

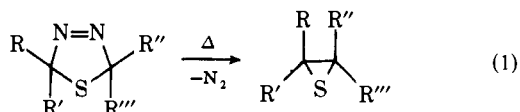
Flash Vacuum Pyrolysis of 1,3-Oxathiolan-5-ones^{1,2}

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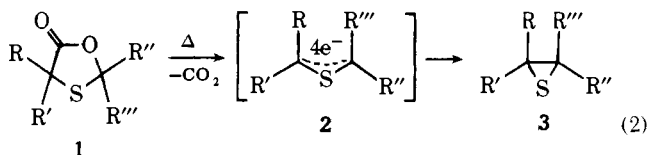
Abstract: Flash vacuum pyrolysis of 1,3-oxathiolan-5-ones causes loss of carbon dioxide with the concomitant formation of the corresponding thiiranes in nearly quantitative yield. The reaction is stereospecific and proceeds by clean inversion of configuration. This suggests a concerted loss of carbon dioxide. Furthermore, substituent effects strongly support the intermediacy of thiocarbonyl ylides. Consequently, this method becomes one of the simplest ways of generating these species.

Thermally induced elimination of neutral molecules is exemplified by the many known chelotropic reactions and other dipolar cycloreversions.³ Of particular interest to the present study is the latter reaction type shown in eq 1⁴ because of the

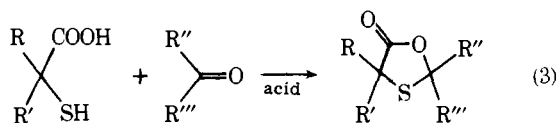


assumed intermediacy of a thiocarbonyl ylide.⁵ Unfortunately, preparation of the thiadiazoline precursors is not trivial and therefore precludes this route as an attractive preparative method.

We have examined the thermal extrusion of carbon dioxide from 1,3-oxathiolan-5-ones (**1**)⁶ as a potentially simple route to thiocarbonyl ylides (**2**) which collapse to thiiranes (**3**) (eq 2).² It is most gratifying to find that flash vacuum pyrolysis⁷



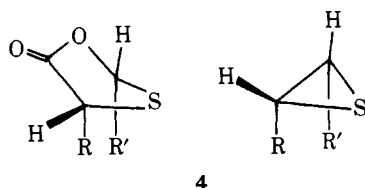
of oxathiolanones gives thiiranes and that the conversion is quite general (see Table I). All yields are excellent so that this reaction represents a preparative method of potential synthetic utility⁸ because of the ease of preparing the starting 1,3-oxathiolan-5-ones (eq 3).⁶



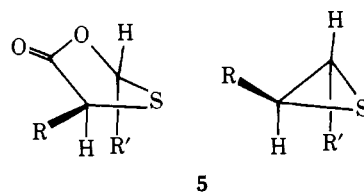
Possibly of even greater importance is proof of the intermediacy of thiocarbonyl ylides as postulated in eq 2. We sought compelling evidence to support this hypothesis.

On the assumption that loss of carbon dioxide is concerted, the conversion of an oxathiolanone into the corresponding thiirane should be stereospecific. In fact, orbital symmetry considerations⁹ require a net inversion of configuration as a consequence of disrotatory ring opening with loss of carbon dioxide followed by conrotatory ring closure of the ylide.

To answer this question requires the unambiguous structural assignment of both starting materials and products by considering the NMR spectra. This is possible because of the conformation of the cis (**4**) and trans (**5**) isomers. The cis



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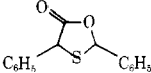
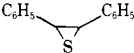
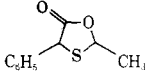

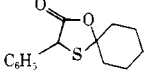
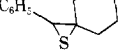
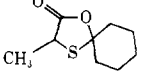
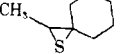
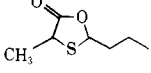
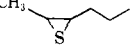
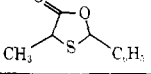
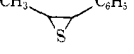
compounds show long-range coupling because of the "W" configuration of the 2,4 hydrogens.¹⁰ An extensive study of the analogous oxygen compounds (1,3-dioxolan-4-ones) also confirms this phenomenon^{11a} and, together with another reactant NMR study on the stereochemistry of thiiranes,^{11b} greatly aided the definitive structural assignments.

With the stereochemistry of the starting materials and products firmly established, we analyzed the results from several systems (see Table II). The most extensively studied compound is 2,4-diphenyl-1,3-oxathiolan-5-one. A mixture which contained 62% of the cis diastereomer yielded a mixture of thiiranes consisting of 65% of the trans isomer. Another mixture containing 40% of the cis oxathiolanone gave a thiirane mixture with 37% of the trans compound present. Fractional sublimation of the starting material gave a third mixture consisting of only 10% of the cis isomer. Pyrolysis gave stilbene thiirane containing 8% of the trans isomer. Sublimation of the starting material also yielded a mixture of oxathiolanones enriched in the cis isomer (89% cis) which gave a thiirane mixture consisting of 86% of the trans isomer. The stereochemical outcome in the other three systems in Table II also is that of clean inversion.

These results clearly show that the oxathiolanone to thiirane conversion is nearly 100% stereospecific (within the error of NMR determination)¹² and goes with inversion of configuration in full agreement with orbital symmetry predictions. This supports the hypothesis of a concerted loss of carbon dioxide which is consistent with a thiocarbonyl ylide intermediate (eq 2). Direct formation of the thiirane ring with no intermediate should result in retention of configuration by analogy with cycloaddition reactions of ketenes ($\pi 2_s + \pi 2_a$)¹³ and cycloeliminations of β -lactones ($\sigma 2_s + \sigma 2_a$).¹⁴

Additional support for the thiocarbonyl ylide can be obtained by considering the effect of substituents on the relative ease of the conversion. If a thiocarbonyl ylide is involved, there should be a strong substituent effect, whereas the rate of a concerted reaction pathway should show very little dependence upon substituents. Examination of the data of Table III reveals that the conversion of 1,3-oxathiolan-5-ones into thiiranes shows a marked, reproducible substituent effect. For example, the diphenyl system undergoes reaction of the lowest temperature (600 °C), whereas the trialkyloxathiolanone requires 750 °C for complete conversion to product. Comparison of the percent reaction at 600 °C also illustrates the dramatic substituent effect. The diphenyl compound goes to completion at 600 °C while systems lacking a phenyl do not react at all at 600 °C. The data of Table III clearly show a trend which parallels

Table I. Preparation of Thiiranes from Oxathiolanones

oxathiolanone	thiirane	% yield ^a
		100 (91)
		95 (89)
		100 (94)
		100 (93)
		98 (95)
		99 (93)

^a The percent yield of both crude material and pure, distilled, or recrystallized product (in parentheses) is given.

that expected by considering the relative stabilization of a thiocarbonyl ylide intermediate and therefore supports the reaction pathway shown in eq 2.

Although strong arguments have been made against the potential diradical character of 1,3 dipoles (including carbonyl ylides),¹⁵ several studies appear to involve 1,3 diradicals.¹⁶ On the basis of the inversion results in various pyrazolines,¹⁶ our results are also consistent with a diradical intermediate. Investigations are currently underway to extend this reaction type to other systems as well as to gain further information on the reaction mechanism.

Experimental Section

General. ¹H NMR spectra were recorded either on a Varian T-60 or a JEOL PFT-100 spectrometer. IR spectra were obtained with a Perkin-Elmer 257 or 297 spectrometer. Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Ga.

General Procedure for the Preparation of 1,3-Oxathiolan-5-ones.

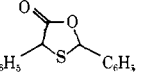
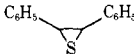
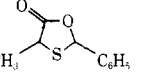
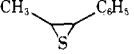
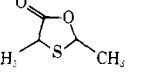

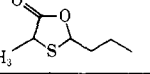
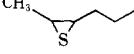
A. Mercapto Acids and Ketones or Benzaldehyde. In a 250-mL flask fitted with a Dean-Stark trap, reflux condenser, and CaCl₂ drying tube were placed 150 mL of benzene, 100 mmol each of the mercapto acid and ketone, and 15 mmol of *p*-TsOH. The solution was refluxed until the theoretical amount of water was collected or until water formation ceased. The reaction mixture was allowed to cool and extracted with either *ice-cold* 10% NaHCO₃ or 10% NaOAc until the aqueous washings were neutral or just basic. Care must be exercised because these products are extremely sensitive to base. The benzene solution was washed twice with distilled water, dried over anhydrous MgSO₄, and concentrated. The crude product was distilled or recrystallized from hexane/benzene.

B. Mercapto Acids and Aldehydes. In a 250-mL flask fitted with a reflux condenser, pressure-equalizing addition funnel, and CaCl₂ drying tube were placed 100 mL of anhydrous ether, 100 mmol of the mercapto acid, and 100–120 mmol of the aldehyde. Freshly distilled BF₃·OEt₂ (125–150 mmol) in 25 mL of dry ether was added dropwise over a 15-min period and stirring was continued for an additional 1 h. Workup was as before.

Preparation of 2,4-Diphenyl-1,3-oxathiolan-5-one. Mercaptophenylacetic acid¹⁷ (5.00 g, 29.8 mmol), benzaldehyde (3.80 g, 35.8 mmol), and *p*-TsOH (0.86 g, 4.5 mmol) in 50 mL of benzene were refluxed for 3 h to give 3.90 g (51.1%) of pure product after recrystallization: mp 94–99 °C; IR (KBr, cm⁻¹) 1765 (C=O); cis/trans, 62/38.

The same reaction mixture when refluxed overnight produced 3.99 g (52.4%) of pure product after recrystallization: mp 94–97 °C; cis/trans, 40/60.

Table II. Stereochemistry of the Oxathiolanone to Thiirane Conversion^a

oxathiolanone	cis/trans ratio	thiirane	cis/trans ratio
	62/38 40/60 10/90 89/11		35/65 63/37 92/8 14/86
	59/41		42/58
	67/33		33/67
	63/37		38/62

^a All percentages are obtained by integration of the ¹H NMR spectra. All values are ±4%.

Three sublimations yielded two mixtures, mp 77–79 (cis/trans, 10/90) and 108–110 °C (cis/trans, 89/11).

¹H NMR (CDCl₃): δ (trans) 5.16 (s, 1 H), 6.55 (s, 1 H), 7.33–7.51 (m, 10 H); (cis) 5.26 (d, *J* = 0.62 Hz, ¹⁸ 1 H) 6.51 (d, *J* = 0.62 Hz, 1 H), 7.33–7.51 (m, 10 H).

Anal. Calcd for C₁₅H₁₂SO₂: C, 70.29; H, 4.72; S, 12.51. Found: C, 70.37; H, 4.78; S, 12.45.

Preparation of 2-Phenyl-4-methyl-1,3-oxathiolan-5-one. Thiolactic acid (10.6 g, 100 mmol), benzaldehyde (12.7 g, 120 mmol), and BF₃·OEt₂ (21.3 g, 150 mmol) gave 9.72 g (50.1%) of pure product: mp 48–56 °C; bp 151–153 °C (3 Torr); IR (KBr, cm⁻¹) 1765 (C=O); cis/trans, 59/41; ¹H NMR (CDCl₃) δ (trans) 1.69 (d, *J* = 7.1 Hz, 3 H), 3.94 (q, *J* = 7.1 Hz, 1 H), 6.48 (s, 1 H), 7.43 (s, 5 H); (cis) 1.64 (d, *J* = 7.1 Hz, 3 H), 4.14 (q of d, *J*_q = 7.1, *J*_d = 0.59 Hz, 1 H), 6.36 (d, *J* = 0.59 Hz, 1 H), 7.43 (s, 5 H).

Anal. Calcd for C₁₀H₁₀SO₂: C, 61.83; H, 5.19; S, 16.5. Found: C, 61.98; H, 5.21; S, 16.44.

Preparation of 2-Methyl-4-phenyl-1,3-oxathiolan-5-one. Mercaptophenylacetic acid (5.00 g, 29.8 mmol), acetaldehyde (2.64 g, 60.0 mmol), and BF₃·OEt₂ (6.33 g, 44.6 mmol) were allowed to react to give 3.55 g (56.3%) of pure product: mp 58–63 °C; bp 104–106 °C (0.2 Torr); IR (KBr, cm⁻¹) 1770 (C=O); cis/trans, 67/33; ¹H NMR (CDCl₃) δ (trans) 1.76 (d, *J* = 6.1 Hz, 3 H), 5.07 (s, 1 H), 5.71 (q, *J* = 6.1 Hz, 1 H), 7.39 (s, 5 H); (cis) 1.78 (d, *J* = 6.1 Hz, 3 H), 5.13 (d, *J* = 0.36 Hz, 1 H), 5.64 (q of d, *J*_q = 6.1, *J*_d = 0.36 Hz, 1 H), 7.39 (s, 5 H).

Anal. Calcd for C₁₀H₁₀SO₂: C, 61.83; H, 5.19; S, 16.51. Found: C, 62.04; H, 5.25; S, 16.37.

Preparation of 2,2-Pentamethylene-4-phenyl-1,3-oxathiolan-5-one. Mercaptophenylacetic acid (5.00 g, 29.8 mmol), cyclohexanone (3.50 g, 35.8 mmol), and *p*-TsOH (0.86 g, 4.5 mmol) gave 6.92 g (93.8%) of pure material: mp 101–102 °C; IR (KBr, cm⁻¹) 1770 (C=O); ¹H NMR (CDCl₃) δ 1.26–1.93 (m, 6 H), 1.93–2.08 (m, 4 H), 5.17 (s, 1 H), 7.40 (s, 5 H).

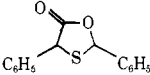
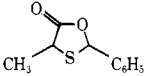
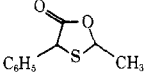
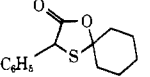
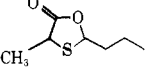
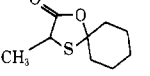
Anal. Calcd for C₁₄H₁₆SO₂: C, 67.71; H, 6.49; S, 12.91. Found: C, 67.66; H, 6.51; S, 12.91.

Preparation of 2-*n*-Propyl-4-methyl-1,3-oxathiolan-5-one. Thiolactic acid (10.6 g, 100 mmol), *n*-butyraldehyde (8.65 g, 120 mmol), and BF₃·OEt₂ (21.28 g, 150 mmol) gave 5.4 g (34%) of pure product: bp 110–111 °C (15 Torr); IR (NaCl, cm⁻¹) 1770 cis/trans, 63/37; ¹H NMR (CDCl₃) δ (trans) 0.98 (t, *J* = 7.3 Hz, 3 H), 1.2–1.7 (m, 2 H), 1.75–2.5 (m, 2 H), 1.60 (d, *J* = 7.1 Hz, 3 H), 3.90 (q, *J* = 7.3 Hz, 1 H), 5.47 (t, *J* = 7.1 Hz, 1 H); (cis) 0.98 (t, *J* = 7.3 Hz, 3 H), 1.2–1.7 (m, 2 H), 1.75–2.5 (m, 2 H), 1.57 (d, *J* = 7.1 Hz, 3 H), 3.97 (q of d, *J*_q = 7.3, *J*_d = 0.49 Hz, 1 H), 5.41 (t of d, *J*_t = 7.1, *J*_d = 0.49 Hz, 1 H).

Anal. Calcd for C₇H₁₂SO₂: C, 52.47; H, 7.55; S, 20.01. Found: C, 52.44; H, 7.54; S, 19.99.

Preparation of 2,2-Pentamethylene-4-methyl-1,3-oxathiolan-5-one. Thiolactic acid (10.6 g, 100 mmol), cyclohexanone (11.7 g, 120 mmol), and *p*-TsOH (2.85 g, 15.0 mmol) gave 17.1 g (91.9%) of pure product: bp 147–149 °C (18 Torr); IR (NaCl, cm⁻¹) 1760 (C=O);

Table III. Effect of Substituents on the Oxathiolanone to Thiirane Conversion^a

oxathiolanone	temp. °C	% conversion	temp at which starting material is completely consumed, °C	% conversion at 600 °C
	550	84		
	600	100	600	100
	550	29		
	600	65	650	65
	650	>99		
	600	45		
	650	>99	650	45
	600	55		
	650	95	700	55
	700	100		
	600	0		
	700	>98	750	0
	750	100		
	600	0		
	650	73	750	0
	700	97		
	750	100		

^a Each run has been repeated at least once and is reproducible. All pyrolyses were conducted in exactly the same way.

¹H NMR (CDCl₃) δ 1.26–1.86 (m, 6 H), 1.60 (d, *J* = 7.1 Hz, 3 H), 1.86–2.20 (m, 4 H), 4.08 (q, *J* = 7.1 Hz, 1 H).

Anal. Calcd for C₉H₁₄SO₂: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.12; H, 7.60; S, 17.14.

General Procedure for Pyrolysis of 1,3-Oxathiolan-5-ones. The sample was heated in a fine stream of nitrogen at a pressure of 0.01–0.5 Torr (adjusted according to the volatility of the starting compound). The vaporized sample then passed through a heated quartz tube (1.0 × 10 cm) and the products were collected on a cold finger (cooled with dry ice/acetone) 2 cm from the end of the hot zone. Typically 15–90 min was required to pyrolyze 0.1–0.5 g by this procedure.

Pyrolysis of 2,4-Diphenyl-1,3-oxathiolan-5-one. The starting material (0.30 g, 1.2 mmol, cis/trans, 62/38) was vaporized at 110 °C (0.05 Torr) with the hot zone at 600 °C. The product was rinsed from the cold finger with distilled ether and concentrated to give the thiirane (100%, cis/trans, 35/65). Recrystallization from methanol gave 0.21 g (0.98 mmol, 84%) of product, mp 34–37 °C.¹⁹

Another mixture of starting material (0.34 g, 1.33 mmol, cis/trans, 40/60) was treated in the same way to give 0.24 g (86%) of product: mp 46–58 °C¹⁹ after recrystallization from methanol; cis/trans, 63/37.

Another mixture (0.020 g, cis/trans, 10/90) was pyrolyzed to give the thiirane mixture: mp 68–71 °C;¹⁹ cis/trans, 98/8.

Another mixture (0.015 g, cis/trans, 89/11) was treated similarly to give the product: mp 35–37 °C¹⁹ cis/trans, 14/86.

Pyrolysis of 2-Phenyl-4-methyl-1,3-oxathiolan-5-one. The starting material (0.36 g, 1.9 mmol, cis/trans, 59/41) was vaporized at 70 °C (0.03 Torr) with the hot zone at 650 °C. The crude product consisted of the thiirane (95%) plus less than 1% of starting material and 4% of propenylbenzene. Distillation gave 0.26 g (93%) of the pure thiirane, bp 53–54 °C (0.5 Torr).²⁰ At 600 °C (0.01 Torr) the product was 65% thiirane and 35% starting material while at 550 °C (0.01 Torr) the product consisted of 29% thiirane and 71% starting material.

¹H NMR (CDCl₃): δ (trans) 1.63 (d, *J* = 5.9 Hz, 3 H), 3.12 (d of q, *J*_d = 5.9, *J*_q = 5.1 Hz, 1 H), 3.57 (d, *J* = 5.1 Hz, 1 H), 7.27 (s, 5 H); (cis) 1.22 (d, *J* = 6.1 Hz, 3 H), 3.17 (m, 1 H), 4.15 (d, *J* = 7.1 Hz, 1 H), 7.32 (s, 5 H).

Pyrolysis of 2-Methyl-4-phenyl-1,3-oxathiolan-5-one. The starting material (0.27 g, 1.4 mmol, cis/trans, 67/33) was vaporized at 70 °C (0.05 Torr) with the hot zone at 650 °C. The crude product was 95% thiirane (cis/trans, 33/67), 4% propenylbenzene, and less than 1% starting material. Distillation gave 0.18 g (89%) of the pure thiirane: bp 52–54 °C (0.5 Torr).²⁰ ¹H NMR (CDCl₃) as before.

Pyrolysis of 2,2-Pentamethylene-4-phenyl-1,3-oxathiolan-5-one. The starting material (0.68 g, 3.7 mmol) was vaporized at 50 °C (0.05

Torr) with the hot zone at 700 °C. The product was pure thiirane (100%). Distillation gave 0.48 g (93%) of thiirane: bp 74–75 °C (0.001 Torr) (the product partially decomposes when distilled at 103–105 °C (0.05 Torr)); ¹H NMR (CDCl₃) δ 1.33–2.03 (m, 10 H), 3.96 (s, 1 H), 7.36 (s, 5 H).

Anal. Calcd for C₁₃H₁₆S: C, 76.41; H, 7.89. Found: C, 76.53; H, 7.90.

Pyrolysis of 2-(*n*-Propyl)-4-methyl-1,3-oxathiolan-5-one. The starting material (0.45 g, 2.8 mmol, cis/trans, 63/37) was vaporized at 50 °C (0.5 Torr) with the hot zone at 750 °C. The product (98%, cis/trans, 38/62) was pure thiirane which was distilled to give 0.31 g (95%): bp 76–80 °C (95 Torr); ¹H NMR (CDCl₃) δ (trans) 0.73–1.18 (m, 3 H), 1.26–2.08 (m, 4 H), 1.52 (d, *J* = 5.3 Hz, 3 H), 2.46–2.93 (m, 2 H), (cis) 0.73–1.18 (m, 3 H), 1.26–2.08 (m, 4 H), 1.50 (d, *J* = 5.3 Hz, 3 H), 2.68–3.25 (m, 2 H).

Anal. Calcd for C₆H₁₂S: C, 62.00; H, 10.41. Found: C, 62.16; H, 10.42.

Pyrolysis of 2,2-Pentamethylene-4-methyl-1,3-oxathiolan-5-one. The starting material (0.60 g, 2.4 mmol) was vaporized at 110 °C (0.05 Torr) with the hot zone at 750 °C to give 100% crude yield of the thiirane. Distillation gave 0.46 g (94%) of the product: bp 83–84 °C (5 Torr); ¹H NMR (CDCl₃) δ 1.40–1.95 (m, 10 H), 1.53 (d, *J* = 6.1 Hz, 3 H), 2.97 (q, *J* = 6.1 Hz, 1 H).

Anal. Calcd for C₈H₁₂S: C, 67.54; H, 9.92. Found: C, 67.28; H, 9.89.

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Preparation of Substituted 2-Pyridones by Thermal Rearrangement of Propargylic Pyrrolidine Pseudoureas

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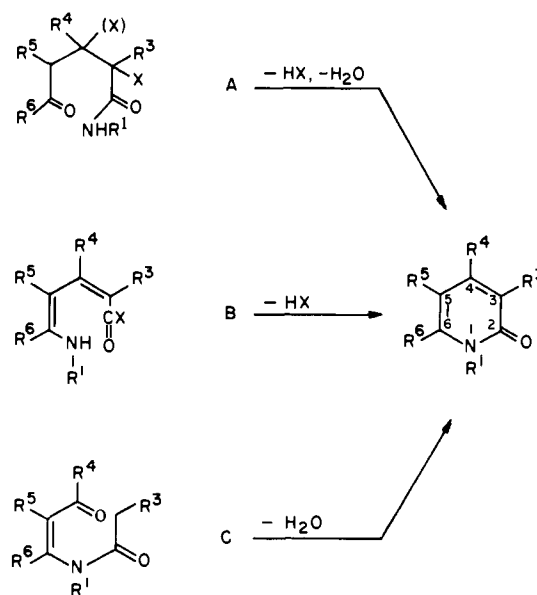
Abstract: A new method for preparing 3,6-dialkyl- (and -diaryl-) 2-pyridones is reported (Scheme II). Secondary propargylic alcohols are condensed with 1-cyanopyrrolidine to yield pseudoureas **1**, which are directly rearranged in refluxing xylene to afford 3,6-disubstituted 2-pyridones **2**. This experimentally simple method is illustrated with nine examples, and the overall yields range from 12 to 79%. This method is most successful (overall yields of 58–79%) for the preparation of 2-pyridones with alkyl substituents at C₆, and either hydrogen, alkyl, or aryl substitution at C₃. When the terminal alkynic carbon of **1** is unsubstituted or phenyl substituted, oxazoles **13–15** are isolated in addition to the corresponding 2-pyridones. Interruption of the thermal rearrangement of pseudourea **1** (R³ = Ph; R⁶ = *t*-Bu) at partial conversion results in the isolation of the (1*Z*,3*E*)-pyrrolidine diene urea **16**, which is converted to 2-pyridone **4** in >95% yield in refluxing xylene. The conversion of **16** → **4** is inhibited by added pyrrolidine; and is accompanied by amine exchange to give the piperidine diene urea **17** when carried out in the presence of piperidine. These experiments demonstrate the intermediacy of diene ureas and diene isocyanates in the propargylic pseudourea to 2-pyridone transformation, and a detailed mechanism for this conversion is proposed (Scheme III).

The 2-pyridone (2(1*H*)-pyridinone) ring is an important structural feature of a number of natural products.^{2,3} Examples are found in the lupinine, lupanine, sparteine, and matrine groups of quinolizidine alkaloids,^{3,4} pyridine alkaloids such as ricinine, and the antitumor agent camptothecin.⁵

The 2-pyridone ring system has not lacked for attention by synthetic chemists.⁶ Syntheses which involve ring closures are particularly important, and three classical approaches of this type are illustrated in Scheme I. The most widely employed method is A.⁶ Usually the ketoamide (or an equivalent) is constructed by C₃–C₄ bond formation, and R³ is, thus, typically⁸ a carbanion stabilizing substituent. A second general approach involves lactamization of a 5-aminodieneoic acid derivative (method B).^{6,9} A third general method involves C–C bond formation via Dieckmann- or aldol-type ring closures,⁶ and C illustrates one common version of this method. The Dieckmann/aldol approach is well suited to preparing di- and tetrahydro derivatives, and has been widely employed in syntheses of camptothecin.^{5,10} With existing methods, 2-pyridones substituted with electron-withdrawing groups (CN, COOR, CONR₂, NO₂) at C₃ are particularly available,⁶ while fewer general methods exist^{6,11,12} for preparing 2-pyridones substituted with alkyl (or aryl) substituents at C₃ and C₆.

A new ring-forming construction of 2-pyridones, which lends itself to the preparation of derivatives with hydrocarbon substituents at C₃ and C₆, was reported by Eloy and Deryckere in 1970.¹³ In this method a 1,3-diene acyl azide is thermolyzed at high temperature (typically 240 °C) to give a substituted

Scheme I



2-pyridone, presumably via electrocyclic ring closure¹⁴ of a (1*Z*)-1,3-diene isocyanate intermediate. Although this 2-pyridone synthesis has not been extensively explored,^{13,14} it would appear limited mainly by the availability of the starting