and 7.70–7.25 (m, 14 H). Anal. Calcd for $C_{23}H_{15}N_4OF_3$: C, 65.71; H, 3.60; F, 13.56; N, 13.33. Found: C, 66.00; H, 3.87; F, 13.35; N, 13.36.

3-[2′-[*N*-(Cyanomethyl)trifluoroacetamido]phenyl]-5,6-diphenyl-1,2,4-triazine (7). To a suspension of **6** (2.50 g, 5.95 mmol) in dry acetone (30 mL) was added bromoacetonitrile (2.85 g, 23.8 mmol). After the mixture was heated to reflux, powdered potassium hydroxide (1.50 g, 26.8 mmol) was added, and the mixture was refluxed for 10 min. The red mixture was filtered, and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (60 g), eluting with 3:1 methylene chloride/hexanes. A fraction with R_f = 0.15/methylene chloride contained 0.58 g (21%) of the alkylated, deacylated material, 3-[2′-[(cyanomethyl)amino]-phenyl]-5,6-diphenyl-1,2,4-triazine. A second fraction (R_f = 0.10, methylene chloride) afforded 0.57 g (21%) of **7** as a bright yellow solid. The yield of **7** was augmented to 42% by reacylation of the deacylated material with excess TFAA in ether: mp 183–184 °C; IR (thin film) 3050, 1705, 1600, 1580, 1500, 1485, 1440, 1385, 1360, 1310, 1260, 1205, 1180, 1160, 1095, 995, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.73–8.51 and 7.75–7.23 (m, 14 H), 4.79 (AB quartet, J_{gem} = 17.4 Hz, 2 H). Anal. Calcd for $C_{25}H_{16}F_3N_5O$: C, 65.36; H, 3.51; F, 12.40; N, 15.24. Found: C, 65.08; H, 3.29; F, 12.18; N, 15.31.

5,6-Dihydro-2,3-diphenyl-6-(trifluoroacetyl)pyrazino-[2,3-*c*]quinoline (8) and 2,3-Diphenylpyrazino[2,3-*c*]-quinoline (9). A solution of **7** (0.60 g, 1.3 mmol) in diphenyl ether (2 mL) was heated at reflux under nitrogen for 2 h. Purification by column chromatography on silica gel (20 g) with 30% ether-/hexanes gave a fraction (R_f = 0.55, ether) that contained one product contaminated with diphenyl ether and a second fraction (R_f = 0.20), which afforded 0.21 g (47%) of **9** as a light orange solid: mp 177–178.5 °C; IR (thin film) 3050, 1610, 1580, 1525, 1420, 1380, 1355, 1210, 1075, 1015, 760, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.58 (s, 1 H), 9.08 (m, 1 H), 8.23 (m, 1 H), 7.97–7.24 (m, 12 H); LRMS, *m/z* (relative intensity) 333 (M^+, 100) 332 (84), 230 (18), 167 (23), 127 (94). Anal. Calcd for $C_{23}H_{15}N_3$: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.65; H, 4.77; N, 12.31.

The first fraction was further purified by column chromatography on silica gel (15 g) with 1:4 ether/hexanes to afford 0.20 g (36%) of **8** as a white solid: mp 163–166 °C; IR (thin film) 3050, 1700, 1600, 1410, 1385, 1275, 1200, 1150, 1085, 750, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.48–8.37 and 7.67–7.29 (m, 14 H), 5.21 (s, 2 H); LRMS, *m/z* (relative intensity) 431 (M^+, 100), 430 (36), 334 (23), 225 (7), 156 (20), 178 (16). Anal. Calcd for $C_{25}H_{16}F_3N_3O$: C, 69.20; H, 3.74; F, 13.21; N, 9.74. Found: C, 69.47; H, 3.99; F, 13.01; N, 9.94.

3-[(2′-Cyanoethyl)thio]-5-phenyl-1,2,4-triazine (11). A solution of 5-phenyl-1,2,4-triazine-3-thione (**10**)[14] (2.00 g, 10.5 mmol) and sodium hydroxide (0.42 g, 10.5 mmol) in water (100 mL) and ethanol (100 mL) was stirred at room temperature. 3-Bromopropionitrile (1.35 g, 10.5 mmol) was added in one portion, and the orange solution was heated at 65–70 °C for 20 h. The solution was concentrated by rotary evaporation, and a red oil separated. The aqueous mixture was extracted with methylene chloride (3 × 100 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of solvent under reduced pressure provided a deep red oil. Purification by column chromatography on silica gel (60 g) and methylene chloride elution afforded 1.67 g (68%) of **11** as a red solid. Recrystallization from isopropyl ether provided a yellow solid: mp 77–78 °C; IR (KBr) 3055, 3030, 2960, 2250, 1600, 1535, 1500, 1440, 1320, 1250, 760, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1 H), 8.20–7.49 (m, 5 H), 3.56 (t, J = 6.8 Hz, 2 H), 3.00 (t, J = 6.8 Hz, 2 H). Anal. Calcd for $C_{12}H_{10}N_4S$: C, 59.49; H, 4.16; N, 23.12; S, 13.23. Found: C, 59.28; H, 3.89; N, 23.18; S, 13.00.

3-[(2′-Cyanoethyl)sulfinyl]-5-phenyl-1,2,4-triazine (12). To a solution of **11** (0.75 g, 3.1 mmol) in methylene chloride (15 mL) stirred in an ice bath was added a cold solution of *m*-chloroperbenzoic acid (0.65 g, 3.1 mmol based on 82.5% purity) in methylene chloride (15 mL) over 10 min. The solution was stirred at 0 °C for 2 h and then allowed to warm to room temperature. Chloroform (10 mL) was added, and the solution was washed with 1 N sodium carbonate (10 mL). The aqueous layer was back-extracted with chloroform (15 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of solvent under reduced pressure gave a yellow oil which upon trituration with a small portion of ethyl acetate provided a yellow solid. Additional material was obtained by diluting the ethyl acetate washings with ether; total yield of **12**, 0.50 g (62%): mp 97–98 °C; IR (thin film) 3050, 3000, 2950, 2930, 2240, 1595, 1530, 1490, 1435, 1320, 1240, 1070, 755, 680 cm^{-1}; ^{1}H NMR (DMSO) δ 10.25 (s, 1 H), 8.48–8.37 and 7.72–7.63 (m, 5 H), 3.63 (m, 2 H), 2.97 (t, J = 7.3 Hz, 2 H); HRMS calcd for $C_{12}H_{10}N_4OS$ 258.0575, found 258.0570.

Registry No. **1a**, 16086-60-5; **1b**, 118207-04-8; **1c**, 118207-07-1; **1d**, 118207-08-2; **1e**, 118207-09-3; **2a**, 106823-32-9; **2b**, 118207-10-6; **2c**, 118207-11-7; **2d**, 118207-12-8; **2e**, 118207-13-9; **3a**, 106823-36-3; **3b**, 118207-14-0; **3d**, 118207-15-1; **3e**, 118207-16-2; **5**, 89213-58-1; **6**, 106823-31-8; **7**, 106823-33-0; **8**, 106823-34-1; **9**, 106823-35-2; **10**, 15969-28-5; **11**, 118207-05-9; **12**, 118207-06-0; salicylhydrazine, 936-02-7; benzil, 134-81-6; phenyl glyoxal monohydrate, 1074-12-0; 1-phenyl-1,2-propanedione, 579-07-7; bromoacetonitrile, 590-17-0; 3-[2′-[(cyanomethyl)amino]phenyl]-5,6-diphenyl-1,2,4-triazine, 118207-17-3; 3-bromopropionitrile, 2417-90-5.

Synthesis of Pyridines by Diels–Alder Reactions of Hetero-Substituted 1,2,4-Triazines with Enamines and an Enaminone

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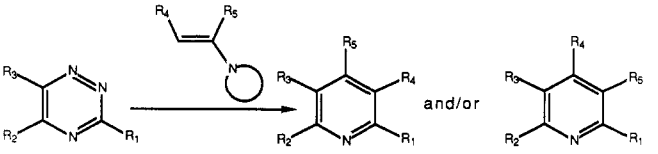
The use of (alkylthio)- and alkoxy-1,2,4-triazines in intermolecular inverse electron demand Diels–Alder reactions with enamine and enaminone dienophiles leads to highly functionalized pyridine derivatives.

Inverse electron demand intermolecular Diels–Alder reactions of 1,2,4-triazines with enamines to yield pyridines has been well documented and exploited (Scheme I).[2] However, the 1,2,4-triazines used in these reactions have been limited to the parent heterocycle (R_1 = R_2 = R_3 = H) or to carbon-substituted derivatives (R_1 = R_2 = R_3 = alkyl, aryl, or alkoxycarbonyl). Additionally, the enamines

Scheme I



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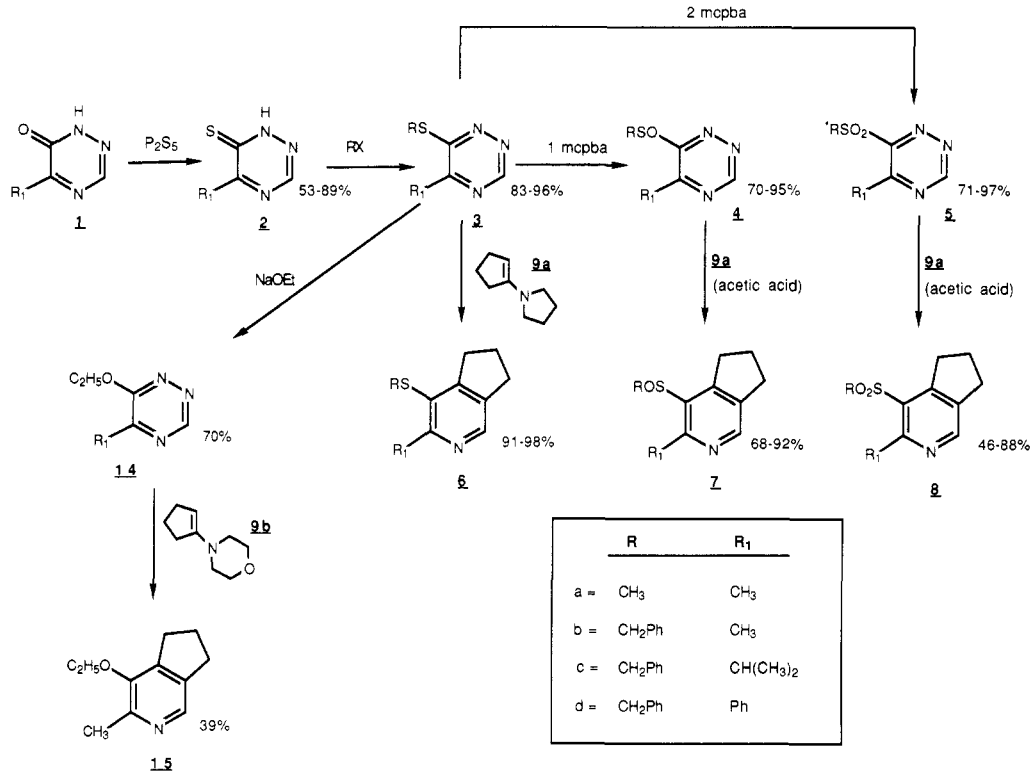
(2) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: New York, 1987.

0022-3263/89/1954-1249$01.50/0

Scheme II

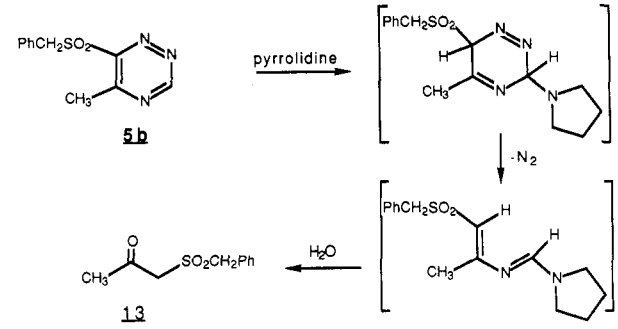


used as dienophiles have generally been derived from simple aldehydes or ketones ($R_4 = R_5 = H$, alkyl, or aryl). We describe in this paper the synthesis of substituted pyridines from (alkylthio)- and alkoxy-1,2,4-triazines and enamines derived from both simple and heterocyclic ketones. The first inverse electron demand Diels–Alder reaction between a 1,2,4-triazine and an enaminone is also detailed.

1,2,4-Triazine-6-thiones **2**, prepared by reaction of the corresponding 1,2,4-triazin-6-ones (**1**)[3] with P_2S_5, were deprotonated with triethylamine; the resulting anions underwent slow alkylation on sulfur at room temperature with reactive alkyl halides (methyl iodide, benzyl bromide). Oxidation of the resulting sulfides **3** with 1 or 2 equiv of *m*-chloroperbenzoic acid led to the corresponding 6-(alkylsulfinyl)- or 6-(alkylsulfonyl)-1,2,4-triazines **4** or **5**, respectively (Scheme II). Both **4** and **5** proved to be extremely sensitive toward nucleophiles, which attacked these compounds at the unsubstituted 3-position leading to decomposition of the triazine.[4] For example, treatment of **5b** with 1 equiv of pyrrolidine at room temperature led to the formation of 1-(benzylsulfonyl)acetone (**13**),[5] apparently by nucleophilic addition of the amine to the 3-position (Scheme III), followed by a retro-Diels–Alder reaction with elimination of nitrogen (which could be observed during the rapid course of the reaction), and subsequent hydrolysis to **13** upon workup.

6-Alkoxy-1,2,4-triazines could thus not be prepared by reaction of **4** or **5** with alkoxides, since attack at position

Scheme III



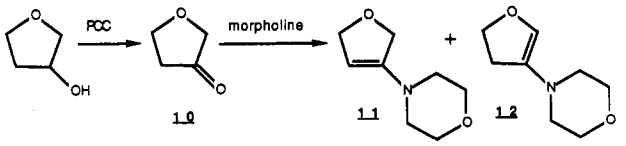
3 predominated.[6] However, the reaction of lower chain (C_3 and less) alkoxides with the less reactive sulfides (**3**) proceeded smoothly (longer chain, less reactive alkoxides led to destruction of the triazine ring). Attempts to prepare 6-alkoxy-1,2,4-triazines by direct O-alkylation of the corresponding 6-ones led to N-alkylation followed by rapid degradation of the triazine ring.

Since 1,2,4-triazine derivatives undergo inverse electron demand ($LUMO_{diene}/HOMO_{dienophile}$) Diels–Alder reactions, electron-donating substituents should retard the rate of reaction, while electron-withdrawing substituents should accelerate the cyclization rate.[2] These predictions were borne out with a series of Diels–Alder reactions of **3**, **4**, **5**, and **14** with pyrrolidino- and morpholinocyclopentene (**9a,b**) (Scheme II). The sulfides **3** reacted with the enamine **9a** in refluxing dioxane (101 °C) overnight to yield 3-(alkylthio)-4,5-cyclopentenopyridines **6** in excellent

(3) Taylor, E. C.; Macor, J. E. *J. Heterocycl. Chem.* **1985**, *22*, 409.
(4) Macor, J. E. Ph.D. Thesis, Princeton University, May, 1986.
(5) (Benzylsulfonyl)acetone was isolated in 43% yield from the reaction of **5b** and pyrrolidine as a white crystalline solid, mp 72.0–73.5 °C: IR (KBr) 1710, 1605, 1495, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.42 (m, 5 H), 4.38 (s, 2 H), 3.86 (s, 2 H), 2.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.4, 131.0, 129.2, 129.1, 127.5, 61.1, 59.7, 32.0; LRMS (relative intensity) *m/z* 212 (2, M^+), 91 (100), 65 (38). Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70; S, 15.11. Found: C, 56.78; H, 5.97; S, 15.32.

(6) Attempts to prepare 6-chloro-5-methyl-1,2,4-triazine as a possible precursor to 6-alkoxy derivatives were unrewarding. This compound could be prepared in low yield (ca. 20%) from the reaction of 5-methyl-1,2,4-triazin-6-one (**1a**) and phosphorus oxychloride in the presence of triethylamine, but the liquid product was not fully characterized: ^1H NMR ($CDCl_3$) δ 9.41 (s, 1 H), 2.71 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.8, 157.7, 155.3, 21.7.

Scheme IV

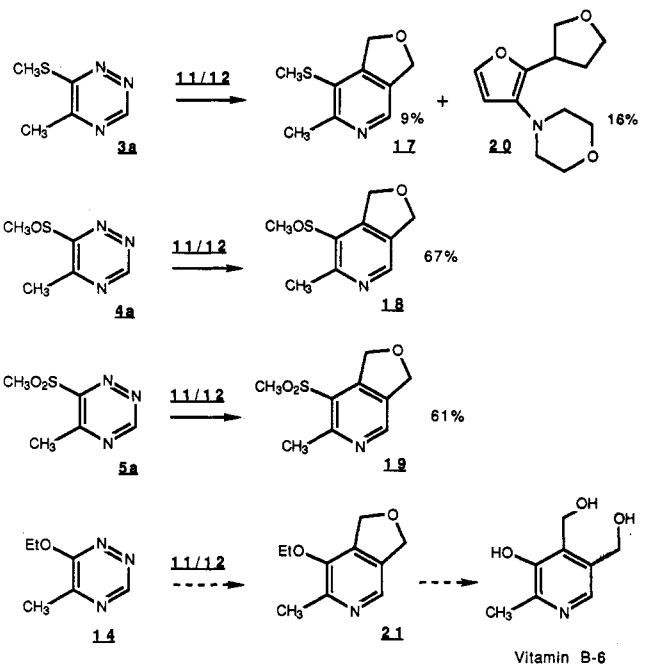


yields. The reaction of **9b**[7] with 6-ethoxy-5-methyl-1,2,4-triazine (**14**), however, was much slower than that with the corresponding sulfide (**3a**), yielding only 39% (61% conversion) of 3-ethoxy-2-methyl-4,5-cyclopentenopyridine (**15**) after 144 h in refluxing chlorobenzene (132 °C).

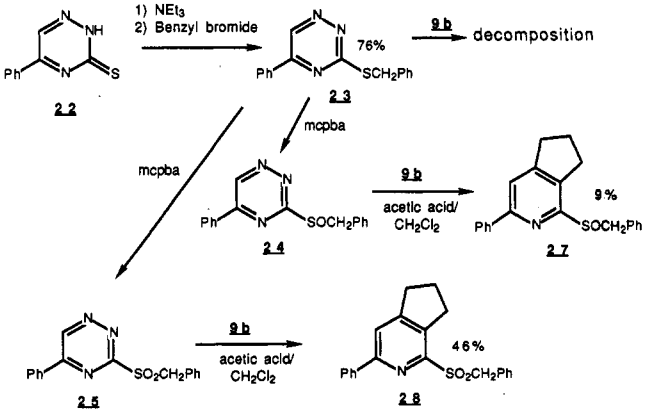
Conversion of the sulfides **3** to the sulfoxides **4** or sulfones **5** reverses the electronic character of the sulfur-linked substituent, and thus in principle should greatly enhance the reactivity of the resulting triazines as dienophilic components in these Diels–Alder reactions. Unfortunately, the sulfoxides **4** and sulfones **5** proved to be so reactive toward the highly nucleophilic enamines **9a,b** (via attack at the unsubstituted 3-position) that treatment with **9a,b** at room temperature produced a rapid, highly exothermic, effervescing reaction, which yielded a variety of degradation products; the desired Diels–Alder reaction products **7** and **8** could be isolated in only ca. 25% yield. For attenuation of the nucleophilicity of the enamine, glacial acetic acid was added to the reaction mixture containing **4** or **5** prior to the addition of the enamine. Subsequent addition of the enamine **9a,b** at room temperature or below led to smooth evolution of nitrogen; after 1–3 h at 0 °C, the Diels–Alder reactions were complete, and the desired pyridine derivatives **7** and **8** could be isolated in good to excellent yields. Scheme II summarizes these results.

For investigation of a possible application of this Diels–Alder reaction methodology to a synthesis of pyridoxine, the enamine **11** (containing some 16% of its double-bond isomer **12**) was prepared from tetrahydrofuran-3-one (**10**)[8] (Scheme IV). Attempts to purify this mixture via distillation were unsuccessful as the material decomposed at the elevated temperatures required for this procedure, and accordingly, the mixture was used directly without further purification (**12** proved to be unreactive as a dienophile and was an innocuous contaminant). Reaction of the enamine **11/12** with the sulfoxide **4a** and with the sulfone **5a** using the room temperature "acidic enamine" conditions described above yielded the highly functionalized pyridines **18** and **19**, respectively (Scheme V). However, reaction of the sulfide **3a** with the enamine **11/12** at the temperature required for cyclization (101 °C) afforded only 9% of the 3-(methylthio)furopyridine **17** (49% conversion); some 80% of starting material **3a** was recovered. Additionally, a byproduct (**20**) arising from decomposition of the enamine was isolated and characterized. It was apparent that the enamine mixture **11/12** was thermally unstable and that it rapidly decomposed at the elevated reaction temperatures required for cycloaddition. When the more electron rich (i.e. less reactive) 6-ethoxy-5-methyl-1,2,4-triazine (**14**) was treated with the enamine **11/12** under a number of different reaction conditions, only recovered **14** and the furan byproduct **20** could be isolated. The limited reactivity of **14** coupled with the thermal instability of the enamine **11/12** led us to abandon this projected approach to pyridoxine.

Scheme V



Scheme VI



3-(Alkylthio)-1,2,4-triazines are well documented;[9] 3-(benzylthio)-1,2,4-triazine (**23**) was thus readily obtained by alkylation of the 3-thione **22**.[10] Oxidation of **23** with 1 and with 2 equiv of MCPBA yielded the sulfoxide **24** and the sulfone **25**, respectively (Scheme VI). A striking difference in reactivity of these 3-(hetero-substituted)-1,2,4-triazines compared with their 6-hetero-substituted counterparts was immediately apparent when we attempted to purify **24** and **25**. Both compounds underwent rapid hydrolytic loss of the 3-substituent; anhydrous workup conditions were therefore required. This susceptibility to nucleophilic displacement of the hetero substituent from the 3-position of the triazine ring in **23**, **24**, and **25** contributed greatly to their inability to participate as efficiently as their 6-substituted analogues **3**, **4**, and **5** in Diels–Alder reactions. Thus, the sulfide **23** was completely decomposed after reaction with **9b** at 101 °C. When the sulfoxide **24** was reacted with **9b** using the "acidic enamine" conditions described above, only 9% of the bicyclic pyridine **27** was isolated. The most reactive dienophile, the sulfone **25**, reacted with **9b** to afford only

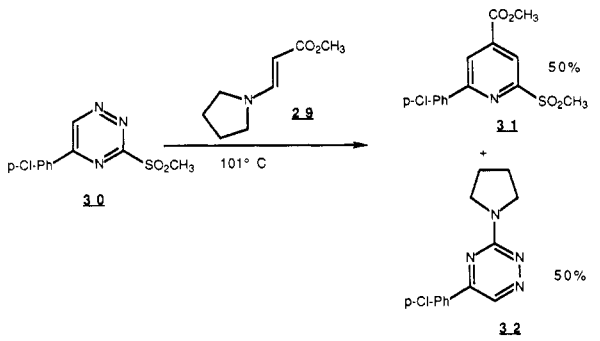
(7) 1-Morpholino-1-cyclopentene (**9b**) is more thermally stable than 1-pyrrolidino-1-cyclopentene (**9a**), and in reactions using elevated temperatures for long periods of time, **9b** was the enamine of choice, even though it appeared to be somewhat less reactive than **9a**.

(8) Gianturco, M. A.; Friedel, P.; Giammarino, A. S. *Tetrahedron* **1964**, *20*, 1763.

(9) Neunhoeffer, H. *The Chemistry of 1,2,3-Triazines, Tetrazines, and Pentazines*, Vol. 33 in the series The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons: New York, 1978; pp 335–346.

(10) Tisler, M. *Croat. Chem. Acta* **1960**, *32*, 123.

Scheme VII



48% of the 2-(benzylsulfonyl)pyridine derivative **28**. These discouraging results are certainly due in large part to the susceptibility of the starting triazines to nucleophilic displacement of the 3-substituent.[11,12]

The use of the enaminone **29**[13] as a dienophilic component in these inverse electron demand Diels–Alder reactions was briefly explored (Scheme VII). Since an enaminone is less electron rich than an enamine (i.e. higher energy HOMO), it was assumed that the enaminone **29** would react best with the most electron poor diene in the series, an (alkylsulfonyl)-1,2,4-triazine. Heating a solution of **29** with the triazine **30**[14] in refluxing anhydrous tetrahydrofuran (66 °C) for 1 day led to the formation (50% yield each) of two products (Scheme VII). One of them proved to be the 3-pyrrolidino-1,2,4-triazine **32**, the product of nucleophilic displacement of methanesulfinate from the starting material by pyrrolidine released during the Diels–Alder reaction. The other product was identified as the 4-carbomethoxy-2-(methoxysulfonyl)pyridine **31**. The regiochemistry of the product was assigned on the basis of proton and carbon NMR spectroscopy and by chemical analogy. The two pyridine protons have isochronous chemical shifts, consistent with a 2,4,6-trisubstituted pyridine; additionally, the reaction of 3-carbethoxy-1,2,4-triazines with enamines occurs with the electron-rich β-position of the enamine reacting at the 6 position of the triazine ring.[1] This regiochemistry should also be observed in the reaction of an enaminone with a 3-(benzylsulfonyl)- or 3-(methylsulfonyl)-1,2,4-triazine. Reaction of 5,6-dimethyl-3-(methylsulfonyl)-1,2,4-triazine (**33**)[14] with **29** resulted only in slow decomposition and did not lead to the expected pyridine. This discouraging result may be associated with the documented ease of deprotonation of 5-methyl-1,2,4-triazines.[15]

Conclusion

The reaction of hetero-substituted 1,2,4-triazines with enamines and enaminones can give rise to highly functionalized pyridine derivatives. The efficiency of these transformations is determined by (1) the stability of the triazine heterocycle to the nucleophilic conditions of the reaction; (2) the inverse electron demand Diels–Alder reactivity of the triazine, which is determined by the nature (electron-donating or electron-withdrawing) of substituents; and (3) the thermal stability of the triazine and of the enamine (or enaminone). Chemically reactive (alkylsulfonyl)- and (alkylsulfinyl)-1,2,4-triazines can be employed as azadienes by using "acidic enamine" conditions in which the nucleophilicity of the participating enamine is attenuated by addition of acetic acid to the reaction mixture. Enaminones can also be employed as dienophiles in inverse electron demand Diels–Alder reactions with reactive 1,2,4-triazines.

Experimental Section

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1320 infrared spectrophotometer, and NMR spectra were obtained on either a JEOL FX-90Q (90 MHz) or a Nicolet QE300 (300 MHz) spectrometer. Mass spectra were determined on a AEI MS-9 instrument, and elemental analyses were carried out by Eli Lilly & Co., Indianapolis, IN. Commercial reagents were utilized without further purification. General procedures listed here represent typical reaction procedures for the class of compounds described.

General Synthesis of 1,2,4-Triazine-6-thiones 2. To a stirred solution of the 1,2,4-triazin-6-one **1**[3] (20.00 mmol) in pyridine (25 mL) at room temperature was added phosphorus pentasulfide (2.95 g, 6.64 mmol, 0.33 equiv) as a solid all at once. The reaction mixture was refluxed under nitrogen for 1–3 h, depending on the substrate. Pyridine was then removed from the reaction solution by evaporation under reduced pressure, the residual solid was suspended in water (40 mL), and the aqueous mixture was extracted with methylene chloride (3 × 40 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure, and the resulting oil or solid was chromatographed on silica gel (approximately 100 g). Elution with 1:2 ether/petroleum ether afforded the 1,2,4-triazine-6-thione **2**.

5-Methyl-1,2,4-triazine-6-thione (2a). The reaction time was 1 h; purification as described yielded **2a** (72%) as an orange solid, mp 173.0–175.0 °C: IR (KBr) 3170, 1585, 1450, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 15.0 (br s, 1 H), 8.60 (s, 1 H), 2.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.1, 173.6, 145.8, 23.6; LRMS (relative intensity) *m/z* 129 (13% of M^+), 127 (47, M^+), 98 (24), 72 (61), 68 (38), 59 (81), 41 (100). Anal. Calcd for $C_4H_5N_3S$: C, 37.78; H, 3.96; N, 33.04; S, 25.21. Found: C, 38.02; H, 4.11; N, 33.26; S, 25.49.

5-Isopropyl-1,2,4-triazine-6-thione (2c). The reaction time was 1 h; purification as described yielded **2c** (53%) as an orange solid, mp 86.0–88.0 °C: IR (KBr) 3140, 1565, 1550, 1465, 1430, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.55 (s, 1 H), 4.06 (sept, J = 6.8 Hz, 1 H), 1.28 (d, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 181.7, 176.0, 146.5, 32.5, 19.5. Anal. Calcd for $C_6H_9N_3S$: C, 46.43; H, 5.84; N, 27.07; S, 20.66. Found: C, 46.22; H, 5.99; N, 26.92; S, 20.82.

5-Phenyl-1,2,4-triazine-6-thione (2d). The reaction time was 3 h; purification as described yielded **2d** (89%) as a dark purple solid, mp 148.0–150.0 °C: IR (KBr) 3150, 1595, 1565, 1435, 1290 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.81 (s, 1 H), 8.18–8.07 (m, 2 H), 7.59–7.35 (m, 3 H), 3.4 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 175.1, 168.3, 146.6, 135.4, 131.1, 129.4, 127.3. Anal. Calcd for $C_9H_7N_3S$: C, 57.12; H, 3.73; N, 22.21; S, 16.94. Found: C, 57.10; H, 3.80; N, 22.03; S, 16.84.

General Procedure for the Synthesis of 6-(Alkylthio)-1,2,4-triazines 3. The alkyl halide was added dropwise to a stirred solution of the 1,2,4-triazine-6-thione **2** (10.00 mmol) and triethylamine (12.00 mmol, 1.2 equiv) in anhydrous tetrahydrofuran (25 mL) at room temperature. The resulting reaction solution was stirred at room temperature for 1–2 h with the exclusion of moisture. A saturated solution of ammonium chloride (20 mL) was then added to the reaction mixture, which was extracted with ether (4 × 20 mL). The ether extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residual oil or solid using silica gel (approximately 100 g) and elution with the appropriate solvent system yielded the 6-(alkylthio)-1,2,4-triazine **3**.

5-Methyl-6-(methylthio)-1,2,4-triazine (3a). The chromatographic eluent was 1:2 ether/petroleum ether; **3a** (83%) was obtained as a pale yellow solid, mp 58.0–59.5 °C: IR (KBr) 1530, 1500, 1420, 1375, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.20 (s, 1 H), 2.72

(11) Reference 9, p 346.
(12) It has recently been observed that carrying out the reaction of 1-pyrrolidinocycloalkenes with several 3-(methylsulfonyl)-1,2,4-triazines under neutral conditions in methylene chloride at 0 °C gives dihydropyridines by loss of *nitrogen only* from the initial cycloadducts. Subsequent aromatization in a separate step then leads to fused pyridines in good yield (Chenard, B. L.; Ronau, R. T.; Schulte, G. K. *J. Org. Chem.* **1988**, *53*, 5175). We thank the authors for a preprint of this work.
(13) Huisgen, R.; Herbig, K.; Siegl, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2526.
(14) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145.
(15) (a) Reference 9, p 5. (b) Suzuki, T.; Okazaki, M.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1986**, *23*, 935.

(s, 3 H), 2.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.3, 157.6, 152.8, 21.2, 12.6. Anal. Calcd for $C_5H_7N_3S$: C, 42.53; H, 5.00; N, 29.76; S, 22.71. Found: C, 42.27; H, 5.06; N, 29.54; S, 22.55.

6-(Benzylthio)-5-methyl-1,2,4-triazine (3b). The chromatographic eluent was 1:4 ether/petroleum ether; **3b** (88%) was obtained as a pale yellow oil that crystallized on cooling, mp 60.0–62.0 °C: IR (KBr) 1600, 1500, 1450, 1420, 1380, 1300, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1 H), 7.47–7.24 (m, 5 H), 4.58 (s, 2 H), 2.44 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.8, 157.4, 153.2, 136.0, 129.1, 128.5, 127.5, 34.0, 21.2. Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34; S, 14.76. Found: C, 60.74; H, 5.18; N, 19.12; S, 14.60.

6-(Benzylthio)-5-isopropyl-1,2,4-triazine (3c). The chromatographic eluent was 1:2 ether/petroleum ether; **3c** (96%) was obtained as a pale yellow oil that crystallized below 0 °C; mp ca. 20 °C: IR (neat) 1600, 1500, 1415, 1400, 1340, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.25 (s, 1 H), 7.50–7.25 (m, 5 H), 4.58 (s, 2 H), 3.12 (sept, J = 6.8 Hz, 1 H), 1.27 (d, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.8, 161.0, 153.5, 136.0, 129.1, 128.5, 127.4, 34.3, 31.7, 19.7. Anal. Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13; S, 13.07. Found: C, 63.87; H, 6.23; N, 16.88; S, 13.11.

6-(Benzylthio)-5-phenyl-1,2,4-triazine (3d). The chromatographic eluent was 1:2 ether/petroleum ether; **3d** (88%) was obtained as a pale yellow solid, mp 106.0–107.5 °C: IR (KBr) 1600, 1505, 1495, 1475, 1455, 1445, 1380, 1310, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.38 (s, 1 H), 7.92–7.72 (m, 2 H), 7.58–7.16 (m, 8 H), 4.55 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.0, 156.1, 153.5, 135.9, 134.3, 131.2, 129.3, 128.7, 128.5, 127.4, 34.2. Anal. Calcd for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04; S, 11.48. Found: C, 69.02; H, 4.79; N, 15.09; S, 11.56.

General Synthesis of 6-(Alkylsulfinyl)-1,2,4-triazines 4. To a stirred solution of the 6-(alkylthio)-1,2,4-triazine (6.00 mmol) in methylene chloride (20 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% technical solid, 1.29 g, 6.35 mmol max, 1.06 equiv max) rapidly as a solid in small portions. The resulting reaction mixture was stirred at 0 °C with exclusion of moisture for 90 min. The reaction mixture was then filtered, and the collected *m*-chlorobenzoic acid was washed with a small amount of ice-cold methylene chloride. The methylene chloride filtrates were combined, washed once with a saturated solution of sodium bicarbonate, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residual oil using silica gel (approximately 50 g) and elution with the appropriate solvent afforded the 6-(alkylsulfinyl)-1,2,4-triazine **4**.

5-Methyl-6-(methylsulfinyl)-1,2,4-triazine (4a). The chromatographic eluent was ether; **4a** (70%) was obtained as a pale yellow oil that crystallized below 0 °C, mp 52.0–53.5 °C: IR (neat) 1510, 1400, 1380, 1285, 1255, 1080–1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1 H), 3.17 (s, 3 H), 2.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 160.2, 157.1, 37.9, 20.7. Anal. Calcd for $C_5H_7N_3OS$: C, 38.20; H, 4.49; N, 26.73; S, 20.40. Found: C, 38.53; H, 4.50; N, 26.74; S, 20.32.

6-(Benzylsulfinyl)-5-methyl-1,2,4-triazine (4b). The chromatographic eluent was 2:3 ether/petroleum ether; **4b** (95%) was obtained as a crystalline white solid, mp 90.5–92.5 °C: IR (KBr) 1505, 1490, 1390, 1270, 1250, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1 H), 7.33–7.21 (m, 3 H), 7.06–6.95 (m, 2 H), 4.62 (d, J = 12.7 Hz, 1 H), 4.41 (d, J = 12.8 Hz, 1 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.4, 160.9, 156.5, 130.1, 128.5, 128.0, 59.6, 19.6 Anal. Calcd for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01; S, 13.74. Found: C, 56.64; H, 4.59; N, 18.06; S, 13.75.

6-(Benzylsulfinyl)-5-isopropyl-1,2,4-triazine (4c). The chromatographic eluent was 1:1 ether/petroleum ether; **4c** (76%) was obtained as a pale yellow oil: IR (neat) 1600, 1515, 1490, 1455, 1405, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1 H), 7.36–7.16 (m, 3 H), 7.16–7.00 (m, 2 H), 4.74 (d, J = 12.5 Hz, 1 H), 4.54 (d, J = 12.5 Hz, 1 H), 3.53–3.08 (m, 1 H), 1.10 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.7, 163.2, 157.3, 130.2, 128.8, 128.6, 128.2, 59.7, 30.2, 21.0, 20.7. Anal. Calcd for $C_{13}H_{15}N_3OS$: C, 59.75; H, 5.79; N, 16.08; S, 12.27. Found: C, 59.50; H, 5.74; N, 15.89; S, 12.43.

6-(Benzylsulfinyl)-5-phenyl-1,2,4-triazine (4d). The chromatographic eluent first was 1:2 ether/petroleum ether and then 1:1 methylene chloride/ether; **4d** (89%) was obtained as a pale yellow solid, mp 135.0–137.0 °C: IR (KBr) 1600, 1515, 1500, 1480, 1455, 1445, 1400, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 7.60–7.37 (m, 5 H), 7.31–7.12 (m, 3 H), 7.12–6.97 (m, 2 H), 4.69 (d, J = 12.2 Hz, 1 H), 4.45 (d, J = 12.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 162.4, 158.0, 157.3, 131.9, 130.1, 129.8, 128.8, 128.6, 128.4, 59.0. Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23; S, 10.86. Found: C, 65.02; H, 4.25; N, 14.36; S, 11.02.

General Synthesis of 6-(Alkylsulfonyl)-1,2,4-triazines 5. To a stirred solution of the 6-(alkylthio)-1,2,4-triazine **3** (6.00 mmol) in methylene chloride (20 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% technical solid, 2.58 g, 12.70 mmol max, 2.12 equiv max) as a solid all at once. The resulting mixture was stirred at room temperature with exclusion of moisture for 3–8 h, depending on the substrate. The reaction mixture was then filtered, and the collected *m*-chlorobenzoic acid was washed with a small amt. of ice-cold methylene chloride. The methylene chloride filtrates were combined, washed with a saturated solution of sodium bicarbonate (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residual oil or solid using silica gel (approximately 50 g) and elution with the appropriate solvent system yielded the 6-(alkylsulfonyl)-1,2,4-triazine **5**.

5-Methyl-6-(methylsulfonyl)-1,2,4-triazine (5a). The reaction time was 3.0 h, and the eluent was 1:2 ether/petroleum ether; **5a** (80%) was obtained as a yellow oil: IR (neat) 1520–1510, 1400, 1330–1300, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.68 (s, 1 H), 3.56 (s, 3 H), 2.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 158.5, 158.1, 39.8, 21.4. Anal. Calcd for $C_5H_7N_3O_2S$: C, 34.68; H, 4.07; N, 24.26; S, 18.51. Found: C, 34.81; H, 4.11; N, 24.25; S, 18.42.

6-(Benzylsulfonyl)-5-methyl-1,2,4-triazine (5b). The reaction time was 3.0 h, and the eluent was methylene chloride; **5b** (97%) was obtained as a pale yellow oil that crystallized upon cooling, mp 57.0–58.5 °C: IR (neat) 1600, 1515, 1495, 1450, 1400, 1320, 1240–1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.61 (s, 1 H), 7.47–7.27 (m, 5 H), 4.98 (s, 2 H), 2.76 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.2, 159.5, 157.8, 131.6, 129.1, 128.7, 126.0, 58.3, 21.5; LRMS (relative intensity) m/z 249 (M^+, 14), 184 (13), 117 (10), 91 (100), 65 (11); HRMS calcd for $C_{11}H_{11}N_3O_2S$ 249.0572, found 249.0574 ± 0.0025. Anal. Calcd for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 53.14; H, 4.21; N, 16.61; S, 12.68.

6-(Benzylsulfonyl)-5-isopropyl-1,2,4-triazine (5c). The reaction time was 4.0 h, and the eluent was 1:4 ether/petroleum ether; **5c** (88%) was obtained as a pale yellow oil: IR (neat) 1600, 1580, 1515–1490, 1450, 1400, 1320, 1150–1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.68 (s, 1 H), 7.45–7.42 (m, 2 H), 7.36–7.33 (m, 3 H), 5.00 (s, 2 H), 3.82 (sept, J = 6.7 Hz, 1 H), 1.25 (d, J = 6.7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.1, 159.8, 158.4, 131.9, 129.3, 128.9, 126.3, 58.7, 31.5, 21.4. Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15; S, 11.56. Found: C, 56.17; H, 5.39; N, 14.91; S, 11.46.

6-(Benzylsulfonyl)-5-phenyl-1,2,4-triazine (5d). The reaction time was 8.0 h, and the eluent was methylene chloride; **5d** (71%) was obtained as a pale yellow crystalline solid, mp 99.5–101.0 °C: IR (KBr) 1600, 1510–1470, 1440, 1390, 1320, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 7.98–7.87 (m, 2 H), 7.55–7.22 (m, 8 H), 4.99 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.3, 157.5, 157.2, 132.7, 132.4, 131.7, 130.3, 129.0, 128.6, 128.5, 126.1, 58.5. Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50; S, 10.30. Found: C, 61.46; H, 4.40; N, 13.34; S, 10.08.

General Procedure for the Diels–Alder Reaction of 6-(Alkylthio)-1,2,4-triazines 3 with Enamines To Form Fused Pyridines 6 and 17. A solution of the 6-(alkylthio)-1,2,4-triazine **3** (3.00 mmol) and the appropriate enamine [**9** or **11**/**12**] (6.00 mmol, 2.0 equiv) in dioxane (10 mL) was heated at reflux (101 °C) for 9–48 h, depending on the substrate. A saturated solution of sodium bicarbonate (10 mL) was added to the reaction solution, which was then extracted with methylene chloride (2 × 20 mL). The methylene chloride extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil or solid was column chromatographed on silica gel (approximately 50 g); elution with the appropriate solvent system yielded the 3,4-fused-5-(alkylthio)pyridine **6** or **17**.

3,4-Cyclopenteno-6-methyl-5-(methylthio)pyridine (6a). The reactants were **3a** and **9b**, the reaction time was 48 h, and the eluent was 1:5 ether/petroleum ether; **6a** (91% actual, 99% conversion) was obtained as a pale yellow oil: IR (neat) 1580, 1545, 1500, 1435, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1 H), 3.13–2.87 (m, 4 H), 2.71 (s, 3 H), 2.29 (s, 3 H), 2.27–1.92 (m, 2 H); ^{13}C NMR

($CDCl_3$) δ 158.5, 158.0, 143.7, 137.7, 127.9, 33.2, 30.7, 24.6, 22.8, 17.7. Anal. Calcd for $C_{10}H_{13}NS$: C, 66.99; H, 7.31; N, 7.81; S, 17.88. Found: C, 67.31; H, 7.44; N, 7.47; S, 18.04.

5-(Benzylthio)-3,4-cyclopenteno-6-methylpyridine (6b). The reactants were **3b** and **9a**, the reaction time was 13 h, and the eluent was 1:3 ether/petroleum ether; **6b** (95%) was obtained as a clear, pale yellow liquid: IR (neat) 1595, 1580, 1540, 1490, 1450, 1430, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.18–6.89 (m, 5 H), 3.78 (s, 2 H), 2.91–2.55 (m, 4 H), 2.59 (s, 3 H), 2.03–1.78 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.8, 159.5, 143.9, 137.7, 137.3, 128.4, 127.9, 126.7, 125.0, 39.1, 33.0, 30.5, 24.3, 22.6; LRMS (relative intensity) *m/z* 255 (32, M^+), 254 (34), 180 (13), 164 (38), 149 (8), 97 (40), 91 (100), 84 (77), 77 (44), 65 (74), 55 (56). Anal. Calcd for $C_{16}H_{17}NS$: C, 75.25; H, 6.71; N, 5.48. Found: C, 74.99; H, 6.58; N, 5.24.

5-(Benzylthio)-3,4-cyclopenteno-6-phenylpyridine (6d). The reactants were **3d** and **9a**, the reaction time was 9 h, and the eluent was 1:2 ether/petroleum ether; **6d** (98%) was obtained as a pale yellow oil: IR (neat) 1600, 1575, 1540, 1495, 1450, 1430, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39 (s, 1 H), 7.70–7.56 (m, 2 H), 7.46–7.31 (m, 3 H), 7.18–7.03 (m, 3 H), 6.92–6.77 (m, 2 H), 3.47 (s, 2 H), 3.00–2.73 (m, 4 H), 2.20–1.79 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.0, 144.2, 140.5, 138.6, 137.5, 129.5, 129.3, 128.6, 128.0, 127.8, 127.6, 126.8, 125.1, 38.9, 33.5, 30.7, 24.5. Anal. Calcd for $C_{21}H_{19}NS$: C, 79.45; H, 6.03; N, 4.41; S, 10.10. Found: C, 79.68; H, 6.12; N, 4.60; S, 10.10.

5-Methyl-6-(methylthio)-2,7-dihydrofuro[3,4-*c*]pyridine (17). The reactants were **3a** and **11/12**, the reaction time was 65 h, and the eluent was 1:4 ether/petroleum ether; **17** (9% actual, 49% conversion based on recovered starting material) was obtained as a clear, colorless oil: IR (neat) 1590, 1560, 1440, 1390, 1355 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (s, 1 H), 5.16 (s, 4 H), 2.74 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.0, 153.5, 140.9, 133.5, 125.4, 73.3, 72.4, 22.5, 17.8. Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.72; S, 17.69. Found: C, 59.92; H, 6.33; N, 7.93; S, 17.42.

Also recovered by chromatography from this reaction as a less polar product was 3-morpholino-2-(3-tetrahydrofuryl)furan (**20**) (16% based on starting enamine) as a clear, colorless oil that crystallized upon cooling, mp 64.0–67.0 °C: IR (KBr) 1620, 1505, 1445, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (d, *J* = 2.0 Hz, 1 H), 6.34 (d, *J* = 2.0 Hz, 1 H), 4.06–3.50 (m, 9 H), 2.85–2.74 (m, 4 H), 2.31–2.06 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 145.3, 140.1, 134.8, 105.5, 71.3, 68.2, 67.1, 53.8, 36.6, 31.1; LRMS (relative intensity) *m/z* 224 (12), 223 (M^+, 100), 195 (12), 180 (11), 164 (32), 134 (33), 120 (20), 108 (13). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56; H, 7.68; N, 6.27. Found: C, 64.47; H, 7.41; N, 6.44.

General Procedure for the Diels–Alder Reaction of 6-(Alkylsulfinyl)-1,2,4-triazines 4 with Enamines To Form Fused 5-(Alkylsulfinyl)pyridines 7 and 18. To a stirred solution of the triazine **4** (3.00 mmol) and glacial acetic acid (8.00 mmol, 2.7 equiv) in anhydrous methylene chloride (10 mL) at 0 °C was added rapidly the enamine **9** or **11/12** (4.00 mmol, 1.3 equiv) dropwise. The resulting effervescing solution was then stirred at room temperature under nitrogen for 5–29 h, depending on the substrate. The resulting reaction solution was evaporated under reduced pressure, and the residual oil was chromatographed on silica gel (approximately 50 g); elution with the appropriate solvent system afforded the 5-(alkylsulfinyl)pyridines **7** or **18**.

5-(Benzylsulfinyl)-3,4-cyclopenteno-6-methylpyridine (7b). The reactants were **4b** and **9a**, the reaction time was 6.0 h, and elution was with ether; **7b** (88%) was obtained as a pale yellow oil: IR (neat) 1580, 1540, 1490, 1445, 1430, 1380, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 7.32–7.17 (m, 3 H), 7.00–6.89 (m, 2 H), 4.24 (s, 2 H), 3.23–2.43 (m, 4 H), 2.34 (s, 3 H), 2.07–1.72 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 154.6, 153.2, 146.6, 140.1, 131.8, 130.3, 129.0, 128.4, 128.2, 59.1, 30.8, 28.8, 25.2, 21.5; LRMS (relative intensity) *m/z* 271 (11, M^+), 255 (6), 165 (5), 91 (100); HRMS calcd for $C_{16}H_{17}NOS$ 271.1031, found 271.1029 ± 0.0027.

5-(Benzylsulfinyl)-3,4-cyclopenteno-6-isopropylpyridine (7c). The reactants were **4c** and **9a**, the reaction time was 13.0 h, and elution was with 1:1 ethyl acetate/petroleum ether; **7c** (68%) was obtained as a pale yellow oil that crystallized upon cooling, mp 84.5–87.5 °C: IR (KBr) 1600, 1570, 1540, 1490, 1465, 1450, 1430, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (s, 1 H), 7.30–7.18 (m, 3 H), 7.06–6.93 (m, 2 H), 4.24 (s, 2 H), 3.37–3.00 (m, 2 H), 2.88–2.47 (m, 3 H), 2.18–1.76 (m, 2 H), 1.25 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.1, 154.4, 147.2, 140.0, 130.8, 130.3, 129.3, 128.5, 128.2, 59.9, 31.4, 31.1, 28.8, 25.3, 22.7, 21.4. Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68; S, 10.71. Found: C, 72.00; H, 7.10; N, 4.93; S, 10.55.

5-(Benzylsulfinyl)-3,4-cyclopenteno-6-phenylpyridine (7d). The reactants were **4d** and **9a**, the reaction time was 5.0 h, and elution was with 1:1 ethyl acetate/petroleum ether; **7d** (92%) was obtained as a pale yellow solid, mp 160.0–162.0 °C: IR (KBr) 1600, 1570, 1530, 1490, 1430, 1370, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (s, 1 H), 7.50–7.05 (m, 8 H), 6.88–6.72 (m, 2 H), 4.03 (d, *J* = 12.8 Hz, 1 H), 3.82 (d, *J* = 12.7 Hz, 1 H), 3.64–3.28 (m, 1 H), 2.93–2.49 (m, 3 H), 2.20–1.78 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.4, 146.7, 141.8, 138.1, 131.8, 130.1, 129.8, 129.3, 129.1, 128.7, 128.5, 128.2, 128.0, 58.5, 30.9, 28.7, 25.3. Anal. Calcd for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74; N, 4.20; S, 9.62. Found: C, 75.39; H, 5.77; N, 4.35; S, 9.40.

5-Methyl-6-(methylsulfinyl)-2,7-dihydrofuro[3,4-*c*]pyridine (18). The reactants were **4a** and **11/12** and the reaction time was 29 h; after 3 h, a second addition of **11/12** (1.0 equiv) was made (2.2 equiv total). Elution with 1:1 ethyl acetate/petroleum ether yielded **18** (67%) as an off-white crystalline solid, mp 140.5–142.0 °C: IR (KBr) 1590, 1550, 1440, 1410, 1390, 1350, 1060–1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.48 (s, 1 H), 5.74 (dd, *J* = 4.4 and 2.2 Hz, 2 H), 5.07 (br m, 2 H), 2.80 (s, 3 H), 2.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.2, 148.4, 143.7, 136.4, 134.7, 71.2, 69.6, 40.3, 21.5. Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; S, 16.25. Found: C, 55.09; H, 5.45; N, 7.05; S, 16.36.

General Procedure for the Diels–Alder Reaction of 6-(Alkylsulfonyl)-1,2,4-triazines 5 with Enamines To Form Fused 5-(Alkylsulfonyl)pyridines 8 and 19. To a stirred solution of the triazine **5** (3.00 mmol) and glacial acetic acid (8.00 mmol, 2.7 equiv) in anhydrous methylene chloride (10 mL) at 0 °C was added rapidly the enamine **9** or **11/12** (4.00 mmol, 1.3 equiv) dropwise. The resulting effervescing solution was then stirred at either 0 °C or at room temperature under nitrogen for 20 min–3 h, depending on the substrate. The resulting reaction solution was evaporated under reduced pressure, and the residual oil was chromatographed on silica gel (approximately 50 g). Elution with the appropriate solvent system afforded the 5-(alkylsulfonyl)pyridines **8** or **19**.

5-(Benzylsulfonyl)-3,4-cyclopenteno-6-methylpyridine (8b). The reactants were **5b** and **9a**, the reaction conditions were 20 min at 0 °C, and elution was with 1:2 ether/petroleum ether; **8b** (66%) was obtained as a white crystalline solid, mp 138.0–139.0 °C: IR (KBr) 1580, 1535, 1490, 1440, 1430, 1410, 1395, 1310, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (s, 1 H), 7.36–7.12 (m, 3 H), 7.10–6.92 (m, 2 H), 4.34 (s, 2 H), 2.87–2.64 (m, 4 H), 2.74 (s, 3 H), 1.99–1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.1, 155.9, 148.1, 139.1, 130.8, 129.1, 128.7, 128.4, 127.7, 62.2, 34.3, 29.6, 24.8, 24.1. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 67.05; H, 5.89; H, 5.89; N, 4.82; S, 11.48.

5-(Benzylsulfonyl)-3,4-cyclopenteno-6-isopropylpyridine (8c). The reactants were **5c** and **9b**, reaction conditions were 30 min at room temperature, and elution was with 1:2 ether/petroleum ether; **8c** (88%) was obtained as a white crystalline solid, mp 135.0–137.0 °C: IR (KBr) 1570, 1535, 1490, 1460, 1450, 1440, 1430, 1305, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.52 (s, 1 H), 7.30–7.18 (m, 3 H), 7.03–6.99 (m, 2 H), 4.34 (s, 2 H), 3.95 (sept, *J* = 6.6 Hz, 1 H), 2.78–2.68 (m, 4 H), 1.79–1.68 (m, 2 H), 1.27 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 165.0, 157.1, 148.9, 139.3, 131.1, 129.0, 128.7, 127.9, 63.3, 34.9, 32.2, 29.9, 25.0, 23.1. Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44; S, 10.16. Found: C, 68.74; H, 6.68; N, 4.57; S, 10.36.

5-(Benzylsulfonyl)-3,4-cyclopenteno-6-phenylpyridine (8d). The reactants were **5d** and **9a**, reaction conditions were 3 h at room temperature, and elution was with ether followed by recrystallization of the resulting solid from ether/hexanes; **8d** (46%) was obtained as an off-white crystalline solid, mp 170.0–171.5 °C: IR (KBr) 1600, 1570, 1530, 1490, 1450, 1440, 1430, 1320, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (s, 1 H), 7.44 (s, 5 H), 7.30–7.18 (m, 3 H), 7.04–6.92 (m, 2 H), 4.04 (s, 2 H), 3.08–2.83 (m, 4 H), 2.06–1.73 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.1, 147.8, 141.0, 139.5, 130.9, 129.5, 128.7, 128.6, 128.5, 128.0, 127.6, 127.1, 62.2, 34.6, 29.8, 24.9. Anal. Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01; S, 9.18. Found: C, 72.29; H, 5.40; N, 4.24; S, 9.40.

5-Methyl-6-(methylsulfonyl)-2,7-dihydrofuro[3,4-*c*]-pyridine (19). The reactants were **5a** and **11/12**, tetrahydrofuran was the reaction solvent, reaction conditions were 0 °C and 90 min, and elution was with 5% methanol in methylene chloride; **19** (61%) was obtained as a white fluffy crystalline solid, mp 169.5–171.0 °C: IR (KBr) 1585, 1550, 1460, 1445, 1410, 1300, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (br s, 1 H), 5.39 (t, J = 2.0 Hz, 2 H), 5.18–5.04 (br m, 2 H), 3.13 (s, 3 H), 2.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.4, 151.0, 145.5, 135.7, 130.6, 74.0, 70.9, 44.0, 23.3. Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57; S, 15.04. Found: C, 50.88; H, 4.94; N, 6.44; S, 14.99.

Tetrahydrofuran-3-one (10). To a stirred solution of tetrahydrofuran-3-ol (17.53 g, 0.20 mol) in acetone (600 mL) at room temperature was added a solution of Jones reagent (2.2 M chromium trioxide, 55.0 mL, 0.121 mol, 0.6 equiv) dropwise at room temperature over the course of 2 h. The resulting reaction mixture was stirred at room temperature for an additional 1 h and filtered, and the filtrate was concentrated by distillation at atmospheric pressure to yield a clear blue liquid (20 mL). This liquid was dissolved in ether (30 mL), and the resulting solution was washed once with a saturated solution of ammonium chloride (30 mL), dried ($MgSO_4$), and fractionally distilled at 60 mmHg to afford tetrahydrofuran-3-one (7.95 g, 0.923 mol, 46%) as a clear, colorless liquid boiling at 62.5 °C at 60 mmHg [lit.[8] bp, 139–140 °C]: IR (neat) 1755, 1430, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.26 (t, J = 7.3 Hz, 2 H), 3.87 (s, 2 H), 2.50 (t, J = 7.3 Hz, 2 H).

3-Morpholino-2,5-dihydrofuran (11)/3-Morpholino-4,5-dihydrofuran (12). A mixture of tetrahydrofuran-3-one (2.31 g, 26.83 mmol), morpholine (4.70 mL, 53.89 mmol, 2.0 equiv), and anhydrous magnesium sulfate (6.0 g) in anhydrous ether (40 mL) was stirred at room temperature with exclusion of moisture for 17 h. Every hour for the first 7 h, additional anhydrous magnesium sulfate (1.0 g) was added to the reaction mixture. The mixture was then filtered, and the filtrate was concentrated by evaporation under reduced pressure to yield a 6:1 mixture of 3-morpholino-2,5-dihydrofuran (**11**)/3-morpholino-4,5-dihydrofuran (**12**) (4.10 g, 26.42 mmol, 99%)[8] as a pale yellow liquid [in the enamine mixture **11/12**, the presence of the lesser isomer [3-morpholino-4,5-dihydrofuran (**12**)] could be confirmed by the proton NMR spectrum of the mixture [C-2 olefinic proton at δ 5.80 (t, J = 2.0 Hz, 1 H)]]: IR (neat) 1630, 1450, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.76–4.42 (m, 3 H), 3.86–3.60 (m, 6 H), 2.92–2.80 (m, 4 H); LRMS (relative intensity) m/z 156 (13% of M^+), 155 (54, M^+), 154 (48), 126 (26), 87 (39), 69 (43), 57 (100), 41 (77); HRMS calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0941 ± 0.0016.

6-Ethoxy-5-methyl-1,2,4-triazine (14). 5-Methyl-6-(methylthio)-1,2,4-triazine (**3a**) (0.71 g, 5.03 mmol) was added to a stirred solution of sodium hydride (60% oil, 0.24 g, 6.00 mmol, 1.2 equiv) in absolute ethanol (15 mL), and the resulting solution was heated at reflux (78 °C) under nitrogen for 30 min. Ethanol was then removed from the reaction solution by evaporation under reduced pressure, and the residue was suspended in a saturated solution of sodium bicarbonate (15 mL). This aqueous mixture was extracted with ether (3 × 20 mL), and the extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield a yellow oil. Column chromatography of this oil on silica gel (approximately 40 g) and elution with 1:1 ether/petroleum ether afforded **14** (0.50 g, 3.54 mmol, 70%) as a pale yellow oil that crystallized upon cooling, mp 31.0–33.5 °C: IR (neat) 1560, 1530, 1470, 1435, 1370, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.07 (s, 1 H), 4.60 (q, J = 7.0 Hz, 2 H), 2.51 (s, 3 H), 1.50 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.4, 153.0, 152.0, 63.7, 18.9, 14.3; LRMS (relative intensity) m/z 139 (53, M^+), 111 (89), 82 (29), 67 (26), 56 (100), 44 (84); HRMS calcd for $C_6H_9N_3O$ 139.0745, found 139.0745 ± 0.0014.

3,4-Cyclopenteno-5-ethoxy-6-methylpyridine (15). A solution of 6-ethoxy-5-methyl-1,2,4-triazine (0.48 g, 3.45 mmol), 1-morpholino-1-cyclopentene (1.70 mL, 10.62 mmol, 3.1 equiv), and chlorobenzene (3 mL) was heated at reflux (132 °C) under nitrogen for 144 h. The reaction was then concentrated by evaporation under reduced pressure. The residual oil was column chromatographed on silica gel (approximately 40 g), and elution with 1:4 ether/petroleum ether yielded **15** (R_f = 0.35 in ether, 0.24 g, 1.35 mmol, 39% actual, 61% conversion) as a pale brown liquid: IR (neat) 1600, 1560, 1460, 1435, 1410, 1380, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1 H), 3.99 (q, J = 7.0 Hz, 2 H), 3.03–2.82 (m, 4 H), 2.47 (s, 3 H), 2.26–1.88 (m, 2 H), 1.38 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.1, 149.0, 143.6, 139.9, 139.3, 67.7, 30.2, 30.1, 25.3, 18.9, 15.7; LRMS (relative intensity) m/z 177 (77, M^+), 149 (85), 148 (100), 77 (38), 44 (99); HRMS calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1156 ± 0.0018. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.30; H, 8.53; N, 7.90.

3-(Benzylthio)-5-phenyl-1,2,4-triazine (23). To a stirred solution of 5-phenyl-1,2,4-triazine-3-thione[10] (4.00 g, 21.14 mmol) and triethylamine (3.10 mL, 22.24 mmol, 1.05 equiv) in anhydrous tetrahydrofuran (50 mL) at 0 °C was added benzyl bromide (2.65 mL, 22.28 mmol, 1.05 equiv) dropwise. The resulting reaction mixture was stirred at 0 °C with exclusion of moisture for 1 h. A saturated solution of ammonium chloride (50 mL) was added to the reaction mixture, which was then extracted with ether (3 × 50 mL). The ether extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield a yellow solid. This solid was dissolved in methylene chloride (25 mL), and the resulting solution was passed through a silica gel filter (approximately 50 g) followed by elution with ether (300 mL). The eluate was evaporated under reduced pressure, and the residual solid was suspended in boiling ether/hexanes (1:1, 50 mL). The undissolved solid from the cooled mixture was filtered to yield **23** (4.47 g, 16.00 mmol, 76%) as a pale orange solid, mp 106.5–108.5 °C: IR (KBr) 1600, 1530, 1490, 1450, 1435, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.32 (s, 1 H), 8.13–8.00 (m, 2 H), 7.59–7.15 (m, 8 H), 4.55 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.9, 154.5, 142.1, 136.7, 133.0, 132.5, 129.2, 129.0, 128.5, 127.5, 127.4, 35.0. Anal. Calcd for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04; S, 11.48. Found: C, 69.03; H, 4.61; N, 15.18; S, 11.67.

3-(Benzylsulfinyl)-5-phenyl-1,2,4-triazine (24). To a stirred solution of 3-(benzylthio)-5-phenyl-1,2,4-triazine (1.21 g, 4.33 mmol) in anhydrous methylene chloride (15 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% technical solid, 0.91 g, 4.48 mmol max, 1.03 equiv max) as a solid all at once. The resulting mixture was stirred at 0 °C with exclusion of moisture for 1 h. The reaction mixture was then filtered, and the filtrate was evaporated under reduced pressure to yield a yellow oil. Column chromatography of this oil on silica gel (approximately 40 g, dried in a vacuum oven at 150 °C overnight) and elution first with 1:1 ether/petroleum ether and then with 5% ethyl acetate in ether afforded **24** (1.15 g, 3.89 mmol, 90%) as a pale yellow solid, mp 124.5–126.0 °C: IR (KBr) 1600, 1535, 1490, 1450, 1440, 1405, 1320, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.70 (s, 1 H), 8.24–8.13 (m, 2 H), 7.67–7.47 (m, 3 H), 7.23 (s, 5 H), 4.58 (d, J = 12.9 Hz, 1 H), 4.40 (d, J = 12.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 156.6, 146.2, 133.5, 131.8, 130.0, 129.4, 129.1, 128.5, 128.4, 128.0, 60.2. Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23; S, 10.86. Found: C, 64.83; H, 4.17; N, 14.07; S, 10.68.

3-(Benzylsulfonyl)-5-phenyl-1,2,4-triazine (25). To a stirred solution of 3-(benzylthio)-5-phenyl-1,2,4-triazine (2.00 g, 7.16 mmol) in anhydrous methylene chloride (30 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% technical solid, 3.00 g, 14.78 mmol max, 2.06 equiv max) as a solid all at once. The resulting mixture was stirred at room temperature with exclusion of moisture for 4 h. The reaction mixture was then filtered, and the filtrate was evaporated under reduced pressure to yield a solid/oil mixture. Trituration of this mixture with anhydrous ether afforded **25** (1.50 g, 4.82 mol, 67%) as a white crystalline solid, mp 98.5–100.0 °C: IR (KBr) 1600, 1535, 1490, 1455, 1440, 1410, 1330–1310, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.78 (s, 1 H), 8.26–8.15 (m, 2 H), 7.66–7.24 (m, 8 H), 4.94 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 157.1, 147.5, 134.0, 131.3, 129.8, 129.6, 129.0, 128.7, 128.2, 126.1, 58.1. Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50; S, 10.30. Found: C, 61.51; H, 4.29; N, 13.24; S, 10.53.

2-(Benzylsulfinyl)-3,4-cyclopenteno-6-phenylpyridine (27). To a stirred solution of 3-(benzylsulfinyl)-5-phenyl-1,2,4-triazine (0.85 g, 2.88 mmol) and glacial acetic acid (0.50 mL, 8.73 mmol, 3.0 eq) in anhydrous methylene chloride (10 mL) at room temperature under nitrogen was added 1-morpholino-1-cyclopentene (**9b**) (0.69 mL, 4.31 mmol, 1.50 equiv) dropwise. The resulting effervescing solution was stirred at room temperature under nitrogen for 3 h, at which time TLC of the reaction showed full consumption of the starting triazine. A saturated solution of sodium bicarbonate (10 mL) was then added to the reaction solution, which was extracted with methylene chloride (2 × 15

mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield a brown oil (1.5 g). Column chromatography of this oil on silica gel (ca. 40 g) and elution with 1:1 ethyl acetate/petroleum ether yielded a brown solid/oil mixture (R_f = 0.6 in ethyl acetate). Trituration of this mixture with ether gave **27** (0.090 g, 0.27 mmol, 9%) as a white crystalline solid, mp 153.5–155.5 °C: IR (KBr) 1595, 1530, 1490, 1450, 1440, 1425, 1360, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08–7.97 (m, 2 H), 7.62 (s, 1 H), 7.53–7.37 (m, 3 H), 7.28–7.12 (m, 3 H), 7.06–6.89 (m, 2 H), 4.43 (d, J = 12.7 Hz, 1 H), 4.20 (d, J = 12.8 Hz, 1 H), 3.05–2.28 (m, 4 H), 2.01–1.69 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.9, 155.0, 139.9, 138.1, 130.4, 129.5, 129.1, 128.6, 128.0, 127.8, 126.7, 117.4, 59.2, 31.8, 28.4, 25.0; LRMS (relative intensity) m/z 333 (10, M^+), 91 (100); HRMS calcd for $C_{21}H_{19}NOS$ 333.1187, found 333.1176 ± 0.0033.

2-(Benzylsulfonyl)-3,4-cyclopenteno-6-phenylpyridine (28). To a stirred solution of 3-(benzylsulfonyl)-5-phenyl-1,2,4-triazine (0.78 g, 2.51 mmol) and glacial acetic acid (0.36 mL, 6.29 mmol, 2.5 equiv) in anhydrous methylene chloride (10 mL) at 0 °C under nitrogen was added 1-morpholino-1-cyclopentene (**9b**) (0.50 mL, 3.12 mmol, 1.24 equiv) dropwise. The resulting effervescing solution was stirred at 0 °C under nitrogen for 30 min and then at room temperature for 30 min. The reaction mixture was concentrated by evaporation under reduced pressure to yield a brown oil. Trituration of this oil with ether (20 mL) with cooling yielded **28** (0.40 g, 1.17 mmol, 46%) as a white crystalline solid, mp 178.0–179.5 °C: IR (KBr) 1600, 1530, 1490, 1445, 1430, 1400, 1310, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12–8.00 (m, 2 H), 7.77 (s, 1 H), 7.55–7.39 (m, 3 H), 7.24 (s, 5 H), 4.77 (s, 2 H), 3.12–2.82 (m, 4 H), 2.13–1.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.1, 155.1, 138.9, 137.6, 131.3, 131.1, 129.5, 128.7, 128.4, 127.9, 126.8, 119.7, 58.1, 32.4, 30.5, 24.6. Anal. Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01; S, 9.18. Found: C, 72.22; H, 5.23; N, 4.13; S, 8.93.

4-Carbomethoxy-6-(4-chlorophenyl)-2-(methylsulfonyl)-pyridine (31). A solution of 5-(4-chlorophenyl)-3-(methylsulfonyl)-1,2,4-triazine[14] (**30**) (0.81 g, 3.00 mmol) and methyl 3-pyrrolidinoacrylate[13] (0.47 g, 3.03 mmol) in anhydrous tetrahydrofuran (25 mL) was heated at reflux (66 °C) under nitrogen for 24 h. The resulting reaction solution was evaporated under reduced pressure, and the residual solid was column chromatographed on silica gel (approximately 40 g) followed by elution with methylene chloride to afford **31** (R_f = 0.4 in methylene chloride) (0.49 g, 1.50 mmol, 50%) as a pale yellow solid, mp 164.5–167.0 °C: IR (KBr) 1725–1715, 1585, 1530, 1480, 1425, 1295, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 8.06 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.5 Hz, 2 H), 4.04 (s, 3 H), 3.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.9, 159.0, 157.8, 140.8, 137.0, 134.5, 129.3, 128.4, 122.9, 118.4, 53.3, 39.8. Anal. Calcd for $C_{14}H_{12}ClNO_4S$: C, 51.62; H, 3.71; Cl, 10.88; N, 4.30; S, 9.84. Found: C, 54.41; H, 3.53; Cl, 10.81; N, 4.54; S, 10.10.

Further elution using ethyl acetate yielded crude 5-(4-chlorophenyl)-3-pyrrolidino-1,2,4-triazine (**32**) (0.40 g, 1.5 mmol, 50% crude) as a pale yellow solid. Trituration of this solid in ether provided the analytically pure sample: IR (KBr) 1590, 1570, 1540–1510, 1475, 1455, 1395 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 8.07–8.03 (m, 2 H), 7.49–7.45 (m, 2 H), 3.73 (br m, 4 H), 2.06 (br m, 4 H). Anal. Calcd for $C_{13}H_{13}ClN_4$: C, 59.89; H, 5.03; Cl, 13.60; N, 21.49. Found: C, 59.95; H, 5.03; Cl, 13.82; N, 21.26.

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Registry No. **1a**, 99702-42-8; **1c**, 99702-44-0; **1d**, 99702-43-9; **2a**, 99702-45-1; **2c**, 99702-47-3; **2d**, 99702-46-2; **3a**, 118459-16-8; **3b**, 99702-48-4; **3c**, 99702-50-8; **3d**, 99702-49-5; **4a**, 118459-17-9; **4b**, 99702-51-9; **4c**, 99702-53-1; **4d**, 99702-52-0; **5a**, 118459-18-0; **5b**, 99702-54-2; **5c**, 99702-56-4; **5d**, 99702-55-3; **6a**, 118459-19-1; **6b**, 99702-57-5; **6d**, 99702-60-0; **7b**, 99702-58-6; **7c**, 99702-62-2; **7d**, 99702-61-1; **8b**, 99702-59-7; **8c**, 118459-20-4; **8d**, 99702-63-3; **9a**, 7148-07-4; **9b**, 936-52-7; **10**, 22929-52-8; **11**, 106183-62-4; **12**, 106183-61-3; **13**, 14790-45-5; **14**, 99702-65-5; **15**, 99702-64-4; **17**, 118459-06-6; **18**, 118459-07-7; **19**, 118459-08-8; **20**, 118459-09-9; **23**, 117504-57-1; **24**, 118459-10-2; **25**, 118459-11-3; **27**, 118459-12-4; **28**, 118459-13-5; **29**, 90087-77-7; **30**, 105783-78-6; **31**, 118459-14-6; **32**, 118459-15-7; tetrahydrofuran-3-ol, 453-20-3; morpholine, 110-91-8; 5-phenyl-1,2,4-triazine-3-thione, 15969-28-5; pyrrolidine, 123-75-1; 6-chloro-5-methyl-1,2,4-triazine, 118459-21-5.

Synthesis of 2,4(5)-Bis(hydroxymethyl)imidazoles and 2,4(5)-Bis[(2-hydroxyethoxy)methyl]imidazoles: Precursors of 2,4(5)-Connected Imidazole Crown Ethers

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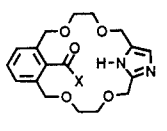
Two syntheses of 1-[(dimethylamino)sulfonyl]-2,4-bis[(2-hydroxyethoxy)methyl]imidazole, **3**, a precursor to imidazole-containing crown ethers, are described. The first involved hydroxymethylation of 1-benzylimidazole with formaldehyde to afford 1-benzyl-2,5-bis(hydroxymethyl)imidazole (**5**) (20% yield), which was elaborated into **3** in four steps. An alternative and more efficient route involved coupling of diamine **17b** with the imino ether obtained from nitrile **11b** to afford imidazoline **18b**. The imidazoline was found to oxidize under Swern conditions, providing a mild new method of imidazole synthesis. Sulfamylation and debenzylation produced **3**. This approach was also applied to the synthesis of 1-[(dimethylamino)sulfonyl]-2,4-bis(hydroxymethyl)imidazole (**2**). Diol **3** was converted into 2,4-connected imidazole crown ethers, one of which (**4**) formed a crystalline complex with water. The complex structure was determined by X-ray crystallography.

As part of an effort directed toward modeling the enzymatic His-Asp couple, we recently described the synthesis of imidazole-containing crown ether **1** in which the imidazole ring was linked from C-2 to C-4(5).[1] To our knowledge this was the first report of a 2,4(5)-connected imidazole crown ether. This is remarkable given the large number of crown ethers that have been synthesized.[2] The



1: X = OH
4: X = OMe

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