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# ACETALS AND KETALS OF 2-(2-PYRIDYL)PROPANE-1,3-DIOL NOVEL PROTECTION FOR CARBONYL GROUPS

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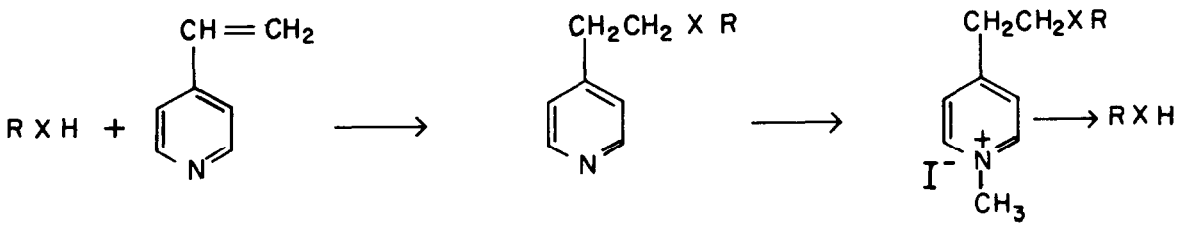
**Abstract**: Aldehydes and ketones are readily converted into the corresponding 1,3-dioxanes by treatment with 2-(2-pyridyl)propane-1,3-diol. The protective group is easily removed under mild base conditions after activation by quaternization with methyl iodide.

We have described the use of β-2- and β-4-pyridylethyl groups for the protection of OH[1], SH[2] and NH[3] functionality. In this work deprotection relied on the reverse Michael reaction which was rendered facile by quaternization at the pyridine N-atom (Scheme 1).

**Scheme I**



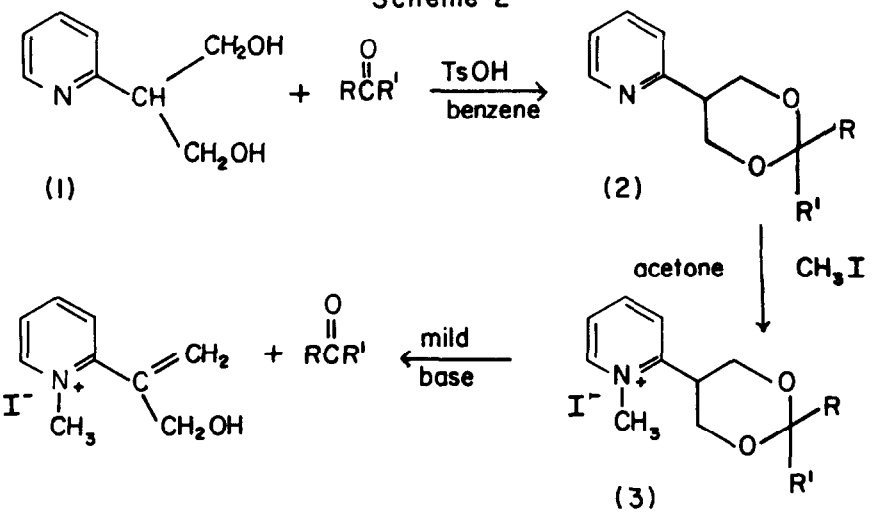

X = O, S, or NR

We reasoned that 5-(2- or 4-pyridyl)-1,3-dioxanes should undergo facile ring cleavage after quaternization because of the analogous reaction sequence shown in Scheme 2, and that this should provide a potentially novel method for the protection of carbonyl functionality. These speculations are now justified by the results reported in the present paper.

A variety of aldehydes and aliphatic ketones were readily converted into the corresponding 1,3-dioxanes (**2a**-**2o**) in good yields by 2-(2-pyridyl)propane-1,3-diol with p-toluenesulfonic acid catalysis as shown in Table 1. The 1,3-dioxanes thus prepared are a mixture of the two expected diastereoisomers as shown by their $^{13}C$ NMR[4] (except in the cases of symmetrical **2m** and **2n**).

Quaternization of the 5-(2-pyridyl)-1,3-dioxanes (**2a**-**2o**) with $CH_3I$ in acetone at 25°C afforded the corresponding pyridinium iodides (**3a**-**3o**), which were fully characterized by their $^{1}H$ and $^{13}C$ spectra[5], and by elemental analysis (Table 2).

Scheme 2




| | R | R' | | R | R' | | R | R' |
|---|---|---|---|---|---|---|---|---|
| a. | Ph | H | f. | m-$NO_2C_6H_4$ | H | k. | $PhCHCH_3$ | H |
| b. | p-$CH_3C_6H_4$ | H | g. | m-$ClC_6H_4$ | H | l. | $CH_3CH_2CH_2$- | H |
| c. | p-$NO_2C_6H_4$ | H | h. | o-$CH_3C_6H_4$ | H | m. | -$(CH_2)_5$- | |
| d. | p-$ClC_6H_4$ | H | i. | o-$ClC_6H_4$ | H | n. | -$(CH_2)_4$- | |
| e. | p-$CH_3OC_6H_4$ | H | j. | $PhCH_2$ | H | o. | $CH_3CH_2CH_2CH_2$ | $CH_3$ |

**Table 1. Preparation and $^1$H NMR Spectra of 1,3-Dioxanes (2)**

| | | | $^1$H NMR (δppm, $CDCl_3$)[a] | | | | |
|---|---|---|---|---|---|---|---|
| No | yield% | m.p.°c | $C_6$PyH(1H) | other PyH | CH-R | $CH_2O$(4H,m) | Py-CH(m) |
| **2a** | 89 | oil | 8.40(d-d) | 6.7-7.9 | 5.50(s) | 4.2-4.8 | 3.0 |
| **2b** | 85 | oil | 8.55(d) | 6.9-8.2 | 5.60(s) | 4.4-4.7 | 2.9[c] |
| **2c** | 98 | 177-179[b] | 8.55(d) | 7.45-7.90 | 5.72(s) | 4.4-4.9 | 3.1 |
| **2d** | 86 | 90-91.5[b] | 8.50(d) | 7,0-7.9 | 5.60(s) | 4.3-4.65 | 3.0 |
| **2e** | 78 | 70-72[b] | 8.35(d) | 6.6-8.0 | 5.25(s) | 4.2-4.5 | 3.05[d] |
| **2f** | 91 | oil | 8.55(m) | 6.95-8.45 | 5.60(s) | 4.0-4.8 | 3.0 |
| **2g** | 87 | oil | 8.47(d) | 6.9-7.9 | 5.50(s) | 4.1-4.6 | 3.0 |
| **2h** | 83 | 64-65[b] | 8.46(d-d) | 6.72-8.05 | 5.65(s) | 4.0-4.65 | 2.90[e] |
| **2i** | 84 | oil | 8.50(d) | 6.75-7.95 | 5.80(s) | 4.0-4.75 | 2.90 |
| **2j** | 94 | oil | 8.55(d) | 6.8-7.75 | 4.80(t) | 3.8-4.50 | 3.10[f] |
| **2k** | 85 | oil | 8.40(d) | 6.80-7.70 | 4.70(d) | 3.85-4.50 | 3.0[g] |
| **2l** | 93 | oil | 8.46(d) | 6.85-7.9 | 4.55(m) | 3.9-4.4 | 2.85[h] |
| **2m** | 86 | oil | 8.47(d-d) | 6.90-7.80 | --- | 3.9-4.6 | 3.2[i] |
| **2n** | 82 | oil | 8.32(d) | 6.7-7.6 | --- | 3.7-4.50 | 3.15[j] |
| **2o** | 65 | oil | 8.25(d) | 6.65-7.35 | --- | 4.0-4.70 | 3.3[k] |

a.aromatic protons overlapped along with the peaks of pyridyl protons.
b.analysis of **2c**: calcd. C, 62.94 ; H, 4.90; N, 9.79%. found: C, 62.28; H, 4.92; N, 9.74%. **2d**: calcd. C, 65.34; H, 5.08; N, 5.08%. found: C, 65.47; H, 5.24; N, 4.87%. **2e**: calcd. C, 70.85; H, 6.27; N, 5.17%. found: C, 70.55; H 6.45; N, 5.01%. **2h**. calcd. C, 75.29; H, 6.67; N, 5.49%. found: C, 75.56; H, 6.78; N, 5.20%. c. 2.35(s,3H,$CH_3$). d. 3.75(s,3H,$OCH_3$). e. 2.33(s,3H,$CH_3$); f. 2.80(d,2H,$CH_2$). g. 2.80(m,1H,CH), 1.40(d,3H,$CH_3$). h. 1.3-1.85(m,4H,$CH_2CH_2$), 0.90(t,3H,$CH_3$). i. 1.3-2.5(m,) j. 2.1(t,4H,$CH_2$), 1.75(t,4H,$CH_2$). k. 2.50 (t, 2H,$CH_2$), 2.2(s,3H,$CH_3$), 1.7(m 4H,$CH_2CH_2$), 0.95(t,3H,$CH_3$).

Table 2. Preparation of Pyridinium Iodide Derivatives (3)

| No | yield% | m.p.°c | analysis calcd. C | H | N | formula | found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 3a | 70 | 172-174 | 50.15 | 4.70 | 3.66 | $C_{16}H_{18}INO_2$ | 50.10 | 4.76 | 3.55 |
| 3b | 82 | 209-210 | 51.39 | 5.04 | 3.53 | $C_{17}H_{20}INO_2$ | 50.88 | 5.17 | 3.35 |
| 3c | 88 | 224-226 | 44.88 | 3.97 | 6.54 | $C_{16}H_{17}IN_2O_4$ | 44.83 | 3.96 | 6.36 |
| 3d | 82 | 218-220 | 46.01 | 4.07 | 3.35 | $C_{16}H_{17}ClINO_2$ | 46.29 | 4.16 | 3.25 |
| 3e | 65 | 185-187 | 49.41 | 4.84 | 3.39 | $C_{17}H_{20}INO_3$ | 49.80 | 4.71 | 3.15 |
| 3f | 75 | 183-185 | 44.88 | 3.97 | 6.54 | $C_{16}H_{17}IN_2O_4$ | 44.39 | 3.92 | 6.25 |
| 3g | 74 | 201-203 | 46.01 | 4.07 | 3.35 | $C_{16}H_{17}ClINO_2$ | 45.96 | 4.13 | 3.22 |
| 3h | 64 | 196-198 | 51.39 | 5.04 | 3.53 | $C_{17}H_{20}INO_2$ | 51.20 | 5.14 | 3.36 |
| 3i | 62 | 205-207 | 46.01 | 4.07 | 3.35 | $C_{16}H_{17}ClINO_2$ | 45.81 | 3.81 | 3.46 |
| 3j | 67 | 171-173 | 51.39 | 5.04 | 3.53 | $C_{17}H_{20}INO_2$ | 51.09 | 5.31 | 3.27 |
| 3k | 69 | 189-191 | 52.57 | 5.35 | 3.41 | $C_{18}H_{22}INO_2$ | 52.56 | 5.45 | 3.36 |
| 3l | 77 | 106-108 | 44.71 | 5.73 | 4.01 | $C_{13}H_{20}INO_2$ | 44.48 | 5.79 | 3.83 |
| 3m | 76 | 151-153 | 48.01 | 5.87 | 3.73 | $C_{15}H_{22}INO_2$ | 47.78 | 5.72 | 3.90 |
| 3n | 70 | 110-112 | 46.55 | 5.54 | 3.88 | $C_{14}H_{20}INO_2$ | 46.89 | 5.31 | 3.52 |
| 3o | 77 | 120-122 | 47.76 | 6.37 | 3.71 | $C_{15}H_{24}INO_2$ | 47.25 | 6.61 | 3.40 |

Previous hydrolyses of acetals and ketals have usually been effected in an acid medium to give the appropriate aldehydes or ketones as treated extensively in the literature[6]. Wet silica gel and activated zinc dust have also been used for deacetalization, but their applicability is restricted[7-8]. The novel pyridinium iodides (3) are readily hydrolyzed to give the corresponding aldehyde or ketone by treatment with a variety of bases under mild conditions: quaternization of the pyridine nitrogen enhances the acidity of the β-hydrogen atoms, facilitating the ring cleavage as shown in Scheme 2. Thus, the aldehydes or ketones were released in good yield by stirring pyridinium iodides (3a-3o) with one equivalent of NaOH in aqueous ethanol at room temperature; furthermore, the pyridinium iodides also underwent deprotection when heated with $K_2CO_3$ in aqueous ethanol (Table 3).

The main advantages of this new protection method are the weakly basic cleavage conditions utilized and the fact that the protecting group needs activation (quaternization) prior to its removal. 2-(4-Nitrobenzene)-5-(2-pyridyl)-1,3-dioxane (2c) was shown to be stable in 0.1M hydrochloric acid solution, although pyridinium iodide (3c) was hydrolyzed by aqueous 0.1M hydrochloric acid solution. Therefore, the 5-(2-pyridyl)-1,3-dioxanes (2) should remain unaffected under various synthetic transformations, especially in acidic medium, of the protected molecule. This new method is particularly recommended for the modification of carbonyl compounds by the addition of functionality which is unstable in an acidic medium.

Table 3. Deprotection of 5-[2-(1-Methylpyridinium)]-1,3-dioxanes Iodides (3)

| base | Pyridinium iodide 3a | 3b | 3c | 3d | 3e | 3f | 3g | 3h | 3i | 3j | 3k | 3l | 3m | 3n | 3o |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NaOH, yield% | 84 | 80 | 88 | 83 | 79 | 95 | 79 | 73 | 84 | 77 | 81 | 70 | 65 | 71 | 60 |
| $K_2CO_3$, yield% | 88 | 82 | 96 | -- | -- | 91 | 85 | -- | 80 | 79 | 77 | -- | 72 | -- | -- |

**Experimental:**

**Preparation of 5-(2-pyridyl)-1,3-dioxane (2), General Procedure:**

2-(2-Pyridyl)propane-1,3-diol (1.53 g, 10 mmol), 10 mmol of the appropriate aldehyde, and p-toluenesulfonic acid monohydrate (2.30 g, 12 mmol) were stirred and refluxed for 4-8 h in benzene (80 ml), the water formed during the reaction was removed azeotropically by means of a Dean-Stark trap. The reaction mixture was washed with $K_2CO_3/H_2O$, extracted with $CHCl_3$, and the extract dried with $MgSO_4$. Evaporation of the solvent gave the acetal.

**5-[2-(1-Methylpyridinium)]-1,3-dioxane iodide (3), General Procedure:**

5-(2-Pyridyl)-1,3-dioxane (2) was treated with excess methyl iodide in acetone at 25°C for 10 h to 3 days. Addition of ether and filtration afforded a solid which on recrystallization from ethanol gave the pyridinium iodide (3).

**Deprotection:**

5-[2-(1-Methylpyridinium)]-1,3-dioxane iodide (3) was stirred with one equivalent of sodium hydroxide (25°C) or potassium carbonate (60°C) in aqueous ethanol overnight. The reaction mixture was extracted with $CHCl_3$ and the extract dried with $MgSO_4$. Evaporation of the solvent gave the aldehyde or ketone, identified by its $^1H$ NMR spectra.

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**References and Notes**

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3. A. R. Katritzky; G. R. Khan; and C. M. Marson, in preparation.
4. A typical $^{13}C$ NMR spectrum is that of (21 R=$CH_2CH_2CH_3$, R'=H). 161.4, 157.6(Py-$C_2$); 121.4, 120.9(Py-$C_3$); 135.8, 135.6(Py-$C_4$); 122.2(Py-$C_5$); 148.8, 148.3 (Py-$C_6$); 101.7, 101.2(CHO); 70.2, 68.9($CH_2O$); 42.1, 41.1(PyCH); 36.5, 36.4($\underline{CH_2}CH_2CH_3$); 16.7, 16.5($CH_2\underline{CH_2}CH_3$); 13.4($CH_3$).
5. Typical NMR spectra are those of (31): $^1H$ NMR (DMSO-$d_6$): 9.1(d,1H,6-Py-H), 8.6(m,2H,3,4-Py-H), 8.1(m,1H,5-Py-H), 4.9(t,1H,CH-O), 4.2-4.6 (m,7H, N-$CH_3$,$CH_2O$), 3.7(m,1H,PyCH), 1.65(m,4H,$CH_2CH_2$), 1.05(t,3H,$CH_3$). $^{13}C$ NMR: 158.6(Py-$C_2$), 125.4(Py-$C_3$), 144.7(Py-$C_4$), 128.1(Py-$C_5$), 146.5(Py-$C_6$), 101.3(CH-O), 67.0($CH_2O$), 46.3(N-$CH_3$), 34.0(Py-CH), 36.3($\underline{CH_2}CH_2CH_3$), 16.4($CH_2\underline{CH_2}CH_3$), 13.4($CH_3$).
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