Competitive Intramolecular Diels–Alder Reaction and Intramolecular Coplanar Cycloamination of 3-(3-Butynylthio)-1,2,4-triazin-5-ones

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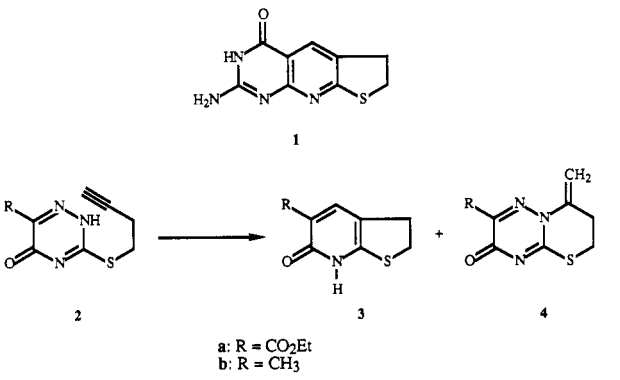
3-(3-Butynylthio)-1,2,4-triazin-5-ones **2** participate in competitive intramolecular Diels–Alder (IDA) and intramolecular coplanar cycloamination (ICC) processes to provide 2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-ones **3** and 8-methylene-7,8-dihydro-3*H*,6*H*-[1,3]thiazino[3,2-*b*]-1,2,4-triazin-3-ones **4**, respectively. In relatively inert aromatic solvent systems, the ratio of IDA to ICC products is markedly dependent on the electronic disposition of the substituent at C-6 of the precursor 1,2,4-triazine **2**. Furthermore, when the substituent at C-6 is electron withdrawing (R = carbethoxy for **2a**), the ratio of IDA to ICC product formation is very sensitive to reaction temperature, with higher temperatures favoring the IDA process. However, this sensitivity to reaction temperature is not observed for **2b** (R = methyl). Utilization of ethanol as the reaction solvent in the presence of triethylamine generally facilitates the ICC vs the IDA process. Without triethylamine, the amount of ICC product is diminished relative to other competitively formed materials. Utilization of deuteriated dimethyl sulfoxide as the reaction solvent leads to completely reversed trends in reactivity and almost exclusive formation of the IDA products **3**.

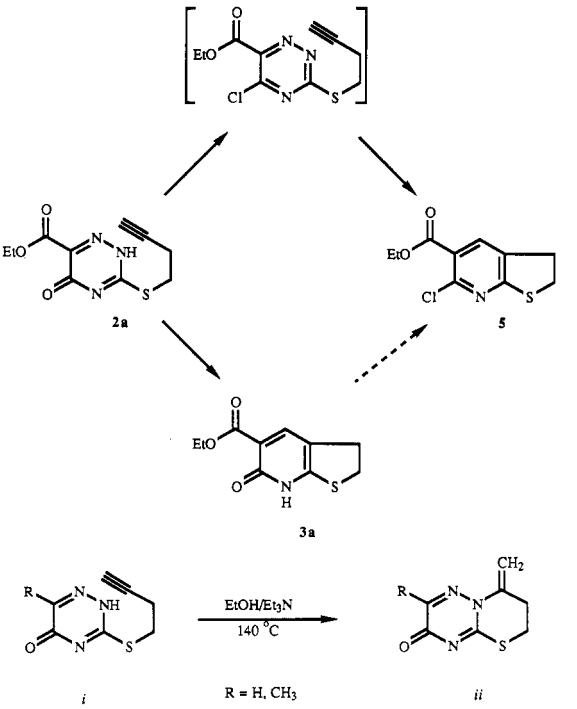
The intramolecular Diels–Alder (IDA) reaction of 3-(3-butynylthio)-1,2,4-triazines has been shown in extensive studies by our group and others to be a convenient route to thieno[2,3-*b*]pyridines.[1] We have further reported the application of this concept to the synthesis of 2-amino-6,7-dihydrothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidin-4-one (**1**)[2] as a part of our research program directed toward the preparation of annulated 5-deazapteridines.[3] In the course of our studies on the synthesis of compound **1**, we examined the thermal reactivity of 3-(3-butynylthio)-1,2,4-triazin-5-ones **2**. We report herein our discovery that these species participate in *competitive* processes providing intramolecular Diels–Alder (IDA) and intramolecular coplanar cycloamination (ICC) products (2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-ones **3** and 8-methylene-7,8-dihydro-3*H*,6*H*-[1,3]thiazino[3,2-*b*]-1,2,4-triazin-3-ones **4**, respectively) (Scheme I) and that the ratio of these products is dependent on the nature of the substituent at C-6 of the precursor 1,2,4-triazine **2**. This dependence is often manifested in a sensitivity of the competitive reaction pathways to reaction temperature and solvent interactions.

The key intermediate in our synthesis of 2-amino-6,7-dihydrothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidin-4-one (**1**) is 5-carbethoxy-6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine (**5**), which is prepared in high yield from **2a** via in situ generated 3-(3-butynylthio)-6-carbethoxy-5-chloro-1,2,4-triazine.[2] We also considered the possibility of preparing **1** by inverting the above sequence of reactions; i.e., by an initial Diels–Alder conversion of **2a** to the dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one **3a** followed by chlorination

Scheme I



Scheme II



to give **5** (Scheme II). However, the earlier work of Sasaki and Shimizu on 1,2,4-triazine systems identical in every respect with **2a** except for the nature of the substitution at C-6 did not bolster our confidence in this conversion,

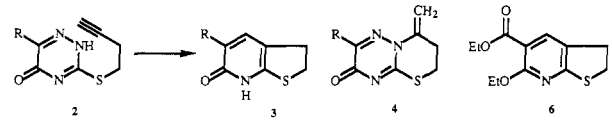
(1) For references to intramolecular Diels–Alder reactions of monocyclic 1,2,4-triazines, see the following: Dienophilic substituent tethered to positions 3 or 6 (nitrogen extrusion): (a) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1985**, *26*, 2419. (b) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 431. (c) Taylor, E. C.; French, L. G. *Tetrahedron Lett.* **1986**, *27*, 1967. (d) Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1986**, *27*, 2107. (e) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (f) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (g) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. (h) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. (i) Seitz, G.; Dietrich, S. *Arch. Pharm. (Weinheim)* **1984**, *317*, 379. (j) Seitz, G.; Gorge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (k) Seitz, G.; Dietrich, S. *Arch. Pharm. (Weinheim)* **1985**, *318*, 1048 and 1051. (l) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. Dienophilic substituent tethered to position 5 (nitrile extrusion): (m) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287.

(2) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Heterocycl. Chem.*, in press.

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

0022-3263/88/1953-5093$01.50/0

Table I. Competitive Thermal Reactions of the 6-Carbethoxy- and 6-Methyl-1,2,4-triazin-5-ones 2a,b



a, R = CO_2Et b, R = CH_3

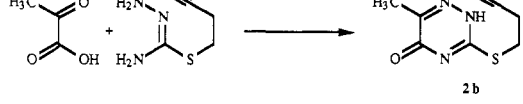
solvent	T (°C)	3b, %	4b, %	3b/4b	3a, %	4a, %	6, %	3a/4a
PhBr	156[a]	17	81	0.2	45	37		1.2
$PhNO_2$	156	5	95	0.1	42	40		1.1
$PhNO_2$	210[a]	15	85	0.2	59	28		2.1
$EtOH/Et_3N$	140	3	83	~0	27	58	14	0.5
EtOH	140	46	52	0.9	29	39	29	0.7
Me_2SO-d_6[b]	140	92	7	13.0	96	3		32
Me_2SO-d_6[b]	170	88	11	8.0	80	19		4.2

[a] Refluxing solvent (all other temperatures maintained by thermostated oil bath). [b] Yields based upon relative ^1H NMR integrations.

as they reported that such compounds underwent an exclusive intramolecular coplanar cycloamination (ICC) reaction (i → ii, Scheme II), with no mention of any Diels–Alder-derived products.[4] Indeed, we have previously described an analogous cyclization of 3-(2′-ethynylanilino)-1,2,4-triazines,[5] and, additionally, Mioque et al. report a similar competitive process in their studies on intramolecular Diels–Alder reactions of pyrimidones.[6] The salient feature of all of these ICC processes is the presence of a tautomerizable ring proton on the respective precursor heterocycles.

In spite of these discouraging precedents, compound **2a** was heated at 156 °C and/or 210 °C in two different aromatic solvents. To our surprise, the IDA product (**3a**) was obtained in larger amounts that the competitively formed ICC product (**4a**), and, additionally, the ratio of IDA to ICC product markedly increased with reaction temperature (Table I). These initial findings prompted us to reexamine the work of Sasaki.[4]

Thus, 3-(3-butynylthio)-6-methyl-1,2,4-triazin-5-one (**2b**), prepared by condensation of *S*-(3-butynyl)thiosemicarbazide[1f] with pyruvic acid,[7] was subjected to analogous thermal conditions as utilized for the 6-carbethoxy derivative **2a**.

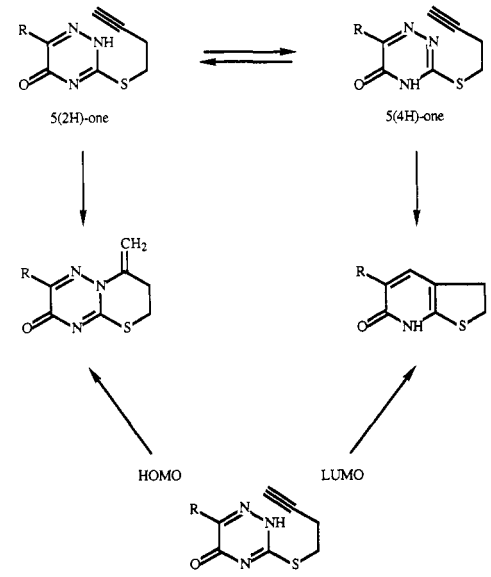


2b

Furthermore, compounds **2a** and **2b** were subjected to Sasaki's original conditions (140 °C/ethanol/0.25 equiv of triethylamine). A slight modification of the Sasaki procedure (omission of the triethylamine from the ethanolic reaction mixture) was also examined. Finally, individual NMR tubes containing deuteriated dimethyl sulfoxide solutions of **2a** and **2b** were heated at 140 °C and 170 °C over a series of fixed time intervals with the course of starting material consumption and competitive product formation followed by proton NMR. The results from these experiments are summarized in Table I.

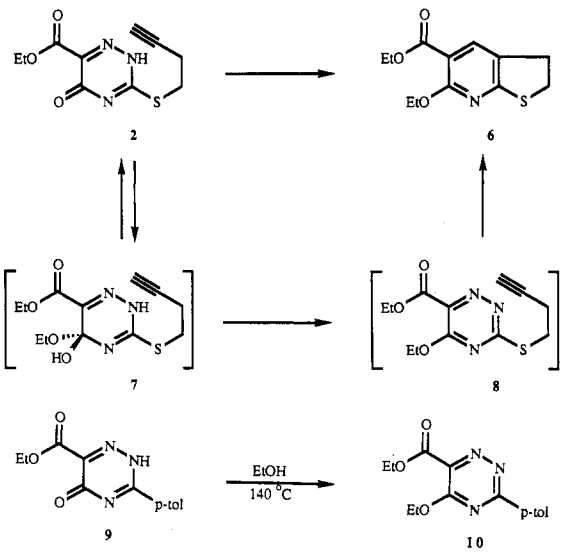
In the aromatic solvent systems (bromobenzene, nitrobenzene), competitive IDA and ICC processes were observed for **2b** (R = methyl) as found earlier for **2a** (R = carbethoxy). However, the amount of IDA product derived from **2b** was considerably less than that from **2a**, and the ratio of products formed was apparently insensitive to changes in reaction temperature. The differences in the ratio of IDA to ICC products at a given reaction temperature can be readily rationalized in terms of the electronic nature of the substituent at C-6 of **2a** and **2b**. The electron-withdrawing carbethoxy substituent of **2a** enhances its Diels–Alder reactivity relative to a competitive coplanar cycloamination because Diels–Alder reactions of heterocyclic azadienes[8] (such as **2a**) are generally inverse electron demand processes. In such situations, the azadiene LUMO is the key frontier molecular orbital; the carbethoxy substituent lowers the LUMO of **2a**, thus increasing frontier orbital overlap in a Diels–Alder reaction. By the same token, the carbethoxy substituent likewise lowers the HOMO energy of **2a**, thus decreasing the likelihood of an intramolecular coplanar cycloamination, which is the consequence of nucleophilic attack of the triazine N-2 on the pendant acetylene electrophile. On the other hand, with compound **2b** the ICC process is significantly favored relative to the IDA process, presumably as a consequence of the electron-donating methyl group at C-6. Both

Scheme III



(4) Sasaki, T.; Shimizu, I. *Heterocycles* **1984**, *22*, 1225.
(5) Taylor, E. C.; Warner, J. C.; Pont, J. L.; Yu, D. Presented at the 11th International Congress of Heterocyclic Chemistry, Heidelberg, FGR, August 1987.
(6) Rougeot, E.; Moskowitz, H.; Mioque, M. *J. Heterocycl. Chem.* **1983**, *20*, 1407.
(7) This synthesis of **2b** was found to be preferable to the method reported by Sasaki (ref 4).
(8) For a review of heterocyclic azadienes in Diels–Alder reactions, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; New York: Academic Press, 1987; p 366.

Scheme IV



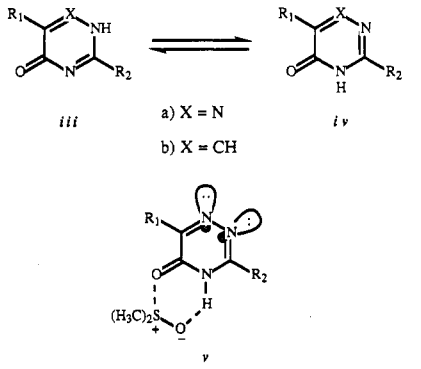
HOMO and LUMO energies of **2b** are raised relative to **2a**, favoring the HOMO governed ICC reaction while disfavoring the LUMO governed IDA reaction (Scheme III).

It seemed possible that the sensitivity of the IDA/ICC ratio to reaction temperature found with **2a** might have been due to funnelling away of an initially but *reversibly* formed ICC product toward a higher energy but *irreversibly* formed IDA product. However, when a purified sample of **4a** was heated in refluxing nitrobenzene over the course of several days, no trace of the dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one **3a** was observed.

1,2,4-Triazin-5-ones have been reported to exist in solution primarily as their 5(2*H*) tautomers.[9,10] This tautomer does not have the *cis*-diene structure requisite for participation in Diels–Alder reactions. Temperature elevation may increase the effective concentration of higher energy *cis*-diene tautomers (such as, for example, the 5-(4*H*)-one), a factor which may, in part, account for the observed IDA/ICC ratios. Although an analogous tautomeric equilibrium shift also probably occurs when the temperature is increased in the environment of **2b**, the IDA/ICC product ratio is apparently unaffected by such a shift due to a prohibitively high barrier for the Diels–Alder reaction (Scheme III).

Subjection of compound **2b** to Sasaki's original conditions led to the isolation of the ICC product **4b** in 83% yield as a white crystalline solid by filtration of the cooled ethanolic reaction mixture. Careful workup of the filtrate gave the corresponding IDA product **3b** in very low (3%) yield. Under the same conditions, **2a** afforded 58% of the ICC product **4a** and 27% of the IDA product **3a**. However, also isolated was 5-carbethoxy-6-ethoxy-2,3-dihydrothieno[2,3-*b*]pyridine (**6**, 14%). Utilization of Sasaki's conditions with **2a** without the addition of triethylamine

Scheme V



to the reaction mixture increased the yield of ethoxypyridine **6** relative to the ICC and IDA products. This byproduct (**6**) presumably arises from initial reversible formation of the hemiketal **7**, followed by loss of water to afford the intermediate 5-ethoxy-1,2,4-triazine **8**, and a subsequent, irreversible Diels–Alder reaction. This mechanism is supported by the observation that 6-carbethoxy-3-(*p*-tolyl)-1,2,4-triazin-5(2*H*)-one[11] (**9**) provides the corresponding 5-ethoxy-1,2,4-triazine **10**[12] under these modified Sasaki conditions (Scheme IV). Compound **2b** similarly subjected to the modified Sasaki conditions yielded nearly a 1:1 mixture of IDA and ICC products. This result lends support to the hypothesis that triethylamine acts as a base under normal Sasaki conditions to deprotonate the ring N–H of **2a** and **2b** thus favoring the ICC process. No ethoxypyridine byproduct was isolated in the case of **2b**, indicating that C-5 is not sufficiently electrophilic in this system (C-6 methyl vs C-6 carbethoxy) to undergo the requisite nucleophilic addition of ethanol.

Utilization of deuteriated dimethyl sulfoxide as the reaction solvent at 140 °C and 170 °C permitted observation of a remarkable reversal in reactivity resulting from what appears to be a pronounced solvent effect. In this instance, the IDA products **3** are produced in large excess relative to the ICC products **4** for both **2a** and **2b** (as determined by ^{1}H NMR). This clear preponderance of the IDA process suggests that the 5(4*H*)-one *cis*-diene tautomers of **2a** and **2b** predominate in dimethyl sulfoxide. This assumption is contrary to the presumed normal prevelance of the 5(2*H*) tautomers of 1,2,4-triazine-5-ones iiia in solution[9] which Paudler suggests is a consequence of deleterious lone pair–lone pair interactions[13] of N-1 and N-2 in the 5-(4*H*)-one tautomer iva.[9a] Paudler further noted that analogous pyrimidin-4-ones, unlike their 1,2,4-triazin-5-one counterparts, exist exclusively in the ortho quinonoid tautomeric form (i.e., the *cis*-diene 4(3*H*)-one ivb) rather than in the para quinonoid 4(1*H*)-one form iiib; in these species, the absence of destabilizing lone pair interactions favors the more highly resonance stabilized 4(3*H*)-one ivb. Based upon these observations, it can be inferred with reasonable confidence that dimethyl sulfoxide solvent molecules interact with **2a** and **2b** so as to lock these 1,2,4-triazines into the 5(4*H*)-one tautomeric structure in spite of the associated repulsive N-1/N-2 interaction (v) (Scheme V).

The intramolecular coplanar cycloamination observed with **2a** and **2b** occurs in a regiochemically clean fashion.

(9) (a) Lee, J.; Paudler, W. W. *J. Heterocycl. Chem.* **1972**, *9*, 995. (b) Daunis, J. *Bull. Soc. Chim. Fr.* **1973**, *6*, 2126. (c) Daunis, J.; Jacquier, R.; Pigiere, C. *Tetrahedron* **1974**, *30*, 3171. (d) Brown, D. J.; Jones, R. L. *Aust. J. Chem.* **1972**, *25*, 2711. (e) Jonas, J.; Gut, J. *Collect. Czech. Chem. Commun.* **1962**, *27*, 1886. (f) Horák, M.; Gut, J. *Collect. Czech. Chem. Commun.* **1963**, *28*, 3392. (g) Pitha, J.; Fiedler, P.; Gut, J. *Collect. Czech. Chem. Commun.* **1966**, *31*, 1864. (h) Uchytilová, V.; Fiedler, P.; Prystas, M.; Gut, J. *Collect. Czech. Chem. Commun.* **1971**, *36*, 1955.

(10) For a discussion of tautomerism in heterocyclic systems, see: Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*, Supplement 1 of *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1976; p 655.

(11) Taylor, E. C.; Martin, S. F. *J. Org. Chem.* **1972**, *37*, 3958.

(12) McDaniel, K. F. Ph.D. Thesis, Princeton University, 1985, p 142.

(13) Taft, R. W.; Anvia, F.; Taagepera, M.; Catalán, J.; Elguero, J. *J. Am. Chem. Soc.* **1986**, *108*, 3237.

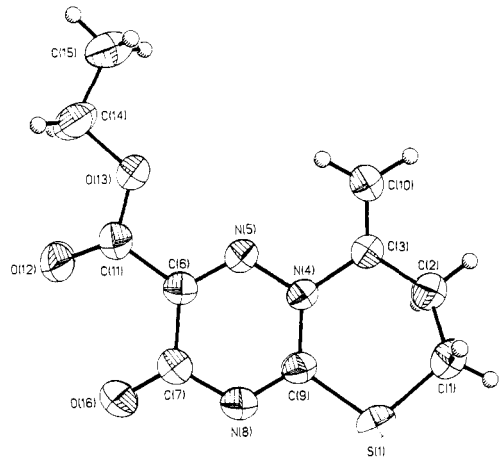
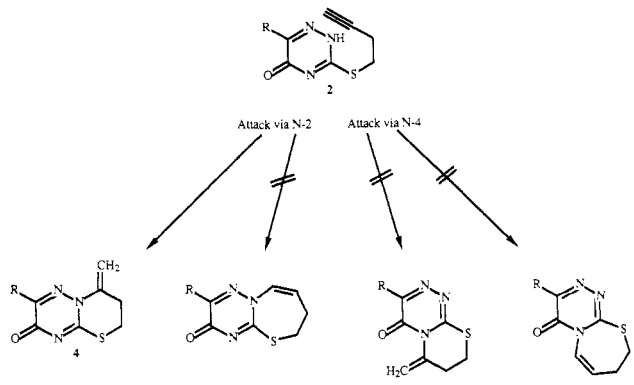


Figure 1. ORTEP drawing of compound **4a**.

Scheme VI



Sasaki[4] and we have presumed that this reaction proceeds via exclusive attack of the triazine N-2 nitrogen (not N-4) upon the internal acetylene carbon (not the terminal carbon). This assumption is consistent with Paudler's observation that for deprotonated 1,2,4-triazin-5-ones, N-2 is more nucleophilic than N-4 due to the aforementioned lone pair repulsion of N-1 and N-2 (a situation analogous to the α-effect[14]). Scheme VI illustrates the gamut of possible regiochemical outcomes of the ICC process, all of which are favored by Baldwin's rules of ring closure.[15]

For confirmation of the course of the intramolecular coplanar cycloamination reaction, an X-ray diffraction analysis was performed on **4a**. With the structure of **4a** thus firmly established (Figure 1), the structure of the other ICC product (**4b**) was confirmed by the correspondence of both ^{1}H and ^{13}C NMR spectra.

Experimental Section

X-ray Structure Determination of 4a ($C_{10}H_{11}N_3O_3S$). The crystallographic data are as follows: monoclinic, $P2_1/n$, a = 6.801 (1), b = 9.257 (2), and c = 17.987 (5) Å, β = 95.50 (2)°, V = 1127.1 (4) Å^3, z = 4, D(calcd) = 1.49 g cm^{-3}, R = 7.4%, R_w = 8.8%. A total of 1524 independent reflections were measured (Nicolet R3m diffractometer, graphite-monochromated Cu Kα radiation, $2\theta_{max}$ = 114°) and corrected for absorption (azimuthal scans of 9 reflections with χ = 90 ± 20°, min trans 0.123, max trans 0.267) after which 1383 with $I \geq 3\sigma(I)$ were considered observed. The structure was solved by direct methods using the SHELXTL package. All non-hydrogen atoms were refined with anisotropic temperature factors; all hydrogen atoms were located and included at idealized positions. The lists of final atomic coordinates, atomic thermal parameters, and molecular dimensions have been deposited as supplementary material.

Instrumentation and Materials. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1320 instrument and are reported in cm^{-1}. ^{1}H and ^{13}C NMR data were obtained with a General Electric QE300 300 MHz instrument and chemical shifts are reported in ppm relative to residual non-deuteriated solvent. Mass spectral data were obtained by Dr. Dorothy Little on a Kratos MS50TC spectrometer. Elemental analyses were performed by Eli Lilly and Co., Indianapolis, IN. Column chromatography was performed on Merck silica gel 60 (240–400 mesh). Preparative TLC was carried out on Analtech silica gel GF uniplates (1500 μm). Commercial reagents were utilized without further purification.

3-(3-Butynylthio)-6-methyl-1,2,4-triazin-5(2*H*)-one (2b). A stirred suspension of *S*-(3-butynyl)thiosemicarbazide hydroiodide (3.04 g, 11.22 mmol) in absolute ethanol (40 mL) was heated to reflux. After a homogeneous solution was obtained, sodium bicarbonate (1.00 g, 11.90 mmol) followed by pyruvic acid (0.99 g, 11.22 mmol) was added to the reaction mixture which was subsequently heated at reflux for 4 h. After this period, the reaction mixture was evaporated under reduced pressure, and the residual pasty solid was triturated with water to afford 3-(3-butynylthio)-6-methyl-1,2,4-triazin-5(2*H*)-one (**2b**) as a white solid: yield 1.72 g (79%); mp 192–193 °C (effervescent dec) (lit.[4] mp 180–182 °C); ^{1}H NMR (DMSO-d_6) δ 13.69 (br s, 1 H), 3.21 (t, J = 7.0 Hz, 2 H), 2.93 (t, J = 2.5 Hz, 1 H), 2.54 (dt, J_1 = 7.0 Hz, J_2 = 2.6 Hz, 2 H), 2.08 (s, 3 H); HRMS calcd for $C_8H_9N_3OS$ m/z 195.0466, found m/z 195.0473.

Thermolysis of the 3-(3-Butynylthio)-1,2,4-triazin-5-(2*H*)-ones 2a,b. Synthesis of 2,3-Dihydrothieno[2,3-*b*]-pyridin-6(7*H*)-ones 3a,b and 8-Methylene-7,8-dihydro-3*H*,6*H*-[1,3]thiazino[3,2-*b*][1,2,4]triazin-3-ones 4a,b. General Procedure A. Stirred suspensions of the 3-(3-butynylthio)-1,2,4-triazin-5(2*H*)-ones **2a,b** in bromobenzene or nitrobenzene were heated for 1–5 h under nitrogen at the temperatures indicated in Table I. The reactions were followed to completion by thin layer chromatography (1:1 ethyl acetate/methylene chloride for **2a**, 5% methanol/methylene chloride for **2b**). The cooled reaction mixtures were filtered through a pad of silica gel and washed with methylene chloride to remove the solvent.

For reactions with **2a**, subsequent elution with 1:1 ethyl acetate/hexanes followed by evaporation of the filtrate under reduced pressure gave the IDA product, 5-carbethoxy-2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one (**3a**), as a pale tan solid. Continued elution with 1:1 ethyl acetate/methylene chloride followed by evaporation of the filtrate under reduced pressure gave the ICC product, 2-carbethoxy-8-methylene-7,8-dihydro-3*H*,6*H*-[1,3]-thiazino[3,2-*b*][1,2,4]triazine (**4a**), as a white solid. The spectral and physical properties of **3a** and **4a** obtained from these reactions were identical with the spectral and physical properties of these compounds described by us elsewhere.[2]

For reactions with **2b**, subsequent elution with 5% methanol/methylene chloride followed by evaporation of the filtrate under reduced pressure afforded a white solid which after purification by preparative TLC (5% methanol/methylene chloride eluent) yielded two compounds: (1) the IDA product, 5-methyl-2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one (**3b**), R_f 0.16 (5% methanol/methylene chloride), mp >210 °C dec; ^{1}H NMR (CDCl$_3$) δ 7.18 (s, 1 H), 3.46 (t, J = 7.8 Hz, 2 H), 3.11 (t, J = 7.9 Hz, 2 H), 2.13 (s, 3 H); ^{1}H NMR (Me$_2$SO-d_6) δ 11.29 (br s, 1 H), 7.20 (s, 1 H), 3.36 (t, J = 8.0 Hz, 2 H), 3.10 (t, J = 7.9 Hz, 2 H), 1.92 (s, 3 H); HRMS calcd for C_8H_9NOS m/z 167.0405, found m/z 167.0402; (2) the ICC product, 2-methyl-8-methylene-7,8-dihydro-3*H*,6*H*-[1,3]thiazino[3,2-*b*][1,2,4]triazine (**4b**), R_f 0.51 (5% methanol/methylene chloride), recrystallized from ethanol as white needles, mp 195.5–196.5 °C (lit.[4] mp 199–200 °C); ^{1}H NMR (CDCl$_3$) δ 5.68 (s, 1 H), 4.88 (d, J = 1.1 Hz, 1 H), 3.16–3.11 (m, 2 H), 3.06–3.02 (m, 2 H), 2.34 (s, 3 H); ^{1}H NMR (DMSO-d_6) δ 5.48 (s, 1 H), 4.94 (s, 1 H), 3.19–3.15 (m, 2 H), 3.00–2.96 (m, 2 H), 2.15 (s, 3 H); ^{13}C NMR (CDCl$_3$) δ 161.62, 159.34, 152.06, 140.30, 104.77, 30.48, 25.81, 17.36; HRMS calcd for $C_8H_9N_3OS$ m/z 195.0466, found m/z 195.0470. Anal. Calcd for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.32; H, 4.69; N, 21.70; S,

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16.59. All yields are reported in Table I.

General Procedure B. Suspensions of **2a,b** in ethanol, with[4] and without the presence of 0.25 equiv of triethylamine, were heated under nitrogen in sealed glass tubes at 140 °C for 36–46 h. After this period, the reaction mixtures were cooled in an ice bath, and the resulting precipitate was collected by filtration to give the corresponding ICC products **4a,b** in pure form. For reactions with **2a**, the filtrates were evaporated under reduced pressure, and the residual material was purified by column chromatography (1:1 ethyl acetate/methylene chloride eluent) to provide additional ICC product **4a** and IDA product **3a**. Also isolated was 5-carbethoxy-6-ethoxy-2,3-dihydrothieno[2,3-*b*]-pyridine (**6**), R_f 0.75 (1:1 ethyl acetate/methylene chloride), mp 38–39 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 4.45 (q, J = 7.1 Hz, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 3.44 (t, J = 8.0 Hz, 2 H), 3.26 (t, J = 8.0, 2 H), 1.44–1.34 (m, 6 H); HRMS calcd for $C_{12}H_{15}NO_3S$ m/z 253.0772, found m/z 253.0783. For reactions with **2b**, the filtrates were evaporated under reduced pressure, and the residual material was purified by preparative TLC (5% methanol/methylene chloride eluent) to yield additional ICC product **4b** and the IDA product **3b**. Yields are reported in Table I. The spectral and physical properties of **3a,b** and **4a,b** derived from these reactions were identical with those described above in General Procedure A and elsewhere.[2]

General Procedure C. NMR tubes containing deuteriated dimethyl sulfoxide solutions of **2a,b** (~10 mg of the triazine in 1 mL of Me_2SO-d_6) were heated at 5–6-h intervals at 140 °C and at 1 h intervals at 170 °C. After each interval, the reaction mixture was analyzed by ^{1}H NMR to determine the extent of reaction. At 140 °C, the starting materials **2a,b** were consumed in ~20 h. At 170 °C, only 3 h were needed for complete disappearance of starting materials. Yields listed in Table I are based upon the ^{1}H NMR peak integration ratio of the pyridine C-4 proton of **3a,b** and one of the exocyclic vinyl methylene protons of **4a,b**.

6-Carbethoxy-5-ethoxy-3-(*p*-tolyl)-1,2,4-triazine (10). A stirred suspension of 6-carbethoxy-3-(*p*-tolyl)-1,2,4-triazin-5-(2*H*)-one[12] (**9**) (0.090 g, 0.35 mmol) in 10 mL of ethanol was heated to 140–145 °C for 43.5 h in a sealed glass tube. After this period, the reaction mixture was evaporated under reduced pressure. The residual material contained 20% of the desired product[12] along with unreacted starting material **10** as determined by ^{1}H NMR peak integration: ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3 H), 1.52 (t, J = 7.0 Hz, 3 H), 2.44 (s, 3 H), 4.5 (q, J = 7.0 Hz, 2 H), 4.70 (q, J = 7.0 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 8.41 (d, J = 8.5 Hz, 2 H).

Registry No. **2a**, 115983-74-9; **2b**, 90997-83-4; **3a**, 115983-75-0; **3b**, 115983-76-1; **4a**, 116025-22-0; **4b**, 90997-87-8; *S*-(3-butynyl)-thiosemicarbazide hydroiodide, 109216-69-5; pyruvic acid, 127-17-3.

Supplementary Material Available: Tables of atomic coordinates, atomic thermal parameters, bond lengths and angles, and figures for **4a** (11 pages). Ordering information is given on any current masthead page.

Synthesis of the Left-Hand Ring of the Antitumor Antibiotic CC-1065 by an Intramolecular Carbenoid Addition Route. Synthesis and Reactivity of 4-Diazo-4,7-dihydroindol-7-ones and Related Compounds

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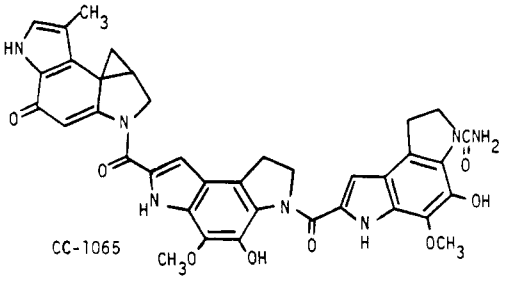
The synthesis of 4-diazo-4,7-dihydroindol-7-ones, which could serve as precursors of the A-ring structure of the antitumor antibiotic CC-1065 by intramolecular carbenoid addition, has been explored. Direct diazo transfer using 7-hydroxy-3-methyl-5-[*N*-(2-propenyl)acetamido]indole gave a 6-diazo-6,7-dihydroindol-7-one. Reduction and diazotiazation of 7-[(ethoxycarbonyl)oxy]-3-methyl-4-nitro-5-[*N*-(2-propenyl)sulfonamido]indole gave 4-diazo-3-methyl-5-[*N*-(2-propenyl)methanesulfonamido]-4,7-dihydroindol-7-one (**2b**). The 1-phenylsulfonyl analogue and a model diazocyclohexadienone, 2-acetamido-4-diazo-5-[*N*-(2-propenyl)methanesulfonamido]cyclohexa-2,5-dienone were also prepared. Photolysis, thermolysis, or transition metal catalyzed decomposition of the diazo compounds leads to mixtures of spirocyclopropanes by intramolecular carbenoid addition and sulfinamido quinones formed by oxygen-transfer from the sulfonyl group to the carbenoid intermediate. The best yields of cyclopropanation in the case of the 4-diazoindol-7-one (**2b**) were obtained with copper catalysts, which provided the methanesulfonyl derivative of the A-ring structure in 45–55% yield.

The highly potent antitumor antibiotic CC-1065 has attracted much attention.[1] The compound has been shown to covalently alkylate DNA in a site-selective manner by cyclopropane ring opening.[2] Beginning with Wierenga's synthesis reported in 1981,[3] a number of syntheses of the left-hand portion of the structure, which possesses the alkylating activity, have been developed.[4]



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