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

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Triacetic acid lactone (1) is readily available either through the acid catalyzed deacetylation of dehydroacetic acid or through microbial transformation of glucose. It is a useful intermediate for the synthesis of penstyrylpyrone (3) and pogostone (4), shown in Figure 1. A related synthetic compound PH797804 (5) is a potent p38 MAPK inhibitor. As part of a program to expand the potential of 1 as a platform chemical, 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.

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.

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](image)

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. Fortunately, the pyridones were readily separable from 1 by differential solubility in ethyl acetate.

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Figure 1. Triacetic acid lactone derivatives
In contrast to the reactivity of 1, tosylate 2\textsuperscript{18} reacted with amines at C-4 (Method A). Adducts 7a-7d were not as polar as the pyridones.\textsuperscript{20} A slight shift of the chemical shifts of the supported the structure assignments. Between 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.

In Scheme 3, the reaction of tosylate in water, of the amine with the keto tautomer at C-4. When reacted with amines at ambient temperature in 35% yield. 21 Later, we found that simply mixing with piperazine afforded the, likely the thermodynamic product, was isolated in 21% yield. 21 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.\textsuperscript{21} Later, we found that simply mixing two equivalents of 1 with piperazine at ambient temperature in water afforded a cleaner product.

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.\textsuperscript{22}

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References


Experimental procedure for the synthesis of 6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate (2) (90%) colorless solid: 4-Hydroxy-6-methyl-2H-pyran-2-one (triacetic acid lactone, T) (0.63 g, 5 mmol) and tosyl chloride (0.955 g, 5 mmol) was dissolved in CH2Cl2 (37.5 mL). Triethylamine (2.05 mL, 15 mmol) was added and the reaction mixture was left stirring at rt. overnight (23 h). CH2Cl2 (50 mL) was added and the organic phase was washed water (25 mL) and brine (25 mL). 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.17

RF = 0.18 (silica gel, hexanes/ EtOAc 3:1); 1H 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; LRMS (ESI-QTOF) calcd for C14H14NO4 [M+H]+ 216.1025, found 216.1024.

Representative procedure for the preparation of pyridines 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°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°C (Lit. 247°C) 18; RF = 0.16 (silica gel, CH2Cl2/ EtOAc 1:1); 1H NMR (300 MHz, Chloroform-d) δ = 8.40 (d, 1H), 7.52 (d, 1H), 4.05 (q, 2H), 2.39 (3H, 1H), 1.24 (3H, 3H) ppm; 13C NMR (126 MHz, Methanol-d4) δ = 165.74, 164.21, 145.70, 100.64 (2C), 37.09, 17.14, 11.18 ppm; LRMS (ESI-QTOF) calcd for C10H16NO2 [M+H]+ 182.1181, found 182.1191.

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (6b) (56%) Light brown solid; mp = 173-175°C; RF = 0.35 (silica gel, CH2Cl2/CH3OH 1:1); 1H NMR (300 MHz, Methanol-d4) δ = 7.35 (d, 2H), 7.31 (d, 2H), 5.97 (s, 1H), 4.94 (s, 1H), 4.33 (d, 2H), 2.15 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for C14H16NO2 [M+H]+ 260.0923, found 260.0927.

4-hydroxy-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one (6c) (29%) White solid: mp = 192-202°C (Lit. 197°C) 19; RF = 0.30 (silica gel, CH2Cl2/ EtOAc 1:1); 1H NMR (300 MHz, Methanol-d4) 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 C16H18NO3 [M+H]+ 286.1209, found 286.1208.

4-hydroxy-1-(4-isopropylbenzyl)-6-methylpyridin-2(1H)-one (6d) (48%) White solid: mp = 221-225°C (Lit. 223°C) 20; RF = 0.24 (silica gel, CH2Cl2/ EtOAc 1:1); 1H NMR (300 MHz, Methanol-d4) δ = 7.22 (d, 2H), 7.07 (d, 2H), 5.86 (d, 1H), 5.50 (d, 1H), 5.19 (s, 2H), 3.77 (s, 3H), 2.20 (3H, s) ppm; LRMS (ESI-QTOF) calcd for C16H18NO3 [M+H]+ 246.1130, found 246.1142. 13C NMR data agreed with the literature.21

1-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(6-methyl-2H-pyran-2-one) (6e) (60%) Yellow solid; mp = 170-172°C (Lit. 170-172°C) 14; RF = 0.43 (silica gel, CH2Cl2/CH3OH 1:1); 1H NMR (300 MHz, Methanol-d4) 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 C16H18NO3 [M+H]+ 182.1181, found 182.1191.

4-hydroxy-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one (6f) (69%) Light yellow solid; mp = 251-255°C; RF = 0.11 (silica gel, CH2Cl2/ EtOAc 1:1); 1H NMR (300 MHz, Methanol-d4) δ = 6.63 (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; 13C NMR (126 MHz, Methanol-d4) δ = 163.37, 159.02, 151.91, 132.02 (2C), 131.43, 115.89, 101.54 (2C), 100.73, 94.46, 52.18, 53.55 (2C), 53.61, 17.52 ppm; LRMS (ESI-QTOF) calcd for C16H18NO3 [M+H]+ 260.0932, found 260.0932.

4-hydroxy-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one (6g) (29%) White solid: mp = 244-247°C (Lit. 252°C) 21; RF = 0.34 (silica gel, CH2Cl2/ EtOAc 1:1); 1H NMR (300 MHz, Methanol-d4) δ = 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 C16H18NO3 [M+H]+ 306.1347, found 306.1347.

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.
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, CHCl3/EtOAc 7:1); 'H NMR (400 MHz, Methanol-d4) δ = 5.67 (s, 4H), 5.03 (s, 4H), 2.92 (s, 16H), 2.05 (s, 12H) ppm; 13C NMR (400 MHz, Methanol-d4) δ = 179.97 (4C), 169.46 (4C), 161.35 (4C), 105.68 (4C), 87.34 (4C), 43.16 (8C), 18.22 (4C) ppm.