# Syntheses of 5-(Alkylaminocarbonyl)-4,6-dimethyl-2-pyridones from *N*-Alkyl-3-oxobutanamides

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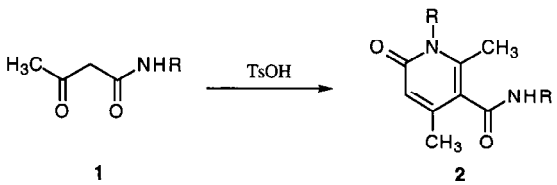
*Received 26 March 1998; revised 7 May 1998*

**Abstract:** 1-Alkyl-5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridones were obtained in high yields from the self-condensation of *N*-alkyl-3-oxobutanamides in the presence of *p*-toluenesulfonic acid as a catalyst at 100–110 °C for 11–24 hours without solvent.

**Key words:** self-condensation, 5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridone, *N*-alkyl-3-oxobutanamide

2-Pyridone derivatives are found in the pyridine nucleotide cycle in plants and also show several physiological activities, such as antifungal and antibiotic.[1] They have been prepared by numerous methods,[1] for example by the oxidation of an *N*-substituted pyridinium salt, by Knovenagel-type reaction, such as cross-condensation of cyanoacetoamide and $\beta$-dicarbonyl compounds by basic catalysts, or by the reaction of 2-pyrones with primary amines.[1–4]

We have been studying the chemistry of $\alpha$-acylketene *O*,*N*-acetals because of their easy synthesis[5] and unique reactivity[6] and have found that they were converted to 2-pyridone derivatives.[7] A mechanistic study of this reaction resulted an efficient synthetic method for 2-pyridone derivatives from *N*-substituted acetoacetamides in the presence of acid. Although this chemistry is considered basic, there were few reports on the synthesis of 2-pyridone derivatives from acetoacetamide derivatives, in which the yields were not satisfactory to our surprise.[8] Moreover, our procedure was quite simple, in which the desired product was obtained by heating a mixture of *N*-substituted acetoacetamide and *p*-toluenesulfonic acid without solvent, and then by column chromatographic purification of the resulting mixture directly. This may be so-called "the environmentally friendly" procedure. Here we wish to describe the detail of this easy and new method.




1 2

Reaction of *N*-propyl-3-oxobutanamide **(1b)** was performed by use of an equimolar amount of *p*-toluenesulfonic acid as a catalyst. When the reaction was performed using a solvent, 4,6-dimethyl-1-propyl-5-(propylaminocarbonyl)-2-pyridone **(2b)** was obtained in moderate yield (for example, benzene: 46%, acetonitrile, 45%, dichloromethane: 14%), while **2b** was obtained in 84% yield when the reaction was performed without solvent at 100–110 °C for 11 hours. The reaction proceeded slowly at lower temperature. Using an equimolar amount of *p*-toluenesulfonic acid was effective for this reaction, while using a half equivalent of acid made the reaction slow, and no reaction occurred without acid. The reaction without solvent was convenient for the separation of the product, because product **2** was obtained by direct column chromatographic purification of the reaction mixture without concentration. The product **2b** was identified by spectroscopic and elemental analyses. Its structure was also confirmed by X-ray crystallographic analysis of a suitable single crystal of **2b** (Figure and Experimental Section). From the X-ray data, bond lengths and angles are reasonable for 2-pyridone structure, and the aminocarbonyl moiety does not resonance with carbon–carbon double bonds in 2-pyridone by sterical demand.

**Table 1.** Synthesis of 1-Alkyl-5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridones **2**[a]

| Product | | Time | Yield[b] | mp |
|---|---|---|---|---|
| **2** | R | (h) | (%) | (°C) |
| **2a** | Me | 12 | 97 | 177.5–178.0 |
| **2b** | Pr | 11 | 84 | 132.5–133.0 |
| **2c** | i-Pr | 24 | 80 | 128.4–129.1 |
| **2d** | $PhCH_2$ | 20 | 92 | 81.2–82.4 |

[a] Satisfactory microanalyses obtained C±0.26, H±0.18, N±0.13; for **2d** this was calculated for the monohydrate.
[b] Yield of the isolated product.

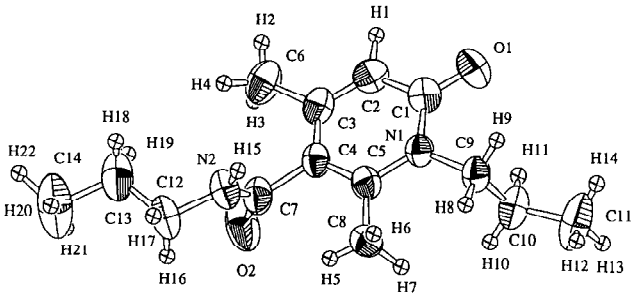



**Figure.** ORTEP Diagram for 4,6-dimethyl-1-propyl-5-(propylaminocarbonyl)-2-pyridone **2b** showing 50% probability thermal ellipsoids.

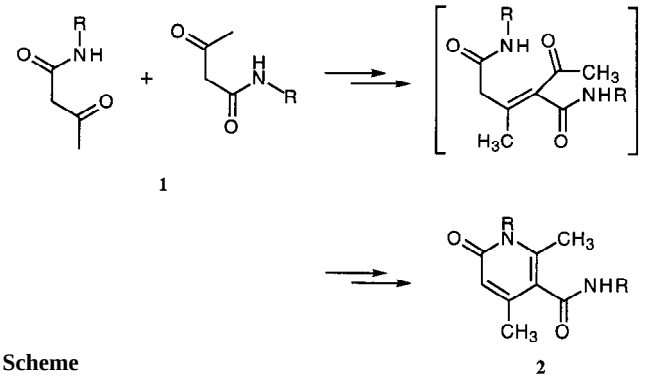
Several *N*-alkyl-3-oxobutanamides **(1)** were reacted under these conditions and converted to 1-alkyl-5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridones **2** in high yields. Representative results are listed in Table 1, and analytical data for identification of the products are given in Table 2.

**Table 2.** Spectral Data of 1-Alkyl-5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridones **2**

| 2 | IR $\nu$ ($cm^{-1}$) | $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$, $J$ (Hz) |
|---|---|---|
| **2a** | 1525, 1640 | 2.14 (s, 3H, C$H_3$), 2.30 (s, 3H, C$H_3$), 2.99 (d, 3H, $J$ = 4.4, C$H_3$), 3.37 (s, 3H, C$H_3$), 6.09 (s, 1H, –C$H$=), 7.42 (br, 1H, N$H$) |
| **2b** | 1522, 1640 | 0.96 (t, 3H, $J$ = 7.6, $CH_2CH_2CH_3$), 1.02 (t, 3H, $J$ = 7.4, $CH_2CH_2CH_3$), 1.61 (sextet, 2H, $J$ = 7.2, $CH_2CH_2CH_3$), 1.67 (sextet, 2H, $J$ = 7.2, $CH_2CH_2CH_3$), 2.14 (s, 3H, C$H_3$), 2.34 (s, 3H, C$H_3$), 3.39 (q, 2H, $J$ = 6.6, $NHCH_2CH_2CH_3$), 3.81 (t, 2H, $J$ = 7.8, $NCH_2CH_2CH_3$), 6.13 (s, 1H, –C$H$=), 6.99 (br, 1H, N$H$) |
| **2c** | 1525, 1640 | 1.26 [d, 3H, $J$ = 6.8, CH(C$H_3$)(C$H_3$)], 1.55 [d, 3H, $J$ = 6.8, CH(C$H_3$)(C$H_3$)], 2.11 (s, 3H, C$H_3$), 2.34 (s, 3H, C$H_3$), 4.24 [d of heptet, 1H, $J$ = 8.0 and 6.8, NHC$H$(C$H_3$)$_2$], 4.43 [br, 1H, NC$H$(C$H_3$)$_2$], 6.05–6.30 (m, 2H, –C$H$= and N$H$) |
| **2d** | 1520, 1640 | 2.15 (s, 3H, C$H_3$), 2.22 (s, 3H, C$H_3$), 4.55 (d, 2H, $J$ = 5.6, $NHCH_2C_6H_5$), 5.17 (s, 2H, $NCH_2C_6H_5$), 6.27 (s, 1H, –C$H$=), 7.07–7.35 (m, 10H, Ar) |

*N*-Isopropyl-3-oxobutanamide **(1c)** also converted to a sterically hindered five-substituted dihydropyridine derivative in 80% yield.

Possible mechanism of this reaction is shown in the Scheme. Double condensations and double dehydrations seem to afford the product. Claisen and Meyer reported the condensation of 3-oxobutanamide giving 5-aminocarbonyl-4,6-dimethyl-2-pyridone in low yield when being heated,[8b] but Kato et al. reinvestigated this reaction and proposed a different structure for the products, 3-acetyl-4-amino-6-methyl-2-pyridone (byproduct, 3%) and 2,6-dimethyl-4-pyrimidone (main product, 52%).[8c, d] Even though pyrolysis of 3-oxobutanamide gave the different products, Sato reported that the self-condensation of *N*-methyl-3-oxobutanamide in benzene in the presence of sulfuric acid afforded the 1,4,6-trimethyl-5-(methylaminocarbonyl)-2-pyridone in 63% yield with only elemental analysis, IR, and UV data.[8a]




**Scheme**

Self-condensation of $\beta$-oxo carbonyl compounds have been reported in only two cases. One is above and another is the condensation of ethyl 3-oxobutanoate in the presence of sulfuric acid to give 5-carbonyl-4,6-dimethyl-2-pyrone in only 27% yield.[9]

This synthetic way gives a facile method for the preparation of 1-alkyl-5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridone derivatives. That is, the starting materials, *N*-substituted 3-oxobutanamides, are easily prepared by the reaction of diketene and primary amines, and the simple operation affords the product. A variety of synthetic procedures were reported for 2-pyridone derivatives, but still most of our products are new compounds. That is to say, our method becomes complementary to others.

Self-condensation of *N*-substituted 3-oxobutanamide was demonstrated to construct 6-membered heterocyclic compound, 2-pyridone derivatives. Using no solvent afforded the product in quite high yields by simple treatment of the reaction mixture.

$^1H$ NMR spectra were measured on a JEOL JNM A-400 (400 MHz) spectrometer using TMS as an internal standard. IR spectra were measured on a Shimadzu IR-408 spectrophotometer. GC-MS were recorded on a Shimadzu GP2000A instrument. Elemental analysis were performed at the Microanalytical Center of Kyoto University. X-ray analysis was conducted on a Rigaku RASA-7R four-circle diffractometer. Mps were measured on a Yanako Model MP and were not corrected.

All solvents were dried by standard methods.[10] Commercially available compounds were used without purification. *N*-Alkyl-3-oxobutanamides **1** were prepared by modified methods according to the literature method.[11]

***N*-Alkyl-3-oxobutanamides 1; General Procedure:**

In a 25-mL flask was placed a mixture of diketene (50 mmol) and MeCN (100 mL). To this was added an amine (50 mmol) slowly at r.t., and the mixture was stirred for 4 h. The resulting mixture was purified by column chromatography (silica gel 60, EtOAc).

***N*-Alkyl-5-(alkylaminocarbonyl)-4,6-dimethyl-2-pyridones 2; General Procedure:**

Into a 25-mL test tube were introduced *N*-alkyl-3-oxobutanamide **1** (2.0 mmol) and anhyd TsOH (0.38 g, 2.0 mmol). The mixture was heated at 100–110 °C for 11–24 h. The resulting mixture was purified by column chromatography (silica gel 60, hexane/EtOAc=1, and EtOAc/acetone=1).

**Crystallographic Data Collections and Structure Determination of 2b:[12]**

The crystals of **2b** suitable for X-ray diffraction studies were prepared by recrystallization from hexane/$Et_2O$. Relevant crystal and data statistics are summarized in Table 3. The unit cell parameter at 20 °C was determined by a least-squares fit to 2$\theta$ values of 25 strong higher reflections. Three standard reflections were chosen and monitored every 150 reflections and showed no significant intensity decay during

**Table 3.** Crystallographic Data for 4,6-Dimethyl-1-propyl-5-(propylaminocarbonyl)-2-pyridone (**2b**)

| Crystal Parameters and Measurement of Intensity Data | | | |
|---|---|---|---|
| Chemical Formula | $C_{14}H_{22}N_2O_2$ | Formula Weight | 250.34 |
| Crystal | colorless, prismatic | Size (mm) | 0.4×0.1×0.4 |
| Crystal System | monoclinic | Space Group | $P2_1/c$ |
| *a* (Å) | 13.204(3) | *b* (Å) | 8.647(3) |
| *c* (Å) | 13.616(3) | $\beta$ (deg) | 107.41(2) |
| V (Å$^3$) | 1483.3(6) | Z | 4 |
| $D_{calc}$ (g/cm$^3$) | 1.121 | | |
| Diffractometer | Rigaku AFC7R | $\mu$ (MoK$\alpha$) (cm$^{-1}$) | 0.75 |
| Radiation (Å) | Mo, 0.71069 (graphite monochromated) | | |
| Scan Type | $\omega$-2$\theta$ | Scan Rate (°/min) | 16 |
| Scan Width (deg) | 1.68+0.30 tan$\theta$ | 2$\theta$ max (deg) | 55.0 |
| No of Unique Data | 3644 | No of obsd. | 1676 (I>3$\sigma$(I)) |
| *R* | 0.063 | $R_W$ | 0.052 |
| Goodness of Fit | 4.53 | Max Shift/Error | 0.16 |

**Table 4.** Selected Bond Distances and Angles for 4,6-Dimethyl-1-propyl-5-(propylaminocarbonyl)-2-pyridone (**2b**)

| Intramolecular Distances (Å) (standard deviation) | | | | | |
|---|---|---|---|---|---|
| O(1)–C(1) | 1.243(4) | O(2)–C(7) | 1.219(4) | N(1)–C(1) | 1.404(4) |
| N(1)–C(5) | 1.385(4) | N(1)–C(9) | 1.479(4) | N(2)–C(7) | 1.322(4) |
| C(1)–C(2) | 1.434(5) | C(2)–C(3) | 1.357(5) | C(3)–C(4) | 1.417(4) |
| C(3)–C(6) | 1.516(5) | C(4)–C(5) | 1.364(4) | C(4)–C(7) | 1.513(4) |
| C(5)–C(8) | 1.498(5) | | | | |

| Selected Bond Angles (deg) (standard deviation) | | | |
|---|---|---|---|
| C(1)–N(1)–C(5) | 122.8(3) | C(1)–N(1)–C(9) | 115.6(3) |
| C(5)–N(1)–C(9) | 121.6(3) | O(1)–C(1)–N(1) | 120.2(3) |
| O(1)–C(1)–C(2) | 124.4(4) | N(1)–C(1)–C(2) | 115.4(3) |
| C(1)–C(2)–C(3) | 122.6(4) | C(2)–C(3)–C(4) | 119.1(3) |
| C(2)–C(3)–C(6) | 119.7(4) | C(4)–C(3)–C(6) | 121.2(4) |
| C(3)–C(4)–C(5) | 120.7(3) | C(3)–C(4)–C(7) | 118.6(3) |
| C(5)–C(4)–C(7) | 120.6(3) | N(1)–C(5)–C(4) | 119.4(3) |
| N(1)–C(5)–C(8) | 117.7(3) | C(4)–C(5)–C(8) | 122.8(3) |

the data collection (less than 3%). The crystal structure was solved by the direct method (Sir) and refined by the full-matrix least squares method. Measured nonequivalent reflections with $I>3.0\sigma(I)$ were used for the structure determination. In the subsequent refinement the function $\Sigma\omega(|F_o|-|F_c|)^2$ was minimized, where $|F_o|$ and $|F_c|$ are the observed and calculated structure factors amplitudes, respectively. The agreement indices are defined as $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $R_w = [\Sigma\omega(|F_o|-|F_c|)^2/\Sigma\omega(|F_o|)^2]^{1/2}$ where $\omega^{-1} = \sigma^2(F_o) = \sigma^2(F_o^2)/(4F_o^2)$. The positions of all non-hydrogen atoms and aromatic hydrogen were found from a difference Fourier electron density map and the positions of other hydrogen atoms were determined by calculations, and then refined anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms. All calculations were performed using the TEXSAN crystallographic software package. Selected bond distances and angles are summarized in Table 4.

*We thank Dr. Takayuki Yamashita for helpful discussions during the course of this work. This work was partially supported by a grant to RCAST at Doshisha University from the Ministry of Education, Japan.*

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