EFFICIENT CATALYTIC FURYLATION OF 2-ACETOXY-5-PYRROLIDONE

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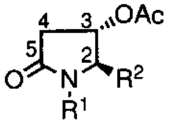
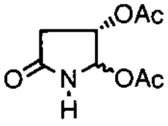
Abstract — 2-Acetoxy-5-pyrrolidone was furylated under a catalytic combination of zinc bromide and chlorotrimethylsilane. The effective catalyst system extremely accelerated the furylation reaction.

In connection to our study on a synthesis of biologically active compounds from 2-pyrrolidone derivatives,[1] we required 3-acetoxy-5-pyrrolidone-2-carboxylate (**1**). Although a nitrile substituent was considered equivalent to a carboxyl, 2-cyano-pyrrolidone (**2**)[2] was hardly hydrolyzed to the carboxylate (**1**) without opening of the pyrrolidone ring. Moreover, when R^1 was hydrogen, cyanation of the acetate (**4**) gave a complex mixture from which the cyanide (**3**) was given in low yield. Furyl substituent, however, could be used as an alternative carboxyl equivalent;[3] besides, the furan moiety would be transformed to an oxygenated C_4 side chain.[4] In this communication, we would like to report an efficient furylation of 2-acetoxy-5-pyrrolidone (**4**) with a catalytic combination system of zinc bromide ($ZnBr_2$) and



1 : R^1=H, R^2=CO_2CH_3
2 : R^1=Bzl, R^2=CN
3 : R^1=H, R^2=CN



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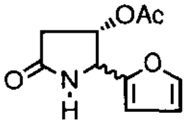
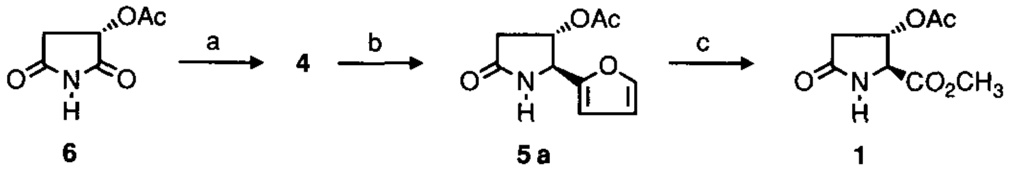


5 a: 2,3-trans
5 b: 2,3-cis



[a] NaBH4, CH_3OH, -15 °C; Ac_2O, Py·$HClO_4$. [b] furan, $ZnBr_2$, $(CH_3)_3SiCl$, CH_3NO_2, -15 °C.
[c] O_3, CH_3OH, -78 °C; CH_2N_2, 0 °C.

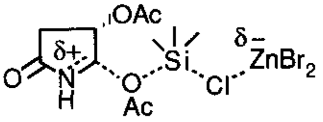
Table 1. Furylation of 2-Acetoxy-5-pyrrolidone (**4**)

Entry	Solvent	Catalyst (equiv.)[a]	Co-catalyst (equiv.)[a]	Temp. °C	Time h	Yield[b] (from **6**)	Ratio[c] (<u>trans</u>/<u>cis</u>)
1	Et_2O	BF_3 (0.1)	—	0	12	0	—
2	CH_2Cl_2	BF_3 (0.8)	—	0	0.5	20	50/50
3	CH_2Cl_2	$TiCl_4$ (0.1)	—	0	12	38	58/42
4	CH_2Cl_2	$AlCl_3$ (0.1)	—	rt[d]	16	21	66/34
5	CH_3NO_2	$ZnBr_2$ (0.1)	—	rt[d]	12	24	67/33
6	CH_3NO_2	$ZnBr_2$ (0.01)	$(CH_3)_3SiCl$ (0.05)	rt[d]	0.5	57	67/33
7	CH_3NO_2	$ZnBr_2$ (0.01)	$(CH_3)_3SiCl$ (0.05)	-15	2	71	67/33
8	CH_2Cl_2	$ZnCl_2$ (0.1)	$(CH_3)_3SiCl$ (0.05)	rt[d]	0.5	54	68/32

[a] Molar equivalent to the imide (**6**).
[b] Yield (%) of the furanolactam (**5**).
[c] Diastereoisomeric ratio.
[d] Room temperature.

chlorotrimethylsilane [$(CH_3)_3SiCl$].

Pyrrolidone diacetate (**4**) prepared from <u>L</u>-malic acid[5] was treated with furan under various conditions in the presence of a Lewis acid. As summarized in Table 1, furylation product (**5**) was obtained after prolonged reaction times with a catalytic amount of Lewis acid, entries 3-5, or in short times accompanying by substantial decomposition of a reaction product, entry 2. Unexpectedly, it was happened to add cyanotrimethylsilane to the reaction mixture containing furan and $ZnBr_2$, for which the furylation was extremely accelerated. We then changed the additive to $(CH_3)_3SiCl$, and found that the product (**5**) was given in moderate yield in short times, entries 6-8. The following is illustrative. To the crude acetate (**4**)[6] obtained from malimide (**6**, 2.35 g, 15 mmol) in nitromethane (20 ml) were added $ZnBr_2$ (33.7 mg, 0.15 mmol), furan (10.9 ml, 150 mmol) and $(CH_3)_3SiCl$ (0.095 ml, 0.75 mmol) at -15 °C. After stirring for 2 h at -15 °C, the reaction mixture was washed with aqueous sodium bicarbonate, and brine, dried (dry $MgSO_4$) and evaporated. Silica gel chromatography of the residue and elution with hexane/ethyl acetate (1/1) gave **5a** (1.52 g, 48% from **6**) and **5b** (764 mg, 23.2% from **6**), respectively.[7] 2,3-trans-Product (**5a**), $J_{2,3}$=0.9 Hz, favored to 2,3-cis-pyrrolidone (**5b**), $J_{2,3}$=7.0 Hz, in a diastereoisomeric ratio of 67:33. The observed acceleration on the furylation reaction implies an enhancement of a catalytic activity of $ZnBr_2$ by complex formation, such as $(CH_3)_3SiCl{\cdot}ZnBr_2$, which may induce a charge separated complex such as **7** prior to the generation of an active iminium ion intermediate (**8**).[8]



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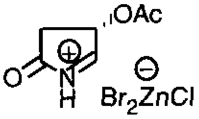

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The furanolactam (**5a**) was ozonized[3] and esterified to afford methyl (2S,3S)-3-acetoxypyroglutamate (**1**), mp 130-131 °C, $[\alpha]_D^{23}$ +60.4° (c 1.00, $CHCl_3$).[9] Overall yield from the imide (**6**) was 42%.

In summary, we observed that the furylation of 2-acetoxy-5-pyrrolidone (**4**) was greatly accelerated with a catalytic combination of $ZnBr_2$ and $(CH_3)_3SiCl$. Using this procedure, we have synthesized (2S,3S)-3-acetoxypyroglutamate (**1**) in short steps and high overall yield. The mechanism of the catalytic system with a combination of $ZnBr_2$ and $(CH_3)_3SiCl$ is now under investigation.

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6) Reduction of the malimide (**6**, 2.35 g, 15 mmol) with sodium borohydride (567 mg, 15 mmol) at -15 °C was followed by acetylation with acetic anhydride (30 ml) and pyridinium perchlorate (268 mg, 1.5 mmol). Because of the lability on silica gel, the acetate (**4**) was used without purification.

7) **5a**: mp 117-118 °C. $[\alpha]_D^{26}$ +65.0° (*c* 1.15, $CHCl_3$). δ_H ($CDCl_3$, 90 MHz) 2.11 (3H, s), 2.34 (1H, dd, *J*=18.0, 2.0 Hz), 2.93 (1H, dd, *J*=18.0, 6.5 Hz), 4.74 (1H, d, *J*=0.9 Hz), 5.34 (1H, ddd, *J*= 6.5, 2.0, 0.9 Hz), 6.26-6.40 (2H, m), 6.72-6.86 (1H, br), 7.39-7.43 (1H, m). **5b**: mp 138-139 °C. $[\alpha]_D^{24}$ -133.7° (*c* 1.00, $CHCl_3$). δ_H ($CDCl_3$, 90 MHz) 1.85 (3H, s), 2.96 (2H, d, *J*=7.0 Hz), 5.08 (1H, d, *J*=7.0 Hz), 5.57 (1H, dt, *J*=7.0, 7.0 Hz), 6.25-6.40 (2H, m), 6.36-6.51 (1H, br), 7.38-7.43 (1H, m).

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9) **1**: δ_H ($CDCl_3$, 500 MHz) 2.11 (3H, s), 2.36 (1H, dd, *J*=17.9, 2.6 Hz), 2.82 (1H, dd, *J*=17.9, 6.8 Hz), 3.80 (3H, s), 4.26 (1H, d, *J*=0.9 Hz), 5.46 (1H, ddd, *J*=6.8, 2.6, 0.9 Hz), 7.33 (1H, br).

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