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Photochemistry of Phenyl-Substituted 1,2,4-Thiadiazoles. ^{15}N-Labeling Studies‡

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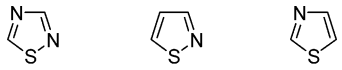
Received January 24, 2003

Irradiation of 5-phenyl-1,2,4-thiadiazole (**6**) resulted in the formation of benzonitrile (**5**), 3-phenyl-1,2,4-thiadiazole (**4**), phenyl- and diphenyl-1,3,5-triazines (**7** and **8**), and a trace quantity of diphenyl-1,2,4-thiadiazole (**9**). The formation of **4** ,**5**, **7**, and **8** can be explained in terms of photoinduced electrocyclic ring closure resulting in the formation of an intermediate 4-phenyl-1,3-diaza-5-thiabicyclo[2.1.0]pentene. ^{15}N-labeling experiments revealed that sulfur can undergo sigmatropic shifts around all four sides of the diazetine ring. Thus, irradiation of **6-4-^{15}N** led to the formation of **6-2-^{15}N** and an equimolar mixture of **4-2-^{15}N** and **4-4-^{15}N**. The thiabicyclo[2.1.0]pentene intermediate is also suggested to undergo sulfur elimination resulting in the formation of phenyldiazacyclobutadiene, which can undergo complete fragmentation to benzonitrile or [4+2] cycloaddition leading to unstable tricyclic adducts, the suggested precursors of the 1,3,5-triazine products **7** and **8**. The observed ^{15}N distribution in **7** and **8** is consistent with this mechanism. Irradiation of **4** led only to the formation of **5**. ^{15}N-labeling experiments show that **4** does not undergo electrocyclic ring closure but reacts exclusively by photofragmentation of the thiadiazole ring.

Introduction

The photochemical properties of 1,2,4-thiadiazoles **1** are intriguing because the ring can be viewed as a combination of an isothiazole **2** and a thiazole **3**. Although the photochemistry of isothiazoles and thiazoles has been extensively studied,[2−16] no accounts of the photochemistry of 1,2,4-thiadiazoles have appeared in the literature. We now report that phenyl-substituted 1,2,4-thiadiazoles



1 2 3

undergo photofragmentation, phototransposition, and an unusual reaction leading to the formation of 1,3,5-triazines. Product distributions in these reactions depend on the position of the phenyl substituent on the thiadiazole ring.

Results and Discussion

Not all phenyl-substituted 1,2,4-thiadiazoles react by all three pathways. Irradiation of a solution of 3-phenyl-1,2,4-thiadiazole (**4**) in acetonitrile, for example, was accompanied by the formation of a finely divided suspension of what was presumed to be elemental sulfur. Gas−liquid chromatographic (GLC) analysis as a function of irradiation time showed the gradual consumption of the reactant and the formation of a GLC-volatile product, which was identified by its retention time and mass spectrum as benzonitrile (**5**). After a total of 120 min of irradiation, quantitative GLC showed that 82% of **4** was

‡ This paper is dedicated to Dr. A. Colin Day (1934−2001), friend and colleague, in recognition of his many contributions to the photochemistry of heteroaromatic compounds.

(1) Presented in part at the 222nd National Meeting of the American Chemical Society, Chicago, IL, August 30, 2001.

(2) Kojima, M.; Maeda, M. *J. Chem. Soc., Chem. Commun.* **1970**, 386-387.

(3) Vernin, G.; Poite, J.-C.; Metzger, J.; Aune, J.-P.; Dou, J. M. *Bull. Soc. Chim. Fr.* **1971**, 1103−1104.

(4) Vernin, G.; Jauffred, R.; Richard, C.; Dou, H. J. M.; Metzger, J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1145−1150.

(5) Riou, C.; Vernin, G.; Dou, H. J. M.; Metzger, J. *Bull. Soc. Chim. Fr.* **1972**, 2673−2678.

(6) Vernin, G.; Poite, J.-C.; Dou, H. J. M.; Metzger, J. *Bull. Soc. Chem. Fr.* **1972**, 3157−3167.

(7) Vernin. G.; Riou, C.; Dou, H. J. M.; Bouscasse, L.; Metzeter, J.; Loridan, G. *Bull. Soc. Chim. Fr.* **1973**, 1743−1751.

(8) Maeda, M.; Kojima, M. *Tetrahedron Lett.* **1973**, 3523−3526.

(9) Riou, C.; Poite, J.-C.; Vernin, G.; Metzger, J. *Tetrahedron* **1974**, *30*, 879−898.

(10) Maeda, M.; Kawahara, A.; Kai, M.; Kojima, M. *Heterocycles* **1978**, *3*, 389−393.

(11) Maeda, M.; Kojima, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 685−692.

(12) Pavlik, J. W.; Pandit, C. R.; Samuel, C. J.; Day, A. C. *J. Org. Chem.* **1993**, *58*, 3407−3410.

(13) Pavlik, J. W.; Tongcharoensirikul, P.; Bird, N. P.; Day, A. C.; Barltrop, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 2292−2300.

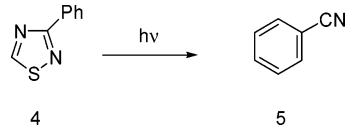
(14) Pavlik, J. W.; Tongcharoensirikul, P.; French, K. M. *J. Org. Chem.* **1998**, *63*, 5592−5603.

(15) Pavlik, J. W.; Tongcharoensirikul, P. *J. Org. Chem.* **2000**, *65*, 3626−3632.

(16) For reviews see: (a) Lablache-Combier, A. In *Photochemistry of Heterocyclic Compounds*; Buchardt, O., Ed.; Wiley: New York, 1976. (b) Padwa, A. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. III, p 501. (c) Lablache-Combier, A. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Ed.; CRC Press: Boca Raton, FL, 1995; p 1063. (d) Pavlik, J. W. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1997; p 57.

(17) All yields reported are percent yields determined by quantitative GLC and based on the number of moles of reactant consumed.

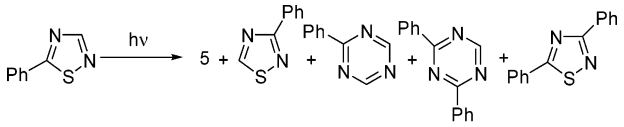
10.1021/jo0340915 CCC: $25.00 © 2003 American Chemical Society
Published on Web 05/14/2003



4 5

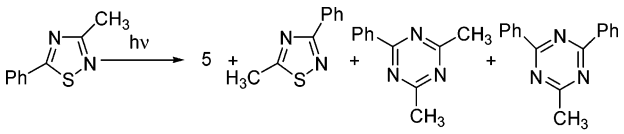
consumed and that benzonitrile (**5**) was formed in 74% yield.[17] These results show that 3-phenyl-1,2,4-thiadiazole (**4**) undergoes only photofragmentation of the thiadiazole ring to yield benzonitrile (**5**).

The photochemistry of 5-phenyl-1,2,4-thiadiazole (**6**) is more complicated. Irradiation of a solution of **6** in acetonitrile for 150 min was accompanied by the consumption of 53% of the reactant and the formation of eight GLC-volatile products. Although three of the most minor products could not be identified, comparison of the GLC retention times and mass spectra with authentic samples allowed the remaining five products to be identified as benzonitrile (**5**), the photofragmentation product, 3-phenyl-1,2,4-thiadiazole (**4**), a phototransposition product, phenyl-1,3,5-triazine (**7**), diphenyl-1,3,5-triazine (**8**), and diphenyl-1,2,4-thiadiazole (**9**). These products were formed in yields of 58%, 18%, 4%, 2%, and trace, respectively.



6 4 7 8 9

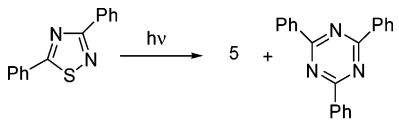
3-Methyl-5-phenyl-1,2,4-thiadiazole (**10**) reacted similarly. Thus, irradiation of a solution of **10** in acetonitrile for 150 min was accompanied by the consumption of 76% of the reactant and the formation of benzonitrile (**5**) in 50% yield, 5-methyl-3-phenyl-1,2,4-thiadiazole (**11**) in



10 11 12 13

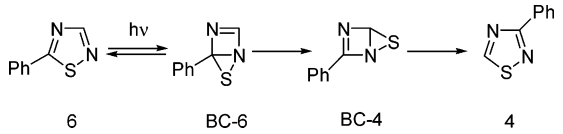
approximately 10% yield, and dimethylphenyl-1,3,5-triazine (**12**) and methyldiphenyl-1,3,5-triazine (**13**) in yields of 33% and 5% respectively. These products were identified by comparison of their GLC-retention times and mass spectra with authentic samples of each compound.

Diphenyl-1,2,4-thiadiazole (**9**) was also observed to undergo photofragmentation and triazine formation. Thus, irradiation of a solution of diphenyl-1,2,4-thiadiazole (**9**) in cyclohexane resulted in the formation of benzonitrile (**5**) and triphenyl-1,3,5-triazine (**14**) in yields of 26% and 52%, respectively.



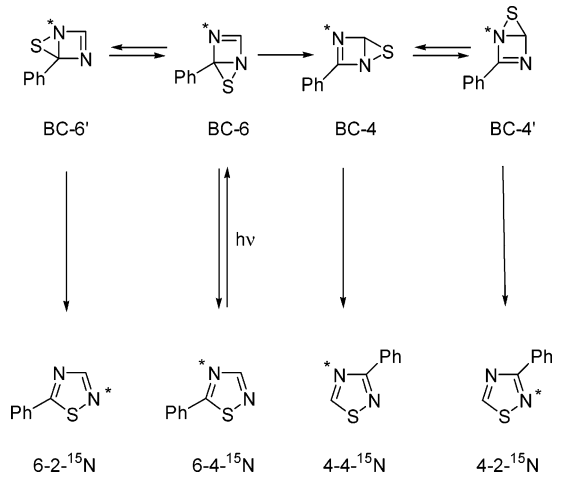
9 14

SCHEME 1



6 BC-6 BC-4 4

SCHEME 2



BC-6' BC-6 BC-4 BC-4'

6-2-^{15}N 6-4-^{15}N 4-4-^{15}N 4-2-^{15}N

Phototransposition. The phototransposition of 5-phenyl-1,2,4-thiadiazole (**6**) to 3-phenyl-1,2,4-thiadiazole (**4**) can be rationalized by a mechanism that has been used to explain the phototransposition reactions of other five-membered heteroaromatic compounds.[16d] Thus, as shown in Scheme 1, upon photochemical excitation **6** is predicted to undergo electrocyclic ring closure leading to the formation of bicyclic intermediate, **BC-6**. Because it is not possible to distinguish between the two nitrogen atoms in **BC-6**, one or two sigmatropic shifts of sulfur would lead to the same bicyclic species, **BC-4**. Rearomatization of this species would lead to the observed phototransposition product, **4**. In addition, sulfur migration in the opposite direction would lead to a bicyclic species identical with **BC-6** except for the interchange of the two ring nitrogens. Rearomatization of this species would lead back to the reactant **6**.

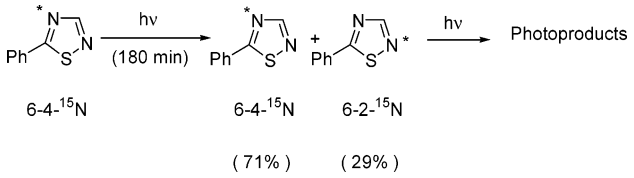
Since it is not possible to distinguish between the two nitrogen atoms in the 1,2,4-thiadiazole ring, it is not possible to distinguish between formation of 3-phenyl-1,2,4-thiadiazole (**4**) by one or two sulfur migrations. Similarly, it is not possible to detect sulfur migration in the opposite direction since that pathway leads back to 5-phenyl-1,2,4-thiadiazole (**6**).

This ambiguity was resolved by studying the photochemistry of 5-phenyl-1,2,4-thiadiazole-4-^{15}N, **6-4^{15}N**. Scheme 2 confirms that if the ^{14}N atom at ring position 4 is replaced by ^{15}N, then the one- and two-step sulfur migrations lead to an equilibrium mixture of **BC-4** and **BC-4′**. Rearomatization of these bicyclic species would result in the formation of 3-phenyl-1,2,4-thiadiazole-4-^{15}N (**4-4-^{15}N**) and 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**), respectively. Furthermore, sulfur migration in the opposite direction and rearomatization would result in the formation of 5-phenyl-1,2,4-thiadiazole-2-^{15}N (**6-2-^{15}N**) via **BC-6′**.

5-Phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) was synthe-

sized from commercially available benzamide-^{15}N.[18] The mass spectrum of **6-4-^{15}N** exhibited a molecular ion at *m*/*z* 163, and a base peak at *m*/*z* 136, which would result from loss of HC^{14}N, but no signal at *m*/*z* 135, which would result from loss of HC^{15}N.

A solution of **6-4-^{15}N** in acetonitrile was irradiated for 180 min. GLC analysis showed that 70% of the reactant had been consumed. The mass spectrum of the recovered ^{15}N-labeled reactant again exhibited an intense signal at *m*/*z* 136 due to the loss of HC^{14}N from 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**). In addition, the spectrum also showed a prominent signal at *m*/*z* 135 due to the loss of HC^{15}N. This signal at *m*/*z* 135 was not present in the mass spectrum of the reactant before irradiation. Its appearance after irradiation indicates that a portion of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) has transposed to 5-phenyl-1,2,4-thiadiazole-2-^{15}N (**6-2-^{15}N**). The *m*/*z* 135/136 ratio of 0.40 indicates that the recovered ^{15}N-labeled reactant consists of 71% of the 4-^{15}N isomer **6-4-^{15}N** and 29% of the 2-N^{15} isomer **6-2-^{15}N**.

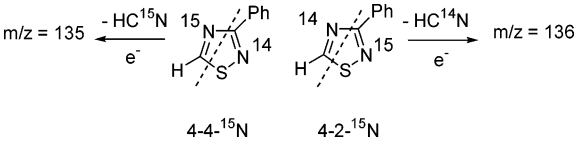


Mass spectral analysis of the ^{15}N-labeled 3-phenyl-1,2,4-thiadiazole (**4-^{15}N**) and phenyl- and diphenyl-1,3,5-triazine photoproducts obtained after this prolonged irradiation also exhibited ^{15}N scrambling. The origin of this scrambling is unclear, however, due to the extensive scrambling in the reactant.

To minimize the extent of ^{15}N-scrambling in the reactant and to preclude the possibility of secondary photolysis of the primary products, the irradiation was carried out for a shorter period of time. In this experiment a solution of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) in acetonitrile (4.0 mL, 2.0×10^{-2}M) was irradiated and analyzed by GLC and mass spectroscopy after each 4.0 min of irradiation.

After 8.0, 12.0, and 16.0 min of irradiation the *m*/*z* 135/136 ratio in the mass spectrum of the ^{15}N-labeled reactant increased from 0.02 at 8.0 min to 0.06 at 12.0 min and 0.080 ± 0.005 at 16.0 min of irradiation. This illustrates the slow phototransposition of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) to 5-phenyl-1,2,4-thiadiazole-2-^{15}N (**6-2-^{15}N**) until after 16.0 min of irradiation the *m*/*z* ratio of 0.080 ± 0.005 indicates that the remaining ^{15}N-labeled reactant consists of 93% **6-4-^{15}N** and 7% **6-2-^{15}N**.

The ^{15}N-labeled 3-phenyl-1,2,4-thiadiazole (**4-^{15}N**) phototransposition product could be unambiguously detected by GLC of the reaction mixture after 8.0 min of irradiation. The mass spectrum of this product at that time exhibited a molecular ion at *m*/*z* 163 and two intense signals of almost equal intensity at *m*/*z* 135 and 136 with a 135/136 ratio of 1.11 ± 0.08. The signal at *m*/*z* 135 must be due to loss of HC^{15}N from a molecule of 3-phenyl-1,2,4-thiadiazole with the ^{15}N atom at ring position 4, **4-4-^{15}N**, whereas the peak at *m*/*z* 136 must originate by loss of



HC^{14}N from a molecule of 3-phenyl-1,2,4-thiadiazole with an ^{15}N atom at ring position 2, as in **4-2-^{15}N**. After 12.0 and 16.0 min of irradiation the *m*/*z* 135/136 ratio was also determined to be 1.07 ± 0.08 and 1.12 ± 0.02, respectively. These ratios show that after 8.0 min of irradiation the ^{15}N-labeled 3-phenyl-1,2,4-thiadiazole product consists of a 50:50 mixture of 3-phenyl-1,2,4-thiadiazole-4-^{15}N (**4-4-^{15}N**) and 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) and that the composition of this mixture remained constant during the entire 16.0 min irradiation period.

The ^{15}N-labeling results are consistent with the electrocyclic ring closure−sulfur migration mechanism shown in Scheme 2. Thus, formation of a 1:1 mixture of **4-2-^{15}N** and **4-4-^{15}N** is consistent with the formation of a 1:1 equilibrium mixture of **BC-4** and **BC-4′**. The observed phototransposition of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) to 5-phenyl-1,2,4-thiadiazole-2-^{15}N (**6-2-^{15}N**) also confirms that sulfur must also shift in the opposite direction to yield ^{15}N-labeled **BC-6′**.

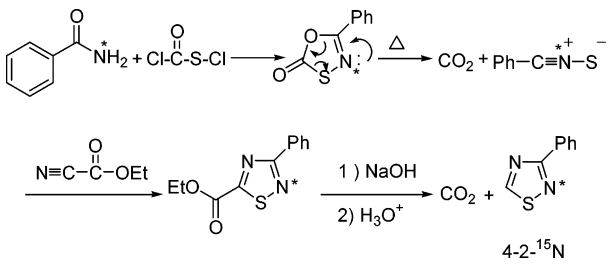
Although 5-phenyl-1,2,4-thiadiazole (**6**) undergoes phototransposition to 3-phenyl-1,2,4-thiadiazole (**4**), the reverse photoisomerization was not observed. As shown in Scheme 1, however, the phototransposition of **6** → **4** involves rearrangement of the initially formed, less-stable bicyclic species **BC-6**, in which the phenyl is substituted at the bridgehead position, to the more stable bicyclic species, **BC-4**, in which the phenyl is in conjugation with the C−N double bond. Thus, conversion of **BC-6** to **BC-4** should compete with the rearomatization of **BC-6** to **6**. The reverse transposition of 3-phenyl-1,2,4-thiadiazole (**4**) to 5-phenyl-1,2,4-thiadiazole (**6**), however, would require that the more stable **BC-4** be converted to the less stable **BC-6**. This reaction is expected to be slow and presumably would not compete with the rearomatization of **BC-4** back to **4**. If formed, however, **BC-4** would be expected to be in equilibrium with **BC-4′**, since these bicyclic species are of equal energy. Indeed, since ^{15}N-substituted-3-phenyl-1,2,4-thiadiazole (**4-^{15}N**) was formed as a 1:1 mixture of **4-2-^{15}N** and **4-4-^{15}N**, this indicates that **BC-4** and **BC-4′** are in equilibrium when formed by rearrangement of **BC-6**. This equilibrium mixture should also result if the ^{15}N-labeled **BC-4′** is formed directly by irradiation of **4-2-^{15}N**. Rearomatization of the equilibrium mixture of **BC-4** and **BC-4′** would result in the reformation of 3-phenyl-1,2,4-thiadiazole (**4**) with interchange of the two ring nitrogen atoms.

To investigate this possible pathway, 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) was synthesized from benzamide-^{15}N by the procedure shown in Scheme 3 developed to synthesize unlabeled **4**.[19] The mass spectrum of **4-2-^{15}N** exhibited a molecular ion at *m*/*z* 163 and a base peak at *m*/*z* 136 due to loss of H−C^{14}N, but no signal at *m*/*z* 135 which would result from loss of H−C^{15}N. This confirms that before irradiation all of the ^{15}N-label is at ring position 2 of the 1,2,4-thiadiazole ring.

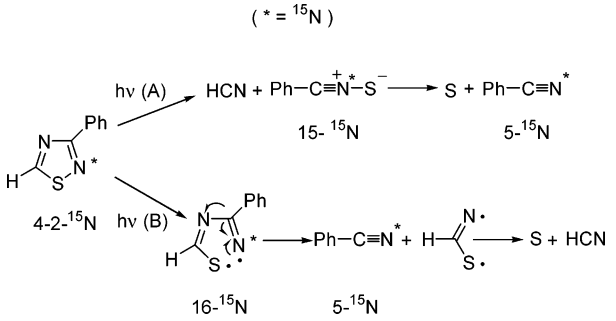
(18) Pavlik, J. W.; Changtong, C.; Tantayanon, S. *J. Heterocycl. Chem.* **2002**, *39*, 237−239.

(19) Howe, R. K.; Franz, J. E. *J. Org. Chem.* **1974**, *39*, 962−964.

SCHEME 3



SCHEME 4



A solution of 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) in acetonitrile was irradiated for a total of 150 min. GLC analysis of the resulting solution showed that 46% of the reactant had been consumed. The mass spectrum of the recovered ^{15}N-labeled reactant was identical with the spectrum obtained before irradiation. Thus, after irradiation the mass spectrum again exhibited a molecular ion at *m*/*z* 163 and a base peak at *m*/*z* 136 due to loss of HC^{14}N from 3-phenyl-1,2,4-thiadiazole with the ^{15}N-label still in ring position 2. No signal, however, could be detected in the mass spectrum at *m*/*z* 135, which would be observed if the molecular ion eliminated H−C^{15}N. This shows that 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) had not transposed to 3-phenyl-1,2,4-thiadiazole-4-^{15}N (**4-4-^{15}N**) during irradiation. This reveals that photochemical excitation of 3-phenyl-1,2,4-thiadiazole (**4**) is not accompanied by electrocyclic ring closure to yield **BC-4**. This pathway apparently cannot compete with the direct photofragmentation pathway leading to benzonitrile (**5**).

Photofragmentation. Irradiation of 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) led to the formation of benzonitrile (**5**). The mass spectrum of this product exhibited a molecular ion at *m*/*z* 104 with no signal detectable at *m*/*z* 103. This shows that the photofragmentation product is exclusively benzonitrile-^{15}N (**5-^{15}N**). This could result from direct fragmentation of the 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) ring (Path A, Scheme 4) leading to hydrogen cyanide and ^{15}N-labeled benzonitrile sulfide (**15-^{15}N**),[20] which is known to eliminate sulfur to provide benzonitrile-^{15}N (**5-^{15}N**).[21] Alternately, by analogy with isothiazole photochemistry,[2−16] photocleavage of the S−N bond[22] (Path B, Scheme 4) would lead to diradical **16-^{15}N**, which would undergo cleavage to provide **5-^{15}N** and ultimately sulfur and hydrogen cyanide. Either pathway is consistent with the observation that photofragmentation of **4-2-^{15}N** yields only **5-^{15}N**.

The photofragmentation of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) is more complicated. The ^{15}N-labeled photofragmentation product could be detected after **6-4-^{15}N** was irradiated in acetonitrile for 4 min. The mass spectrum of this product exhibited molecular ions at *m*/*z* 103 and 104, due to the formation of benzonitrile-^{14}N (**5-^{14}N**) and benzonitrile-^{15}N (**5-^{15}N**) in a ratio of 0.17. After 8.0, 12.0, and 16.0 min of irradiation this ratio gradually increased to 0.24, 0.27, and 0.32, respectively. Thus, after 16.0 min of irradiation, when the reactant consisted of 93% 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) and 7% 5-phenyl-1,2,4-thiadiazole-2-^{15}N (**6-2-^{15}N**), the photofragmentation product was a mixture of 76% benzonitrile-^{15}N (**5-^{15}N**) and 24% benzonitrile-^{14}N (**5-^{14}N**). This shows that there is more ^{15}N scrambling in the photofragmentation product than in the ^{15}N-labeled reactant. Formation of benzonitrile (**5**), therefore, cannot occur only by direct photofragmentation of the 1,2,4-thiadiazole ring but requires another pathway, or pathways, that allow for a greater amount of ^{15}N-scrambling.

Triazine Formation. Irradiation of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**6-4-^{15}N**) in acetonitrile also led to the formation of the ^{15}N-labeled triazine products. After 8.0 min of irradiation the mass spectrum of the ^{15}N-labeled phenyl-1,3,5-triazine (**7**) exhibited molecular ions at *m*/*z* 158 and 159 in a ratio of 0.84 ± 0.02. After 12.0 and 16.0 min of irradiation this ratio remained unchanged and was determined to be 0.80 ± 0.04 and 0.85 ± 0.01, respectively. These ratios show that phenyl-1,3,5-triazine was formed with 46% of the molecules containing one ^{15}N atom and 54% containing two ^{15}N atoms.

After 8.0 min of irradiation GLC analysis of the same irradiated solution also revealed the formation of diphenyl-1,3,5-triazine (**8**). After 8.0, 12.0, and 16.0 min of irradiation the mass spectrum of this product exhibited molecular ions at *m*/*z* 234 and 235 with almost equal intensities. The ratio could be measured accurately after 16.0 min of irradiation and was found to have a value of 1.14 ± 0.03. This shows that 53% of the diphenyl-1,3,5-triazine molecules contained one ^{15}N atom while 47% were formed with two ^{15}N atoms. These results show that the ^{15}N-labeled phenyl and diphenyl-1,3,5-triazines are each formed with essentially equal amounts of mono- and di-^{15}N-labeled molecules.

It is plausible that triazines **7** and **8** can also arise from bicyclic species **BC-6**. Thus, in addition to heteroatom migration leading to transposition (Scheme 1), **BC-6**

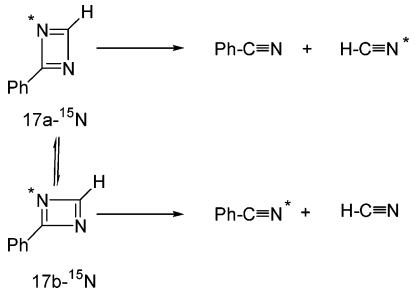
(20) It is interesting to note that the base peak in the mass spectrum of 3-phenyl-1,2,4-thiadiazole-2-^{15}N (**4-2-^{15}N**) is observed at *m*/*z* 136, consistent with the elimination of HCN and the formation of benzonitrile sulfide-^{15}N (**15-^{15}N**).

(21) Paton, R. M. *Chem. Soc. Rev.* **1989**, *18*, 33−52.

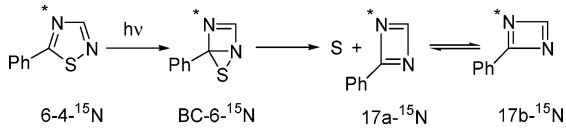
(22) Photocleavage of the bond between the two heteroatoms is a major pathway for five-membered heteroaromatic compounds containing two adjacent heteroatoms and initiates the N_2-C_3 interchange pathway by which isoxazoles,[23a−k] pyrazoles,[24−27] and isothiazoles are[14] converted to oxazoles, imidazoles, and thiazoles. This pathway would result in the conversion of 1,2,4-thiadiazoles to 1,3,4-thiadiazoles which were not among the products observed in this study.

(23) (a) Kurtz, D. W.; Schechter, H. J. *J. Chem. Soc., Chem. Commun.* **1966**, 689−690. (b) Ullman, E. G.; Singh, B. *J. Am. Chem. Soc.* **1966**, *88*, 1844−1845. (c) Ullman, E. G.; Singh, B. *J. Am. Chem. Soc.* **1967**, *89*, 6911−6916. (d) Singh, B.; Zweig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199−1206. (e) Nishiwaki, T.; Nakano, A.; Matsuoka, J. *J. Chem. Soc. C* **1970**, 1825−1829. (f) Nishiwaki, T.; Fujiyama, F. *J. Chem. Soc., Perkin Trans.* **1972**, 1456−1459. (g) Wamhoff, H. *Chem. Ber.* **1972**, *105*, 748−752. (h) Good, R. H.; Jones, G. *J. Chem. Soc. C* **1971**, 1196−1198. (i) Goeth, H.; Gagneux, A. R.; Eugster, C. H.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 137−142. (j) Padwa, A.; Chen, E.; Ku, A. *J. Am. Chem. Soc.* **1975**, *97*, 6484−6491. (k) Dietliker, K.; Gilgen, P.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 2074−2099.

SCHEME 5



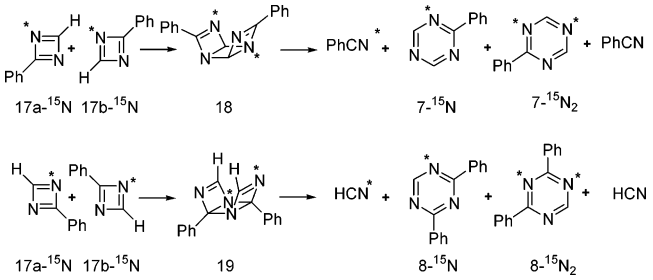
would also be expected to undergo thermal and/or photochemical elimination of sulfur.[28−35] Starting with ^{15}N-labeled **6-4-^{15}N**, electrocyclic ring closure and sulfur elimination would lead to ^{15}N-labeled phenyldiazacyclobutadiene, which presumably would exist as an equilibrium mixture of **17a-^{15}N** and **17b-^{15}N**. Several reaction



pathways can be envisioned for this species. First, as shown in Scheme 5, complete fragmentation of **17a-^{15}N** and **17b-^{15}N** would yield benzonitrile-^{14}N (**5-^{14}N**) and benzonitrile-^{15}N (**5-^{15}N**) in a 1:1 ratio. This constitutes a second photofragmentation pathway which, moreover, leads to more ^{15}N-scrambling in benzonitrile formation than is predicted by the direct fragmentation pathway. This would be consistent with the observed ^{15}N-labeling distribution in benzonitrile (**5**).

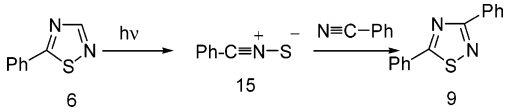
Second, by analogy with cyclobutadiene, **17a** and **17b** would also be expected to undergo [4+2] cycloaddition leading to the formation of unstable tricyclic adducts.[36,37] Although there are numerous orientations for this [4+2] cycloaddition, two examples are shown in Scheme 6. In the first case, tricyclic species **18** could eliminate benzonitrile-^{15}N (**5-^{15}N**) or benzonitrile-^{14}N (**5-^{14}N**) to form phenyl-1,3,5-triazines with either one or two ^{15}N atoms per molecule. Alternatively, as shown in the second

SCHEME 6

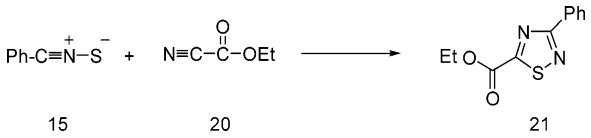


example, the tricyclic adduct **19** would be expected to eliminate HC-^{15}N or HC-^{14}N resulting in the formation of mono- or di-^{15}N-labeled diphenyl-1,3,5-triazine, respectively. This mechanistic pathway predicts that the triazines would be formed as a 1:1 mixture of mono- and di-^{15}N-labeled compounds, which is very close to the observed ratio.

Trapping Experiments. Direct photofragmentation of 3-phenyl-1,2,4-thiadiazole (**4**) and 5-phenyl-1,2,4-thiadiazole (**6**) could lead to the formation of benzonitrile (**5**) via the intermediacy of benzonitrile sulfide (**15**). Indeed, formation of diphenyl-1,2,4-thiadiazole (**9**) as a product from irradiation of 5-phenyl-1,2,4-thiadiazole (**6**) seems to suggest a mechanism involving trapping of photochemically generated benzonitrile sulfide (**15**) by benzonitrile (**5**). Similarly, Howe and Franz have shown that thermally generated benzonitrile sulfide **15** can be ef-



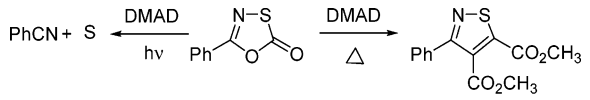
fectively trapped in 1,3-dipolar cycloaddition reactions with acetylenes[38] or by reaction with ethyl cyanoformate **20** to yield ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate (**21**).[19]



To test for the intermediacy of benzonitrile sulfide **15** in these reactions, solutions of thiadiazoles **4** and **6** in acetonitrile solvent containing 5.0 equiv of ethyl cyanoformate **20** were irradiated for 210 or 300 min, respectively. GLC analysis showed the consumption of 78% of **4** and 74% of **6**. In each case, in addition to the expected products observed after irradiation of **4** or **6** in the absence of ethyl cyanoformate **20**, GLC analysis showed the formation of a new product with a retention time of approximately 19 min. The mass spectrum of this new product exhibited a molecular ion at *m*/*z* 234 and a fragmentation pattern identical with the fragmentation pattern of an authentic sample of ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate (**21**).[19] The formation of this product is convincing evidence that irradiation of **4** or **6** results in the formation of benzonitrile sulfide (**15**), which is captured by cycloaddition with ethyl cyanoformate (**20**).

(24) Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313−6302.
(25) Pavlik, J. W.; Connors, R. E.; Burns, D. S.; Kurzweil, E. M. *J. Am. Chem. Soc.* **1993**, *115*, 7645−7652.
(26) Pavlik, J. W.; Kebede, N.; Bird, N. P.; Day, A. C.; Barltrop, J. A. *J. Org. Chem.* **1995**, *60*, 8138−8139.
(27) Pavlik, J. W.; Kebede, N. *J. Org. Chem.* **1997**, *62*, 8325−8334.
(28) Coffen, D. L.; Poon, Y. C.; Lee, M. L. *J. Am. Chem. Soc.* **1971**, *93*, 4627−4628.
(29) Kellogg, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 2344−2346.
(30) Padwa, A.; Au, A.; Lee, G. A.; Owens, W. *J. Org. Chem.* **1975**, *40*, 1142−1149.
(31) Umemoto, T.; Otsubo, T.; Misumi, S. *Tetrahedron Lett.* **1974**, 1573−1576.
(32) Kellogg, R. M.; Prins, *J. Org. Chem.* **1974**, *39*, 2366−2374. Block, E.; Page, J.; Toscano, J. P.; Wang, C.-W.; Zhang, X.; DeOrazio, R.; Guo, C.; Sheridan, R. S.; Towers, G. H. N. *J. Am. Chem. Soc.* **1996**, *118*, 4719−4720.
(33) Padwa, A.; Au, A.; Lee, G. A.; Owens, W. *J. Org. Chem.* **1945**, *40*, 1142−1149.
(34) Nakayama, J.; Shimomura, M.; Iwamoto, M.; Hoshino, M. *Heterocycles* **1985**, *23*, 1907−1910.
(35) Block, E.; Page, J.; Toscano, J. P.; Wang, C.-W.; Zhang, X.; DeOrazio, R.; Guo, C.; Sheridan R. S.; Towers, G. H. N. *J. Am. Chem. Soc.* **1996**, *118*, 4719−4720.
(36) Masamune, S.; Suda, M.; Ona, H.; Leichter, L. M. *J. Chem. Soc., Chem. Commun.* **1972**, 1268−1269.
(37) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 880−885.
(38) Howe, R. K.; Franz, J. E. *J. Chem. Soc., Chem. Commun.* **1973**, 524−525.

The yields of the cycloaddition product **21** were small, however, ranging from ~0.1% in the case of **4** to ~0.5% upon irradiation of **6**. These low yields suggest that either a photofragmentation pathway involving the intermediacy of benzonitrile sulfide (**15**) is a very minor reaction pathway or photochemically generated benzonitrile sulfide (**15**) is less efficiently trapped than the thermally generated species. Some evidence suggests that this may be the case. Thus, although thermal decarboxyation of 5-phenyl-1,3,4-oxathiazol-2-one (**22**) in one molar excess of dimethyl acetylenedicarboxylate (DMAD) led to the formation of dimethyl 3-phenylisothiazole-4,5-dicarboxylate (**23**) in 90% yield, the corresponding irradiation of **22** in the presence of the same trapping agent led only to the formation of benzonitrile (**5**) and sulfur.[39]



5 22 23

Conclusion

Photofragmentation leading to benzonitrile (**5**) formation is a major reaction pathway for phenyl-1,2,4-thiadiazoles. 3-Phenyl-1,2,4-thiadiazole (**4**) reacts only by this pathway and ^{15}N-labeling experiments suggest that **5** is formed either by direct fragmentation of the thiadiazole ring or from the 1,5-diradical formed by photocleavage of the S−N bond. In addition to fragmentation, 5-phenyl-1,2,4-thiadiazole (**6**) also undergoes phototransposition to 3-phenyl-1,2,4-thiadiazole (**4**) and photoconversion to phenyl- and diphenyl-1,3,5-triazines (**7** and **8**). These reactions are suggested to originate in electrocyclic ring closure in **6** leading to 4-phenyl-1,3-diaza-5-thiabicyclo-[2.1.0]pent-2-ene (**BC-6**). Sulfur migration and rearomatization would account for the observed phototransposition while sulfur elimination would lead to phenyldiazacyclobutadiene **17**. This species could undergo complete fragmentation to benzonitrile (**5**) or [4+2] cycloaddition leading to unstable tricyclic adducts, the suggested precursors of the 1,3,5-triazine products **7** and **8**. The distribution of ^{15}N in the phototransposition and triazines products is consistent with this mechanistic interpretation.

Experimental Section

General Procedures. ^1H, ^{13}C, and ^{15}N NMR spectra were recorded at 400.1, 100.6, and 40.5 MHz, respectively. ^{15}N chemical shifts are reported in ppm downfield from $NH_{3(l)}$ and were measured relative to aqueous $Na^{15}NO_3$, which was used as an external standard and taken to absorb at 378.4 ppm downfield from $NH_{3(l)}$. Mass spectra were recorded with an HP 5970B mass selective detector interfaced to an HP588 capillary gas chromatograph. GLC was performed with use of a 15-m × 3-μm Carbowax-20M bonded phase column employing the following temperature program: 140 °C (4 min), 20 °C/min to 180 °C (14 min), 20 °C/min to 240 °C (30 min). Preparative layer chromatography was carried out on 20-cm × 20-cm glass plates coated with 2 mm Kieselgel 60 F_{254} (Merck).

Preparation of Starting Materials and Products. Compounds previously described in the literature were prepared as follows: 3-phenyl-1,2,4-thiadiazole (**4**) by cycloaddition of benzonitrile sulfide (**15**) with ethyl cyanoformate followed by saponification and decarboxylation of the ethyl ester;[19] **15** by decarboxylation of 5-phenyl-1,3,4-oxathiazole-2-one prepared by condensation of chlorocarbonylsulfenyl choride with benzamide;[40] 5-phenyl-1,2,4-thiadiazole (**6**) and 3-methyl-5-phenyl-1,2,4-thiadiazole (**10**) by condensing thiobenzamide with *N*,*N*-dimethylformamide dimethylacetal or *N*,*N*-dimethylacetamide dimethylacetal followed by cyclization of the resulting amidines with hydroxylamine-*O*-sulfonic acid;[41] diphenyl-1,2,4-thiadiazole (**9**) by reaction of thiobenzamide with nitrous acid;[42] phenyl-1,3,5-triazine (**7**) and diphenyl-1,3,5-triazine (**8**) as a mixture by condensing formamidine hydrochloride and benzamidine hydrochloride followed by separation by steam distillation;[43] and 2,4-dimethyl-6-phenyl-1,3,5-triazine (**12**) and 2-methyl-4,6-diphenyl-1,3,5-triazine (**13**) by condensation of *N*-[(dimethylamino)ethylidene]benzamide and either acetamidine or benzamidine in refluxing THF.[44] Benzonitrile (**5**) and triphenyl-1,3,5-triazine (**14**) were commercially available.

3-Phenyl-1,2,4-thiadiazole-2-^{15}N (4-2-^{15}N): Prepared from benzamide-^{15}N by the procedure developed to synthesize the unlabeled compound;[41] ^1H NMR ($CDCl_3$) δ 7.51−7.56 (m, 3H), 8.37−8.39 (m, 2H), 9.90 (d, 1H, $J_{^1H,^{15}N}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ (DEPT-135) 128.7 (+), 129.2 (+), 131.0 (+), 132.8 (0), 173.1 (+) 174.5 (0) (d, $J_{^{13}C,^{15}N}$ = 3.0 Hz); ^{15}N NMR ($CDCl_3$) δ 258.4; MS *m*/*z* (%) 163 (80), 136 (100), 104 (23), 77 (26), 51, (14).

5-Phenyl-1,2,4-thiadiazole-4-^{15}N (6-4-^{15}N): Prepared by converting benzamide-^{15}N to thiobenzamide-^{15}N,[45] and proceeding according to the method developed to synthesize the unlabeled compound;[19] ^1H NMR (acetone-d_6) δ 7.58−7.61 (m, 3H), 8.06−8.08 (m, 2H), 8.84 (d, 1H, $J_{^1H,^{15}N}$ = 13.9 Hz); ^{13}C NMR (acetone-d_6) δ (Dept-135) 128.2 (+), 130.3 (+), 131.1 (0) (d, $J_{^{13}C,^{15}N}$ = 3.8 Hz), 188.6 (+); ^{15}N NMR (acetone-d_6) δ 302.2 (d, $J_{^1H,^{15}N}$ = 13.9 Hz); MS *m*/*z* (%) 163 (88), 136 (100), 105 (92), 104 (24), 77 (59), 59 (64).

Irradiation and Analysis Procedures. To monitor reactions on an analytical scale, a solution of the reactant (4.0 mL, 2.0×10^{-2}M) in the appropriate solvent was placed in a Pyrex tube (7.0 mm inside diameter × 13.0 cm long), sealed with a rubber septum, purged with argon for 10 min, and irradiated in a Rayonet reactor equipped with 16 3000-Å lamps for the appropriate length of time. Preparative-scale reactions were carried out as indicated.

Reaction progress was monitored by removing aliquots at specified times for GLC analysis. Retentions of all products are given relative to the appropriate reactant. Quantitative GLC analysis of reactant consumption and product formation was accomplished by using calibration curves constructed for the reactants and products by plotting detector responses versus five standards of known concentrations. Correlation coefficients ranged from 0.991 to 0.998. After irradiation, the resulting solutions were concentrated to ~0.1 mL and analyzed by GC-MS. Retention times and fragmentation patterns were compared with those of authentic samples of products.

All of the following irradiation are on an analytical-scale unless otherwise indicated.

3-Phenyl-1,2,4-thiadiazole (4). GLC analysis after 120 min of irradiation showed the consumption of **4** (81.6%) and the formation of benzonitrile (**5**) (74.1%) with a relative retention of 0.22. MS *m*/*z* (%) 103 (100), 77 (11), 76 (66), 75 (34), 74 (18), 73 (11), 653 (11), 52 (11), 51 (23).

(39) Franz, J. E.; Black, L. L. *Tetrahedron Lett.* **1970**, 1381−1384.

(40) Muhlbauer, E.; Weiss, W. British Patent 1,079,348, 1967; *Chem. Abstr.* **1968**, *68*, 69000W.

(41) Lin, Y.-I.; Lang, S. A., Jr.; Petty, S. R. *J. Org. Chem.* **1980**, *45*, 3750−3753.

(42) Bahadir, M.; Siegfried, N.; Harun, P.; Korte, F. *J. Agric. Food Chem.* **1979**, *24*, 815−818.

(43) Schaefer, F.; Hechenbleikner, I.; Peters, G.; Wystrach, V. P. *J. Am. Chem. Soc.* **1959**, *81*, 1466−1470.

(44) Chen, C.; Dagnino, R.; McCarthy, J. *J. Org. Chem.* **1995**, *60*, 8428−8430.

(45) King, L. C.; Miller, F. M. *J. Am. Chem. Soc.* **1949**, *71*, 367−368.

5-Phenyl-1,2,4-thiadiazole (6). GLC analysis after 150 min of irradiation showed the consumption of **6** (53%) and the formation of benzonitrile (**5**) (58%), relative retention 0.38 [MS *m*/*z* (%) 103 (100), 77 (11), 76 (66), 75 (34), 74 (18), 73 (11), 63 (11), 52 (11), 51 (23)], phenyl-1,3,5-triazine (**7**) (4%), relative retention 0.94 [MS *m*/*z* (%) 157 (75), 104 (100), 103 (29), 75 (18), 76 (24), 51 (13), 50 (13)], 3-phenyl-1,2,4-thiadiazole (**4**) (18%), relative retention 1.14 [MS *m*/*z* (%) 162 (75), 135 (100), 103 (25), 91 (10), 77 (32), 76 (20), 51 (18), 50 (15)], diphenyl-1,3,5-triazine (**8**) (2%), relative retention 3.77 [MS *m*/*z* (%) 233 (57), 130 (17), 103 (100), 76 (26)], and diphenyl-1,2,4-thiadiaole (**9**) (trace), relative retention 4.0 [MS *m*/*z* (%) 238 (35), 135 (100), 103 (19), 77 (22), 76 (12), 51 (12)].

3-Methyl-5-phenyl,1,2,4-thiadiazole (10). GLC analysis after 150 min of irradiation showed the consumption of **10** (76%) and the formation of benzonitrile (**5**) (56%), relative retention 0.42 [MS *m*/*z* (%) as above], 2,4-dimethyl-6-phenyl-1,3,5-triazine (**12**) (33%), relative retention 0.96 [MS *m*/*z* (%) 185 (55), 103 (100), 82 (33), 76 (28)], 5-methyl-3-phenyl-1,2,4-thiadiazole (**11**) (∼10%), relative retention 1.13 [MS *m*/*z* (%) 176 (54), 135 (100), 103 (19), 77 (39)], and 2-methyl-4,6-diphenyl-1,3,5-triazine (**13**) (7%), relative retention 2.33 [MS *m*/*z* (%) 247 (31), 103 (100), 76 (19)].

Diphenyl-1,2,4-Thiadiazole (9). GLC analysis after 5 min of irradiation showed the consumption of **9** (12.9%) and the formation of benzonitrile (**5**) (35%), relative retention (0.11) [MS *m*/*z* (%) as above]. At a higher oven temperature a second product eluted showing the formation of triphenyl-1,3,5-triazine (**14**), relative retention 3.5 [MS *m*/*z* (%) 309 (64), 103 (100), 76 (14)].

5-Phenyl-1,2,4-thiadiazole-4-^{15}N (6-4-^{15}N). GLC-MS analysis after the specified irradiation time showed the following ratios: for unconsumed **6-4-^{15}N**, *m*/*z* 135:136 0.02 (8.0 min), 0.06 (12.0 min), 0.080 ± 0.005 (16.0 min), 0.40 (180 min); for benzonitrile (**5**), *m*/*z* 103:104, 0.17 (4.0 min), 0.24 (8.0 min), 0.27 (12.0 min), 0.32 (16.0 min); for 3-phenyl-1,2,4-thiadiazole (**4**), *m*/*z* 135:136, 1.11± 0.08 (8 min), 1.07 ± 0.08 (12.0 min), 1.12 ± 0.02 (16 min); for phenyl-1,3,5-triazine (**7**), *m*/*z* 158: 159, 0.84 ± 0.02 (8.0 min), 0.80 ± 0.04 (12. min), 0.85 ± 0.01 (16.0 min); and for diphenyl-1,3,5-triazine (**8**), *m*/*z* 234:235, 1.14 ± 0.03 (16.0 min).

3-Phenyl-1,2,4-thiadiazole-2-^{15}N (4−2-^{15}N). GLC and GLC-MS analysis after 150 min of irradiation showed consumption of **4-2-^{15}N** (46%) but no change in the mass spectrum of the unconsumed reactant and the formation of benzonitrile-^{15}N (**5-N^{15}**) (71%) with a relative retention of 0.27. MS *m*/*z* (%) 104 (100), 76 (70), 50 (15).

Preparative-Scale Irradiation of 5-Phenyl-1,2,4-Thiadiazole-4-^{15}N (6-4-^{15}N). A solution of 5-phenyl-1,2,4-thiadiazole-4-^{15}N **(6-4-^{15}N)** in acetonitrile (8.0 mL, 2.0 × 10^{-2}M) was placed in a Pyrex tube (7.0 mm inside diameter × 20 cm long), sealed with a rubber septum, purged with argon for 30 min, and irradiated in a Rayonet reactor equipped with 16 3000-Å lamps until GLC analysis showed 40% consumption of the reactant. The resulting solution was concentrated under reduced pressure and the residue was subjected to preparative layer chromatography (silica gel, CH_2Cl_2−hexane, 4:1). After 4 elutions, the band at R_f 0.69 gave unconsumed 5-phenyl-1,2,4-thiadiazole-^{15}N: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.53 (m, 3H), 7.95−7.98 (M, 2H), 8.69 (d, 1H, J = 13.9 Hz). The band at R_f 0.39 gave 3-phenyl-1,2,4-thiadiazole-^{15}N: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.50 (m, 3H), 8.32−8.34 (m, 2H), 9.87 (d, J = 11.1 Hz); 9.87 (d, J = 1.5 Hz).

Preparative-Scale Irradiation of Diphenyl-1,2,4-Thiadiazole (9). A solution of diphenyl-1,2,4-thiadiazole (**9**) in cyclohexane was placed in a Pyrex tube (2.5 cm inside diameter × 30 cm long), sealed with a rubber septum, purged with argon for 30 min, and irradiated in a Rayonet reactor equipped with 16 3000-Å lamps until GLC analysis showed complete consumption of the reactant. The resulting solution was concentrated and the residue subjected to silica gel (100 g) flash column chromatography. The column (68 cm long × 3.5 cm diameter) was eluted with hexane:dichloromethane (1:1) and fractions (15 mL) were collected and analyzed by thin-layer chromatography. Fractions 13−16 were concentrated to yield triphenyl-1,3−5-triazine (**14**) as a while solid: mp 235−237 °C (lit.[46] mp 237−238 °C); 0.169 (0.52 mmol, 52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 129.0, 129.3, 132.9, 136.6, 172.0; MS *m*/*z* (%) 309 (10), 104 (13), 103 (100), 77 (12), 76 (19), 51 (8).

Irradiation of 3-Phenyl-1,2,4-Thiadiazole (4) or 5-Phenyl-1,2,4-Thiadiazole (6) in the Presence of Ethyl Cyanoformate. Trapping of Benzonitrile Sulfide (15). Solutions of 3-phenyl-1,2,4-thiadiazole (**4**) and 5-phenyl-1,2,4-thiadiazole (**6**) in acetonitrile (4.0 mL, 2.0 × 10^{-2}M) each containing ethyl cyanoformate (0.1 mL, 1 × 10^{-1} M) in Pyrex tubes were sealed with a rubber septa, purged with argon for 30 min, and irradiated in a Rayonet Reactor equipped with 16 3000-Å lamps for 210 or 300 min, respectively. GLC analysis showed the consumption of **4** (−78%) and **6** (−74%). In addition to the products observed in the absence of ethyl cyanoformate, GLC analysis showed the formation of ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate **21** (∼0.1% from **4** and ∼0.5% from **6**), MS *m*/*z* (%) 234 (50), 162 (14), 135 (100), 103 (21), 77 (19), 41 (12).

Acknowledgment. We are grateful to Dr. Lawrence Scott, Department of Chemistry, Boston College, for an insightful discussion regarding the mechanistic understanding of triazines formation.

JO0340915

(46) Forsberg, J. H.; Spaziano, V. T.; Klump, S. P.; Sanders, K. M. *J. Heterocycl. Chem.* **1988**, *25*, 767−770.