SYNTHESIS OF 3,3,5-TRIMETHOXY-2-PYRROLIDINONE AND ITS DERIVATIVES

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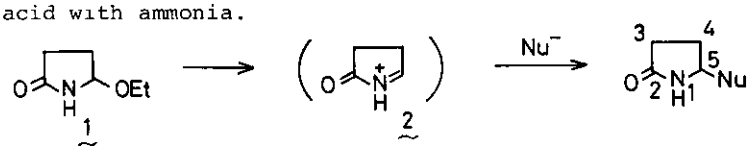
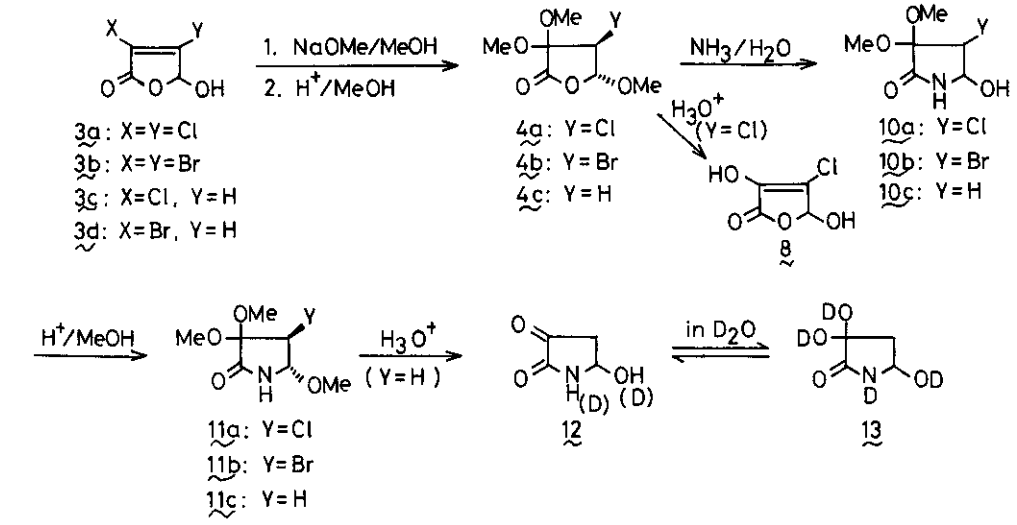
Abstract ——A convenient synthesis of 3,3,5-trimethoxy-2-pyrrolidinone (11a-c) by using a reaction of α-halo-β-formylacrylic acid [3-halo-5-hydroxy-2(5H)-furanone] (3a-d) with alkoxide is described. An investigation for synthesis of 2,3-pyrrolidinediones is also mentioned.

In our previous report,[1] we showed that 5-ethoxy-2-pyrrolidinone (1) was a useful intermediate for the synthesis of 5-amino-2-pyrrolidinone derivatives, because the ethoxy group at the 5-position was easily substituted by the reaction with nucleophiles via a highly reactive intermediate, iminium ion (2). This result suggested that 5-alkoxy-2-pyrrolidinones were expected to be valuable reagents to modify amino groups in biological substances such as amino acids or nucleosides. In this communication, we describe a new synthesis of more functionalized 2-pyrrolidinones, 3,3,5-trimethoxy-2-pyrrolidinones (11a-c) and its related compounds, by using a convenient reaction of α-halo-β-formylacrylic acid [3-halo-5-hydroxy-2(5H)-furanone] (3a-d) with alkoxide followed by a reaction of pseudoesters of β-formylpropionic acid with ammonia.



Treatment of mucochloric acid (3a) with sodium methoxide (3 eq. mol) in methanol [-10 → +5°C, 24 hr] followed by acidification with methanolic hydrogen chloride afforded slightly yellow oil, which on preparative medium pressure liquid chromatography[2] gave the methoxylactone (4a) as colorless crystals in 50% yield,



3a: X=Y=Cl
3b: X=Y=Br
3c: X=Cl, Y=H
3d: X=Br, Y=H

4a: Y=Cl
4b: Y=Br
4c: Y=H

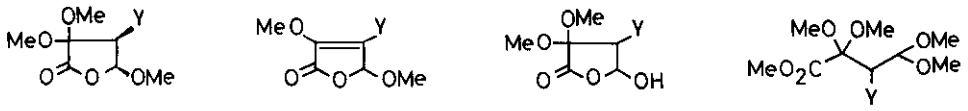
8

10a: Y=Cl
10b: Y=Br
10c: Y=H

11a: Y=Cl
11b: Y=Br
11c: Y=H

12

13



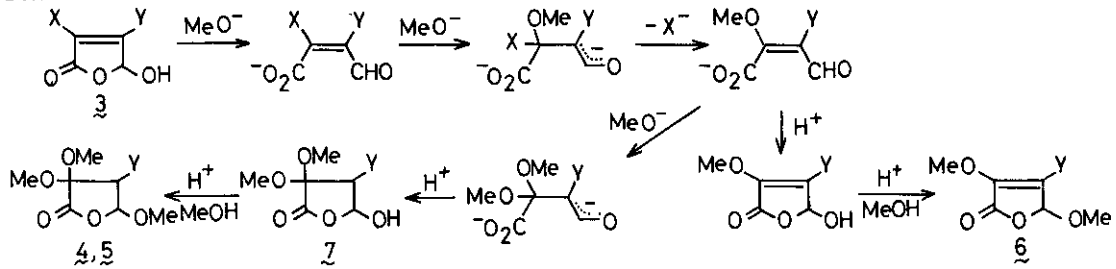
5a: Y=Cl
5b: Y=Br

6a: Y=Cl
6b: Y=Br
6c: Y=H

7a: Y=Cl
7b: Y=Br
7c: Y=H

9a: Y=Cl
9b: Y=Br
9c: Y=H

Scheme 1.



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4, 5

7

6

Table 1. Reaction of α-halo-β-formylacrylic acids (3a-d) with sodium methoxide.

Starting Materials	Reaction Conditions	Products(%)[c] 3	4	5	6	7	9	Physical data of methoxylactones(4a-c) mp(°C)	IR(cm^{-1})	NMR(δ, $CDCl_3$)	$J_{H_4H_5}$
3a	-10→+5°C 24hr	-	50	8	7	4	-	90[a]	1795(C=O)	4.06(H_4) 5.22(H_5)	5Hz
3b	-10→+5°C 4hr	25	25	4	2	5	-	93[a]	1795(C=O)	4.13(H_4) 5.37(H_5)	5Hz
3c	-10→+5°C 4hr	-	43		-	-	6	55[ab]	1785(C=O)	2.25(H_4) 5.48(H_5) 2.68(H_4')	5Hz 5.5Hz ($J_{H_4H_4'}$=13Hz)
3d	-10→+5°C 15hr	-	41		-	-	3				

a) Recrystallized from hexane. b) bp 109°C(6mmHg).
c) Satisfactory elemental analyses were obtained for 4 and 5. Physical data are listed in the last section of this paper, except for 4.

along with lesser amount of 5a (8%), 6a (7%), and 7a (4%). The structures of these products were determined by spectral analyses and by chemical conversion with 10% hydrochloric acid to the known mucoxychloric acid (8)[3], respectively. 4a and 5a were briefly hydrolyzed with 1% hydrochloric acid to give the hydroxylactone (7a), quantitatively. Treatment of 7a with methanol in the presence of catalytic amount of hydrogen chloride at room temperature regenerated a mixture of 4a and 5a (10:1), but when refluxed in methanol, 7a gave a mixture of 4a and 9a (1:1). Because 4a was always predominant in these reactions, the relative configuration of 4a was recognized as trans and that of 5a as cis. A mechanism for the formation of these compounds is assumed as shown in Scheme 1. Analogously, the reactions of mucobromic acid (3b), 3-chloro-5-hydroxy-2(5H)-furanone (3c), and 3-bromo-5-hydroxy-2(5H)-furanone (3d) with sodium methoxide were carried out to give the corresponding methoxylactones (4b and 4c) in moderate yields (see Table 1). Because these lactones (4a-c) were regarded as the pseudoesters of β-formylpropionic acid, they were expected to undergo ammonolysis to give hydroxylactams[4]. Thus, 4a-c were treated with aqueous ammonia under ice cooling to give the desired hydroxylactams (10a-c), respectively (see Table 2). The conversion of 10a-c to the corresponding methoxylactams (11a-c) was performed by refluxing a methanol solution containing a catalytic amount of hydrogen chloride (see Table 3). A considerable amount of cis-isomers was not detected.

Finally, the synthesis of 2,3-pyrrolidinediones was attempted. Hydrolysis of 10c or 11c with 10% hydrochloric acid [room temp., 10 min] followed by careful evaporation of water gave the unstable ketolactam (12)[5] in 55% yield. The structure of 12 was confirmed as keto-form by its NMR spectrum (in DMSO) which showed typical signals of ABX system. In contrast with above result, it was found that 12 existed in D_2O as the equilibrium mixture (1:1) of the keto-form (12) and the gem-diol-form (13)[6]. However, neither the enol tautomer nor open-chain isomer were detected. On the other hand, deketalization of 11a and 11b, having halogen atom at the 4-position, was not established even under a drastic condition [reflux, 10% HCl]. This result suggests that the stability of a ketal function at the 3-position increased by the electron withdrawing effect of an adjacent halogen atom. In conclusion, the reaction described above provides a convenient method for the synthesis of 3,3,5-trialkoxy-2-pyrrolidinones. Further investigation to introduce

Table 2. Synthesis of 5-hydroxy-2-pyrrolidinones (10a-c)

Starting Materials	Reaction Conditions	Product (%)	Physical data of 10a-c mp(°C)	IR(cm^{-1})		NMR(δ, Acetone-d_6)	
4a	0°C, 5min	75	163	1715(C=O)	1702(C=O)	4.08(H_4)	5.07(H_5)
4b	0°C, 30min	85	158	1715(C=O)	1703(C=O)	4.22(H_4)	5.22(H_5)
4c	0°C, 5min	76	oil	1710(C=O)		2.12(H_4) 2.53(H_4,)	5.27(H_5)

Table 3. Synthesis of 5-methoxy-2-pyrrolidinones (11a-c)

Starting Materials	Reaction Conditions	Product (%)	Physical data of 11a-c mp(°C)	IR(cm^{-1})	NMR(δ, $CDCl_3$)		$J_{H_4H_4'}$	$J_{H_4H_5}$
10a	reflux, 1hr	99	137[a]	1728(C=O)	4.12(H_4)	4.78(H_5)		2Hz
10b	reflux, 1hr	91	144[a]	1725(C=O)	4.15(H_4)	4.95(H_5)		2Hz
10c	reflux, 1hr	71	86[a]	1720(C=O)	2.15(H_4) 2.45(H_4,)	4.83(H_5)	14Hz	3Hz 6Hz

a) Recrystallized from hexane.

nitrogen functions at the 5-position by the reaction of the methoxylactams (11a-c) with nucleophiles such as nucleosides is now undertaken.

REFERENCES AND NOTES

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2) SiO_2: Iatrobeads 6RS-8060; solvent: hexane-acetone; flow rate: 20 ml/min. pressure: 1 kg/cm^2.

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5) 12, mp ~250°C(decomp.); IR(KBr)cm^{-1}: 3200(br, NH, and OH), 1760(C=O), 1710(C=O); NMR(DMSO-d_6)δ: 2.34 and 3.01(2H, AB of ABX, J_{AB}=19.5Hz, H_4), 5.1(1H, br, OH), 5.38(1H, X of ABX, J_{AX}=2Hz, J_{BX}=6Hz, H_5), 10.1(1H, br, NH); MS m/z: 115(M^+).

6) NMR(D_2O)δ: 2.23 and 2.70(2H, AB of ABX, J_{AB}=13.5Hz, H_4 of 13), 2.68 and 3.25 (2H, AB of ABX, J_{AB}=19.5Hz, H_4 of 12), 4.75(4H, s, exchangeable proton), 5.39 (1H, X of ABX, J_{AX}=3Hz, J_{BX}=6Hz, H_5 of 13), 5.70(1H, X of ABX, J_{AX}=2Hz, J_{BX}= 6Hz, H_5 of 12).

7) 5a, mp 103°C; IR(KBr)cm^{-1}: 1785(C=O); NMR($CDCl_3$)δ: 3.43, 3.48, and 3.72(3H×3, s, CH_3), 4.50(1H, d, J=4Hz, H_4), 5.62(1H, d, J=4Hz, H_5). 5b, mp 105°C; IR(KBr) cm^{-1}: 1785(C=O); NMR($CDCl_3$)δ: 3.43, 3.45, and 3.68(3H×3, s, CH_3), 4.43(1H, d,

J=4Hz, H_4), 5.40(1H, d, J=4Hz, H_5). 6a, mp 35°C; IR(KBr)cm^{-1}: 1780(C=O), 1680 (C=C); NMR($CDCl_3$)δ: 3.52 and 4.15(3H×3, s, CH_3), 5.67(1H, s, H_5). 6b, mp 54°C; IR(KBr)cm^{-1}: 1780(C=O), 1665(C=C); NMR($CDCl_3$)δ: 3.53 and 4.17(3H×2, s, CH_3), 5.65(1H, s, H_5). 9a, oil; NMR($CDCl_3$)δ: 3.38, 3.42, 3.50, and 3.80(3H×5, s, CH_3), 4.33(1H, d, J=5Hz, H_β), 4.57(1H, d, J=5Hz, H_γ). 9c, oil; NMR($CDCl_3$)δ: 2.25(2H, d, J=5Hz, H_β), 3.33(12H, s, CH_3×4), 3.80(3H, s, CH_3), 4.45(1H, t, J= 5Hz, H_γ).

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