Synthesis of Some 2-Aminofurans from Cyanoacetone Enolate and Their Rearrangement to 3-Cyanopyrroles with Ammonia

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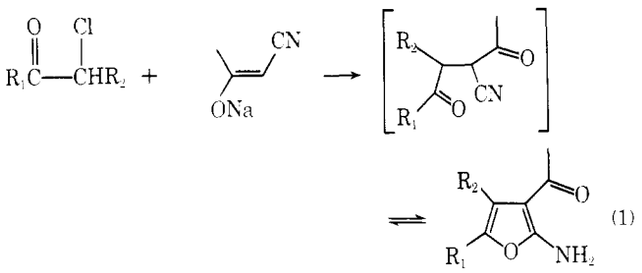
Condensation of the sodium enolate of cyanoacetone with α-chloro ketones having a nitrile, ester, ketone, or amide group on the carbon atom bearing the chlorine gave 2-aminofurans, 2-hydroxypyrroles, or 2-hydroxyfurans depending on the group present in the chloro ketone. Reaction of 2-amino-3-acetylfurans with ammonia produced rearranged pyrroles having methyl and cyano groups in the 2 and 3 positions, respectively. The structures assigned were proven by X-ray crystallography of a representative product, 2-amino-3-acetyl-4-cyano-5-methylfuran.

Cyanoacetone[1] is a compound lacking in both stability and availability and accordingly has rather limited utility in preparative organic chemistry. In contrast, the sodium enolate is readily available as a dry powder from 5-methylisoxazole[2] and can be stored indefinitely. While investigating the chemistry of this stable derivative, an easily accessible group of 2-aminofurans was discovered.[3]

The condensation reaction involved is shown in eq 1 in



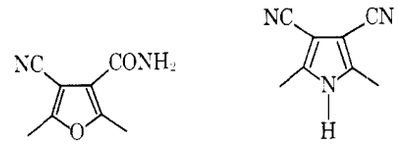
(1)

generalized form. Related condensations utilizing malononitrile and ethyl cyanoacetate were reported by Westöö in 1959.[4] In the examples studied, R_1 is a methyl group. In the successful cases, R_2 is a nitrile, ester, or ketone function and evidently needs to be an electron-withdrawing group of this sort.

The aminofuran **4** was obtained in the first instance as a byproduct in the preparation of α-chloro-α-cyanoacetone (**3**). The formation of **4** was the result of incomplete chlorination of 5-methylisoxazole as shown in Scheme I.[5]

The aminofuran **4** can be prepared quite simply by chlorinating half of any given quantity of 5-methylisoxazole followed by treatment of the resulting mixture with NaOEt in EtOH and heating the resulting precipitate of sodium enolates in water buffered with $NaHCO_3$.

The structure of compound **4** could not be unequivocally assigned on the basis of spectral and analytical data. For example, the (incorrect) carboxamide structure **5**, suggested obliquely by the reaction (of **4**) with hot aqueous ammonia to give the known[6] pyrrole **6**, was a possible alternative. To clear

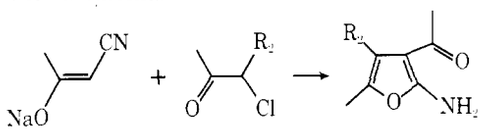


5 **6**

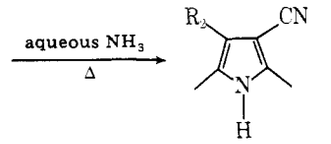
up the structural ambiguity regarding the position of substituents on the furan ring, an X-ray crystallographic structure determination was carried out, proving that the aminofuran structure **4** was correct (Figure 1).

The reorganization of functional groups occurring during the transformation of the furan **4** into the pyrrole **6** is assumed to proceed through the open dicyano–diketone. A published analogy to this rearrangement is the base-induced rearrangement of ethyl 2-amino-4-phenylthiophene-3-carboxylate to 2-hydroxy-3-cyano-4-phenylthiophene.[7]

The corresponding aminofurans **9** and **11** were obtained when the cyanoacetone enolate was condensed with ethyl 2-chloroacetoacetate and with 3-chloro-2,4-pentanedione. These products also rearranged to cyanopyrroles by treatment with ammonia.

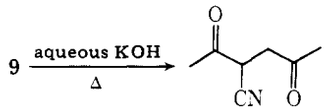


7, R_2 = COOEt **9**, R_2 = COOEt
8, R_2 = $COCH_3$ **11**, R_2 = $COCH_3$



10, R_2 = COOEt
12, R_2 = $COCH_3$

A result which supports the contention that reversal of the furan ring closure is involved in the rearrangement was obtained by heating the ester **9** with aqueous potassium hydroxide, which yielded 3-cyano-2,5-hexanedione (**13**).



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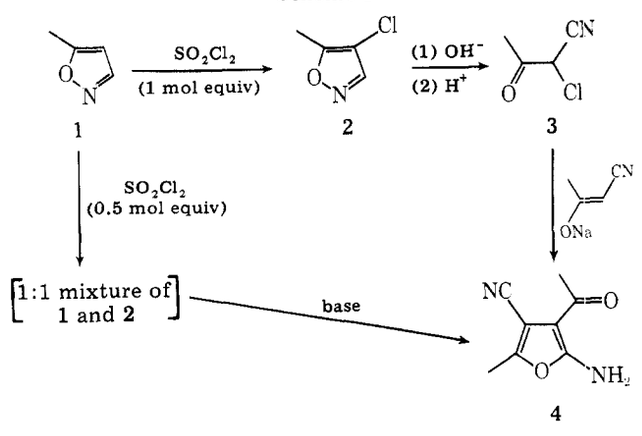
When the group R_2 in the generalized reaction was a primary amide group, an alternative mode of cyclization prevailed and a hydroxypyrrole was obtained rather than an aminofuran. The product in this case, compound **15**, aggres-

Scheme I



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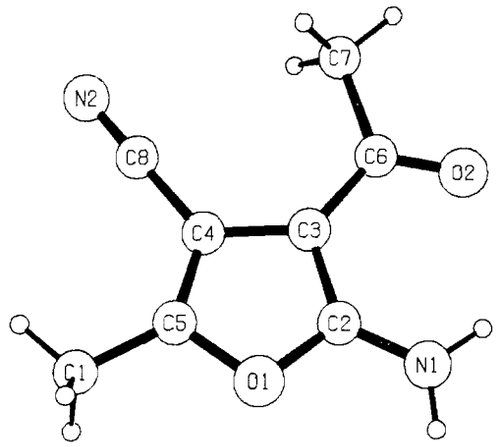
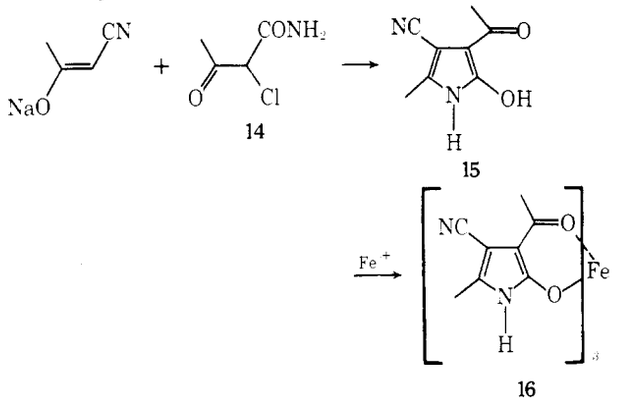
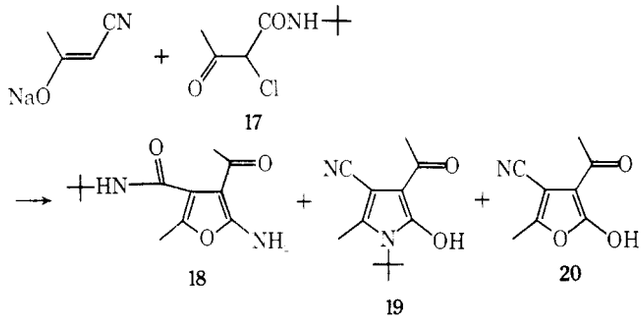


Figure 1. X-ray crystallographic structure of **4**.

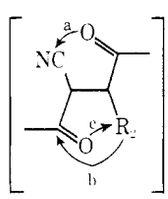
sively chelates iron, forming the dark purple tris complex **16**. The affinity of **15** for even trace amounts of iron leaves vacuum sublimation as the most practical method of preparing colorless samples. Compound **15** was unchanged by exposure to hot aqueous ammonia.



In the case of a secondary amide where R_2 = *t*-BuNHCO–, the existence of three competing modes of cyclization became evident, resulting in a mixture of the products **18**, **19**, and **20**.



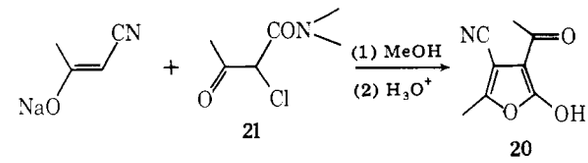
Compounds **18** and **19** are the result of cyclization modes



R_2	cyclization mode
CN	a
COOEt	a
$COCH_3$	a
$CONH_2$	b
CONHBu-*t*	a, b, c
$CONMe_2$	c

a and b encountered in the earlier examples. Compound **20** results from cyclization mode c followed by elimination of *tert*-butylamine from the tetrahedral intermediate.

Finally, when the group R_2 is a tertiary amide group, i.e., dimethylamide, the chemistry reverts to the simple situation in which a single product is formed. Cyclization mode c prevails, and the hydroxyfuran **20** is obtained in good yield.



Experimental Section[9]

α-Chloro-α-cyanoacetone (3). 5-Methylisoxazole (83 g, 1 mol) was treated with sulfuryl chloride (155 g, 1.15 mol) dropwise through a condenser at such a rate as to maintain a gentle reflux. Upon completion of the addition, refluxing was continued for 1 h by heating. After cooling, the flask was connected to a water aspirator for a brief period to remove HCl and SO_2. The crude 4-chloro-5-methylisoxazole (114 g) was added to a solution of NaOH (60 g, 1.5 mol) in water (500 mL) and rinsed in with more water (200 mL). This mixture was swirled with intermittent cooling in such a way as to let the reaction proceed without getting hot. When a clear solution had formed, it was chilled in ice and treated with 200 mL of concentrated hydrochloric acid (ca. 2 mol). The resulting yellow solution was saturated with NaCl and extracted three times with ether. The combined extracts were dried over Na_2SO_4, and the ether was evaporated. Distillation of the residue at 20 mm gave 89 g (76%) of colorless liquid distilling mostly at 85 °C; the temperature rose quickly to 100 °C near the end of the distillation. The product partly crystallized to a slush on standing in the refrigerator. A sample of the crystals washed with ether/hexane had mp 32–37 °C: IR (neat liquid) 3200, 2230, 1745, and 1630 cm^{-1} (the spectrum of the solid (Nujol) is very similar but with a much more intense band at 1625 cm^{-1} than at 1745 cm^{-1}); NMR ($CDCl_3$) four singlets at 2.20 (CH_3, enol), 2.46 CH_3, ketone), 5.01 (CH, ketone), and 7.10 (OH, enol) ppm. The peaks ascribed to the ketone are stronger when the NMR solution is prepared from a liquid specimen, and those ascribed to the enol are stronger when a solid specimen is used. The mass spectrum had peaks at *m/e* 117 (M^+) and 43 (100); the UV spectrum in EtOH had a λ_{max} 234 mμ (ε 10 550).

Anal. Calcd for C_4H_4ClNO: C, 40.87; H, 3.43; Cl, 30.16; N, 11.92. Found: C, 40.76; H, 3.59; Cl, 29.47; N, 11.32.

2-Amino-3-acetyl-4-cyano-5-methylfuran (4). (a) A solution of α-chloro-α-cyanoacetone (13.7 g, 0.117 mol) and the sodium enolate of cyanoacetone (12.5 g, 0.119 mol) in water (150 mL) was heated on the steam bath for 30 min. The orange-yellow precipitate which formed on cooling was filtered, washed with water, air-dried (10.8 g), and taken up in CH_2Cl_2, some insoluble material being discarded. The solution was concentrated with the addition of hexane to give after chilling 9.0 g (47%) of colorless crystals with mp 182–184 °C: IR (Nujol) 3250, 2240, 1675, 1635, 1600, and 1510 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6/D_2O washed) 2.40 and 2.43 ppm (singlets) (before the D_2O wash, the NH_2 signal appeared at 7.4 ppm and the CH_3 singlets were not resolved); mass spectrum, *m/e* 43 (100), 149, and 164 (M^+).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.60; H, 4.95; N, 16.97

(b) Sulfuryl chloride (13.5 g, 0.1 mol) was added gradually through a condenser to 5-methylisoxazole (16.6 g, 0.2 mol). The mixture was heated on a steam bath for 1 h and then chilled in ice. A sodium ethoxide solution prepared by dissolving sodium (5 g) in ethanol (100 mL) was added dropwise with stirring and continued cooling. After dilution with ether, the precipitated salts were collected and dissolved in water (200 mL) containing sodium bicarbonate (10 g). Heating and workup as in (a) afforded 5.75 g (35%) of compound **4** in two crops.

2,5-Dimethyl-3,4-dicyanopyrrole (6). A mixture of aminofuran **4** (6.3 g) and concentrated aqueous ammonia (125 mL) was stirred at reflux for 14 h. The precipitate which formed was collected after cooling and air-dried to give 3.9 g of crude product. Purification by vacuum sublimation afforded 3.3 g (59%) of very pale yellow crystals with mp 247–248 °C (lit.[6] mp 239 °C): IR (Nujol) 3200, 2230, 1615, and 1540 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) 2.34 (s, 6 H) and 11.5 (broad, 1 H) ppm; mass spectrum, *m/e* 144 (100) and 145 (M^+).

Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.09; H, 5.04; N, 28.72.

2-Amino-3-acetyl-5-methyl-4-furancarboxylic Acid Ethyl

Ester (9). A solution of the sodium enolate of cyanoacetone (10.5 g, 0.1 mol) and ethyl 2-chloroacetoacetate (16.5 g, 0.1 mol) in water (100 mL) was heated on the steam bath for 90 min. The brownish precipitate which formed on cooling was collected (15.5 g) and taken up in ethanol. Some insoluble material was filtered off, and the filtrate was concentrated by boiling with the addition of water. The product separated in colorless leaflets, giving 9.95 g (47%) with mp 147–149 °C: IR (Nujol) 3400, 3100, 1720, 1650, and 1620 cm^{-1}; NMR ($CDCl_3$) 1.38 (t, 3 H, J = 7 Hz), 2.40 (s, 6 H), 4.36 (q, 2 H), and 6.4 (broad s, 2 H) ppm; mass spectrum, m/e 43 (100), 165, and 211 (M^+).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.97; H, 6.18; N, 6.59.

2,5-Dimethyl-4-cyanopyrrole-3-carboxylic Acid Ethyl Ester (10). A mixture of compound **9** (5.5 g) in concentrated aqueous ammonia (100 mL) was stirred at reflux for 4 h. After cooling, the precipitate was collected and air-dried, giving 4.4 g of crude product. Recrystallization from methylene chloride/ethanol/hexane gave 3.25 g (65%) of colorless crystals with mp 150–152 °C (lit.[6] mp 152 °C); IR (Nujol) 3200, 2220, and 1675 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) 1.40 (t, 3 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 4.33 (q, 2 H), and 11.0 (broad, 1 H) ppm; mass spectrum, m/e 147, 163 (100), and 192 (M^+).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.44; H, 6.21; N, 14.62.

2-Amino-3,4-diacetyl-5-methylfuran (11). A solution of 3-chloro-2,4-pentanedione (26 g, 0.2 mol) and the sodium enolate of cyanoacetone (21 g, 0.2 mol) in water (100 mL) and methanol (200 mL) was heated to reflux on a steam bath for 90 min. Concentration under reduced pressure and chilling formed a precipitate which was collected, washed with water, and air-dried. An orange-red impurity was removed by trituration with methylene chloride, leaving 13.1 g (36%) of pale yellow needles with mp 168–169 °C: IR (KBr) 3375, 1660, and 1640 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) 2.17 (s, 3 H), 2.33 (s, 3 H), 2.44 (s, 3 H), and 7.4 (broad s, 2 H) ppm; mass spectrum, m/e 43 (100) and 181 (M^+).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.69; H, 5.99; N, 7.95.

2,5-Dimethyl-3-cyano-4-acetylpyrrole (12). Compound **11** (13.1 g) and concentrated aqueous ammonia (200 mL) were heated to reflux for 90 min. After cooling, the product was collected and dried to give 6.8 g (58%) of pink-white crystals. Recrystallization from methanol gave colorless crystals with mp 214–216°C: IR (KBr) 3210, 3145, 2215, and 1625 cm^{-1}; NMR (Me_2SO-d_6) 2.27 (s, 3 H), 2.37 (s, 6 H), and 11.80 (broad, 1 H) ppm; mass spectrum, m/e 147 (100) and 162 (M^+).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.75; H, 6.11; N, 17.16.

3-Cyano-2,5-hexanedione (13). A solution prepared from compound **9** (40 g), potassium hydroxide (80 g), water (100 mL), and methanol (400 mL) was heated at reflux for 4 h. After cooling, the solution was acidified with 3 N HCl and water and methanol were evaporated under reduced pressure. The residue was extracted with ethanol. The extract was filtered and evaporated, and the resulting residue was extracted with methylene chloride. This extract was filtered and evaporated, and the residue was vacuum distilled to give 16.25 g of impure product. Chromatography on silica gel (1 kg) afforded 12 g of material which on redistillation gave 9.2 g (35%) of pale yellow liquid with bp 71–78 °C (0.1 mm) [lit.[10] bp 106–108 (3 mm) and 137–138 °C (15–16 mm)]: IR (film) 3300 (enol), 2260, 2220 (enol), and 1725 cm^{-1}; NMR ($CDCl_3$) 2.17 (s, 3 H), 2.42 (s, 3 H), 3.03 (m, eight lines, J_{AB} = 18.0 Hz, J_{AX} = 5.3 Hz, and J_{BX} = 6.5 Hz, 2 H), and 3.79 (m, four lines, 1 H) ppm; mass spectrum, m/e 43 (100) and 139 (M^+).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 59.93; H, 6.64; N, 9.85.

2-Chloroacetoacetamide (14). α-Chloro-α-cyanoacetone (80 g) was combined with concentrated HCl (100 mL) and cooled in ice to control the exothermic hydrolysis. After standing overnight, a precipitate of ammonium chloride was filtered out and washed with ether. The filtrate was evaporated to a small volume, and ether was added. This mixture was dried with Na_2SO_4, filtered, and evaporated, and the residue was taken up in warm CH_2Cl_2, dried again, and evaporated. The residue solidified on standing; it was triturated with a small volume of CH_2Cl_2, filtered, washed with CH_2Cl_2, and then dried to give 28.5 g (31%) of the amide (in three crops). An analytical sample prepared by vacuum sublimation had mp 78–85 °C (lit.[11] mp 76–77 °C): IR ($CHCl_3$) 3200–3500, 1730 (shoulder), 1650, 1630, and 1575 cm^{-1}; NMR ($CDCl_3$) 2.11 and 2.40 (CH_3 of ketone and enol), 4.80 (CH of ketone), and 6.5 (broad, NH_2 and OH of enol) ppm; mass spectrum, m/e 43 (100) and 135 (M^+).

Anal. Calcd for $C_4H_6ClNO_2$: C, 35.44; H, 4.46; Cl, 26.15; N, 10.33. Found: C, 35.39; H, 4.50; Cl, 26.31; N, 10.36.

2-Hydroxy-3-acetyl-4-cyano-5-methylpyrrole (15). A solution prepared from 2-chloroacetoacetamide (1.35 g), the sodium enolate of cyanoacetone (1.05 g), and sodium bicarbonate (0.85 g) in *distilled* water (20 mL) was heated on a steam bath for 45 min. The solution was cooled, diluted with distilled water, and acidified with 3 N HCl. The product was collected, washed with water, and air-dried to give 1.2 g (73%) of light tan powder. A sublimed sample gave pale yellow crystals with mp 206–209 °C: IR (Nujol) 3100, 2200, 1655, and 1620 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) 2.17 (s, CH_3), 2.30 (s, CH_3), 8.4 (broad, NH or OH), and 11.2 (broad, NH or OH) ppm; mass spectrum, m/e 164 (100, M^+).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.97; H, 5.18; N, 17.52.

Iron(III) Complex of 2-Hydroxy-3-acetyl-4-cyano-5-methylpyrrole (16). A solution of compound **15** (1 g) in ethanol (20 mL) was treated dropwise with excess ferric acetate in ethanol. The latter was prepared by dissolving ferric chloride (2 g) in ethanol (25 mL) and adding sodium acetate (5 g) followed by removal of sodium chloride by filtration. The purple solution of the complex was diluted to 250 mL with water, and the precipitate was collected on Whatman No. 42 filter paper. After washing and drying, 1.2 g of product was obtained. Recrystallization (a) from chloroform and (b) from acetone/hexane gave 900 mg (81%) of dark purple fine needles with mp >330 °C: IR (KBr) 3270, 2215, 1610, 1580, and 1510 cm^{-1}; UV–vis (CH_2Cl_2) 240 nm (ϵ 24 750), 255 sh (19 600), 296 (15 355), 340 sh (8135), and 555–565 (3820).

Anal. Calcd for $C_{24}H_{21}FeN_6O_6$: C, 52.86, H, 3.88; N, 15.41; Fe, 10.24. Found: C, 52.22; H, 3.99; N, 15.49; Fe, 10.56.

2-Chloro-*N*-*tert*-butylacetoacetamide (17). Diketene (42 g, 0.5 mol) was mixed with ca. 200 mL of ice and water in a 2-L three-neck flask. A solution of *tert*-butylamine (37.5 g, 0.5 mol) in water (150 mL) was added gradually with stirring, and more ice was added as needed to keep the reaction at or below 20 °C. The solution was stirred for 20 min after completing the addition, acidified with concentrated HCl (400 mL), and cooled to 10 °C with an ice/acetone bath. Aqueous sodium hypochlorite ("Chlorox"; 750 mL, 0.5 mol) was then added dropwise with rapid mechanical stirring. The product was filtered out, washed with water, and air-dried for several hours to give 78.5 g (81.8%) of colorless solid. An analytical sample was recrystallized from methylene chloride/hexane to give colorless crystals with mp 105–108 °C: IR (Nujol) 3300, 3100, 1750, 1660, and 1570 cm^{-1}; NMR ($CDCl_3$) 1.44 (s, 9 H), 2.43 (s, 3 H), 4.73 (s, 1 H), and 6.4 (broad, NH) ppm; mass spectrum, m/e 57 (100) and 191 (M^+).

Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; Cl, 18.50; N, 7.31. Found: C, 50.31; H, 7.44; Cl, 18.44; N, 7.17.

Condensation of Cyanoacetone Sodium Enolate with Compound 17. Preparation of 18, 19, and 20. A mixture of **17** (19.2 g, 0.1 mol) and cyanoacetone sodium enolate (10.5 g, 0.1 mol) in water (100 mL) was heated on the steam bath. Addition of sodium bicarbonate (10 g) led to the formation of a clear brown solution. Heating was continued for 1 h, during which time small amounts of solid material subliming on the flask wall were washed back in with a little ethanol (6 mL). Pale yellow platelets of 2-amino-3-acetyl-4-(*N*-*tert*-butylcarboxamide)-5-methylfuran (**18**) separated upon chilling. These were collected, washed with water, and air-dried to give 2.1 g (8.8%) of **18**. A sample recrystallized from aqueous ethanol had mp 63–67 °C: IR ($CHCl_3$) 3480, 3425, 3340, 1645, 1585, and 1510 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) 1.47 (s, 9 H), 2.33 (s, 3 H), 2.37 (s, 3 H), and 6.8 (broad, 3 H, NH) ppm; mass spectrum, m/e 43, 137, 165 (100), and 238 (M^+).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.41; H, 7.73; N, 11.56.

The filtrate was acidified with 3 N HCl, causing a gum to separate. After stirring at room temperature for 4 days, this material was taken up in methylene chloride and chromatographed on 130 g of silica gel. Elution with methylene chloride gave compounds **19** and **20**. Recrystallization of the fractions rich in **19** from aqueous ethanol gave 1.15 g (5.2%) of 1-*tert*-butyl-2-hydroxy-3-acetyl-4-cyano-5-methylpyrrole (**19**). A sample recrystallized from aqueous ethanol had mp 83–85 °C: IR (Nujol) 3100, 2215, 1640, and 1570 cm^{-1}; NMR ($CDCl_3$) 1.62 (s, 9 H), 2.40 (s, 3 H), 2.50 (s, 3 H), and 13.4 (broad, OH) ppm; mass spectrum, m/e 57, 146, 164 (100), and 220 (M^+).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 64.68, H, 7.03; N, 12.47.

Recrystallization of the fractions rich in **20** from aqueous ethanol gave 450 mg (2.7%) of 2-hydroxy-3-acetyl-4-cyano-5-methylfuran as colorless crystals with mp 130–132 °C (a diamorph with mp 148–150 °C was also obtained): IR ($CHCl_3$) 3100 (broad), 2230, 1725, and 1635 cm^{-1}; NMR ($CDCl_3$) 2.33 (s, 3 H), 2.38 (s, 3 H), and 10.97 (s, OH) ppm; mass spectrum, m/e 43 (100) and 165 (M^+).

Anal. Calcd for $C_8H_7NO_3$: C, 58.19; H, 4.27; N, 8.48. Found: C, 58.14; H, 4.36; N, 8.58.

Further elution of the column gave a viscous syrupy material.

***N,N*-Dimethyl-2-chloroacetoacetamide (21).** Diketene (42 g, 0.5 mol) was mixed with ice and water (200 mL) and treated with 25% aqueous dimethylamine (90 mL). On completion of the addition, the solution was allowed to warm to room temperature and stirred for 30 min. It was then cooled with an ice bath, acidified with concentrated HCl (250 mL), and treated with aqueous sodium hypochlorite ("Chlorox"; 800 mL) by rapid dropwise addition. After warming to room temperature, the resulting mixture was extracted three times with 400-mL portions of methylene chloride. After drying and evaporation of solvent, the product was vacuum distilled to give 67.65 g (83%) of pale yellow liquid with bp 97–98 °C (0.05 mm): IR (film) 1730 and 1645 cm^{-1}; NMR ($CDCl_3$) 2.40 (s, 3 H), 3.03 (s, 3 H), 3.20 (s, 3 H), and 5.30 (s, 1 H) ppm; mass spectrum, *m/e* 43 and 163 (M^+).

Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16, Cl, 21.67; N, 8.56. Found: C, 44.31; H, 6.29, Cl, 21.73; N, 8.66.

2-Hydroxy-3-acetyl-4-cyano-5-methylfuran (20). A solution of compound **21** (3.28 g, 0.02 mol) in methanol (10 mL) was treated with the sodium enolate of cyanoacetone (2.1 g, 0.02 mol) and heated on a steam bath for 10 min. It was then cooled and acidified with 3 N HCl. After standing at room temperature for 20 h, the crystals of **20** were collected, washed with cold water, and air-dried. This crop of 2 g, together with a second crop, gave 2.2 g (66.7%) of the higher melting diamorph with mp 148–150 °C. Identity with the sample obtained previously was established by IR and mass spectra and TLC.

Crystallography. Crystals of compound **4** for structure analysis were grown from aqueous ethanol. The crystal data were as follows: space group Ia; a = 7.488 Å; b = 15.297 Å; c = 7.071 Å; β = 97.05°; Z = 4; d_{calcd} = 1.356 g/cm^3; and μ (Cu Kα) = 8.5 cm^{-1}.

The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation; θ–2θ scans; pulse height discrimination). The size of the crystal used for data collection was approximately 0.05 × 0.08 × 0.45 mm; the data were not corrected for absorption. Of the 822 accessible reflections for $\theta < 76°$, 638 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[8] and refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.040 and R_w = 0.038 for the 638 observed reflections. The final difference map had no peaks greater than ±0.2 eA^{-3}.

The C–N and C=O bond lengths of the amino and ketone functions, assumed on the basis of the very weak basicity of **4** to be involved in a resonance interaction, are 1.32 and 1.23 Å, respectively.

Acknowledgment. The interest and suggestions provided by Dr. Willy Leimgruber are greatly appreciated.

Registry No.—**1,** 5765-44-6; **2,** 7064-36-0; **3** ketone form, 60930-76-9; **3** enol form, 67271-59-4; **4,** 67271-60-7; **6,** 67271-61-8; **7,** 609-15-4; **8,** 1694-29-7; **9,** 67271-62-9; **10,** 67271-63-0; **11,**67271-64-1; **12,** 67271-65-2; **13,** 4439-88-7; **14,** 67271-66-3; **15,** 67271-67-4; **16,** 67271-81-2; **17,** 67271-68-5; **18,** 67271-69-6; **19,** 67271-70-9; **20,** 67271-71-0; **21,** 5810-11-7; cyanoacetone sodium enolate, 67271-72-1; ammonia, 7664-41-7; diketene, 674-82-8; *tert*-butylamine, 75-64-9; dimethylamine,124-40-3.

Supplementary Material Available: Final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles of **4** (Tables I–IV, respectively) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) H. Dahn and H. Hauth, *Helv Chim. Acta,* **47,** 1424 (1964).
(2) L. Claisen, *Chem. Ber.,* **25,** 1776 (1892).
(3) Simple aminofurans are rare; see, for example, A. P. Dunlop and F. N. Peters, "The Furans", Reinhold, New York, N.Y., 1953, p 183.
(4) G. Westöö, *Acta Chem. Scand.,* **13,** 692 (1959).
(5) Cf. A. Quilico and R. Justoni, *Rend., R. Ist. Lomb. Sci. Lett.,* **69,** 587 (1936); *Chem. Abstr.,* **32,** 7455 (1938).
(6) J. A. Bilton and R. P. Linstead, *J. Chem. Soc.,* 922 (1937).
(7) K. Gewald, H. Jablokoff, and M. Hentschel, *J. Prakt. Chem.,* **317,** 861 (1975). See also O. Meth-Cohn and B. Narine, *J. Chem. Res. (S),* 294 (1977).
(8) G. Germain, P. Main, and M. M Woolfson, *Acta Crystallogr., Sect. A,* **27,** 368 (1971).
(9) Melting points are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137, Digilab FTS-14, and CEC-110B instruments. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our Microanalytical laboratory.
(10) R. Justoni, *Gazz. Chim. Ital.,* **71,** 41, 375 (1941).
(11) J. L. Mostek, U.S. Patent 2 434 507, 1948), to the Sinclair Refining Co.; *Chem. Abstr.,* **42,** 2615 (1948).

Cyclic Sulfamides: Synthesis of Some Fused Tetrahydrobenzo- and Tetra- and Dihydroheterothiadiazinone 2,2-Dioxides[1]

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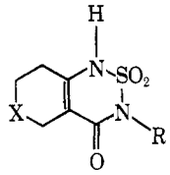
General methods for the synthesis of the title compounds (**1–3**) are described. The two key steps in these syntheses are the regiospecific sulfamoylation of primary enamino esters **9** and an acid-catalyzed ring closure procedure which offers distinct advantages over existing methods. Thus, the title compounds bearing bulky alkyl groups on N-3 are available in high yield from available β-keto esters.

In 1962 Cohen and Klarberg reported a new class of fused ring sulfamides, the 2,1,3-benzothiadiazin-4-one 2,2-dioxides.[2] The subsequent discovery that certain alkylated derivatives of this class of compounds possess uniquely selective phytotoxic properties[3] has made further synthesis in this area a relevent problem. This paper details general methods for the synthesis of some reduced and heterosubstituted reduced forms of these fused ring cyclic sulfamides, including the 5,6,7,8-tetrahydro-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxides **1**, the dihydro-2,1,3-thiopyranothiadiazin-4-one 2,2-dioxides **2**, and the tetrahydro-2,1,3-pyridothiadiazin-4-one 2,2-dioxides **3**.

Our initial synthetic efforts in this area involved attempted direct formation of the desired ring system by condensation



1, X = CH_2
2, X = S
3, X = N–R′

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