

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

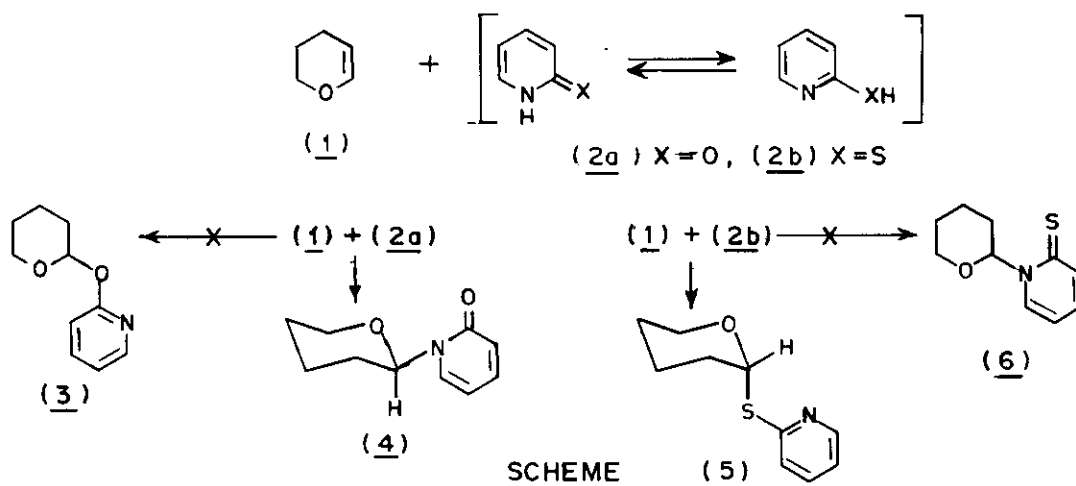
Hari Babu Mereyala

National Chemical Laboratory, Poona 411008, India

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

Protonated pyridine-2-thiyl group is an excellent leaving group. Synthetic utility of this group was demonstrated in performing glycosidation<sup>2</sup> and macrolactonization<sup>3</sup> 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<sup>2</sup>, respectively<sup>3,7</sup>.

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).



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.,<sup>1</sup>

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<sup>1</sup> 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<sup>1</sup> 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<sup>1b,4</sup> of heterocyclic compounds, which exhibit prototropic tautomerism,<sup>5,6</sup> 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  $\delta$ 8.44 in the PMR spectrum (entry VII) is characteristic of a pyridine-2-thiyl group<sup>7</sup>. N-Alkylated 2-pyridinethiones, however, exhibit a very significant chemical shift difference in their PMR spectra [ $\delta$ 6.63-7.70 (4H)] (entry III) when compared with their 2-alkylated mercaptopyridines [ $\delta$ 7.09-8.42 (4H)] (entry IV and V). Likewise, a singlet at  $\delta$ 158.35 (C-2) in the  $^{13}C$ -spectrum is diagnostic of a pyridine-2-thiyl group<sup>8</sup> (entry IV and V), whereas structure (6) would be expected to show a singlet around  $\delta$ 180.00 for the thioamide carbon<sup>8</sup> ( $R_2N-RC=S$ ) (entry III). UV [245(9032), 287 (4283)]<sup>12</sup> 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<sup>7</sup>.

Structure elucidation of compound (4): In a similar way, appearance of H-5 at  $\delta$ 7.74 (most downfield signal) in the PMR (entry I), a strong IR absorption at  $1655\text{ cm}^{-1}$  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 distinguish 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 <sup>§</sup>	COMPOUND	<sup>1</sup> H-NMR (ppm, CDCl <sub>3</sub> )	<sup>13</sup> C (ppm, CDCl <sub>3</sub> )	UV (MeOH) λ <sub>max</sub> , nm (ε)	IR (ν cm <sup>-1</sup> , CHCl <sub>3</sub> )	Ref.
I	N-Methyl-2-pyridone	3.55(s, 3H, N-CH <sub>3</sub> ), 6.15(t, H-5), 6.57(d, H-3), 7.30(m, 2H, H-4 & H-6).	41.8(q, N-CH <sub>3</sub> ), 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 <sub>3</sub> ), 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 <sub>3</sub> ), 111.0, 116.7, 138.3(3d, C-4, 5, 3), 147.4(4d, 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 <sub>3</sub> ), 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 <sub>3</sub> ), 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 <sub>3</sub> ), 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 <sub>3</sub> ), 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(4d, 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)	<sup>a</sup> 1.50-2.40(m, 6H, -CH <sub>2</sub> -pyranyl), 3.52-3.91(m, H-6'), 4.10-4.30(m, H-6'), 5.94(d x d, H-2', J <sub>1</sub> =9.88, J <sub>2</sub> =2Hz), 6.24(d x d, H-5, J <sub>1</sub> =6.84, J <sub>2</sub> =2Hz), 6.55(d x d, H-3, J <sub>1</sub> =9.5, J <sub>2</sub> =2Hz), 7.30(d x d x d, H-4, J <sub>1</sub> =9.5, J <sub>2</sub> =6.84, J <sub>3</sub> =2.28Hz), 7.60(d x d, H-6, J <sub>1</sub> =6.84, J <sub>2</sub> =2.28Hz).	<sup>b</sup> 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) <sup>c</sup>	<sup>a</sup> 1.60-2.20(m, 6H, CH <sub>2</sub> -pyranyl), 3.66(d x d x d, H-6', J <sub>1</sub> =12, J <sub>2</sub> =11, J <sub>3</sub> =5Hz), 4.11(d x d x d, H-6' J <sub>1</sub> =12, J <sub>2</sub> =7, J <sub>3</sub> =5Hz), 5.94(d x d, H-2', J <sub>1</sub> =6, J <sub>2</sub> =4Hz), 7.00(d x d x d, H-4, J <sub>1</sub> =7, J <sub>2</sub> =5, J <sub>3</sub> =1Hz), 7.29(d x d x d, H-2, J <sub>1</sub> =8, J <sub>2</sub> =J <sub>3</sub> =1Hz), 7.50(d x d x d, H-3, J <sub>1</sub> =8, J <sub>2</sub> =7, J <sub>3</sub> =1.9Hz), 8.44(d x d x d, H-5, J <sub>1</sub> =5, J <sub>2</sub> =1.9, J <sub>3</sub> =1).	<sup>b</sup> 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) Bruker, WH-90FT(90MHz); b) 22.63 MHz; c) bp 95°C/0.01 Torr; Elemental analysis: Found C, 61.52; H, 6.88; N, 7.01; S, 16.65. C<sub>10</sub>H<sub>13</sub> 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<sup>11</sup>, 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<sup>1</sup> on heterocyclic bases.

#### REFERENCES

<sup>†</sup>NCL Communication No. 4044

1. a) H. Kuhmstedt and G. Wagner, Arch. Pharm., 1968, 301, 660.  
b) "Heterocyclic Compounds" Vol. 14, Suppl. Part 3, ed by R. A. Abramovitch, John Wiley & Sons, Inc., 1974, p.756 and references cited therein.
2. S. Hanessian, C. Bacquet and N. Lohong, Carbohydr. Res., 1980, 80, C17.
3. E. J. Corey and K. C. Nicolaou, J. Am. Chem. Soc., 1974, 96, 5614.
4. a) H. Kuhmstedt and G. Wagner, Arch. Pharm., 1969, 302, 213.  
b) N. Takahayashi, J. Pharm. Soc. Jap., 1956, 76, 1296.  
c) K. Eichenberger, R. Rometsch and J. Druey, Helv.Chim.Acta, 1956, 39, 1755.  
d) E. Spinner, J. Chem. Soc., 1960, 1237.
5. "Heterocyclic Compounds", Special topics in heterocyclic chemistry, Vol. 30, ed. by A. Weissberger and E.C. Taylor, John Wiley & Sons, Inc., 1977, p.99.
6. "Heterocyclic Compounds" Vol. 28, ed. by R.N. Castle, John Wiley & Sons, Inc., 1973, pp. 756-779.
7. Peter G. M. Wuts and Sean S. Bigelow, J. Org. Chem., 1983, 48, 3492.
8. I. W. J. Still, N. Plavac, D. M. McKinnon and M. S. Chauhan, Can. J. Chem., 1976, 54, 280.
9. P. W. Von Ost Walden and J. D. Roberts, J. Org. Chem., 1971, 36, 3792.
10. S. F. Mason, J. Chem. Soc., 1959, 1253.
11. P. Beak and J. T. Lee Jr., J. Org. Chem., 1969, 34, 2125.
12. C. Djerassi and G. R. Pettit, J. Am. Chem. Soc., 1954, 76, 4470.  
[2-Ethylthiopyridine, UV(EtOH),  $\lambda_{\max}$ , nm( $\epsilon$ ), 250(7943), 293(3467)].
13. "The Aldrich Library of Infrared Spectra", ed. III, 1981, C. J. Pouchert.
14. a) L. Stefaniak, Tetrahedron, 1976, 32, 1065.  
b) V. Vogeli and W. von Philipsborn, Org. Mag. Res., 1973, 5, 551.  
c) C. J. Turner and G.W.H. Cheeseman, ibid., 1974, 6, 663.
15. G. B. Barlin and J. A. Benbow, J. Chem. Soc. Perkin II, 1974, 790.
16. 'Sadtlter Research Laboratories Inc' 1981.

Received, 6th May, 1986