methods of preparation, and comparison of the obtained data with those presented in literature.

Phosphinites. The phosphinites were prepared from the corresponding alcohols and $(C_6H_5)_2PCl$ according to the procedure described by Koole et al.[1a]

Tetrahydrofurfuryl Diphenylphosphinite. Bp: 154–156 °C (0.01 mm). Yield: 74%. ^1H NMR ($CDCl_3$): δ 1.58–1.97 (m, 4 H, $H_{2'}/H_{3'}$), 3.62–3.94 (m, 4 H, $H_{1'}/POCH_2$), 4.09 (m, 1 H, $H_{4'}$), 7.19–7.58 (m, 10 H, Ar H). ^{13}C NMR ($CDCl_3$): δ 25.4 ($C_{2'}$), 27.7 ($C_{3'}$), 68.0 ($C_{1'}$), 71.0 ($C_{5'}$), 78.1 ($C_{4'}$), 127.9–130.4 (Ar C), 141.8 (ipso C). ^{31}P NMR ($CDCl_3$): δ 115.9.

Cyclopentylmethyl Diphenylphosphinite. Bp: 161–163 °C (0.01 mm). Yield: 65%. ^1H NMR ($CDCl_3$): δ 1.15–1.82 (m, 8 H, cyclopentane H), 2.26 (m, 1 H, $H_{4'}$), 3.71 (dd, 2 H, $POCH_2$), 7.20–7.60 (m, 10 H, Ar H). ^{13}C NMR ($CDCl_3$): δ 25.4 ($C_{1'}/C_{3'}$), 29.3 ($C_{1'}/C_{2'}$), 41.0 ($C_{4'}$), 74.2 ($C_{5'}$), 128.0–130.5 (Ar C), 142.3 (ipso C). ^{31}P NMR ($CDCl_3$): δ 112.2.

Phosphinates. The phosphinates were obtained by oxidation of the corresponding phosphinates. An ozone-oxygen stream was passed through a solution of the phosphinate in dry dichloromethane at 0 °C. After 1 h the solution was sparged with oxygen and allowed to warm to room temperature. Evaporation of the solvent yielded the desired phosphinates, as was confirmed by ^{31}P NMR and elemental analysis.

Tetrahydrofurfuryl Diphenylphosphinate (3a). ^1H NMR (CD_3COCD_3): δ 1.78–2.11 (m, 4 H, $H_{2'}/H_{3'}$), 3.79 (m, 2 H, $H_{1'}$), 4.07 (m, 2 H, $POCH_2$), 4.22 (m, 1 H, $H_{4'}$), 7.55–8.08 (m, 10 H, Ar H). ^{13}C NMR (CD_3COCD_3): δ 27.1 ($C_{2'}$), 29.1 ($C_{3'}$), 68.4 ($C_{1'}$), 69.5 ($C_{5'}$), 78.9 ($C_{4'}$), 130.0–134.2 (Ar C), 142.1 (ipso C). ^{31}P NMR: δ 39.4. Anal. Calcd for $C_{17}H_{19}O_3P$: C, 67.54; H, 6.34. Found: C, 67.48; H, 6.36.

Cyclopentylmethyl Diphenylphosphinate (3b). ^1H NMR: δ 1.03–1.79 (m, 8 H, cyclopentane H), 2.16 (m, 1 H, $H_{4'}$), 3.76 (t, 2 H, $POCH_2$), 7.23–7.81 (m, 10 H, Ar H). ^{13}C NMR: δ 26.2 ($C_{1'}/C_{3'}$), 29.9 ($C_{1'}/C_{2'}$), 41.3 ($C_{4'}$), 70.0 ($C_{5'}$), 129.7–133.8 (Ar C). ^{31}P NMR: δ 38.4. Anal. Calcd for $C_{18}H_{21}O_2P$: C, 71.99; H, 7.05. Found: C, 72.13; H, 6.94.

Solvolysis Experiments. In order to investigate the course of the solvolysis reactions and to allow the determination of the specific rate constants belonging to these reactions, the following typical procedure was employed.

A solution of 16.5 mmol of the desired alkyl diphenylphosphinate in 25 mL of dry CH_3OH was prepared in a 100-mL double-walled reaction vessel, which was connected to a constant-temperature bath with a sufficiently large capacity, ensuring a temperature of 25 ± 0.1 °C.

To eliminate the possibility of a reaction of the phosphinate ester with the solvent, the solution was kept at 25 °C in the reaction vessel overnight. Comparison of the ^{31}P NMR spectra recorded before and after this period of time showed that no reaction had taken place.

To the resulting solution was added 16.5 mmol of freshly prepared $NaOCH_3$ in 25 mL of CH_3OH, leaving an equimolar solution of the alkyl diphenylphosphinate and methoxide. At regular intervals small aliquots of the reaction mixture were taken from the reaction vessel and transferred into a NMR tube equipped with a small reference tube providing an external deuterium lock; the ^{31}P NMR spectrum of the sample was scanned and integrated. In this way the disappearance of the alkyl diphenylphosphinate signal was measured and the specific reaction rate of the solvolysis reaction was determined.

Several experimental runs using different phosphinate and methoxide concentrations were performed in order to appoint the exact reaction order and to exclude any irregularities influencing the accuracy of the determination of the specific rate constant. An analogous procedure was applied for the experimental runs in which both phosphinates were allowed to react simultaneously.

Acknowledgment. This investigation has been supported in part by the Netherlands Foundation for Chemical Research (SON), with financial aid from the Netherlands Organization for Scientific Research (NWO).

Registry No. **1a**, 91237-87-5; **1b**, 91237-90-0; **3a**, 91237-85-3; **3b**, 91237-89-7; $(C_6H_5)_2PCl$, 1079-66-9; tetrahydrofurfurol, 97-99-4; cyclopentylmethanol, 3637-61-4.

Synthesis and Competitive Thermal Transformations of 3-[[2′-(2-Propynylthio)phenyl]amino]-1,2,4-triazines

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Received September 8, 1988

Intramolecular Diels–Alder reactions of 1,2,4-triazines[1] have been shown in extensive studies by our group and others to provide convenient access to a wide array of condensed pyridine, pyrimidine, and pyrazine heterocycles.[2] We have recently applied this concept to the preparation of a series of 6,7-annulated pteridine and deazapteridine derivatives as a part of our program directed toward the synthesis of folate antimetabolites.[3] The investigation described herein was prompted by interest in extending such intramolecular Diels–Alder reactions to the preparation of annulated azepine[4] and thiepin[5] derivatives as potential medicinal agents. Seitz has recently reported that 1,2,4-triazines tethered with simple acetylenic side chains of appropriate length undergo intramolecular Diels–Alder reactions, albeit in very low yield under brutal conditions, to give a variety of azepino-, oxepino- and thiepinopyridines (Scheme I).[2k] We felt that utilization of a side chain incorporating an appropriate pendant group might facilitate the formation of a seven-membered annulated ring by buttressing the dienophilic side chain into a conformation requisite for cycloaddition (i.e., the Thorpe–Ingold effect).[2c,d,6] A benzene ring was chosen as the incorporated pendant group (Scheme II) because of ample precedent for the effectiveness of such a strategy[2c] and because of synthetic expediency. We report herein on an intriguing series of thermal molecular rearrangements observed in the course of an investigation of such a system.

The 3-(methylsulfonyl)-1,2,4-triazines **1**[2g] were treated with 2-aminothiophenol to provide the 3-[(2′-aminophenyl)thio]-1,2,4-triazines **2**. Stirring a THF solution of

(1) For a comprehensive review of heterocyclic azadienes in Diels–Alder reactions, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: New York, 1987.

(2) For references to intramolecular Diels–Alder reactions of monocyclic 1,2,4-triazines, see the following. Dienophilic substituent tethered to positions 3 or 6 (nitrogen extrusion): (a) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1985**, *26*, 2419. (b) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 431. (c) Taylor, E. C.; French, L. G. *Tetrahedron Lett.* **1986**, *27*, 1967. (d) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 2107. (e) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (f) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (g) Taylor, E. C.; Macor J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. (h) Seitz, G.; Dietrich, S. *Arch. Pharm.* **1984**, *317*, 379. (i) Seitz, G.; Gorge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (j) Seitz, G.; Dietrich, S. *Arch. Pharm.* **1985**, *318*, 1048 and 1051. (k) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. Dienophilic substituent tethered to position 5 (nitrile extrusion): (l) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287.

(3) (a) Taylor, E. C.; Warner, J. C.; Pont, J. L. *J. Org. Chem.* **1988**, *53*, 800. (b) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. (c) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 3568.

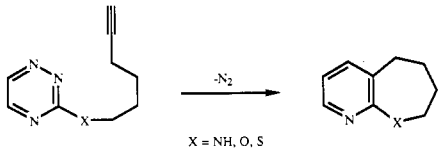
(4) For a comprehensive review of the chemistry of azepines, see: Rosowski, A. In *Azepines, Parts I and II*, Vol. 43 in the series The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C.; Eds.; Wiley-Interscience: New York, 1984.

(5) For a comprehensive review of the chemistry of oxepins and thiepins; see: Rosowski, A. In *7-Membered Heterocyclic Compounds Containing Oxygen and Sulfur*, Vol. 26 in the series The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C.; Eds.; Wiley-Interscience: New York, 1972.

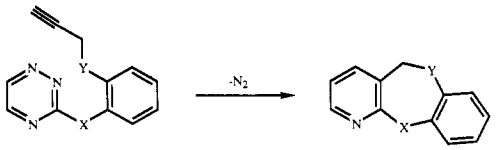
(6) Fischer, K.; Hünig, S. *J. Org. Chem.* **1987**, *52*, 564.

0022-3263/89/1954-1456$01.50/0

Scheme I



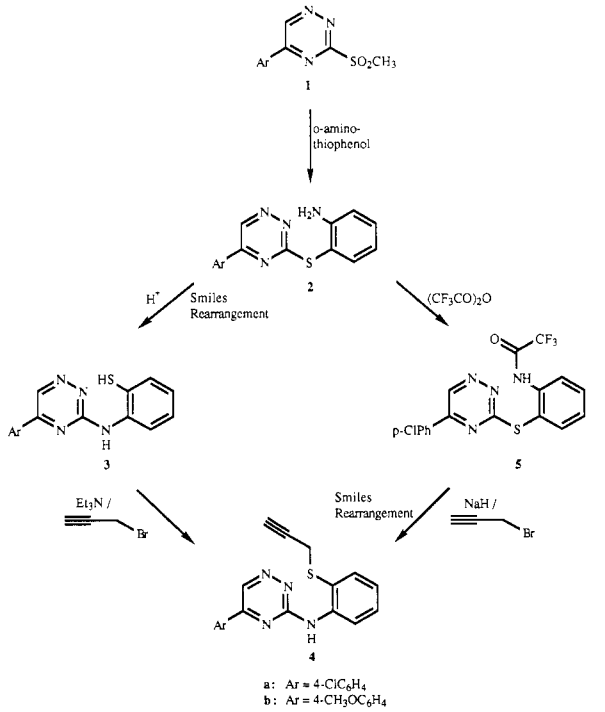
Scheme II



2 in the presence of 1–2 mol % of *p*-toluenesulfonic acid led to an acid-catalyzed Smiles rearrangement[7,8] to give the 3-[(2′-mercaptophenyl)amino]-1,2,4-triazines **3**. Alkylation of **3** with propargyl bromide, after initial deprotonation with triethylamine, smoothly afforded the 3-[[2′-(2-propynylthio)phenyl]amino]-1,2,4-triazines **4**. An alternate route to **4a** (Ar = 4-ClC_6H_4) involved conversion of the precursor **2a** to its trifluoroacetyl derivative **5**, followed by deprotonation of **5** with sodium hydride in the presence of propargyl bromide; an in situ Smiles rearrangement, sulfur alkylation, and detrifluoracetylation gave **4a** (Scheme III).

Heating the dienophile-tethered species **4** in refluxing bromobenzene (bp 156 °C) over the course of 2–5 days (consumption of **4** was followed by TLC) afforded the anticipated fused 1,5-benzothiazepines **6**,[9] but in yields that were consistently less than 5%. The major reaction products were the pyrido[3,2-*b*][1,4]benzothiazines **7**[10] and the 3-(2*H*-1-benzothiopyran-8-ylamino)-1,2,4-triazines **8**. Plausible mechanisms for the formation of **7** and **8** involve a series of thermal rearrangements that have been previously observed for simple propargyl phenyl sulfides (Scheme IV).[11] Compounds **7** presumably arise via initial "thiopropynylic" rearrangement of the propynylthio precursors **4** to the corresponding allenes **9**, followed by an intramolecular Diels–Alder reaction across the internal double bond of the allene functionality and final aromatization of the cycloaddition products **10**. We suggest that the formation of **8** involves an initial thio-Claisen rearrangement to the allene intermediates **11**. Subsequent aromatization to **12**, [1,5]-sigmatropic shift to **13**, and 6π electrocyclic ring closure then leads to **8**. Whether these suggested reaction pathways are unimolecular processes is not clear; Kwart, for example, has shown that for allyl phenyl sulfides, analogous thermal rearrangements proceed through both unimolecular and bimolecular pathways.[12] In retrospect, it is not unreasonable that formation of **7** and **8**, involving six-membered transition states, is preferred to formation of the Diels–Alder product **6**, which

Scheme III



proceeds through an entropically less favorable seven-membered transition state.

Experimental Section

General. Melting points are uncorrected and were determined in open capillary tubes on a Thomas-Hoover apparatus. Infrared data were obtained from a Perkin-Elmer 1320 infrared spectrometer. ^1H and ^{13}C NMR data were obtained with a General Electric QE300 300 MHz instrument, and chemical shifts are reported in ppm downfield with residual solvent as internal standard. Mass spectral data were obtained by Dr. Dorothy Little on a Kratos MS50TC spectrometer. Elemental analyses were performed by Eli Lilly and Co., Indianapolis, IN. Column chromatography was performed on Merck silica gel 60 (240–400 mesh). Preparative TLC was carried out on Analtech silica gel GF uniplates (1500 μm).

Materials. Commercial reagents were utilized without further purification. Anhydrous solvents were distilled before use—tetrahydrofuran from benzophenone ketyl; methylene chloride from calcium hydride.

3-[(2′-Aminophenyl)thio]-5-(4′-chlorophenyl)-1,2,4-triazine (2a). A mixture of 5-(4′-chlorophenyl)-3-(methylsulfonyl)-1,2,4-triazine (**1a**)[2g] (3.34 g, 12.39 mmol) and 2-aminothiophenol (3.10 g, 24.79 mmol) in anhydrous THF (95 mL) was stirred under nitrogen for 6 h. After this period, the reaction mixture was cooled (ice bath) and filtered and the collected solid was washed with cold THF to provide **2a** (2.39 g, 61%) as yellow needles, mp 165–165.5 °C: IR (KBr) 3440, 3340, 1620, 1595, 1540, 1485, 1445, 1310, 1290, 1235, 1185, 1165, 1100, 1090, 1015, 840, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.38 (s, 1 H), 7.95 (d, J = 8.6 Hz, 2 H), 7.54–7.51 (m, 1 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.34 (t, J = 8.1 Hz, 1 H), 6.90–6.81 (m, 2 H), 4.34 (bs, 2 H). Anal. Calcd for $C_{15}H_{11}N_4SCl$: C, 57.23; H, 3.52; N, 17.80; S, 10.19; Cl, 11.26. Found: C, 57.43; H, 3.60; N, 17.95; S, 10.38; Cl, 11.43.

3-[(2′-Aminophenyl)thio]-5-(4′-methoxyphenyl)-1,2,4-triazine (2b) was prepared as above for **2a** from 5-(4′-methoxyphenyl)-3-(methylsulfonyl)-1,2,4-triazine (**1b**)[3b] (1.92 g, 7.25 mmol) and 2-aminothiophenol (1.80 g, 14.49 mmol); yield of pale yellow flakes, 1.12 g (50%); mp 147–149 °C: IR (KBr) 3420, 3330, 1610, 1585, 1545, 1510, 1480, 1440, 1410, 1310, 1260, 1240, 1215, 1190, 1085, 1035, 975, 840, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.32 (s, 1 H), 7.98 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.32 (t, J = 6.8 Hz, 1 H), 7.01–6.97 (m, 2 H), 6.88–6.79 (m, 2 H), 4.34 (bs, 2 H), 3.89 (s, 3 H); HRMS calcd for $C_{16}H_{14}N_4OS$ m/z 310.0888, found m/z 310.0880. Anal. Calcd for $C_{16}H_{14}N_4OS$: C, 61.92; H,

(7) For a review of the Smiles rearrangement, see: Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1971**, *18*, 99.

(8) For examples of acid-catalyzed Smiles rearrangements of 1,3,5-triazines, see: Harayama, T.; Okada, K.; Sekiguchi, S.; Matsui, K. *J. Heterocycl. Chem.* **1970**, *7*, 981.

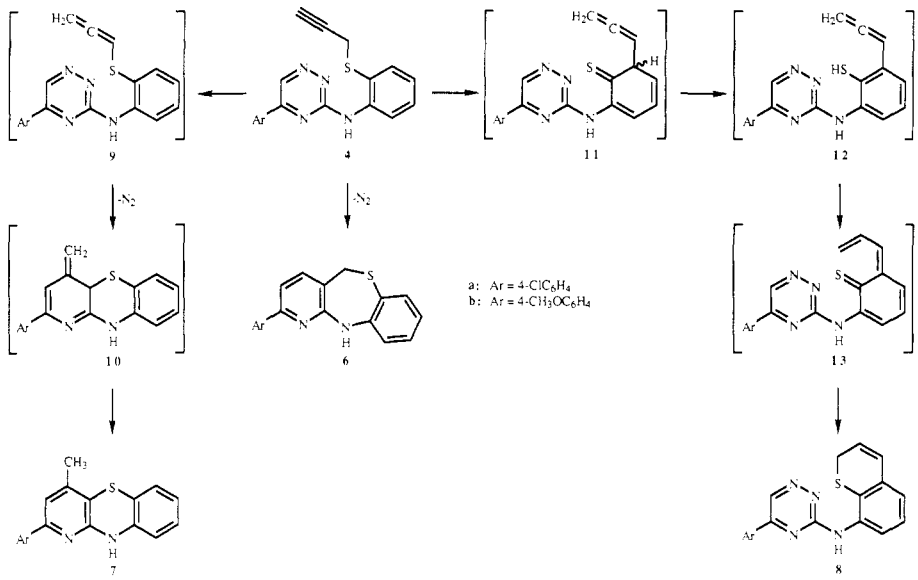
(9) The parent 5,11-dihydropyrido[3,2-*c*][1,5]benzothiazepine has been prepared from 2-chloro-3-(chloromethyl)pyridine and 2-aminothiophenol by Gadient, F.; Jucker, E.; Lindenmann, A.; Taeschler, M. *Helv. Chim. Acta* **1962**, *217*, 1860.

(10) N^{10} derivatives of 10*H*-pyrido[3,2-*b*][1,4]benzothiazines are currently in clinical use as antihistamic, antitussive, and antiemetic agents. See (a) Pasutto, F. M.; Knaus, E. *Can. J. Chem.* **1979**, *57*, 2371. (b) Schuler, W. A.; Klebe, H. *Liebigs Ann. Chem.* **1962**, 172. (c) Yale, H. L.; Sowinski, F. *J. Am. Chem. Soc.* **1958**, *80*, 1651.

(11) Kwart, H.; George, T. J. *J. Chem. Soc., Chem. Commun.* **1970**, *433*.

(12) Kwart, H.; Johnson, N. A. *J. Am. Chem. Soc.* **1977**, *99*, 3441.

Scheme IV



4.55; N, 18.05; S, 10.33. Found: C, 61.69; H, 4.39; N, 18.15; S, 10.13.

5-(4′-Chlorophenyl)-3-[(2′-mercaptophenyl)amino]-1,2,4-triazine (3a). A suspension of **2a** (0.50 g, 1.59 mmol) in methylene chloride (40 mL) containing *p*-toluenesulfonic acid (0.005 g, 0.03 mmol, 2 mol %) was stirred under nitrogen at room temperature for 47 h and evaporated under reduced pressure, and the residual yellow solid was triturated with ether to afford **3a** as a yellow solid (0.44 g, 88%), mp 137.5–139.5 °C: IR (KBr) 3360, 3250, 3050, 1580, 1520, 1440, 1410, 1310, 1285, 1090, 1060, 1010, 835, 740, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.22 (s, 1 H), 8.38 (d, J = 7.8 Hz, 1 H), 8.25 (bs, 1 H), 8.10 (d, J = 8.6 Hz, 2 H), 7.60–7.55 (m, 1 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.41–7.36 (m, 1 H), 7.08 (t, J = 7.37 Hz, 1 H), 3.28 (bs, 1 H); HRMS calcd for $C_{15}H_{11}N_4SCl$ m/z 314.0393, found m/z 314.0387.

5-(4′-Chlorophenyl)-3-[(2′-trifluoroacetamidophenyl)-thio]-1,2,4-triazine (5). A stirred suspension of **2a** (1.35 g, 4.29 mmol) in anhydrous ether (30 mL) and trifluoroacetic anhydride (3.0 mL, 21 mmol) was stirred under nitrogen for 45 min. After this period, the homogeneous reaction mixture was evaporated under reduced pressure to afford a violet-white solid, which was triturated in 1:10 ether/petroleum ether to provide **5** (1.95 g, 100%) as a silvery white solid. The analytical sample was obtained by column chromatography purification (1:1 hexanes/ethyl acetate eluent); mp 128.5–130 °C: IR (KBr) 3340, 3080, 1700, 1580, 1520, 1485, 1435, 1390, 1340, 1300, 1270, 1230, 1160, 1080, 995, 900, 835, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.47 (s, 1 H), 9.27 (bs, 1 H), 8.36 (d, J = 8.2 Hz, 1 H), 7.97 (d, J = 8.7 Hz, 2 H), 7.79 (d, J = 7.8 Hz, 1 H), 7.68 (t, J = 7.8 Hz, 1 H), 7.53 (d, J = 8.8 Hz, 2 H), 7.36 (t, J = 7.6 Hz, 1 H); HRMS calcd for $C_{17}H_{10}N_4OSF_3Cl$ m/z 410.0216, found m/z 410.0189. Anal. Calcd for $C_{17}H_{10}N_4OSF_3Cl$: C, 49.71; H, 2.45; N, 13.64; F, 13.87; Cl, 8.63. Found: C, 49.58; H, 2.74; N, 13.25; F, 14.00; Cl, 8.62.

5-(4′-Chlorophenyl)-3-[[2′-(2-propynylthio)phenyl]-amino]-1,2,4-triazine (4a). Method A. A stirred solution of **3a** (0.20 g, 0.64 mmol) in anhydrous THF (15 mL) was treated with triethylamine (0.10 mL, 0.72 mmol). There was an immediate color change from yellow to red. Propargyl bromide (0.09 mL, 0.8 mmol, 80% solution in toluene) was then added, whereupon the color changed back from red to yellow, and a precipitate formed. The reaction mixture was stirred under nitrogen for 1 h and then filtered through a silica gel pad, eluting with 1:1 ethyl acetate/methylene chloride (50 mL). The filtrate was evaporated under reduced pressure, and the residual pasty yellow solid was purified by column chromatography (1:1 hexanes/ethyl acetate eluent) to provide **4a** as a yellow solid (0.18 g, 80%), mp 131.5–132.5 °C: IR (KBr) 3300, 3180, 1580, 1515, 1495, 1440, 1300, 1215, 1070, 1050, 1005, 830, 750, 720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.24 (s, 1 H), 8.79 (bs, 1 H), 8.65 (d, J = 8.1 Hz, 1 H), 8.13 (d, J = 8.5 Hz, 2 H), 7.74–7.71 (m, 1 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.54–7.47 (m, 1 H), 7.14–7.09 (m, 1 H), 3.35 (d, J = 2.6 Hz, 2 H), 2.23 (t, J = 3.0 Hz, 1 H); HRMS calcd for $C_{18}H_{13}N_4SCl$ m/z 352.0549, found m/z 352.0523. Anal. Calcd for $C_{18}H_{13}N_4SCl$: C, 61.27; H, 3.71; N, 15.88; S, 9.09; Cl, 10.05. Found: C, 61.51; H, 3.92; N, 15.82; S, 9.37; Cl, 9.87.

Method B. To a stirred solution of **5** (1.00 g, 2.44 mmol) in anhydrous THF (35 mL) was added all at once sodium hydride (0.08 g, 2.7 mmol, 80% oil dispersion). When the initial effervescence subsided, propargyl bromide (0.73 g, 4.87 mmol, 80% solution in toluene) was added, and the reaction mixture was stirred under nitrogen for 14.5 h, and then heated at reflux for an additional 12 h. It was then evaporated under reduced pressure, and the residual dark yellow oil was purified by column chromatography (methylene chloride eluent) to afford **4a** (0.30 g, 35% actual yield, 59% yield based upon recovered starting material) as a yellow solid. The spectral and physical properties of this material were identical with those reported above for **4a** prepared by method A.

5-(4′-Methoxyphenyl)-3-[[2′-(2-propynylthio)phenyl]-amino]-1,2,4-triazine (4b). A stirred suspension of **2b** (0.48 g, 1.55 mmol) in anhydrous THF (10 mL) to which a crystal of *p*-toluenesulfonic acid had been added was heated at reflux under nitrogen for 40 min. Thin layer chromatography indicated the complete formation of 3-[(2′-mercaptophenyl)amino]-5-(4′-methoxyphenyl)-1,2,4-triazine (**3b**) (R_f = 0.39, 1:1 hexanes/ethyl acetate). Because this material consistently decomposed upon attempted isolation, full characterization was not carried out. The crude reaction mixture was cooled and treated with triethylamine (0.22 mL, 1.55 mmol) at once via syringe. The mixture immediately became red. After 3 min, propargyl bromide (0.17 mL, 1.55 mmol, 80% solution in toluene) was added, whereupon the color slowly reverted from red to yellow. The mixture was then stirred under nitrogen for 6.5 h and filtered and the filtrate evaporated under reduced pressure. The residual green resin was taken up in ~3 mL of methylene chloride and filtered through a silica gel pad with subsequent elution with 1:1 hexanes/ethyl acetate (400 mL). The filtrate was evaporated under reduced pressure to afford **4b** (0.48 g, 89%) as a yellow solid, mp 120–121 °C: ^1H NMR ($CDCl_3$) δ 9.19 (s, 1 H), 8.69 (bs, 1 H), 8.68–8.66 (m, 1 H), 8.16 (d, J = 6.9 Hz, 2 H), 7.71–7.68 (m, 1 H), 7.50–7.44 (m, 1 H), 7.09–7.05 (m, 3 H), 3.91 (s, 3 H), 3.51 (d, J = 2.5 Hz, 2 H), 2.21 (t, J = 2.7 Hz, 1 H); HRMS calcd for $C_{19}H_{16}N_4OS$ m/z 348.1045, found m/z 348.1053.

Thermal Transformations of 5-(4′-Chlorophenyl)-3-[[2′-(2-propynylthio)phenyl]amino]-1,2,4-triazine (4a). Method A. A stirred suspension of **4a** (5.06 g, 14.36 mmol) in bromobenzene (30 mL) was heated at reflux under nitrogen with the consumption of starting material followed by thin layer chromatography (1:1 hexanes/ethyl acetate eluent). After 49.5 h, the reaction mixture was cooled to room temperature and filtered through a silica gel pad, which was then eluted successively with hexanes (350 mL), methylene chloride (600 mL), and 1:1 hex-

anes/ethyl acetate (500 mL). The latter two fractions were separately evaporated under reduced pressure, and the residual materials were purified as described below to provide the three thermal transformation products **6a**, **7a**, and **8a**.

2-(4′-Chlorophenyl)-5,11-dihydropyrido[3,2-*c*][1,5]benzothiazepine (6a) was obtained as a pale red solid (0.05 g, 1%) upon column chromatography (80% methylene chloride/hexanes as eluent); mp 154–156 °C: R_f = 0.64 in methylene chloride; ^{1}H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2 H), 7.53 (bs, 1 H), 7.44–7.41 (m, 2 H), 7.39–7.36 (m, 1 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.24–7.18 (m, 1 H), 7.09 (d, J = 7.7 Hz, 1 H), 6.98–6.95 (m, 1 H), 6.91–6.86 (m, 1 H), 3.90 (s, 2 H); HRMS calcd for $C_{18}H_{13}N_2SCl$ m/z 324.0488, found m/z 324.0473.

2-(4′-Chlorophenyl)-4-methyl-10*H*-pyrido[3,2-*b*][1,4]benzothiazine (7a). The methylene chloride fraction obtained from the above reaction was sequentially evaporated under reduced pressure to afford **7a** as orange needles (1.66 g). The residue remaining after a third crop of crystals was obtained was purified by column chromatography (80% methylene chloride/hexanes eluent) to afford 0.14 g of additional product (39% total yield), mp 198–199 °C: R_f = 0.60 in methylene chloride; ^{1}H NMR ($CDCl_3$) δ 7.84–7.79 (m, 2 H), 7.40–7.36 (m, 2 H), 7.02–6.96 (m, 3 H), 6.85–6.79 (m, 1 H), 6.55 (bs, 1 H), 6.52 (d, J = 7.8 Hz, 1 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.99, 152.10, 144.86, 140.90, 137.63, 135.22, 129.37, 128.30, 128.17, 127.05, 123.51, 117.28, 117.08, 115.37, 113.04, 20.00; HRMS calcd for $C_{18}H_{13}N_2SCl$ m/z 324.0488, found m/z 324.0482. Anal. Calcd for $C_{18}H_{13}N_2SCl$: C, 66.56; H, 4.03; N, 8.62; S, 9.87; Cl, 10.91. Found: C, 66.85; H, 3.90; N, 8.51; S, 9.89; Cl, 11.08.

3-(2*H*-1-Benzothiopyran-8-ylamino)-5-(4′-chlorophenyl)-1,2,4-triazine (8a). Method A. The 1:1 hexanes/ethyl acetate fraction was evaporated under reduced pressure to afford **8a** in a trace amount (R_f = 0.58 in 1:1 hexanes/ethyl acetate). The spectral and physical properties of this compound were identical with those of **8a** prepared as described below under method B.

Method B. A stirred suspension of **4a** (0.04 g, 0.11 mmol) in bromobenzene (8 mL) was heated at reflux under nitrogen for 75.5 h. After this period, the reaction mixture was cooled to room temperature and filtered through a silica gel pad, eluting successively with hexanes (200 mL), methylene chloride (200 mL), and ethyl acetate (200 mL). The methylene chloride fraction was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (1:1 hexanes/ethyl acetate as eluent) to afford 0.01 g of an orange solid identified by ^{1}H NMR ($CDCl_3$) as a mixture of the 1,5-benzothiazepine **6a** and the 1,4-benzothiazine **7a** (5% and 20% yield, respectively, based upon relative NMR peak integrations). The spectral properties of these materials were identical with those of **6a** and **7a** prepared as described above.

The ethyl acetate fraction was evaporated under reduced pressure, and the residual oil was purified twice by preparative thin layer chromatography (1:1 hexanes/ethyl acetate as eluent) to afford 3-(2*H*-1-benzothiopyran-8-ylamino)-5-(4′-chlorophenyl)-1,2,4-triazine (**8a**) (0.02 g, 50%) as a yellow solid, mp 164–166 °C: IR (KBr) 3290, 1585, 1540, 1520, 1460, 1420, 1300, 1280, 1090, 1060, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.21 (s, 1 H), 8.12–8.09 (m, 3 H), 7.59–7.53 (m, 3 H), 7.21 (t, J = 7.8 Hz, 1 H), 6.93 (d, J = 7.3 Hz, 1 H), 6.59 (dt, J_1 = 10.1 Hz, J_2 = 1.3 Hz, 1 H), 6.07–6.00 (m, 1 H), 3.50 (dd, J_1 = 5.3 Hz, J_2 = 1.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.45, 154.75, 138.97, 138.80, 135.17, 133.24, 132.34, 130.10, 129.69, 128.95, 125.58, 123.79, 122.57, 122.04, 121.44, 24.94; HRMS calcd for $C_{18}H_{13}N_4SCl$ m/z 352.0549, found m/z 352.0537.

Thermal Transformations of 5-(4′-Methoxyphenyl)-3-[[2′-(2-propynylthio)phenyl]amino]-1,2,4-triazine (4b). A stirred suspension of **4b** (0.40 g, 1.15 mmol) in bromobenzene (10 mL) was heated at reflux under nitrogen for 67.5 h and filtered through a silica gel pad, with successive elution with hexanes (250 mL), methylene chloride (600 mL), and 1:1 hexanes/ethyl acetate (400 mL). The latter two fractions were separately evaporated under reduced pressure, and the residual materials were purified as described below to provide the three thermal transformation products **6b**, **7b**, and **8b**.

2-(4′-Methoxyphenyl)-5,11-dihydropyrido[3,2-*c*][1,5]benzothiazepine (6b) was obtained as a pale yellow solid (0.01 g, 3%), mp 149–151 °C, upon column chromatography (methylene chloride eluent, R_f = 0.16 in methylene chloride): ^{1}H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2 H), 7.52 (bs, 1 H), 7.38–7.35 (m, 1 H), 7.30 (d, J = 7.7 Hz, 1 H), 7.23–7.18 (m, 1 H), 7.07 (d, J = 7.6 Hz, 1 H), 7.01–6.95 (m, 3 H), 6.90–6.84 (m, 1 H), 3.91 (s, 2 H), 3.87 (s, 3 H); HRMS calcd for $C_{19}H_{16}N_2OS$ m/z 320.0983, found m/z 320.0975.

2-(4′-Methoxyphenyl)-4-methyl-10*H*-pyrido[3,2-*b*][1,4]benzothiazine (7b). The methylene chloride fraction was evaporated under reduced pressure, and the residual orange solid was purified by column chromatography (methylene chloride eluent) to provide **7b** (0.08 g, 22%) as a pale orange solid, mp 167.5–169 °C: R_f = 0.15 in methylene chloride; ^{1}H NMR ($CDCl_3$) δ 7.84–7.81 (m, 2 H), 7.01–6.93 (m, 5 H), 6.84–6.78 (m, 1 H), 6.61 (bs, 1 H), 6.52–6.49 (m, 1 H), 3.85 (s, 3 H), 2.23 (s, 3 H); HRMS calcd for $C_{19}H_{16}N_2OS$ m/z 320.0983, found m/z 320.0976.

3-(2*H*-1-Benzothiopyran-8-ylamino)-5-(4′-methoxyphenyl)-1,2,4-triazine (8b). The 1:1 hexanes/ethyl acetate fraction was evaporated under reduced pressure, and the residual dark resin was purified by column chromatography (1:1 hexanes/ethyl acetate eluent) to provide **8b** as a yellow solid (0.07 g, 18%), mp 143.5–145.5 °C: R_f = 0.41 in 1:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 9.16 (s, 1 H), 8.15–8.09 (m, 3 H), 7.50 (bs, 1 H), 7.18 (t, J = 7.9 Hz, 1 H), 7.05–7.02 (m, 2 H), 6.88 (d, J = 7.4 Hz, 1 H), 6.58 (dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz, 1 H), 6.05–5.98 (m, 1 H), 3.90 (s, 3 H), 3.48 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 2 H); HRMS calcd for $C_{19}H_{16}N_4OS$ m/z 348.1045, found m/z 348.1039.

Registry No. **1a**, 105783-78-6; **1b**, 114954-25-5; **2a**, 118632-00-1; **2b**, 118632-01-2; **3a**, 118632-02-3; **3b**, 118632-03-4; **4a**, 118632-04-5; **4b**, 118632-05-6; **5**, 118632-06-7; **6a**, 118632-07-8; **6b**, 118632-08-9; **7a**, 118632-09-0; **7b**, 118657-03-7; **8a**, 118632-10-3; **8b**, 118632-11-4; 2-aminothiophenol, 137-07-5; propargyl bromide, 106-96-7.

N-Bromoacetamide as a Selective Reagent for the Functionalization of the 10,11 Double Bond of Avermectin B1a

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Received July 25, 1988 (Revised Manuscript Received November 14, 1988)

The avermectins and related milbemycins are a class of extremely potent anthelminthic and pesticidal agents.[1] In addition to being the focus of total synthetic efforts,[2] these unique macrolactonic structures are the target of transformation and derivatization with the goals of improving and/or shifting the spectrum of activity. One important advance from these efforts has been the selective hydrogenation of the 22,23 double bond of avermectin B1a (1) with Wilkinson's catalyst to produce ivermectin (3).[3] Since that discovery we have continued to explore the selective functionalization of the other double bonds. In particular, modification of the 8,9 or 10,11 double bonds became of interest since it appears that the 8,9,10,11-diene chromophore is responsible for the isomerization and photodecomposition of the avermectins.[4] Our investiga-

(1) (a) Fisher, M.; Mrozik, H. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 14, p 553. (b) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, 87.

(2) (a) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dube, D.; Andre, C. *Pure Appl. Chem.* **1987**, *59*, 299. (b) Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119 and references cited in these publications.

(3) Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskola, P.; Lusi, A.; Peterson, L. H.; Woods, M. F.; Fisher, M. H. *J. Med. Chem.* **1980**, *23*, 1134.

(4) Mrozik, H.; Eskola, P.; Reynolds, G. F.; Arison, B. H.; Smith, G. M.; Fisher, M. H. *J. Org. Chem.* **1988**, *53*, 1820.

0022-3263/89/1954-1459$01.50/0