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CHEMISTRY OF HETEROCYCLIC COMPOUNDS. 10. KETALIZATION OF 2-PYRIDYLKETONES UNDER BASIC CONDITIONS

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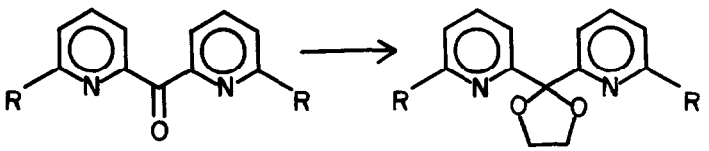
Cyclic ketals are one of the most important protecting groups for ketones.[2] These 2,2-disubstituted-1,3-dioxolanes are normally prepared by condensation of ethylene glycol with ketones under acidic conditions. During our efforts directed toward syntheses of heteromacrocycles, we required a simple synthesis of 2,2-di-(6-bromo-2-pyridyl)-1,3-dioxolane (2b). Initial attempted conversion of the simpler di-2-pyridylketone (1a)[3] into the corresponding ketal 2a under diverse conditions [e.g. Protecting Group Reagent: ethylene glycol; Catalyst: p-toluenesulfonic acid, anhydrous hydrochloric acid, or sulfuric acid; Solvent: benzene, toluene, xylene, or mesitylene; Temperature: 80°-195°; Time: 8-36 hours] were all unsuccessful with one exception [1a, ethylene glycol, xylene and a catalytic amount of sulfuric acid were refluxed for 10 hours]. In this way 1a was converted (20%) into 2a. When p-toluenesulfonic acid was used as catalyst, the major side product was 2-hydroxyethyl p-toluenesulfonate: yellow oil;[4] t.l.c. R_f 0.40 [cyclohexane-ethyl acetate (1:1)]; i.r. ($CHCl_3$) 3700, 2900, 1600, 1400, 1350, 1180, 1100, 920, 818 cm^{-1}; nmr ($CDCl_3$-1% TMS) δ 2.37 (s, 3H, Ar-CH_3), 3.62 (broad s, 1H, O-H), 3.73 (t, J = 5Hz, 2H, -CH_2OH), 4.10 (t, J = 5Hz, 2H, -CH_2OSO_2-), 7.33 (d, J = 8.5, 2H, 3,5-Ar-H), and 7.81 (d, J = 8.5, 2H, 2,6 Ar-H). However, under numerous combinations of the above conditions, attempted transformation of 1b into the desired 2b was futile.



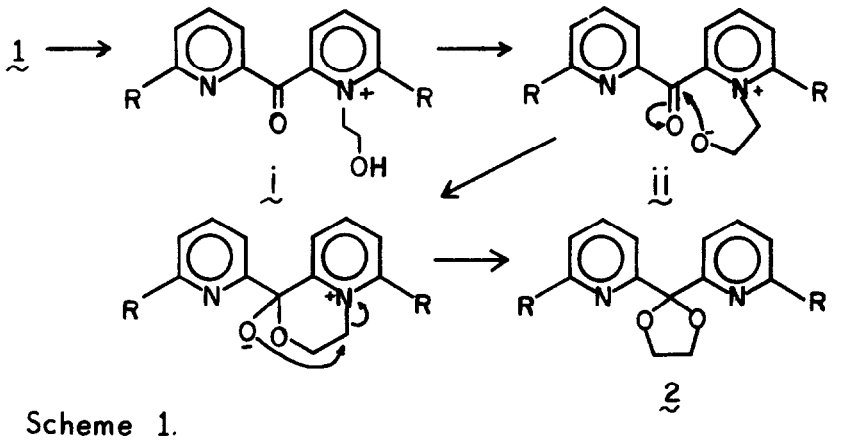
1 (a, R = H; b, R = Br) 2 (a, R = H; b, R = Br)

We herein describe a new method for ketalization of 1 utilizing 2-chloro- or 2-bromoethanol under basic conditions. The simplicity of experimental operations is indicated by the following preparation.

2,2-Di-(2-pyridyl)-1,3-dioxolane (2a): To a solution containing 1.06 g (0.57 mmol) of di-2-pyridylketone in 40 ml of redistilled 2-chloroethanol was added 12g of anhydrous lithium carbonate. The reaction mixture was refluxed for 5 hours, after which most excess solvent was removed by reduced pressure (water aspirator) distillation. A chloroform suspension of the residue was filtered and the filtrate was evaporated giving a crude product, which was chromatographed [Silica Gel P, cyclohexane-ethyl acetate (4:1)] affording 550 mg (45%) of white crystalline ketal:[5] m.p. 164-166° (needles from petroleum ether); t.l.c. R_f 0.14 [cyclohexane-ethyl acetate(1:1)]; i.r. (KBr) 1575, 1460, 1435, 1225, 1120, 1090, 1010, 990, 945, 805 cm^{-1}; n.m.r. ($CDCl_3$-1% TMS) δ 6.10 (s, 4H, $-OCH_2$), 7.0-8.0 (m, 6H, pyr-H), and 8.5 (d, 2H, 6-pyr-H).

Di-(6-bromo-2-pyridyl)ketone ketal (2b)[5] [m.p. 146-148°; t.l.c. R_f 0.41; i.r. (KBr) 1460, 1272, 1107, 1042, 1006, 807, 788, 754, 740, 710 cm^{-1}; n.m.r. ($CDCl_3$-1% TMS) δ 4.14 (s, 4H, $-OCH_2-$), 7.35 (dd, J = 2.0 and 7.0 Hz, 3 or 5-pyr-H), 7.58 (dd, J = 7.0 and 7.7 Hz, 4-pyr-H), 7.82 (dd, J = 2.0 and 7.7 Hz, 5 or 3-pyr-H)] was prepared from 1b[5] [m.p. 153-156°; t.l.c. R_f 0.6; i.r. ($CHCl_3$) 1690 (C=O), 1426, 1220, 1126, 986, 966, 825 cm^{-1}, n.m.r. ($CDCl_3$-1% TMS) δ 7.65 (m, J = 4.0 and 2.5 Hz, 3 or 5-pyr-H) and 8.0 (m, J = 4.0 and 2.5 Hz, 4-pyr-H)] in an identical manner except for the substitution of 2-chloroethanol by 2-bromoethanol which has a higher reflux temperature and circumvents potential halogen exchange.[6]

The possible reaction pathway (Scheme 1) can be envisioned to proceed through initial quaternization[7] of 1 with the β-haloethanol. Intermediate i with lithium carbonate generates



Scheme 1.

zwitterion ii, which attacks the highly electrophilic ketonic carbon. Subsequent nucleophilic attack at the β-carbon atom affords the desired ketal.

Further studies are in progress to elucidate the overall generality of this ketalization procedure.

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1. This work was supported by the National Institute of Neurological Diseases and Stroke (PHS Grant No. 5-R01-MS-09930) the donors of the Petroleum Research Fund, administered by the American Chemical Society and the Research Corporation.

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