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Synthesis of 2*H*-1,2-Benzothiazine 1,1-Dioxides via Heteroannulation Reactions of 2-Iodobenzenesulfonamide with Ketone Enolates under $S_{RN}1$ Conditions[§]

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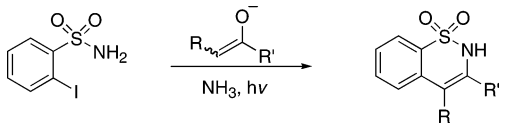

2-Iodobenzenesulfonamide (**1a**) underwent photostimulated $S_{RN}1$ reactions in liquid NH_3 with the potassium enolates derived from acetone, pinacolone, butanone, and 3-methyl-2-butanone to give fair to good yields of 2*H*-1,2-benzothiazine 1,1-dioxides **2**. Reductive dehalogenation of **1a** was found to predominate in photoinduced reactions of **1a** with 3-pentanone, 2-methyl-3-pentanone, and 2,4-dimethyl-3-pentanone, the extent of reduction being proportional to the number of β-hydrogen atoms present in the ketone enolate. Isotopic labeling studies with 2,4-dimethyl-3-pentanone-d_{14} (**24**) confirmed the major role of the β-hydrogens in the reduction process. Reactions of **1a** with cyclopentanone, cyclohexanone, and cyclooctanone enolates afforded new tricyclic benzothiazine derivatives **26**−**29**. Attempts to extend the heteroannulation reaction to the preparation of 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides **3** (R = H, Ph) through reactions of **1a** with *tert*-butyl acetate and ethyl phenylacetate enolates resulted only in hydrodehalogenation of **1a**. However, oxazoline anion **30**, a synthetic equivalent of ethyl phenylacetate, was successfully employed in an alternative $S_{RN}1$-based synthesis of benzothiazine **3** (R = Ph).

Introduction

The synthetic utility of the radical chain nucleophilic aromatic substitution ($S_{RN}1$) reaction is well established and has been the subject of several comprehensive reviews.[1] A particularly useful application of this reaction has been the facile construction of benzo-fused heterocyclic ring systems via reactions of 2-substituted aryl halides with ketone enolates and subsequent cyclodehydration of the intermediate $S_{RN}1$ substitution products as outlined in Scheme 1.

This substitution−cyclization process pioneered by Beugelmans[2] has been applied to the synthesis of indoles,[3] azaindoles,[4] benzofurans,[5] isoquinolones,[6]

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(1) For reviews on $S_{RN}1$ reactions, see: (a) Rossi, R. A.; de Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*; ACS Monograph 178; American Chemical Society: Washington, DC, 1983. (b) Bowman, W. R. *Chem. Soc. Rev.* **1988**, *17*, 283. (c) Rossi, R. A.; Pierini, A. B.; Palacios, S. M. In *Advances in Free Radical Chemistry*; Tanner, D. D., Ed.; JAI Press: Greenwich, CT, 1990; Chapter 5; *J. Chem. Educ.* **1989**, *66*, 720. (d) Norris, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergammon: New York, 1991; Vol. 4. (e) Saveant, J.-M. *Tetrahedron* **1994**, *50*, 10117. (f) Rossi, R. A.; Pierini, A. B.; Penenory, A. B. In *The Chemistry of Functional Groups, Suppl. D, The Chemistry of Halides, Pseudo-halides and Azides*; Patai S., Rappoport, Z., Eds.; Wiley: New York, 1995; Chapter 24. (g) Rossi, R. A.; Pierini, A. B.; Santiago, A. N. *Org. React.* **1999**, *54*, 1−271.

(2) Beugelmans, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 547−556.

(3) (a) Beugelmans, R.; Roussi, G. *J. Chem. Soc., Chem. Commun.* **1979**, 950−951. (b) Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1547−1548. (c) Boujlel, K.; Simonet, J.; Roussi, G.; Beugelmans, R. *Tetrahedron Lett.* **1982**, *23*, 173−176. (d) Beugelmans, R.; Chbani, M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 306−313.

(4) (a) Beugelmans, R.; Boudet, B.; Quintero, L. *Tetrahedron Lett.* **1980**, *21*, 1943−1944. (b) Fontan, R.; Galvez, C.; Viladoms, P. *Heterocycles* **1981**, *16*, 1473−1474. (c) Estel, L.; Marsais, F.; Quéquiner, G. *J. Org. Chem.* **1988**, *53*, 2740−2744.

(5) Beugelmans, R.; Ginsburg, H. *J. Chem. Soc., Chem. Commun.* **1980**, 508−509.

(6) (a) Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729−731. (b) Beugelmans, R.; Ginsburg, H.; Bois-Choussy, M. *J. Chem Soc., Perkin Trans. 1* **1982**, 1149−1152. (c) Beugelmans, R.; Bois-Choussy, M. *Tetrahedron* **1992**, *48*, 8285−8294.

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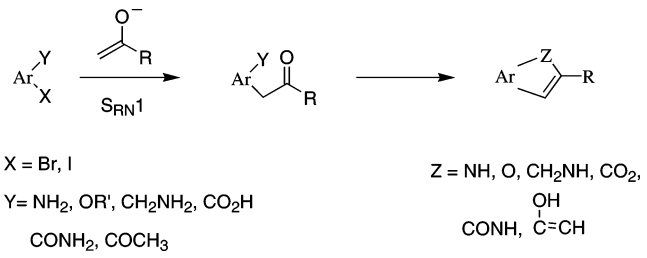
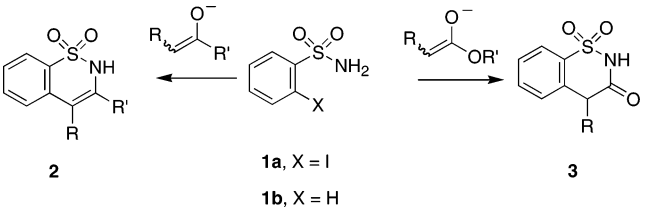
SCHEME 1



SCHEME 2



isocumarones,[6b] isoquinolines,[7] quinolines,[7c] benzo[*c*]phenanthridines,[6b,8] benzo[*c*]phenanthridones,[8] berberines,[6b] 3-benzazepines,[9] 3-benzoxepines,[9] furo[3,2-*h*]quinolines,[10] furo[3,2-*b*]pyridines,[10] benz[*e*]indoles,[11] and benz[*g*]indoles.[11] In light of this synthetic versatility, we became interested in determining if 2-iodobenzenesulfonamide (**1a**) might also participate in photoinduced $S_{RN}1$ reactions with ketone and ester enolates and thus afford convenient access to the biologically important[12] benzothiazine ring system (Scheme 2). Specifically, reactions of **1a** with ketone enolates would furnish either 3-substituted or 3,4-disubstituted-2*H*-1,2-benzothiazine 1,1-dioxides **2**, whereas ester enolates would afford 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides **3**. These heterocyclic annulation reactions represent a potentially convenient one-step approach to the preparation of benzothiazines **2** and **3** that compares very favorably with earlier multistep syntheses of these ring systems.[12a,13] We now report that the success of $S_{RN}1$ reactions of **1a** with ketone enolates does occur but is dependent on the nature of the enolate, with hydrodehalogenation (reduction) of **1a** being a competing side reaction when β-hydrogen atoms are present adjacent to the site of deprotonation of the ketone. With ester enolates, reduction of **1a** becomes the major or exclusive mode of reaction.

Results and Discussion

Photostimulated reactions of **1a** with both ketone and ester enolates were carried out in the presence of 4 equiv of the appropriate potassium enolate generated by means of KNH_2 in liquid NH_3. The results of reactions of ketone enolates with **1a** are summarized in Table 1. In general, enolates derived from methyl ketones reacted cleanly and efficiently with **1a** under the influence of near-UV (350 nm) irradiation to afford good yields (67−90%) of the corresponding benzothiazines **2** (entries 1, 3, and 6). Evidence that these substitution reactions were proceeding via the photoinduced radical-chain $S_{RN}1$ mechanism was provided by the failure of **1a** to react with pinacolone enolate in the absence of illumination (entry 2). In the case of 3-methyl-2-butanone (entry 6) where two different enolates are possible, a single product, **2g**, was obtained in 67% yield from the reaction of **1a** with the enolate formed by deprotonation at C-1. This result is consistent with the estimated equilibrium composition of enolates for 3-methyl-2-butanone which favors the C-1 enolate by a factor of 49:1.[14] The reaction of the enolate mixture from butanone with **1a** afforded benzothiazines **2c** and **2d** in a ratio of 2:1, respectively (entry 4). Similar product mixtures have been reported for $S_{RN}1$ reactions of butanone enolate with other substrates.[5,15] Although it was not possible to achieve separation of regioisomers **2c** and **2d** using the normal workup procedure, pure **2c** was ultimately obtained in 27% yield following selective aerial oxidation of **2d** to the 4-hydroxy compound,[16] which facilitated its separation from **2c** by flash chromatography, vide infra. In contrast to the favorable results obtained with methyl ketone enolates, yields of benzothiazine products were low in reactions with ethyl ketone enolates (entries 7 and 8) where reduction of substrate **1a** to benzenesulfonamide (**1b**) predominated. For example, reaction of **1a** with 3-pentanone afforded 20% of the desired benzothiazine **2f** along with 42% of **1b**. With 2-methyl-3-pentanone, the yield of the expected benzothiazine **2g** was only 9%, while 58% of **1b** was isolated. These results indicate that the reduction of **1a** is favored over the more sterically constrained process (substitution) as the size of the R-groups of the enolate increases. Furthermore, this increase in size corresponds to an increase in the number of β-hydrogens in the enolate, suggesting the involvement of these hydrogens in the reduction process.[17] Another factor contributing to the modest yields of benzothiazines **2f** and **2g** was the difficulty encountered in purifying these compounds due to their tendency to undergo aerial oxidation to the corresponding alcohols **4** and **5**.[18] Small amounts of cyclohexenone **6** and pyridine derivative **7** from dimerization reactions of 3-pentanone and 2-methyl-3-

(7) (a) Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron Lett.* **1982**, *23*, 2313−2314. (b) Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron* **1984**, *40*, 311−314. (c) Beugelmans, R.; Bois-Choussy, M. *J. Org. Chem.* **1991**, *56*, 2518−2522.

(8) Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933−4938.

(9) Beugelmans, R.; Ginsburg, H. *Heterocycles* **1985**, *23*, 1197−1203.

(10) Beugelmans, R.; Bois-Choussy, M. *Heterocycles* **1987**, *26*, 1863−1871.

(11) Beugelmans, R.; Chbani, M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 729−733.

(12) (a) Sianesi, E.; Redaelli, R.; Magistretti, M. J.; Massarani, E. *J. Med. Chem.* **1973**, *16*, 1133−1137. (b) Lombardino, J. G. *Chron. Drug Discovery* **1982**, *1*, 173−200. (c) Camoutsis, C.; Catsoulacos, P. *J. Heterocycl. Chem.* **1992**, *29, 569−570*. (d) Proudfoot, J. R.; Patel, U. R.; Dyatkin, A. B. *J. Org. Chem.* **1997**, *62*, 1851−1853.

(13) (a) Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1971**, *14*, 973−977. (b) Catsoulacos, P. *J. Heterocycl. Chem.* **1971**, *8*, 947−950. (c) Hauser, C. R.; Wantanabe, H.; Mao, C.-L.; Barnish, I. T. *J. Org. Chem.* **1969**, *34*, 919−926.

(14) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 1324−1325.

(15) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 3020−3025.

(16) The facile oxidation of **2d** compared to that of **2c** is probably due to relief of steric interactions between the C-4 methyl group in **2d** and the aryl hydrogen at C-5. This oxidation process likely proceeds via epoxidation of the C-3,4 double bond leading to pyrimidalization of the C-4 carbon.

(17) (a) Bunnett, J. F.; Sundberg, J. E. *J. Org. Chem.* **1976**, *41*, 1702−1706. (b) Semmelhack, M. F.; Bargar, T. M. *J. Org. Chem.* **1977**, *42*, 1481−1482. (c) Wolfe, J. F.; Moon, M. P.; Sleevi, M. C.; Bunnett, J. F.; Bard, R. R. *J. Org. Chem.* **1978**, *43*, 1019−1020. (d) Semmelhack, M. F.; Bargar, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 7765−7774.

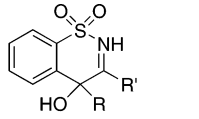
(18) In an identical experiment, when the reaction mixture from **1a** and potassio-2-methyl-3-pentanone was treated with H_2O_2, 18% of pure **5** was obtained.

TABLE 1. Reactions of 1a with Ketone Enolates

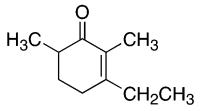
entry	enolate derived from	irradiation time, min	product	yield,[a] %	1b
1	pinacolone	8	**2a** (R = H, R′ = *t*-Bu)	80	
2	pinacolone	15[b]	*c*		
3	acetone	8	**2b** (R = H, R′ = Me)	90	
4	butanone	15	**2c** (R = H, R′ = Et); **2d** (R = R′ = Me)	31;[d] 16	9
5	butanone	15	**2c** (R = H, R′ = Et)	27[e]	
6	3-methyl-2-butanone	8	**2e** (R = H, R′ = *i*-Pr)	67	6
7	3-pentanone	15	**2f** (R = Me, R′ = Et)	20[d,f]	42
8	2-methyl-3-pentanone	15	**2g** (R = Me, R′ = *i*-Pr)	9[d,g]	58
9	2,4-dimethyl-3-pentanone	8			90[h]
10	cyclopentanone	15	**26** -$(CH_2)_3$-	45	10
11	cyclohexanone	15	**27** -$(CH_2)_4$-	45	29
12	cyclooctanone	45	**28** -$(CH_2)_6$-	65[i]	

[a] Yields of pure products after chromatography and recrystallization. [b] Dark reaction. [c] 90% of **1a** recovered. [d] Anaerobic workup. [e] Aerobic workup. [f] Cyclohexenone **6** (10%) and a trace of alcohol **4** were also obtained. [g] Pyridine **7** (1%) and alcohol **5** were also produced. [h] Ketone dimer **8** (86%) was also obtained. [i] Yield of oxidation product **29**.

pentanone, respectively, were also isolated from these reactions.



4, R = CH_3, R' = C_2H_5
5, R = CH_3, R' = $(CH_3)_2CH$



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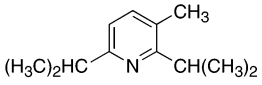
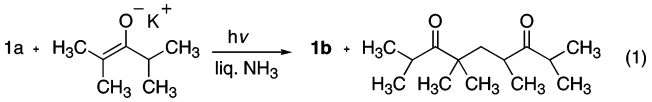


7

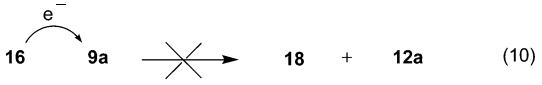
Treatment of **1a** with potassio-2,4-dimethyl-3-pentanone (**10**) under photostimulation led to rapid (8 min) and complete reduction of **1a** to benzenesulfonamide (**1b**) with concomitant generation of an equivalent amount of ketone dimer **8** (eq 1). Similar results were reported by



10 **8** (1)

Bunnett and Sundberg[17a] for the $S_{RN}1$ reaction of iodobenzene (**9a**) with enolate **10**. However, this reaction was extremely sluggish and only 20% of benzene and dimer **8** were obtained after a 3 h irradiation period along with 32% of the expected substitution product and 48% of recovered **9a**. Thus, the rate and extent of reduction of substrates **1a** and **9a** by enolate **10** are markedly different. These differences may be rationalized by consideration of the diverse mechanistic pathways leading to the reduction of these two substrates (Scheme 3). In contrast to the slow, nonchain character previously ascribed to the reduction of **9a**,[17c] we propose that the reduction of **1a** proceeds via a rapid radical-chain process.

The commonly accepted initiation and propagation steps for substitution reactions occurring via the radical-chain $S_{RN}1$ mechanism are shown in eqs 2−5 of Scheme 3. In the case of iodobenzene (**9a**), phenyl radical **13a** generated in eq 3 may either combine with enolate **10**, ultimately leading to substitution product **15** (eqs 4, 5), or abstract a β-hydrogen atom from enolate **10** to yield the reduction product benzene (**17**), as shown in eq 6. On the other hand, in the reaction of **1a** with enolate **10**, the more sterically constrained benzenesulfonamide radical **13b** apparently reacts exclusively by β-hydrogen atom abstraction from **10** to afford benzenesulfonamide (**1b**) and enolate radical anion **16** (eq 6). At this point, the different rates of reduction of iodobenzene (**9a**) and 2-iodobenzenesulfonamide anion (**9b)** may be rationalized in terms of their ability to accept an electron from radical anion **16**. The slow reduction of **9a** has been attributed to the reluctance of resonance-stabilized radical anion **16** to transfer an electron to the π-system of iodobenzene (**9a**) to generate radical anion **12a** (eq 10) through which



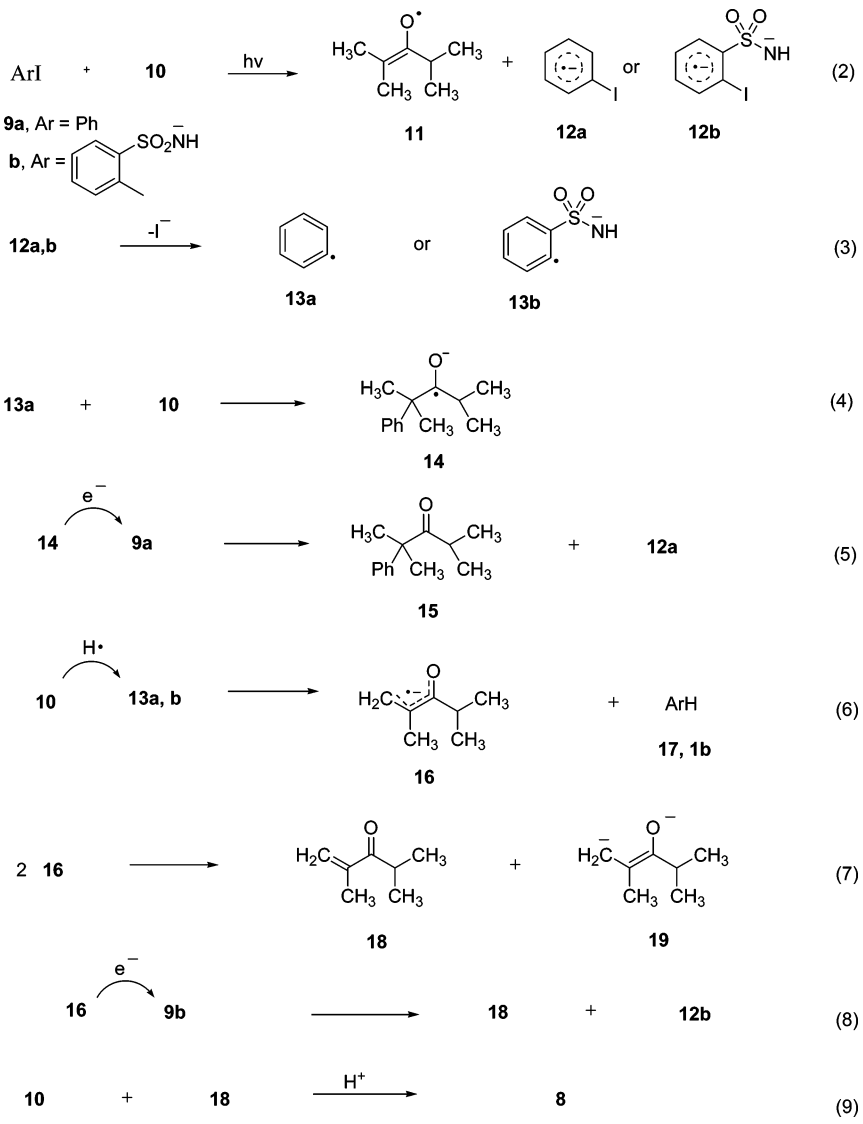
16 **9a** **18** + **12a** (10)

reduction may occur via a radical chain, i.e., eqs 3, 6, and 10. Rather, it was postulated that **16** alternatively undergoes a chain-breaking disproportionation reaction to provide enone **18** for subsequent Michael reaction with enolate **10** to give ketone dimer **8**[17c] (eqs 7, 9). In contrast to **9a**, the more easily reducible aryl ring of **9b** may accept an electron from **16** according to eq 8. This chain propagating step provides both enone **18**, required for the production of dimer **8**, and radical dianion **12b** needed to continue the reduction cycle (eqs 3, 6, and 8). Thus, the reduction of **9b** and formation of **18** are both part of the same rapid, radical-chain process. Evidence for such radical-chain character in the reduction mechanism was obtained when the reaction of **1a** with enolate **10** was severely inhibited by the presence of 10 mol % of the radical scavenger di-*tert*-butyl nitroxide (DTBN), resulting in the recovery of 88% of **1a**.

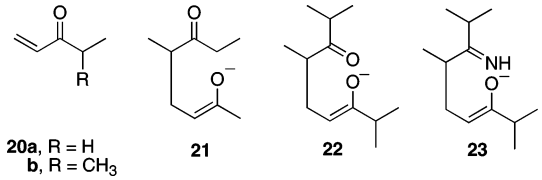
It is likely that ketone dimerization products **6** and **7** obtained in the reactions of **1a** with 3-pentanone and 2-methyl-3-pentanone, respectively, (entries 7 and 8, Table 1) also arise via mechanisms that feature Michael addition of the enolate to the corresponding enone **20a,b**[19] as the key step. Subsequent intramolecular aldol condensation of Michael adduct **21** from 3-pentanone and

(19) It is postulated that enones **20a,b** likely arise via electron-transfer steps analogous to step 7 of Scheme 3.

SCHEME 3



20a followed by dehydration would yield cyclohexenone **6**. The genesis of pyridine derivative **7** may be envisioned in a similar sequence of steps that include condensation of NH_3 with the Michael addition product **22** to give imine **23** followed by cyclodehydration and aerial oxidation of the penultimate dihydropyridine intermediate.



To substantiate the role of β-hydrogen atom abstraction in the reduction of **1a** with enolate **10** and to uncover other potential hydrogen atom sources, a series of deuterium labeling experiments was conducted. The results of this study are summarized in Table 2. Irradiation of **1a** in the presence of the potassium enolate derived from 2,4-dimethyl-3-pentanone-d_{14} (**24**)[20] in liquid NH_3 for 30 min afforded a 55% isolated yield of benzenesulfonamide (**1b**), which by mass spectral analysis was found to be 80% d_1 and 20% d_0 (entry 1). The location of the incorporated deuterium was shown by ^{13}C NMR and ^2H NMR to be exclusively *ortho* to the sulfonamide function. These results show that intermolecular β-hydrogen atom transfer from the enolate is the major but perhaps not the only mode of reduction. Although the reduction of aryl radicals via hydrogen atom transfer

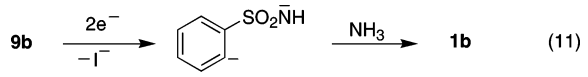
TABLE 2. Deuterium Labeling Studies of the Photostimulated Reduction of 1a

entry	aryl halide	enolate from	solvent	% d_1[a]
1	**1a**	$[(CD_3)_2CD]_2C{=}O$	NH_3	80
2	**1a**	$[(CH_3)_2CH]_2C{=}O$	ND_3	5
3	**1a**, *N*-d_2[b]	$[(CH_3)_2CH]_2C{=}O$	ND_3	5[c]
4	**1a**, *N*-d_2[b]	$[(CH_3)_2CD]_2C{=}O$	ND_3	6[c]

[a] Based on the ratio of $C_6H_5^{\bullet+}$ to $C_6H_4D^{\bullet+}$ from the mass spectrum after correction for the ^{13}C natural abundance. [b] Generated in situ from 2-iodobenzenesulfonyl chloride and ND_3. [c] ^2H NMR analysis showed deuterium was not incorporated exclusively at the *ortho* position.

(20) Compound **24** was prepared in 95% purity (98 atom %D) in three steps from 2-propanol-d_8.

from solvents such as THF,[21] DMSO,[22] and CH_3CN[22] in $S_{RN}1$ reactions has been documented in studies using deuterated solvents, no such experimental evidence has been offered for reduction through abstraction of hydrogen atoms from liquid NH_3. A two-electron reduction of 2-iodobenzenesulfonamide anion (**9b**) and subsequent protonation by NH_3 as proposed previously by Bunnett[17a] was deemed a plausible reduction pathway for the production of nondeuterated benzenesulfonamide (**1b**) (eq 11).

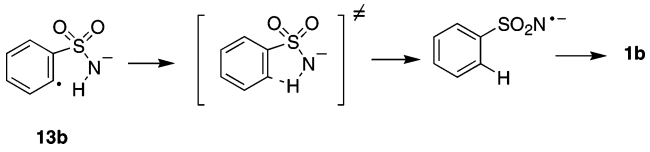


(11)

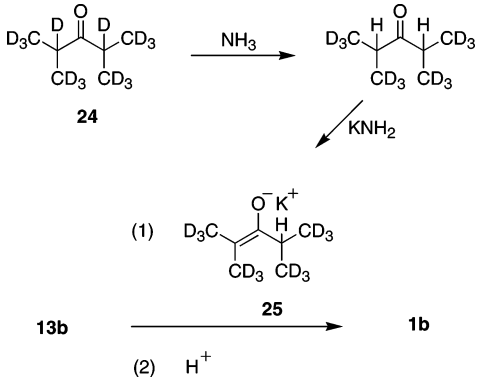
We also considered other possible hydrogen atom donors that might be involved in the formation of **1b**. It is conceivable that aryl radical **13b** might abstract a hydrogen atom from the adjacent sulfonamide group via a five membered cyclic activated complex to ultimately yield **1b** (Scheme 4). Based on the likelihood of hydrogen−deuterium exchange between the NH_3 solvent and the α-deuterium atoms of deuterated ketone **24**, another reduction scheme involving hydrogen atom transfer from the un-ionized α-carbon of enolate **25** might account for the formation of **1b** (Scheme 5). To test these hypotheses, further labeling experiments were conducted (Table 2). The reaction of sulfonamide **1a** with unlabeled enolate **10** in liquid ND_3 resulted in 5% of deuterium incorporation (entry 2), indicating that a two-electron reduction mechanism could be a possible minor source of **1b**. However, because of the possibility of deuterium exchange between ND_3 and the sulfonamide hydrogens or the α-protons of the ketone prior to the reduction, this experiment can neither exclude nor support mechanisms featuring deuterium atom transfer from those sources. Therefore, two more labeling experiments were performed. Reaction of *N*-d_2-2-iodobenzenesulfonamide with unlabeled enolate **10** in liquid ND_3 (entry 3) again afforded only 5% of **1b**-d_1 and thus did not provide evidence for intramolecular hydrogen atom transfer from the sulfonamide function. Similarly, treatment of *N*-d_2-2-iodobenzenesulfonamide with 2,4-dideuterio-2,4-dimethyl-3-pentanone enolate in liquid ND_3 (entry 4) ruled out a reduction mechanism involving the α-hydrogen atom of the enolate and confirms the results of the initial labeling study that it is the β-hydrogens of the enolate that are primarily involved in the reduction of **1a**. At this time, we must conclude that small amounts of impurities with labile hydrogen atoms likely account for the nondeuterated benzenesulfonamide obtained in the reaction of **1a** with the perdeuterated enolate of **24**.

Enolate anions derived from cyclic ketones have been reported to participate in photoinduced $S_{RN}1$ reactions with a variety of aryl halides to afford good to excellent yields of substitution products.[3a,4b,6a,7b,17a,23−25] We were, therefore, interested in determining if sulfonamide **1a** would also function as a suitable substrate in photostimulated reactions with cyclic ketone enolates. We have now found that **1a** undergoes substitution−cyclization

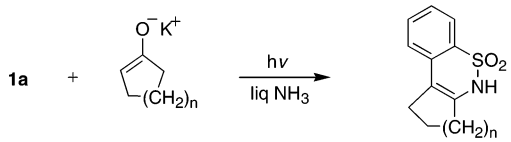
SCHEME 4



SCHEME 5



reactions with potassium enolates derived from cyclopentanone, cyclohexanone, and cyclooctanone under photostimulation to afford fair to good yields of tricyclic 1,2-benzothiazine derivatives **26**−**28**, respectively (eq 12, entries 10−12, Table 1).



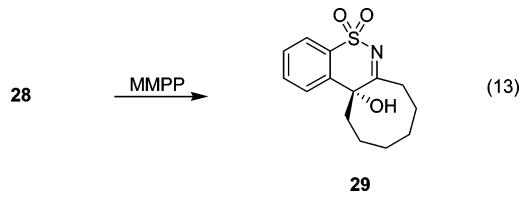
(12)

26, n=1
27, n=2
28, n=4

These new heterocycles have properties that are interesting in their own right. Unlike all other ketone-derived products prepared during the course of this study, which are protonated by the NH_4Cl employed to quench the reaction mixture, compound **26** required acidification of the NH_4Cl solution with 5% HCl to pH 3 for isolation.[26] Heterocycles **27** and **28** are of interest as a result of their sensitivity toward oxidants. It was noted earlier that benzothiazines **2f** and **2g** also exhibited a similar susceptibility toward oxidation. Although compound **27** can be obtained in pure form with some difficulty, the isolation of compound **28** was unsuccessful because of rapid aerial oxidation. Consequently, the yield of **28** was quantified by oxidation to the corresponding alcohol **29** with magnesium monoperoxyphthalate hexahydrate (MMPP) (eq 13). An X-ray crystal structure was determined to verify the structure of **29**.

Although substitution was favored over reduction in all reactions of **1a** with cyclic ketone enolates, competing reduction was responsible for the lower yields observed with cyclopentanone and cyclohexanone compared with

(21) Quintard, J.-P.; Hauvette-Frey, S.; Pereyre, M. *J. Organomet. Chem.* **1978**, *159*, 147−164.
(22) M'Halla, F.; Pinson, J.; Saveant, J. M. *J. Electroanal. Chem.* **1978**, *89*, 347−361.
(23) Komin, A.; Wolfe, J. F. *J. Org. Chem.* **1977**, *42*, 2481−2486.
(24) Hay, J. V.; Wolfe, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 3702−3706.
(25) Nair, V.; Chamberlain, S. D. *J. Am. Chem.. Soc.* **1985** *107*, 2183−2185.
(26) Compound **26** was readily soluble in a 10% $NaHCO_3$ solution.



(13)

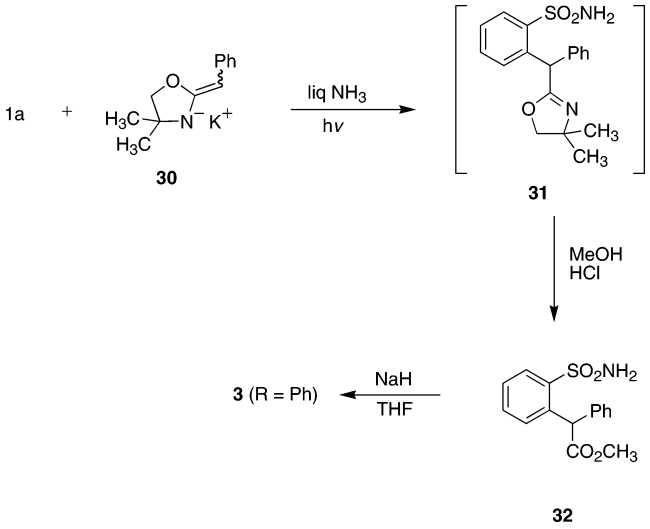
cyclooctanone (Table 1). Presumably, cyclooctanone enolate is a poor hydrogen atom donor since no benzenesulfonamide could be detected in its reaction with **1a**. This predominance of substitution in reactions of **1a** with cyclic ketone enolates was somewhat surprising in light of an earlier report by Beugelmans[6a] that the analogous $S_{RN}1$ reaction of 2-bromobenzamide with cyclohexanone enolate favored reduction over substitution by a 2:1 ratio.

In contrast to the efficient synthesis of 1,2-benzothiazine 1,1-dioxides achieved using methyl and cyclic ketones, attempts to extend this reaction to the preparation of 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides **3** via reactions of **1a** with ester enolates were unsuccessful. Photostimulation of **1a** in the presence of the potassium enolate of either *tert*-butyl acetate or ethyl phenylacetate resulted in the reduction of **1a**, and none of the expected benzothiazine products **3** (R = H) or **3** (R = Ph) were obtained. However, we were able to prepare benzothiazine **3** (R = Ph) by an alternative route starting with potassio-2-benzyl-4,4-dimethyl-2-oxazoline (**30**)[27] as a ethyl phenylacetate enolate equivalent as outlined in Scheme 6. Substrate **1a** underwent photoassisted $S_{RN}1$ aromatic substitution in the presence of 3 equiv of anion **30** to yield an inseparable mixture of **31** and oxazoline ring opened products derived from **31** (^{1}H NMR analysis), along with 27% of benzenesulfonamide (**1b**). Methanolysis of this mixture afforded a 25% yield of methyl ester **32** from which benzothiazine **3** (R = Ph) was obtained through cyclization by means of NaH in THF.

Conclusions

In the present study, we report a convenient and efficient synthesis of certain 3-substituted-2*H*-1,2-benzothiazine 1,1-dioxides **2** involving photoinduced $S_{RN}1$ reactions of 2-iodobenzenesulfonamide (**1a**) with methyl ketone enolates in liquid NH_3. This heteroannulation process was also applied to the preparation of the previously unknown tricyclic heterocycles **26**−**28** from reactions of **1a** with cyclic ketones. Hydrodehalogenation of **1a** was found to compete with substitution in reactions with acyclic ketone enolates possessing β-hydrogen atoms, the extent of reduction being proportional to the number of β-hydrogens present in the enolate. The photostimulated reaction of **1a** with potassio-2,4-dimethyl-3-pentanone resulted in rapid and complete reduction of **1a** via a radical-chain mechanism featuring β-hydrogen atom transfer from the ketone enolate to the intermediate aryl radical. Attempts to prepare 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides **3** (R = H, Ph) through reactions of **1a** with potassium ester enolates derived from *tert*-butyl acetate and ethyl phenylacetate, respectively, were unsuccessful and resulted only in the reduction of **1a**.

SCHEME 6



However, the preparation of benzothiazine **3** (R = Ph) was accomplished by employing the oxazoline ester equivalent **30** of ethyl phenylacetate in an $S_{RN}1$ reaction with **1a** followed by cyclization of the resulting substitution product **32**.

Experimental Section

^{1}H and ^{13}C NMR spectra were measured at either 270 or 400 MHz. Chemical shift values are reported relative to TMS (^{1}H) or NMR solvent (^{13}C), either $CDCl_3$ (77.0 ppm) or acetone-d_6 (206.0 ppm). ^{2}H NMR spectra were recorded at 200 MHz, and deuterium chemical shifts are referenced to acetone-d_6 (2.04 ppm). Photostimulated reactions were carried out in an inert atmosphere using a Rayonet RPR-240 photoreactor equipped with four 12.5 W lamps emitting maximally at 350 nm. Flash chromatography was performed using 230−400 mesh Kiesegel 60 silica gel. Unless otherwise stated, all chemical reagents from commercial sources were used as received. Di-*tert*-butyl nitroxide was prepared from 2-methyl-2-nitropropane as previously described.[28]

General Procedure for Photostimulated Reactions of 2-Iodobenzene-sulfonamide (1a)[29] in Liquid NH_3. 3-*tert*-Butyl-2*H*-1,2-benzothiazine 1,1-Dioxide (2a). Anhydrous NH_3 was condensed under nitrogen flow into a vacuum jacketed photoreaction tube equipped with a metal stirring bar and sidearm adapter surmounted by a dry ice condenser and stopper. A catalytic quantity of ferric nitrate was then added, followed by the portionwise addition of potassium metal (2.21 g, 56.5 mmol). After the dark blue color was discharged, pinacolone (4.25 g, 42.4 mmol) was added via syringe and the solution was stirred for 5 min. The lights of the photoreactor were then turned on and **1a** (3.00 g, 10.6 mmol) was added as a solid in portions. The slightly heterogeneous mixture was then irradiated for 8 min. The resulting homogeneous reaction mixture was quenched by pouring slowly (caution!) over excess solid NH_4Cl in a 2-L beaker and the NH_3 was allowed to evaporate overnight. The solid residue was partitioned between CH_2Cl_2 and H_2O and the separated aqueous layer was extracted twice more with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography of the residue with hexanes−EtOAc (7:3) and recrystallization from CCl_4 gave 2.0 g (80%) of (**2a**), mp 193−195 °C, (lit.[30] mp 196−199 °C).

(27) Wong, J.-W.; Natalie, K. J.; Nwokogu, G. C.; Pisipati, J. S.; Flaherty, P. T.; Greenwood, T. D.; Wolfe, J. F. *J. Org. Chem.* **1997**, *62*, 6152−6159.

(28) Hoffman, A. K.; Feldman, A. M.; Geblum, E.; Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639−646.

(29) Leffler, J. E.; Jaffe, H. *J. Org. Chem.* **1975**, *40*, 797−799.

3-Methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (2b). Flash chromatography of the oily reaction mixture with $CHCl_3$−EtOAc (4:1) followed by recrystallization from $CHCl_3$−hexane afforded colorless crystals of **2b**, mp 110−112 °C. IR (KBr) 3300−3100, 1665, 1425, 1315, 1180, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 6.04 (s, 1H), 7.13 (br s, 1H), 7.30−7.87 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.9, 105.3, 121.2, 126.4, 126.6, 130.1, 132.2, 133.7, 137.0; MS (70 eV) *m/z* (rel intensity) 195 (100), 130 (100), 117 (80), 90 (20); HRMS calcd for $C_9H_9NO_2S$ 195.0354, found 195.0351.

3-Ethyl-2*H*-1,2-benzothiazine 1,1-Dioxide (2c) and 3,4-Dimethyl-2*H*-1,2-benzothiazine 1,1-Dioxide (2d). Following flash chromatography with $CHCl_3$, 1.2 g of an inseparable solid mixture of **2c** and **2d** was obtained. ^1H NMR analysis of the mixture indicated a ratio of 2:1 for 183c:184c. HR-GCMS calcd for $C_{10}H_{11}NO_2S$ 209.0510, found 209.0510 for **2c** and 209.0498 for **2d**. Further elution with $CHCl_3$−EtOAc (4:1) afforded 0.15 g (9%) of benzenesulfonamide, mp 150−152 °C. In an identical experiment, when the crude solid reaction mixture was pulverized and exposed to the air for 12 h, subsequent flash chromatography with $CHCl_3$−EtOAc (9:1) and recrystallization from CCl_4 gave 0.60 g (27%) of **2c** as colorless crystals, mp 116.5−118 °C. IR (KBr) 3225, 1660, 1425, 1315, 1170, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, 7.5 Hz, 3H), 2.40 (q, J = 7.5 Hz, 2H), 6.02 (s, 1H), 7.24−7.69 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.3, 27.2, 103.9, 121.2, 126.6, 130.5, 132.1, 133.7, 142.2; MS (70 eV) *m/z* (rel intensity) 209 (92), 194 (2), 144 (25), 130 (100). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.30; H, 5.28; N, 6.66.

3-(1-Methylethyl)-2*H*-1,2-benzothiazine 1,1-Dioxide (2e). Following flash chromatography using hexanes−EtOAc (4:1) and recrystallization from hexanes−EtOAc (6:1), 1.59 g (67%) of **2e**[30] was obtained as small colorless prisms, mp 107.5−109 °C. ^{13}C NMR ($CDCl_3$) δ 20.3, 33.2, 102.9, 121.0, 126.6, 126.8, 130.7, 131.9, 133.7, 146.2. The eluent was changed to hexanes−EtOAc (1:1) and 0.1 g (6%) of benzenesulfonamide was obtained as a light tan solid, mp 150−152 °C.

3-Ethyl-4-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (2f). The residue from evaporation of the NH_3 was extracted first with hexane and then with CH_2Cl_2. The hexane extract was concentrated in vacuo to yield an oil that was chromatographed with hexanes−EtOAc (5:1) to afford 0.17 g of a yellow oil, which was distilled in a Kugelrohr apparatus at 40−45 °C (0.5 mm) to give 0.10 g of (±)-3-ethyl-1,6-dimethyl-2-cyclohexene-1-one (**6**), which was 99% pure by GPC analysis. IR (thin film) 3050−2900, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.6 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.60 (m, 1H), 1.74 (t, J = 1.5 Hz, 3 H), 1.92−2.33 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 10.6, 11.7, 15.7, 28.2, 49.8, 129.6, 159.0, 202.0; MS (70 eV) *m/z* (rel intensity) 152 (46), 137 (8), 123 (4), 110 (100), 67 (71). Concentration of the CH_2Cl_2 extract followed by flash chromatography of the resulting solid with hexanes−EtOAc (2:1) afforded 0.47 g (20%) of **2f**, mp 130.5−132 °C. IR (KBr) 3100−3350, 1655, 1425, 1320, 1180, 785 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 2.15 (s, 3H), 2.44 (q, J = 7.5 Hz, 2H), 6.97 (br s, 1H), 7.38−7.87 (m, ArH, 4H); ^{13}C NMR ($CDCl_3$) δ 11.7, 13.4, 25.8, 109.9, 121.1, 124.3, 126.5, 131.9, 135.4, 137.1; MS (70 eV) *m/z* (rel intensity) 223 (100), 144 (57), 104 (35), 77 (27), 56 (33); HRMS calcd for $C_{11}H_{13}NO_2S$ 223.0667, found 223.0681. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.20; H, 5.90; N, 6.27. Found: C, 58.94; H, 5.90; N, 6.20. The eluent was then changed to CH_2Cl_2-EtOAc (1:1) and a trace of alcohol **4**, followed by 0.70 g (42%) of benzenesulfonamide (**1b**) were obtained.

When this reaction was repeated and the crude reaction mixture was pulverized and exposed to the air for 24 h, 0.29 g (12%) of (±)-3-ethyl-4-hydroxy-4methyl-4*H*-1,2-benzothiazine 1,1-dioxide (**4**), mp 160−161 °C, was isolated by flash chromatography. IR (KBr) 3560, 1670, 1320, 1205, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H), 1.66 (s, 3H), 2.90−2.96 (m, 3H), 7.44−7.80 (m, 4H); ^{13}C NMR (acetone-d_6) δ 9.3, 28.2, 30.6, 124.8, 124.9, 128.9, 132.5, 133.2; MS (CI mode) *m/z* (rel intensity) 240 (45), 222 (100), 120 (15), 105 (40). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85. Found: C, 55.18; H, 5.46; N, 5.81.

3-(1-Methylethyl)-4-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (2g). The liquid NH_3 solution was evaporated to a volume of ca. 10 mL and 250 mL of hexane was added cautiously and then heated on a steam bath to remove the remainder of the NH_3. The hexane solution was decanted and combined with a second hexane wash of the salts. Concentration of the hexane solution gave a brown oil that was dissolved in 40 mL of CCl_4. The CCl_4 solution was extracted with a 5% HCl solution and the acidic extract was neutralized with 10% NaOH and then extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous K_2CO_3, vacuum filtered through a 1-in. plug of silica gel to remove colored impurities and concentrated. Preparative TLC ($CHCl_3$) gave 0.02 g (1%) of 2,6-(1-methylethyl)-3-methylpyridine (**7**) as the first band, which was 95% pure by GPC analysis. IR (thin film) 1605, 1585, 1485, 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, J = 4.1 Hz, 6H), 1.77 (d, J = 4.2 Hz, 6H), 2.27 (s, 3H), 2.96 (m, J = 4.1 Hz, 1H), 3.20 (m, J = 4.1 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 21.7, 22.6, 31.5, 35.9, 117.1, 126.3, 137.7, 163.6, 163.9; MS (70 eV), *m/z* (rel intensity) 177 (25), 176 (30), 162 (100), 149 (70). The solid residue from the original hexane extraction was extracted with EtOAc and the combined extracts were concentrated to give 1.77 g of an orange solid, which was washed with hot CCl_4 leaving 0.95 g (58%) of crude **1b**, mp 145−150 °C. The CCl_4 solution was concentrated to an orange oil that was chromatographed using CH_2Cl_2−hexane (9:1) to afford 0.23 g (9%) of **2g** as a colorless solid, mp 143−145 °C. IR (KBr) 3300, 1315, 1190, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.9 Hz, 6H), 2.18 (s, 3H), 3.18 (m, J = 6.9 Hz, 1H), 6.90 (br s, 1H), 7.38−7.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.4, 19.4, 29.3, 110.1, 121.1, 124.6, 126.6, 131.8, 132.2, 135.7, 140.0; MS (70 eV) *m/z* (rel intensity) 273 (100), 222 (55), 158 (47), 104 (57), 77 (28); HRMS calcd for $C_{12}H_{15}NO_2S$ 237.0646, found 237.0796. Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.76; H, 6.33; N, 5.91. Found: C, 60.48; H, 6.32; N, 6.01. The eluent was changed to CH_2Cl_2−2% MeOH and 0.09 g of (±)-4-hydroxy-3-(1-methylethyl)-4-methyl-2*H*-1,2-benzothiazine 1,1-dioxide **5**, mp 194−196 °C was obtained. Recrystallization from CCl_4 yielded 0.06 g (2%) of pure **5**, as clear colorless needles, mp 195.5−196.5 °C. IR (KBr) 3535, 1645, 1350, 1180, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 6.7 Hz, 3H) 1.67 (s, 3H), 2.96 (br s, 1H), 3.65 (m, J = 6.7 Hz, 1H), 7.59−7.92 (m, 4H); ^{13}C NMR (acetone-d_6) δ 21.2, 21.4, 32.8, 70.4, 124.6, 126.3, 129.2, 133.6, 143.0, 198.8; MS (CI mode) *m/z* (rel intensity) 254 (60), 236 (100), 222 (10), 212 (17), 120 (20), 105 (60). Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.97; N, 5.53. Found: C, 56.66; H, 5.97; N, 5.47. In a similar reaction, when the orange oil obtained by concentration of the hot CCl_4 extract was dissolved in $CHCl_3$ and stirred for 2 h with a solution of 20 mL of 1% $NaHCO_3$ and 0.5 mL of 30% H_2O_2, 0.49 g (18%) of **5** was obtained following chromatography and recrystallization from CCl_4.

Reaction of 1a with the Enolate Anion Derived from 2,4-Dimethyl-3-pentanone. To a stirred solution of 43.8 mmol of KNH_2 in 500 mL of liquid NH_3 was added 2,4-dimethyl-3-pentanone (4.00 g, 35.1 mmol) followed by **1a** (2.48 g, 8.77 mmol) and the mixture was irradiated for 8 min. The residue obtained upon quenching the reaction and evaporation of the NH_3 was extracted with 300 mL of hexane. Concentration of the hexane solution yielded 2.0 g (86%) of 2,4,4,6,8-pentamethylnonane-3,7-dione (**8**).[17c] Further extraction of the solid residue with hot EtOAc gave 1.48 g (90%) of **1b**, mp 150−152 °C. When this reaction was repeated in the presence of 10 mol % of DTBN, 2.57 g (88%) of **1a** was recovered along with 0.08 g (5%) of **1b** and 0.09 g (4%) of **8**.

(30) Takeuchi, Y.; Liu, Z.; Satoh, A.; Shiragami, T.; Shibata, N. *Chem. Pharm. Bull.* **1999**, *47*, 1730−1733.

Reaction of 1a with the Enolate Derived from 2,4-Dimethyl-3-pentanone-d_{14} (24). To a solution of the potassium enolate of **24** prepared from 9.76 mmol of KNH_2 and **24** (1.00 g, 7.80 mmol) was added **1a** (0.55 g, 1.90 mmol). The mixture was irradiated for 30 min, quenched over NH_4Cl, and worked up as before to afford 0.11 g of **1b**, mp 150−154 °C. The mass spectrum indicated that this compound was 80% d_1 and 20% d_0. The ^2H NMR (acetone) showed only one resonance of δ 7.96 relative to acetone-d_6 as an internal reference.

Reaction of 1a with the Enolate Derived from 2,4-Dimethyl-3-pentanone in Liquid ND_3. To a stirred solution of 5.50 mmol of KND_2 in 50 mL of liquid ND_3 was added 2,4-dimethyl-3-pentanone (0.50 g, 4.38 mmol) followed by **1a** (0.31 g, 1.10 mmol). The reaction mixture was irradiated for 30 min and then quenched by the introduction of excess MeOD. The solution was then transferred to a beaker containing 3 g of NH_4Cl, the ND_3 was allowed to evaporate, and **1b** was isolated as before. The mass spectrum assay indicated it to be 95% d_0 and 5% d_1. The ^2H NMR spectrum showed one weak resonance at δ 7.96 relative to acetone-d_6.

Reaction of *N,N*-Dideuterio-2-iodobenzenesulfonamide with 2,4-Dimethyl-3-pentanone Enolate in Liquid ND_3. 2-Iodobenzenesulfonyl chloride[29,31] (0.40 g, 1.32 mmol) was added to a stirred solution of the enolate prepared from 7.0 mmol of KND_2 and 2,4-dimethyl-3-pentanone (0.50 g, 4.38 mmol) in 50 mL of liquid ND_3 and the resulting reaction mixture was irradiated for 30 min. Excess MeOD was then added and the solution was poured into a beaker containing 3 g of NH_4Cl. The ND_3 was evaporated and the residue was treated as previously described. The benzenesulfonamide thus obtained analyzed 95% d_0 and 5% d_1. Two weak resonances were present in the ^2H NMR spectrum at δ 7.96 and δ 7.64[32] in a ratio of intensities of 2:1, respectively.

Reaction of *N,N*-Dideuterio-2-iodobenzenesulfonamide with the Enolate from 2,4-Dideuterio-2,4-dimethyl-3-pentanone in Liquid ND_3. To a stirred solution of 6.40 mmol of KND_2 in 50 mL of liquid ND_3 was added 2,4-dideuterio-2,4-dimethyl-3-pentanone (0.50 g, 4.38 mmol) followed by 2-iodobenzenesulfonyl chloride (0.33 g, 1.09 mmol) and the mixture was irradiated for 45 min. MeOD was then added and the resulting solution was poured onto 3 g of NH_4Cl contained in a beaker. Evaporation of the ND_3 yielded a solid residue, which was treated as before to obtain benzenesulfonamide that was 94% d_0 and 6% d_1 by mass spectral analysis. The ^2H NMR spectrum consisted of two weak resonances at δ 7.96 and δ 7.64 in a ratio of 3:1.

1,2,3,4-Tetrahydrocyclopenta[*c*][1,2]benzothiazine 5,5-Dioxide (26). The solid residue remaining after evaporation of NH_3 was dissolved in water and 1 g of sodium thiosulfate was added to discharge the iodine color. This solution was then acidified to pH 3 with 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to a brown oil, which was chromatographed using hexanes−EtOAc (6:4). A yellow oil was obtained that crystallized from CCl_4 to give 1.06 g (45%) of **26** as a colorless solid, mp 184−187 °C. An analytical sample was prepared by recrystallization from toluene, mp 186.5−188 °C. IR (KBr) 3175, 1660, 1305, 1160, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (m, 2H), 2.72−2.88 (m, 4H), 7.00 (br s, 1H), 7.28−7.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.5, 29.1, 33.4, 115.6, 122.0, 123.7, 130.1, 132.1, 132.2, 138.4; MS (70 eV) *m/z* (rel intensity) 221 (100), 204 (12), 156 (35), 129 (20), 77 (8). Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.01; N, 6.33. Found: C, 59.61; H, 5.02; N, 6.31. Further elution gave 0.17 g (10%) of benzenesulfonamide, mp 149−152 °C.

7,8,9,10-Tetrahydro-6*H*-dibenzo[*c,e*][1,2]thiazine 5,5-Dioxide (27). The residue, which was still moist with liquid NH_3, was partitioned between water and $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, filtered, and concentrated to an oil that was chromatographed using hexanes−EtOAc (6:4) to obtain 1.13 g (45%) of **27**, mp 146−148 °C, followed by 0.48 g (29%) of benzenesulfonamide. An analytical sample of **27** was prepared by recrystallization from toluene, mp 148.5−150 °C. IR (KBr) 3350−3150, 1650, 1315, 1170, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.40 (m, 2H), 2.50 (m, 2H), 6.98 (br s, 1H), 7.25−7.89 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.2, 24.5, 29.2, 111.9, 121.2, 123.0, 126.5, 131.8, 131.9, 134.4, 134.8; MS (70 eV) *m/z* (rel intensity) 235 (100), 221 (20), 207 (40), 170 (52), 89 (25); HRMS calcd for $C_{12}H_{13}NO_2S$: 235.0667, found 235.0678. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.30; H, 5.60; N, 5.91.

(±)-8,9,10,11-Tetrahydro-11a-hydroxy-7*H*-cycloocta[*c*][1,2]-benzothiazine 5,5-Dioxide (29). The residue was extracted with 400 mL of refluxing hexane. The hexane solution was decanted and concentrated to an oil containing mostly cyclooctanone. The solid residue remaining from the hexane extraction was partitioned between water and CH_2Cl_2. The CH_2Cl_2 solution was separated, dried over Na_2SO_4, filtered, and concentrated to yield 3.03 g of an immobile oil. The oil was dissolved in 120 mL of 80% 2-propanol, 6.55 g (10.6 mmol) of 80% magnesium monoperoxyphthalate hexahydrate was added, and the solution was stirred at room temperature for 4 h and then heated at 40 °C for 4h in an oil bath. The solution was cooled, 3 g of sodium thiosulfate was added, and the solvent was remove in vacuo. The residue was partitioned between 5% $NaHCO_3$ and CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4, filtered, and concentrated to yield 2.40 g of a yellow solid. Flash chromatography of this solid with hexanes−EtOAc (6:4) and recrystallization from CCl_4 gave 1.04 g (35%) of pure **29**, mp 182−185 °C. Concentration of mother liquor and recrystallization from toluene afforded another 0.88 g (30%) of **29**, mp 180−183 °C. An X-ray crystal structure was determined from the crystals of **29** that separated from CCl_4. IR (KBr) 3600−3400, 2970, 1625, 1325, 1175, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23−2.15 (m, 10H), 2.54 (m, 1H), 3.24 (s, 1H), 3.41 (m, 1H), 7.36−7.73 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.8, 25.1, 27.7, 28.0, 36.1, 46.2, 71.8, 124.2, 125.3, 128.5, 131.9, 132.8, 197.9; MS (CI mode) *m/z* (rel intensity) 280 (30), 264 (100), 262 (42). Anal. Calcd for $C_{14}H_{17}NO_3S$; C, 60.18; H, 6.13; N, 5.01. Found: C, 60.15; H, 6.09; N, 4.95.

Reaction of 1a with the Enolate Derived from *tert*-Butyl Acetate. To a stirred solution of KNH_2 prepared by the addition of potassium (1.26 g, 32.6 mmol) to 400 mL of liquid NH_3 was added *tert*-butyl acetate (3.16 g, 27.3 mmol) and **1a** (1.63 g, 5.76 mmol). The heterogeneous mixture was irradiated for 2 h and then poured onto excess NH_4Cl in a beaker. Evaporation of the NH_3 yielded a solid residue to which was added 100 mL of 1 M HCl and the resulting cloudy solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and concentrated to give 1.19 g of a 1:1 solid mixture of **1a**/benzenesulfonamide by ^1H NMR.

Reaction of 1a with the Enolate Derived from Ethyl Phenylacetate. Ethyl phenylacetate (2.32 g, 14.1 mmol) was added to a solution of 17.6 mmol of KNH_2 in 300 mL of liquid NH_3 followed by the addition of **1a** (1.00 g, 3.53 mmol). The heterogeneous mixture was irradiated for 1 h and quenched with NH_4Cl, and the NH_3 was evaporated. The residue was washed with 50 mL of hexanes−ether (4:1) to remove unreacted ester and then dissolved in 100 mL of H_2O containing 1 g of sodium thiosulfate and the solution was acidified to pH 3 with 2 M HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and concentrated to give 0.48 g (87%) of crude benzenesulfonamide containing unreacted **1a**.

Preparation of Methyl α-(2-Sulfamoylphenyl)phenylacetate (32) by the Reaction of 1a with the Anion Derived from 2-Benzyl-4,4-dimethyl-2-oxazoline (30). To a stirred solution of 52.6 mmol of KNH_2 in 800 mL of NH_3 was added the oxazoline (8.00 g, 42.4 mmol) and **1a** (4.00 g,

(31) Chau, M. M.; Kice, J. L. *J. Org. Chem.* **1977**, *42*, 3265−3270.

(32) The source of the small amount of aryl deuterium at δ 7.64 and its position on the sulfonamide ring were not determined.

(33) Sheldrick, G. M. *SHELXTL NT*, version 6.12; Bruker Analytical X-ray Systems: Inc. Madison, WI, 2001.

14.1 mmol). The slightly heterogeneous mixture was irradiated for 30 min, producing a homogeneous green solution. The residue obtained after quenching the reaction with NH_4Cl was suspended in a solution containing 1 g of sodium thiosulfate in 100 mL of H_2O. The mixture was acidified to pH 3 and was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over Na_2SO_4, filtered, and concentrated to an oil that was chromatographed using hexanes−EtOAc (7:3) to give the recovered oxazoline, benzenesulfonamide (0.61 g, 27%) and 2.49 g of a mixture of substitution products resulting from opening of the oxazoline ring. This mixture was treated with refluxing methanolic HCl overnight and concentrated, and the oily residue was chromatographed with CH_2Cl_2−CH_3CN (9:1) to afford 1.04 g (25%) of **32** as a colorless oil that solidified on standing. An analytical sample was obtained by recrystallization from CH_2Cl_2−hexane as white needles, mp 99−101 °C. IR (KBr) 3370, 3280, 1745, 1350, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 4.80 (br s, 2H), 6.18 (s, 1H) 7.26−8.10 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 52.5, 127.6, 128.6, 128.9, 131.6, 132.8, 136.9, 137.5, 140.3, 172.9; MS (CI mode), *m/z* (rel intensity) 306 (15), 289 (100), 274 (20), 246 (30), 225 (25). Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 58.95; H, 4.97; N, 4.58.

4-Phenyl-3,4-dihydro-1,2-benzothiazin-3(2*H*)-one 1,1-Dioxide (**3**, R = Ph). To a slurry of NaH (0.12 g of a 60% dispersion in mineral oil, 3.0 mmol) in 10 mL of THF was added dropwise a solution of **32** (0.30 g, 0.98 mmol) in 20 mL of THF. The resulting solution was stirred for 3 h and cooled to 0°C and 2 M HCl was added cautiously dropwise until pH 1 was achieved. The THF solution was separated and concentrated on a rotary evaporator to a pale yellow oil that was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), and concentrated. The resulting oil was dissolved in 1 mL of ether. The dropwise addition of hexane to the ethereal solution caused crystallization of 0.19 g of **3** (R = Ph), mp 198−200°C. Recrystallization from ether−hexane provided pure **3** (R = Ph) as colorless crystals, 0.15 g (56%), mp 200−201°C. ^1H NMR ($CDCl_3$) δ 4.59 (br s, 1H), 6.02 (s, 1H), 7.14 (m, 2H), 7.36 (m, 3H), 7.69 (t, 1H), 7.85 (t, 1H), 7.98 (d, 1H), 8.16 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 48.6, 123.3, 128.4, 128.7, 129.0, 129.5, 132.4, 133.8, 137.2, 170.3. Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.13. Found: C, 61.39; H, 4.11; N, 5.20.

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Supporting Information Available: X-ray crystallographic data file in CIF format and ORTEP plot for **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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