

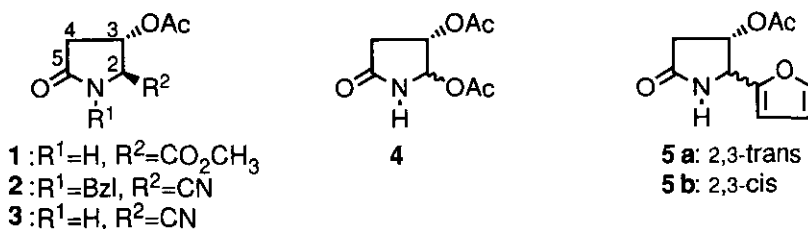
EFFICIENT CATALYTIC FURYLATION OF 2-ACETOXY-5-PYRROLIDONE

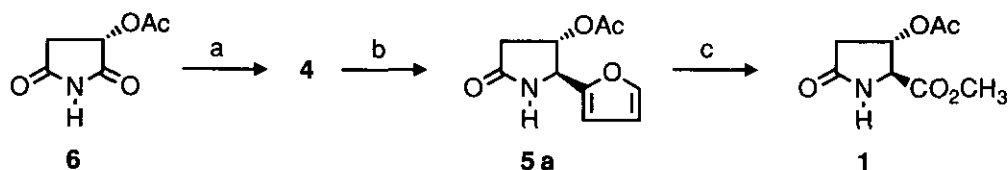
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Abstract — 2-Acetoxy-5-pyrrolidone was furylated under a catalytic combination of zinc bromide and chlorotrimethylsilane. The effective catalyst system extremely accelerated the furylation reaction.

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 R¹ 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 C₄ 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 (ZnBr₂) and





^a NaBH₄, CH₃OH, -15 °C; Ac₂O, Py·HClO₄. ^b furan, ZnBr₂, (CH₃)₃SiCl, CH₃NO₂, -15 °C.

^c O₃, CH₃OH, -78 °C; CH₂N₂, 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 ₂ O	BF ₃ (0.1)	—	0	12	0	—
2	CH ₂ Cl ₂	BF ₃ (0.8)	—	0	0.5	20	50/50
3	CH ₂ Cl ₂	TiCl ₄ (0.1)	—	0	12	38	58/42
4	CH ₂ Cl ₂	AlCl ₃ (0.1)	—	rt ^d	16	21	66/34
5	CH ₃ NO ₂	ZnBr ₂ (0.1)	—	rt ^d	12	24	67/33
6	CH ₃ NO ₂	ZnBr ₂ (0.01)	(CH ₃) ₃ SiCl (0.05)	rt ^d	0.5	57	67/33
7	CH ₃ NO ₂	ZnBr ₂ (0.01)	(CH ₃) ₃ SiCl (0.05)	-15	2	71	67/33
8	CH ₂ Cl ₂	ZnCl ₂ (0.1)	(CH ₃) ₃ SiCl (0.05)	rt ^d	0.5	54	68/32

^a Molar equivalent to the imide (6).

^b Yield (%) of the furanolactam (5).

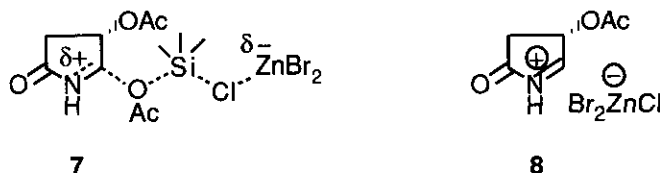
^c Diastereoisomeric ratio.

^d Room temperature.

chlorotrimethylsilane [(CH₃)₃SiCl].

Pyrrolidone diacetate (4) prepared from *L*-malic acid⁵ 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 $(\text{CH}_3)_3\text{SiCl}$, 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 $(\text{CH}_3)_3\text{SiCl}$ (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 $(\text{CH}_3)_3\text{SiCl}\cdot\text{ZnBr}_2$, which may induce a charge separated complex such as **7** prior to the generation of an active iminium ion intermediate (**8**).⁸



The furanolactam (**5a**) was ozonized³ and esterified to afford methyl (2S,3S)-3-acetoxypyroglutamate (**1**), mp $130-131^\circ\text{C}$, $[\alpha]_{\text{D}}^{23} +60.4^\circ$ (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 $(\text{CH}_3)_3\text{SiCl}$. 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 $(\text{CH}_3)_3\text{SiCl}$ 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. $[\alpha]_D^{26} +65.0^\circ$ (c 1.15, CHCl₃). δ_H (CDCl₃, 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. $[\alpha]_D^{24} -133.7^\circ$ (c 1.00, CHCl₃). δ_H (CDCl₃, 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 (CDCl₃, 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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