Photolysis of 1 and Characterization of Photoproducts. Compound 1 (200 mg) was dissolved in 50 mL of dry CH_3CN previously distilled from CaH_2 and placed in a Pyrex glass vessel. Cyclohexane (50 mL) also was added to the glass vessel, forming two immiscible layers. Only the acetonitrile solution layer was irradiated with an Oriel 200-W Hg–Xe lamp using a Corning 0-52 cut-off filter, i.e., $h\nu > 340$ nm. The solution was continuously purged with argon during the irradiation. The cyclohexane layer (upper layer) was removed periodically and replenished with fresh cyclohexane, thus removing the nonionic photoproducts in order to eliminate secondary photochemistry. The combined cyclohexane extract was flash evaporated and subjected to silica gel chromatography using a Harrison Research chromatotron (Model 7924) to remove **3** from **2**. Compound **3** and also compound **4**, which remained in the acetonitrile, were characterized by ^1H NMR and comparison to authentic samples that were synthesized independently. The mixture of photoisomers was subjected to careful chromatotron chromatography and was characterized by a combination of ^1H NMR in $CDCl_3$ and mass spectrometry.

^1H NMR and Mass Spectral Characterization of Photoproducts 4a–e. 9-(Methylthio)-10-(*p*-cyanobenzyl)-anthracene (2a): ^1H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 5.07 (s, 2 H), 9.11 (d, 2 H, Ar), 8.18 (d, 2 H, Ar), 7.20–7.65 (m, 8 H, remaining Ar); mass spectrum (FDMS), m/e = 339.

4-(*p*-Cyanobenzyl)-9-(methylthio)anthracene (2b): ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H), 4.63 (s, 2 H), 8.51 (s, 1 H, Ar), 8.89 (d, 2 H, Ar), 7.99 (d, 1 H, Ar), 7.20–7.65 (m, 8 H, remaining Ar); mass spectrum (FDMS), m/e = 339.

3-(*p*-Cyanobenzyl)-9-(methylthio)anthracene (2c): ^1H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 4.24 (s, 2 H), 8.48 (s, 1 H, Ar), 8.98 (d, 2 H, Ar), 7.95 (d, 2 H, Ar), 7.20–7.65 (m, 7 H, remaining Ar); mass spectrum (FDMS), m/e = 339.

2-(*p*-Cyanobenzyl)-9-(methylthio)anthracene (2d): ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 4.31 (s, 2 H), 8.43 (s, 1 H, Ar), 8.96 (d, 2 H, Ar), 8.07 (d, 2 H, Ar), 7.20–7.65 (m, 7 H, remaining Ar); mass spectrum (FDMS), m/e = 339.

1-(*p*-Cyanobenzyl)-9-(methylthio)anthracene (2e): ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 5.26 (s, 2 H), 8.49 (s, 1 H, Ar), 8.76 (d, 1 H, Ar), 8.06 (d, 2 H, Ar), 7.20–7.65 (m, 8 H, remaining Ar); mass spectrum, m/e = 339.

A Study of the Scope of the [4 + 2] Cycloaddition Reactions of Unactivated 1,3-Oxazin-6-ones

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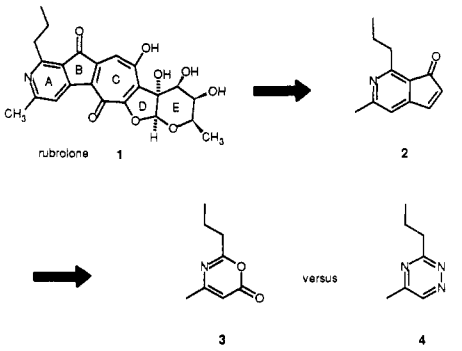
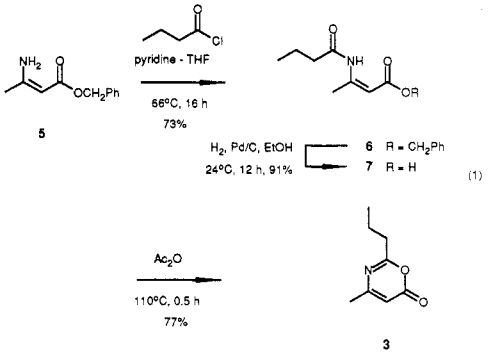
Rubrolone (1),[2] a red tropoloalkaloid[3] isolated from *Streptomyces enchinoruber* and unambiguously identified in a single-crystal X-ray structure determination, bears the unique tautomeric azaleno[2,3-*c*]pyridine-2,5,13-trione aglycon characteristic of a class of structurally related agents.[2] In a continued exploration of the inverse electron demand Diels–Alder reaction of heterocyclic azadienes[4]

Scheme I



and in efforts to define the relative and complementary scope of the 1,2,4-triazine[4,5] versus 1,3-oxazin-6-one[6] → pyridine Diels–Alder reactions applicable to the total synthesis of rubrolone, we have examined the potential for unactivated 1,3-oxazin-6-one participation in inverse electron demand Diels–Alder reactions. Herein we detail the preparation of 4-methyl-2-propyl-1,3-oxazin-6-one (**3**), the scope of its participation in [4 + 2] cycloaddition reactions, and its potential for rubrolone AB ring construction (Scheme I).

The preparation of **3** is summarized in eq 1 and is based on the 1,3-oxazin-6-one synthesis introduced by Barker[7] and subsequently improved and developed by Steglich.[6] Acylation of benzyl 3-aminocrotonate employing butyryl chloride followed by clean catalytic hydrogenolysis of the benzyl ester and subsequent dehydration (Ac_2O, 110 °C, 0.5 h) provided **3**. As noted in the work of Steglich,



attempts to promote the ester hydrolysis of **6** (3.0 equiv of LiOH, 3:1 THF–H_2O, 23 °C) served to preferentially deacylate the activated amide and provided **5**. Additional mild dehydrating agents including dicyclohexylcarbodiimide (DCC), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI), and bis(2-oxo-3-oxazolidinyl)phosphinic chloride were successful in promoting the closure of **7** to provide **3** but were found to suffer from isolation procedures that hydrolyze the moisture-sensitive 1,3-oxazin-6-one **3**.

The results of the investigation of the scope of the participation of **3** in [4 + 2] cycloaddition reactions are summarized in Table I. Nucleophilic, electron-rich acetylenes (ynamines; Table I, entries 1 and 2) participate in a well-defined regiospecific [4 + 2] cycloaddition reaction

(1) National Institutes of Health research career development award recipient, 1983–88 (CA 01134). Alfred P. Sloan research fellow, 1985–89.

(2) Isolation and structure identification: Schuep, W.; Bount, J. F.; Williams, T. H.; Stempel, A. *J. Antibiot.* **1978**, *31*, 1226. Palleroni, N. J.; Reichelt, K. E.; Mueller, D.; Epps, R.; Tabenkin, B.; Bull, D. N.; Schuep, W.; Berger, J. *J. Antibiot.* **1978**, *31*, 1218. Total synthesis: Kelly, T. R.; Echavarren, A.; Whiting, A.; Weibel, F. R.; Miki, Y. *Tetrahedron Lett.* **1986**, *27*, 6049.

(3) In addition to rubrolone, naturally occurring tropoloalkaloids include the following. (a) Colchicine and congeners: Capraro, H. G.; Brossi, A. *The Alkaloids*; Academic Press: Orlando, 1984; Vol. 23, pp 1–70. (b) Grandirubrine: Buck, K. T. *The Alkaloids*; Academic Press: San Diego, 1984; Vol. 23, pp 301–325.

(4) For recent reviews, see: Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: Orlando, 1987.

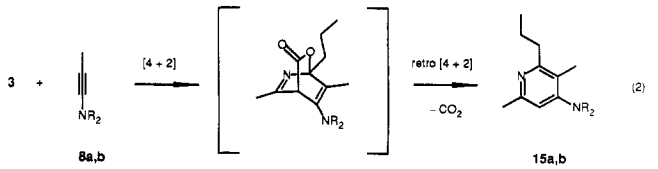
(5) Neunhoeffer, H.; Wiley, P. F. *Chemistry of Heterocyclic Compounds*; Wiley Interscience: New York, 1978; Vol. 33, pp 226–228. Neunhoeffer, H. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: London, 1984; Vol. 3, pp 421–429.

(6) Review: Steglich, W.; Jeschke, R.; Buschmann, E. *Gazz. Chim. Ital.* **1986**, *116*, 361.

(7) Barker, C. C. *J. Chem. Soc.* **1954**, 317. See also: Ming, Y.-f.; Horlemann, N.; Wamhoff, H. *Chem. Ber.* **1987**, *120*, 1427.

0022-3263/89/1954-0714$01.50/0

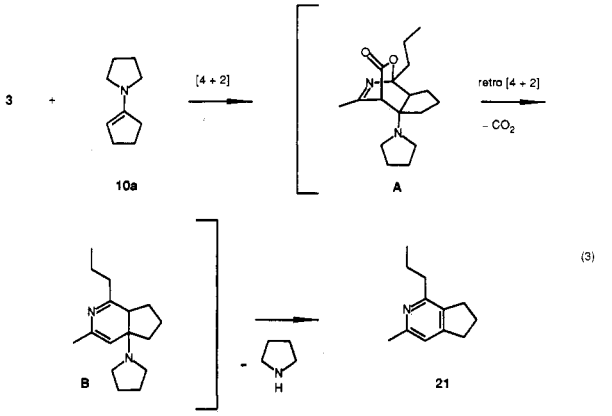
with **3** which was determined to be accompanied by the retro Diels–Alder loss of carbon dioxide with direct pyridine introduction under the reaction conditions (75–80 °C), eq 2. In accord with prior studies, the cycloaddition



proceeds across C-2/C-5 of the 1,3-oxazin-6-one **3** with the nucleophilic carbon of the electron-rich alkyne attaching to C-2.[6] Less nucleophilic alkynes (ethoxyacetylene, phenylacetylene, and 1,4-dimethoxybut-2-yne) and electron-deficient alkynes (dimethyl acetylenedicarboxylate) failed to react productively with **3** under thermal (140–165 °C), pressure-promoted (10 kbar, dichloromethane),[8] or Lewis acid catalyzed reaction conditions.[9]

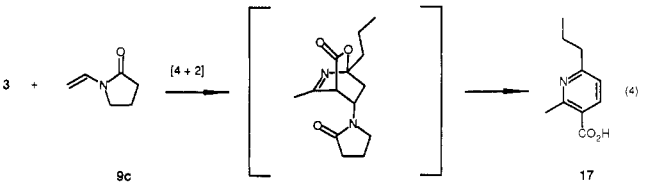
Selected nucleophilic olefins [ketene acetals, 110 °C (Table I, entry 9) > enol ethers, 140 °C (Table I, entry 4) > enol acetates, 160 °C (Table I, entry 5)] were found to participate in dependable, regiospecific [4 + 2] cycloaddition reactions with **3** following an order of reactivity that correlates well with the nucleophilic character of the dienophile. A subsequent thermal retro Diels–Alder reaction with loss of carbon dioxide (100–160 °C) presumably precedes aromatization. Similar to observations detailed in prior investigations of the [4 + 2] cycloaddition reactions of 1,2,4-triazines,[4,5] alkyl substitution of an enol ether or enol acetate is sufficient to slow or prevent its participation in a [4 + 2] cycloaddition reaction with **3** (cf. Table I, entries 7, 8, and 10 versus entries 4 and 5).[10] The modest reactivity of enol ethers and enol acetates coupled with the additional destabilizing steric interactions necessarily present in both the exo *or* endo transition state of the [4 + 2] cycloaddition of alkyl-substituted enol ethers with **3** retard or preclude a successful reaction, Figure 1. This is apparent upon comparison of the thermal reaction conditions required for the Diels–Alder reaction of **3** with ethyl vinyl ether (140 °C; Table I, entry 4) versus 2-methoxypropene (225 °C; Table I, entry 7) in which the presence and position of the additional dienophile methyl substituent is sufficient to substantially decelerate the [4 + 2] cycloaddition of 2-methoxypropene despite its increased reactivity.

In contrast to enol ethers and enol acetates, enamines and enamides [enamines, 25–120 °C (Table I, entries 11–15) > enamides, 110 °C (Table I, entry 6) > enol ethers (140–225 °C)] were found to react readily with **3** but may suffer competitive reactions to the subsequent, slow loss of carbon dioxide, eq 3. In initial efforts, the intermediate formation of the enamine–oxazinone **3** [4 + 2] cycloadduct (e.g. A, eq 3) was established by ^1H NMR spectroscopy.[11]



Attempts to isolate the sensitive [4 + 2] cycloadducts by chromatography (SiO_2) induced decarboxylation (e.g. B, eq 3) and subsequent amine elimination (aromatization) and suggested that the slow, thermal elimination of carbon dioxide and the sluggish aromatization could be facilitated by conducting the reaction process in the presence of a mild, protic acid. Thus, in selected instances the reaction of enamines with **3** in a benzene–acetic acid mixture (1:1–1:2, 25–80 °C; Table I, entries 12–14) was found to provide a suitable, single-step operation for conducting the enamine–1,3-oxazin-6-one **3** [4 + 2] cycloaddition under conditions that may not hamper the initial [4 + 2] cycloaddition reaction and which serve to facilitate the subsequent retro Diels–Alder reaction ($-CO_2$) and problematic aromatization ($-R_2NH$).[12]

Interestingly, in the room-temperature pressure-promoted [4 + 2] cycloaddition reaction of enamide **9c** with **3** (Table I, entry 6b) an apparent fragmentation (25 °C) and subsequent aromatization (–2-pyrrolidinone) intervenes to provide the 2-methyl-6-propylpyridine-3-carboxylic acid (**17**) as the exclusive reaction product (eq 4). This



unanticipated course of the reaction of **9c** with **3** is not observed with other olefinic dienophiles but is comparable to the subsequent fragmentation reactions observed in olefin–oxazole [4 + 2] cycloaddition reactions.[4]

Experimental Section

^{13}C NMR chemical shifts are relative to chloroform-*d* (77.0 ppm). The pressure-promoted Diels–Alder reactions were carried out in a Psika PA32-381 14-kbar pressure generator employing Monoplex DDA (C.P. Hall) as the pressure transmission fluid. Flash chromatography[13] was performed on 230–400 mesh silica gel (SiO_2). All purified reaction products proved homogeneous to chromatographic and spectroscopic techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), and acetonitrile

(8) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999.

(9) Ethoxyacetylene (1.3 equiv, mesitylene, 150 °C, 13 h), phenylacetylene (1.7 equiv, mesitylene, 150 °C, 17 h; 1.0 equiv, mesitylene, 1.0 equiv of $BF_3{\cdot}OEt_2$, 0–23 °C, 10 h), 1,4-dimethoxybut-2-yne (1.6 equiv, xylene, 120–150 °C, 35 h), and dimethyl acetylenedicarboxylate (1.1 equiv, mesitylene, 164 °C, 24 h) failed to react with **3**.

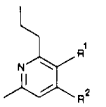
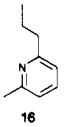
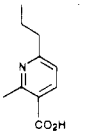
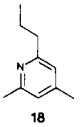
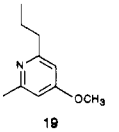
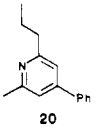
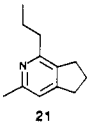
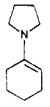
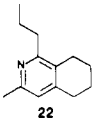
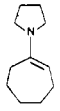
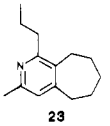
(10) 3,4-Dihydro-2*H*-pyran (15 equiv, mesitylene, 80–170 °C, 120 h), 1,2-bis(trimethylsilyloxy)cyclopentene (1.0 equiv, xylene, 120–170 °C, 60 h), and less nucleophilic olefins including 4-methoxy-3-buten-2-one (2.1 equiv, xylene, 80–140 °C, 96 h; 2.0 equiv, dichloromethane, 24 °C, 13 kbar, 96 h), 4,4-dimethoxy-3-buten-2-one (1.4 equiv, mesitylene, 164 °C, 24 h; 3.7 equiv, dichloromethane, 24 °C, 13 kbar, 96 h), and methyl 4-pyrrolidino-2-buten-1-oate (1.1 equiv, mesitylene, 150 °C, 16 h; 1.1 equiv, dichloromethane, 24 °C, 13 kbar, 48 h; 1.7 equiv, xylene–acetic acid (2:1), 110 °C, 28 h) failed to react with **3**. In addition, 1,3-oxazin-6-one **3** failed to react with ethyl vinyl ether upon treatment with tris(*p*-bromophenyl)ammonium pentachloroantimonate ($(p\text{-}BrC_6H_4)_3NSbCl_5$, 0.2 equiv, 0–25 °C, CH_2Cl_2, 15 h); cf. Pabon, R. A.; Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 5158.

(11) For example, the [4 + 2] cycloadduct of oxazinone **3** with **10a** exhibits a diagnostic ^1H NMR singlet at 3.90 ppm attributed to the bridgehead proton.

(12) Gas evolution (CO_2) occurs immediately upon the addition of acetic acid to a solution of **10a** or **10b** and **3** in benzene. For related observations, see: Boger, D. L.; Dang, Q. *Tetrahedron* **1988**, *44*, 3379.

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table I. [4 + 2] Cycloaddition Reactions of 4-Methyl-2-propyl-1,3-oxazin-6-one (3)

entry	dienophile		reaction conditions: equiv,[a] solvent, temp °C (time, h)	product[b]	% yield[c]
					
1	$R^1 = CH_3$, $R^2 = NEt_2$	**8a**[d]	2.0, C_6H_6, 80 (6)	**15a** **15b** **15c**	83
2	$R^1 = CH_3$, $R^2 = NBn_2$	**8b**[e]	1.0, toluene, 75 (7)		69
3	$R^1 = H$, $R^2 = OEt$	**8c**[f]	1.3, mesitylene, 150 (13)		no reaction
4	CH_2=CHOEt	**9a**	7.5, xylene, 140 (48)		56
5	CH_2=CHOAc	**9b**	40, mesitylene, 164 (48)	**16**	58
6a		**9c**	1.2, xylene, 110 (96)		39
6b			1.2, CH_2Cl_2, 10 kbar, 24 (96)	**17**	60
7	CH_2=C(CH_3)OCH_3	**9d**	15.0, mesitylene, 225 (15)		79
8	CH_2=C(CH_3)OAc	**9e**	15.0, mesitylene, 225 (45)	**18**	no reaction
9	CH_2=C(OCH_3)$_2$	**9f**[g]	2.0, xylene, 110 (34)		72
	CH_2=C(X)Ph			**19**	
10	X = $OSi(CH_3)_3$	**9g**[d]	2.2, xylene, 225 (40)		no reaction
11	X = morpholino	**9h**[d]	2.7, xylene, 110 (13)	**20**	69
					
12a	X = pyrrolidino	**10a**[h]	2.5, xylene, 120 (0.5)		31
12b			5.7, C_6H_6–CH_3CO_2H (1:1), 24 (10)		50
13a	X = morpholino	**10b**[h]	2.1, toluene, 10 kbar, 24 (96)		30
13b			2.7, toluene, 23–110 (30)		15
13c			5.5, C_6H_6–CH_3CO_2H (1:1), 24 (10)	**21**	55
14a		**11**[h]	3.4, xylene, 110 (10)		19
14b			1.7, neat, 80 (16)		no reaction
14c			2.7, C_6H_6–CH_3CO_2H (2:1), 24–80 (14)	**22**	no reaction
15		**12**[h]	2.0, neat, 80 (4)		58
				23	

[a] Mole equivalents of dienophile. [b] All products exhibited the expected or previously reported ^1H NMR, IR, and EI/CIMS characteristics consistent with the assigned structure. All new compounds provided HRMS exact mass information and/or satisfactory CHN elemental analysis. [c] All yields are based on pure material isolated by chromatography (SiO_2). [d] Reference 15. [e] Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. [f] Available commercially from Alfa. [g] Available commercially from Wiley. [h] The morpholino and pyrrolidino enamines were prepared in benzene with the aid of the azeotropic removal of water; ref 16.

(CH_3CN) were distilled from phosphorus pentoxide. Mesitylene, toluene, xylene, benzene (C_6H_6), and acetic anhydride were distilled from calcium hydride. Acetic acid was distilled from chromium trioxide and acetic anhydride. All extraction and chromatographic solvents; dichloromethane (CH_2Cl_2), ethyl ether (Et_2O), ethyl acetate (EtOAc), and hexane; were distilled prior to use. All other solvents and reagents were used as received from commercial sources. Reactions requiring anhydrous conditions or an inert atmosphere were performed under a positive atmosphere of argon or nitrogen (N_2).

Benzyl (*Z*)-3-Butanamido-2-butenoate (6). A solution of benzyl 3-aminocrotonate[14] (**5**, 6.7 g, 35 mmol) and pyridine (5.7 g, 72 mmol, 2.1 equiv) in tetrahydrofuran (100 mL) was treated with butyryl chloride (3.8 g, 35 mmol, 1.0 equiv) and was warmed at reflux (16 h). The reaction mixture was cooled to room temperature and filtered. The collected solid was washed with ether (2 × 50 mL). The combined filtrate was diluted with ether (150 mL) and washed with 2 M aqueous hydrochloric acid (3 × 100

(14) Davoll, J. *J. Chem. Soc.* **1953**, 3802. An improved, more convenient preparation of **5** was employed: treatment of methyl 3-aminocrotonate (Aldrich) with potassium carbonate (1.0 equiv) in benzyl alcohol (2.4 equiv) under reduced pressure (20 mm, 55 °C, 5 h) provided **5** (76%), bp 135–138 °C (0.35 mm) [lit. bp 134–148 °C (2 mm)].

mL), water (3 × 100 mL), and saturated aqueous sodium chloride (1 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5.0 × 25 cm, CH_2Cl_2 eluant) provided pure **6** (6.7 g, 9.2 g theoretical, 73%) as a gold oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 11.09 (br s, 1 H, N*H*), 7.35 (s, 5 H, C_6H_5), 5.14 (s, 2 H, OCH_2), 4.96 (s, 1 H, C=C*H*CO_2), 2.39 (s, 3 H, C=CCH_3), 2.33 (t, 2 H, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.71 (hextet, 2 H, J = 7.4 Hz, $CH_2CH_2CH_3$), 0.98 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3273, 3034, 2965, 2875, 1719, 1672, 1632, 1490, 1456, 1439, 1378, 1256, 1188, 1150, 1081, 1059, 1002, 905, 808, 745, 697 cm^{-1}; EIMS, m/e (relative intensity) 261 (M^+, 4), 173 (4), 126 (4), 91 (base); CIMS (isobutane), m/e (relative intensity) 262 (M + H^+, base); HRMS, m/e 261.1365 ($C_{15}H_{19}NO_3$ requires 261.1362). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.57; N, 5.36. Found: C, 68.71; H, 7.33; N, 5.50.

(*Z*)-3-Butanamido-2-butenoic Acid (7). A solution of **6** (2.4 g, 9.2 mmol) and activated 10% palladium on carbon (182 mg, 0.08 wt equiv) in absolute ethanol (40 mL) was placed under an atmosphere of hydrogen (1 atm) and was stirred at 24 °C (12 h). The reaction mixture was filtered through Celite, and the Celite was washed with absolute ethanol (3 × 50 mL). The combined filtrate was concentrated in vacuo to afford **7** (1.43 g, 1.57 g theoretical, 91%) as a low-melting white solid: mp 65–66 °C (benzene); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 10.98 (br s, 1 H, CO_2H), 7.6–6.8 (br s, 1 H, N*H*), 4.93 (q, 1 H, J = 0.7 Hz, C=C*H*CO_2), 2.43 (d, 3 H, J = 0.7 Hz, C=CCH_3), 2.33 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.75 (hextet, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 0.98 (t, 3 H, J = 7.5 Hz, $CH_2CH_2CH_3$); IR (melt) ν_{max} 3500–3000, 2963, 2879, 1720, 1625, 1440, 1389, 1263, 1159, 1093, 829, 730, 710 cm^{-1}.

The carboxylic acid **7** was found to decompose slowly upon storage and was subjected to the conditions of cyclization to 1,3-oxazin-6-one **3** upon isolation.

4-Methyl-2-propyl-1,3-oxazin-6-one (3). A solution of **7** (1.43 g, 8.36 mmol) in acetic anhydride (10 mL, 106 mmol, 12.7 equiv) was warmed at 110 °C (0.5 h). The reaction mixture was cooled to room temperature, and the excess acetic anhydride and acetic acid were removed by distillation under reduced pressure. Bulb-to-bulb distillation (100 °C at 1.0 mm) provided **3** (990 mg, 1.28 g theoretical, 77%) as a gold oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 5.97 (s, 1 H, C=C*H*CO), 2.59 (t, 2 H, J = 7.6 Hz, $CH_2CH_2CH_3$), 2.22 (s, 3 H, CCH_3), 1.80 (hextet, 2 H, J = 7.6 Hz, $CH_2CH_2CH_3$), 1.01 (t, 3 H, J = 7.6 Hz, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 169.6 (*C*=O), 165.8 (N=*C*O), 159.4 (CH_3C=CH), 105.9 (C=*C*H), 36.8 ($CH_2CH_2CH_3$), 23.5 (*C*CH_3), 19.6 (CH_2CH_3), 13.6 (CH_2CH_3); IR (neat) ν_{max} 2967, 2935, 2877, 1763, 1671, 1576, 1388, 1353, 1260, 1121, 842 cm^{-1}; EIMS, m/e (relative intensity) 153 (M^+, 3), 138 (5), 125 (85), 110 (base); CIMS (isobutane), m/e (relative intensity) 154 (M + H^+, base); HRMS, m/e 153.0786 ($C_8H_{11}NO_2$ requires 153.0790); UV (ether) 270 (ϵ 6700), 216 nm (ϵ 5500). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.93; H, 7.52; N, 9.14.

4-(Diethylamino)-2,5-dimethyl-6-propylpyridine (15a). A solution of **3** (50 mg, 0.33 mmol) in benzene (1 mL) under an atmosphere of nitrogen was treated with 1-diethylaminopropyne[15] (**8a**, 72 mg, 0.65 mmol, 2.0 equiv) and was warmed at 80 °C (6 h). The reaction mixture was cooled to room temperature and was concentrated in vacuo. Flash chromatography (SiO_2, 2.0 × 12.5 cm, 15% Et_2O–CH_2Cl_2 eluant) afforded **15a** (60 mg, 72 mg theoretical, 83%) as a dark yellow oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.58 (s, 1 H, C3-H), 3.05 (q, 4 H, J = 7.1 Hz, NCH_2), 2.75 (t, 2 H, J = 7.9 Hz, N=C$CH_2CH_2CH_3$), 2.47 (s, 3 H, N=CCH_3), 2.17 (s, 3 H, C=CCH_3), 1.68 (hextet, 2 H, J = 7.9 Hz, $CH_2CH_2CH_3$), 1.04 (t, 6 H, J = 7.1 Hz, NCH_2CH_3), 1.01 (t, 3 H, J = 7.9 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 2966, 2932, 2871, 1585, 1556, 1464, 1380, 1338, 1201, 1168, 819, 789 cm^{-1}; EIMS, m/e (relative intensity) 220 (M^+, 10), 205 (61), 191 (base), 163 (89); CIMS (isobutane), m/e (relative intensity) 221 (M + H^+, base); HRMS, m/e 220.1935 ($C_{14}H_{24}N_2$ requires 220.1939).

4-(Dibenzylamino)-2,5-dimethyl-6-propylpyridine (15b): gold oil (133 mg, 193 mg theoretical, 69%); ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.24 (m, 10 H, C_6H_5), 6.48 (s, 1 H, C3-H), 4.13 (s, 4 H, NCH_2), 2.78 (t, 2 H, J = 7.7 Hz, N=C$CH_2CH_2CH_3$), 2.38 (s, 3 H, CCH_3), 2.37 (s, 3 H, CCH_3), 1.69 (hextet, 2 H, J = 7.7 Hz, $CH_2CH_2CH_3$), 1.01 (t, 3 H, J = 7.7 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3086, 3063, 3029, 2960, 2929, 2870, 1583, 1555, 1495, 1453, 1398, 1364, 1266, 1116, 1029, 794, 736, 699 cm^{-1}; EIMS, m/e (relative intensity) 344 (M^+, 1), 329 (1), 316 (6), 253 (53), 225 (36), 91 (base); CIMS (isobutane), m/e (relative intensity) 345 (M + H^+, base); HRMS, m/e 344.2254 ($C_{24}H_{28}N_2$ requires 344.2253).

6-Methyl-2-propylpyridine (16): colorless oil (167 mg, 300 mg theoretical, 56%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.47 (t, 1 H, J = 7.6 Hz, C4-H), 6.95 (dd, 2 H, J = 7.6, 3.3 Hz, C3- and C5-H), 2.73 (t, 2 H, J = 7.8 Hz, $CH_2CH_2CH_3$), 2.53 (s, 3 H, CCH_3), 1.73 (hextet, 2 H, J = 7.8 Hz, $CH_2CH_2CH_3$), 0.97 (t, 3 H, J = 7.8 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3063, 2962, 2933, 2873, 1592, 1579, 1457, 1376, 1236, 1223, 1156, 1191, 789, 774, 752, cm^{-1}; EIMS m/e (relative intensity) 135 (M^+, 1), 134 (6), 120 (20), 107 (base); CIMS (isobutane), m/e (relative intensity) 136 (M + H^+, base); HRMS, m/e 135.1046 ($C_9H_{13}N$ requires 135.1048). Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.55; H, 9.80; N, 10.33.

2-Methyl-6-propylpyridine-3-carboxylic Acid (17). A solution of **3** (180 mg, 1.18 mmol) in CH_2Cl_2 (0.2 mL) was treated with *N*-vinyl-2-pyrrolidinone (**9c**, 156 mg, 1.4 mmol, 1.2 equiv). The reaction mixture was sealed under argon in a Teflon tube sealed with brass screw clamps and placed under 10 kbar of pressure at ambient temperature (96 h). Flash chromatography of the residue (SiO_2, 2.0 × 15 cm, 0–100% Et_2O–CH_2Cl_2 gradient elution) afforded **17** (127 mg, 211 mg theoretical, 60%) as a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 10.42 (br s, 1 H, CO_2H), 8.34 (d, 1 H, J = 8.1 Hz, C4-H), 7.17 (d, 1 H, J = 8.1 Hz, C5-H), 2.95 (s, 3 H, CCH_3), 2.90 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.79 (hextet, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 0.99 (t, 3 H, J = 7.5 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3100, 2965, 2933, 2874, 1712, 1591, 1466, 1392, 1241, 1152, 788 cm^{-1}; EIMS, m/e (relative intensity) 179 (M^+, 1), 178 (4), 164 (15), 151 (base); CIMS (isobutane), m/e (relative intensity) 189 (M + H^+, base); HRMS, m/e 179.0927 ($C_{10}H_{13}NO_2$ requires 179.0946). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.35; H, 7.57; N, 7.79.

4,6-Dimethyl-2-propylpyridine (18): colorless oil (93 mg, 117 mg theoretical, 79%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.79 and 6.77 (2 s, 1 H each, C3- and C5-H), 2.68 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 2.48 (s, 3 H, CCH_3), 2.27 (s, 3 H, CCH_3), 1.71 (hextet, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 0.96 (t, 3 H, $CH_2CH_2CH_3$); IR (neat) ν_{max} 2961, 2931, 2873, 1610, 1456, 1376, 1123, 791 cm^{-1}; EIMS, m/e (relative intensity) 149 (M^+, 2), 148 (10), 134 (22), 121 (base); CIMS (isobutane), m/e (relative intensity) 150 (M + H^+, base); HRMS, m/e 149.1204 ($C_{10}H_{15}N$ requires 149.1204).

4-Methoxy-6-methyl-2-propylpyridine (19): yellow oil (98 mg, 136 mg theoretical, 72%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.50 (s, 2 H, C3- and C5-H), 3.82 (s, 3 H, OCH_3), 2.69 (t, 2 H, J = 7.3 Hz, $CH_2CH_2CH_3$), 2.49 (s, 3 H, N=CCH_3), 1.72 (hextet, 2 H, J = 7.3 Hz, $CH_2CH_2CH_3$), 0.97 (t, 3 H, J = 7.3 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3006, 2901, 2872, 1597, 1466, 1442, 1350, 1334, 1316, 1193, 1154, 1059, 847 cm^{-1}; EIMS, m/e (relative intensity) 165 (M^+, 1), 164 (6), 137 (base); CIMS (isobutane), m/e (relative intensity) 166 (M + H^+, base); HRMS, m/e 165.1141 ($C_{10}H_{15}NO$ requires 165.1154). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.53; H, 9.46; N, 8.62.

6-Methyl-4-phenyl-2-propylpyridine (20): yellow oil (206 mg, 298 mg theoretical, 69%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.63 (d, 2 H, J = 8.2 Hz, phenyl C2-H), 7.46 (m, 3 H, phenyl C3- and C4-H), 7.18 (s, 2 H, pyridine C3- and C5-H), 2.81 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 2.61 (s, 3 H, CCH_3), 1.79 (hextet, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.01 (t, 3 H, J = 7.5 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3060, 3034, 2960, 2931, 2871, 2606, 1556, 1498, 1452, 1404, 764, 733, 697 cm^{-1}; EIMS, m/e (relative intensity) 211 (M^+, 2), 210 (5), 196 (15), 184 (12), 183 (base), 147 (45); CIMS (isobutane), m/e (relative intensity) 212 (M + H^+, base); HRMS, m/e 211.1363 ($C_{15}H_{17}N$ requires 211.1361).

3-Methyl-1-propyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (21). A mixture of **3** (130 mg, 0.85 mmol) and 1-(4-morpholino)cyclopentene[16] (**10b**, 710 mg, 4.6 mmol, 5.5 equiv) in

(15) Available commercially from Fluka.

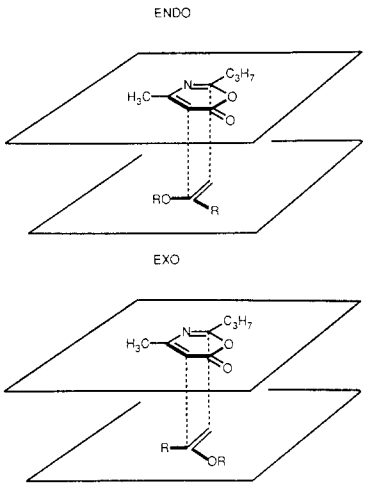


Figure 1.

benzene (2 mL) was treated with glacial acetic acid (2 mL) and was stirred at 24 °C (10 h). The reaction mixture was extracted with benzene (3 × 10 mL), and the combined extracts were washed with water (2 × 10 mL) and saturated aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5.0 × 15 cm, 0–100% Et_2O–CH_2Cl_2 gradient elution) afforded **21** (82 mg, 149 mg theoretical, 55%) as a gold oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.87 (s, 1 H, C4-H), 2.85 (t, 4 H, J = 7.5 Hz, C5-H_2 and C7-H_2), 2.70 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 2.49 (s, 3 H, CCH_3), 2.06 (p, 2 H, J = 7.5 Hz, C6-H_2), 1.69 (hextet, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 0.98 (t, 3 H, J = 7.5 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3066, 2959, 2871, 2847, 1602, 1573, 1457, 1390, 1377, 1123, 856 cm^{-1}; EIMS, m/e (relative intensity) 175 (M^+, 9), 174 (13), 160 (20), 147 (base), 146 (49); CIMS (isobutane), m/e (relative intensity) 176 (M + H^+, base), 89 (47); HRMS, m/e 175.1363 ($C_{12}H_{17}N$ requires 175.1361).

3-Methyl-1-propyl-5,6,7,8-tetrahydroisoquinoline (22): gold oil (21 mg, 111 mg theoretical, 19%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.73 (s, 1 H, C4-H), 2.73 (t, 4 H, J = 8.1 Hz, $CH_2(CH_2)_2CH_2$), 2.71 (t, 2 H, J = 7.4 Hz, $CH_2CH_2CH_3$), 2.48 (s, 3 H, CCH_3), 1.87–1.60 (m, 6 H, $CH_2CH_2CH_2CH_2$ and $CH_2CH_2CH_3$), 1.01 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 2960, 2953, 2869, 1596, 1561, 1451, 1399, 1375, 1088, 860, 789 cm^{-1}; EIMS, m/e (relative intensity) 189 (M^+, 30), 174 (31), 160 (base); CIMS (isobutane), m/e (relative intensity) 190 (M + H^+, base); HRMS, m/e 189.1516 ($C_{13}H_{19}N$ requires 189.1518).

3-Methyl-1-propyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]-pyridine (23): gold oil (70 mg, 120 mg theoretical, 58%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.83 (s, 1 H, C4-H), 2.82 (m, 6 H, $CH_2CH_2CH_3$ and $CH_2(CH_2)_3CH_2$), 2.54 (s, 3 H, CCH_3), 1.85 (p, 4 H, J = 5.5 Hz, $CH_2CH_2CH_2CH_2CH_2$), 1.67 (m, 4 H, $CH_2CH_2CH_3$ and $(CH_2)_2CH_2(CH_2)_2$), 0.98 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 2958, 2924, 2852, 1595, 1563, 1455, 1390, 976, 830, 788 cm^{-1}; EIMS, m/e (relative intensity) 203 (M^+, 11), 188 (16), 175 (48), 160 (43), 147 (base); CIMS (isobutane), m/e (relative intensity) 204 (M + H^+, base); HRMS, m/e 203.1672 ($C_{14}H_{21}N$ requires 203.1674).

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Registry No. 1, 65445-21-8; **3**, 118170-48-2; **5**, 43107-11-5; **6**, 118170-49-3; **7**, 118170-50-6; **8a**, 4231-35-0; **8b**, 75371-82-3; **8c**, 14273-06-4; **9a**, 109-92-2; **9b**, 108-05-4; **9c**, 88-12-0; **9d**, 116-11-0; **9e**, 108-22-5; **9f**, 922-69-0; **9g**, 13735-81-4; **9h**, 7196-01-2; **10a**, 7148-07-4; **10b**, 936-52-7; **11**, 1125-99-1; **12**, 14092-11-6; **15a**, 118170-51-7; **15b**, 118170-57-3; **16**, 5397-28-4; **17**, 118170-52-8; **18**, 6753-29-3; **19**, 118170-53-9; **20**, 118170-54-0; **21**, 118170-55-1; **22**, 94384-37-9; **23**, 118170-56-2; $H_3C(CH_2)_2COCl$, 141-75-3.

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Hydration of Nitriles to Amides Promoted by Mercury(II) Acetate in Acetic Acid

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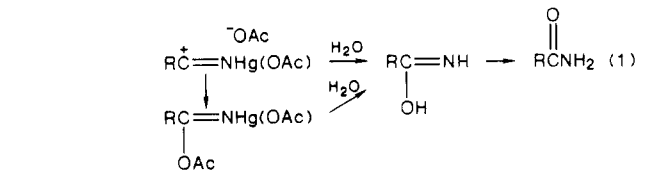
During a study of the chemical reactivity of 7-chloro-7-cyano-6b,7,8,8a-tetrahydrocyclobut[*a*]acenaphthylene (1′),[2] we observed that treatment of 1′ with silver acetate in refluxing acetic acid invariably produced the corresponding amides and rearranged products containing the carbonamide function. To test our hypothesis that silver acetate was acting as a catalyst to transform the nitrile, we subjected benzonitrile to refluxing acetic acid in the presence and absence of silver acetate and with sodium acetate and refluxing acetic acid. Benzamide was formed in 20 h only in the presence of silver acetate. Other nitriles were treated similarly but silver acetate proved to be a poor catalyst for many nitrile hydrations. The fact that mercury salts are often used as catalysts in alkyne chemistry[3] and that mercury(II) acetate (2′) is used in oxymercuration reactions of double bonds[4] led us to study the hydration of nitriles in refluxing acetic acid catalyzed by 2′.

An array of methods is available for the hydration of nitriles to amides.[5] A recent report describes the use of active reduced copper in water at 100 °C in a sealed bottle.[6] The method is effective but requires an inert atmosphere to maintain the activity of the copper catalyst. The catalytic effect of 2′ requires no special precautions and the results are summarized in Table I. Appropriate controls were run in the absence of catalyst and reaction times were extended such that only traces of nitrile could be detected by thin-layer chromatography or GLC. In some cases the reaction was complete in 5 h but most reactions were run at reflux for 70 h. The mechanism in eq 1 is proposed to



explain the catalytic effect of mercury(II) acetate and is equally applicable to silver ion catalysis. Because no special precautions are taken to exclude water from the acetic acid, water is probably present at low concentration. Thus, the intermediate that is hydrated could either be the iminium-stabilized carbocation or the imino acetate ester.

The reaction conditions are moderate and they may be useful in cases where strong acids could be detrimental to other functional groups. The cyclopropyl nitrile was hydrated intact without disruption of the cyclopropyl ring and it exhibited the shortest reaction time to completion.

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