Functionalization of Substituted 2(1*H*)-Pyridones. V. The Synthesis of 1,2-Dihydro-2-oxo-3,5-pyridinedicarboxylic Acid Derivatives Through a Novel Dianion Route

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A new pyridone dianion was prepared by halogen-metal exchange from 5-bromo-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid, *t*-butyl ester and two equivalents of *n*-butyllithium. This 1,5-dianion readily reacted at C_5 with electrophiles. Quenching with carbon dioxide gave the previously unreported 1,2-dihydro-2-oxo-3,5-pyridine dicarboxylic acid, 3-*t*-butyl ester. The 5-carboxyl groups were selectively converted to the ethyl ester and the ethyl amide through the 5-imidazolide. The 3-*t*-butyl ester was easily removed from all derivatives with acid hydrolysis.

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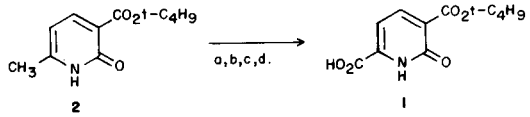
As part of our search for new pyridone side chains for β-lactam nuclei [1], we became particularly interested in certain pyridone diacids. The 1,6-dihydro-6-oxo-2,5-pyridinedicarboxylic acid (**1**) was prepared [2] with the 5-acid moiety selectively protected from the 6-methyl pyridone ester **2** (Equation 1) by employing some pyridone dianion chemistry initially developed by Hauser [3] and later extended for broader utility [4]. The unknown 1,2-dihydro-2-oxo-3,5-pyridinedicarboxylic acid **3** could not be obtained by such a route, and a new methodology involving a new pyridone dianion was required. The preparation and chemistry of this dianion **6** is the subject of this report.

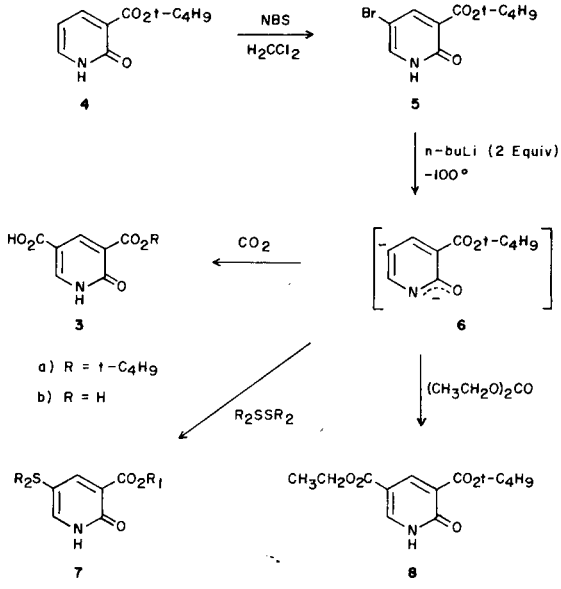


Eq. 1

a) 2 equivalents LDA; b) benzophenone;
c) $SOCl_2$, pyridine; d) O_3, H_2O_2

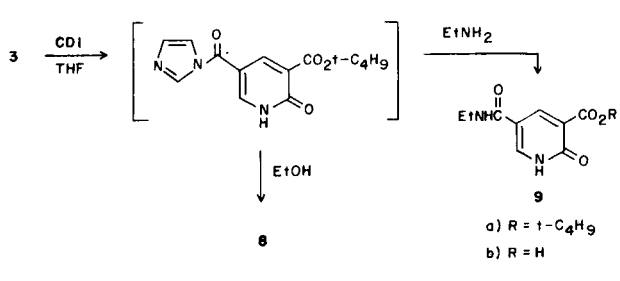
A direct carboxylation of the simple pyridone **4** (Scheme 1) was desired but formation of an anion at the electronegative 5-position of the 2-pyridone **4** was unknown. In fact, the ease of electrophilic addition at position 5 [5] of such pyridones suggested than an anion at this carbon would not be stable. Several initial attempts to form such an anion with *n*-butyllithium or *t*-butyllithium gave mixtures and tars, so a halogen-metal exchange was considered. When the pyridone **4** was treated with *N*- bromosuccinimide at room temperature, facile bromination occurred in good yield to give the 5-bromopyridone **5**. This bromopyridone **5** was treated with *n*-butyllithium at −78° and then quenched with deuterium oxide. Some incorporation of deuterium (~ 30%) at C_5 was observed, but the major reaction was decomposition from attack of both the *n*-butyllithium and the dianion itself with the *t*-butyl ester. Lowering the temperature to −100° (hexane, liquid nitrogen) resulted in clean and complete halogen-metal exchange to

Scheme 1



a) R_1 = t-C_4H_9, R_2 = $-CH_2CH_3$
b) R_1 = H, R_2 = $-CH_2CH_3$
c) R_1 = t-C_4H_9, R_2 = −Ph
d) R_1 = H, R_2 = −Ph

Scheme 2



the dianion **6**, which was quenched with deuterium oxide to give 96% incorporation of deuterium at C_5 in the recovered **4**. Quenching with dry carbon dioxide and warming to −35° gave the desired diacid **3** (75%) selectively protected at the C_3-carboxyl. The dianion **6** was also reacted with diethylcarbonate to give the diester **8** in 91% yield.

In an effort to prepare the 5-ethyl or phenyl sulfide derivatives of the pyridone **4** we initially attempted without success, to displace the 5-bromo substituent of **5** with the lithio salts of ethyl or phenyl mercaptans. When the dianion **6** was treated with ethyl or phenyl disulfide however, the desired 5-sulfides **7** were readily obtained.

Since the pyridone diacid **3** was protected at the 3-carboxyl as the *t*-butyl ester, derivatization at the C_5 carboxyl was easily achieved. Treatment of **3** with 1,1-carbonyldiimidazole in THF followed by ethylamine or ethanol gave the amide **9** or diester **8** in good yields (Scheme 2).

In all cases, the *t*-butyl ester was readily cleaved to the free acid with trifluoroacetic acid, or depending on the group at C_5, with aqueous acid hydrolysis.

This new dianion methodology employing the simple pyridone **4** should be a valuable synthetic alternative for the preparation of many other 5-substituted 2-pyridones, where the incoming group is an electrophile, since it eliminates the need for a 2-substituted-1,3-dialdehyde equivalent. The scope of this dianion chemistry is under investigation.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Beckman IR9 grating dispersion instrument. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian EM-390 or Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corporation B-NC12 data acquisition system. Chemical shifts are reported as δ values in ppm from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. Column chromatography was performed with E. Merck "Silica Gel 60," 70-230 mesh ASTM. Tetrahydrofuran (THF) was dried and distilled from sodium aluminum hydride just prior to use. Solutions were dried using magnesium sulfate and concentrated on a rotary evaporator at 30-45° at pressures of 10-20 mm. *n*-Butyllithium in heptane was from Foote Chemical Company and its activity was determined by titration [7]. All moisture sensitive reactions were carried out under dry nitrogen.

1,2-Dihydro-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**4**).

To 10 g (72 mmoles) of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid [6] in 150 ml of dry THF was added 23.3 g (2 equivalents) of 1,1-carbonyldiimidazole and the mixture was heated at 60° for three hours. Upon cooling the solids were filtered giving 11.12 g of the imidazolide which was used without purification. This imidazolide was added in portions to 1.0 ℓ of *t*-butanol containing 6.67 g (59 mmoles, 1.0 equivalents) of potassium *t*-butoxide. The mixture was heated to 50° for 48 hours. It was then concentrated, suspended in chloroform and extracted twice with water. The chloroform was dried and concentrated to give 10.1 g (92%) of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid, *t*-butyl ester, (**4**) as a white solid, mp 134-140° dec; ir: 3200, 1730, 1660, 1605, 1560 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (dd, J = 7 Hz, J = 2 Hz, 1H, Ar), 7.7 (dd, J = 7 Hz, J = 2 Hz, 1H, Ar), 6.4 (dd, J = 7 Hz, J = 7 Hz, 1H, Ar), 1.6 (s, 9H, C_4H_9).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.66; N, 7.18. Found: C, 61.21; H, 6.38; N, 7.25.

5-Bromo-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**5**).

To 10 g (51 mmoles) of **4** in 200 ml of dichloromethane was added 10.0 g (56 mmoles) of *N*-bromosuccinimide. The mixture was stirred at room temperature overnight. It was then extracted with water and concentrated to a light brown oil. Purification by column chromatography (chloroform 6:hexane 3:ethanol 1) gave 8.5 g (57%) of **5** as a white solid, mp 77-78°; ir: 2980, 1730, 1650, 1600, 1550 cm^{-1}; nmr (deuteriochloroform): δ 8.2 (d, J = 2 Hz, 1H, Ar), 8.1 (d, J = 2 Hz, 1H, Ar), 1.6 (s, 9H, C_4H_9).

Anal. Calcd. for $C_{10}H_{12}BrNO_3$: C, 43.79; H, 4.38; N, 5.11. Found: C, 43.99; H, 4.38; N, 4.77.

Preparation of the Dianion **6**. A General Procedure. Synthesis of 1,2-Dihydro-2-oxo-3,5-pyridinedicarboxylic Acid, 5-*t*-Butyl Ester (**3a**).

To 3.0 g (10.9 mmoles) of **5** in 75 ml of dry THF was added at −100° (hexane, liquid nitrogen), 14.2 ml of 1.63 *N* *n*-butyllithium (2.1 equivalents), keeping the temperature below −90°. After six hours at −100° the mixture was treated with a stream of dry carbon dioxide for five hours, and was allowed to warm to −35° overnight. The mixture was poured over ice and saturated ammonium sulfate solution. It was extracted with chloroform which was dried and concentrated to give 1.95 g (75%) of **3a** as a white solid, mp 294-296° dec; ir: 3440, 1725, 1640, 1565 cm^{-1}; nmr (deuteriochloroform): δ 12.6 (s, 1H, CO_2H), 8.2 (d, J = 2 Hz, 1H, Ar), 8.1 (d, J = 2 Hz, 1H, Ar), 1.5 (s, 9H, C_4H_9).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.19; H, 5.29; N, 5.51.

The acid **3a** was also obtained in 60% yield by hydrolysis of the diester **8** with 2.0 equivalents of 2*N* sodium hydroxide in ethanol for 24 hours. The product obtained in this manner was identical to the material described above.

1,2-Dihydro-2-oxo-3,5-pyridinecarboxylic Acid (**3b**).

To 500 mg (2.1 mmoles) of the *t*-butyl ester **3a** was added 17 ml of acetic acid and 3 ml of 3*N* hydrocyhloric acid. The mixture was heated at 100° for two hours and diluted with water. Upon cooling the solids were filtered to give 0.33 g (85%) of **3b** as a tan powder, mp 323-325° dec; ir: 3200-2800 br, 1718, 1639, 1609 cm^{-1}; nmr (DMSO-d_6): δ 13.7 (s, br, 3H), 8.59 (d, J = 3 Hz, 1H, Ar), 8.39 (d, J = 3 Hz, 1H, Ar).

Anal. Calcd. for $C_7H_5NO_5$: C, 45.87; H, 2.73; N, 7.65. Found: C, 45.67; H, 2.89; N, 7.63.

1,2-Dihydro-2-oxo-3,5-pyridinecarboxylic Acid 3-*t*-Butyl, 5-Ethyl Diester (**8**).

Using the general procedure, 1.53 g (5.58 mmoles) of **5** was converted to the dianion **6**, which was treated with 4.0 g (6.1 equivalents) of diethylcarbonate. The general workup gave, after purification by column chromatography (chloroform 4:hexane 5:ethanol 1), 1.36 g (91%) of **8** as a white powder, mp 156-158°; ir: 1720, 1670, 1650 cm^{-1}; nmr (deuteriochloroform): δ 8.5 (d, J = 3 Hz, 1H, Ar), 8.35 (d, J = 3 Hz, 1H, Ar), 4.25 (q, J = 7 Hz, 2H, CH_2CH_3), 1.56 (s, 9H, C_4H_9), 1.35 (t, J = 7 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.43; H, 6.37; N, 5.24. Found: C, 58.22; H, 6.66; N, 4.90.

Alternatively **8** could be prepared from **3** by treatment with 2 equivalents of 1,1-carbonyldiimidazole in THF for two hours at 50°, followed by an excess of ethanol. The product obtained was identical in all respects to **8** described above.

5-Ethylthio-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid, (**7b**) and *t*-Butyl Ester (**7a**).

Following the general procedure 3.00 g (10.9 mmoles) of **5** was converted to the dianion **6** and was quenched with 1.99 ml (1.5 equivalents) of ethyldisulfide in 10 ml of THF. The general workup gave, after column purification (chloroform 3:hexane 6:ethanol 1) 1.99 g (75%) of **7b** as a faint yellow low melting slightly impure solid, ir: 3240, 1730, 1645, 1595 cm^{-1}; nmr (deuteriochloroform): δ 8.2 (d, J = 3 Hz, 1H, Ar), 8.05 (d, J = 3

Hz, 1H, Ar), 2.8 (q, J = 7 Hz, 2H, CH_2CH_3), 1.6 (s, 9H, C_4H_9), 1.3 (t, J = 7 Hz, 3H, CH_2CH_3).

This material was dissolved in 50 ml of dichloromethane, 1 ml of dimethoxybenzene and 1.0 ml of trifluoroacetic acid. After two hours at 0°, the mixture was brought to room temperature and concentrated. The residue was treated with 25 ml of ether:pentane 1:1 and the solids that formed were filtered and dried to give 1.25 g (76% from **7b**) of **7a**, mp 199-201° dec; ir: 3490, 1730, 1630, 1590; nmr (DMSO-d_6): 8.4 (d, J = 2 Hz, 1H, Ar), 8.1 (d, J = 2 Hz, 1H, Ar), 2.85 (q, J = 9 Hz, 2H, CH_2CH_3), 1.2 (t, J = 9 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_8H_9NO_3S$: C, 48.24; H, 4.52; N, 7.04. Found: C, 47.93; H, 4.58; N, 6.76.

1,2-Dihydro-2-oxo-5-phenylthio-3-pyridinecarboxylic Acid (**7d**) and *t*-Butyl Ester (**7c**).

Following the general procedure 3.00 g (10.9 mmoles) of **5** was converted to the dianion **6** and was quenched with 2.61 g (1.1 equivalents) of phenyldisulfide. The general workup gave, after recrystallization from hexane-chloroform (12:1) 2.88 g (87%) of **7c** as a faint yellow solid, mp 166-167°; ir: 3460, 1740, 1650, 1600, 1585, 1555; nmr (deuteriochloroform): δ 8.15 (d, J = 2 Hz, 1H, Ar), 8.05 (d, J = 2 Hz, 1H, Ar), 7.15 (s, 5H, phenyl), 1.55 (s, 9H, C_4H_9).

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.00; H, 5.80; N, 4.73.

This material was treated with trifluoroacetic acid as in the preparation of **7b**, and gave 2.0 g (85% from **7d**) of the acid **7c** as a pale yellow solid, mp 236-240 dec; ir: 3450, 3050, 1735, 1625, 1590, 1540 cm^{-1}; nmr (DMSO-d_6): δ 13.7 (s, 1H, O*H*), 8.1 (m, 2H, Ar), 7.2 (s, 5H, phenyl).

Anal. Calcd. for $C_{12}H_8NO_3S$: C, 58.30; H, 3.64; N, 5.67. Found: C, 57.89; H, 3.81; N, 5.40.

5-[(Ethylamino)carbonyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**9b**) and *t*-Butyl Ester (**9a**).

To 2.0 g (8.36 mmoles) of the acid **3** was added 50 ml of dry THF and 5 ml of dry *N,N*-dimethylformamide. The mixture was heated to 50° for three hours and cooled. The solids were filtered and quickly treated with a mixture of 3 ml of anhydrous ethylamine in 50 ml of dichloromethane. The reaction was stirred for one hour at 25° and was then extracted twice with water. The dichloromethane was dried and concentrated to give a crude white solid. This material was purified by column chromatography (chloroform 9:ethanol 1) to give 1.75 g (79%) of **9a** as a white solid: mp 102-110° dec; ir: 3300, 1730, 1640, 1545 cm^{-1}; nmr (deuteriochloroform): δ 8.5 (d, J = 2 Hz, 1H, Ar), 8.4 (d, J = 2 Hz, 1H, Ar), 7.5 (t, J = 5 Hz, 1H, N*H*CH_2CH_3), 3.5 (m, 2H, CH_2CH_3), 1.5 (s, 9H, C_4H_9), 1.3 (t, J = 7 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.65; H, 6.77; N, 10.53. Found: C, 58.35; H, 6.79; N, 10.74.

This material was dissolved in 75 ml of dichloromethane, 1.5 ml of dimethoxy benzene and 2.0 ml of trifluoroacetic acid at 0°. After two hours, the mixture was concentrated and the solids triturated with ether:pentane (1:1) to give 1.31 g (94%) of the acid **9b** as a white solid, mp 284-285°; ir: 3330, 1725, 1640, 1550 cm^{-1}; nmr (DMSO-d_6): δ 13.3 (s, 1H, O*H*), 8.9 (d, J = 2 Hz, 1H, Ar), 8.7 (t, J = 6 Hz, 1H, N*H*CH_2CH_3), 8.45 (d, J = 2 Hz, 1H, Ar), 3.3 (m, 2H, CH_2CH_3), 1.15 (t, J = 6 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.33; H, 4.88; N, 13.10.

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