A Novel Synthesis of 2,3-Disubstituted-4-pyridones from 4-Methoxypyridine

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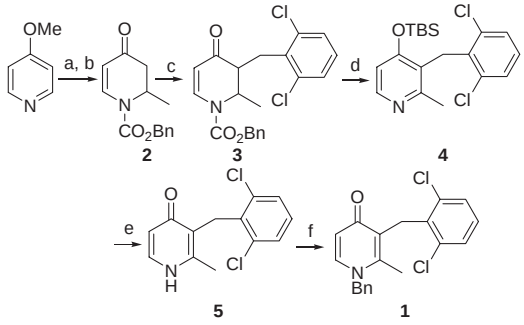
Novel 2,3-disubstituted 4-pyridone derivatives were prepared from 4-methoxypyridine through aldol condensation and isomerization of *exo*-olefin as key reactions, in fairly good to high yields.

4-Pyridone derivatives are important as synthetic intermediates for the preparation of natural products and as biologically active compounds.[1] We have been screening our compound library for enoyl-ACP reductase (FabI)[2] inhibitors as antibacterial agents. And we found a novel 4-pyridone derivative **1** as a FabI inhibitor. Compound **1** exhibited not only FabI-inhibitory activity, but also antibacterial activity against *Staphylococcus aureus*.

For structure optimization studies, we required a convenient and accessible method to synthesize a range of 4-pyridone derivatives. The conventional methods can be roughly classified as follows: (1) cyclization of triketones,[3] (2) reaction of primary and secondary enamines with diketene,[4] and (3) conversion of natural products, such as maltol or kojic acid, in the presence of an appropriate amine.[5] Though a number of synthetic methods have been reported for 4-pyridone derivatives, it is still difficult to prepare 2,3-disubstituted 4-pyridones because the methods generally need multiple steps or involve troublesome intermediates, such as triketones. Here, we would like to report a convenient method for synthesizing a wide range of 2,3-disubstituted 4-pyridone derivatives.

We planned to use *N*-acylated 2,3-dihydropyridine-4(1*H*)-ones as synthetic intermediates.[6] The racemic 2,3-dihydropyridine-4(1*H*)-ones can be easily prepared by the addition of organometallics such as Grignard reagent to 1-acyl-4-methoxypyridinium salts.[7] 2,3-Dihydropyridine-4(1*H*)-one **2**[8] was prepared in 94% yield from commercially available 4-methoxypyridine, by introduction of the methyl group into 4-methoxypyridine via nucleophilic addition using methylmagnesium bromide in the presence of carbobenzyloxy chloride.[9] Compound **3** was prepared from the lithium enolate of **2** with 2,6-dichlorobenzyl bromide. Although we examined several methods for oxidation of compound **3**, aromatization reaction did not occur. We finally found that dehydrogenation of the TBS enol ether of compound **4** with DDQ afforded compound **5** in 34% yield. 4(1*H*)-Pyridone **5** was treated with benzyl bromide in the presence of NaH in DMF, to afford **1** in 37% yield. The overall yield was only 8% from compound **2** (Scheme 1). Since these synthetic methods have multiple steps and low overall yield, we considered the synthesis of 3-(1-hydroxyalkyl)-2,3-dihydro-4-pyridone **6** by using the aldol reaction with **2**. The reaction of **2** with 2,6-dichlorobenzaldehyde was carried out in THF at $-78\,^{\circ}C$ in the presence of lithium hexamethyldisilazide and the corresponding aldol adduct **6** was obtained in 95% yield. The hydroxy group of compound **6** was converted into methanesulfonylate by treatment with methanesulfonyl chloride under ice cooling in 94% yield. Elimination of the methanesulfonyloxy group and isomerization



Reagents: (a) BnOCOCl (1 equiv.), CH_3MgBr (1.2 equiv.), THF, -25 °C; (b) 3 M HCl, r.t. (94% for two steps); (c) 2,6-dichlorobenzyl bromide (1.5 equiv.), LiHMDS (1.2 equiv.), THF, 0 °C (95%); (d) TBSOTf (1.5 equiv.), Et_3N (2 equiv.), CH_2Cl_2, 0 °C to r.t. (71%); (e) DDQ (1.2 equiv.), $NaHCO_3$ (1.2 equiv.), 1,4-dioxane, r.t. (34%); (f) BnBr (1.5 equiv.), NaH (1.5 equiv.), DMF, r.t. (37%); Overall yield was 8% from compound **2** to **5** (4 steps).

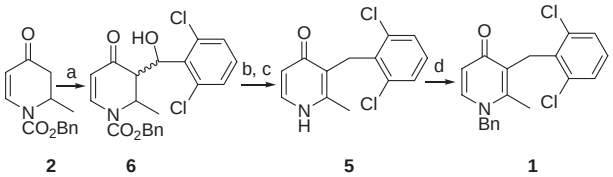
Scheme 1. Synthesis of compound **1**.[11]

of the *exo*-olefin by using potassium *tert*-butoxide gave the desired 4(1*H*)-pyridone **5** in 82% yield (two steps).

As described previously, the 1-benzyl-4-pyridone was obtained in 37% yield, together with 4-benzyloxypyridine in 25% yield, using DMF in the presence of sodium hydride (Scheme 1). The desired 1-benzylated 4-pyridone was prepared in 92% yield by changing the reaction solvent from DMF to THF. Compound **1** was obtained in 67% overall yield (Scheme 2).

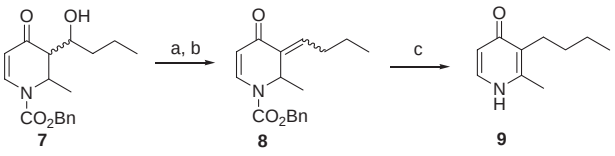
However, when the above methods were applied to aliphatic aldehydes, the desired 4(1*H*)-pyridones were not obtained at all. Since the *exo*-olefin **8**[10] was isolated from the reaction mixture (*E*:*Z* = 1:4), we examined isomerization of the *exo*-olefin to form the 4(1*H*)-pyridone. The desired 4(1*H*)-pyridone **9** was obtained in high yield through isomerization of **8** by using catalytic palladium under a hydrogen atmosphere (Scheme 3). Therefore, it was possible to prepare a wide range of 2,3-disubstituted 4(1*H*)-pyridones by using the two procedures.

Finally, these methods were applied to prepare the 2,3-disubstituted 4(1*H*)-pyridone derivatives listed in Table 1. The



Reagents: (a) 2,6-dichlorobenzaldehyde (1.3 equiv.), LiHMDS (1.1 equiv.), THF, -78 °C (98%); (b) MsCl (2 equiv.), pyridine, 0 °C to r.t. (94%); (c) ^tBuOK (3 equiv.), THF, 0 °C (87%); (d) BnBr (1.3 equiv.), NaH (1.3 equiv.), THF, r.t. (92%); Overall yield was 67% from compound **2** to **5** (4 steps).

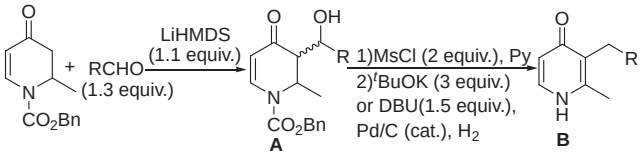
Scheme 2. Improved synthesis method of compound **1**.



Reagents: (a) MsCl (2 equiv.), pyridine, 0 °C to r.t. (94%); (b) DBU (1.5 equiv.), THF, r.t. (85%); (c) H_2, 10%Pd/C (cat.), r.t. (93%).

Scheme 3. Isomerization of **8** to **9** by using Pd/C.

Table 1. Synthesis of 3-substituted 4(*H*)-pyridone derivatives



Entry	R	Yield/%[c] A	B	Entry	R	Yield/%[c] A	B
1[a]		36,	75	6[a]		97,	79
2[a]		48,	77	7[a]		79,	37
3[a]		98,	82	8[b]		97,	57
4[a]		90,	41	9[b]	^{n}Pr	quant,	70
5[a]		78,	32				

[a]Potassium *tert*-butoxide was used. [b]DBU and Pd/C, H_2 was used. [c]Isolated yield.

desired 2,3-disubstituted 4(1*H*)-pyridones were obtained in fairly good yields.

Thus, we have developed a new and efficient method to prepare various 2,3-disubstituted 4-pyridones from 4-methoxypyridine through aldol condensation and isomerization of *exo*-olefin as key reactions, in good to high yields. Further studies on 4-pyridones, including 5- and 6-substituted derivatives, are in progress.

References and Notes

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9 When the other Grignard reagents such as ethylmagnesium or butylmagnesium bromide were used for addtion of 4-methoxypyridine, desired 2,3-dihydropyridines were obtained 81 or 99%, respectively. Each 4-pyridone derivative obtained through aldol condensation and isomerization of *exo*-olefin in 11 or 22% total yield.

10 The aldol adduct **7** that was similarly prepared (Scheme 2) was treated with DBU under mild reaction conditions to afford compound **8**.

11 A typical experimental procedure is as follows; to a solution of **2**[8] (5.0 g, 20.4 mmol) in THF (60 mL) at −78 °C was added 1 M lithium bis(trimethylsilyl)amide in THF (22.4 mL). The resulting mixture was stirred at 0 °C for 30 min and cooled to −78 °C, then a solution of 2,6-dichlorobenzaldehyde (4.64 g, 26.5 mmol) was added and stirring was continued at −78 °C for 1 h. The mixture was poured into saturated NH_4Claq (200 mL). Usual work-up and separation by column chromatography on silica gel afforded **3** (8.4 g, 98%) as a colorless oil. Next, to a solution of the prepared **3** (1.61 g, 3.83 mmol) in pyridine (10 mL) at 0 °C was added mesyl chloride (0.445 mL, 5.75 mmol). The resulting mixture was stirred at room temperature for 3 h then poured into water (150 mL). Usual work up and separation by column chromatography on silica gel gave **4** (1.79 g, 94%) as a colorless oil. To a solution of **4** (1.00 g, 2.01 mmol) in THF (35 mL) was added potassium *tert*-butoxide (1.13 g, 10.0 mmol). The resulting solution was stirred at room temperature for 10 min then poured into 5% NH_4Claq (100 mL). Usual work up and separation by column chromatography on silica gel afforded **5** (469 mg, 87%) as a white powder. Finally, to a solution of **5** (100 mg, 0.373 mmol) in THF (3 mL) was added sodium hydride (19.4 mg, 0.485 mmol as a 60% dispersion in mineral oil), followed by benzyl bromide (0.0577 mL, 0.485 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with ethyl acetate and washed with 5% NaClaq. Usual work up and separation by column chromatography on silica gel gave **1** (123 mg, 92%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (3H, s), 4.36 (2H, s), 5.01 (2H, s), 6.38 (1H, d, J = 7.6 Hz), 6.96–7.06 (3H, m), 7.21–7.39 (6H, m): HRMS (FAB$^+$) m/z: calcd for $C_{20}H_{18}Cl_2NO$ $(M + H)^+$: 358.0765, found: 358.0775.

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