

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

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Abstract: A facile and efficient one-pot synthesis of substituted pyridine-2,4(1*H*,3*H*)-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(1*H*,3*H*)-diones in high yields.

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

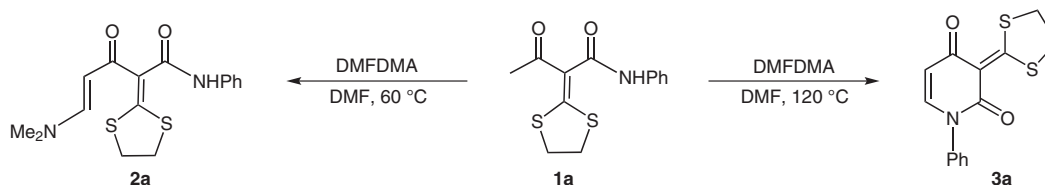
Over the few past decades, the utility of α -oxoketene *S,S*-acetals as versatile intermediates in organic synthesis has been recognized.¹ As three carbon 1,3-bielectrophilic synthons, α -oxoketene *S,S*-acetals have been widely applied in the synthesis of substituted and/or fused aromatic structural 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 heterocycles by reaction with heteronucleophiles, such as hydrazine, hydroxylamine, guanidine, amidines, enamines, and diamines.⁶

During the course of our studies on the chemistry of α -oxoketene *S,S*-acetals, we successfully developed novel strategies for the synthesis of highly substituted six-membered carbocycles⁷ and heterocycles,⁸ relying upon the utilization of alkenylketene *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 nucleophile. Considering the synthetic importance of alkenylketene *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(1*H*,3*H*)-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(1*H*,3*H*)-dione (**3a**) was obtained in 91% yield



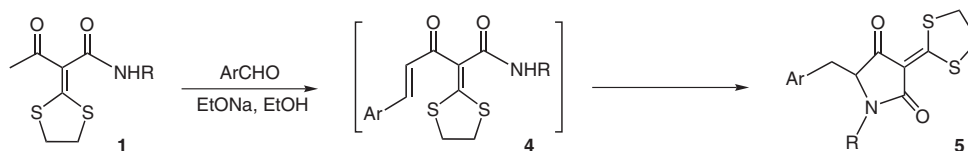
Scheme 1 Reaction of **1a** with *N,N*-dimethylformamide dimethyl acetal in *N,N*-dimethylformamide

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Scheme 2 Intramolecular anti-Michael addition reaction reported by Bi²⁰

(Scheme 1, Table 1, entry 1). It is assumed that the formation of **3a** involved tandem Aldol-type condensation and aza-nucleophilic vinyl substitution (S_NV) reactions,¹³ 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 substituted pyridine-2,4(1*H*,3*H*)-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 amide function of **1** is crucial for the pyridine-2,4(1*H*,3*H*)-dione synthesis.

Actually, substituted pyridine-2,4(1*H*,3*H*)-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.^{14,15} In the present work, we provided a facile and efficient one-pot synthesis of substituted pyridine-2,4(1*H*,3*H*)-diones **3** from readily available acyl(carbamoyl)ketene *S,S*-acetals **1**. It should be noted that the pyridine-2,4(1*H*,3*H*)-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 synthons in other transformations. For example, the characteristic 1,3-dithiolan-2-ylidene group has the potential to be converted into thioesters,^{11,16} enamines,¹⁷ 1,3-dithiolan-2-yl,¹⁸ and aromatic rings¹⁹ 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 tetramic 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 (S_NV , 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**.

3-(1,3-Dithiolan-2-ylidene)-1-phenylpyridine-2,4(1*H*,3*H*)-dione (**3a**); Typical Procedure

To a soln of **1a** (2.0 mmol) in DMF (10 mL) was added DMFDMA (3.0 mmol) in one portion at r.t. under stirring. The mixture was heated to 120 °C and stirred for 2.0 h. When the substrate **1a** had been consumed (monitored by TLC), the mixture was poured into

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

Entry	Substrate 1	Ar	Time (h)	Product 3	Yield ^a (%)
1	1a	Ph	2.0	3a	91
2	1b	4-MeC ₆ H ₄	1.5	3b	90
3	1c	2-MeC ₆ H ₄	1.5	3c	88
4	1d	2,4-Me ₂ C ₆ H ₃	2.0	3d	84
5	1e	4-MeOC ₆ H ₄	1.0	3e	90
6	1f	2-MeOC ₆ H ₄	1.5	3f	87
7	1g	2,5-MeO ₂ C ₆ H ₃	1.5	3g	86
8	1h	2-MeO-5-ClC ₆ H ₃	1.5	3h	93
9	1i	4-ClC ₆ H ₄	1.5	3i	92
10	1j	2-ClC ₆ H ₄	1.0	3j	94

^a Isolated yield.

sat. aq NaCl (50 mL). The mixture was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic phases were washed with H₂O (3 × 20 mL), dried (MgSO₄), 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.

¹H NMR (500 MHz, CDCl₃): δ = 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).

¹³C NMR (125 MHz, CDCl₃): δ = 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 C₁₄H₁₁NO₂S₂: 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-(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, 724 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 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).

¹³C NMR (125 MHz, CDCl₃): δ = 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 C₁₅H₁₃NO₂S₂: C, 59.38; H, 4.32; N, 4.62. Found: C, 59.42; H, 4.44; N, 4.70.

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.

¹H NMR (500 MHz, CDCl₃): δ = 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).

¹³C NMR (125 MHz, CDCl₃): δ = 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 C₁₅H₁₃NO₂S₂: C, 59.38; H, 4.32; N, 4.62. Found: C, 59.25; H, 4.20; N, 4.75.

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.

¹H NMR (500 MHz, CDCl₃): δ = 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).

¹³C NMR (125 MHz, CDCl₃): δ = 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 C₁₆H₁₅NO₂S₂: C, 60.54; H, 4.76; N, 4.41. Found: C, 60.39; H, 4.85; N, 4.50.

3-(1,3-Dithiolan-2-ylidene)-1-(4-methoxyphenyl)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.

¹H NMR (500 MHz, CDCl₃): δ = 3.38–3.41 (m, 2 H), 3.43–3.45 (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).

¹³C NMR (125 MHz, CDCl₃): δ = 37.5, 38.4, 55.8, 108.1, 114.8, 118.5, 128.2, 133.3, 141.9, 159.5, 162.6, 179.8, 191.5.

Anal. Calcd for C₁₅H₁₃NO₃S₂: C, 56.41; H, 4.10; N, 4.39. Found: C, 56.27; H, 4.21; N, 4.46.

3-(1,3-Dithiolan-2-ylidene)-1-(2-methoxyphenyl)pyridine-2,4(1*H*,3*H*)-dione (3f)

Yellow solid; mp 238–240 °C.

IR (KBr): 1630, 1576, 1500, 1429, 1398, 1325, 1280, 1256, 1015, 909, 826, 744 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.36–3.38 (m, 2 H), 3.40–3.41 (m, 2 H), 3.80 (s, 3 H), 5.93 (d, *J* = 8.0 Hz, 1 H), 7.01–7.05 (m, 2 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.26–7.27 (m, 1 H), 7.37–7.40 (m, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 37.2, 38.1, 55.8, 107.4, 112.2, 118.5, 120.8, 128.5, 129.2, 130.2, 142.4, 154.8, 162.2, 179.9, 190.7.

Anal. Calcd for C₁₅H₁₃NO₃S₂: C, 56.41; H, 4.10; N, 4.39. Found: C, 56.57; H, 4.18; N, 4.51.

1-(2,5-Dimethoxyphenyl)-3-(1,3-dithiolan-2-ylidene)pyridine-2,4(1*H*,3*H*)-dione (3g)

Yellow solid; mp 228–230 °C.

IR (KBr): 2832, 1630, 1580, 1510, 1419, 1399, 1283, 1233, 1042, 810 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.36–3.39 (m, 2 H), 3.41–3.44 (m, 2 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 5.94 (d, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 2.5 Hz, 1 H), 6.94–6.97 (m, 2 H), 7.09 (d, *J* = 8.0 Hz, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 37.5, 38.3, 56.1, 56.6, 107.7, 113.6, 115.2, 115.6, 118.8, 129.3, 142.5, 149.3, 153.8, 162.3, 180.1, 190.9.

Anal. Calcd for C₁₆H₁₅NO₄S₂: C, 55.00; H, 4.33; N, 4.01. Found: C, 54.87; H, 4.41; N, 3.96.

1-(5-Chloro-2-methoxyphenyl)-3-(1,3-dithiolan-2-ylidene)pyridine-2,4(1*H*,3*H*)-dione (3h)

Yellow solid; mp 210–212 °C.

IR (KBr): 3070, 1627, 1582, 1500, 1411, 1330, 1289, 1247, 1015, 911, 811 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.37–3.40 (m, 2 H), 3.42–3.44 (m, 2 H), 3.79 (s, 3 H), 5.94 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 9.0 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 2.5 Hz, 1 H), 7.34–7.36 (dd, *J*₁ = 9.0 Hz, *J*₂ = 2.5 Hz, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 37.5, 38.4, 56.4, 108.0, 113.5, 118.4, 125.5, 129.5, 129.7, 130.2, 142.0, 153.9, 162.1, 179.9, 191.3.

Anal. Calcd for C₁₅H₁₂ClNO₃S₂: C, 50.92; H, 3.42; N, 3.96. Found: C, 51.13; H, 3.37; N, 4.07.

1-(4-Chlorophenyl)-3-(1,3-dithiolan-2-ylidene)pyridine-2,4(1*H*,3*H*)-dione (3i)

Yellow solid; mp 231–233 °C.

IR (KBr): 1624, 1574, 1489, 1395, 1287, 1255, 1089, 1015, 910, 818, 760 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.40–3.42 (m, 2 H), 3.43–3.45 (m, 2 H), 5.99 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.0 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 37.3, 38.2, 108.5, 118.0, 128.2, 129.5, 134.1, 138.6, 140.7, 162.0, 179.4, 191.9.

Anal. Calcd for $C_{14}H_{10}ClNO_2S_2$: C, 51.93; H, 3.11; N, 4.33. Found: C, 51.81; H, 3.19; N, 4.42.

1-(2-Chlorophenyl)-3-(1,3-dithiolan-2-ylidene)pyridine-2,4(1H,3H)-dione (3j)

Yellow solid; mp 199–201 °C.

IR (KBr): 1627, 1577, 1541, 1479, 1423, 1397, 1371, 1246, 1155, 1054, 813, 760 cm^{-1} .

1H NMR (500 MHz, $CDCl_3$): δ = 3.38–3.41 (m, 2 H), 3.43–3.46 (m, 2 H), 6.00 (d, J = 8.0 Hz, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 7.36–7.41 (m, 3 H), 7.38–7.56 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.3, 38.2, 108.1, 118.0, 127.9, 129.9, 130.3, 130.5, 132.4, 137.5, 140.9, 161.7, 179.6, 191.6.

Anal. Calcd for $C_{14}H_{10}ClNO_2S_2$: C, 51.93; H, 3.11; N, 4.33. Found: C, 51.78; H, 3.06; N, 4.21.

(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, 1417, 1354, 1322, 1265, 1177, 1088, 758 cm^{-1} .

1H NMR (500 MHz, $CDCl_3$): δ = 2.89 (s, 3 H), 3.15 (s, 3 H), 3.31–3.35 (m, 4 H), 5.49 (d, J = 12.5 Hz, 1 H), 7.05 (t, J = 7.5 Hz, 1 H), 7.29 (t, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.69 (d, J = 12.5 Hz, 1 H), 9.60 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.3, 37.7, 38.5, 45.2, 93.5, 120.1, 124.1, 126.2, 129.3, 139.8, 153.8, 159.8, 166.8, 181.4.

Anal. Calcd for $C_{16}H_{18}N_2O_2S_2$: C, 57.46; H, 5.42; N, 8.38. Found: C, 57.39; H, 5.50; N, 8.24.

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