Triacetic Acid Lactone as a Common Intermediate for the Synthesis of 4-Hydroxy-2-pyridones and 4-Amino-2-pyrones

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-pyrone
Triacetic acid lactone
Amine
4-amino-2-pyrones
4-hydroxy-2-pyridones

ABSTRACT

At ambient temperature, triacetic acid lactone reacts with amines to produce 4-amino-2-pyrones. If the temperature is raised to 100 °C, 4-hydroxy-2-pyridones are generated.

Triacetic acid lactone (**1**) is readily available either through the acid catalyzed deacetylation of dehydroacetic acid or through microbial transformation of glucose.[1] It is a useful intermediate for the synthesis of penstyrylpyrone (**3**)[2] and pogostone (**4**)[3], shown in Figure 1. A related synthetic compound PH797804 (**5**)[4] is a potent p38 MAPK inhibitor. As part of a program to expand the potential of **1** as a platform chemical[5], we studied the reaction of **1** and its tosylate **2** with amines. A number of groups have reported limited studies of **1** with primary amines and with glycine.[6-10]

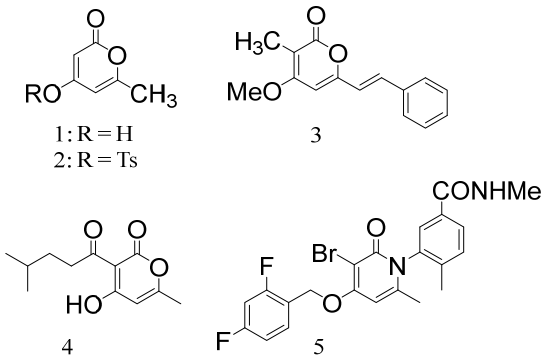
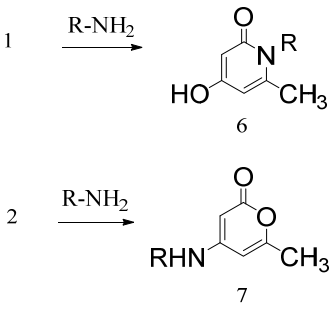


Figure 1. Triacetic acid lactone derivatives

Reaction of 1.1 equivalents of a primary amine with **1** at 100 °C in water afforded 2-pyridones **6**, as shown in Scheme 1. The structure assignment of **6a** was supported by a shift in the NMR resonance of the methyl group at C-6 and by a strong NOE interaction between the methyl group at C-6 and the methylene of the ethyl group.



Scheme 1. Reaction with amines

The products of primary amines with **1** are shown in Figure 2. Both aliphatic and aromatic amines react with **1**. The pyridones **6a-6g** were polar solids whose insolubility made them difficult to purify by silica gel chromatography.[19] Fortunately, the pyridones were readily separable from **1** by differential solubility in ethyl acetate.

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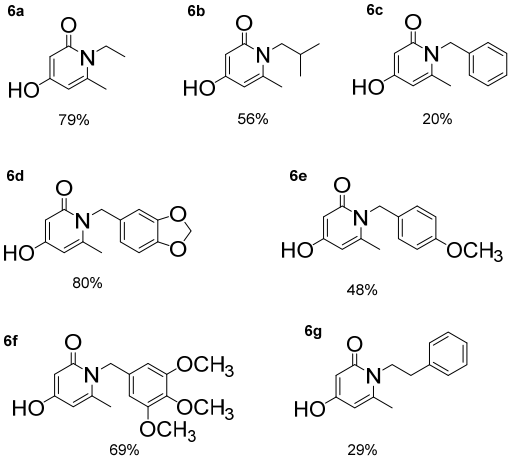


Figure 2. Pyridone derivatives

In contrast to the reactivity of **1**, tosylate **2**[18] reacted with amines at C-4 (Method A). Adducts **7a**-**7d** were not as polar as the pyridones.[20] A slight shift of the chemical shifts of the hydrogens at C-3 and C-5 plus the strong NOE interaction between the hydrogens at C-3 and C-5 with the methylene in **7a** supported the structure assignments.

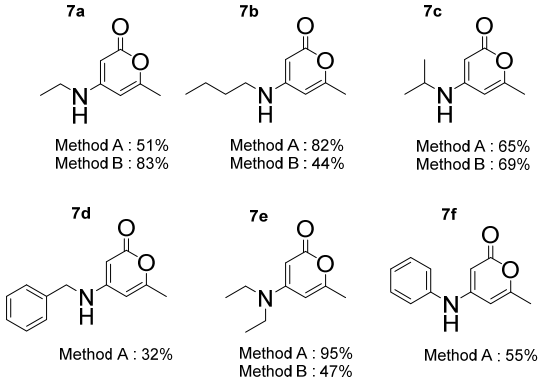
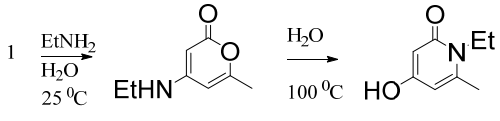


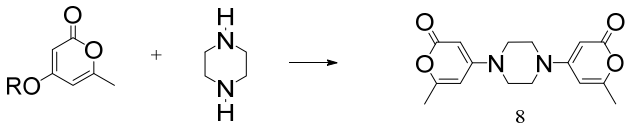
Figure 3. 4-amino-2-pyrone derivatives

We subsequently found that **1** reacted with amines *at ambient temperature* in water to form **7** (Method B). We attribute the remarkable chemoselectivity of this addition to the rapid reaction of the amine with the keto tautomer at C-4. When **7a** was boiled in water, **6a**, likely the thermodynamic product, was isolated in 35% yield.



Scheme 2. Reaction with amines at ambient temperature and 100 ^{0}C

We also examined the reactions with diamines. As shown in Scheme 3, the reaction of tosylate **2** with piperazine afforded the 2:1 adduct **8** in 21% yield.[21] Later, we found that simply mixing two equivalents of **1** with piperazine at ambient temperature in water afforded a cleaner product.



Scheme 3. Reaction with diamines

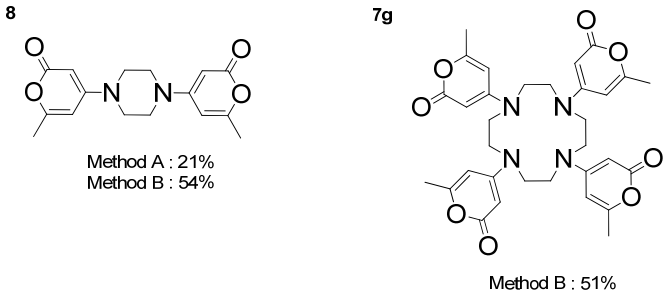


Figure 4. Products with diamine and tetramine

Triacetic acid lactone constitutes a useful platform for the direct introduction of nitrogen functionality. The reactions proceed in good yields and are operationally convenient. The extension to the reactions of **1** or **2** with diamines and tetramines leads rapidly to new materials.[22]

Acknowledgments

We thank the NSF Engineering Center for Biorenewable Chemicals (CBiRC) which was awarded NSF grant EEC-0813570 for support of this research. Jashaun Bottoms, an undergraduate at Tuskegee University, was a 2015 CBiRC REU participant.

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18. Experimental procedure for the synthesis of *6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate* (**2**) (96%) colorless solid: 4-Hydroxy-6-methyl-2H-pyran-2-one (triacetic acid lactone, **1**) (0.63 g, 5 mmol) and tosyl chloride (0.955 g, 5 mmol) was dissolved in CH_2Cl_2 (37.5 mL). Triethylamine (2.05 mL, 15 mmol) was added and the reaction mixture was left stirring at rt. overnight (23 h). CH_2Cl_2 (50 mL) was added and the organic phase was washed with water (25 mL) and brine (25 mL). The organic phase was dried over MgSO4. After concentration in vacuo the crude product was purified by column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the desired product.[11] Rf = 0.18 (silica gel, hexanes/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.82 (d, 2H), 7.37 (d, 2H), 6.00 (s, 1H), 5.80 (s, 1H), 2.45 (s, 3H), 2.23 (s, 3H) ppm.
19. Representative procedure for the preparation of pyridones **6a-6g**: A mixture of triacetic acid lactone (**1**) (0.5 g, 3.96 mmoL, 1 eq) and primary amine (4.35 mmoL, 1.1 eq) in water (2.5 mL) was heated to 100 ^{0}C overnight. After completion of the reaction (TLC monitoring), the reaction mixture was cooled down and the precipitate was filtered and washed with ethyl acetate and dried under vacuum to obtain the desired product.[12]
1-ethyl-4-hydroxy-6-methylpyridin-2(1H)-one (**6a**) (79%) Light brown solid: mp 240-242 ^{0}C (Lit. 247 ^{0}C) [6]; Rf = 0.16 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.92 (d, 1H), 5.72 (d, 1H), 4.05 (q, 2H), 2.39 (s, 3H), 1.24 (t, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.74, 164.21, 145.70, 100.64 (2C), 37.09, 17.14, 11.18 ppm; LRMS (ESI-QTOF) calcd for $C_8H_{12}NO_2$ [*M* + H]$^+$ 154.0868, found 154.0872.
4-hydroxy-1-isobutyl-6-methylpyridin-2(1H)-one (**6b**) (56%) Light brown solid: mp 173-175 ^{0}C; Rf = 0.35 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.92 (d, 1H), 5.73 (d, 1H), 3.85 (d, 2H), 2.37 (s, 3H), 2.26-2.05 (m, 1H), 1.04-0.80 (m, 6H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.41, 164.67, 146.18, 100.54, 94.73, 48.51, 26.18, 17.90, 17.20 (2C) ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{16}NO_2$ [*M* + H]$^+$ 182.1181, found 182.1191.
1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (**6c**) (20%) White solid: mp 219-220 ^{0}C (Lit. 217 ^{0}C) [6]; Rf = 0.30 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 7.33 (m, 2H), 7.27 (m, 1H), 7.11 (m, 2H), 5.97 (d, 1H), 5.82 (d, 1H), 5.32 (s, 2H), 2.25 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{13}H_{14}NO_2$ [*M* + H]$^+$ 216.1025, found 216.1040. ^{13}C NMR data agreed with the literature.[14]
1-(benzo[1,3]dioxol-5-ylmethyl)-4-hydroxy-6-methylpyridin-2(1H)-one (**6d**) (80%): mp 206-209 ^{0}C; Rf = 0.30 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 6.76 (s, 1H), 6.72 (d, 1H), 6.69 (d, 1H), 5.94 (s, 2H), 5.92 (d, 1H), 5.68 (d, 1H), 5.13 (s, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ = 163.85, 155.28, 147.80, 146.57, 145.65, 133.25, 120.72, 108.65, 108.58, 101.35, 101.30, 99.40, 45.55, 20.37 ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{14}NO_4$ [*M* + H]$^+$ 260.0923, found 260.0932.
4-hydroxy-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one (**6e**) (48%) White solid: mp 221-225 ^{0}C; Rf = 0.24 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 7.27 (d, 2H), 7.07 (d, 2H), 5.86 (d, 1H), 5.50 (d, 1H), 5.19 (s, 2H), 3.77 (s, 3H), 2.20 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{16}NO_3$ [*M* + H]$^+$ 246.1130, found 246.1142. ^{13}C NMR data agreed with the literature.[15]
4-hydroxy-6-methyl-1-(3,4,5-trimethoxybenzyl)pyridin-2(1H)-one (**6f**) (69%) Light yellow solid: mp 251-255 ^{0}C; Rf = 0.11 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 6.43 (s, 2H), 5.97 (d, 1H), 5.82 (d, 1H), 5.26 (s, 2H), 3.80 (s, 6H), 3.76 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 163.37, 159.92, 151.91, 132.02 (2C), 131.43, 115.89, 101.54 (2C), 100.73, 94.46, 58.12, 53.55 (2C), 45.61, 17.52 ppm; LRMS (ESI-QTOF) calcd for $C_{16}H_{20}NO_5$ [*M* + H]$^+$ 306.1341, found 306.1347.
4-hydroxy-6-methyl-1-phenethylpyridin-2(1H)-one (**6g**) (29%) White solid: mp 244-247 ^{0}C (Lit. 252 ^{0}C) [6]; Rf = 0.34 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 7.35-7.14 (m, 5H), 5.85 (d, 1H), 5.77 (d, 1H), 4.17 (t, 2H), 2.97 (t, 2H), 2.12 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{16}NO_2$ [*M* + H]$^+$ 230.1181, found 230.1173. NMR data agreed with the literature.[16]
20. Representative procedure for the preparation of 4-aminopyrones **7a-7f**:
Method A: A mixture of 6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate (2) (0.08 g, 0.3 mmoL, 1 eq) and amine (0.66 mmoL, 2.2 eq) in ethanol (4 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product. **Method B**: A mixture of triacetic acid lactone **(1)** (0.17 g, 1.4 mmoL, 1 eq) and amine (1.54 mmoL, 1.1 eq) in water (1.5-2 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product.
4-(ethylamino)-6-methyl-2H-pyran-2-one (**7a**) (Method A: 51%, Method B: 83%) Colorless liquid: Rf = 0.11 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.92 (s, 1H), 5.72 (s, 1H), 3.32 (m, 2H), 2.39 (s, 3H), 1.24 (t, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 163.68, 157.62, 152.78, 97.77, 89.99, 35.12, 27.46, 16.60 ppm; LRMS (ESI-QTOF) calcd for $C_8H_{12}NO_2$ [*M* + H]$^+$ 154.0868, found 154.0871.
4-(butylamino)-6-methyl-2H-pyran-2-one (**7b**) (Method A: 82%, Method B: 44%) White solid: mp >260 ^{0}C; Rf = 0.24 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.75 (s, 1H), 4.86 (s, 1H), 2.93 (m, 2H), 1.64 (m, 2H), 1.41 (m, 2H), 0.93 (t, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 160.55, 160.06, 154.39, 102.35, 85.08, 42.10, 37.52, 18.34, 18.01, 11.06 ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{16}NO_2$ [*M* + H]$^+$ 182.1181, found 181.1176.
4-(isopropylamino)-6-methyl-2H-pyran-2-one (**7c**) (Method A: 65%, Method B: 69%) White solid: mp >260 ^{0}C; Rf = 0.13 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.76 (s, 1H), 5.21 (s, 1H), 3.63 (m, 1H), 2.13 (s, 3H), 1.20 (d, 6H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.87, 158.99, 156.69, 97.95, 76.32, 41.94, 19.01 (2C), 16.63 ppm; LRMS (ESI-QTOF) calcd for $C_9H_{14}NO_2$ [*M* + H]$^+$ 168.1025, found 168.1030.
4-(benzylamino)-6-methyl-2H-pyran-2-one (**7d**) (Method A: 32%) White solid: mp 126-130 ^{0}C; Rf = 0.43 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 7.41 – 7.17 (m, 5H), 5.90 (s, 1H), 4.94 (s, 1H), 4.33 (d, 2H), 2.15 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{13}H_{14}NO_2$ [*M* + H]$^+$ 216.1025, found 216.1034. ^{13}C NMR data agreed with the literature.[17]
4-(diethylamino)-6-methyl-2H-pyran-2-one (**7e**) (Method A: 95%, Method B: 47%) Yellow solid: mp 96-98 ^{0}C; Rf = 0.30 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.80 (d, 1H), 4.99 (d, 1H), 3.41 (q, 4H), 2.21 (s, 3H), 1.19 (t, 6H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.56, 160.24, 156.37, 94.74, 77.67, 42.67 (2C), 17.09 (2C), 16.63 ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{16}NO_2$ [*M* + H]$^+$ 182.1181, found 182.1189.
6-methyl-4-(phenylamino)-2H-pyran-2-one (**7f**) (Method A: 55%) White solid: mp 192-195 ^{0}C (Lit. 195-196 ^{0}C) [13]; Rf = 0.43 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Acetone-*d*$_6$) δ = 7.48 – 7.36 (m, 2H), 7.32 – 7.14 (m, 3H), 5.95 (d, 1H), 5.27 (d, 1H), 2.14 (s, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.54, 160.18, 156.21, 141.31, 127.65 (2C), 123.91, 121.73 (2C), 97.47, 79.47, 16.84 ppm; LRMS (ESI-QTOF) calcd for $C_{12}H_{12}NO_2$ [*M* + H]$^+$ 202.0868, found 202.0879.
21. Experimental procedure for the preparation *of 4,4'-(piperazine-1,4-diyl)bis(6-methyl-2H-pyran-2-one)* (**8**) (Method A: 21%, Method B: 54%) white solid : **Method A**: A mixture of 6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate (2) (0.1 g, 0.36 mmoL, 2 eq) and piperazine (0.18 mmoL, 1 eq) in ethanol (8 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product. **Method B**: A mixture of triacetic acid lactone **(1)** (0.15 g, 1.2 mmoL, 2 eq) and piperazine (0.6 mmoL, 1 eq) in water (1.5 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product: Rf = 0.13 (silica gel, CH_2Cl_2/EtOAc 7:1); ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ = 5.77 (s, 2H), 4.86 (s, 2H), 3.11 (s, 8H), 2.14 (s, 6H) ppm; ^{13}C NMR (400 MHz, Methanol-*d*$_4$) δ = 179.72 (2C), 169.40 (2C), 161.39 (2C), 105.51 (2C), 87.39 (2C), 42.94 (4C), 18.22 (2C) ppm; LRMS (ESI-QTOF) calcd for $C_{16}H_{19}N_2O_4$ [*M* + H]$^+$ 303.1345, found 303.1347.
22. Experimental procedure for the preparation of *4,4',4'',4'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(6-*

methyl-2H-pyran-2-one) (**7g**) (51%) White solid: A mixture of triacetic acid lactone **(1)** (0.14 g, 1.1 mmoL, 4 eq) and cyclen (0.047 g, 0.27 mmoL, 1 eq) in water (2 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product: Rf = 0.14 (silica gel, CH_2Cl_2/EtOAc 7:1); ^{1}H NMR (400 MHz, Methanol-d_4) δ = 5.67 (s, 4H), 5.03 (s, 4H), 2.92 (s, 16H), 2.05 (s, 12H) ppm; ^{13}C NMR (400 MHz, Methanol-d_4) δ = 179.97 (4C), 169.46 (4C), 161.35 (4C), 105.68 (4C), 87.34 (4C), 43.16 (8C), 18.22 (4C) ppm.