A Facile One-Pot Synthesis of Substituted Pyridine-2,4(1H,3H)-diones from Acyl(carbamoyl)ketene S,S-Acetals

Yunhui Li,a Wenliang Li,a,b Rui Zhang,b Yang Zhou,b Dewen Dong*a

a School of Chemistry and Environmental Engineering, Changchun University of Science and Technology, Changchun 130022, P. R. of China
b Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, P. R. of China
Fax +86(431)85098635; E-mail: dwdong@ciac.jl.cn

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Abstract: A facile and efficient one-pot synthesis of substituted pyridine-2,4(1H,3H)-diones has been developed. Subjected to N,N-dimethylformamide dimethyl acetal (DMFDMA) in N,N-dimethylformamide at 120 °C, a series of acyl(carbamoyl)ketene S,S-acetals were converted into the corresponding substituted pyridine-2,4(1H,3H)-diones in high yields.

Key words: annulation, N,N-dimethylformamide dimethyl acetal, Michael addition, α-oxoketene S,S-acetals, pyridine-2,4(1H,3H)-diones

Over the past few decades, the utility of α-oxoketene S,S-acetals as versatile intermediates in organic synthesis has been recognized.1 As three carbon 1,3-bielectrophilic synths, α-oxoketene S,S-acetals have been widely applied in the synthesis of substituted and/or fused aromatic structural frameworks by reaction with organometallic nucleophiles, such as Grignard reagents,2 Reformatsky reagents,3 organolithium reagents,4 and organocuprate reagents.5 Also they have been extensively exploited for the construction of five- and six-membered carbocycles7 and heterocycles,8 relying upon the utilization of acyl(carbamoyl)ketene S,S-acetals, derived from aldol condensation of acylketene S,S-acetals with aldehydes,9 as a five-carbon 1,5-bielectrophilic species in the formal [5+1] annulation with various nucleophiles. Considering the synthetic importance of acyl(carbamoyl)ketene S,S-acetals, we recently investigated the aldol condensation reaction of 3-(1,3-dithiolan-2-ylidene)pentane-2,4-dione in water and obtained both mono- and double-condensed products,10 which were, in turn, further used for the synthesis of thiopyrano[2,3-b]thiopyran-4,5-diones via a double formal [5+1] annulation.11 In connection with our previous work and our continuing interest in the synthesis of valuable heterocycles, we examined the reaction of acyl(carbamoyl)ketene S,S-acetals 1 with N,N-dimethylformamide dimethyl acetal. As a result, we achieved a convenient one-pot synthesis of substituted pyridine-2,4(1H,3H)-diones. Herein, we wish to report our results. Substrates, acyl(carbamoyl)ketene S,S-acetals 1, were prepared according to our published procedure.12 With a series of substrates 1a–j in hand, we then selected 2-(1,3-dithiolan-2-ylidene)-3-oxo-N-phenylbutanamide (1a) as a model compound to examine its behavior under different conditions.

Thus, the reaction of 1a with N,N-dimethylformamide dimethyl acetal (1.5 equiv) in N,N-dimethylformamide was first attempted at room temperature. Unfortunately, no reaction was observed as monitored by TLC. When 1a was subjected to N,N-dimethylformamide dimethyl acetal (1.5 equiv) in N,N-dimethylformamide at 60 °C, the reaction proceeded smoothly and furnished a product, which was characterized as (E)-5-(dimethylamino)-2-(1,3-dithiolan-2-ylidene)-3-oxo-N-phenylpent-4-enamide (2a) (86% yield), on the basis of its spectral and analytical data (Scheme 1). It was very interesting that when the reaction of 1a with N,N-dimethylformamide dimethyl acetal (1.5 equiv) was performed in N,N-dimethylformamide at 120 °C, 3-(1,3-dithiolan-2-ylidene)-1-phenylpyridine-2,4(1H,3H)-dione (3a) was obtained in 91% yield.

Scheme 1 Reaction of 1a with N,N-dimethylformamide dimethyl acetal in N,N-dimethylformamide

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amide dimethyl acetal (1.5 equiv) was carried out in dimethylformamide at 120 °C, and some of the results are summarized in Table 1. It was observed that all the reactions of acyl(carbamoyl)ketene S,S-acetals proceeded smoothly to afford the corresponding substituted pyridine-2,4(1H,3H)-diones 3b–j in high yields (up to 94%). When 2-(1,3-dithiolan-2-ylidene)-N-methyl-3-oxobutanamide was subjected to identical conditions, unfortunately, no major product was obtained from the intractable reaction mixture. The results reveal that the N-aryl amine function of 1 is crucial for the pyridine-2,4(1H,3H)-dione synthesis.

Actually, substituted pyridine-2,4(1H,3H)-diones and their benzo-fused derivatives represent an important class of aza-heterocycles that are widely distributed among a large number of alkaloids that have useful biological and pharmacological activities. In the present work, we provided a facile and efficient one-pot synthesis of substituted pyridine-2,4(1H,3H)-diones 3 from readily available acyl(carbamoyl)ketene S,S-acetals 1. It should be noted that the pyridine-2,4(1H,3H)-dione of type 3 obtained possess very rich functionality, such as α,β-unsaturated carbonyl and β-dicarbonyl groups, and, in particular, the α-oxoketene S,S-acetal moiety, which may render them extremely versatile as valuable synths in other transformations. For example, the characteristic 1,3-dithiolan-2-ylidene group has the potential to be converted into thioesters, 13,16 enamines, 17 1,3-dithiolan-2-yl, 18 and aromatic rings 19 through ring-opening, reduction, substitution, and cycloaromatization reactions, respectively.

It is worth mentioning that in Bi’s recent work on anti-Michael additions of amide anions to enones, they developed a regiospecific approach to tetrmeric acid derivatives as shown in Scheme 2.20 They found that the varied aryl substituents at β-position of enones 4 had a lower effect on the anti-Michael addition. In contrast, the anti-Michael adduct was not obtained in our present work, which suggested that the character of substituents, i.e. their electronic effect, at the β-position of the enone plays a crucial role in the regioselectivity of the cyclization. 21

In summary, a facile and efficient synthesis of pyridine-2,4-diones starting from acyl(carbamoyl)ketene S,S-acetals is described, which involves tandem Aldol-type condensation and aza-nucleophilic vinyl substitution (SNV, aza-Michael addition/elimination) reactions. The simple execution, readily available substrates, mild conditions, high yields, and wide range of synthetic potential of the products make this protocol very attractive.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. 1H NMR and 13C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard at 25 °C on a Varian Inova-500 spectrometer. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm⁻¹. Elemental analyses were conducted on a PE-2400 analyzer (Perkin-Elmer). Petroleum ether (PE) used was the fraction boiling in the range 60–90 °C. Selected data are given for compounds 3a–j.

![Scheme 2](https://example.com/scheme2.png)

**Scheme 2** Intramolecular anti-Michael addition reaction reported by Bi.20

(Scheme 1, Table 1, entry 1). It is assumed that the formation of 3a involved tandem Aldol-type condensation and aza-nucleophilic vinyl substitution (SNV) reactions, which can be regarded as a formal [5+1] annulation.

To examine the scope of the one-pot cyclization reaction, a range of reactions of acyl(carbamoyl)ketene S,S-acetals 1 bearing various amide groups with N,N-dimethylformamide dimethyl acetal (1.5 equiv) was carried out in N,N-dimethylformamide at 120 °C, and some of the results are summarized in Table 1. It was observed that all the reactions of 1b–j with N,N-dimethylformamide dimethyl acetal proceeded smoothly to afford the corresponding branched pyridine 3b–j in high yields (up to 94%). When 2-(1,3-dithiolan-2-ylidene)-N-methyl-3-oxobutanamide was subjected to identical conditions, unfortunately, no major product was obtained from the intractable reaction mixture. The results reveal that the N-aryl amine function of 1 is crucial for the pyridine-2,4(1H,3H)-dione synthesis.

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### Table 1 One-Pot Synthesis of Substituted Pyridine-2,4(1H,3H)-diones

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<th>Entry</th>
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<th>Product 3</th>
<th>Yield (%)</th>
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<td>3d</td>
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<td>1.0</td>
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</table>

* Isolated yield.

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sat. aq NaCl (50 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 20 mL), and the combined organic phases were washed with H$_2$O (3 × 20 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, PE:EtOAc, 1:3) to give 3a (91% yield) as a yellow solid; mp 222–224 °C.

IR (KBr): 3066, 1624, 1517, 1491, 1389, 1332, 1287, 1075, 910, 822, 771 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 3.38–3.40 (m, 2 H), 3.42–3.45 (m, 2 H), 5.98 (d, $J = 8.0$ Hz, 1 H), 7.26 (d, $J = 8.0$ Hz, 1 H), 7.34 (t, $J = 8.0$ Hz, 2 H), 7.39 (t, $J = 8.0$ Hz, 1 H), 7.46–7.49 (m, 2 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 37.3, 38.2, 108.1, 118.2, 126.9, 128.3, 129.4, 140.2, 141.3, 162.1, 179.6, 191.5.

Anal. Calcd for C$_{15}$H$_{13}$NO$_2$S$_2$: C, 59.38; H, 4.32; N, 4.62. Found: C, 59.26; H, 3.92; N, 4.76.

3-(1,3-Dithiolan-2-ylidene)-1-(4-tolyl)pyridine-2,4(1'H,3'H)-dione (3b)

Yellow solid; mp 218–220 °C.

IR (KBr): 2904, 1627, 1576, 1512, 1391, 1326, 1288, 1108, 910, 821 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.39 (s, 3 H), 3.38–3.39 (m, 2 H), 3.41–3.43 (m, 2 H), 5.96 (d, $J = 8.0$ Hz, 1 H), 7.20 (d, $J = 8.5$ Hz, 2 H), 7.24 (d, $J = 8.0$ Hz, 1 H), 7.27 (d, $J = 8.5$ Hz, 2 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 21.1, 37.2, 38.1, 107.9, 118.3, 126.6, 130.0, 137.6, 138.3, 141.5, 162.2, 179.6, 191.3.

Anal. Calcd for C$_{14}$H$_{11}$NO$_2$S$_2$: C, 58.11; H, 3.83; N, 4.84. Found: C, 58.02; H, 3.92; N, 4.76.

3-(1,3-Dithiolan-2-ylidene)-1-(2-tolyl)pyridine-2,4(1'H,3'H)-dione (3c)

Yellow solid; mp 183–185 °C.

IR (KBr): 3058, 1623, 1576, 1427, 1396, 1331, 1278, 907, 811, 730 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.19 (s, 3 H), 3.37–3.40 (m, 2 H), 3.43–3.46 (m, 2 H), 5.97 (d, $J = 8.0$ Hz, 1 H), 7.10 (d, $J = 8.0$ Hz, 1 H), 7.20 (d, $J = 7.5$ Hz, 1 H), 7.23–7.33 (m, 3 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 17.7, 37.3, 38.2, 107.9, 118.3, 127.2, 127.8, 129.1, 131.2, 135.7, 139.3, 141.3, 161.9, 179.7, 191.4.

Anal. Calcd for C$_{15}$H$_{13}$NO$_2$S$_2$: C, 59.38; H, 4.42; N, 4.62. Found: C, 59.24; H, 4.44; N, 4.70.

1-(2,4-Dimethylphenyl)-3-(1,3-dithiolan-2-ylidene)pyridine-2,4(1'H,3'H)-dione (3d)

Yellow solid; mp 169–171 °C.

IR (KBr): 2920, 1626, 1579, 1505, 1425, 1404, 1326, 1280, 1257, 818 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.14 (s, 3 H), 2.36 (s, 3 H), 3.36–3.40 (m, 2 H), 3.42–3.45 (m, 2 H), 5.96 (d, $J = 8.0$ Hz, 1 H), 7.06–7.11 (m, 3 H), 7.14 (s, 1 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 17.6, 21.1, 37.3, 38.1, 107.8, 118.3, 127.5, 127.8, 131.8, 135.3, 136.7, 139.0, 141.6, 162.1, 179.8, 191.3.

Anal. Calcd for C$_{15}$H$_{13}$NO$_2$S$_2$: C, 60.54; H, 4.46; N, 4.41. Found: C, 60.39; H, 4.85; N, 4.62.

1-(4-Methoxyphenyl)-3-(1,3-dithiolan-2-ylidene)pyridine-2,4(1'H,3'H)-dione (3e)

Yellow solid; mp 238–240 °C.

IR (KBr): 2907, 1628, 1575, 1510, 1401, 1323, 1289, 1241, 1026, 817 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 3.38–3.41 (m, 2 H), 3.48–3.45 (m, 2 H), 3.85 (s, 3 H), 5.96 (d, $J = 8.5$ Hz, 1 H), 6.98 (d, $J = 9.0$ Hz, 2 H), 7.23–7.27 (m, 3 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 37.3, 38.2, 107.8, 118.0, 128.5, 134.1, 138.6, 140.7, 162.0, 179.4, 191.9.

Synthesis of Pyridine-2,4(1'H,3'H)-diones 3413

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(1H,3H)-dione (3j)
Yellow solid; mp 199–201 °C.
IR (KBr): 1627, 1577, 1541, 1479, 1423, 1397, 1371, 1246, 1155, 1177, 1088, 758 cm–1.

(E)-5-(Dimethylamino)-2-(1,3-dithiolan-2-ylidene)-3-oxo-N-phenylpent-4-enamide (2a)
Yellow solid; mp 198–200 °C.
IR (KBr): 2923, 1630, 1541, 1491, 1440, 1375, 1409, 1617, 1796, 1916.

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