followed by sequential treatment with (phenylthio)trimethylsilane and acetone as described above gave the optically active 1,3-diol synthon **4**. The oxirane **6** and the tetraalkyltin **7** were both prepared from synthon **4**. Reduction of **4** and coupling with ethylene oxide gave alcohol **5**.[8] Acid-catalyzed migration of the acetonide to the more stable terminal position, followed by desilylation and dehydration,[23] gave oxirane **6**. Tetraalkyltin **7**[18] and oxirane **6** were coupled by sequentially treating a solution of the two compounds with *n*-BuLi and boron trifluoride etherate at −78 °C to give alcohol **8** in 62% yield. Transmetalation proceeds faster than oxirane opening, and boron trifluoride etherate activates the oxirane for coupling. Desilylation and acid hydrolysis gave decanehexol **9**.[8] The internal bisacetonide prepared from **9** has $^1$H NMR and COSY spectra consistent with the data reported for the corresponding lienomycin degradation product, confirming the relative stereochemistry. The convergent synthesis of decanehexol **9** from 1,3-diol synthon **4** required only six linear steps and demonstrates the effectiveness of this new method for assembling the alternating polyol chains found in polyene macrolide antibiotics.

(23) Holand, S.; Epsztein, R. *Synthesis* **1977**, 706-708.

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**Supplementary Material Available:** Preparation of compounds **2** and **5**, as well as spectral data for compounds **2**, **5**, and **9** (1 page). Ordering information is given on any current masthead page.

# *Articles*

## Diels–Alder Reactions of 1,2,4-Triazines. Synthesis of Thieno[2,3-*c*]pyridines and 3,4-Dihydro-2*H*-thiopyrano[2,3-*c*]pyridines from 6-(Alkynylthio)-1,2,4-triazines

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Intramolecular Diels–Alder reactions of 6-(alkynylthio)-1,2,4-triazines are shown to give 2,3-dihydrothieno[2,3-*c*]pyridines and 3,4-dihydro-2*H*-thiopyrano[2,3-*c*]pyridines. 1-Oxo-2,3-dihydrothieno[2,3-*c*]pyridines synthesized in this fashion from the corresponding 6-(alkynylsulfinyl)-1,2,4-triazines are readily aromatized to thieno[2,3-*c*]pyridines by an acetic anhydride induced Pummerer reaction.

Inverse electron demand intramolecular Diels–Alder reactions of 1,2,4-triazines tethered to an appropriate dienophilic side chain provide a versatile and remarkably effective route to a broad variety of fused pyridines and pyrimidines.[2,3] Several years ago we developed a convenient synthesis of 1,2,4-triazin-6-ones[4] and their corresponding 6-thiones.[3k] Alkylation of the latter with 4-halo-1-butynes and 5-halo-1-pentynes, utilizing procedures analogous to those previously employed for the preparation of 3-(alkynylthio)-1,2,4-triazines,[3f] provides a family of tethered diene–dienophile pairs that are attractive intermediates for the preparation of thieno[2,3-*c*]pyridines and 3,4-dihydro-2*H*-thiopyrano[2,3-*c*]pyridines. The present paper describes these transformations in full detail.[3a]

It should be noted that thienopyridines, although not found in nature, have attracted considerable attention as components of synthetic antibiotics, as agricultural chemicals, and as dyestuffs. Previous syntheses have invariably utilized preformed pyridines or thiophenes as starting materials and have required strenuous, and often low-yielding, reaction conditions and difficultly accessible starting materials.[5] accessible starting materials.[4,5] By contrast, the conversions described below utilize readily accessible 1,2,4-triazines[3k,4,6] and alkynyl alkylating agents,

(1) Present address: Pfizer Central Research, Chas. Pfizer and Co., Groton, CT 06340.

(2) (a) For a general discussion of intramolecular Diels–Alder reactions of 1,2,4-triazines, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (b) Taylor, E. C. *Bull. Soc. Chim. Belg.* **1988**, *97*, 599.

(3) For some specific recent references to intramolecular Diels–Alder reactions of monocyclic 1,2,4-triazines, see the following: (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) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. (i) Taylor, E. C.; Pont, J. L.; van Engen, D.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 5093. (j) Taylor, E. C.; French, L. G. *J. Org. Chem.* **1989**, *54*, 1245. (k) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1989**, *54*, 1249. (l) Seitz, G.; Dietrich, S. *Arch. Pharm.* (Weinheim, Ger.) **1984**, *317*, 379. (m) Seitz, G.; Gorge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (n) Seitz, G.; Dietrich, S. *Arch. Pharm.* (Weinheim, Ger.) **1985**, *318*, 1048 and 1051. (o) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. (p) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287.

(4) Taylor, E. C.; Macor, J. E. *J. Heterocycl. Chem.* **1985**, *22*, 409.

(5) For a review of the syntheses, uses, and chemistry of thienopyridines, see: Barker, J. M. The Thienopyridines. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1977; Vol. 21, pp 65-119.

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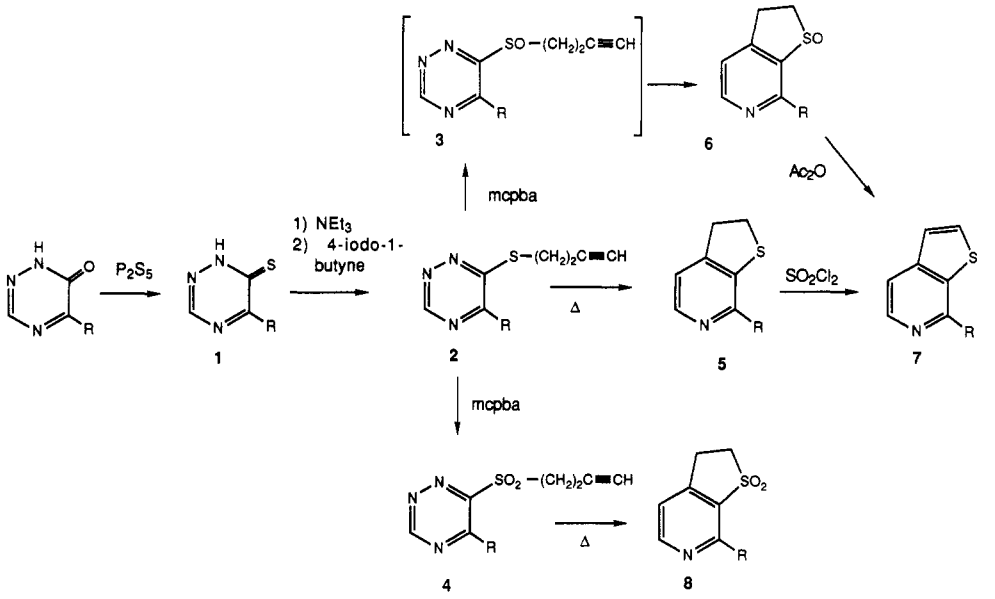
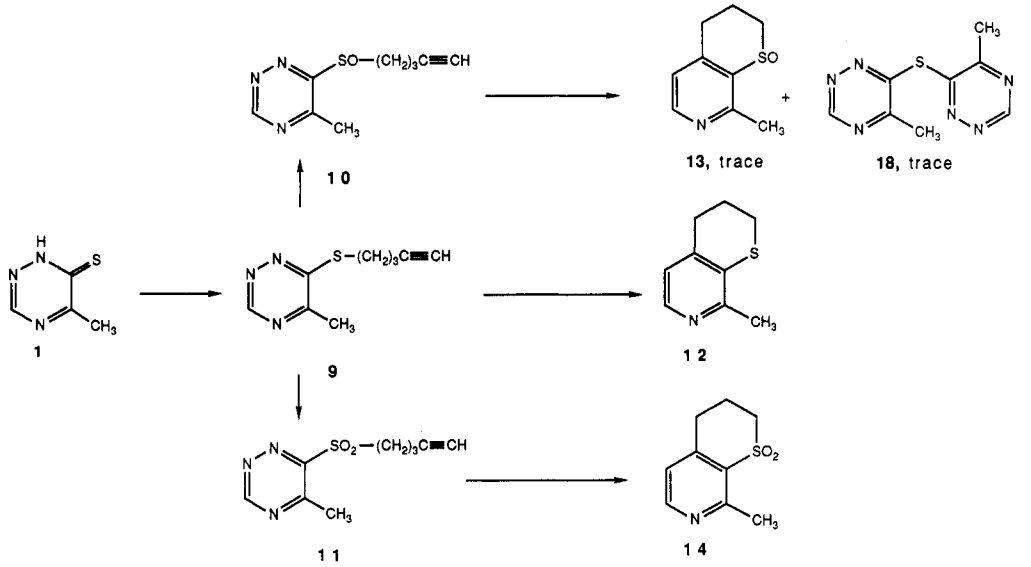
**Scheme I**[a]



[a] R = $CH_3$ (**a**), $CH(CH_3)_2$ (**b**), Ph (**c**).

**Scheme II**



thus permitting (at least in principle) wide variations in the placement and nature of substituents in the final bicyclic products.

Thus, alkylation of a series of 1,2,4-triazin-6-thiones **1a–c**[3k] with 4-iodo-1-butyne[7] in the presence of triethylamine gave the 6-(3-butynylthio)-1,2,4-triazines **2a–c** (see Scheme I). Heating **2a** in refluxing dioxane under nitrogen for 21 h afforded the 2,3-dihydrothieno[2,3-*c*]pyridine **5a** in 69% yield. By contrast, the sulfoxide **3a** (prepared from **2a** with 1 equiv of *m*-chloroperbenzoic acid (mcpba) at 0 °C) cyclized *at room temperature* over a period of 27 h to give the 1-oxo-2,3-dihydrothieno[2,3-*c*]pyridine **6a**, also in 69% yield. Oxidation of **2a** with 2 equiv of mcpba gave the sulfone **4a**, which cyclized smoothly to the 1,1-dioxo-2,3-dihydrothieno[2,3-*c*]pyridine **8a** in 75% yield (for the two steps); this more sluggish cyclization reaction required 27 h of refluxing in THF. The observed ease of the intramolecular Diels–Alder reaction (SO ≫ $SO_2$ > S) parallels precisely that observed previously with the isomeric 3-(3-butynylthio)-, 3-(3-butynylsulfinyl)-, and 3-(3-butynylsulfonyl)-1,2,4-triazines. This reactivity order appears to be a balance of electron-withdrawing ($SO_2$ > SO > S) and C–S–C bond angle (SO < S < $SO_2$) effects, as discussed previously for the 3-substituted 1,2,4-triazine isomeric series,[2b,3f] and further supported by later studies on 2-substituted pyrimidines.[8]

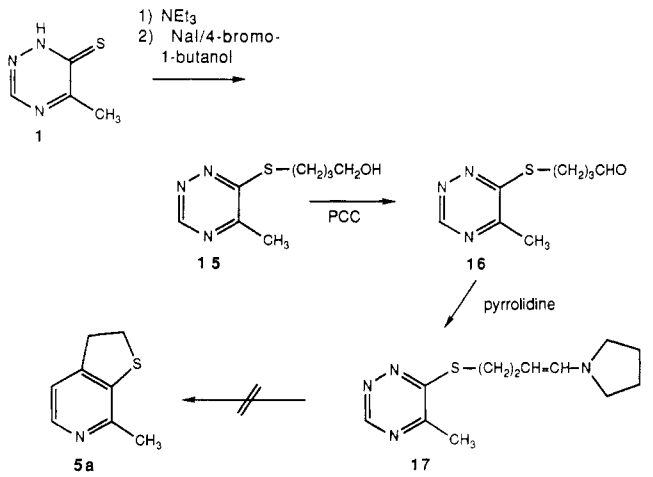
The 6-(3-butynylsulfinyl)-1,2,4-triazines **3b** and **3c** were prepared from **2b** and **2c** in analogous fashion and were cyclized to the dihydrothieno[2,3-*c*]pyridines **6b** and **6c** either at room temperature (27 h) or in refluxing methylene chloride (4–5 h). Aromatization of these 1-oxo-2,3-dihydrothieno[2,3-*c*]pyridines (**6a–c**) to **7a–c** could be readily effected by heating with acetic anhydride (Pum-

(6) For a comprehensive review of 1,2,4-triazine syntheses and chemistry, see: Neunhoffer, H. The Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons: New York, 1978; Vol. 33, pp 189–1072.

(7) Eglington, G.; Whiting, M. C. *J. Chem. Soc.* **1950**, 3650.

(8) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 803.

**Scheme III**




merer rearrangement); this procedure proved more convenient and gave higher yields of the fully aromatic thienopyridines than did direct oxidation of **5** with sulfuryl chloride.

Alkylation of **1a** with 5-chloro-1-pentyne under Finkelstein conditions yielded the homologous 6-(4-pentynylthio)-1,2,4-triazine **9**. Oxidation with 1 equiv of mcpba gave the sulfoxide **10**, while 2 equiv of mcpba gave the sulfone **11** (see Scheme II). The results of attempted intramolecular Diels–Alder reactions with these homologous intermediates differed significantly from those observed with their lower homologues **2–4**, as described above. Much more vigorous conditions were required for the conversion of **9** to 3,4-dihydro-2*H*-thiopyrano[2,3-*c*]-pyridine **12** (refluxing bromobenzene for 64 h; 57% yield), although this observation is not surprising in view of the known dependency of the intramolecular Diels–Alder reaction on the length of the tether separating diene from dienophile.[9] The sulfoxide **10** gave only a trace of the expected 1-oxo-3,4-dihydro-2*H*-thiopyrano[2,3-*c*]pyridine **13**;[10] no reaction whatsoever took place below 100 °C, while decomposition was rapid above this temperature. The only other product identified under these latter conditions was the symmetrical sulfide **18**,[11] which was apparently formed by a complex series of decomposition pathways involving elimination of the 4-pentynyl side chain to give a 1,2,4-triazine-6-sulfenic acid, which then may have disproportionated to a sulfide and a sulfonic acid; interaction of these latter two decomposition products presumably then gave rise to the sulfide **18**. Again by contrast, the sulfone **11** cyclized *quantitatively* to the 1,1-dioxo-3,4-dihydro-2*H*-thiopyrano[2,3-*c*]pyridine **14** in refluxing bromobenzene over a period of 12 h.

A brief attempt was made to explore an alternative route to thieno[2,3-*c*]pyridines by utilization of an electron-rich equivalent of the terminal acetylene tethered dienophile in **2a** (i.e., the corresponding enamine). In fact, this concept of utilizing an electron-rich enamine as the tethered dienophile rather than its (apparently) less reactive acetylene had been successful in the 3-substituted 1,2,4-triazine series. The thione **1a** was alkylated with 4-bromo-1-butanol[12] (Finkelstein conditions), and the resulting product (**15**) was oxidized with pyridinium chlorochromate to the aldehyde **16** (52% yield) (see Scheme III). (This three-step procedure was preferable to direct alkylation of **1** with 4-bromo-1-butanal because of the troublesome synthesis and stability of this latter intermediate.) Conversion of **16** to its pyrrolidine enamine **17** proceeded quantitatively under standard conditions. However, all attempts to effect an intramolecular Diels–Alder reaction of **17** proved fruitless; no reaction took place at room temperature, and heating brought about rapid decomposition. Since the orbital coefficients of the LUMO of **17** should be larger at C-3 than at C-6, while the HOMO of the enamine should have its larger coefficient at the more electron rich $\beta$-carbon atom, HOMO–LUMO overlap is minimized for an enamine tethered through C-6 of the 1,2,4-triazine and maximized for a C-3-tethered enamine. This interpretation is in full accord with our experimental observations.[3f]

## Experimental Section

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from 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 an 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 conditions for the class of compounds described.

**General Procedure for the Synthesis of 6-(3-Butynylthio)-1,2,4-triazines 2.** To a stirred solution of the 1,2,4-triazine-6-thione 1[7] (6.00 mmol) and triethylamine (0.88 mL, 6.3 mmol, 1.05 equiv) in anhydrous THF (10 mL) at room temperature was rapidly added, dropwise, a solution of 4-iodo-1-butyne[7] (1.13 g, 6.3 mmol, 1.05 equiv) in anhydrous THF (5 mL). The resulting solution was stirred at room temperature with the exclusion of moisture for 24 h. A saturated solution of ammonium chloride (25 mL) was then added, and the resulting aqueous mixture was extracted with ether (3 × 25 mL). The ether extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure, and the residual oil was chromatographed by using silica gel (approximately 40 g) and eluting with the appropriate solvent system to afford the 3-(3-butynylthio)-1,2,4-triazine **2**.

**6-(3-Butynylthio)-5-methyl-1,2,4-triazine (2a).** The chromatographic eluent was 1:3 ether/petroleum ether. Compound **2a** was obtained in 90% yield as a pale yellow oil, which crystallized below room temperature: IR (neat) 3280, 2110, 1495, 1420, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.22 (s, 1 H), 3.53 (t, $J$ = 6.9 Hz, 2 H), 2.74 (dt, $J$ = 6.9 and 2.6 Hz, 2 H), 2.51 (s, 3 H), 2.13 (t, $J$ = 2.6 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 161.3, 157.7, 153.0, 81.7, 70.0, 28.5, 21.1, 18.6.

Anal. Calcd for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.88; H, 4.93; N, 23.23; S, 17.63.

**6-(3-Butynylthio)-5-isopropyl-1,2,4-triazine (2b).** The chromatographic eluent was 2:3 methylene chloride/petroleum ether. Compound **2b** was obtained in 70% yield as a clear, pale yellow liquid: IR (neat) 3280, 2110, 1495, 1460, 1430, 1390 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.27 (s, 1 H), 3.53 (t, $J$ = 6.6 Hz, 2 H), 3.18 (sept, $J$ = 6.6 Hz, 1 H), 2.74 (dt, $J$ = 6.6 and 2.6 Hz, 2 H), 2.11 (t, $J$ = 2.6 Hz, 1 H), 1.31 (d, $J$ = 6.6 Hz, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.0, 160.5, 153.3, 81.8, 69.8, 31.5, 28.6, 19.7, 18.6.

Anal. Calcd for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; N, 20.27; S, 15.47. Found: C, 57.69; H, 6.33; N, 20.15; S, 15.34.

**6-(3-Butynylthio)-5-phenyl-1,2,4-triazine (2c).** The chromatographic eluent was 2:3 methylene chloride/petroleum ether.

(9) Ciganek, E. The Intramolecular Diels–Alder Reaction. *Org. React. (N.Y.)* **1984**, *32*, 44–45.

(10) The spectral data for 8-methyl-1-oxo-3,4-dihydrothiopyrano[2,3-*c*]pyridine were as follows: $^1H$ NMR ($CDCl_3$) $\delta$ 8.44 (d, $J$ = 5.3 Hz, 1 H), 7.02 (d, $J$ = 5.3 Hz, 1 H), 3.64–3.24 (m, 2 H), 2.91 (s, 3 H), 2.64–2.44 (m, 2 H), 2.20–2.00 (m, 2 H); LRMS, $m/z$ (relative intensity) 182 (13% of $M^+$), 181 (81, $M^+$), 164 (100), 152 (19), 131 (19), 51 (39). This compound could presumably be prepared independently by controlled oxidation of **12**; such transformations have been routinely effected in analogous systems (see refs 3f,k).

(11) The spectral data for **18** were as follows: $^1H$ NMR ($CDCl_3$) $\delta$ 9.41 (s, 2 H), 2.68 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 161.5, 159.0, 155.5, 21.9; LRMS, $m/z$ (relative intensity) 221 (13% of $M^+$), 220 (42, $M^+$), 165 (22), 152 (40), 110 (100), 45 (56).

(12) Vedjs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.* **1979**, *44*, 3230.

Compound **2c** was obtained in 85% yield as a pale yellow crystalline solid: mp 93.5–94.5 °C; IR (KBr) 3210, 2100, 1595, 1495, 1480, 1440, 1425, 1385 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.38 (s, 1 H), 7.96–7.76 (m, 2 H), 7.60–7.43 (m, 3 H), 3.47 (t, $J$ = 7.0 Hz, 2 H), 2.70 (dt, $J$ = 6.9 and 2.6 Hz, 2 H), 2.06 (t, $J$ = 2.6 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.1 156.4, 153.3, 134.1, 131.2, 128.7, 128.4, 81.8, 69.9, 29.5, 18.5.

Anal. Calcd for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.41; S, 13.29. Found: C, 64.85; H, 4.39; N, 17.22; S, 13.40.

**7-Methyl-2,3-dihydrothieno[2,3-*c*]pyridine (5a).** A solution of 6-(3-butynylthio)-5-methyl-1,2,4-triazine (**2a**) (0.90 g, 5.02 mmol) in anhydrous dioxane (5 mL) was heated at reflux (101 °C) under nitrogen for 21 h. The resulting solution was concentrated by evaporation under reduced pressure, and the residual oil was chromatographed by using silica gel (approximately 40 g) and elution with 1:1 ether/petroleum ether to afford **5a** (0.52 g, 3.44 mmol, 69%) as a clear, pale yellow oil: IR (neat) 1570, 1555, 1425, 1395 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.14 (d, $J$ = 5.1 Hz, 1 H), 6.95 (d, $J$ = 5.1 Hz, 1 H), 3.33–3.31 (m, 4 H), 2.45 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 151.1, 148.7, 144.8, 137.6, 117.3, 36.2, 32.1, 23.5; LRMS, $m/z$ (relative intensity) 151 (100, $M^+$), 150 (60), 136 (10), 109 (12), 69 (11), 39 (16).

Anal. Calcd for $C_8H_9NS$: C, 63.53; H, 6.00; N, 9.26; S, 21.20. Found: C, 63.20; H, 6.05; N, 9.13; S, 21.48.

**Direct Synthesis of 1-Oxo-2,3-dihydrothieno[2,3-*c*]pyridines 6 from 2.** To a stirred solution of the 6-(3-butynylthio)-1,2,4-triazine **2** (4.00 mmol) in anhydrous methylene chloride (15 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% tech solid, 0.84 g, 4.13 mmol max, 1.03 equiv max) as a solid all at once. The resultant reaction mixture was then stirred at room temperature under nitrogen for 1 h, by which time full conversion of **2** to the intermediate 6-(3-butynylsulfinyl)-1,2,4-triazine **3** was complete (as determined by TLC). The reaction mixture was then either further stirred at room temperature under nitrogen or heated in methylene chloride under reflux (39 °C) under nitrogen for a time that depended on the substrate. When full conversion of **3** was complete (as determined by TLC), the reaction mixture was concentrated by evaporation under reduced pressure, and the residual oil/solid was chromatographed by using silica gel (approximately 40 g) and eluting with the appropriate solvent system.

**7-Methyl-1-oxo-2,3-dihydrothieno[2,3-*c*]pyridine (6a).** The reaction time was 27 h at room temperature, and the chromatographic eluent was first ether (200 mL) and then 15% methanol in ether. Compound **6a** was obtained in 69% yield as a white, crystalline solid: mp 104.5–106.0 °C; IR (KBr) 1580, 1550, 1450, 1415, 1395, 1015 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.55 (d, $J$ = 5.1 Hz, 1 H), 7.28 (d, $J$ = 5.3 Hz, 1 H), 4.12–3.71 (m, 1 H), 3.52–3.19 (m, 3 H), 2.85 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 157.4, 152.8, 151.8, 139.9, 118.6, 51.0, 31.7, 22.1; LRMS, $m/z$ (relative intensity) 168 (10), 167 (100, $M^+$), 151 (37), 150 (58), 97 (24).

Anal. Calcd for $C_8H_9NOS$: C, 57.46; H, 5.43; N, 8.38; S, 19.17. Found: C, 57.23; H, 5.44; N, 8.30; S, 18.91.

**7-Isopropyl-1-oxo-2,3-dihydrothieno[2,3-*c*]pyridine (6b).** The reaction time was 5 h in refluxing methylene chloride (39 °C), and the chromatographic eluent was first ether (200 mL) and then 5% methanol in ether. Compound **6b** was obtained in 84% yield as a clear, colorless oil: IR (neat) 1570, 1555, 1465, 1450, 1425, 1410, 1040–1010 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.68 (d, $J$ = 5.1 Hz, 1 H), 7.26 (d, $J$ = 5.1 Hz, 1 H), 4.11–3.07 (m, 5 H), 1.39 (d, $J$ = 6.8 Hz, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 166.1, 153.1, 152.1, 139.2, 118.6, 51.1, 34.0, 31.9, 21.9; LRMS, $m/z$ (relative intensity) 195 (18, $M^+$), 177 (100), 164 (33); HRMS calcd for $C_{10}H_{13}NOS$ 195.0718, found 195.0719 ± 0.002.

**1-Oxo-7-phenyl-2,3-dihydrothieno[2,3-*c*]pyridine (6c).** The reaction time was 4 h at room temperature, and the chromatographic eluent was first ether (200 mL) and then 10% methanol in ether. Compound **6c** was obtained in 95% yield as a clear, colorless oil: IR (neat) 1600, 1575, 1560, 1490, 1450, 1430, 1035–1020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.77 (d, $J$ = 5.1 Hz, 1 H), 8.07–7.96 (m, 2 H), 7.60–7.49 (m, 3 H), 7.40 (d, $J$ = 5.1 Hz, 1 H), 4.31–3.95 (m, 1 H), 3.56–2.86 (m, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 157.6, 154.6, 151.8, 139.9, 137.8, 129.3, 128.8, 128.2, 119.4, 50.7, 31.9; LRMS, $m/z$ (relative intensity) 230 (19), 229 (100, $M^+$), 212 (84), 185 (21), 77 (19); HRMS calcd for $C_{13}H_{11}NOS$ 229.0561, found 229.0564 ± 0.0022.

**General Procedure for the Dehydration (Pummerer Reaction) of 6 to Thieno[2,3-*c*]pyridines 7.** A solution of the 1-oxo-2,3-dihydrothieno[2,3-*c*]pyridine **6** (3.00 mmol) in acetic anhydride (10 mL) was heated at reflux under nitrogen for 1–4 h, depending on the substrate. The resulting reaction solution was then concentrated by evaporation under reduced pressure, and the residue was chromatographed by using silica gel (approximately 40 g) and eluting with 1:1 ether/petroleum ether.

**7-Methylthieno[2,3-*c*]pyridine (7a). Method A.** The reaction time was 1 h. Compound **7a** was obtained in 88% yield as a clear, colorless liquid: IR (neat) 1570, 1550, 1475, 1450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.37 (d, $J$ = 5.5 Hz, 1 H), 7.58 (d, $J$ = 5.3 Hz, 1 H), 7.46 (d, $J$ = 5.9 Hz, 1 H), 7.25 (d, $J$ = 5.3 Hz, 1 H), 2.75 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 152.1, 144.5, 141.7, 134.6, 131.0, 123.2, 115.5, 22.4.

The spectral and physical properties of **7a** were identical with those previously reported for 7-methylthieno[2,3-*c*]pyridine.[13]

**7-Isopropylthieno[2,3-*c*]pyridine (7b).** The reaction time was 1.5 h. Compound **7b** was obtained in 85% yield as a clear, colorless liquid: IR (neat) 1570, 1550, 1475, 1460, 1450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.47 (d, $J$ = 5.5 Hz, 1 H), 7.56 (d, $J$ = 5.5 Hz, 1 H), 7.46 (d, $J$ = 5.5 Hz, 1 H), 7.28 (d, $J$ = 5.3 Hz, 1 H), 3.38 (sept, $J$ = 6.8 Hz, 1 H), 1.45 (d, $J$ = 6.8 Hz, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 161.1, 144.8, 142.7, 133.9, 130.3, 123.4, 115.5, 35.5, 21.1.

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90; S, 18.09. Found: C, 67.55; H, 6.04; N, 7.86; S, 18.27.

**7-Phenylthieno[2,3-*c*]pyridine (7c).** The reaction time was 4 h. Compound **7c** was obtained in 93% yield as a clear, pale yellow liquid: IR (neat) 1565, 1545, 1475, 1450, 1440 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.58 (d, $J$ = 5.5 Hz, 1 H), 8.14–7.97 (m, 2 H), 7.62–7.39 (m, 5 H), 7.29 (d, $J$ = 5.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 153.4, 145.9, 143.1, 139.5, 133.9, 131.7, 129.1, 128.5, 128.0, 123.2, 116.4.

Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.55; S, 15.18. Found: C, 73.71; H, 4.41; N, 6.55; S, 14.91.

**7-Methylthieno[2,3-*c*]pyridine (7a). Method B (from 5a).** To a stirred mixture of **5a** (0.38 g, 2.51 mmol) and potassium carbonate (0.40 g, 3.12 mmol, 1.24 equiv) in methylene chloride (10 mL) at 0 °C was added sulfuryl chloride (0.22 mL, 2.74 mmol, 1.1 equiv). This reaction mixture was stirred at room temperature with exclusion of moisture for 3 h, and then triethylamine (0.42 mL, 3.01 mmol, 1.2 equiv) and additional sulfuryl chloride (0.22 mL, 2.74 mmol, 1.1 equiv) were added. The reaction mixture was then stirred overnight at room temperature with exclusion of moisture. A further addition of triethylamine (0.42 mL, 3.01 mmol, 1.2 equiv) and sulfuryl chloride (0.11 mL, 1.31 mmol, 0.55 equiv) was then made, and the resulting reaction mixture was stirred at room temperature for 6 h. Water (10 mL) was added, and the aqueous layer was adjusted to pH 10 with 1 N sodium hydroxide. The methylene chloride layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 20 mL). The combined methylene chloride extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residual liquid as described above yielded **7a** (0.20 g, 1.34 mmol, 53%) as a clear, pale yellow liquid with physical and spectral properties identical with those of the material prepared as described above by method A.

**1,1-Dioxo-7-methyl-2,3-dihydrothieno[2,3-*c*]pyridine (8a).** To a stirred solution of **2a** (0.60 g, 3.35 mmol) in anhydrous methylene chloride (15 mL) at 0 °C was rapidly added *m*-chloroperbenzoic acid (80–85% tech solid, 1.45 g, 7.14 mmol max, 2.13 equiv max) as a solid in small portions. The resulting reaction mixture was stirred at room temperature with exclusion of moisture for 24 h, cooled, and filtered and the collected solid washed with a little cold methylene chloride. The combined filtrates were evaporated under reduced pressure to yield 6-(3-butynylsulfonyl)-5-methyl-1,2,4-triazine (**4a**) as a yellow oil. A solution of this oil in anhydrous THF (15 mL) was heated at reflux (66 °C) under nitrogen for 27 h. THF was then removed by evaporation under reduced pressure, and the resulting oil was chromatographed by using silica gel (approximately 40 g) followed by elution with ether to afford **8a** (0.46 g, 2.51 mmol, 75%) as

(13) Dressler, M. L.; Joullie, M. M. *J. Heterocycl. Chem.* **1970**, *7*, 1257 (bp 102–103 °C at 2.5 mmHg; $^1H$ NMR ($CDCl_3$) $\delta$ 8.38, 7.50, 7.36, 7.18, 2.72).

a white, crystalline solid: mp 123.5–125.0 °C; IR (KBr) 1580, 1560, 1460, 1425, 1290, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.59 (d, $J$ = 5.1 Hz, 1 H), 7.21 (d, $J$ = 5.3 Hz, 1 H), 3.62–3.26 (m, 4 H), 2.78 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 154.4, 152.1, 146.7, 133.5, 119.5, 49.6, 24.5, 20.4; LRMS, $m/z$ (relative intensity) 185 (6), 184 (11), 183 ($M^+$, 100), 134 (30), 118 (28), 93 (13), 91 (15), 52 (22); HRMS calcd for $C_8H_9NO_2S$ 183.0354, found 183.0346 ± 0.0018.

Anal. Calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64; S, 17.50. Found: C, 52.74; H, 5.05; N, 7.61; S, 17.72.

**5-Methyl-6-(4-pentynylthio)-1,2,4-triazine (9).** A mixture of **1a** (0.99 g, 7.78 mmol), triethylamine (1.10 mL, 7.89 mmol, 1.0 equiv), sodium iodide (2.33 g, 15.54 mmol, 2.0 equiv), and 5-chloro-1-pentyne (1.65 mL, 15.60 mmol, 2.0 equiv) in acetone (50 mL, water < 0.5%) was heated at reflux under nitrogen for 18 h. A saturated solution of sodium bicarbonate (20 mL) was added to the reaction mixture, which was then extracted with methylene chloride (2 × 50 mL). The combined methylene chloride extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a black oil. Column chromatography of this oil using silica gel (approximately 50 g) and elution with 1:4 ether/petroleum ether afforded **9** (1.03 g, 5.33 mmol, 69%) as a pale yellow oil: IR (neat) 3280, 2120, 1500, 1425, 1380, 1275 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.20 (s, 1 H), 3.49 (t, $J$ = 7.0 Hz, 2 H), 2.50 (s, 3 H), 2.50–2.32 (m, 2 H), 2.18–1.84 (m, 2 H), 2.03 (t, $J$ = 2.6 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 161.8, 157.6, 153.0, 82.7, 69.1, 28.6, 27.5, 21.0, 17.5.

Anal. Calcd for $C_9H_{11}N_3S$: C, 55.93; H, 5.74; N, 21.74; S, 16.59. Found: C, 55.85; H, 5.75; N, 21.46; S, 16.68.

**5-Methyl-6-(4-pentynylsulfinyl)-1,2,4-triazine (10).** To a stirred solution of **9** (0.79 g, 4.09 mmol) in anhydrous methylene chloride (20 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% tech solid, 0.88 g, 4.33 mmol max, 1.06 equiv max) as a solid all at once. The resulting mixture was stirred at 0 °C with exclusion of moisture for 2 h and then concentrated by evaporation under reduced pressure. The residual oil was dissolved in ether (3 mL), and this solution was passed through a silica gel filter (approximately 30 g) followed first by elution with petroleum ether (50 mL), then with 1:1 ether/petroleum ether (50 mL), and finally with ether (300 mL). The final ether eluate was evaporated under reduced pressure to yield **10** (0.74 g, 3.54 mmol, 87%) as a pale yellow, crystalline solid: mp 64.5–66.0 °C; IR (KBr) 3280, 2110, 1505, 1430, 1395, 1065 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.58 (s, 1 H), 3.49 (t, $J$ = 7.5 Hz, 2 H), 2.89 (s, 3 H), 2.57–2.34 (m, 2 H), 2.26–1.91 (m, 2 H), 2.04 (t, $J$ = 2.6 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 164.8, 160.6, 157.0, 82.0, 70.0, 51.5, 21.4, 20.8, 17.7; LRMS (20 eV), $m/z$ (relative intensity) 209 ($M^+$, 11), 208 (100); LRMS (70 eV), $m/z$ (relative intensity) 208 (4), 192 (30), 181 (12, $[M^+] - N_2$), 165 (70), 146 (79), 88 (100), 67 (98), 65 (97).

Anal. Calcd for $C_9H_{11}N_3OS$: C, 51.66; H, 5.30; N, 20.07; S, 15.32. Found: C, 51.72; H, 5.42; N, 19.79; S, 15.20.

**5-Methyl-6-(4-pentynylsulfonyl)-1,2,4-triazine (11).** To a stirred solution of **9** (0.62 g, 3.21 mmol) in anhydrous methylene chloride (15 mL) at 0 °C was added *m*-chloroperbenzoic acid (80–85% tech solid, 1.45 g, 7.14 mmol max, 2.22 equiv max) as a solid all at once. The resulting mixture was stirred at room temperature with exclusion of moisture for 4 h and filtered and the filtrate washed with a saturated solution of sodium bicarbonate (2 × 10 mL). It was then dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. Chromatography of this oil using silica gel (approximately 40 g) and elution with methylene chloride afforded **11** (0.50 g, 2.22 mmol, 69%) as a clear, colorless oil, which crystallized upon cooling: mp 83.5–85.5 °C; IR (KBr) 3280, 2110, 1510, 1425, 1400, 1315, 1135 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.67 (s, 1 H), 3.99–3.82 (m, 2 H), 2.95 (s, 3 H), 2.57–2.10 (m, 4 H), 2.09 (t, $J$ = 2.6 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.8, 159.0, 157.9, 81.7, 70.3, 51.0, 21.4, 21.4, 17.5.

Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N, 18.65; S, 14.23. Found: C, 48.21; H, 4.79; N, 18.53; S, 14.21.

**8-Methyl-2,3-dihydrothiopyrano[2,3-*c*]pyridine (12).** A solution of **9** (0.39 g, 2.02 mmol) in bromobenzene (3 mL) was heated at reflux (156 °C) under nitrogen for 64 h. The dark colored solution was then chromatographed by using silica gel (approximately 40 g) and eluted with 1:2 ether/petroleum ether to yield **9** ($R_f$ = 0.55 in ether, 0.07 g, 0.36 mmol, 18% recovered) followed by **12** ($R_f$ = 0.25 in ether, 0.19 g, 1.15 mmol, 57% actual, 69% conversion) as a clear, pale yellow liquid: IR (neat) 1570, 1540, 1455, 1425, 1385, 1055 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.02 (d, $J$ = 5.1 Hz, 1 H), 6.74 (d, $J$ = 5.1 Hz, 1 H), 3.10–2.97 (m, 2 H), 2.76 (t, $J$ = 6.2 Hz, 2 H), 2.43 (s, 3 H), 2.18–1.92 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 153.9, 143.1, 141.7, 129.2, 122.0, 29.3, 27.6, 22.2, 21.7; HRMS calcd for $C_9H_{11}NS$ 165.0612, found 165.0611 ± 0.0017.

**1,1-Dioxo-8-methyl-2,3-dihydrothiopyrano[2,3-*c*]pyridine (14).** A solution of **11** (0.38 g, 1.69 mmol) in bromobenzene (3 mL) was heated at reflux (156 °C) under nitrogen for 12 h and then passed through a silica gel filter (approximately 30 g) followed by an elution first with ether (100 mL) and then with 20% methanol in ether (200 mL). The methanol/ethanol eluate was evaporated under reduced pressure to yield **14** (0.33 g, 1.67 mmol, 99%) as an off-white, crystalline solid: mp 163.5–165.5 °C; IR (KBr) 1580, 1540, 1420, 1390, 1305–1285, 1110 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.43 (d, $J$ = 5.1 Hz, 1 H), 7.00 (d, $J$ = 5.1 Hz, 1 H), 3.49–3.36 (m, 2 H), 2.99 (t, $J$ = 5.9 Hz, 2 H), 2.92 (s, 3 H) 2.56–2.37 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 156.9, 150.3, 145.6, 134.4, 121.7, 53.4, 29.3, 23.4, 20.1.

Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; S, 16.25. Found: C, 54.64; H, 5.42; N, 7.24; S, 16.04.

**6-[(4-Hydroxybutyl)thio]-5-methyl-1,2,4-triazine (15).** A solution of **1a** (1.27 g, 9.99 mmol), triethylamine (1.46 mL, 10.47 mmol, 1.05 equiv), 4-bromobutan-1-ol[12] (1.60 g, 10.46 mmol, 1.05 equiv), and sodium iodide (1.50 g, 10.01 mmol, 1.0 equiv) in acetone (25 mL, water <0.5%) was stirred at room temperature with exclusion of moisture for 15 h. The resulting mixture was concentrated under reduced pressure, and the residual oil was suspended in a saturated solution of sodium bicarbonate (25 mL). This aqueous mixture was extracted with methylene chloride (3 × 25 mL), and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual brown oil was chromatographed by using silica gel (approximately 100 g) followed by elution with 1:1 ether/petroleum ether to afford **15** (1.13 g, 5.67 mmol, 57%) as a clear, colorless oil: IR (neat) 3400, 1500, 1425, 1380, 1280 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.17 (s, 1 H), 3.70 (t, $J$ = 6.3 Hz, 2 H), 3.43 (br s, 1 H), 3.37 (t, $J$ = 7.1 Hz, 2 H), 2.48 (s, 3 H), 1.93–1.84 (m, 2 H), 1.79–1.60 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 162.6, 158.2, 152.9, 61.7, 31.8, 29.5, 25.2, 21.5.

Anal. Calcd for $C_8H_{13}N_3OS$: C, 48.22; H, 6.58; N, 21.09; S, 16.09. Found: C, 47.96; H, 6.29; N, 21.13; S, 15.90.

**6-[(4-Oxobutyl)thio]-5-methyl-1,2,4-triazine (16). Method A.** To a stirred mixture of pyridinium chlorochromate (1.04 g, 4.82 mmol, 1.1 equiv) in anhydrous methylene chloride (30 mL) at room temperature was added dropwise a solution of **15** (0.87 g, 4.37 mmol) in anhydrous methylene chloride (5 mL). The resulting reaction mixture was stirred at room temperature under nitrogen for 3 h and then passed through a silica gel filter (approximately 60 g) followed by elution with ether (500 mL). The filtrate was evaporated under reduced pressure, and the residual green oil was chromatographed over silica gel (approximately 40 g) followed by elution with 1:1 ether/petroleum ether to afford **16** (0.45 g, 2.28 mmol, 52%) as a pale yellow oil: IR (neat) 2720, 1725, 1500, 1420, 1410, 1380, 1300, 1275 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.82 (t, $J$ = 1.3 Hz, 1 H), 9.20 (s, 1 H), 3.42 (t, $J$ = 6.9 Hz, 2 H), 2.69 (dt, $J$ = 6.9 and 1.3 Hz, 2 H), 2.50 (s, 3 H), 2.30–2.06 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 200.7, 161.6, 157.7, 152.8, 42.3, 28.6, 21.1, 21.0.

Anal. Calcd for $C_8H_{11}N_3OS$: C, 48.71; H, 5.62; N, 21.30; S, 16.25. Found: C, 48.97; H, 5.42; N, 21.45; S, 16.05.

**Method B.** To a solution of **1a** (0.51 g, 4.01 mmol) and triethylamine (0.60 mL, 4.30 mmol, 1.07 equiv) in anhydrous THF (15 mL) at room temperature were added 4-bromo-1-butanal[12] (0.70 g, 4.64 mmol, 1.15 equiv) and sodium iodide (0.65 g, 4.34 mmol, 1.08 equiv), and the reaction mixture was stirred at room temperature with exclusion of moisture for 34 h. A saturated solution of sodium bicarbonate (15 mL) was added to the reaction mixture, which was then extracted with methylene chloride (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the residual brown oil was chromatographed over silica gel (approximately 40 g) followed by elution with 1:2 ether/petroleum ether to afford **16** (0.46 g, 2.33 mmol, 58%) as a pale brown oil identical in all respects with the material obtained by method A.

**6-[(4-Pyrrolidino-3-butenyl)thio]-5-methyl-1,2,4-triazine (17).** A mixture of **16** (0.51 g, 2.59 mmol), anhydrous magnesium sulfate (0.40 g, 3.32 mmol, 1.3 equiv), pyrrolidine (0.43 mL, 5.15

mmol, 2.0 equiv), and anhydrous ether (25 mL) was stirred at room temperature under nitrogen for 9.5 h. The resulting mixture was filtered, and the filtrate was evaporated under reduced pressure to yield **17** (0.65 g, 2.60 mmol, 100%) as a pale brown liquid: IR (neat) 1645, 1620, 1565, 1500, 1420 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.16 (s, 1 H), 6.29 (d, $J$ = 13.6 Hz, 1 H), 4.14–4.05 (m, 1 H), 3.34 (t, $J$ = 7.2 Hz, 2 H), 3.01–2.96 (m, 4 H), 2.47 (s, 3 H), 1.85–1.79 (m, 4 H), 1.75–1.67 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 162.9, 158.0, 152.9, 137.6, 94.7, 49.1, 32.1, 30.1, 25.0, 21.6.

**Registry No.** **1a**, 99702-45-1; **1b**, 99702-47-3; **1c**, 99702-46-2; **2a**, 100037-81-8; **2b**, 100037-82-9; **2c**, 100037-83-0; **4**, 100037-84-1; **5a**, 100037-71-6; **6a**, 100037-73-8; **6b**, 100037-74-9; **6c**, 100037-75-0; **7a**, 30433-74-0; **7b**, 100037-76-1; **7c**, 100067-45-6; **8a**, 100037-72-7; **9**, 122624-40-2; **10**, 122624-41-3; **11**, 122624-42-4; **12**, 122624-43-5; **14**, 122624-44-6; **15**, 122624-45-7; **16**, 122624-46-8; **17**, 122624-47-9; 4-iodo-1-butyne, 43001-25-8; 4-bromobutanol, 33036-62-3; 4-bromo-1-butanal, 38694-47-2; pyrrolidine, 123-75-1; 5-chloro-1-pentyne, 14267-92-6.

# Asymmetric Reduction of the Prochiral Carbon–Carbon Double Bond of Methyl 2-Chloro-2-alkenoates by Use of Fermenting Bakers' Yeast

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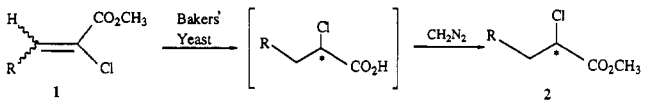
Asymmetric reduction of (*E*)- and (*Z*)-methyl 2-chloro-2-alkenoates by use of fermenting bakers' yeast gave (*R*)- and (*S*)-2-chloroalkanoic acids in 25–92% ee and ≥98% ee, respectively. The chemical yields were 10–40% for 2-chloropentenoate and 2-chloroheptenoate, but 65–70% for 2,4,4-trichloro- and 2,4,4,4-tetrachlorobutenoates. The substrates were found to be reduced after hydrolysis to the acids. The reactivity and stereoselectivity of the reduction were discussed. The reduction products, (*R*)- and (*S*)-2,4,4-trichlorobutanoic acids, were transformed to (*S*)- and (*R*)-2-amino-4,4-dichlorobutanoic acids, respectively.

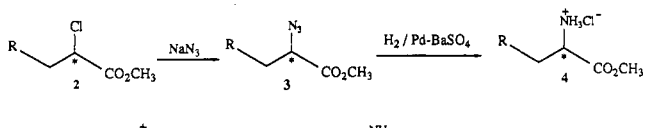
In a previous paper,[1] we have reported that (*E*)- and (*Z*)-methyl 2,4,4-trichloro-2-butenoate (**1e**) were reduced to (*R*)- and (*S*)-2,4,4-trichlorobutanoic acids (**2e**), respectively, by use of fermenting bakers' yeast (*Saccharomyces cerevisiae*) (eq 1). The *R* and *S* acids **2e** were effectively




| R | | | |
|---|---|---|---|
| a | $CH_3CH_2$ | d | $CH_2Cl$ |
| b | $(CH_3)_2CH$ | e | $CHCl_2$ |
| c | $CH_3(CH_2)_3$ | f | $CCl_3$ |

(1)

converted to optically pure L- and D-armentomycin (**5e**),[2] both enantiomers of a naturally occurring antibiotic agent (eq 2). The remarkable feature of this reduction is the




| R | | | |
|---|---|---|---|
| b | $(CH_3)_2CH$ | | |
| e | $CHCl_2$ | | |

(2)

highly effective stereochemical control for each geometrical isomer to produce the (*R*)- and (*S*)-α-chloro acids **2e** selectively. The *E* isomer [(*E*)-**1e**] was reduced to (*R*)-**2e** in 92% ee (60% yield), while the *Z* isomer [(*Z*)-**1e**] was reduced to (*S*)-**2e** in 98% ee (65% yield). This result attracts interest in view of the mechanism of bakers' yeast reduction and the methodology of organic synthesis.

Although many optically active α-halo acids or esters have been prepared by using naturally occurring chiral acids such as α-amino acids[3] or lactic acid[4] as starting materials, the asymmetric syntheses have been rather rare. Reported syntheses include a microbial hydrogenation of the carbon–carbon double bond of α-halo substituted enoate anions by using *Clostridium* sp. La 1[5] and an asymmetric halogenation of camphor-10-sulfonic acid derived esters with *N*-bromo- or *N*-chlorosuccinimide.[6] The present method reduces the carbon–carbon double bond of α-chloro alkenoate by use of easily available bakers' yeast. The scope and limitation of the method and its application to the preparation of α-amino acids are fully described.

## Results and Discussion

**Preparation of the Substrate.** The substrates **1** were readily prepared by starting from aldehydes and methyl α-chloroacetoacetate according to the method reported.[7] The products obtained were a mixture of *E* and *Z* isomers except for the case of R = $CCl_3$, where only the *Z* isomer was produced. The separation was carried out by using a silica gel column. Determination of the *E* and *Z* geometry for **1a–c** was made by using the chemical shift of the olefinic hydrogen on the basis of the downfield shift for

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