these questions but also to resolve some of the aforementioned anomalies reported in

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[1] Present address: IBM Laboratories, East Fishkill, NY.

[2] Padwa, A. *Rearrangements in Ground and Excited States*; De Mayo, P., Ed.; Academic: New York, 1980; Vol. 3, pp 518–529.

[3] (a) Singh, B.; Ullman, E. F. *J. Am. Chem. Soc.* **1967**, *89*, 6911–6916; (b) Singh, B.; Zweig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199–1206.

[4] Dietliker, K.; Gilgen, P.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 2074–2099.

[5] Padwa, A.; Chen, E.; Ku, A. *J. Am. Chem. Soc.* **1975**, *97*, 6484–6491.

[6] These conclusions have been questioned on kinetic and conformational grounds by Schmid et al. Cf. ref 4.

[7] Ferris, J. P.; Trimmer, R. W. *J. Org. Chem.* **1976**, *41*, 13–19.

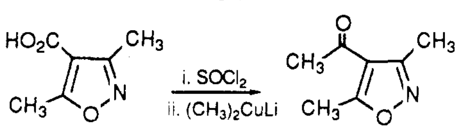
[8] Tanaka, H.; Matsushita, T.; Osamura, Y.; Nishimoto, K. *Int. J. Quantum Chem.* **1980**, *18*, 463–468.

[9] (a) Sauers, R. R.; Van Arnum, S. D. *Tetrahedron Lett.* **1987**, *28*, 5797–5800. (b) Sauers, R. R.; Hagedorn, A. A.; Van Arnum, S. D.; Gomez, R. P.; Moquin, R. V. *J. Org. Chem.* **1987**, *52*, 5501–5505.

the literature. To these ends we prepared and examined the photochemistry of the following compounds: 3,5-dimethyl-4-acetylisoxazole (**4**), 3,5-dimethyl-4-benzoylisoxazole (**5**), 3-methyl-4-acetyl-5-phenylisoxazole (**13**), 3-phenyl-4-benzoyl-5-methylisoxazole (**14**), and 3,5-diphenyl-4-acetylisoxazole (**17**).

Syntheses

3,5-Dimethyl-4-acetylisoxazole (**4**) was prepared by a new procedure from the reaction of 3,5-dimethyl-4-isoxazolylcarboxylic acid chloride with lithium dimethylcopper (eq 3). The corresponding phenyl ketone **5** was obtained by reaction of 3,5-dimethylisoxazole-4-carboxaldehyde with phenylmagnesium bromide followed by oxidation of the intermediate alcohol with Jones reagent (eq 4). 3-Methyl-4-acetyl-5-phenylisoxazole (**13**) was prepared by in situ addition of acetonitrile oxide to 4-phenyl-3-butyn-2-one.



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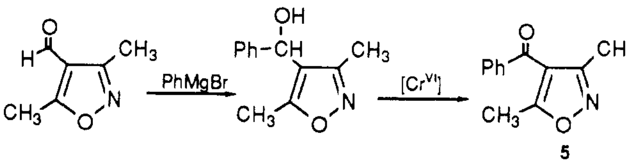
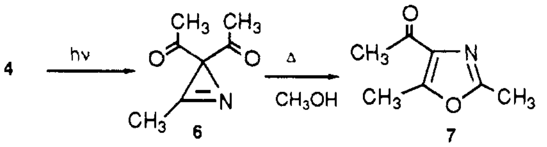


5 (4)

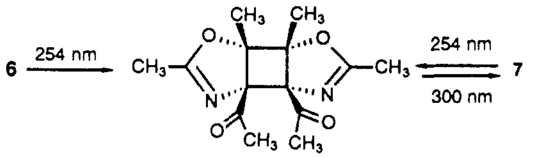
Preparative Photolyses

Compound 4. Irradiation of the acetylisoxazole **4** was carried out under a variety of conditions and monitored by ^{1}H NMR spectroscopy. Irradiations in acetonitrile, methanol-d_4, benzene, dioxane, and dimethoxyethane at 254, 300, and/or 350 nm gave rise to a single product, 2*H*-azirine **6**. Irradiation in benzene with a Corex filter also gave **6** and much tarry material. Compound **6** was characterized by an elemental analyses, ^{1}H NMR spectrum (two singlets, area ratio 2:1 at δ 2.15 and 2.50), ^{13}C NMR (five peaks), and thermolysis to produce oxazole **7** (eq 5).



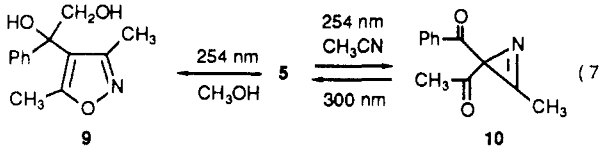
6 **7** (5)

Irradiation of **6** at 254 nm converted it to compound **8** that showed three different methyl groups in the ^{1}H NMR spectrum and seven different carbon atoms in a ^{13}C NMR experiment. The structure of this product was assigned on the basis of an exact mass determination, which showed it to have twice the molecular weight of **6**, and the fact that it could also be produced quantitatively from oxazole **7** by irradiation at 254 nm (eq 6). The structure and stereochemistry are assigned by analogy with the results from the related esters (carbalkoxy in place of acetyl).[10]



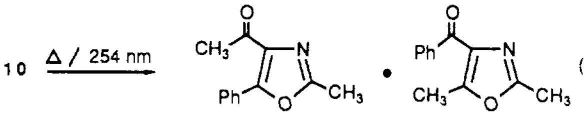
8 (6)

Compound 5. Irradiation of **5** in methanol solution at 254 nm gave rise to a mixed pinacol **9** as the major product. Identification was based on NMR, IR, and mass spectroscopic analyses and periodic acid cleavage to **5** (eq 7).



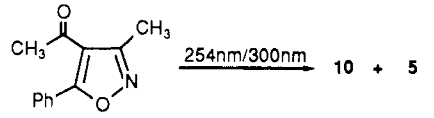
9 **10** (7)

From a preparative scale irradiation in acetonitrile (Vycor filter), we isolated a compound identified as 2*H*-azirine **10**, an 8:1 mixture of oxazoles **11** and **12**, an unstable ketene imine,[9a,11,12] and a small amount of benzoylacetone. Although all attempts to isolate a derivative of the ketene imine by trapping with nucleophiles were unsuccessful,[12] we were able to characterize the methanol adduct by ^{1}H NMR (see the Experimental Section). The 2*H*-azirine **10** was isolated and characterized by an IR absorption band at 5.57 μm[12] and its further conversion to oxazoles **11** and **12** on thermolysis[5] at 235 °C or irradiation at 254 nm (eq 8). The oxazoles were identified by comparison with authentic samples. Irradiation of **10** or **5** at 300 nm produced a 95:5 photoequilibration mixture of isoxazole **5** and 2*H*-azirine **10** (eq 7). Under these conditions, no ketene imine was detected.



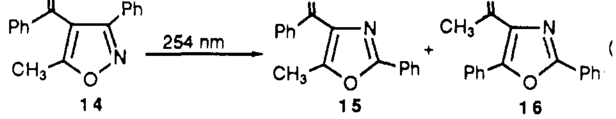
11 **12** (8)

3-Methyl-4-acetyl-5-phenylisoxazole (13). A preparative scale irradiation of **13** in acetonitrile at 300 nm gave rise to a 20% yield of 2*H*-azirine **10** and an 80% yield of a 2:1 mixture of isoxazole **5** and isoxazole **13**, respectively (eq 9). An experiment at 254 nm yielded **5**, **10**, ketene imine, and oxazoles **11** and **12**.



13 (9)

3-Phenyl-4-benzoyl-5-methylisoxazole (14). Preparative scale irradiation of **14** in acetonitrile with an immersion lamp and Vycor filter gave rise to a 53% recovery of mass that was comprised of starting material (40%), benzoylacetone (14%), and 46% of a 1:9 mixture of oxazoles **15** and **16** (eq 10). The presence of *both* **15** and **16** was demonstrated by comparisons of ^{1}H NMR and ^{13}C NMR spectra with those of authentic samples. Control experiments showed that **15** and **16** were not interconverted at either 254 or 300 nm and that **14** itself was stable at wavelengths >300 nm. The same oxazoles were formed in ca. equal amounts on thermolysis[5] of **14** at 245 °C.



14 **15** **16** (10)

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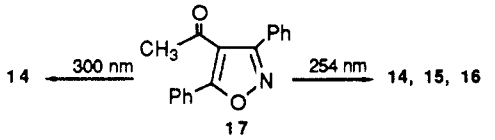
[10] Dworschak, H.; Weygard, F. *Chem. Ber.* **1968**, *101*, 302–307.

[11] For an example of one case in which a ketene imine was isolated from an isoxazole photolysis, see: Kurtz, D. W.; Schechter, H. *Chem Commun.* **1966**, 689–690.

[12] Sato, T.; Yamamoto, K.; Fukui, K.; Saito, K.; Haykawa, K.; Yoshiie, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 783–787.

3,5-Diphenyl-4-acetylisoxazole (17). The isomeric isoxazole 17 was converted to 14 on irradiation at 300 nm in either benzene or acetonitrile. Irradiation at 254 nm resulted in formation of 14–16 and small amounts of benzoylacetone (eq 11). Irradiation in the presence of 0.076 M 1,4-diazabicyclo[2.2.2]octane (DABCO) at 254 nm partially quenched the isomerization of 17 whereas the same concentration of DABCO completely quenched the conversion of 17 to 14 upon irradiation at 300 nm.

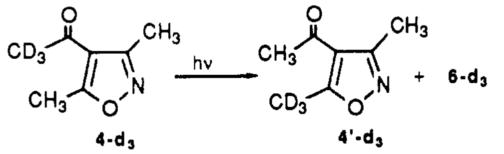


(11)

Quantum Yields. Quantum yields for ketone disappearances were measured for 4 (ϕ_{-K} = 0.23 at 254 nm, 0.32 at 300 nm), 14 (ϕ_{-K} = 0.0094 at 254 nm), and 17 (ϕ_{-K} = 0.083 at 300 nm).

Mechanistic Studies

The photoisomerization of 4 could be quenched by 2-methoxy-1,3-butadiene, and a minimum triplet state lifetime of ~1 × 10^{-10} s was calculated by a standard Stern–Volmer analysis (slope 2.1 M^{-1}).[13] Irradiation of the trideuterio analogue 4-d_3 at either 254 or 300 nm led to partial scrambling of the label into the 5-position with an estimated quantum yield of ca. 0.04 (eq 12). Irradiation of 4 in methanol-*O-d* did not lead to incorporation of deuterium atoms on either of the methyl carbons in 4 recovered from partial photoisomerizations at 254 or 300 nm.[14]

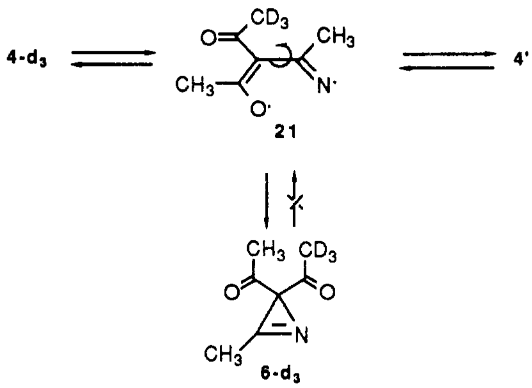


(12)

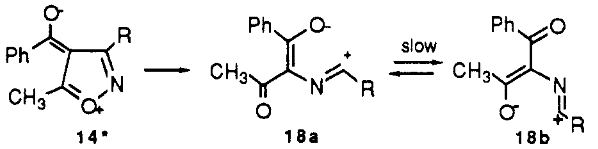
Flash photolysis experiments were carried out with 5 and 14 in an effort to detect transient intermediates and/or excited states. The ketones were examined in acetonitrile with a 14-ns, 70–90-mJ, 351-nm pulse from a XeF excimer laser. From 5 we observed a transient absorption spectrum that had maxima at ca. 320 and 480 nm. The transient decayed with a lifetime of 276 ns and was quenched in the presence of 0.01 M biphenyl to give rise to a typical biphenyl T–T absorption spectrum with absorption maximum at 360 nm.[15] Similarly, ketone 14 gave rise to a transient (τ = 48 ns) with a maximum at ca. 320 nm and a weak shoulder at ca. 412 nm. Strong absorption appeared at 365 nm in the presence of 0.01 M biphenyl.

Efforts were made to detect a 2*H*-azirine during the course of irradiation of 14 at 254 nm. A peak appeared in the ^{1}H NMR spectrum at δ 2.47 that built up to ca. 12% conversion and then steadily decreased. This same absorption appeared during irradiations of 17 (10%) and is believed to be associated with the methyl group of 2-acetyl-2-benzoyl-3-phenyl-2*H*-azirine. Attempts to trap this material with water, acetic acid, trifluoroacetic acid, sodium cyanoborohydride, or 1,3-diphenylisobenzofuran were unsuccessful. Irradiation at 300 nm of a sample containing this peak did not produce a definitive change, but the peak gradually disappeared simply on standing at 25 °C. Irradiations of 14 in the presence of D_2O did not lead to incorporation of deuterium in the methyl group of material recovered from incomplete photoisomerizations.[14]

Scheme I



A series of experiments was designed to investigate the behavior of the postulated zwitterionic precursors of oxazoles. It is generally believed that these moieties, represented as 18a and 18b by Padwa et al.,[5] are produced by carbon–carbon bond cleavage of intermediate 2*H*-azirines[2] although these workers proposed that a specific conformer 18a (R = Ph) was formed from a charge separated excited state 14*. If cyclization of 18a to form 14 were faster than rotational equilibrium with 18b (eq 13), one would expect unusual product ratios. Since this proposal is unprecedented, we carried out experiments that were designed to generate the zwitterions by an alternative pathway. Photodecomposition of 2-diazo-1-phenyl-1,3-butanedione (19) has been shown by Tomioka et al. to produce acetylbenzoylcarbene (20) in competition with Wolff rearrangement.[16] Upon irradiation of 19 at 350 nm in benzonitrile or acetonitrile we obtained mixtures of oxazoles and other products in both cases (eq 14).[17] Using benzonitrile as solvent, we obtained a 1.5:1.0 mixture of 16 and 15 (^{1}H NMR) and with acetonitrile a 1.5:1.0 mixture of 11 and 12 was obtained.



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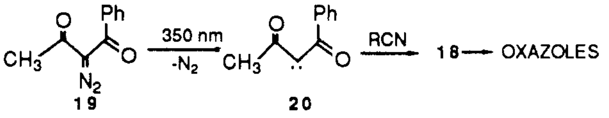

(14)

Discussion

The isolation of 2*H*-azirine 6 from irradiations of 4 is exceptional in that earlier workers did not report the ap-

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[13] It is likely that the quenching rate for this diene proceeds at a diffusion-controlled rate, 2 × 10^{10} M^{-1} s^{-1}. Cf.: Schore, N. E.; Turro, N. J. *J. Am. Chem. Soc.* **1975**, *97*, 2482–2488.

[14] Matsuura, T.; Kitaura, Y. *Tetrahedron* **1969**, *25*, 4487–4499.

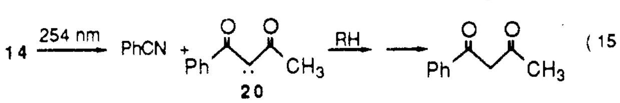
[15] Casal, H. L.; McGimpsey, W. G.; Scaiano, J. C.; Bliss, R. A.; Sauers, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 8255–8259. Under similar conditions, a transient spectrum obtained from 3-benzoyl-5-phenylisoxazole was attributed to a nitrile ylide. See footnote 36 in: Barik, R.; Kumar, C. V.; Das, P. K.; George, M. V. *J. Org. Chem.* **1985**, *50*, 4309–4317.

[16] Tomioka, H.; Hayashi, N.; Asano, T.; Izawa, Y. *Bull Chem. Soc. Jpn.* **1983**, *56*, 758–761.

[17] For examples of oxazole formation from a ketocarbene and a nitrile, see: Huisgen, R.; Binsch, G.; Konig, H. *Chem. Ber.* **1964**, *97*, 2868–2883. Barcus, R. L.; Wright, B. B.; Platz, M. S.; Scaiano, J. C. *Tetrahedron Lett.* **1983**, *24*, 3955–3958. For Lewis acid catalyzed examples, see: Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657–3664. For an example in which a carbene was trapped by a nitrile to form a nitrile ylide see: Barcus, R. L.; Wright, B. B.; Platz, M. S.; Scaiano, J. C. *Tetrahedron Lett.* **1983**, *24*, 3955–3958.

pearance of **6** and isolated only oxazole **7** from their photolyses.[5] When we attempted to reproduce their experiment, we found only the photodimer of **7**.[18] The isolation of 2*H*-azirine **6** was fortuitous in that it enabled us to more definitively evaluate the genesis of the methyl scrambling process discovered by Schmid et al.[4] Although these workers observed methyl scrambling during photoisomerization of 3-phenyl-4-acetyl-5-methylisoxazole, they were unable to unequivocally evaluate the role of 2*H*-azirine in their analysis because it was not detected. In our system, we observed methyl scrambling of **4**-d_3 under conditions in which 2*H*-azirine **6**-d_3 is formed but is photochemically stable. We conclude that scrambling must have occurred *before* 2*H*-azirine formation via a (triplet) diradical intermediate **21** or its equivalent[3,19] (Scheme I). The low efficiency of scrambling indicates that reclosure to isoxazole is relatively rapid compared to bond rotations and that the intermediate does not survive long enough to achieve symmetry with respect to the acyl groups.

Formation of benzoylacetone from irradiation of **14** is an unprecedented reaction, and some effort was expended to probe the origin of this material. Initially, we entertained the idea that an excited state of **14** underwent photocleavage to produce benzonitrile and acetylbenzoylcarbene (**20**), which could abstract hydrogen from the solvent to produce benzoylacetone (eq 15). This conjecture was based on the observations of Tomioka et al. who found benzoylacetone upon irradiation of **19** in methanol.[16] Because we could find no evidence in acetonitrile for the other products that would be expected if this mechanism were in operation, e.g., succinonitrile and benzonitrile, it seems likely that a photohydrolysis is involved that may be induced by nucleophilic attack of water on a charge-separated excited state of the kind suggested by Padwa et al.,[5] i.e., **14***. In support of this contention, we showed that the addition of water enhanced the yield of benzoylacetone. Unfortunately, we were unable to find evidence for the formation of benzonitrile oxide or its dimer, diphenylbenzofuroxazan, although it was demonstrated that the latter was not stable under the irradiation conditions.



(15)

Summary

Each of the ketones examined rearranged (in part) to oxazoles upon irradiation into the isoxazole chromophore with 254-nm light, and three of the ketones led to isolable 2*H*-azirines. Because there is at least indirect evidence for the formation of 2*H*-azirines in the case of **14** (transitory ^{1}H NMR peaks and formation of both oxazoles), we see no compelling reason to postulate an ad hoc mechanism for the formation of **14**.[5]

In an effort to develop a comprehensive scheme that encompasses the available experimental facts, the following observations must be accommodated:

(a) Photoisomerizations under all conditions are inefficient. Quantum yields for ketone loss are less than 0.30, yet there are no other chemically observable mechanisms for internal conversion, e.g., photoenolization.

(b) Aromatic ketones are less reactive than aliphatic ketones.

(c) Irradiations at 254 nm produce (in part) product-forming manifolds different that are different from those produced by irradiations at longer wavelengths. For example, ketene imine formation is accessible only by irradiation of either 2*H*-azirine **10** or acetylisoxazole **13** at 254 nm; irradiations at 300 nm produce benzoylisoxazole **5**, but not ketene imine. In addition, DABCO completely quenches isomerization of isoxazole **17** to **14** on irradiation with 300-nm light but not with 254-nm light.

(d) Differing ratios of isomeric oxazoles are produced depending on whether the precursors are isoxazoles or nitriles plus diazoketone.

Conclusions

(a) We conclude that both physical and chemical modes of deactivation are responsible for the low quantum yields of these reactions. Since the lowest lying excited states of the phenyl ketones are triplet states as shown by flash spectroscopy, it is likely that some of the inefficiency of the phenyl ketone reactions at 254 nm is due to intramolecular energy transfer from an upper-level reactive state to a low-lying state that it is localized mainly in the carbonyl group as an n,π^* triplet. This aspect of 4-acylisoxazole photochemistry was noted in earlier studies of 5-*endo*-(4-acylisoxazolyl)norbornenyl systems in which excitation at 254 nm led to both 2*H*-azirines and oxetanes.[9] It was proposed that oxetane resulted from a carbonyl n,π^* triplet state formed via intersystem crossing/internal conversion of an upper excited state since excitation at 300 nm led only to oxetane. Because it was estimated that only 22% of the upper states decayed to the oxetane-forming n,π^* state, the inefficiency associated with 2*H*-azirine formation was not limited by oxetane formation and was attributed to radiationless decay process(es) derived from an upper-level excited state.

The most obvious chemical mechanism for rationalizing the inefficiency of these photoisomerizations is reclosure of ring-opened intermediates, e.g., diradical **21**.[19] What was not anticipated about this conclusion is the high efficiency of this process: 70–99%. This is evidenced not only by the uniformly low quantum yields for ketone loss but also by the results of the methyl scrambling experiments in which case reclosure competed favorably with bond rotations as outlined in Scheme I. As a further consequence of this conclusion, the apparent contradiction between the lack of reactivity of **14** on irradiation at long wavelengths with its short triplet-state lifetime (48 ns) can be rationalized by assuming that ring opening occurs rapidly from the lowest triplet state and that reclosure back to the ground state of **14** is the predominant fate of the biradical.[20]

(b) We estimate that the aliphatic triplet-state reactions proceed as much as $\sim 3 \times 10^3$ times faster than in the aromatic systems. This estimate is based on a calculated

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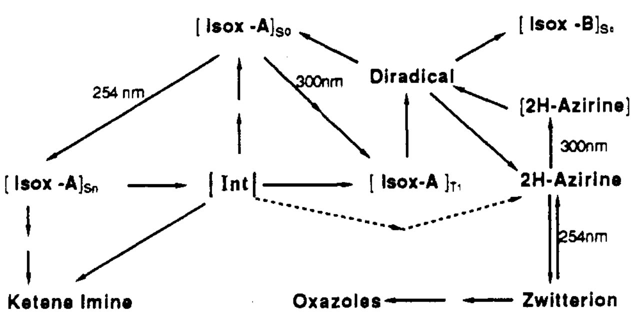
(18) In a private communication A. Padwa suggested that small differences in reaction conditions may have been responsible for this discrepancy.

(19) The first intermediate in these reactions is generally drawn as a diradical, i.e., **21**, although most authors have not been explicit about the multiplicity and electronic configuration of this species.[2-4,7] For a discussion of structures of nitrenes derived from vinyl azides, see: Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176–3180. Calculations by Tanaka et al.[8] show that the configuration of the lowest energy singlet state of isoxazole itself is n,π^* and lies at 5.31 eV above the ground state. Homolytic cleavage of the N–O bond from this state might be expected to lead to a s,π radical, but this configuration may not necessarily be of lowest energy. The configurations of the lowest two triplet states were shown to be π,π^* and are of lower energy.

(20) Under similar conditions, the lifetime of benzophenone triplet was $\sim 4 \times 10^{-6}$ s. An alternative explanation takes note of the opportunity for carbonyl–phenyl deactivation in **13** (but not in **5**) analogous to the situation encountered by Scaiano and Nicodem with 2-phenylbenzophenone. Cf.: Scaiano, J. C.; Nicodem, D. E. *Can. J. Chem.* **1984**, *62*, 2346–2350.

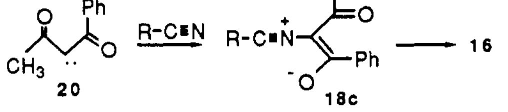
Scheme II



reaction rate constant of 1 × 10^{10} s^{-1} for **4** and an estimated upper limit of 3.6 × 10^6 s^{-1} for **5**. With **14** the ratio of reactivities is ~500. Although the exact reason for these reactivity differences is unknown, it may be the result of the greater exothermicity of the reactions of alkyl ketones vs aromatic ketones.[21]

(c) Since interconversions can be selectively initiated between isoxazoles and 2*H*-azirines without formation of ketene imine using long-wavelength light, we conclude that two different intermediates must be involved. Although we cannot rule out ketene imine formation via concerted reactions from an upper-level excited state, a simple rationale for these observations is to assume that an electronically distinct version of **21** is involved in ketene imine formation.[19]

(d) The experiments with diazophenylbutanedione support the idea advanced by Padwa et al.[5] that the ratio of isomeric oxazoles produced from **18** is a function of the initial conformation of the acyl groups; i.e., bond rotations are slow compared to collapse of the zwitterion. Since the acetyl oxazole **16** is the predominant product in all cases, there may be an electronic preference in addition to steric factors. These results are consistent with the conclusions of Tomioka et al.[16] who rationalized their findings in terms of preferred conformations of the diazo ketone and corresponding carbene. As shown in eq 16 capture of the carbene in conformation **20** by a nitrile would generate a zwitterion **18c** represented in the more usual form with a linear CNC bond.[3,4,7] Rapid collapse of the latter would lead to **16**. Since there is no reason to expect that the initial conformations of the zwitterionic species generated from the 2*H*-azirines would be identical with those originating from the carbene precursors, different ratios of oxazoles would be produced.



(16)

The minimum level of complexity that encompasses these results is shown in Scheme II in which Int is the species that is distinguished from the diradical **21** because it forms ketene imine. As noted by Ferris and Trimmer[7] this moiety has characteristics of a vinylnitrene,[19] but in contrast to their conclusions the intermediate cannot be the sole precursor of 2*H*-azirines in isoxazole **5**. Because photoequilibration of 2*H*-azirine **10** with **5** occurs independently of ketene imine formation, it is more appropriate to place intermediate **21** at a later stage in the progression of events. We came to a similar conclusion in an earlier study of 3-acetyl-5-methylisoxazole in which case direct irradiation produced a nitrile and 2*H*-azirine but irradiation under acetone-sensitized conditions led only to oxazole, presumably via 2*H*-azirine formation. Finally, until compelling evidence requires modification of the scheme, 2*H*-azirines are shown as intermediates for oxazole formation.

In conclusion, this work has provided several new mechanistic details about the photochemical interconversions and rearrangements of isoxazoles and 2*H*-azirines and has clarified some inconsistencies in the literature. Although the exact nature and number of intermediates involved in these transformations still remain unknown and may vary from system to system, we have highlighted the roles of multiple intermediates and excited states.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 727b spectrometer or a Mattson Cygnus 100 (A) spectrometer. Proton NMR spectra were determined in $CDCl_3$ or as noted with tetramethylsilane as internal standard. Spectra labeled ^1H NMR were determined on Varian Model T-60 spectrometer. ^1H NMR(A) and ^{13}C NMR spectra were determined on a Varian VXR-200 spectrometer. Integration data (±10%) were consistent with the assigned structures. Methyl peaks only are reported for compounds that contain aromatic rings. Absorption spectra were obtained in HPLC grade acetonitrile on a Cary Model17D spectrometer. The time-resolved spectral data were obtained with a Lambda Physik EMG 101 excimer laser source operating at 351 nm and emitting 14-ns light pulses at ~90 mJ. The detection unit consisted of a 1000-W Oriel xenon arc lamp, a 1-in. Uniblitz shutter, grating monochromator, and an RCA 4840 photomultiplier tube wired in a five-dynode configuration. The transient data were acquired by a Tektronix 7912AD transient digitizer and analyzed by a Tektronix 4052A computer. The digitizer was capable of generating a 512-point trace with a minimum resolution of 500 ps/point. Mass spectral data were obtained from a VG Model 7070 EQ high-resolution spectrometer. Elemental analyses were performed by G. Robertson, Madison, NJ. Analytical and small-scale preparative irradiations were carried out in a Rayonet reactor equipped with 254-, 300-, or 350-nm bulbs. Preparative reactions were carried out in an immersion apparatus with a 450-W Hanovia lamp and the appropriate filter. All solutions were thoroughly deaerated with nitrogen before irradiation.

3-Methyl-4-acetyl-5-phenylisoxazole (13). To a stirred solution of 4-phenyl-3-butyn-2-one (0.500 g, 3.47 mmol) and 1.1 equiv of triethylamine (0.53 mL) in 7 mL of methylene chloride cooled to −10 °C was added 3.8 mL of methylhydroxamoyl chloride[22] solution in methylene chloride (0.323 g, 3.45 mmol) over ca. a 20-min period. The reaction mixture was stirred for 1 h at −10 °C and ca. 3 h at 25 °C and stored overnight at 4 °C. The methylene chloride solution was washed with water (2 × 15 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 0.610 g of an orange oil. The oil was chromatographed on a silica gel column with 10% ethyl acetate/hexanes as the eluent. A fast-moving fraction containing 0.226 g of unreacted 4-phenyl-3-butyn-2-one was recovered, as well as a slow-moving fraction containing 0.282 g of the desired isoxazole as a slightly yellow oil. The oil was purified by column chromatography with the same eluent system to yield 0.280 g (40%) of pure 3-methyl-4-acetyl-5-phenylisoxazole as a clear oil; IR (film) 5.96 μm; UV λ_{max} (CH_3CN) 263 nm (ε 9900); ^1H NMR(A) singlets at δ 2.423, 2.183 (CD_3CN) and 2.478, 2.209 ($CDCl_3$). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 72.11; H, 5.56; N, 7.06.

3-Phenyl-4-benzoyl-5-methylisoxazole (14): mp 117 °C (lit.[23] mp 116–117 °C); ^1H NMR(A) methyl group singlets at δ 2.422 (CD_3CN) and 2.495 ($CDCl_3$).

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(21) There is good analogy in the diminished type I reactivity of aromatic vs aliphatic ketones. See: Wagner, P. J.; McGrath, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 3849–3851. Lewis, F. D.; Hilliard, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 3852–3858.

(22) McGillivray, G.; ten Krooden, E. S. *Afr. J. Chem.* **1986**, *39*, 54–56.

(23) (a) Renzi, G.; Dal Piaz, V.; Musante, C. *Gazz. Chem. Ital.* **1968**, *98*, 656–666. (b) Triebs, A.; Sutter, W. *Chem. Ber.* **1951**, *84*, 96–100.

3,5-Diphenyl-4-acetylisoxazole (17): mp 95–97 °C (lit.[5] mp 94–95 °C); ^1H NMR(A) methyl group singlets at δ 2.143 (CD_3CN) and 2.176 ($CDCl_3$).

2,5-Dimethyl-4-acetyloxazole (7): mp 47–48 °C (lit.[5,23] mp 46–47, 48–49 °C); ^1H NMR(A) singlets at δ 2.45, 2.50, 2.60.

2-Phenyl-4-benzoyl-5-methyloxazole (15). A three-necked, round-bottomed flask was charged with 0.410 g (1.85 mmol) of the 2-phenyl-5-methyl-4-oxazolecarboxylic acid chloride (mp 133–135 °C; lit.[5,24] mp 135–136, 133–135 °C) and 25 mL of benzene. The stirred solution was placed in a cold water bath, and 0.32 g (2.4 mmol) of $AlCl_3$ was added slowly followed by stirring for 0.5 h. The reaction mixture was heated at reflux at 3 h and stirred for an additional 18 h at 25 °C. The reaction mixture was poured into 75 mL of water, and the reaction flask was rinsed with ether and concentrated HCl. The layers were shaken and separated, and the aqueous layer was extracted with 50 mL of ether (2X). The combined organic layers were washed with 50 mL of water (2X) and 50 mL of 0.1 M Na_2CO_3 and dried over $MgSO_4$. The solvent was removed in vacuo to yield 450 mg of wet yellow solid. The crude product was stirred with ethyl alcohol for several hours to convert unreacted acid chloride back to the ethyl ester. The ethyl ester and the desired phenyl ketone were separated on a silica gel column (7.5% ethyl acetate/hexanes) to yield 131 mg (27%) of **15** and 177 mg of ethyl ester. The product was further purified by chromatography on a silica gel column two more times followed by sublimation at 68 °C (0.1 Torr) and crystallization from $MeOH/H_2O$ to yield 82 mg (17%) of **15** as white needles: mp 63–64 °C (lit.[5] mp 61–62 °C); IR (Nujol) 6.05 μm; UV λ_{max} (CH_3CN) 272 nm (ε 27000); ^1H NMR(A) singlets at δ 2.686 (CD_3CN) and 2.751 ($CDCl_3$); ^{13}C NMR δ 12.9, 126.5, 126.9, 128.2, 128.8, 130.4, 130.6, 132.8, 135.6, 137.5, 157.3, 158.5, 188.0.

2,5-Diphenyl-4-acetyloxazole (16): mp 101–102 °C (lit.[25] mp 101–102 °C); UV λ_{max} (CH_3CN) 214, 293 nm (ε 20000, 19200); ^1H NMR(A) singlets at δ 2.626 (CD_3CN) and 2.703 ($CDCl_3$); ^{13}C NMR δ 29.1, 126.6, 127.2, 128.1, 128.5, 128.9, 130.5, 130.9, 135.4, 153.0, 158.6, 194.7.

3,5-Dimethyl-4-acetylisoxazole (4). A solution of 1.41 g (0.01 mol) of 3,5-dimethylisoxazole-4-carboxylic acid was treated with 5 mL of thionyl chloride and the resultant mixture stirred overnight at 25 °C. Two 14-mL quantities of toluene were added followed by evaporations under reduced pressure. A solution of the crude acid chloride in 4 mL of anhydrous ether was added dropwise at −78 °C to a solution of lithium dimethylcopper prepared from 42 mL of 2.2 M methyllithium and a slurry of 3.8 g (0.020 mol) of copper(I) iodide in 25 mL of dry ether (prepared at −78 °C, allowed to warm to 0 °C, recooled to −78 °C). The resulting mixture was stirred at −78 °C for 20 min and −10 °C for 15 min and added to a solution containing 18 mL of concentrated NH_4OH and 360 mL of saturated NH_4Cl. The aqueous layer was extracted three times with ether and the combined extracts were washed with water, 2 M HCl and 5% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the ether yielded an oil that was crystallized from ligroin to give 0.58 g (42%) of **4**. After sublimation at 60–70 °C (2.5 Torr) it showed the following: mp 45 °C (lit.[5] mp 46–47 °C); UV λ_{max} (CH_3CN) 255, 300 nm (ε 7949, 48); ^1H NMR ($CHCl_3$) and IR data agreed with published values; ^1H NMR singlets at δ 2.35, 2.40, 2.65 (CD_3CN) and 1.75, 1.95, 2.15 (C_6H_6).

3,5-Dimethyl-4-(acetyl-*d*$_3$)isoxazole (4-*d*$_3$) was prepared by an exchange reaction in which a solution of sodium deuterioxide in deuterium oxide (0.040 g of sodium in 10 mL of D_2O) was stirred at 25 °C with a solution of 0.35 g of **4** in benzene. After 2 h, the layers were separated and the aqueous layer was extracted with benzene. The benzene extracts were washed with D_2O, dried over molecular sieves, and evaporated to give 0.33 g of **4**-d_3 after sublimation at 60–70 °C (2.5 Torr): ^1H NMR singlets at δ 1.75, 1.95 (C_6H_6) and 2.35, 2.60 (CD_3CN).

3,5-Dimethyl-4-benzoylisoxazole (5). To a solution of 0.91 g (0.0072 mol) of 3,5-dimethyl-4-isoxazolecarboxaldehyde[26] in 17 mL of anhydrous ether was added 3 mL of an ethereal solution of phenylmagnesium bromide (3 M) at 25 °C. After being stirred for 80 min, the reaction was quenched with saturated NH_4Cl solution and the aqueous layer was removed and extracted with 25 mL of ether. The combined extracts were washed with NH_4Cl, dried over $MgSO_4$, and evaporated to give 1.12 g of carbinol **9**. The crude alcohol was oxidized at 0 °C with 3.1 mL of Jones reagent (3.4 M K_2CrO_4 in 4 M H_2SO_4). Saturated aqueous $NaHCO_3$ solution was added, and the mixture was filtered. The aqueous phase was extracted with more ether, and the combined extracts were washed with $NaHCO_3$ and brine and dried over $MgSO_4$. After evaporation of the ether there was obtained 0.9 g (81%) of ketone **5**, bp 40–41 °C (0.24 Torr). After flash chromatography (10% ethyl acetate/hexanes) it showed the following: mp 58 °C; IR (CCl_4) 6.23 μm; ^1H NMR (CCl_4) δ 2.20 (s), 7.60 (m); UV λ_{max} (CH_3CN) 244, 321 nm (ε 13500, 136). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.88; H, 5.27; N, 7.12.

2-Methyl-4-acetyl-5-phenyloxazole (11). (a) Ethyl (2-Acetamidobenzoyl)acetate. To a clean, dry 250-mL round-bottomed flask were added 16.59 g (75.0 mmol) of ethyl benzoylacetate oxime, 21.23 mL (0.225 mol) of acetic anhydride, and 28.3 mL of acetic acid. To the stirred solution were added 0.375 g of sodium acetate and 0.0375 g of $HgCl_2$. A condenser was attached to the flask, and Zn powder (14.71 g, 0.225 mol) was added in small portions. The reaction mixture was refluxed for 40 min, after which the cooled mixture was filtered. The solids were rinsed with ether, and the combined organic layers were washed with water (3 × 50 mL) and 1 M K_2CO_3 (1X). The combined aqueous layers were made basic by adding solid K_2CO_3 and were then extracted with ether (2 × 75 mL). All organic layers were then combined and dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to yield 15.85 g of an orange oil that crystallized eventually. Recrystallization from ethyl acetate/hexanes afforded 8.171 g (44%) of the amide as yellow-brown crystals. An analytical sample was prepared by flash chromatography of a 0.590-g portion of the crude product on a silica gel column with 25% ethyl acetate/hexanes as the eluent followed by crystallization from ethyl acetate/hexanes to yield 0.129 g of the pure amide as white crystals: mp 83–85 °C; IR (Nujol) 3.05, 5.72, 5.89, 6.11 μm; ^1H NMR(A) singlet at δ 2.09. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.66; H, 5.91; N, 5.53.

(b) Ethyl 2-Methyl-5-phenyl-4-oxazolecarboxylate. A solution of 4.012 g (16.1 mmol) of the amide in 10 mL of chloroform was cooled to 0 °C in an ice/salt bath. Thionyl chloride (1.40 mL, 1.2 equiv) was added to the stirred solution, and the temperature was maintained at 0 °C for 30 min. The solution was stirred overnight at 25 °C. Because the reaction was incomplete as shown by thin-layer chromatography, the mixture was refluxed for an additional 45 min. An additional 0.30 mL (4.10 mmol) of $SOCl_2$ was added, and the mixture was refluxed for 1 h followed by stirring overnight at 25 °C. Excess thionyl chloride was quenched with 25 mL of 1 M K_2CO_3, the layers were separated, and the solvent was removed under reduced pressure. The residue was redissolved in 25 mL of ether, and the aqueous layer was extracted with ether (2X). The ether layers were combined, washed with water (1X), and dried over $MgSO_4$, and the solvent was removed in vacuo to yield 3.601 g (97%) of ethyl 2-methyl-5-phenyl-4-oxazolecarboxylate as a brown solid. An analytical sample was prepared by subliming a 0.710-g sample at 56 °C (0.025 Torr) to yield 0.544 g of pure oxazole as white crystals: mp 61–63 °C; IR (Nujol) 5.85 μm; ^1H NMR(A) singlet at δ 2.54. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.39; H, 5.57; N, 5.86.

(c) 2-Methyl-5-phenyl-4-oxazolecarboxylic Acid. A 250-mL round-bottomed flask was charged with 2.682 g (0.0116 mol) of the ethyl ester, 13 mL of 95% ethanol, and 13 mL of 2 N NaOH. A few more milliliters of water was added to facilitate stirring, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was washed with ether (2X), and the combined ether layers were washed with water (1X). All aqueous layers were combined, and acidification with concentrated HCl resulted in precipitation of a white solid. Vacuum filtration afforded 1.860 g of a brown-yellow solid that was recrystallized from ethanol/H_2O to yield 1.586 g (67%) of the acid as a yellow powder. An analytical sample was prepared by repeated sublimation at 110 °C (0.025 Torr): mp 186–187 °C; IR (Nujol) 3.77, 5.87 μm; ^1H NMR(A) δ 2.63 (s, 3H).

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Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.88; H, 4.50; N, 6.76.

(d) 2-Methyl-4-acetyl-5-phenyloxazole (11). a 100-mL round-bottomed flask equipped with a condenser and drying tube were charged with 1.200 g (59.1 mmol) of the acid and 5 mL of thionyl chloride. The magnetically stirred solution was refluxed for 20 min and stirred at 25 °C overnight. Two separate portions of $CHCl_3$ were added followed by removal under reduced pressure to yield 1.318 g (100%) of the acid chloride.

A 250-mL three-necked, round-bottomed flask was equipped with a thermometer, condenser, dropping funnel, and a three-way stopcock. The system was evacuated and filled with dry N_2 (2X), and the glassware was flame-dried on the second evacuation. Nitrogen was passed continuously through the system, and the stopcock was replaced with a serum stopper. A suspension of Cu_2I_2 (2.26 g, 0.0119 mol) in 15 mL of anhydrous ether was added, and the stirred suspension was cooled to −78 °C in a dry ice/chloroform bath. Twenty milliliters of a 1.4 M solution of methyllithium in ethyl ether was added dropwise through the serum stopper, resulting in the formation of a black solution. The reaction mixture was allowed to warm to 0 °C in an ice bath for 15 min, recooled to −78 °C, and then stirred at low temperature for another 45 min. The acid chloride dissolved in 17 mL of dry ether and added quickly with a syringe, and the mixture was stirred at −78 °C for 40 min and 20 min at −10 °C. Saturated NH_4Cl (210 mL) and concentrated NH_4OH (11 mL) were added, and the solution was stirred vigorously for 15 min. The layers were separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined extracts were washed with water (3 × 30 mL), 2 M HCl (1 × 50 mL), and 0.5 M $NaHCO_3$ (1 × 50 mL) and dried over $MgSO_4$. The ether was removed in vacuo to yield 0.780 g of a brown solid that was chromatographed on a silica gel column with 15% ethyl acetate/hexanes. Sublimation at 53 °C (0.05 Torr) afforded 0.310 (26%) of oxazole **11** as white crystals: mp 78–79 °C; IR (Nujol) 5.98 μm; UV λ_{max} (CH_3CN) 221, 296 nm (ϵ 11 000, 11 100); ^{1}H NMR(A) singlets at δ 2.512, 2.484 (CD_3CN) and 2.589, 2.530 ($CDCl_3$); ^{13}C NMR δ 13.8, 29.0, 127.2, 127.9, 128.4, 130.3, 134.3, 153.2, 158.8, 194.2. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.78; H, 5.52; N, 6.85.

Irradiations of 4. (a) Preparative (300–350 nm). A solution of 1.39 g of **4** in 100 mL of dry benzene was irradiated for 19 h at 350 nm at which time no isoxazole remained and only 2*H*-azirine could be seen by ^{1}H NMR. The solvent was removed in vacuo, and a 0.30-g sample of the residue was flash chromatographed (35% ethyl acetate/hexanes) to give 0.24 g of crude **6**. A second chromatography gave pure 2*H*-azirine **6** as a colorless oil in a 50% recovery: ^{1}H NMR δ 2.20 (s, 6 H), 2.55 (s, 3 H); ^{13}C NMR δ 11.8, 28.6, 50.8, 155.1, 202.9; IR (film) 5.55 μm; UV λ_{max} (CH_3CN) 254, 300 nm (ϵ 8404, 114). Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.30; H, 6.69; N, 10.20.

(b) Corex Filter. Irradiation of 0.015 M **4** in benzene through a Corex filter with use of a Hanovia immersion lamp produced a mixture that contained 2*H*-azirine **6** as the major component and considerable amounts of intractable products.

(c) Analytical. Irradiations of **4** under the following conditions gave only 2*H*-azirine **6** (^{1}H NMR): (i) 14 h at 350 nm (0.1 M) and 16.5 h (0.016 M) at 300 nm in benzene; (ii) 0.30 M in methanol-d_4 at 300 nm for 22 h with no deuterium incorporation; (iii) 0.5 M in acetonitrile-d_3 at 300 nm, 92% complete after 17 h, no further change observed after 41 h.

(d) Preparative (254 nm). A 0.4 M solution of **4** in acetonitrile (15 mL) was irradiated in a quartz tube at 254 nm for 45 h. The solvent was removed under stream of nitrogen, and the residue was purified by flash chromatography (35% ethyl acetate/hexanes) to give 0.0265 g (18%) of **8**: mp 107–108 °C after sublimation at 37 °C (0.75 Torr); IR 5.80 μm; ^{1}H NMR δ 1.50 (s, 3 H), 2.05 (s, 3 H), 2.30 (s, 3 H); exact mass calcd for $C_{14}H_{18}N_2O_4$ 278.126 657 2, found 278.126 46.

(e) Analytical. Irradiations under the following conditions led to formation of **6** initially and on longer times to dimer **8**; at no time was any significant amount of oxazole **7** observed: (i) 0.1 M in acetonitrile-d_3; (ii) 0.4 M in dimethoxyethane (57 h); (iii) in methanol-*O*-d_1 after 3 h, only **6** was present, after 12 h, conversion to dimer **8** was ca. 75% complete, no deuterium incorporation observed by ^{1}H NMR.

Irradiation of 4-d_3. A solution of **4**-d_3 (0.55 M) in CD_3CN containing 20 μL of dioxane was degassed by the freeze/thaw method (four cycles) and sealed under nitrogen. The sample was irradiated at 300 nm and monitored by ^{1}H NMR as a function of time. The peak at δ 2.35 (acetyl methyl) decayed slower than the one at δ 2.60 (C-3 methyl), and a new signlet appeared at δ 2.20 that is assigned to the acetyl group of **4′**-d_3. New peaks attributed to 2*H*-azirine **6**-d_3 appeared at δ 2.15 and 2.55. With the area of the dioxane peak as an internal standard, the concentrations of **4**-d_3, **4′**-d_3, and **6**-d_3 were calculated as a function of time. The average ratio of **4′**-d_3 to **6**-d_3 at four different times was 0.155.

Irradiation of 7. Irradiation of 0.4 mL of a 0.11 M solution of **7** in acetonitrile-d_3 for 15 min at 254 nm in a quartz NMR tube gave rise to dimer **8** exclusively as shown by ^{1}H NMR.

Irradiation of 8. A solution of dimer **8** in benzene (0.0538 M) in a pyrex NMR tube was irradiated for 3 h at 300 nm. Removal of the solvent gave a residue with an ^{1}H NMR spectrum identical with that of oxazole **7**.

Stern–Volmer plot. Five solutions containing variable amounts of 1-methoxy-1,3-butadiene (0.054–1.03 M) and isoxazole **4** (1.0 M) in benzene were deaerated with dry nitrogen and irradiated at 350 nm in parallel with control samples that contained no quencher. Values of ϕ_0/ϕ were calculated from ^{1}H NMR measured peaks heights of the 2*H*-azirine and isoxazole methyl protons to calculate the rate of 2*H*-azirine formation. A plot of ϕ_0/ϕ vs quencher concentration gave a straight line with slope 2.14 ± 0.21 M^{-1}.

Thermolysis of 6. (a) A solution of **6** in benzene (0.4 mL, 0.188 M) was heated at 70 °C in a sealed NMR tube and monitored by ^{1}H NMR as function of time. The rate of formation of oxazole **7** was monitored by comparing the height of the 2*H*-azirine peaks to the tetramethylsilane peak. A linear plot of ln [**6**] vs time was obtained from which a rate constant of 4.5×10^{-3} s^{-1} was obtained. After 476 h, the solvent was removed and the residue was sublimed to give 0.003 g of oxazole **7**, identified by ^{1}H NMR.

(b) A solution of 2*H*-azirine **6** in methanol (0.030 g in 5 mL) was heated at reflux for 7 h after which the solvent was evaporated. The residue was purified by flash chromatography (40% ethyl acetate/hexanes) to give 0.015 g of oxazole **7**, identified by ^{1}H NMR.

Thermolysis of 8. An NMR tube containing 0.4 mL of a 0.10 M solution of dimer **8** and tetramethylsilane in benzene was sealed and heated at 70 °C for 3 h. The rate of decrease of the peaks attributable to **8** was followed as a function of time with TMS as an internal standard. A rate constant of 6.8×10^{-2} s^{-1} was calculated. After removal of the solvent and sublimation of the residue at 27 °C (50 Torr) there was obtained 0.006 g (52%) of oxazole **7**, identified by ^{1}H NMR.

Irradiation of 5 in Methanol. Pinacol 9. Two milliliters of a solution of **5** in methanol (0.25 M) was irradiated at 254 nm for 5 h. The residue after evaporation of the solvent was purified by flash chromatography (35% ethyl acetate/hexanes) to give a 25% yield of pinacol **9**: mp 100–101 °C after sublimation at 90 °C (5 Torr); ^{1}H NMR δ 2.00 (s, 3 H), 2.40 (s, 3 H), 3.20 (br s, 2 H), 4.00 (br s, 1 H), 7.25 (s, 5 H); ^{13}C NMR δ 12.0, 12.9, 13.0, 68.6, 74.8, 116.7, 126.0, 127.8, 128.4, 142.2, 160.0, 165.7; mass spectrum (CI) *m/e* 234 (M + 1). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.70; H, 6.78; N, 5.90. Found: C, 66.94; H, 6.48; N, 6.00.

Cleavage of 0.018 g (7.7×10^{-5} mol) of **9** with 0.020 g (8.8×10^{-5} mol) of periodic acid in 1.0 mL of water was carried out over 15 h at 25 °C. Extraction of this solution with $CDCl_3$ gave a solution of isoxazole **5** identified by ^{1}H NMR.

Irradiation of 5 in Methanol-d_4 or D_2O. Irradiation of **5** in CD_3OD or 4:1 CD_3CN/D_2O with 300-nm light for 27.5 and 19 h, respectively, did not result in significant change in the integrated ratio of aliphatic to aromatic protons as monitored by ^{1}H NMR. Similar experiments at 254 nm likewise did not result in loss in intensity of methyl proton absorptions.

Irradiation of 5 in Acetonitrile-d_3. (a) Analytical Scale (254 nm). Irradiation of a 0.10 M solution of **5** in CD_3CN at 254 nm for 24 h led to a complex mixture of products of which the major product (32%) showed ^{1}H NMR(A) absorptions at δ 3.566 (s) and 2.378 (s). Addition of 5 μL of methanol gave rise to a new set of peaks after 6 h: δ 3.465 (s), 2.92 (d, *J* = 5 Hz), 2.082 (s). Removal of the solvent under a stream of nitrogen gave rise to an oil that was dissolved in $CDCl_3$ and examined by ^1H NMR(A). The major peaks at δ 3.551 (s, 3 H), 2.960, 2.955 (br d, 3 H), and 2.153 (s, 3 H) were assigned to OCH_3, NCH_3, and CCH_3, respectively.[27]

(b) Preparative Scale (254 nm). A solution of 503 mg of **5** in 225 mL of acetonitrile was irradiated for ~17 h in a 450-W immersion apparatus with a Vycor filter sleeve. Analysis of an evaporated aliquot by ^1H NMR(A) revealed the presence of **5** (40%), ketene imine (29%), **10** (9%), and **11** (20%). The solvent was removed by rotary evaporation at low temperature, but no evidence for ketene imine could be found by thin-layer analysis. Flash chromatography (15% ethyl acetate/hexanes) resulted in a 47% recovery of starting mass in the following four fractions: (a) oxazole **12**, **5**, and benzoylacetone (4%, 44%, 7%); (b) mixture of oxazole **11** and **5** (21% and 7%); (c) oxazole **11** (9%); (d) 2*H*-azirine **10** (8.5%). No evidence could be found for the ketene imine in any of the fractions; apparently it did not survive the workup procedure.

(c) Analytical Scale (300 nm). Irradiation of a 0.10 M solution of **5** in CD_3CN gave a solution that contained 2*H*-azirine **10** (~5%) and **5** (~95%) within 2 h. No change in this ratio or any new absorptions were observed upon further irradiation for 20 h.

2-Acetyl-2-benzoyl-3-methyl-2*H*-azirine (10) was characterized by the following spectral data: IR(A) (film) 5.58, 5.91 μm; UV λ_{max} (CH_3CN) 251, 286 nm (ε 14 000, 1500); ^1H NMR(A) singlets at δ 2.648, 1.946 (CD_3CN) and 2.637, 2.094 ($CDCl_3$). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.38; H, 5.36; N, 6.96.

Irradiation of 10. (a) 300 nm. Irradiation of a 0.064 M solution of **10** in CD_3CN for 18 h gave rise to a photoequilibrium mixture of **5** and **10** in the ratio of ca. 95:5.

(b) 254 nm. Irradiation of a 0.080 M solution of **10** in CD_3CN for 3 h gave rise to a complex mixture that contained isoxazole as the major constituent (74%), oxazoles **11** (9%) and **12** (4%), ketene imine (6%), and starting material (7%).

Thermolysis of 3-Methyl-2-acetyl-2-benzoyl-2*H*-azirine (10). The azirine (0.0545 g, 0.271 mmol) was placed in a small glass ampule and sealed under N_2. After the mixture was heated at 238 °C for 42 min, a dark oil was obtained analysis of which by ^1H NMR(A) showed complete conversion to a 1:1 mixture of **11** and **12** with a trace of both isoxazoles. Flash chromatography on a silica gel column (10% ethyl acetate/hexanes) afforded two fractions. The faster moving fraction was rechromatographed (12.5% ethyl ether/petroleum ether) to yield 0.0190 g (35%) of pure **2,5-dimethyl-4-benzoyloxazole (12)** as a white solid: mp 60–61 °C; IR (KBr) 6.10 μm; ^1H NMR(A) singlets at δ 2.564, 2.411 (CD_3CN) and 2.612, 2.460 ($CDCl_3$). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.58; H, 5.39; N, 6.91.

Irradiation of 13. (a) 300 nm. Irradiation of a 0.18 M solution of **13** in CD_3CN for 1.35 h at 300 nm gave rise to a mixture of 2*H*-azirine **10** (23%) and isoxazole **5**. A preparative scale experiment with 420 mg in 10 mL of CH_3CN was irradiated for 7.15 h. Flash chromatography (15% ethyl acetate/hexanes) of the crude product gave rise to two fractions: (a) 337 mg of a 2:1 mixture of **5** and **13**; (b) 82 mg (20%) of **10** as a light yellow oil.

(b) 254 nm. Irradiation of a 0.10 M solution of **13** in CD_3CN for 2.15 h at 254 nm gave rise to a mixture of 2*H*-azirine **10** (8.2%), isoxazole **5** (74.5%), and minor amounts of ketene imine (6.2%) and oxazoles by ^1H NMR(A).

Irradiation of 14. (a) 300 nm. A sample of **14** was irradiated for 40 h in CD_3CN (0.076 M). No change in the ^1H NMR(A) spectrum was observed.

(b) 254 nm. A sample of **14** in CD_3CN (0.15 M) was irradiated for 13.5 h. Oxazoles **15** (7%) and **16** (28%), benzoylacetone (5%), an unknown methyl-containing compound at ∂ 2.47 (12%), and starting material (47.5%) were seen by ^1H NMR(A). A preparative scale run in an immersion apparatus with a Vycor filter utilized 1.032 g of **14** in 225 mL of CH_3CN. After irradiation for 114 h the solvent was removed by rotary evaporation in vacuo. Benzoylacetone was removed by extraction with 1 N NaOH and isolated by acidification with concentrated HCl. After extraction with methylene chloride, the residue (128 mg) was purified by flash chromatography with 7.5% ethyl acetate/hexanes to yield 68 mg (14%) of an off-white solid that was identified by comparison of its ^1H NMR(A) with that of an authentic sample. The other products were isolated from the residue by flash chromatography (7.5% ethyl acetate/hexanes). The total recovery of mass corresponded to 53%, and fractions were obtained that were composed of the following compounds: **14** (40%), a 1:9 mixture of oxazoles **15** and **16** (46%). The oxazole mixture was assayed by comparisons of both ^1H NMR(A) and ^{13}C NMR data in $CDCl_3$ with data of the pure components. No additional peaks were seen in either spectrum. Control experiments demonstrated the stability of **15** and **16** to irradiation conditions.

Irradiation of 17. (a) 300 nm. Irradiation of a 0.076 M solution of **17** in CD_3CN resulted in complete conversion to **14** in 3.25 h. In the presence of 0.076 M 1,4-diazabicyclo[2.2.2]octane no reaction was observed under these conditions.

(b) 254 nm. Irradiation of a 0.051 M solution of **17** in CD_3CN for 4.5 h gave rise to starting material (23%), **14** (29%), oxazole **15** (6%), oxazole **16** (27%), unknown methyl-containing product at ∂ 2.47 (10%), and benzoylacetone (6%) by ^1H NMR(A). In the presence of 0.076 M 1,4-diazabicyclo[2.2.2]octane the rate of disappearance of **17** was reduced by a factor of ca. 1.5.

Irradiation of Diazobenzoylacetone in the Presence of Benzonitrile. A solution of 0.106 g of **19**[28] (0.56 mmol) in 2.0 mL (20 mmol) of benzonitrile was placed in a Pyrex ampule fitted with a serum cap and a syringe needle to allow escape of nitrogen. After irradiation at 350 nm for 18.5 h, the excess solvent was removed by evaporation at 10 Torr. The residue (111 mg) showed a 1.5:1 ratio of **16** to **15** by ^1H NMR(A). Flash chromatography gave 25 mg of pure oxazoles in a 1.4:1 ratio.

Irradiation of Diazobenzoylacetone in the Presence of Acetonitrile. A similar experiment with 157 mg (0.85 mmol) of **19** in 8.0 mL (304 mmol) of acetonitrile led (4.75 h) to 136 mg of crude oxazoles **16** and **15** in a ratio of 1.5:1 by ^1H NMR(A). Flash chromatography gave two fractions: 29 mg of a 1:1 mixture of pure oxazoles and a second fraction (28 mg) that was mainly **16** by ^1H NMR(A).

Quantum Yields. The concentration of **4** was monitored by means of changes in ultraviolet absorption at 229 nm. Conversion was kept to <10%, and corrections were made for light absorption by **6**. Light intensity was monitored by potassium ferric oxalate actinometry (ϕ^{254nm} 1.28; ϕ^{300nm} 1.24).[29] The oxalate was recrystallized before use, and all manipulations were performed under diffuse red light or in darkness. Irradiations were carried out in 13-mm quartz tubes into which were placed 3 mL of a solution containing 1.835 g of oxalate in 25 mL of 0.1 N sulfuric acid. The solutions were deaerated with a stream of dry nitrogten and irradiated in a carousel in parallel with the samples. Analyses of the actinometer solutions were carried out on 0.1-mL aliquots added to a premixed solution of 2 mL of 0.1% aqueous *o*-phenanthroline solution, 0.5 mL of 1 M aqueous sodium acetate, and 0.9 mL of 0.1 M sulfuric acid. The resulting solution was diluted to 10 mL and kept in the dark for 1 h at 25 °C after which the concentration of Fe^{2+} was calculated from the absorbance of the complex at 540 nm (ε 110 50).

Three milliliters of 0.105 M solutions of **4** in acetonitrile was placed in 13-mm quartz tubes equipped with stopcocks and degassed by four successive freeze–thaw cycles. Irradiations were commenced with 254-n or 300-nm lamps in which case a Pyrex breaker was placed around the samples to serve as a filter. The average quantum yields for duplicate runs were $\phi^{254nm}(-K) = 0.23 \pm 0.03$ and $\phi^{300nm}(-K) = 0.32 \pm 0.03$.

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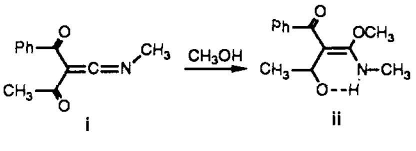
[27] These assignments are in good agreement with data of Sauers and Van Arnum[9a] and Sato et al.[12] for closely related structures. The structures of the ketene imine (i) and the methanol adduct (ii) are believed to be those shown or geometric isomers.



i
ii

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Quantum yields for **14** and **17** were determined in a similar way with **4** as an actinometer: $\phi^{254\text{nm}}(-\mathbf{14}) = 0.0.0094 \pm 0.001$; $\phi^{300\text{nm}}(-\mathbf{17}) = 0.083 \pm 0.004$.

Flash Photolysis Experiments. Triplet absorption spectra were obtained at 25 °C on ~3 mL of acetonitrile solutions of **5** (0.0087 M) and **14** (0.010 M) and benzophenone (0.005 M) that were thoroughly purged with argon. Benzophenone triplet decay (2.78×10^5 s^{-1}) was monitored at 480 nm. The absorption spectra were generated by measuring absorbances at 5-nm intervals in the range 290–580 nm. Because of photochemical instability, the triplet absorption spectrum of isoxazole **5** was a composite of measurements taken from different samples. In addition, the spectrum was recorded in both sweep directions in which case small differences in optical densities were observed. Both compounds had a strong absorption peak at ca. 320 nm, and in addition, **5** showed a broad maximum at 480 nm and **14** showed a shoulder at 410 nm. The transient lifetimes in the absence of biphenyl were 276 and 48 ns, respectively. In the presence of 0.01 M biphenyl a new absorption appeared at 360–365 nm. Quenching rates were calculated from lifetime measurements in the presence and absence of biphenyl: **5**, 8.3×10^8 M^{-1} s^{-1}; **14**, 2.0×10^9 M^{-1} s^{-1}.

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Photochemical Reactivity of Halofuran and Halothiophene Derivatives in the Presence of Arylalkenes and Arylalkynes

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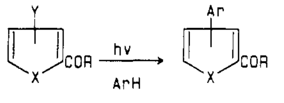
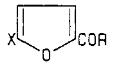
The photochemical reactions of 5-iodothiophene-2-carbaldehyde (**4a**), 2-acetyl-5-iodothiophene (**4b**), 5-bromofuran-2-carbaldehyde (**3a**), and 5-iodofuran-2-carbaldehyde (**3b**) with arylalkenes **5** (styrene), **7** (2-vinylthiophene), **10** (2-vinylfuran), **12** (4-methyl-5-vinylthiazole), and **16** (benzofuran) are reported. All of the reactions give the corresponding substitution products as a cis–trans mixture. The photochemical reaction of **4a** and **4c** (methyl 5-iodothiophene-2-carboxylate) with arylalkynes is also reported: in this case the reaction of **4a** and **4c** with phenylacetylene (**18**) furnishes the substitution products (**19** and **26**, respectively) deriving from an attack on the alkyne moiety, while the reaction with 2-ethynylthiophene (**20**) and 2-ethynylfuran (**23**) furnishes a mixture deriving from the attack both on the alkyne and on the heterocyclic ring. The ratio between these two products can be modified by changing the concentrations of the reagents. The mechanism of these reactions is discussed on the basis of photochemical and electrochemical properties of the reagents in terms of an electron-transfer process. The experimental results are explained in terms of ΔG values, and they are in agreement with the formation of both a solvent-separated pair and a contact radical ion pair.

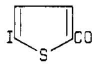
In our previous papers we described the photochemical behavior of halofuran[1] and halothiophene[2] derivatives when irradiated in the presence of an aromatic or heteroaromatic compound. Under these conditions, compound **1** is converted into the corresponding aryl or heteroaryl derivative **2** in high yields.



1 2

In this paper we report our results on the photochemical reactivity of 5-halofuran-2-carbaldehyde **3** and 5-iodothiophene-2-carbaldehyde, methyl ketone, or methyl carboxylate **4** when they are irradiated in the presence of aryl- and heteroarylalkenes and -alkynes. In fact, it is well-known that both aryl-substituted alkenes, such as styrene, and alkynes, such as phenylacetylene, give the photoaddition products.[3,4]





3

a: X = Br
b: X = I

4

a: R = H
b: R = CH_3
c: R = OCH_3

In our case we wanted to verify whether photochemical reactions occur on the aromatic ring or whether the presence of an unsaturated side chain could influence the reaction pattern giving photoaddition products.

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