Photochemistry of 3- and 5-Phenylisothiazoles. Competing Phototransposition Pathways

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5-Phenylisothiazole undergoes phototransposition via the electrocyclic ring closure−heteroatom migration pathway and by the N_2-C_3 interchange reaction pathway. The latter route is enhanced by the addition of triethylamine (TEA) to the reaction medium and by increasing the polarity of the solvent. In addition to phototransposition, 5-phenylisothiazole also undergoes photocleavage to 2-cyano-1-phenylethenethiol which was trapped by reaction with benzyl bromide to yield 2-cyano-1-phenylethen-1-ylbenzyl thioether. 3-Phenylisothiazole also phototransposes by both reaction pathways, but the product distribution is not affected by the addition of TEA or by changing the solvent polarity.

Introduction

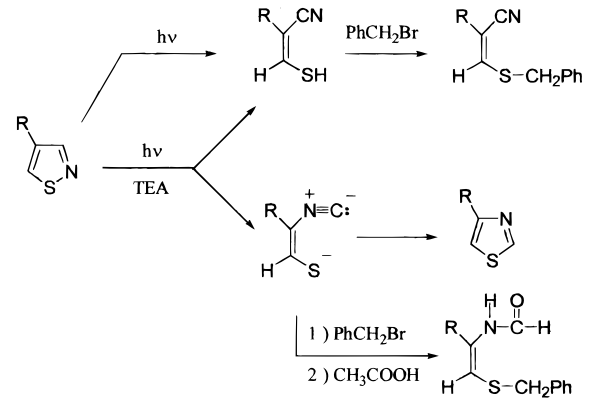
Work in this laboratory has recently shown (Scheme 1) that 4-substituted isothiazoles undergo photocleavage in benzene solvent to yield cyanothiols which can be trapped as their benzyl thioether derivatives.[1] The addition of a small amount of a base such as triethylamine (TEA) to the reaction media has a profound effect on the photoreaction. Under these conditions 4-substituted thiazoles, the expected P_4 phototransposition products, are also formed.[2,3] This work also revealed that the 4-substituted isothiazole → 4-substituted thiazole P_4 transposition occurs by way of isocyanosulfide intermediates which in some cases can be observed spectroscopically and can be trapped as their *N*-formylaminobenzyl thioether derivatives. In the absence of trapping agents, these isocyanosulfides can also cyclize to 4-substituted thiazoles, the observed P_4 transposition product.[1]

In the present work we have explored the effects of TEA and solvent polarity on the photochemistry of 3- and 5-phenylisothiazoles and have searched for the isocyano intermediates in the photorearrangements of these compounds.

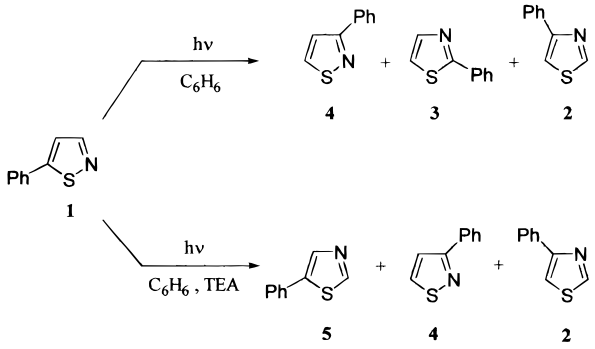
Results and Discussion

To determine the effect of TEA on the photochemistry of 5-phenylisothiazole (**1**), two solutions of **1** in benzene (3.0 mL, 2.2×10^{-2} M), without and with TEA (1.4×10^{-2} M), were simultaneously irradiated on a merry-go-round apparatus for 30 min. Gas liquid chromatographic (GLC) analysis of the resulting solutions showed that in the absence of TEA 32% of the reactant had been

Scheme 1



consumed and that 3-phenylisothiazole (**4**), 2-phenylthiazole (**3**), and 4-phenylthiazole (**2**) were formed in yields of 5%, 2%, and 15%, respectively. Whereas these are the products anticipated via the P_5, P_6, and P_7 permutation pathways, GLC analysis did not reveal the formation of any 5-phenylthiazole (**5**), the product expected by the P_4 pathway which involves interchange of the N_2-C_3 atoms.



4 **3** **2** **1** **5** **4** **2**

GLC analysis revealed that addition of TEA to the solution resulted in several changes to the reaction. First, in the presence of TEA, the consumption of **1** increased from 32% to 44%. Second, although 5-phenylthiazole (**5**) was not observed as a product in the absence of TEA, in

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

(2) For a discussion of permutation pattern analysis in aromatic phototransposition chemistry, see: (a) Barltrop, J. A.; Day, A. C. *J. Chem. Soc., Chem. Commun.* **1975**, 177. (b) Barltrop, J. A.; Day, A. C.; Moxon, P. D.; Ward, R. W. *J. Chem. Soc., Chem. Commun.* **1975**, 786. (c) Barltrop, J. A.; Day, A. C.; Ward, R. W. *J. Chem. Soc., Chem. Commun.* **1978**, 131.

(3) For five-membered heterocycles containing two heteroatoms, there are 12 different ways of transposing the five ring atoms resulting in 12 permutation patterns identified P_1-P_{12}. For a table showing these permutation patterns, see: Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313.

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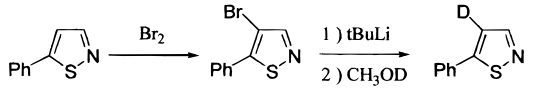
the presence of TEA it is the major product formed in 14% yield. In addition, although TEA had no effect on the yield of 3-phenylisothiazole (**4**), the yields of 4-phenylthiazole (**2**) and 2-phenylthiazole (**3**) decreased from 15% and 2% to 4% and 0%, respectively. Finally, GLC analysis showed that TEA was not consumed during the photolysis.

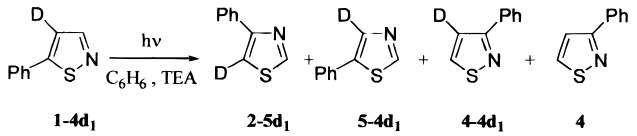
The permutation patterns[2,3] for these transpositions were unambiguously determined by synthesizing and studying the photochemistry of 4-deuterio-5-phenylisothiazole (**1**-4d$_1$), a molecule in which each isothiazole ring position is uniquely labeled. This was prepared by lithium−halogen exchange of 4-bromo-5-phenylisothiazole **6** using *tert*-butyllithium and quenching 4-lithio-5-



phenylisothiazole **7** with CH_3OD. The mass spectrum of the resulting product exhibited a molecular ion at *m*/*z* 162 but no signal at *m*/*z* 161, confirming complete deuteration and an intense peak at *m*/*z* 135 due to loss of H−C(3)≡N indicating that the deuterium is located at position 4 of the isothiazole ring.[5,6] This was confirmed by the ^{1}H NMR spectrum which exhibited a singlet at δ 8.45 due to the H-3 proton but no signal at δ 7.40 where the C-4 proton of **1** is known to absorb.[7]

A benzene solution of 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) (50 mL, 2.0×10^{-2} M) containing TEA (7.5×10^{-2} M) was irradiated for 30 min after which GLC analysis showed that 49% of the reactant was consumed and that 5-phenylthiazole (**5**), 3-phenylisothiazole (**4**), and 4-phenylthiazole (**2**) were formed in yields of 19%, 9%, and 8%, respectively.

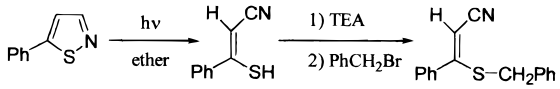
The photolysate was also examined by GC-MS. The mass spectrum of the unconverted 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) was identical to the spectrum before photolysis, showing that no deuterium was lost or scrambled in the reactant during the irradiation. The mass spectrum of deuterated 4-phenylthiazole (**2**) exhibited a molecular ion at *m*/*z* 162 and an intense peak at *m*/*z* 135 due to loss of H−C(2)≡N. This shows that the deuterium is located at position 5 of the 4-phenylthiazole (**2**) ring and that the product is 5-deuterio-4-phenylthiazole (**2**-5d$_1$) formed from 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) by a mechanism consistent with the P_7 permutation.



Preparative layer chromatography of the photolysate residue provided two major products. The band at R_f = 0.3 provided a yellow oil which was identified as 4-deuterio-5-phenylthiazole (**5**-4d$_1$) on the basis of the ^{1}H NMR spectrum which exhibited a singlet at δ 8.73 due to the H-2 proton of 5-phenylthiazole (**5**) but no signal at δ 8.05 where the H-4 proton is known to absorb. This confirms that 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) has phototransposed to 4-deuterio-5-phenylthiazole (**5**-4d$_1$) by the N_2−C_3 interchange mechanism which is consistent with the P_4 permutation pathway. The second band at R_f = 0.75 provided a yellow oil that was identified by ^{1}H NMR as a mixture of 4-deuterio-3-phenylisothiazole (**4**-4d$_1$) and undeuterated 3-phenylisothiazole (**4**). Thus, the ^{1}H NMR spectrum of this material exhibited a singlet at δ 8.69 due to H-5 of **4**-4d$_1$ and a doublet of low intensity at δ 7.61 (J = 4.71 Hz) due to H-4 coupled with H-5 of undeuterated 3-phenylisothiazole (**4**). Integration of these signals and analysis of the *m*/*z* 162 and 161 peaks in the mass spectrum indicates that the isolated product is a mixture of 4-deuterio-3-phenylisothiazole (**4**-4d$_1$), demanded by the P_5 permutation pathway, and undeuterated 3-phenylisothiazole (**4**) in a ratio of 57:43. Interestingly, when **1**-4d$_1$ was irradiated in benzene without TEA, the ratio of **4**-4d$_1$:**4** was 10.1. Thus, in the presence of TEA, considerably more deuterium−hydrogen exchange occurs during the phototransposition reaction.

The residues remaining after evaporation of the solvent from the irradiated solutions of 5-phenylisothiazole **(1)** were also examined by infrared spectroscopy in order to detect the formation of photocleavage products. These spectra showed a weak absorption at 2209 cm^{-1}, characteristic of a nitrile functional group, but no absorption in the 2100 cm^{-1} region where an isocyanide would be expected to absorb. This suggests that 5-phenylisothiazole **(1)** has undergone photocleavage leading presumably to 2-cyano-1-phenylethenethiol **(8)**, the expected photocleavage product of **1**.

In an attempt to trap **8** as its benzyl thioether derivative, a solution of **1** in diethyl ether was irradiated until after 30 min GLC analysis showed that greater than 90% of the reactant had been consumed. TEA and then benzyl bromide were added to the solution. After standing overnight, preparative layer chromatography allowed isolation of 2-cyano-1-phenylethen-1-ylbenzyl thioether **(9)** as a yellow oil in 10.3% yield.



As required by this structural assignment, the mass spectrum of this product exhibited a molecular ion at *m*/*z* 251, consistent with a molecular formula of $C_{16}H_{13}NS$, and a base peak at *m*/*z* 91, as expected for a benzyl derivative. Furthermore, the infrared spectrum exhibited a sharp absorption at 2210 cm^{-1} for the nitrile functional group. The ^{1}H NMR spectrum showed a singlet at δ 3.88 assigned to the benzyl protons and a singlet due to the vinyl proton at δ 5.44 with an integrated ratio of 2:1. In addition to signals for the phenyl carbons, the ^{13}C NMR spectrum exhibited absorptions due to the benzyl, cyano, and vinyl carbons at δ 37.7, 116.6, and 162.1, respectively. These spectral properties are consistent with the assigned structure.

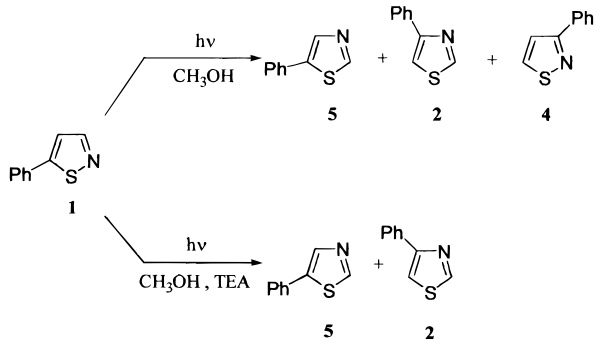
Close inspection of the ^{1}H NMR spectrum also revealed weak absorptions at δ 4.00 and 5.23 which may be due to the benzyl and vinyl protons of a second stereoisomer of the benzyl thioether **9**. The vinyl protons of the (*Z*)-

(4) All reported yields are absolute yields and are based on the quantity of reactant consumed.

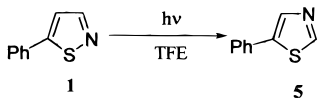
(5) Salmona, G.; Vincent, E.-J. *Org. Mass. Spectrum* **1978**, *13*, 119.
(6) Clarke, G. M.; Grigg, R.; Williams, D. H. *J. Chem. Soc. B* **1966**, 339.
(7) Staab, A.; Mannschreck, A. *Chem. Ber.* **1965**, *98*, 1111.

and (*E*)-isomers of **9** are estimated to absorb at δ 5.75 and δ 5.16, respectively.[8] Since the vinyl protons of the major and minor stereoisomers of **9** were observed at δ 5.44 and upfield at δ 5.23, the major isomer was assigned the (*Z*)-configuration. Isolation of **9** provides excellent evidence that 5-phenylisothiazole (**1**) has undergone photocleavage to yield cyanothiol **8**.

The photochemistry of 5-phenylisothiazole (**1**) was also investigated in methanol and 2,2,2-trifluoroethanol (TFE) solvents with and without added TEA. Solutions of **1** in methanol (3.0 mL, 2.1×10^{-2} M) without and with TEA (1.5×10^{-2} M) were irradiated simultaneously on a merry-go-round apparatus for 30 min. GLC analysis showed that in the absence of TEA 33% of **1** had been consumed and that 5-phenylthiazole (**5**), 4-phenylthiazole (**2**), and 3-phenylisothiazole (**4**) had been formed in yields of 23%, 6%, and 2%, respectively.[9] GLC analysis also revealed that in the presence of TEA the consumption of **1** increased to 51% and that the only photoproducts observed are 5-phenylthiazole (**5**) and 4-phenylthiazole (**2**) in yields of 34% and 2%, respectively. Interestingly,

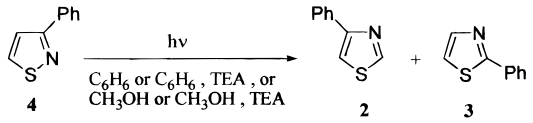


this shows that the phototransposition becomes more regioselective with increasing polarity of the solvent. Indeed, when **1** was irradiated in the more polar TFE solvent (3.0 mL, 2.0×10^{-2} M), 5-phenylthiazole (**5**) was the only product observed. Thus, GLC analysis showed that in the absence of TEA 5-phenylthiazole (**5**) was formed in 32% yield while in the presence of TEA (1.5×10^{-2} M) the yield of **5** was increased to 42%. Again, TEA was not consumed during these irradiations. Finally, in either methanol or TFE solvent, 4-deuterio-5-phenylisothiazole (**1**-4d_1) was converted to 4-deuterio-5-phenylthiazole (**5**-4d_1), showing that the increased solvent polarity has not changed the permutation pathway for the phototransposition reaction.



When the irradiated solution of **1** in TFE containing TEA was allowed to react with benzyl bromide, the infrared spectrum of the residue left after evaporation of the solvent showed weak absorptions at 2211 and at 2099 cm^{-1}, suggesting the presence of both cyano- and isocyanobenzyl thioethers. These results again implicate an isocyanothiol in the phototransposition of 5-phenylisothiazole **(1)**.

Vernin and Maeda previously reported that 3-phenylisothiazole **(4)** phototransposes to 4-phenylthiazole **(2)**, the expected P_6 permutation product, in ether or benzene solvent but not to 2-phenylthiazole **(3)**, the expected P_4 permutation product.[11−14] In our laboratory, two solutions of 3-phenylisothiazole **(4)** (3.0 mL, 2.0×10^{-2} M) in benzene in the absence or presence of TEA (1.5×10^{-2} M) were irradiated simultaneously for 3.0 h on a merry-go-round apparatus. GLC analysis showed that in the absence of TEA 34% of 3-phenylisothiazole **(4)** was consumed and that 4-phenylthiazole **(2)** and 2-phenylthiazole **(3)** were formed in 42.1% and 2.6% yields, respectively. When the irradiation was carried out in the presence of TEA, GLC analysis showed that the consumption of 3-phenylisothiazole **(4)** was increased to 51% and that 4-phenylthiazole **(2)** and 2-phenylthiazole **(3)** were formed in 12.9% and 2.4% yields, respectively. The decrease in the yield of 4-phenylthiazole **(2)** from 42.1% to 12.9% was found to be due to the instability of **2** upon prolonged irradiation in the presence of TEA.[15,16] The yields of 2-phenylthiazole **(3)** in the two reactions show that TEA has little affect on the formation of this compound. Finally, the infrared spectra of the residues left after evaporation of the solvent from these reactions did not show absorptions that would suggest the formation of products containing cyano or isocyano functional groups.



3-Phenylisothiazole **(4)** was also irradiated in methanol solvent under the conditions described above. GLC analysis showed that in the absence of TEA 36% of 3-phenylisothiazole **(4)** had been consumed while 4-phenylthiazole **(2)** and 2-phenylthiazole **(3)** were formed in yields of 16.8% and 4.9%, respectively. In the same manner as for the reaction carried out in benzene, when 3-phenylisothiazole **(4)** was irradiated in methanol containing TEA, the consumption of **4** was increased to 56% whereas 4-phenylthiazole **(2)** and 2-phenylthiazole **(3)** were formed in yields of 8.7% and 3.3%, respectively.

4-Phenylthiazole **(2)** is the product expected if 3-phenylisothiazole **(4)** transposes via a P_6 permutation pathway. This permutation was confirmed by studying the phototransposition of 5-deuterio-3-phenylisothiazole (**4**-5d_1) synthesized from 3-phenylisothiazole **(4)** by base-

(8) Frieboln, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 2nd; Ed.; VCH Publishers: New York, 1993; pp 139−143.

(9) Ohashi[10] also reported that 5-phenylisothiazole (**1**) phototransposes to 5-phenylthiazole (**5**) but made no mention of the formation of 4-phenylthiazole (**2**) or 3-phenylisothiazole (**4**).

(10) Ohashi, M.; Iio, A.; Ezaki, A.; Yonezawa, T. *Heterocycles* **1975**, *1*, 69.

(11) Maeda, M.; Kojima, M. *J. Chem. Soc., Perkin Trans 1* **1977**, 239.

(12) Maeda, M.; Kawahara, A.; Kai, M.; Kojima, M. *Heterocycles* **1975**, *5*, 389.

(13) Vernin, G.; Poite, J. C.; Metzger, J.; Aune, J. P.; Dou, H. J. M. *Bull. Soc. Chim. Fr.* **1971**, 1103.

(14) Vernin, G.; Riou, C.; Dou, H. J. M.; Bouscasse, L.; Metzger, J.; Loridan, G. *Bull. Soc. Chim. Fr.* **1973**, 1743.

(15) Although irradiation of 4-phenylisothiazole **10** in the presence of TEA for 30 min results in the formation of 4-phenylthiazole **2** in 70% yield,[16] independent experiments show that prolonged irradiation of **2** in the presence of TEA results in substantial loss of the heterocycle.

(16) The acidity of the C-2 hydrogen of 4-phenylthiazole **2** is enhanced upon photochemical excitation.[17] In the presence of TEA, excited **2** is no doubt efficiently deprotonated which may enhance its reactivity.

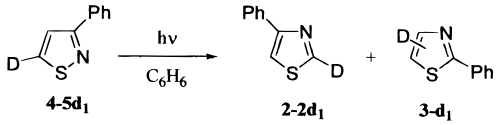
Table 1. Quantum Yield Results

reactant (solvent)	Φ (consumption)
1 (C_6H_{12})	0.24 ± 0.01
1 (C_6H_{12}/TEA)	0.24 ± 0.01
4 (C_6H_{12})	0.20 ± 0.03

Table 2. Spectroscopic and Photophysical Properties

	λ_{max} (nm)	log ϵ	Φ_f (×10⁴)	τ_f (ps)	τ_p (ms)	E_{S_1}	E_{T_1}
4	271	4.24	100	68	215	97	66
1	265	4.18	4.2	2.4	45	98	64

catalyzed hydrogen−deuterium exchange.[17] A solution of 5-deuterio-3-phenylisothiazole (**4**-5d$_1$) in benzene (3.0 mL, 2.0×10^{-2} M) was irradiated, and the deuterated 4-phenylthiazole formed was analyzed by mass spectroscopy. The major mass spectral fragmentation pathway for 4-phenylthiazole **(2)** involves loss of H−C(2)≡N, resulting in the formation of an *m*/*z* 134 fragment. In the mass spectrum of deuterated 4-phenylthiazole formed from 5-deuterio-3-phenylisothiazole (**4**-5d$_1$), the spectrum exhibited a molecular ion at *m*/*z* 162 and a base peak at *m*/*z* 134 showing that fragmentation has resulted in the loss of D−C(2)≡N. This shows that the C-5-deuterium of **4**-5d$_1$ has transposed to position 2 of the 4-phenylthiazole ring to yield 2-deuterio-4-phenylthiazole (**2**-2d$_1$) as



4-5d$_1$ **2-2d$_1$** **3-d$_1$**

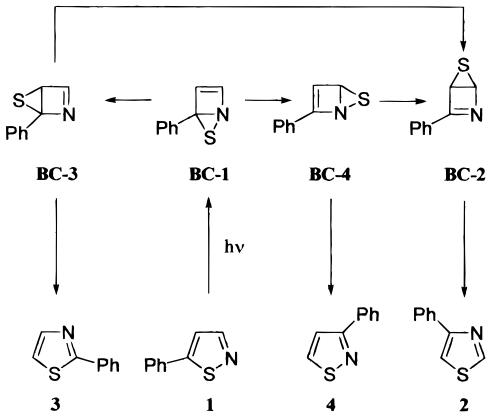
demanded by the P_6 permutation pathway. Deuterated 2-phenylthiazole was also formed in this reaction, but the yield was too low to allow determination of the position of the deuterium.

Quantum Yields. The quantum yields for the consumption of isothiazoles **1** and **4** were determined in triplicate in cyclohexane solutions. In the case of **1**, the quantum yield for consumption was also measured in cyclohexane containing TEA. These values are shown in Table 1. 1,3-Cycloheptadiene was used as the actinometer.[18]

Spectroscopic Properties. 3-Phenylisothiazole **(4)** and 5-phenylisothiazole **(1)** exhibit structureless absorption spectra in methylcyclohexane solvent (Table 2) with extinction coefficients consistent with $\pi \rightarrow \pi^*$ transitions. Both compounds exhibit very weak fluorescence and phosphorescence in methylcyclohexane. Discernible O,O bands in the fluorescence and phosphorescence spectra of **4** and **1** indicate that E_{S_1} values are 97 and 98 kcal mol^{-1} while E_{T_1} values are 66 and 64 kcal mol^{-1}, respectively. The quantum yields of fluorescence at room temperature were measured relative to hexaphenylbenzene[19] and are shown in Table 2. The measured fluorescence and phosphorescence lifetimes at room temperature and at 77 K, respectively, are also shown in Table 2. The lifetimes of S_1 and T_1 and the energy gaps are consistent with π,π^* configurations.

Sensitized Irradiations. The photoreactions of 3-phenylisothiazole **(4)** (E_T = 66 kcal mol^{-1}) and 5-phenylisothiazole **(1)** (E_T = 64 kcal mol^{-1}) could not be sensitized in cyclohexane by butyrophenone (E_T = 74.7 kcal mol^{-1}) despite the observation that both **4** and **1** efficiently quench the Norrish type II reaction of the sensitizer with rate constants (k_q) of 3.88×10^9 and 5.00×10^9 M^{-1} s^{-1}, respectively.

Scheme 2

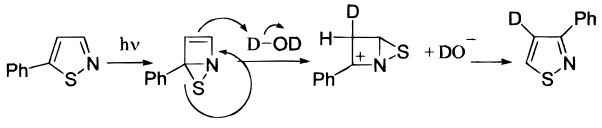


Mechanistic Discussion. Deuterium labeling shows that the phototransposition of 5-phenylisothiazole **(1)** and 3-phenylisothiazole **(4)** involves competition between electrocyclic ring closure−sulfur migration and the P_4 interchange of N_2 and C_3 of the isothiazole ring.

As shown in Scheme 2, 5-phenylisothiazole **(1)** can be converted to 3-phenylisothiazole **(4)**, the P_5 permutation product, via a single sulfur walk, **1** + *hν* → **BC-1** → **BC-4** → **4**, whereas 4-phenylthiazole **(2)**, the P_7 permutation product, is formed via a double walk, process **1** + *hν* → **BC-1** → **BC-4** → **BC-2** → **2** and/or **1** + *hν* → **BC-1** → **BC-3** → **BC-2** → **2**. Although **BC-1** is expected to rearrange mainly to **BC-4**, which is more stable than **BC-3**, the latter pathway via **BC-3** must account for at least a portion of the transposition since the formation of 2-phenylthiazole **(3)**, the P_6 permutation product, implicates the existence of **BC-3** on the transposition pathway. The formation of 4-phenylthiazole **(2)** as the major product most likely reflects the fact that **BC-2** is the most stable bicyclic intermediate.

4-Deuterio-5-phenylisothiazole (**1**-4d$_1$) was observed to phototranspose in benzene to 4-deuterio-3-phenylisothiazole (**4**-4d$_1$) with approximately 10% H−D exchange, and a much greater amount of exchange was observed when the irradiation was carried out in benzene−TEA.

Previous work in this laboratory has shown that 5-phenylisothiazole **(1)** undergoes phototransposition in benzene−D_2O to yield a mixture of 3-phenylisothiazole **(4)** and 4-deuterio-3-phenylisothiazole (**4**-4d$_1$).[17] Mechanistically, we suggested that the initially formed **BC-1** undergoes deuterium incorporation and simultaneous sigmatropic shift of sulfur to yield **4**-4d$_1$ via (4D-4-H-**BC-4**)$^+$. In the present case, 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) phototransposed to 4-deuterio-3-phenylisothiazole (**4**-4d$_1$) with exchange of a small quantity of deuterium



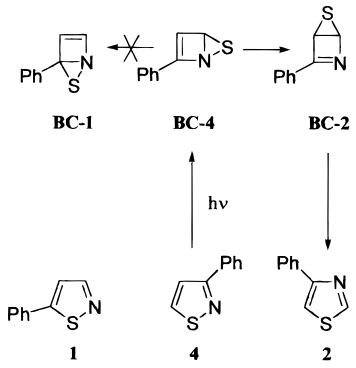
1 **BC-1** **(4D-4H-BC-4)$^+$** **4-4d$_1$**

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

(18) Numao, N.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1997**, 1661.

(19) Berlman, I. B. *Handbook of Fluorescence Spectra of Aromatic Molecules*, 2nd ed.; Academic Press: New York, 1971; p 237.

Scheme 3



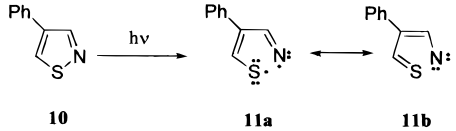
for hydrogen at position 4. This must be due to a small quantity of H_2O in the benzene solvent. The extent of H−D exchange was substantially enhanced when the photolysis of **1**-4d_1 was carried out in the presence of TEA. In this case TEA presumably deprotonates (4D-4H-**BC-4**)$^+$ to yield **4** and H-TEA$^+$ which is a better proton donor in the exchange reaction.

As shown in Scheme 3, 3-phenylisothiazole **(4)** can be converted to 4-phenylthiazole **(2)** via a single sulfur walk, **4** + *hν* → **BC-4** → **BC-2** → **2**. This is consistent with deuterium labeling which shows that 3-phenylisothiazole **(4)** transposes to 4-phenylthiazole **(2)** by way of a P_6 permutation pathway. Failure to observe 5-phenylthiazole **(1)** as a product in this reaction indicates that **BC-4** partitions only between **4** and **BC-2** and not the significantly less stable bicyclic species **BC-1**.

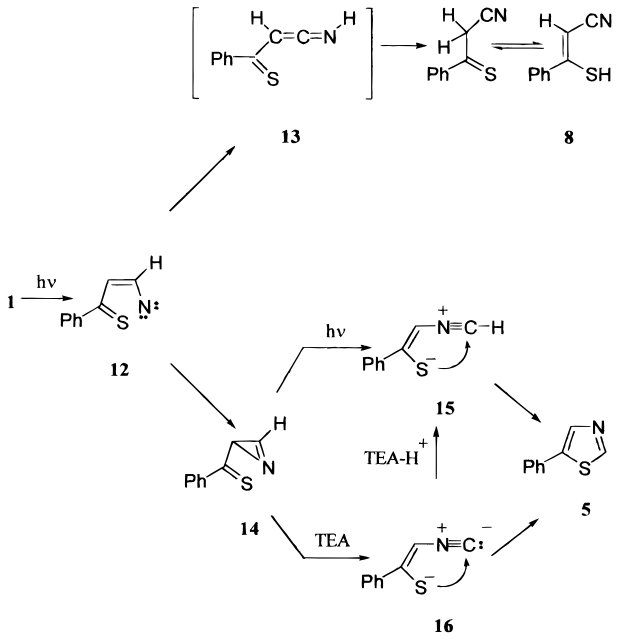
Although the conversion of 5-deuterio-3-phenylisothiazole (**4**-5d_1) to 2-deuterio-4-phenylthiazole (**2**-2d_1) confirmed that the transposition occurs via the P_6 permutation pathway, deuterated 2-phenylthiazole was not formed in sufficient quantity to allow determination of the position of the deuterium. Accordingly, in this reaction it is not possible to unambiguously determine the permutation pattern since both the P_4 N_2−C_3 interchange and the double sulfur walk P_7 pathways lead coincidentally to the same product, 2-phenylthiazole **(3)**.

The conversion of 3-phenylisothiazole **(4)** to 2-phenylthiazole **(3)** via the P_7 pathway is unlikely, however, since it would require a pathway (Scheme 2) involving **4** + *hν* → **BC-4** → **BC-2** → **BC-3** → **3**. 4-Phenylthiazole **(2)**, however, phototransposes only to 3-phenylisothiazole **(4)** and not to 2-phenylthiazole **(3)**. This reveals that **BC-2** partitions only between **2** and **BC-4** and not to the significantly less stable bicyclic species **BC-3**. The absence of the formation of 5-phenylisothiazole **(1)** from 3-phenylisothiazole **(4)** makes walk in the opposite direction, i.e., **4** + *hν* → **BC-4** → **BC-1** → **BC-3** → **3**, also unlikely. In view of these arguments, it is more likely that 2-phenylthiazole **(3)** is formed from 3-phenylisothiazole **(4)** via the P_4 permutation pathway.

4-Phenylisothiazole **(10)** undergoes photocleavage and phototransposition exclusively by the P_4 N_2−C_3 interchange pathway. Both of these reactions are initiated by photochemically breaking of the S−N bond, resulting in the formation of a species that can be viewed as diradical **11a** or as *β*-thioformylvinyl nitrene **11b**. This species, as



Scheme 4

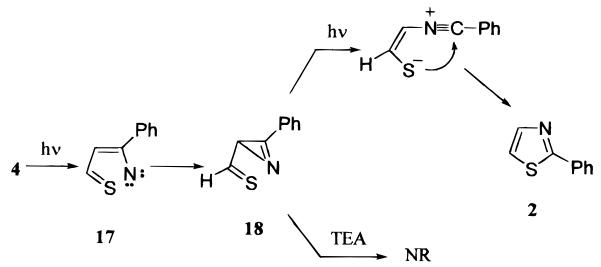


well as the transition state leading to it, is appreciably stabilized by the *β*-phenyl group. This stabilization thus assists photocleavage of the S−N bond relative to other possible reactions. As a result, 4-phenylisothiazole **(10)**, which has a quantum yield of consumption of 0.41, is the most reactive of the phenylisothiazole isomers. 5-Phenylisothiazole **(1)** and 3-phenylisothiazole **(4)** react less efficiently and have quantum yields of consumption of 0.20 and 0.13, respectively, reflecting the lack of stabilization exerted by the phenyl group from the 3 and 5 positions. Moving the phenyl group from C_4 to C_5 or C_3 not only decreases reactivity of the P_4 N_2−N_3 interchange pathway but also allows the slower electrocyclic ring closure to compete with breaking of the S−N bond. Thus, both 3-phenyl- and 5-phenylisothiazoles **(4** and **1)** react by both the P_4 N_2−C_3 interchange pathway and the electrocyclic ring closure−heteroatom migration pathway leading to P_5, P_6, and P_7 phototransposition products. Interestingly, the same structure−reactivity trends were observed in the three isomeric phenyl-substituted 1-methylpyrazoles.[20]

In addition to recyclizing to isothiazole reactant **1**, *β*-thiocarbonyl vinyl nitrene **12** (Scheme 4) would be expected to rearrange to cyanothiol **8**, possibly by way of thiocarbonylketene **13**. Isomerization to nitriles is a well-documented reaction of terminal vinyl nitrenes.[21] In addition, **12** would also be expected to be in equilibrium with thiocarbonylazirine **14**.[22] Two reaction pathways can be envisioned for this azirine. First, on the basis of the known photochemistry of azirines,[23,24] **14** would be expected to undergo photochemical opening of the C−C bond resulting in the formation of nitrile ylide **15**, a likely

(20) Pavlik, J. W.; Kebede, N. *J. Org. Chem.* **1997**, *62*, 8325.
(21) See: Hassner, A. In *Azides and Nitrenes. Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, 1984; pp 35−94, and references therein.
(22) Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176.
(23) Padwa, A.; Smolanoff, J.; Tremper, A. *Tetrahedron Lett.* **1974**, 29; *J. Am. Chem. Soc.* **1975**, *97*, 4682.
(24) (a) Padwa, A. *Acc. Chem. Res.* **1976**, *9*, 371. (b) Griffin, G. W.; Padwa, A. In *Photochemistry of Heterocyclic Compounds*; Buchardt, O., Ed.; John Wiley and Sons: New York, 1976.

Scheme 5



precursor of the P_4 thiazole transposition product **5**. The concentration of **14**, however, would be expected to be low. This pathway would therefore be expected to be of limited efficiency since azirine **14** would not be able to compete with isothiazole **1** for the incident light. In the absence of other ring expansion pathways, the yield of 5-phenylthiazole **(5)** would be low. In the presence of a suitable base such as TEA, the base would be expected to deprotonate azirine **14**, resulting in its conversion to isocyanide **16**.[25] Reprotonation of **16** at carbon also leads to nitrile ylide **15** and, after cyclization, 5-phenylthiazole **5**, the P_4 phototransposition product. This mechanistic pathway thus explains the observed increase in the yield of thiazole **5** upon addition of TEA to the reaction mixture.

This mechanistic pathway is also consistent with the observed photochemistry of 3-phenylisothiazole **(4)**. Thus, in the absence of an α-H, thioformylvinyl nitrene **17** (Scheme 5), derived from **4**, cannot rearrange to a nitrile. This accounts for our inability to observe a nitrile absorption band in the crude product mixtures. In addition, in the absence of a hydrogen at C_3, the deprotonation−ring opening−cyclization pathway for the formation of the P_4 transposition product, which was available for the conversion of azirine **14** to 5-phenylthiazole **5**, is not available for the conversion of azirine **18** to 2-phenylthiazole **2**. In the case of **4**, the addition of TEA is not expected to enhance the yield of the P_4 phototransposition product. The only phototransposition pathway thus must involve the less efficient photochemical ring opening of azirine **18**, accounting for the low yield of **2**.

Conclusion. Phenylisothiazoles undergo phototransposition via their $S_1(\pi,\pi^*)$ states. Unlike 4-phenylisothiazole (**10**), which transposes exclusively via the N_2-C_3 interchange pathway, 3- and 5-phenylisothiazoles (**4** and **1)** transpose by both the N_2-C_3 interchange pathway and the electrocyclic ring closure−heteroatom migration pathway. In the case of 5-phenylisothiazole (**1)**, the N_2-C_3 interchange pathway is affected by the presence of TEA in the reaction medium and by the solvent polarity. For example, although upon irradiation in benzene **1** transposes only by the electrocyclic ring closure−heteroatom migration pathway, when the photoreaction is carried out in TFE solvent containing TEA **1** transposes regiospecifically by the N_2-C_3 interchange pathway. 3-Phenylisothiazole (**4)** also phototransposes by both transposition pathways, but in this case the product distribution is not affected by the solvent polarity or the presence of TEA.

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Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively. GLC was performed using a 30 m × 0.25 μm Supelcowax 10 bonded phase column. Preparative layer chromatography was carried out on 20 cm × 20 cm glass plates coated with 2 mm Kieselgel 60_{254} (Merck).

Materials. Benzene was purified by being refluxed over calcium hydride followed by fractional distillation. Diethyl ether was purified by being refluxed over a 40% dispersion of sodium in paraffin containing benzophenone until the benzophenone ketyl radical was bright blue followed by fractional distillation. Methanol was purified by being refluxed over magnesium methoxide followed by fractional distillation. 2,2,2-Trifluoroethanol (NMR grade) and triethylamine (99.5%) were obtained from Aldrich Chemical Co. and used as received.

Synthesis of Reactants and Products. Phenylisothiazoles and phenylthiazoles **1**−**5** were synthesized by procedures previously described.[17]

5-Deuterio-3-Phenylisothiazole (4−5d$_1$). 3-Phenylisothiazole (**4**) (0.25 g, 1.44 mmol) was added to CH_3OD (10 mL) containing sodium metal (0.13 g, 5.4 mmol), and the flask was tightly closed and allowed to stand at room temperature in the dark for 5 days. The resulting solution was added to aqueous HCl (5 M, 50 mL), and the mixture was extracted with dichloromethane (3 × 100 mL). The extract was dried (Na_2SO_4) and concentrated to yield a colorless oil (0.25 g) which was distilled (Kugelrohr) to give 5-deuterio-3-phenylisothiazole (**4**-5d$_1$) as a colorless oil: bp (oven temperature) 120 °C (1.5 Torr); 0.22 g (1.36 mmol, 88% yield); ^1H NMR ($CDCl_3$) δ 7.35−7.50 (m, 3H), 7.55 (s, 1H), 7.85−8.05 (2H, m); MS *m*/*z* (%), 162 (100).

4-Bromo-5-phenylisothiazole (6). Bromine (4.5 g, 28.2 mmol) was added dropwise over a period of 30 min to a stirred mixture of 5-phenylisothiazole (**1**), (1.41 g, 8.8 mmol) anhydrous potassium acetate (1.34 g, 14.0 mmol), and glacial acetic acid (30 mL). The reaction mixture was stirred at room temperature overnight and then refluxed for 2 h. The reaction mixture was cooled to room temperature and treated with aqueous sodium bisulfite (33%, 10 mL). The solution was made basic with aqueous sodium hydroxide (20%), extracted with dichloromethane (3 × 80 mL), dried (anhydrous Na_2SO_4), and evaporated to dryness to a yellow solid (2.1 g). The crude product was distilled (Kugelrohr, 130 °C, 0.5 Torr) to yield a colorless liquid that solidified to give 4-bromo-5-phenylisothiazole (**6**) as a white solid (1.9 g, 7.9 mmol, 89.8% yield): mp 50−52 °C; ^1H NMR (200 MHz), $CDCl_3$) δ 8.36 (s, 1H), 7.66−7.58 (m, 2H), 7.52−7.43 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 161.0, 159.5, 129.8, 129.2, 129.0, 128.4, 106.0; MS *m*/*z* (%) 243(4.8), 242(10.4), 241(100). Anal. Calcd for C_9H_6NSBr: C, 45.02; H, 2.52, N, 5.83; Br, 33.28. Found: C, 45.03, H, 2.47; N, 5.79; Br, 33.19.

4-Deuterio-5-Phenylisothiazole (1−4d$_1$). *tert*-Butyllithium (1.7 M in pentane, 4.0 mL, 6.8 mmol) was added dropwise to a stirred solution of 4-bromo-5-phenylisothiazole (**6**) (1.44 g, 6.0 mmol) in anhydrous ether (30 mL) at −110 °C (ethanol/liquid N_2) under argon. After addition was complete, the solution was stirred at −110 °C for 1 h, quenched by the addition of CH_3OD (4.0 mL), and allowed to warm to room temperature. The suspension was filtered, and the filtrate was concentrated. Distillation of the residue (Kugelrohr, 120 °C, 0.5 Torr) gave a colorless liquid that solidified to give 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) as a white solid (0.90 g, 5.56 mmol, 93% yield): mp 47−48 °C; ^1H NMR (200 MHz, $CDCl_3$ δ 8.45 (s, 1H), 7.62−7.57 (m, 2H), 7.46−7.38 (m, 3H); MS *m*/*z* (%), 164 (5), 163 (11), 162 (100), 135 (36).

Irradiation and Analysis Procedures. Photoreactions of phenylisothiazoles **1** and **4** on an analytical scale were monitored by GLC and by IR spectroscopy. To determine the effect of TEA on the photoreactions of **1** and **4** in a particular solvent, two solutions of **1** or **4** (3.0 mL, 2.0 × 10^{-2} M) in benzene, methanol, or TFE in the absence or presence of TEA (1.5 × 10^{-2} M) were placed in quartz tubes (0.7 cm inside diameter × 12 cm long) which were sealed with rubber septae,

purged with argon for 30 min, and irradiated simultaneously in a Rayonet photochemical reactor equipped with a merry-go-round and eight low-pressure Hg lamps.

GLC Analysis. Quantitative GLC analysis of reactant consumption and product formation was accomplished using calibration curves constructed for **1**−**5** by plotting detector responses versus 10 standards of known concentrations. Correlation coefficients ranged from 0.995 to 0.999. At 190 °C **1**−**5** elute in the order 2-phenylthiazole (**3**), 5-phenylisothiazole (**1**), 5-phenylthiazole (**5**), 3-phenylisothiazole (**4**), and 4-phenylthiazole (**2**) with retentions [relative to 5-phenylisothiazole (**1**)] of 0.92, 1.0, 1.14, 1.16, and 1.30, respectively.

IR Analysis. An aliquot (2.0 mL) of the irradiated solution was evaporated under reduced pressure. The residue was dissolved in methylene chloride (0.1 mL), and this solution was allowed to evaporate on a sodium chloride disk. The residual oil was covered with a second disk and the infrared spectrum recorded.

Preparative Scale Irradiations. A solution of the reactant was dissolved in the appropriate solvent and the mixture placed in a quartz tube [1.45 cm inside diameter × 13 cm long (for 10.0 mL) or 2.5 cm inside diameter × 30 cm long (for 50.0 or 90.0 mL)] which was closed with a rubber septum, purged with argon for 30 min, and irradiated in a Rayonet reactor while the solution was continuously purged with a fine stream of argon.

Irradiation of 4-Deuterio-5-phenylisothiazole (1−4d$_1$) in Benzene. 4-Deuterio-5-phenylisothiazole (**1**-4d$_1$) (0.14 g, 0.86 mmol) was dissolved in benzene (50.0 mL) and irradiated in a Rayonet reactor equipped with 16 low-pressure Hg lamps until GLC analysis showed that 97% of **1**-4d was consumed.

An aliquot (0.5 mL) of the resulting solution was evaporated to dryness, redissolved in benzene (0.020 mL), and analyzed by GLC-MS. 4-Deuterio-5- phenylisothiazole (**1**-4d$_1$) exhibited a base peak due to the molecular ion at $m/z = 162$ and a strong signal at $m/z = 135$. 5-Deuterio-4-phenylthiazole (**2**-5d$_1$) exhibited a base peak due to the molecular ion at $m/z = 162$ and an intense signal at $m/z = 135$.

The remaining solution (49.5 mL) was evaporated to dryness, and the residue (0.12 g) was subjected to preparative layer chromatography (silica gel, CH_2Cl_2). The band at R_f 0.75 gave deuterated 3-phenylisothiazole **(4)** as a yellow oil (0.005 g): ^{1}H NMR (200 MHz, $CDCl_3$), δ 8.69 (brs, 1.0H), 7.98−0.790 (m, 2H), 7.61 (d, $J = 4.71$ Hz, 0.1H), 7.50−7.39 (m, 3H); MS *m*/*z* (%), 164 (5.1), 163 (12.2), 162 (100), 61 (26.4), 135 (24.0).

Irradiation of 4-Deuterio-5-phenylisothiazole (1−4d$_1$) in Benzene Containing TEA. 4-Deuterio-5-phenylisothiazole (**1**-4d$_1$) (0.16 g, 0.99 mmol) and TEA 0.5 mL) were dissolved in benzene (50.0 mL) in a quartz tube and treated and irradiated as above until GLC analysis showed that 49% of **1**-4d$_1$ was consumed.

An aliquot (0.5 mL) of the resulting solution was treated and analyzed as above. 4-Deuterio-5-phenylisothiazole (**1**-4d$_1$) exhibited signals *m*/*z* (%), 164 (5.2), 163 (11.4), 162 (100), and 135 (35.8). Deuterated 4-phenylthiazole (**2**-5d$_1$) exhibited signals at *m*/*z* (%), 162 (100), 161 (3.8), 135 (91.6), and 134 (12.9).

The remaining solution (49.5 mL) was evaporated, and the residue (0.16 g) was subjected to preparative layer chromatography (silica gel, CH_2Cl_2). The band at $R_f = 0.32$ gave 4-deuterio-5-phenylthiazole (**5**-4d$_1$) as a yellow oil (0.012 g): ^{1}H NMR (200 MHz, $CDCl_3$), δ 8.73 (s, 1H), 7.59−7.29 (m, 5H); MS *m*/*z* (%), 164 (4.9), 163 (11.6), 162 (100), 135 (85.7), 134 (27.4). The band at $R_f = 0.75$ gave a mixture of 3-phenylisothiazole **(4)** and 4-deuterio-3-phenylisothiazole (**4**-4d$_1$) as a yellow oil (0.006 g): ^{1}H NMR (200 MHz, $CDCl_3$), δ 8.71−8.69 (brs, 1.4H), 7.98−7.90 (m, 2H), 7.61 (d, $J = 4.17$ Hz, 0.6H), 7.50−7.39 (m, 3H); MS *m*/*z* (%), 164 (4.6), 163 (12.9), 162 (100).

Irradiation of 4-Deuterio-5-phenylisothiazole (1−4d$_1$) in TFE. 4-Deuterio-5-Phenylisothiazole (**1**-4d$_1$) (0.032 g, 0.2 mmol) was dissolved in freshly distilled TFE (10.0 mL) and irradiated in a Rayonet reactor equipped with eight low-pressure Hg lamps for 30 min. An aliquot (0.5 mL) of the irradiated solution was evaporated to dryness, redissolved in CH_2Cl_2 (0.02 mL), and analyzed by GLC-MS. The peak due to 4-deuterio-5-phenylisothiazole (**1**-4d$_1$) exhibited signals at *m*/*z* (%), 164 (5.1), 163 (11.2), 162 (100), 135 (36.2). The peak due to 4-deuterio-5-phenylthiazole (**5**-4d$_1$) exhibited signals at *m*/*z* (%), 164 (5.2), 163 (11.4), and 162 (100).

Irradiation of 5-Phenylisothiazole (1) in Diethyl Ether. Trapping of Cyanosulfide 8. 5-Phenylisothiazole (**1**) (0.050 g, 0.31 mmol) was dissolved in freshly distilled diethyl ether (90 mL) and irradiated in a Rayonet reactor equipped with eight low-pressure Hg lamps. TEA (5.0 mL) was added followed by benzyl bromide (0.10 mL, 0.14 g 0.84 mmol). The reaction mixture was allowed to stand overnight at room temperature and filtered, and the filtrate was evaporated to dryness to leave a yellow oil. The combined residue (0.38 g) from two such reactions was subjected to preparative layer chromatography (silica gel, CH_2Cl_2:hexane 6:4). The band at $R_f = 0.35$ gave 2-cyano-1-phenylethen-1-ylbenzyl thioether **(9)** as a slightly unstable yellow oil (0.016 g, 0.064 mmol, 10.3% yield): ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.43−6.00 (m, 5H, 5.44 (s, 1H), 3.88 (s, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 162.1, 136.4, 136.2, 130.7, 128.9, 128.8, 128.5, 128.1, 127.5, 116.6, 97.1, 37.7; MS *m*/*z* (%), 253 (1.0), 252 (2.9), 251 (15.5), 91 (100).

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