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Abstract
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Keywords
2-pyrene, Triacetic acid lactone, Amine, 4-amino-2-pyrones, 4-hydroxy-2-pyridones

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

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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.

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.

![Figure 1. Triacetic acid lactone derivatives](image)

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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 amines at C-4 (Method A). Adducts 2:1 adduct T 21.4 reacted with piperazine afforded the 2:1 adduct 8 in 21% yield.\textsuperscript{21} 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**

18. Precipitate was filtered and washed with ethyl acetate and dried.

19. 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 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.12 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.

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 (15.2 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% (3%); Colorless liquid: LRMS (ESI-QTOF) calcd for C10H16NO2 [M + H]+ 182.1181, found 182.1181.

4-(butylamino)-6-methyl-2H-pyran-2-one (7b) (Method A: 82%); Method B: 44% White solid: mp >260°C; RF = 0.24 (silica gel, CHCl3/ EtOAc 1:1); 1H NMR (300 MHz, Methanol-d4) δ = 5.75 (s, 1H), 4.86 (s, 1H), 2.93 (m, 2H), 1.42 (m, 2H), 0.93 (s, 3H) ppm; 13C NMR (126 MHz, Methanol-d4) δ = 165.55, 156.50, 105.85, 154.39, 100.68, 105.68, 36.49, 28.83, 21.75 ppm; LRMS (ESI-QTOF) calcd for C13H21NO [M + H]+ 216.1025, found 216.1034. 13C NMR data agreed with the literature.17

4-(4-hydroxy-6-methyl-1-phenethylpyridin-2(1H)-one (6f) (Method A: 29%)
White solid: mp 126-130°C; RF = 0.43 (silica gel, CHCl3/ EtOAc 1:1); 1H NMR (300 MHz, Methanol-d4) δ = 5.75 (s, 1H), 4.94 (s, 1H), 4.33 (d, 2H), 2.15 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for C13H20NO5 [M + H]+ 306.1341, found 306.1342.
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); ¹H 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.