ADDITION OF 2(1H)-PYRIDINETHIONE TO 3,4-DIHYDRO(2H)-PYRAN+

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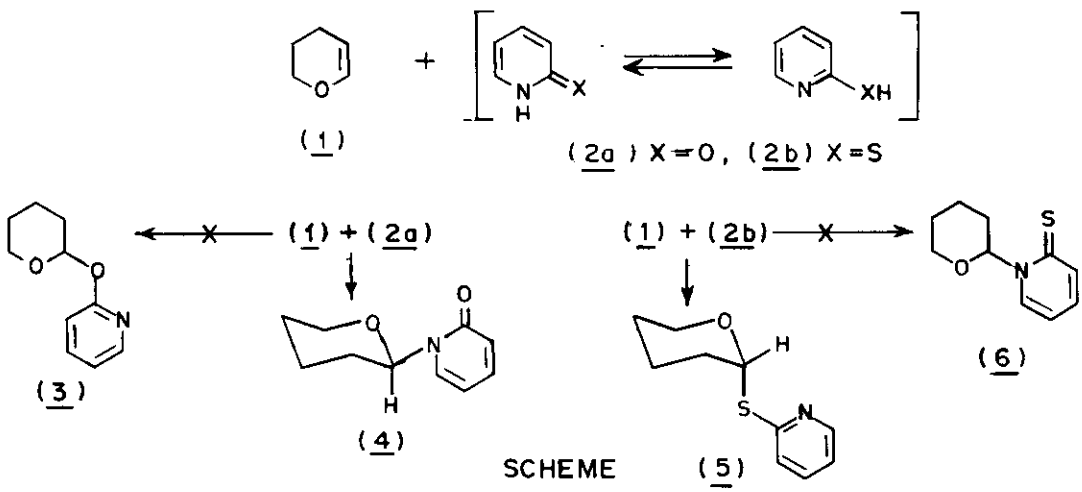
Abstract - The title reaction gave [tetrahydro-2H-pyran-2'-yl]-2-thiopyridine (5) rather than 1-tetrahydropyranyl-2-pyridinethione (6) as was earlier reported.[1]

Protonated pyridine-2-thiyl group is an excellent leaving group. Synthetic utility of this group was demonstrated in performing glycosidation[2] and macrolactonization[3] reactions under very mild conditions. Thiopyridyl ethers and esters required for such transformations are generally made either from their corresponding hydroxy or the halogenated compounds using 2,2'-dithiodipyridine-R_3P and 2-mercaptopyridine - KOH[2], respectively[3,7].

In a programme to find new and simpler methods of preparing such thiopyridyl compounds, addition of 2(1H)-pyridinethione (2b) to 3,4-dihydro(2H)pyran (1) was tried (Scheme).



SCHEME

The reaction between (1) and (2b) (equimolar, CH_2Cl_2, cat. PTSA, reflux 20 min) gave (5) in 42% yield. This observation is contrary to the report of Wagner et al.,[1]

where (6) was reported to have been formed, when (1) and (2b) were reacted (equimolar, C_6H_6-DMF, cat. PTSA, 70-80°C, 4 h). Due to this discrepancy Wagner's procedure[1] was repeated. But the compound isolated was found to be (5). Likewise, the reaction of (1)+(2a) (equimolar, C_6H_6-DMF, cat. PTSA, 70-80°C, 4 h) of the same authors was also repeated[1] and it gave (4) as was reported. In either reaction, (CH_2Cl_2 or C_6H_6-DMF, cat. PTSA) compounds (3) and (6) were not found even as minor compounds.

Though extensive investigations have been carried out and reviewed on the addition reactions[1b,4] of heterocyclic compounds, which exhibit prototropic tautomerism,[5,6] enough evidence was not presented on the structure of the reaction products specially when X = O or S as in (2a) and (2b). Hence, a systematic structure elucidation is presented here to distinguish between pairs (3), (4) and (5), (6), together with published data for other reference compounds (Table).

Structure elucidation of compound (5): Appearance of H-6 at δ8.44 in the PMR spectrum (entry VII) is characteristic of a pyridine-2-thiyl group[7]. N-Alkylated 2-pyridinethiones, however, exhibit a very significant chemical shift difference in their PMR spectra [δ6.63-7.70 (4H)] (entry III) when compared with their 2-alkylated mercaptopyridines [δ7.09-8.42 (4H)] (entry IV and V). Likewise, a singlet at δ158.35 (C-2) in the ^{13}C-spectrum is diagnostic of a pyridine-2-thiyl group[8] (entry IV and V), whereas structure (6) would be expected to show a singlet around δ180.00 for the thioamide carbon[8] (R_2N-R<u>C</u>=S) (entry III). UV [245(9032), 287 (4283)][12] spectrum is also characteristic of compound (5) (entry VII). Whereas, UV of a conjugated dienone chromophore as in (6) would be clearly different (entry III). IR spectra (entry V and VII) are not really helpful in distinguishing structures (5) and (6). Conformation of (5) at C-2' shown is based on the comparison of the chemical shift value and the coupling constants[7].

Structure elucidation of compound (4): In a similar way, appearance of H-5 at δ7.74 (most downfield signal) in the PMR (entry I), a strong IR absorption at 1655 cm^{-1} and a very characteristic UV [228(5996), 302 (5280)] (entry I) confirm the formation of compound (4) in the reaction between (1) and (2a). ^{13}C-Data (entry I and II) is not particularly useful in this case to dinstinguish structures (3) and (4). Conformation of (4) at C-2' is again based on the comparison of the chemical shift value and coupling constants.

TABLE

ENTRY§	COMPOUND	^{1}H-NMR (ppm, $CDCl_3$)	^{13}C(ppm, $CDCl_3$)	UV(MeOH) λ max,nm(ε)	IR(ν cm^{-1},$CHCl_3$)	Ref.
I	N-Methyl-2-pyridone	3.55(s,3H,N-CH_3),6.15(t,H-5), 6.57(d,H-3),7.30(m,2H,H-4&H-6).	41.8(q,N-CH_3),104.8,119.1, 139.5, 139.5(4d,C-5,3,4,6), 161.8(s,C-2).	226(6100), 297(5700).	3030(w),1665(s),1585(s), 1535(s),1315(m),1150(m), 1050(m),870(m),	9, 8, 10,13
II	2-Methoxy-pyridine	3.90(s,3H,OCH_3),6.63-6.92(m,2H, H-3&H-5),7.36-7.67(m,H-4),8.19 (m,H-6).	60.9(q,OCH_3),111.0,116.7, 138.3(3d,C-4,5,3),147.4 (d,C-6),164.9(s,C-2).	269(3230)	3020(w),1590(s),1560(s), 1430(s),1315(s),1280(s), 1260(s),1040(s), 775(s).	10,13, 14
III	1-Methyl-2-(1H)-pyridine-thione	3.99(s,3H,N-CH_3),6.63(m,H-5),7.18 (m,H-4),7.61(m,H-3),7.70(m,H-6).	46.0(q,N-CH_3),134.1,135.8, 141.0(3d,C-3,4,6),180.2 (s,C-2).	281(13600), 351(7040).	3010(w),1610(m),1540(s), 1410(s),1135(s),1110(s), 750(s).	14,15, 16
IV	2-Methyl-thio-pyridine	2.61(s,3H,S-CH_3)7.10(m,H-5), 7.25(m,H-3),7.60(m,H-4),8.58(m,H-6).	13.2(q,S-CH_3),119.0,121.4, 135.7,149.3(4d,C-5,3,4,6), 159.9(s,C-2).	-	-	8, 12, 15
V	2,2'-Dithiodi-pyridine	7.09(m,2H,H-5,5'),7.60(m,4H,H-3,3'& H-4,4'),8.42(m,2H,H-6,6').	119.6,121.1,137.3(3d,C-3,3', C-4,4',C-5,5'),149.5(d,C-6, 6')158.8(s,C-2,2').	236(14300), 280(9030).	3030(w),1565(s),1450(s), 1425(s),1150(m),1110(m), 1040(m), 990(m), 775(s).	13,16
VI	(4)	[a]1.50-2.40(m,6H,-CH_2-pyranyl),3.52-3.91(m,H-6'),4.10-4.30(m,H-6'), 5.94(d x d,H-2',J_1=9.88,J_2=2Hz), 6.24(d x d,H-5,J_1=6.84,J_2=2Hz), 6.55(d x d,H-3,J_1=9.5,J_2=2Hz), 7.30(d x d x d,H-4,J_1=9.5,J_2=6.84, J_3=2.28Hz),7.60(d x d,H-6,J_1=6.84, J_2=2.28Hz).	[b] 22.8,25.2,31.9(3t,C-3', C-4'.C-5')69.1(t,C-6'), 82.5(d,C-1'),106.1,120.4, 133.0,139.4(4d,C-3,C-4,C-5, C-6),161.5(s,C-2).	228(5996), 302(5280).	3080(w),2920(m),1660(s), 1580(s),1530(s),1440(w), 1290(m),1250(s),1200(m), 1180(s),1140(m),1090(s).	
VII	(5)[c]	[a]1.60-2.20(m,6H,CH_2-pyranyl),3.66 (d x d x d,H-6',J_1=12,J_2=11,J_3=5Hz), 4.11(d x d x d.H-6'J_1=12,J_2=7,J_3=5Hz), 5.94(d x d,H-2',J_1=6,J_2=4Hz),7.00(d x d x d,H-4,J_1=7,J_2=5,J_3=1Hz),7.29(d x d x d,H-2,J_1=8,J_2=J_3=1Hz),7.50(d x d x d,H-3,J_1=8,J_2=7,J_3=1.9Hz),8.44 (d x d x d,H-5,J_1=5,J_2=1.9,J_3=1).	[b] 21.5,25.5,31.4(3t,C-3',C-4', C-5'),64.4(t,C-6'),81.8(d,C-2').120.0,122.9,136.3,149.5 (4d,C-3,C-4,C-5,C-6),158.3 (s, C-2).	245(9032), 287(4283).	3040(w),2940(s),2850(m), 1570(s),1550(s),1445(s), 1550(s),1445(s),1410(s), 1330(m),1280(m),1120(s), 1100(s),1070(s),1030(s), 1000(s), 890(m).	

a) Brucker, WH-90FT(90MHz); b) 22.63 MHz; c) bp 95°C/0.01 Torr; Elemental analysis: Found C, 6152; H, 6.88; N, 7.01; S, 16.65. $C_{10}H_{13}$ NOS requires C, 61.51; H, 6.71; N, 7.17; S, 6.41%.

§ Entries I to V; data have been previously reported.

Formation of (4) and (5) thus indicates a reversal in the chemical reactivity[11], in the addition reactions of 2-hydroxy and 2-mercaptopyridines (2a) and (2b) to 3,4-dihydro(2H)pyran (1). Based on the above observation it would appear necessary to check the several alkylations reported[1] on heterocyclic bases.

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