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(9) (a) Reference 3a, pp 65–89. (b) Reference 3b, pp 86–109.
(10) (a) Pasto, D. J.; Johnson, C. R. "Organic Structure Determination"; Prentice-Hall: Englewood Cliffs, N.J., 1969; p 186. (b) Pihlaja, K.; Nikkila, A.; Neuvonen, K.; Keskinen, R. *Acta Chem. Scand., Ser. A* **1976**, *30*, 457–460.
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(12) 1,3-Oxathiolan-5-ones are also known to undergo slow cis–trans isomerization; see ref 10b.
(13) Reference 3a, pp 163–168.
(14) Mageswaran, S.; Sultanbawa, M. U. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 884–890.
(15) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403–419.
(16) Clarke, T. C.; Wendling, L. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1975**, *97*, 5638–5640; **1977**, *99*, 2740–2750, and references cited therein.
(17) Prepared by the reaction of α-bromophenylacetic acid with sodium sulfide nonahydrate (Levene, P. A.; Mori, T.; Mikeska, L. A. *J. Biochem. (Tokyo)* **1927**, *75*, 337–365) followed by reduction of the disulfide with zinc in acetic acid. See: Wardell, N. In "Chemistry of the Thiol Group", Patai, S., Ed.; Wiley: New York, 1974; Part 2, pp 220–229.
(18) The error in chemical shifts and coupling constants is ±0.12 Hz.
(19) The cis compound has mp 77–78 °C and the trans has mp 53–54 °C. The ^{1}H NMR spectra agreed perfectly with the published assignments. See: Ketcham, R.; Shah, V. P. *J. Org. Chem.* **1963**, *28*, 229–230.
(20) Literature boiling points are 84–86 (5 Torr) (cis) and 77–79 °C (2 Torr) (trans): Gottarelli, G.; Samori, B.; Moretti, I.; Torre, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1105–1111.

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

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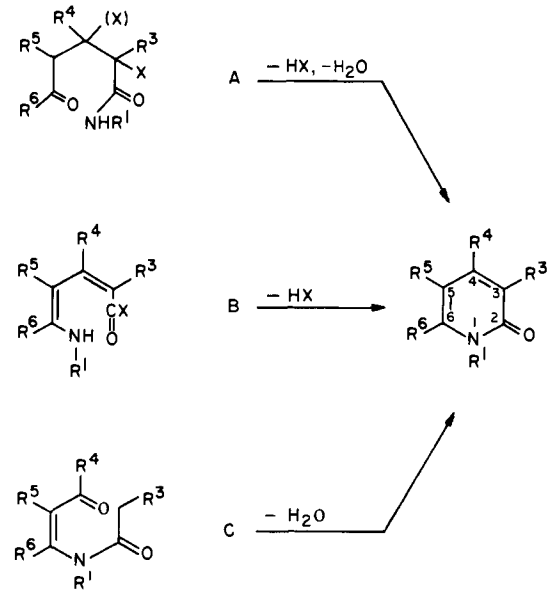
Abstract: A new method for preparing 3,6-dialkyl- (and -diaryl-) 2-pyridones is reported (Scheme II). Secondary propargylic alcohols are condensed with 1-cyanopyrrolidine to yield pseudoureas **1**, which are directly rearranged in refluxing xylene to afford 3,6-disubstituted 2-pyridones **2**. This 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 C_6, and either hydrogen, alkyl, or aryl substitution at C_3. 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** (R^3 = Ph; R^6 = *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 C_3–C_4[7] bond formation, and R^3 is, thus, typically[8] a carbanion stabilizing substituent. A second general approach involves lactamization of a 5-aminodienoic 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, $CONR_2$, NO_2) at C_3 are particularly available,[6] while fewer general methods exist[6,11,12] for preparing 2-pyridones substituted with alkyl (or aryl) substituents at C_3 and C_6.

A new ring-forming construction of 2-pyridones, which lends itself to the preparation of derivatives with hydrocarbon substituents at C_3 and C_6, 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 closure[14] 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

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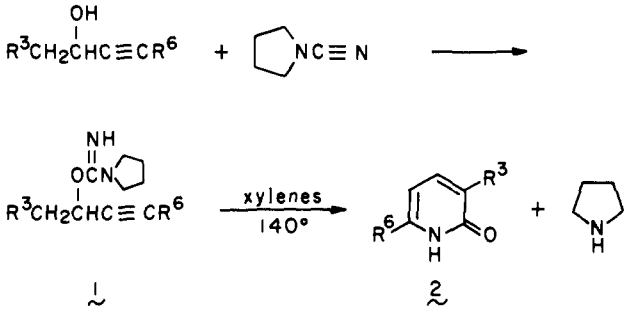
Table I. Preparation of Substituted 2-Pyridones from Propargylic Alcohols[a]

2-pyridone	R^3	R^6	rearr[b] condn, h	isolated yield, %[c]
3	Me_3C	Me_3C	72	68 (83)
4	Ph	Me_3C	12	63
5	Me	n-C_3H_7	24	79
6	n-C_3H_7	n-C_3H_7	24	64
7	H	2-C_3H_7	72	58
8	Me	Me	24	75
9	Et	Ph	20	46[d]
10	Ph	Ph	24	29 (34)
11	Et	H	24	12

[a] According to Scheme II. [b] A xylene solution (0.02–0.05 M) of the crude pseudourea was heated at reflux for the indicated time. [c] Overall yield from propargylic alcohol of recrystallized 2-pyridone. Yields in parentheses are based on consumed alcohol. [d] Rearrangement conducted at 0.01 M in the presence of 2 equiv of *N,N*-diisopropylethylamine.

Scheme II



dienoic acid and the thermal stability of the substituents involved.

In 1977 we reported[15] that pyrrolidine pseudoureas[16] of secondary propargylic alcohols undergo a complex rearrangement when heated in xylene to give substituted 2-pyridones in good yield. In this paper we present the details of our investigations of this experimentally simple 2-pyridone synthesis. We also report experiments which establish the intermediacy of diene ureas and diene isocyanates in the propargylic pseudourea to 2-pyridone transformation.

Results

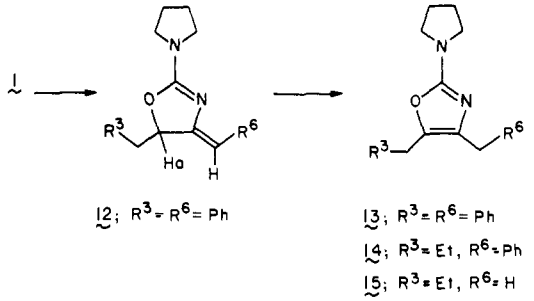
Scheme II illustrates the method. The results obtained with a representative group of nine secondary propargylic alcohols are summarized in Table I.

Preparation of Pyrrolidine Pseudoureas.[17] In the majority of our experiments, pseudoureas **1** were prepared by the potassium alkoxide catalyzed reaction of a secondary propargylic alcohol and 1-cyanopyrrolidine,[18] following an inverse addition procedure we had previously reported.[19] This method (procedure A in the Experimental Section) of pseudourea preparation has proven reliable for large-scale preparations (>20 mmol), but has failed (>50% of the starting alcohol was unchanged) on a number of occasions in smaller reactions. With an aim of finding a simpler and more reproducible procedure, we have examined in detail the reaction of 1-phenyl-1-hexyn-3-ol and 1-cyanopyrrolidine.[20] Results are summarized in Table II. Several points are noteworthy: (1) Yields were similar with either normal or inverse addition. (2) Sodium hydride is the preferred catalyst, since the pseudourea prepared with this agent was less colored and was formed in slightly higher yield (entries 2 and 3). (3) The reaction is complete after 4 h at room temperature, and the yield of pseudourea is unchanged after 20 h, but decreases thereafter (entries 3–8). (4) Ether is the preferred solvent since pseudoureas formed in ether were nearly colorless. (5) The condensation is best conducted in dilute solution (entries 1, 2, and 10). (6) Oxazoles and oxazolines (vide infra) were formed in significant amounts if the condensation was conducted without solvent, or if an excess of acetic acid was used to quench the reaction. These experiments suggest that the *preferred method for preparing pyrrolidine pseudoureas is to employ sodium hydride and ether, follow the simpler normal addition procedure, and to quench the reaction carefully with 1 equiv (based on the catalyst) of acetic acid.* Pyrrolidine pseudoureas of tertiary alcohols cannot be prepared in this manner, since the equilibrium for pseudourea formation is apparently unfavorable.[19]

2-Pyridone Formation. Freshly prepared unpurified pseudoureas were conveniently rearranged in refluxing xylene to yield the crystalline 2-pyridone products (Table I). Thermal rearrangements were conducted in dilute solution (0.01–0.05 M) in order to minimize polymerization[14] of diene urea and diene isocyanate intermediates (vide infra).

The 2-pyridione products were characterized by analytical and spectroscopic data, and in the cases of the known 2-pyridones **7**,[21] **8**,[13] and **10**[12a] by comparison with literature melting points. The best evidence that the new 2-pyridones have the assigned structures comes from ^{13}C NMR data, which are summarized in Table III. Although 2-pyridone itself has been extensively studied by ^{13}C NMR techniques,[22] the ^{13}C NMR data summarized in Table III are apparently the first reported for substituted 2-pyridones. The substituent shifts[23] observed for C_3 and C_6 are entirely consistent with the assigned structures, and shift comparisons within the group (e.g., between **5** and **6**) make structural assignments unambiguous.

When the terminal alkynic carbon of pseudourea **1** was unsubstituted or phenyl substituted (R^6 = H or Ph), oxazoles **13–15** were isolated in addition to the corresponding 2-pyridones. Oxazoles **13–15** result from intramolecular addition of the imine nitrogen to the triple bond[24,25] followed by tautomerization (eq 1). In the case of pseudourea **1** (R^3 = R^6 =



(1)

Ph), the intermediate 4-alkylidene-4,5-dihydrooxazole **12** (mp 142–143 °C) was also isolated. Oxazoline **12** was characterized by ^1H NMR absorptions for the vinylic hydrogen and H_a at δ 5.1–5.4, a doublet (J = 5 Hz) for the benzyl methylene at δ 3.0, and by conversion to oxazole **13** upon treatment with silica gel. The Z stereochemistry that is assigned to the exocyclic double bond in **12** is consistent with our demonstration in a related series[25] that intramolecular addition of the imine nitrogen is not a unimolecular reaction and as a result occurs in an antarafacial fashion. Intramolecular nucleophilic addition becomes the dominant process when the neat pseudoureas are heated, or in certain cases left at room temperature for several days. For example, crystalline **12** was deposited in 33% yield when pseudourea **1** (R^3 = R^6 = Ph) was stored at room temperature for 4 days. Pseudourea **1** (R^3 = Et; R^6 = Ph) was similarly >60% decomposed when stored at room temperature for 3 days, but could be successfully stored at 0 °C in the presence of 1–5% of triethylamine as a dilute (0.5 M) solution in hexane.

Since the conversion of a propargylic pseudourea to an al-

Table II. The Reaction of 1-Phenyl-1-hexyn-3-ol with 1-Cyanopyrrolidine under a Variety of Base-Catalyzed Conditions[a]

entry	catalyst (equiv)	solvent	[ROH] M[b]	addition mode[c]	reaction conditions,[d] temp, °C (time, h)	pseudourea yield,[e] %
1	KH (0.15)	THF	1.0	I	25 (20)	63-70[f]
2	KH (0.15)	THF	0.25	I	25 (20)	76
3	NaH (0.15)	THF	0.25	I	25 (20)	84
4	NaH (0.15)	THF	0.25	I	25 (48)	72
5	NaH (0.15)	THF	0.25	N	0 (0.5)	20
6	NaH (0.15)	THF	0.25	N	25 (1)	70
7	NaH (0.15)	THF	0.25	N	25 (4)	89
8	NaH (0.15)	THF	0.25	N	25 (20)	81-90[g]
9	NaH (0.15)	Et_2O	0.25	N	25 (20)	85
10	KH (0.15)	none	neat	I	25 (20)	<35[h]

[a] Reactions were conducted on a 10-mmol scale. [b] Final concentration of the starting alcohol in the reaction mixture after the addition with 1-cyanopyrrolidine was completed. Unless otherwise noted, the alcohol and 1-cyanopyrrolidine in equal volumes of the indicated solvent were mixed. [c] Normal (N) or inverse (I) addition. Normal addition means 1-cyanopyrrolidine was added to the alcohol-alkoxide solution. [d] Addition was carried out within 5 min at −5 °C. The reaction mixture was maintained as indicated and then quenched by adding 0.15 equiv of acetic acid. [e] By ^1H NMR integration of the pseudourea methine hydrogen and the C_6H_5 hydrogens. [f] Range of three preparations. [g] Range of five preparations. [h] No starting alcohol remained. The corresponding oxazole and oxazoline were apparent in the ^1H NMR.

Table III. ^{13}C NMR Spectra of Substituted 2-Pyrridones[a]

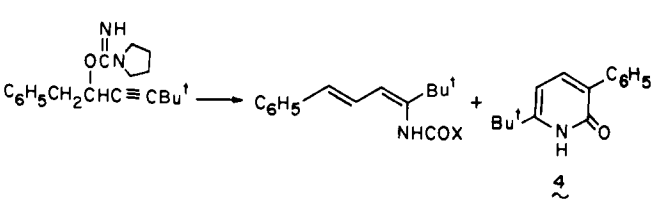
2-pyridone	R^3	R^6	^{13}C NMR C_2	C_3	C_4	C_5	C_6	other
	H	H	162.3	119.8	140.8	104.8	135.2	from ref 22b
3	Me_3C	Me_3C	164.2	131.1	135.5	100.9	154.3	28.6, 29.1, 34.5
4	Ph	Me_3C	163.5	127.9	139.1	101.7	156.3	29.0, 34.9, 127.3, 127.9, 128.4, 136.8
5	Me	C_3H_7	165.9	125.5	139.1	104.8	147.2	13.6, 16.1, 22.1, 34.9
6	C_3H_7	C_3H_7	165.6	131.1	137.4	104.7	147.3	12.9, 13.7, 22.3, 23.1, 31.0, 32.7
7	H	2-C_3H_7	166.0	117.0	141.9	102.3	156.0	21.7, 32.1
8	Me	Me	165.6	125.4	139.2	105.5	142.6	16.1, 18.8
9	Et	Ph	164.9	133.8	137.2	104.5	144.0	12.8, 23.3, 126.5, 129.1, 129.6, 137.2
11	Et	H	165.1	135.0	137.2	106.8	131.8	12.6, 23.2
	Me	H	165.7	129.4	139.1	106.8	132.2	16.1

[a] In $CDCl_3$; chemical shifts are given in parts per million from internal Me_4Si; assignments are consistent with the multiplicities observed in off-resonance decoupled spectra.

kylidenedihydrooxazole (eq 1) involves formation of a new C-H bond, we explored the extent to which the yield of 2-pyridone **9** could be increased by reaction conditions that reduce the concentration of proton acids. Results are summarized in Table IV. The yield of 2-pyridone **9** was improved by conducting the rearrangement at 0.01 M, but was unaffected by the presence of minor amounts of 1-phenyl-1-hexyn-3-ol in the starting pseudourea sample. The yield of **9** was also slightly improved by conducting the reaction in the presence of 2-4 equiv of *N,N*-diisopropylethylamine. Under the best conditions, 2-pyridone **9** was isolated in 54% yield.

As a general procedure for 2-pyridone synthesis, we suggest that freshly prepared crude pseudoureas be employed, and that the solution thermolysis be conducted as dilute as possible.

Isolation of Diene Urea Intermediates. When the thermal rearrangement (xylene, 140 °C) of pseudourea **1** (R^3 = Ph; R^6 = *t*-Bu) was terminated after 5 h, diene urea **16** (mp 142-143 °C) was isolated in 5% yield, in addition to 2-pyridone **4** (59% yield). The stereochemical assignment for **16** follows from ^1H NMR paramagnetic shift experiments, which resulted in the largest induced shift for the central vinylic hydrogen, and resolved the vinylic coupling constants (J = 16 and 10 Hz). When this rearrangement was conducted at 110 °C and was monitored by ^1H NMR (benzene-d_6), the formation of diene urea **16** was observed to reach a maximum of ca. 60% at 28 h, and decrease thereafter. When diene urea **16** was heated at reflux in xylene for 7 h, it was converted to 2-pyridone **4** in >95% yield. Diene ureas **18** and **19** (stereochemistry not determined, but presumably 1*Z*,3*E*) were also isolated in small amounts when thermal rearrangements of pseudoureas **1** (R^3 = H; R^6 = 2-C_3H_7, and R^3 = Et; R^6 = H, respectively) were conducted in refluxing xylene as described in Table I.

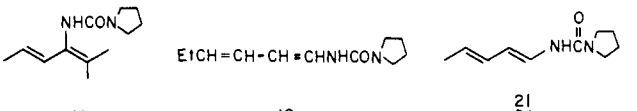


4

16, X = N

17, X = N

20, X = CCl_3



18 **19** **21**

In order to explore the possible intermediacy of diene isocyanates in the diene urea to 2-pyridone conversion, diene urea **16** was heated at reflux in xylene in the presence of 5 equiv of piperidine. Termination of this reaction after 2 h resulted in the isolation of the piperidine diene urea **17** (17%) in addition to recovered **16** (37%) and 2-pyridone **4** (25%). In order to establish that the process which resulted in amine exchange was on the diene urea to 2-pyridone pathway, the conversion of **16** → **4** was examined in the presence of pyrrolidine. The results summarized in Figure 1 show that added pyrrolidine

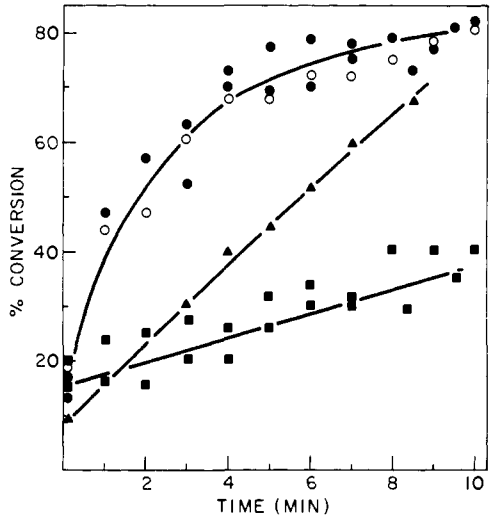


Figure 1. The rate of formation of 2-pyridone **4** from diene urea **16** in benzene-d_6 at 140.0 °C in the absence and in the presence of added pyrrolidine; initial diene concentration = 0.19 M (contained 15% of **4**) for all runs: (●) no additives; (○) contained chlorobenzene (0.20 M); (▲) contained pyrrolidine (0.11 M); (■) contained pyrrolidine (0.23 M).

significantly reduces the rate of formation of 2-pyridone **4**. This rate retardation is not a bulk medium effect, since chlorobenzene (whose dielectric constant is similar to that of pyrrolidine)[26] produced no effect at the same concentration level. Inhibition by pyrrolidine was also apparent in reactions conducted in the absence of added pyrrolidine, since these reactions yielded first-order kinetic plots with pronounced downward curvature.

That both the acyl substituent and diene stereochemistry are important for the facile conversion of diene urea **16** to 2-pyridone **4** is apparent in the following observations. Diene trichloroacetamide **20**[27] afforded no trace of pyridone **4** when heated at reflux in xylene for 72 h, and the (1*E*,3*E*)-diene urea **21**[28] was converted only *slowly* (<10% after 19 h, 60% after 1 week) to 3-methyl-2-pyridone.

Discussion

Mechanism. The results reported here, together with previous studies in our laboratory,[19,27,29] allow the mechanism for the complex transformation of a propargylic pseudourea to a substituted 2-pyridone to be specified in detail (Scheme III). The conversion is initiated by [3,3]-sigmatropic rearrangement[19] of pseudourea **1** to yield allene **22**. Subsequent tautomerization produces the (1*Z*,3*E*)-diene urea **24**. The kinetic preference which is observed in this, and related reactions,[27,29] for forming the diene with the *Z* configuration about the 1,2-double bond is attributed to the second tautomerization (**23** → **24**) occurring via a [1,5]-sigmatropic hydrogen migration. The cis α,β-unsaturated *N*-acylimine **23** is either the highly favored kinetic tautomer of **22** (preferential protonation at C_2 cis to the C_3 hydrogen) or is in rapid equilibrium with the corresponding trans isomer.[29] Reversible elimination of pyrrolidine from **24** affords diene isocyanate **25**, which undergoes electrocyclic ring closure[13,14,30] to yield ultimately 2-pyridone **2**.

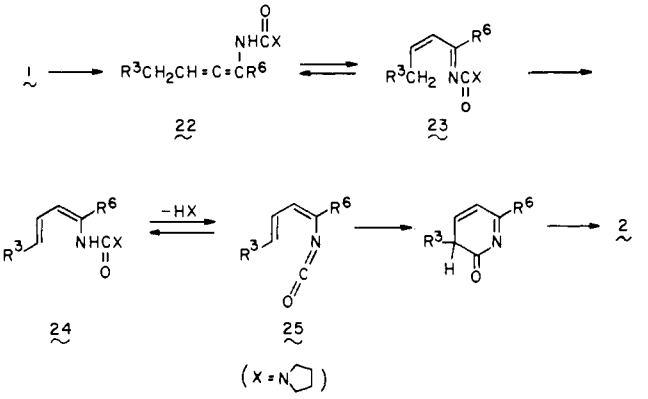
The mechanism of Scheme III is supported by our isolation of the (1*Z*,3*E*)-diene urea **16**, and the demonstration that it was converted to the corresponding 2-pyridone in nearly quantitative yield under the solution thermolysis conditions. Although diene isocyanates have not been directly observed or isolated,[31] their intervention is strongly implicated by the amine exchange which was observed when the conversion of diene urea **16** to 2-pyridone **4** was conducted in the presence of piperidine. The observation that pyrrolidine is a competitive

Table IV. Isolated Yield of 2-Pyridone **9** from Thermal Rearrangement of Pseudourea **1** (R^3 = Et; R^6 = Ph) under Various Reaction Conditions

starting pseudourea purity, %	starting pseudourea concn, M	additives	isolated yield, %[b]
>95[c]	0.05		33
>95[c]	0.01		45[d]
87	0.01		48[e]
>95[c]	0.01	2 equiv of *i*-Pr_2NEt	53[d]
>95[c]	0.01	4 equiv of *i*-Pr_2NEt	54
85	0.01	0.05 equiv of bis-(trimethylsilylacetamide)	38[3]

[a] Thermal rearrangements were conducted in refluxing xylene for 20 h. [b] Isolation procedure was identical for all reactions. [c] Chromatographically homogeneous.[36] Contained no starting alcohol by ^1H NMR analysis. [d] Average of two experiments. [e] Yield is corrected for the purity of the starting pseudourea.

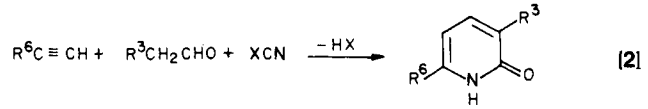
Scheme III



inhibitor for the **16** → **4** conversion is consistent with capture of the diene isocyanate by pyrrolidine to re-form **16**, and demonstrates conclusively that the diene isocyanate is an intermediate on the 2-pyridone-forming reaction pathway.

It is interesting to note that the success of the 2-pyridone synthesis reported here stems in large part from the fact that diene urea **24** is an excellent source of the critical diene isocyanate **25**. Thermal cracking[31] of diene urea **24** provides **25** in a low steady-state concentration, thus favoring unimolecular electrocyclic ring closure rather than a polymerization pathway for this reactive intermediate, and the stereochemistry of **24** assures that **25** will be produced with the 1*Z* stereochemistry required for electrocyclic ring closure.

Synthetic Applications. The method reported here allows the 2-pyridone ring to be assembled in a simple fashion from aldehyde, alkyne, and cyanamine components (eq 2). As an



[2]

example, 3-methyl-6-propyl-2-pyridone (**5**) was prepared from 4-octyn-3-ol (derived from[32] propanal and 1-lithio-1-pentyne) in 78% yield, a 71% overall yield from propanal. With this method a variety of 3,6-dialkyl- (and -aryl-) 2-pyridones can be prepared in moderate to excellent yield in an experimentally simple fashion. This synthesis is highest yielding for the preparation of 2-pyridones with alkyl substituents (either primary, secondary, or tertiary) at C_6, and either hydrogen, alkyl, or aryl substitution at C_3. It is significant that the propargylic pyrrolidine pseudourea to 2-pyridone conversion occurs readily in refluxing xylene, which is 100 °C below the temperatures reported[13,14] for 2-pyridone syntheses that in-

volve thermal rearrangements of diene acyl azides. Whether the propargylic pseudourea method or the diene acyl azide method[13,14] for preparing 2-pyridones substituted with alkyl (or aryl) substituents at C_3 and C_6 is preferred for a specific case will depend primarily on the availability of the starting propargylic alcohol or dienoic acid.

The competing formation of oxazoles, which is responsible for the lower yields of 2-pyridones when R^6 = H or Ph, should be subject to experimental control. For example, one would predict[25,27] that reducing the basicity of the imine nitrogen should reduce complications from competing intramolecular addition pathways. Experiments of this type, which are aimed at optimizing the X substituent of Scheme III, are continuing.[33]

Experimental Section[34]

1-Cyanopyrrolidine.[18] The following improved procedure was employed. A solution of pyrrolidine (35.5 g, 0.5 mol) and 100 mL of anhydrous ether was stirred rapidly and cooled to 0 °C. A solution of cyanogen bromide (26.5 g, 0.25 mol, freshly distilled, bp 60–62 °C) and 100 mL of anhydrous ether was added dropwise over 90 min, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 2 h, the two layers which resulted were separated by decantation, and the lower layer (containing impure pyrrolidine hydrobromide) was extracted with 50 mL of ether. The ethereal extracts were concentrated and distilled (10-cm Vigreux column) giving 17.2 g (71%) of pure 1-cyanopyrrolidine: bp 42–44 °C (0.33 mm); IR (film) 2220 (C≡N), 1280, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 3.1–3.5 (m, NCH_2), 1.7–2.0 (m, NCH_2CH_2).

Impure samples of 1-cyanopyrrolidine show absorption in the infrared at 3430–3700 cm^{-1} and are *not* suitable for use in pseudourea synthesis.

Preparation of Pyrrolidine Pseudoureas. Representative procedures are detailed below. It is essential that pure 1-cyanopyrrolidine and dry alcohols be used in these preparations. The procedure of choice will depend on the specific propargylic alcohol. We feel that *procedure B is preferred* and should be examined initially. Procedure A was utilized for most of the pseudoureas prepared in this study. The hydrolytic and thermal instabilities of pyrrolidine pseudoureas make them difficult to purify, although they can be chromatographed on silica gel if 10–25% of Et_3N is added to the eluant.[36] Some propargylic pseudoureas also decompose within hours at room temperature. For these reasons we suggest that crude pseudoureas be used immediately for the thermal rearrangement step.

Method A. Inverse Addition/KH/THF. 4-Octyn-3-yl 1-Pyrrolidinecarboximidate (1, R^3 = Me; R^6 = *n*-C_3H_7). A dry 25-mL round-bottomed flask was flushed with N_2, charged with 4-octyn-3-ol (2.52 g, 20 mmol, dried over activated 4-Å molecular sieves) and 10 mL of THF, and cooled to below 0 °C in an ice–salt bath. Potassium hydride (0.46 mL, a 24.8% suspension in mineral oil, 3.0 mmol) was carefully added via syringe, and the resulting alcohol–alkoxide solution was then added dropwise (double-needle transfer) to a solution of 1-cyanopyrrolidine (1.92 g, 20 mmol) in 10 mL of THF at −5 to −10 °C. Addition was complete in 15 min, and the solution was allowed to warm to room temperature. After 20 h the solution was concentrated, hexane (50 mL, containing 3 mmol of acetic acid) was added, the mixture was shaken for 30 s, and a small amount of insoluble residue was removed by filtration through Celite. Concentration yielded 4.51 g of the crude pseudourea as a light yellow oil. Pseudourea **1** (R^3 = Me; R^6 = *n*-C_3H_7) showed characteristic absorptions in the IR (film) at 3350 (N—H), 1620 (C=N), and 1040 (C—O—C) cm^{-1}, and in the ^1H NMR spectrum ($CDCl_3$) for the C_3 methine hydrogen (δ 5.1, m) and the NH hydrogen (δ 4.5, s). The ^1H NMR spectrum also indicated that this sample was contaminated with less than 10% of the starting alcohol (δ 4.1, m, C*H*OH).

Method B. Normal Addition/NaH/Ether. 1-Phenyl-1-hexyn-3-yl 1-Pyrrolidinecarboximidate (1, R^3 = Et; R^6 = Ph). A dry 50-mL round-bottomed flask was flushed with N_2, charged with NaH (63 mg, a 57% suspension in oil, 1.5 mmol), and cooled to 0 °C. A solution of 1-phenyl-1-hexyn-3-ol (1.74 g, 10 mmol, dried over activated 4-Å molecular sieves) in 20 mL of ether was added dropwise over 10–15 min. The reaction mixture was stirred for 1 h at room temperature, and then cooled to 0 °C in an ice–salt bath, and treated dropwise with 1-cyanopyrrolidine (0.96 g, 0.92 mL, 10 mmol). Addition was complete within 10 min, and the solution was allowed to warm to room temperature. After 20 h, the solution was rapidly concentrated at room temperature, and 10 mL of hexane and a magnetic stirring bar were added. The hexane solution was stirred rapidly and was treated dropwise with 20 mL of a 0.075 M solution of acetic acid in hexane. A change in color from dark yellow to bright yellow was apparent when 1 equiv of acid had been added, and the addition was terminated at this point. Filtration through Celite removed a small amount of insoluble material, and concentration yielded 2.63 g of crude pseudourea **1** (R^3 = Et; R^6 = Ph) as a light yellow liquid: IR (film) 3350 (N—H), 1620 (C=N), 1050 (C—O—C) cm^{-1}; ^1H NMR (CCl_4) δ 7.0–7.7 (m, C_6H_5), 5.7 (br t, J = 7 Hz, C*H*OR), 4.7 (s, NH), 2.8–3.4 (m, NCH_2). The ^1H NMR spectrum indicated that this sample was contaminated with 15% of the starting alcohol (δ 4.4, t, C*H*OH), but was free of contaminating oxazoline (characteristic aromatic absorptions at δ 7.5–7.9, see **12**) and oxazole **14** (characteristic t, δ 2.26). This sample was >60% decomposed when stored as the neat liquid for 3 days at room temperature. Storage of this pseudourea in a refrigerator (−5 °C) as a 0.5 M solution in 95:5 hexane–triethylamine for 2 weeks, however, resulted in no decomposition.

Pseudourea **1** (R^3 = Et; R^6 = Ph) could be purified by chromatography on silica gel[36] using a 70:15:15 mixture of hexane–triethylamine–ethyl acetate as eluant. With this eluant the TLC behavior was as follows: 1-phenyl-1-hexyn-3-ol (R_f 0.47), 1-cyanopyrrolidine (R_f 0.37), pseudourea (R_f 0.3).

Preparation of 2-Pyridones by Thermal Rearrangement of Propargylic Pyrrolidine Pseudoureas. 6-Propyl-3-methyl-2(1*H*)-pyridinone (5). A 2.25-g portion of crude pseudourea **1** (R^3 = Me; R^6 = *n*-C_3H_7; prepared from 4-octyn-3-ol as described above) was dissolved in 300 mL of xylene, the air was replaced with N_2,[35] and the solution was heated at reflux under a N_2 atmosphere for 24 h. The reaction mixture was allowed to cool to room temperature, and 39 mg (0.34 mmol) of 1-pyrrolidinecarboxamide (mp 210–213 °C)[37] was isolated by filtration. The concentrated filtrate was purified by chromatography on silica gel (100 g, 10:1 to 1:1 hexane–acetone) to yield three fractions: an early fraction (0.14 g) that was mineral oil; an intermediate fraction (0.21 g) that was a mixture of 2-pyridone **5**, 4-octyn-3-ol, and two unknown components; and a third crystalline fraction that yielded 1.04 g (69%) of pure **5**, mp 58–60 °C. An additional 155 mg (10%) of **5** (pure by ^1H NMR) was isolated from the second fraction by bulb-to-bulb distillation. Two recrystallizations from pentane afforded an analytical sample of **5**: mp 60–61 °C; IR (KBr) 3400 (N—H), 1640 (C=O), 1580, 1470, 1170, 1020, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.6 (br s, NH), 7.22 (dq, J = 7, 1 Hz, C_4 H), 5.85 (d, J = 7 Hz, C_5 H), 2.50 (unsymm t, J = 7 Hz, $CH_2CH_2CH_3$), 2.05 (s, CH_3), 2.0–2.7 (m, $CH_2CH_2CH_3$), 0.94 (unsymm t, J = 7 Hz, CH_2CH_3); mass spectrum, *m/z* (rel intensity) 151 (36), 136 (20), 123 (100), 105 (12), 94 (37). Anal. ($C_9H_{13}NO$) C, H, N.

3,6-Di-*tert*-butyl-2(1*H*)-pyridinone (3). In a similar manner the crude pseudourea (prepared by procedure A, contained 25% starting alcohol by ^1H NMR) formed from 0.91 g (5.0 mmol) of 2,2,7,7-tetramethyl-5-octyn-4-ol was heated at reflux in 150 mL of xylene for 3 days. The reaction mixture was cooled to room temperature, and 458 mg (44%) of 2-pyridone **3**, mp 273–275 °C, was isolated by filtration. An additional 244 mg of **3** (mp 273 °C, total yield 68%) was obtained from the concentrated filtrate by trituration with hot hexane. Bulb-to-bulb distillation (80 °C, 0.01 mm) of the hexane-soluble material resulted in the isolation of 167 mg (18% recovery) of 2,2,7,7-tetramethyl-5-octyn-4-ol. An analytical sample of **3** was prepared by recrystallization from benzene: mp 273 °C; IR (KBr) 3400 and 3230 and 3120 (N—H), 1625 (C=O), 1610, 1060, 932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.3 (br s, NH), 7.25 (d, J = 7 Hz, C_4 H), 5.96 (d, J = 7 Hz, C_5 H), 1.32 (s, two $C(CH_3)_3$). Anal. ($C_{13}H_{21}NO$) C, H, N.

6-*tert*-Butyl-3-phenyl-2(1*H*)-pyridinone (4). In a similar manner the crude pseudourea (1.66 g, prepared by procedure A, contained 15% starting alcohol by ^1H NMR) formed from 1.01 g (5.0 mmol) of 5,5-dimethyl-1-phenyl-3-hexyn-2-ol was heated at reflux in 150 mL of xylene for 12 h. Concentration and trituration with cold hexane afforded 719 mg (63%) of 2-pyridone **4**, mp 217–218 °C. One recrystallization from benzene–acetone (1:2) afforded an analytical sample: mp 217–218 °C; IR (KBr) 3400 (N—H), 1630 (C=O), 1460, 1380, 900, 780, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.3 (br s, NH), 7.7–7.9 (m, phenyl H), 7.56 (d, J = 7 Hz, C_4 H), 7.2–7.5 (m,

phenyl H), 6.20 (d, J = 7 Hz, C_5 H), 1.33 (s, $C(CH_3)_3$); mass spectrum m/z (rel intensity) 227.131 (99) ($C_{15}H_{17}NO$ requires 227.131), 212 (100), 194 (11), 185 (32). Anal. ($C_{15}H_{17}NO$) C, H, N.

3,6-Dipropyl-2(1*H*)-pyridinone (6). In a similar manner the crude pseudourea (5.50 g, prepared by procedure A, contained 15% starting alcohol by ^{1}H NMR) formed from 3.08 g (20 mmol) of 6-decyn-5-ol was heated at reflux in 1 L of xylene for 24 h. Concentration and trituration with cold benzene yielded 110 mg (0.96 mmol) of 1-pyrrolidinecarboxamide[37] (mp 209–212 °C). Purification of the concentrated filtrate by chromatography on silica gel (9:1 hexane–acetone) afforded 2.30 g (64%) of 2-pyridone **6**, a light yellow oil which was homogeneous by TLC (R_f 0.6; 3:1 hexane–acetone). Bulb-to-bulb distillation (150 °C, 0.02 mm) and recrystallization from hexane at −10 °C yielded an analytical specimen: mp 41–41.5 °C; IR (Nujol) 3400 (N—H), 1640 (C=O), 1575, 1155, 1050, 960, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.3 (br s, NH), 7.10 (br d, J = 6 Hz,[38] C_4 H), 5.82 (d, J = 8 Hz,[38] C_5 H), 2.1–2.7 (m, $CH_2CH_2CH_3$), 0.7–2.0 (m, CH_2CH_3); mass spectrum m/z (rel intensity) 179.129 (77) ($C_{11}H_{17}NO$ requires 179.131), 164 (74), 137 (100), 122 (29). Anal. ($C_{11}H_{17}NO$) C, H, N.

6-Isopropyl-2(1*H*)-pyridinone (7) and *N*-[(*E*)-2-Methyl-2,4-hexadien-3-yl]-1-pyrrolidinecarboxamide (18). In a similar manner the crude pseudourea (1.05 g, prepared by procedure A, contained 6% starting alcohol by ^{1}H NMR) formed from 0.56 g (5.0 mmol) of 5-methyl-3-hexyn-2-ol was heated at reflux in 150 mL of xylene. ^{1}H NMR analysis after 24 h indicated the presence of diene protons; so reflux was continued for 3 days. Concentration afforded a solid (mp 119–128 °C) that was recrystallized from hexane–acetone (3:1) to yield 0.364 g (53%) of pure 2-pyridone **7**, mp 129–131 °C (lit.[21] 129–130 °C). Purification of the recrystallization residues by a combination of dry column chromatography (aluminum oxide, ethyl acetate) and preparative TLC (silica gel, 2:3 hexane–ethyl acetate) yielded an additional 36 mg (5%) of **7** (mp 129–131 °C, 58% total yield) and 47 mg (4.5%) of *N*-[(*E*)-2-methyl-2,4-hexadien-3-yl]-1-pyrrolidinecarboxamide (**18**): mp 125–127 °C (after recrystallization from 3:1 hexane–acetone); IR (KBr) 3280 (N—H), 1636 (C=O), 1510, 1393, 960 ((*E*)-HC=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.41 (d, J = 15 Hz, C_4 H), 5.60 (dq, J = 15, 6.6 Hz, C_5 H), 5.0 (br s, NH), 3.41 (m, NCH_2), 1.86 (s, CH_3), 1.76 (s, CH_3); mass spectrum m/z (rel intensity) 208.157 (46) ($C_{12}H_{20}N_2O$ requires 208.158), 193 (25), 110 (32), 98 (96), 70 (66), 56 (100).

3,6-Diphenyl-2(1*H*)-pyridinone (10), 5-(Phenylmethyl)-4-(phenylmethylene)-2-(1-pyrrolidinyl)-4,5-dihydrooxazole (12), and 4,5-Bis(phenylmethyl)-2-(1-pyrrolidinyl)oxazole (13). Following procedure A, but using NaH instead of KH as the base catalyst, 2.22 g (10 mmol) of 1,4-diphenyl-3-butyn-2-ol was converted to 3.3 g of the crude pseudourea **1** (R^3 = R^6 = Ph, contained 15% of the starting alcohol by ^{1}H NMR). This pseudourea was not stable when stored at 25 °C and the neat liquid developed a noticeable precipitate within a few hours. Filtration of this mixture after 4 days, followed by washing with ether, yielded 1.01 g (33%) of the alkylidenedihydrooxazole (**12**), mp 141–143 °C. Recrystallization from hexane–acetone (1:1) yielded an analytical specimen of **12**: mp 142–143 °C; IR (KBr) 1680 (C=N), 1603, 1420, 730, 720, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.9–8.0 (m, phenyl H), 5.1–5.4 (m, C_5 H and =CH), 3.2–3.7 (m, NCH_2), 3.0 (d, J = 6 Hz, CH_2 Ph), 1.6–2.1 (m NCH_2CH_2). Anal. ($C_{21}H_{22}N_2O$) C, H, N.

Concentration of the filtrate described above afforded a light yellow liquid (1.13 g), which was shown by ^{1}H NMR analysis to be a 1.5:4:4.5 mixture of **12**, 1,4-diphenyl-3-butyn-2-ol, and oxazole **13**. Adsorption of 203 mg of **12** on silica gel and, after 4 days, elution with acetone afforded 180 mg (89%) of oxazole **13**, a colorless liquid, 90% pure by ^{1}H NMR. Dry column chromatography of a sample of comparable material (silica gel, 9:1 hexane–acetone) afforded an analytical specimen of oxazole **13**: colorless liquid; IR (film) 1670, 1625, 1500, 1460, 1410, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (s, C_6H_5), 7.20 (s, C_6H_5), 3.65 (s, two CH_2Ph), 3.1–3.6 (m, NCH_2), 1.6–2.0 (m, NCH_2CH_2); mass spectrum m/z (rel intensity) 318.174 (100) ($C_{21}H_{22}N_2O$ requires 318.173), 241 (18), 227 (13), 131 (17), 98 (21), 91 (27).

In a similar manner, 1.11 g (5 mmol) of 1,4-diphenyl-3-butyn-2-ol was converted to the crude pseudourea **1** (R^3 = R^6 = Ph). In an attempt to reduce the formation of alkylidenedihydrooxazole **12**, this material was *immediately* dissolved in 180 mL of xylene and heated at reflux for 22 h. The reaction mixture was cooled to room temperature and 360 mg (29%) of 2-pyridone **10**, mp 258–260 °C (lit.[12a] 260–261 °C), was isolated by filtration. Separation of the concentrated filtrate by chromatography on silica gel (100 g, 10:1 hexane–acetone) afforded 613 mg (39%) of oxazole **13** (pure by TLC) and 110 mg (0.5 mmol) of recovered 1,4-diphenyl-3-butyn-2-ol.

3-Ethyl-2(1*H*)-pyridinone (11), 4-Methyl-5-propyl-2-(1-pyrrolidinyl)oxazole (15), and *N*-(1,3-Hexadienyl)-1-pyrrolidinecarboxamide (19). In a similar manner the crude pseudourea (prepared by procedure B, contained <5% starting alcohol by ^{1}H NMR) formed from 0.98 g (10 mmol) of 1-hexyn-3-ol was *immediately* dissolved in 300 mL of xylene and heated at reflux for 24 h. Concentration and trituration with cold benzene yielded 263 mg (2.3 mmol) of 1-pyrrolidinecarboxamide. The concentrated filtrate was purified by chromatography on silica gel (60 g, 5:1 to 1:1 hexane–acetone) to yield four fractions. An early fraction contained mineral oil. A second fraction yielded 610 mg (31%) of oxazole **15**, a colorless liquid (R_f 0.7, 1:1 hexane–acetone). A sample of comparable material was purified by high-performance liquid chromatography (μ-Porasil, 1:1 hexane–ethyl acetate) to give an analytical specimen: IR (film) 1670, 1610, 1400, 1200, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.2–3.6 (m, NCH_2), 2.43 (t, J = 6 Hz, $CH_2CH_2CH_3$), 1.98 (s, CH_3), 1.7–2.2 (m, NCH_2CH_2), 1.1–1.7 (m, $CH_2CH_2CH_3$), 0.93 (t, J = 6 Hz, CH_3CH_2); mass spectrum m/z (rel intensity) 194.142 (15) ($C_{11}H_{18}N_2O$ requires 194.142), 165 (100), 123 (8).

A third fraction yielded 119 mg (6%) of the sensitive diene **19** (stereochemistry unknown but probably 1*Z*,3*E*): mp 120–130 °C; TLC (R_f 0.2, trace impurity R_f 0.0, 3:1 hexane–acetone); IR (KBr) 3400 and 3200 (N—H), 1660 and 1640 and 1610 (C=O), 1490, 1360, 970 ((*E*)-CH=CH), 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.8–6.9 (m, vinylic H and NH), 3.0–3.5 (m, NCH_2), 1.5–2.4 (m, CH_3CH_2 and NCH_2CH_2), and 1.01 (t, J = 6 Hz, CH_3); mass spectrum m/z (rel intensity) 194 (8), 98 (78), 55 (100). Attempted recrystallization of a sample of comparable material was unsuccessful and resulted in polymerization.

A fourth fraction yielded 145 mg (12%) of 2-pyridone **11**, mp 120–121 °C.[39] Recrystallization from hexane–acetone (4:1) afforded an analytical specimen: mp 121–121.5 °C; IR (KBr) 3400 (N—H), 1646 (C=O), 1618, 1570, 1480, and 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (two d, J = 7 Hz, C_4 H and C_6 H), 6.24 (t, J = 7 Hz, C_5 H), 2.50 (q, J = 7.2 Hz, CH_2CH_3), 1.17 (t, J = 7.2 Hz, CH_3). Anal. (C_7H_9NO) C, H, N.

3-Ethyl-6-phenyl-2(1*H*)-pyridinone (9) and 4-(Phenylmethyl)-5-propyl-2-(1-pyrrolidinyl)oxazole (14). In a similar manner a sample of the crude pseudourea (200 mg, prepared as detailed above by procedure B, contained 13% starting alcohol by ^{1}H NMR) prepared from 1-phenyl-1-hexyn-3-ol was heated at reflux in 75 mL of xylene for 20 h. Concentration afforded a semisolid, which was washed with hot hexane (2 × 5 mL). The residue was dissolved in hot acetone and filtered through a short plug of silica gel (0.5 g) using 10 mL of hot acetone as the eluant. Concentration and successive trituration with 5 mL of 5:1 hexane–acetone and 5 mL of hexane afforded 60.8 mg (45%) of pure 2-pyridone **9** as a white insoluble residue, mp 164–165 °C. One recrystallization from $CHCl_3$ yielded an analytical specimen: mp 164–166 °C; IR (Nujol) 3260 and 3400 (N—H), 1640 (C=N), 1610, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.6–8.0 (m, phenyl H), 7.52 (d, J = 6 Hz, C_4 H), 7.2–7.5 (m, phenyl H), 6.52 (d, J = 6 Hz, C_5 H), 2.52 (q, J = 7 Hz, CH_2CH_3), 1.20 (t, J = 7 Hz, CH_3). Anal. ($C_{13}H_{13}NO$), C, H, N.

Chromatography (silica gel, 1:10 to 1:1 ether–hexane) of the concentrated hexane triturate from a comparable preparation that employed 175 mg of the crude starting pseudourea yielded 66 mg (38%) of oxazole **14** as a yellow oil, ca. 90% pure by ^{1}H NMR. An analytical specimen was obtained by preparative TLC (silica gel, 1:1 ether–hexane): a light yellow oil; IR (film) 1660, 1610, 1400, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2 (s, phenyl), 3.60 (s, CH_2Ph), 2.9–3.5 (m, NCH_2), 2.26 (unsymm t, J = 7 Hz, $CH_2CH_2CH_3$). Table IV summarizes the results obtained when pseudourea **1** (R^3 = Et; R^6 = Ph) was thermolyzed on a 200-mg scale under various reaction conditions. 2-Pyridone **9** (mp 164–166 °C) was isolated by the procedure detailed above.

***N*-[(3*Z*,5*E*)-2,2-Dimethyl-6-phenyl-3,5-hexadien-3-yl]-1-pyrrolidinecarboxamide (16). Isolation from Thermal Rearrangement at 100 °C in Decalin.** A solution of 2.37 g (8.0 mmol, contained 15% starting alcohol by ^{1}H NMR) of crude pseudourea **1** (R^3 = Ph; R^6 = *t*-Bu) and 100 mL of decalin was heated in an oil bath at 100 ± 10 °C for 11 h. The reaction mixture was cooled to room temperature and 425 mg of a crystalline solid (mp 204–208 °C) was isolated by filtration.

Partitioning of this material between hot benzene and water (1:1) resulted in the isolation of 381 mg (21%) of 2-pyridone **4** (R_f 0.5, 2:1 hexane–acetone) from the benzene layer and 35 mg of 1-pyrrolidinecarboxamide from the aqueous layer. Concentration (ca. 50 °C, 0.2 mm) of the decalin filtrate afforded 1.76 g of a pale brown semisolid material which yielded 784 mg (33%) of diene **16** as a white crystalline material, mp 140–142 °C, upon trituration with hexane. An additional 95 mg of impure diene **16** (mp 130–135 °C) and 260 mg (1.3 mmol) of 5,5-dimethyl-1-phenyl-3-hexyn-2-ol was obtained by dry column chromatography (4:1 hexane–acetone) of the triturate. Two recrystallizations from 4:1 hexane–acetone afforded an analytical specimen of diene **16**: mp 142–143 °C; TLC R_f 0.4, 2:1 hexane–acetone; IR (KBr) 3330 (N—H), 1650 (C=O), 1600, 1470, 960 ((*E*)-CH=CH), 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1–7.5 (m, C_6H_5), 6.88 (apparent dd, J = 9.5, 16 Hz, C_5 H), 6.50 (d, J = 16 Hz, C_6 H), 6.12 (d, J = 9.5 Hz, C_4 H), 5.24 (br s, NH), 3.3–3.6 (m, NCH_2), 1.7–2.1 (m, NCH_2CH_2), and 1.16 (s, $C(CH_3)_3$). Anal. ($C_{19}H_{26}N_2O$) C, H, N.

The stereochemistry assigned for **16** was consistent with the results of ^1H NMR experiments, which were conducted in the presence of europium tris(2,2,6,6-tetramethylheptanedionate), and yielded the following observed shifts (ppm mol^{-1} mol^{-1}): 3.3 for C_4 H, 7.5 for C_5 H, 1.2 for C_6 H.

Diene urea **16** was also isolated in 5% yield when the thermolysis of pseudourea **1** (R^3 = Ph; R^6 = *t*-Bu) was conducted for 5 h in refluxing xylene.

Conversion of Diene Urea 16 to 2-Pyridone 4. A solution of diene urea **16** (114 mg, 0.38 mmol) and 5 mL of xylene was heated at reflux, and the reaction was monitored by TLC. After 6.5 h **16** was no longer detectable. Concentration afforded 85 mg (99%) of nearly pure 2-pyridone **4**, mp 215–217 °C. Recrystallization from 1:1 hexane–acetone yielded 71 mg (82%) of pure **4**, mp 217–218 °C.

Conversion of Diene Urea 16 to 2-Pyridone 4 in the Presence of Piperidine. Trapping of the Diene Isocyanate Intermediate to Give Diene Urea 17. A solution of diene urea **16** (129 mg, 0.43 mmol), piperidine (204 mg, 2.4 mmol), and 6 mL of xylene was heated at reflux for 2 h. Concentration afforded 130 mg of solid material. The ^1H NMR spectrum indicated that this material was a 32:43:25 mixture of starting diene urea **16**, 2-pyridone **4**, and the piperidine diene urea **17**. The characteristic features of this spectrum are the *tert*-butyl singlets at δ 1.37 due to 2-pyridone **4**, and at δ 1.15 due to diene ureas **16** and **17**, and the multiplet at δ 1.4–1.7, which arises from the six hydrogens at C_3 and C_4 of the piperidine ring of diene **17**. Recrystallization of the crude product from acetone afforded 14 mg (0.062 mmol) of 2-pyridone **4**, mp 217–219 °C. The concentrated filtrate was purified by chromatography on silica gel (ca. 10 g, 7:1 hexane–ethyl acetate) to yield three fractions. The first fraction yielded 10 mg (0.044 mmol) of **4**, mp 215–218 °C. An intermediate fraction (37 mg) was a 65:35 mixture (^1H NMR analysis) of diene urea **17** (0.085 mmol) and 2-pyridone **4** (0.046 mmol). A third semisolid fraction was chromatographically homogeneous diene urea **16** (45 mg, 0.151 mmol).

The second fraction was purified by high-performance LC (μ-Porasil, 5:1 hexane–ethyl acetate) to afford an analytical specimen of *N*-(2,2-dimethyl-6-phenyl-3,5-hexadien-3-yl)-1-piperidinecarboxamide (**17**): an oil; an apparent mixture of stereoisomers by high-performance LC; IR (film) 3340 (N—H), 1650, 1640, 1510, 960 ((*E*)-CH=CH), 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.6 (m, C_6H_5), 5.9–7.1 (m, vinylic H), 5.3 (br s, NH), 3.1–3.6 (m, NCH_2), 1.4–1.7 (m, piperidine C_3H and C_4H), 1.13 (s, $C(CH_3)_3$); mass spectrum *m/z* (rel intensity) 312.220 (55) ($C_{20}H_{28}N_2O$ required 312.220), 227 (25), 221 (16), 212 (11), 200 (19), 184 (11), 144 (14), 112 (100), 84 (17).

Conversion of *N*-[(1*E*,3*E*)-1,3-Pentadienyl]-1-pyrrolidinecarboxamide (21) to 3-Methyl-2-pyridone. A solution of (*E*,*E*)-diene **21**[28] (720 mg, 4.0 mmol), ca. 20 mg of 4-*tert*-butylcatechol, and 160 mL of xylene was heated at reflux. The reaction was monitored by TLC and ^1H NMR. The ^1H NMR spectrum indicated that there was <10% conversion to 3-methyl-2-pyridone after 19 h, and TLC analysis after 43 h indicated only slight conversion. The reaction was terminated after 1 week, and the reaction mixture purified by chromatography on silica gel (hexane–acetone) to afford 269 mg (62%) of 3-methyl-2-pyridone, mp 140 °C (lit.[40] 140 °C).

Kinetic Study of the Conversion of Diene Urea 16 to 2-Pyridone 4. Competitive Inhibition by Pyrrolidine. Reactions were conducted at 140.0 ± 0.1 °C in sealed, degassed NMR tubes. Reactions were followed by removing the tubes from a constant temperature oil bath at the indicated times and recording the ^1H NMR spectrum at room temperature. Trioxane (0.035 M, δ 4.7) was employed as an internal standard. The data summarized in Figure 1 were obtained by monitoring the increase in the C_5 proton (d, δ 6.2) of 2-pyridone **4** as a function of time. Qualitatively similar results were obtained by monitoring the decrease in the vinylic protons of diene **16**.

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Nucleophilic Esterolytic and Displacement Reactions of a Micellar Thiocholine Surfactant[1]

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Abstract: The thiol-functionalized surfactant *N*-*n*-cetyl-*N*,*N*-dimethyl-*N*-(β-thioethyl)ammonium chloride, **4** (16-SH), was synthesized. Under micellar conditions at pH 7, excess micellar 16-SH cleaved *p*-nitrophenyl acetate (PNPA) with k_ψ^{max} = 2.16 s^{-1} (corresponding to k_{cat} = 144 L/mol·s) and the formation of 16-SAc. Corresponding data for *p*-nitrophenyl hexanoate (PNPH) were 6.68 s^{-1} and 1037 L/mol·s, respectively. S_N2 reactions between 16-SH and iodoacetamide were also examined; at pH 7, excess micellar 16-SH gave k_ψ^{max} = 1.68 s^{-1} and k_{cat} = 44.8 L/mol·s. Relative to suitable model reactions with thiocholine, micellar kinetic advantages for 16-SH reactions at pH 7 were 251 (PNPA), 2820 (PNPH), and 32 (iodoacetamide); at pH 8, the PNPA cleavage exhibited a micellar advantage of 485. The origins of these catalytic factors are discussed, and the esterolytic reactivity of 16-SH is compared with that of other functional surfactants. Deacetylation of 16-SAc is also examined.

Strong interest in the use of functional surfactant micelles as esterolytic reagents,[2] coupled with the high nucleophilicity of thiolate anions and the appreciable acidity of thiols, has focused attention on the synthesis and properties of thiol surfactants. The micellar reactivity of these reagents is both intrinsically interesting and related to the properties of the cysteine proteinases papain, ficin, and stem bromelain.[3]

Surfactant derivatives of cysteine have been prepared by Heitmann (**1**),[4] Moss et al. (**2**),[5] and Murakami (**3**).[6] A simpler and somewhat more reactive thiol surfactant is the long-chain thiocholine derivative, **4**, prepared in our laboratory[7] and, independently, by Tonellato (Br^- form).[8] In this report, we provide full details of the preparation of **4**, its esterolytic reactivity toward *p*-nitrophenyl acetate (PNPA) and *p*-nitrophenyl hexanoate (PNPH), and its S_N2 reactions with iodoacetamide. Additionally, we discuss the comparative reactivities of surfactants **1**–**4** and of such "comicellar" reagents as alkane thiols,[9] coenzyme A,[10] and glutathione,[10] each solubilized in micellar alkyltrimethylammonium bromide solutions.

n-$C_{11}H_{23}CONHCHCOO^-(H^+)$
|
CH_2SH

1

n-$C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2CH_2NHCOCHNH_2\ Cl^-$
|
CH_2SH

2

n-$C_{16}H_{33}NHCOCHNHCOCH_2CH_2\overset{+}{N}(CH_3)_3\ Br^-$
|
CH_2SH

3

n-$C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2CH_2SH\ Cl^-$

4 (16-SH)

Results

Synthesis. Choline surfactant **5** (16-OH) was converted to its triflate derivative with triflic anhydride in CH_2Cl_2/pyridine. Self-phase-transfer catalytic conversion[11] of the triflate to **6** (16-SAc, X = OTf) was achieved by stirring the CH_2Cl_2 solution with excess aqueous sodium thioacetate. Ion exchange of **6** to its water-soluble chloride form, followed by deprotection with deoxygenated 3 N aqueous HCl, lyophilization, and recrystallization from CH_2Cl_2/ether, gave **4** (16-SH). Spectroscopic properties of **4** and its precursors appear in the Experimental Section.

n-$C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2CH_2OH\ Br^-$

5 (16-OH)

n-$C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2CH_2SCOCH_3\ X^-$

6 (16-SAc)

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