172 °C (from *n*-hexane–benzene); IR (Nujol) 3200 cm^{-1}; NMR δ 1.83 (6 H, s), 2.37 (3 H, s), 2.50 (3 H, s), 3.33 (2 H, s), 5.6 (1 H, broad s), 6.1–7.0 (4 H, m); MS *m/e* (rel intensity) 375 (46), 374 (15), 360 (32), 358 (14), 332 (100), 43 (85). Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$: C, 63.83; H, 5.10; N, 3.72. Found: C, 64.08; H, 5.15; N, 3.50.

The product mixture labeled A was chromatographed on a silica gel column (200 g) by elution with hexane–diisopropyl ether (4:1). First fractions gave **3b** (0.51 g): mp 170 °C (from *n*-hexane–chloroform); NMR δ 1.38 (3 H, t, J = 3.1 Hz), 2.30 (6 H, s), 2.51 (3 H, s), 5.20 (2 H, q, J = 3.1 Hz), 6.8–7.4 (5 H, m). Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$: C, 63.83; H, 5.10; N, 3.72. Found: C, 63.61; H, 5.18; N, 3.54. Subsequent fractions contained **7** (0.98 g).

3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4-(2-methoxybenzyl)-5-methylisoxazole [6b]. Compound **6a** (0.37 g) was dissolved in 0.05 M methanolic sodium methoxide (20 mL) and treated with methyliodide (2.1 g). After the solution was refluxed for 5 h, the solvent was removed under reduced pressure, and the residue was taken up with water and extracted with ether. The organic solution was dried over sodium sulfate and evaporated, and the residue was absorbed onto a silica gel column (30 g). Elution with benzene–ethyl acetate (9:1) gave **6b** (0.18 g): mp 115 °C (from diisopropyl ether); NMR δ 1.85 (6 H, s), 2.43 (3 H, s), 2.54 (3 H, s), 3.39 (2 H, s), 3.60 (3 H, s), 6.3–7.2 (4 H, m); MS *m/e* (rel intensity) 389 (27), 374 (22), 358 (42), 346 (46), 43 (100). Anal. Calcd for $C_{21}H_{21}Cl_2NO_2$: C, 64.62; H, 5.43; N, 3.59. Found: C, 64.67; H, 5.24; N, 3.54.

Acknowledgment. The author thanks Mr. Domenico Dal Chiele for the technical assistance in determining NMR and mass spectra.

Registry No. 1, 13456-86-5; **2a**, 1595-40-0; **2b**, 1595-41-1; **3a**, 70288-44-7; **3b**, 70288-45-8; **4a**, 70288-46-9; **4b**, 70288-47-0; **5**, 70288-48-1; **6a**, 70288-49-2; **6b**, 70288-50-5; **7**, 70288-51-6; **8**, 53960-28-4; 3-phenoxy-1-butyne, 1596-40-3.

Synthesis and Properties of Pyrrolin-2-ones

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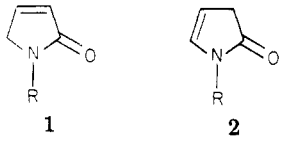
Received September 19, 1978

We were interested in the synthesis of Δ^3-pyrrolin-2-one (**1a**) as a potential monomer but were somewhat puzzled



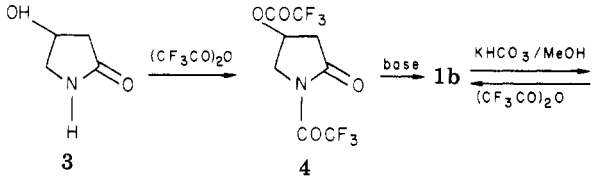
1 2

a, R = H
b, R = $COCF_3$
c, R = CH_3

by the conflicting properties attributed to this compound in the literature.

Langebeck and Boser[2] reported a preparation of **1a** that melted at 140 °C. This material was obtained from the hydrazinolysis of methyl 4-phthalimidocrotonate followed by the ring closure of the presumed methyl 4-aminocrotonate intermediate. Rapoport and Bordner[3] assigned structure **1a** for the material, mp 165 °C, obtained from the decarboethoxylation of *N*-(ethoxycarbonyl)-Δ^3-pyrrolin-2-one. The latter compound was hydrolyzed in dilute NaOH, acidified, and then sublimed. Bocchi et al.[4] synthesized a mixture of Δ^3- and Δ^4-pyrrolin-2-ones, **1a** and **2a**, respectively, by oxidation of pyrrole with aqueous hydrogen peroxide in 25–30% yield. The mixture consisted of nine parts **1a** and one part **2a** as analyzed by ^1H NMR. The isomeric mixture was a viscous, white, and hygroscopic liquid similar to the compound prepared by Grob and Ankli,[5] by hydrolysis and decarboxylation of 4-(ethoxycarbonyl)-Δ^4-pyrrolin-2-one, to which structure **2a** was assigned. We have repeated and confirmed the work of Bocchi's group. Furthermore, we were able to isolate pure **1a** from the mixture of isomers by preparative liquid chromatography and low-temperature crystallization. To a limited extent, we were able to follow the interconversion of the two isomers.

A new synthesis of **1a** and **2a** was carried out in 30–35% overall yield starting from methyl 4-bromocrotonate. Reaction of this material with potassium phthalimide gave methyl 4-phthalimidocrotonate,[6] which upon acid hydrolysis produced 4-amino-3-hydroxybutyric acid.[7] Cyclization of the amino acid yielded 4-hydroxypyrrolidin-2-one (**3**).[8] **3** was trifluoroacetylated completely to *N*,*O*-bis(trifluoroacetyl)-4-hydroxypyrrolidin-2-one (**4**). Base treatment of **4** readily gave *N*-(trifluoroacetyl)-Δ^3-pyrrolin-2-one (**1b**). This structure was assigned based on comparison with the ^1H NMR and ^{13}C NMR spectra of the unsubstituted pyrrolin-2-ones. Hydrolysis of **1b** with methanolic $KHCO_3$ gave the isomeric mixture of **1a** and **2a**. This mixture has properties similar to the pyrrolinones prepared from the peroxide oxidation of pyrrole.



3 4

1a + 2a

Δ^3-Pyrrolin-2-one (**1a**, 99.5% pure) is a very pale yellow material that melts at 23–27 °C. We were not successful in obtaining Δ^4-pyrrolin-2-one (**2a**) in purity greater than 84% because of fast isomerization. Neat samples were stored at −10 and 24 °C and analyzed quickly by ^1H NMR at 24 °C for isomer composition. **1a** (99.5%) remained essentially unchanged after storing for 27 days at −10 °C. Under these conditions enriched **2a** (74%) isomerized to nine parts **1a** and one part **2a**. **1a** was unstable at 24 °C. The isomer ratio was half-way to the equilibrium composition after 1 day. This point, a 9:1 mixture of **1a** and **2a**, was finally reached after 14 days at 24 °C.

The isomerization occurred via tautomerization to the enol as evidenced by the accelerated isomerization and concurrent deuterium–hydrogen exchange in positions 3 and 5 in CH_3OD solution in the presence of a base catalyst.

N-Methylpyrrolin-2-ones **1c** and **2c** were also prepared by the peroxide oxidation of *N*-methylpyrrole. Like the unsubstituted pyrrolin-2-ones an equilibrium isomer ratio of nine parts Δ^3 to one part Δ^4 was also obtained. As would be expected, the replacement of the amide hydrogen with an electron-donating methyl group decreased the acidity

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of the methylene protons. This in turn caused slower enolization and hence slower isomerization. A 98:2 Δ^3 to Δ^4 isomer of *N*-methylpyrrolin-2-one was only slightly changed after 1 week at 24 °C. The equilibrium composition was reached after 24 days at 24 °C.

It is interesting that **1b** was the only isomer we were able to isolate out of two possible *N*-(trifluoroacetyl)pyrrolin-2-ones. This was true whether **1b** was prepared from **4** or from a mixture of **1a** and **2a**. It is thus apparent that **1b** is thermodynamically much more stable than **2b**.

In summary, we conclude that Δ^3-pyrrolin-2-one and Δ^4-pyrrolin-2-one are both low-melting solids that cannot exist as pure isomers at room temperature. The derivatives *N*-methyl- and *N*-(trifluoroacetyl)pyrrolin-2-ones are better candidates for polymerization studies if one wishes to start with a pure Δ^3 isomer.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian T-60A and CFT-20 spectrometers, respectively. Me_4Si was used as internal standard. The pyrrolin-2-one isomer compositions were determined by comparing the two sets of vinylic and methylene proton integrations obtained from the ^{1}H NMR spectra. IR spectra were obtained on Beckman IR-9. UV analysis was done on Beckman DK-2A.

Methyl 4-Phthalimidocrotonate.[6] Potassium phthalimide (424 g, 2.29 mol) was added over 1.5 h to the rapidly stirred solution of methyl 4-bromocrotonate (Shawnee Chemical Corp. **Caution**: *this material may cause severe burns and allergic reactions*) (405 g, 2.26 mol) and DMF (1625 mL), while keeping the temperature below 50 °C. The solution was allowed to come to room temperature over 2 h. $CHCl_3$ (2.5 L) was added and the organic layer was extracted twice with 4 L of H_2O and dried over Na_2SO_4. The residue obtained after the removal of $CHCl_3$ in vacuo was recrystallized from MeOH yielding 330–400 g (60–75% yield) of fine crystals, mp 104–105 °C (lit.[2] 100 °C).

4-Hydroxypyrrolidin-2-one (3). The procedure described below was adapted from the method of Balenovic et al.[7] for the synthesis of the unisolated intermediate 4-amino-3-hydroxybutyric acid and the method of Tomita[8] for the final cyclization to **3**. A stirred mixture of methyl 4-phthalimidocrotonate (150 g, 0.612 mol) and 1.5 L of 6 N HCl was refluxed for 16 h. The mixture was then kept at 0–5 °C for 4 h and the precipitated phthalic acid was filtered and washed twice with 50 mL of H_2O. The combined filtrates and washings were evaporated in vacuo at 50 °C to 500 mL and cooled and additional phthalic acid was filtered off and washed with 20–40 mL of H_2O. The mother liquor was reduced to a syrup and 250 mL of glyme was added causing precipitation. The solids were filtered, washed with Et_2O, and air-dried. The product, 4-amino-3-hydroxybutyric acid hydrochloride, was dissolved in a minimum amount of H_2O and neutralized with 0.95 equiv of solid NaOH at 0–5 °C. The pH was then adjusted to 7 with 50% w/v NaOH solution. The liquid was again evaporated in vacuo at 60 °C and the resulting solid mixture of 4-amino-3-hydroxybutyric acid and NaCl was distilled in a Kugelrohr apparatus. The fraction collected at 130–150 °C (0.05–0.1 mm) was redistilled a second time. **3** was obtained: white solid, 34 g (55% yield); mp 118–120 °C (lit. 118–119 °C); mass spectrum *m/e* 101; ^{1}H NMR (Me_2SO-d_6) δ 7.5 (br, NH), 5.1 (br, OH), 4.4 (br, C4-H), 3.2 (m, C5-H_2), 2.2 (m, C3-H_2); ^{13}C NMR (Me_2SO-d_6) δ 176.2 (C-2), 66.2 (C-4), 51.0 (C-5), 40.3 (C-3).

***N*-(Trifluoroacetyl)-Δ^3-pyrrolin-2-one (1b).** This was synthesized in two steps from **3** using one reaction flask. Trifluoroacetic anhydride (58 mL, 411 mmol) was added over 15–20 min to 11.95 g (118.3 mmol) of **3** with stirring at 5–10 °C. When all of **3** had dissolved the solution was refluxed for 1.5 h. Excess anhydride and acid were removed in vacuo at <50 °C. The residue, crude *N,O*-bis(trifluoroacetyl)-4-hydroxypyrrolidin-2-one, was a viscous amber liquid: ^{1}H NMR ($CDCl_3$) δ 5.68 (br, C4-H), 4.2 (m, C5-H_2), 3.08 (m, C3-H_2). **4** was taken up in 60 mL of CH_2Cl_2 and Et_3N[10] (20 mL, 142 mmol) in 40 mL of CH_2Cl_2 was added dropwise over 15 min to the stirred solution of **4** at 5–10 °C. Elimination of trifluoroacetic acid to form **1b** was instantaneous as indicated by ^{1}H NMR analysis of the reaction mixture. The excess reagents were removed in vacuo and the residue was distilled in a Kugelrohr apparatus at 0.05–0.1 mm at 50–90 °C. The product **1b** was sublimed twice at 55–60 °C (0.05–0.1 mm), yielding 13 g (61% yield) of colorless crystals: mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.6 (m, C4-H), 6.2 (m, C3-H), 4.6 (m, C5-H_2); ^{13}C NMR ($CDCl_3$) δ 171.8 (C-2), 148.0 (C-4), 126.8 (C-3), 51.1 (C-5); IR (KBr) 1185 (CF_3), 1600 (C=C), 1710 and 1720 cm^{-1} (C=O); UV (Et_2O) λ_{max} 228 nm (ϵ 9455); mass spectrum *m/e* 179. Anal. Calcd for $C_6H_4F_3NO_2$: C, 40.22; H, 2.23; N, 7.82. Found: C, 40.14; H, 2.40; N, 7.88.

1b was also synthesized from the trifluoroacetylation of a mixture of **1a** and **2a**. Freshly distilled pyrrolin-2-ones (1.08 g, 13 mmol) were dissolved in 3 mL of $CDCl_3$ and 2.2 mL (15.8 mmol) of Et_3N. ^{1}H NMR analysis of the resulting mixture for vinylic protons showed a 85:15 **1a** to **2a** molar ratio. The solution was cooled to −70 °C and trifluoroacetic anhydride (2.0 mL, 14.2 mmol) in 2 mL of $CDCl_3$ was added dropwise over 5 min. ^{1}H NMR analysis of the reaction mixture did not show two distinct sets of vinylic protons similar to **1a** and **2a**. Excess reagents were evaporated off and the residue was sublimed as previously described, yielding colorless crystals of **1b**.

Δ^3- and Δ^4-Pyrrolin-2-ones 1a and 2a. The procedure described below yielded mixture of **1a** and **2a** having properties identical with the mixture obtained from the aqueous peroxide oxidation of pyrrole.[4] Crude **1b** was prepared from **4** (49 mmol) by the previously described procedure except that pyridine (70 mmol) was used instead of triethylamine. The crude product containing **1b**, pyridinium trifluoroacetate, excess pyridine, and CH_2Cl_2 was mixed with 30 mL of MeOH and 12 g (120 mmol) of $KHCO_3$. The mixture was stirred at 24 °C for 1.5 h, evaporated in vacuo at 35 °C to a thick syrup, and 90 mL of a 7:2 $CHCl_3$/dioxane mixture was added. The slurry was dried with Na_2SO_4 and filtered and the mother liquor was evaporated in vacuo at 35 °C, leaving an amber oil residue. This product was distilled in a Kugelrohr apparatus at 60–80 °C (0.05–0.1 mm), yielding 3.5 g (86%) of almost colorless oil. ^{1}H NMR analysis of the freshly distilled material showed eight parts **1a** and two parts **2a**. This mixture equilibrated on standing to nine parts **1** and one part **2a**. Essentially the same mixture of **1a** and **1b** was obtained when purified crystalline **1b** was treated with $KHCO_3$ in MeOH or with aqueous NaOH under the conditions or ref 3. The yield in the latter case was 48%.

^{1}H NMR ($CDCl_3$): **1a**, δ 8.0 (br, NH), 7.2 (m, C4-H), 6.2 (m, C3-H), 4.1 (m, C5-H_2); **2a**, δ 9 (br, NH), 6.5 (m, C5-H), 5.3 (m, C4-H), 3.0 (m, C3-H_2). ^{1}H NMR (D_2O): **1a**, δ 7.4 (m, C4-H), 6.2 (m, C3-H), 4.2 (m, C5-H_2); **2a**, δ 6.5 (m, C5-H), 5.5 (m, C4-H), 3.1 (m, C3-H_2). Deuterium exchange for C3-H and C5-H was observed in the ^{1}H NMR of pyrrolin-2-ones in CH_3OD. This exchange was faster in the presence of CH_3ONa. ^{13}C NMR (acetone-d_6): **1a**, δ 175.6 (C-2), 147.6 (C-4), 127.7 (C-3), 49.5 (C-5); **2a**, δ 130.9 (C-5), 105.18 (C-4), 37.18 (C-3), not enough signal to see C-2 (C=O). UV (H_2O) λ_{max} 198 nm (ϵ 10 500); (EtOH) λ_{max} 225 nm (ϵ 3100). IR ($CHCl_3$) 3465, 3230 (NH), 1690 (C=O), 1580 and 1602 cm^{-1} (C=C). Mass spectrum *m/e* 83. Anal. Calcd for C_4H_5NO: C, 57.80; H, 6.07; N, 16.87. Found: C, 57.65; H, 6.15; N, 16.84.

Purification of Δ^3-Pyrrolin-2-one (1a). Crystallization. An equilibrium mixture of **1a** and **2a** (3.2 g) was dissolved in 90 mL of Et_2O. While under N_2 and with stirring, the solution was brought down to −7 °C over 1 h and kept at −7 to −10 °C for 4 h. The solids were filtered under an N_2 blanket through a cooled filter funnel, and washed twice with 10 mL of −70 °C Et_2O. The solids were transferred to a flask by dissolving in $CHCl_3$ and evaporating the solvent in vacuo at <15 °C. Nearly colorless crystals, 1.5 g (47% yield), mp 23–27 °C, were obtained. ^{1}H NMR analysis showed the product was pure **1a**. LC showed the presence of ≤0.5% **2a**.

Preparative Liquid Chromatography of Pyrrolin-2-one 1a and 2a.[11] Pyrrolin-2-ones (0.6 g) from pyrrole oxidation were

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(10) For the desired elimination product, pyridine and Et_3N were satisfactory; however, Et_3N was preferred. Triethylammonium trifluoroacetate was easier to separate from **1b** than pyridinium trifluoroacetate.

chromatographed in a 2.54 × 50 cm Sephadex LH-20 column using methyl acetate as solvent (4.3 mL/min) and a refractive index detector. After a forecut of about 450 mL, **2a** was eluted within 90 mL followed immediately by **1a** (300 mL). The purity of **2a** isolated after solvent evaporation was 84% (^{1}H NMR, LC). Material, mp 23–27 °C, obtained by evaporation of the middle third portion of the second peak was 99.9% pure **1a** (LC). Traces of succinimide and 3-methylpyrrolin-2-one were found in intermediate fractions.

***N*-Methylpyrrolin-2-ones (1c and 2c).** This procedure was adopted from Atkinson et al.[9] *N*-Methylpyrrole (192 g, 2.37 mol) and pyridine (320 mL) were heated at 90 ± 2 °C. H_2O_2 (240 mL, 30% w/v, 2.17 mol) was added over 1.5 h with stirring at the same temperature. The reaction was not exothermic. Heating was continued for an additional 5 h and the mixture was left at 24 °C overnight. The mixture was heated again at 90 °C and a pinch of PbO_2 was added to destroy any remaining peroxide. Most of the pyridine and unreacted *N*-methylpyrrole were removed by evaporation in vacuo at 40 °C. The residue was extracted with 200 mL of $CHCl_3$, the extract was dried with Na_2SO_4, and the solvent was evaporated. Repeated fractional distillation at 40–41 °C (0.1 mm) yielded 40 g (19% yield) of light yellow liquid. The product was a 9:1 mixture of **1c** and **2c**, respectively: ^{1}H NMR (neat) **1c**, δ 7.3 (m, C4-H), 6.2 (m, C3-H), 4.1 (m, C5-H_2), 2.9 (s, CH_3); **2c**, δ 6.7 (m, C5-H), 5.3 (m, C4-H), 3.0 (m, C3-H_2), 3.0 (s, CH_3).

Enrichment of *N*-Methyl-Δ^3-pyrrolin-2-one (1c). An isomeric mixture of **1c** and **2c** (9:1 molar ratio, respectively) (2.7 g) was dissolved in 16 mL of Et_2O and made slightly cloudy with the addition of 10 mL of hexanes. The mixture was cooled over 3 h with stirring to −5 °C under N_2. The liquid was decanted off quickly and the solid was washed twice by decantation with 10 mL of 1.6:1 v/v Et_2O/hexanes at −70 °C. The solid recovered after evaporation of the solvent in vacuo was 2.2 g (81% yield) of 98% **1b** and 2% **2b**.

Acknowledgments. We wish to thank Dr. William J. Boyle, Jr., for helpful discussions and assistance in the preparation of this paper.

Registry No. **1a**, 4031-15-6; **1b**, 70399-10-9; **1c**, 13950-21-5; **2a**, 27406-82-2; **2b**, 70399-11-0; **2c**, 22124-67-0; **3**, 25747-41-5; **4**, 70399-12-1; methyl 4-phthalimidocrotonoate, 54238-27-6; potassium phthalimide, 1074-82-4; methyl 4-bromocrotonoate, 1117-71-1; 4-amino-3-hydroxybutyric acid hydrochloride, 51085-21-3; 4-amino-3-hydroxybutyric acid, 352-21-6; *N*-methylpyrrole, 96-54-8.

(11) This procedure was developed in cooperation with Louis Palmer, Separation Labs, Allied Chemical Corp., Morristown, N.J.

Alkyl Substituent Effects on Rates of Arylnitrile Oxide Cycloadditions

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Received February 6, 1979

Alkyl substituents may either accelerate or decelerate the rates of attack by electrophiles on alkenes. The gas-phase proton affinity of ethylene is increased as the number or size of attached alkyl groups is increased,[2] and this behavior is for the most part paralleled by rates of acid-catalyzed hydration.[3] The results reflect the cation-stabilizing effects of alkyl substituents. However, for other electrophiles such as bromine,[4] carbenes,[5] and boranes,[6] increasing the number or size of alkyl substituents causes first acceleration and then deceleration, the latter a reflection of the steric effects of alkyl substituents.

Table I. Rates of Cycloadditions of Benzonitrile Oxides to Alkylethylenes in CCl_4 (L/(mol s) × 10^{-3})

alkene			substituted BNO[a]	
R	R′	IP[11]	*p*-NO_2 (25 °C)	*p*-MeO (20 °C)
H	H	10.52		
Me	H	9.90	13.4	2.41[b]
Et	H	9.79	12.9	2.41
Pr	H	9.68	12.6	2.38
Bu	H	9.64	12.9	2.39
i-Pr	H	9.69	11.3	2.08
t-Bu	H	9.61	7.26	1.44
Me	Me	9.40	4.79	0.691

[a] BNO = Benzonitrile oxide. [b] The propene rate was measured at −12.5 °C and was found to be identical (0.090 × 10^{-3} L/(mol s)) to that of 1-butene at the same temperature.

Less is known about the influence of alkyl substituents on concerted 1,3-dipolar cycloadditions. Huisgen and co-workers have reported that the relative rates of cycloadditions of benzonitrile oxide to ethylene, propene, and 1-hexene are 1:0.32:0.31,[7] which suggests that the steric, rather than the electronic, influence of alkyl substituents is being manifested. We report here a study of the rates of cycloadditions of *p*-methoxy- and *p*-nitrobenzonitrile oxides (MBNO and NBNO, respectively) to a series of simple alkenes—propene, 1-butene, 1-pentene, 1-hexene, 3-methyl-1-butene, 3,3-dimethyl-1-butene, and isobutene. Our goal was, first, to determine the influence of the "classic" series of alkyl substituents on rates of cycloadditions of relatively electrophilic 1,3 dipoles[7,8] and, second, to determine whether increasing the electrophilicity of the nitrile oxide would cause the electron-donor influence of the alkyl substituents to be manifested. Third, we wished to have quantitative rate data to compare with theoretical treatments of 1,3-dipolar cycloaddition rates.[9,10]

Results and Discussion

The cycloadditions studied here all gave, within the experimental limits of detection (by NMR), only the 5-substituted isoxazolines:

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