A Facile and Efficient Synthesis of 3,5-Disubstituted Tetronic Acids in Aqueous Media Involving Acid-Catalyzed Intramolecular Oxa-Pyridylethylation

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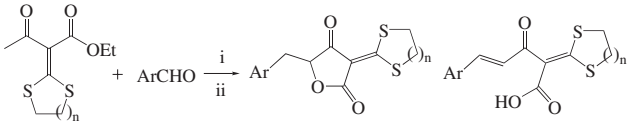
Abstract: A facile and efficient one-pot synthesis of 3-[bis(alkylthio/alkylamino)methylene]-5-(pyridyl/quinoylmethyl) furan-2,4(3*H*,5*H*)-diones **3** and **10**, based on a sequential aldol condensation and lactonization reaction between α-oxo ketene-*S*,*S*-acetals **1** and pyridine/qinoline-carboxaldehydes **2** in aqueous media, has been developed. A mechanism involving an acid-catalyzed intramolecular oxa-pyridylethylation reaction is proposed for the formation of the lactone ring.

Key words: aqueous media, tetronic acid derivatives, α-oxo ketene-*S*,*S*-acetals, oxa-pyridylethylation, α-oxo ketene-*N*,*N*-acetals

Tetronic acid derivatives (TADs), e.g. vitamin C and penicillic acid, have attracted much attention for their presence in many natural products along with a large array of useful biological and pharmacological activities.[1,2] To date, extensive work has been reported on the synthetic methodology for this kind of compounds and their practical applications. Generally, TADs can be principally synthesized either by the modification of the pre-constructed core scaffold of a TAD[3] or through the construction of 3-oxo-γ-lactone ring from appropriately substituted open chain precursors.[4] Nevertheless, to match the increasingly scientific and practical demands for TADs, it is still of continued interest and great importance to explore novel and efficient synthetic approaches for such compounds. On the other hand, α-oxo ketene-*S*,*S*-acetals are emerging as a kind of versatile intermediate[5] in the construction of heterocyclic[6] and carbocyclic[7] compounds over the last several decades. Pak and co-workers reported the aldol condensation of α-oxo ketene-*S*,*S*-acetals **1** with aryl aldehydes which was followed by ester hydrolysis and decarboxylation to give alkenoyl ketene dithoacetals **4**.[8] In our previous work,[9,10] we found that halodecarboxylation could further take place after the aldol condensation of α-oxo ketene-*S*,*S*-acetals **1** with some aryl aldehydes. As a part of further investigation of this kind of α-oxo ketene-*S*,*S*-acetals, we here wish to report a novel synthetic method for 3,5-disubstituted TADs **3** involving tandem aldol condensation and acid-catalyzed lactonization reaction of α-oxo ketene-*S*,*S*-acetals **1** with the selected heteroaryl aldehydes, as well as the further transformation to TADs **10** by the displacement reaction with various amines.



1 (n = 1, 2) **2** **3** (Ar = 4-Pyridyl, 2-Pyridyl, 2-Quinoyl) **4**

Scheme 1 *Reagents and conditions*: (i) NaOH, EtOH–H_2O (2:1, v/v), r.t., 0.5–1.0 h; (ii) HCl aq (1 N), r.t., 0.5–2.0 h.

The initial study was performed on the aldol condensation between α-oxo ketene-*S*,*S*-acetal **1a** (n = 1) and 4-pyridinecarboxaldehyde **2a** in the presence of NaOH according to the procedure described in literature (Scheme 1).[8] The only product was obtained from the resulting reaction mixture in excellent yield and identified as 3-(1,3-dithiolan-2-ylidene)-5-(pyridin-4-ylmethyl)furan-2,4(3*H*,5*H*)-dione (**3a**) on the basis of its elemental analysis, ^{1}H NMR and ^{13}C NMR spectra and single crystal X-ray analysis. The product is thus a tetronic acid derivative instead of an alkenoyl ketene dithioacetal **4**.

In an attempt to extend the scope of this novel reaction, α-oxo ketene-*S*,*S*-acetal **1b** and some other aryl aldehydes were selected and examined in this protocol. Consequently, a range of TADs **3b–f** were successfully synthesized in very high yields following the same one-pot procedure. Some of the results are summarized in Table 1.[11] However, when the protocol was applied to 3-pyridinecarboxaldehyde **2d**, 4-nitrobenzaldehyde **2e** and 2-nitrobenzaldehyde **2f**, only the corresponding α-carboxyl-α-alkenoyl ketene dithioacetals **4g–i** were obtained in excellent yields, and no lactonization product was detected. The results reveal that the chemical structures of the aryl aldehydes strongly affect the orientation of the final aldol condensation products.

To collect more information, some supporting experiments were conducted on the reaction of **1a** and **2a**. In one experiment, the condensation reaction of **1a** with **2a** was carried out in the presence of NaOH in absolute ethanol at room temperature for 0.5 hour. The sodium carboxylate **5a** (Scheme 2) was formed and isolated from the reaction mixture in 98% yield. It is worth noting that **5a** is quite stable under ambient atmosphere. In another experiment, where the aqueous solution of **5a** was acidified with dilute acetic acid at 0 °C, the mixture of **4a** and **3a** was obtained in 95% total yield (**4a**:**3a** = 1:4, according to ^{1}H NMR spectra). The results reveal that α-carboxyl-α-alkenoyl ketene dithioacetal **4a** was very labile under acidic condi-

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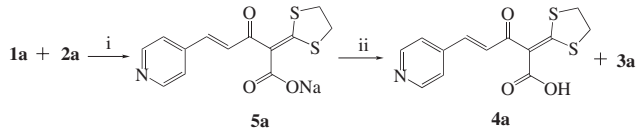
Table 1 Reactions between α-Oxo Ketene-*S*,*S*-acetals **1a**,**b** and Aryl Aldehydes **2a–f**

Entry	Substrates		n	Ar	Product	Time (h)	Yield (%)[a]
	1	**2**					
1	**1a**	**2a**	1	4-Pyridyl	**3a**	1.0	95
2	**1b**	**2a**	2	4-Pyridyl	**3b**	1.0	93
3	**1a**	**2b**	1	2-Pyridyl	**3c**	2.5	88
4	**1b**	**2b**	2	2-Pyridyl	**3d**	2.5	91
5	**1a**	**2c**	1	2-Quinoyl	**3e**	1.0	90
6	**1b**	**2c**	2	2-Quinoyl	**3f**	1.0	94
7	**1a**	**2d**	1	3-Pyridyl	**4g**	3.0	95
8	**1a**	**2e**	1	4-$O_2NC_6H_4$	**4h**	3.0	93
9	**1a**	**2f**	1	2-$O_2NC_6H_4$	**4i**	3.0	93

[a] Isolated yields.

tions. Apparently, the one-pot reaction to the tetronic acid derivatives **3** involves a sequential aldol condensation and acid induced cyclization of intermediate **4**. Considering both carbonyl and pyridyl group as electron-withdrawing groups, the lactonization seems to be a regioselective Michael-type addition.[12] As a matter of fact, the novel lactonization should be classified as a pyridinium-directed intramolecular oxa-pyridylethylation reaction.



Scheme 2 *Reagents and conditions*: (i) NaOH, EtOH, 0.5 h; (ii) HOAc (20%, aq), 0 °C, 10 min.

Pyridylethylation has been extensively studied over the last several decades.[13–21] Various nucleophiles including sulfur,[14] nitrogen,[15] carbon,[16] phosphorus,[17] selenium,[18] and silicon[19] have proven to be effective in this pyridylethylation reaction. However, there are few reports on the oxygen nucleophiles employed in the pyridylethylation. Doering et al. gave an example of oxa-pyridylethylation of 2-vinylpyridine with ethanol catalyzed by sodium ethoxide.[13] The reaction was carried out under strongly basic condition and its yield was very low (20%). Their attempts, together with that from other research groups, to develop oxa-pyridylethylation under acidic conditions were unsuccessful.[20,21] To the best of our knowledge, the lactonization of **4** to give tetronic acid derivatives **3** is the first example of acid-catalyzed intramolecular oxa-pyridylethylation reaction.

To gain the much more clear insight into the mechanism of this novel oxa-pyridylethylation reaction, the deuterium labeling experiment was then carried out. After the treatment of sodium salt **5a** with 1.5 equivalents CF_3CO_2D in D_2O for one hour at ambient temperature, the

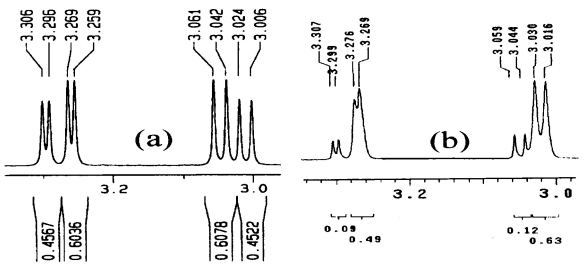
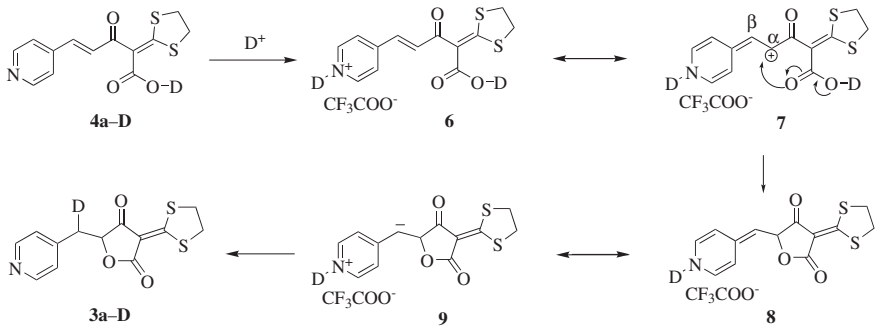


Figure 1 ^{1}H NMR spectra of the methylene of (a) **3a** and (b) **3a-D**.

deuterated tetronic acid derivative **3a-D** was obtained in 89% yield. Comparing the ^{1}H NMR spectra of **3a** and **3a-D**, it is observed that there are obvious changes occurring at the range of δ = 3.0–3.3 ppm (Figure 1). The disappearance of the ^2J coupling in the ^{1}H NMR spectrum of **3a-D** indicates that the methylene group is deuterated during the lactonization process. However, the fact that **4g**, **4h** and **4i** are inert to lactonization under the same reaction conditions suggests that the deuteration might commence from the protonation of the pyridyl ring instead of the direct addition of D^+ to the double bond.[22]

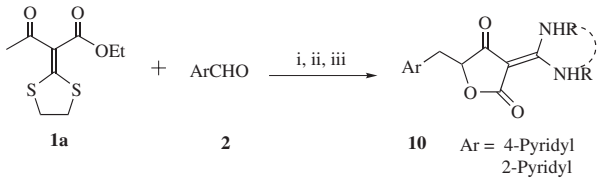
As has been widely known, the electronegative nitrogen imposes the electron deficiency on the α- and γ-positions of pyridine, and the electron deficiency can be extended to a double bond conjugated in the α- and γ-positions but impossible in the β-position due to the resonance interactions of the double bonds.[13,18,23] Therefore, a plausible mechanism is proposed for the lactonization (Scheme 3, **3a-D** as an example). The lactonization is initiated by the protonation of **4a-D** at the basic nitrogen of pyridyl ring and leads to the formation of a strong electrophilic site at the α-position of intermediate **7** through the resonance of the pyridinium ring. An intramolecular pyridylethylation then takes place while the attack of the nucleophilic oxygen atom of carboxyl group to the electrophilic site and give a lactonized intermediate **8**. Through a quick



Scheme 3 A proposed mechanism for the lactonization.

resonance recovery to the pyridinium ring, intermediate **8** is transformed into intermediate **9** bearing a negative charge carbon. Accompanied with the protonation of this carbon anion and a subsequent deprotonation of the pyridinium ring in the presence of $NaHCO_3$, the intermediate **9** affords the final product **3a-D**. From the mechanism, it is not difficult to understand why the deuteration occurs on the methylene group and no deuterated evidence on the pyridyl ring is detected.

In the present work, we combined ketene dithioacetal group and tetronic acid ring in the same molecules, which makes compounds **3** having the potential to become highly valuable organic intermediates. It is reported by some researchers that the selective 1,4-reduction of α-oxo ketene-*S*,*S*-acetals has been achieved in Mg/MeOH or Zn/HOAc systems.[24] In these cases, the carbonyl groups are leaving intact. These results suggest that there might exist the feasibility to convert compounds **3** to protected β-keto aldehydes, which is very useful for organic synthesis as most natural TADs bears 3-acyl substituent. The investigation aimed at this is ongoing in our laboratory.



Scheme 4 *Reagents and conditions*: (i) NaOH, EtOH–H_2O (2:1, v/v), r.t., 0.5–1.0 h; (ii) HCl (1 N), r.t., 0.5–2.0 h; (iii) RNH_2, r.t., 0.5–2.5 h.

On the other hand, α-oxoketene-*S*,*S*-acetals can be used as 1,3-electrophilic 3-carbon equivalents due to the push–pull character of the ketene dithioacetal group. Indeed, numerous works on the displacement of the bisalkylthio groups of α-oxo ketene-*S*,*S*-acetals with varied amines to give α-oxo ketene-*N*,*N*-acetals have been reported.[5,25] These researches encourage us to envisage the protocol to combine the lactonization with the displacement reaction together. In the present work, one-pot synthesis of TADs **10**, 5-pyridinemethyl-3-bis(alkylamino)methylenefuran-2,4-diones, was achieved by addition of the selected amines directly to the reaction mixture of **1a** and **2a**,**b** when the lactonization reaction was completed (monitored by TLC), as shown in Scheme 4.[26] A range of TADs **10a–i** was obtained in moderate to high yields, some of the results are listed in Table 2.

In summary, we have presented here a facile, one-pot synthetic route to a range of tetronic acid derivatives, 3-[bis(alkylthio/alkylamino)methylene]-5-(pyridyl/quinoyl methyl)furan-2,4(3*H*,5*H*)-diones **3** and **10**, and proposed a mechanism for the lactonization. Associated with readily available starting materials, mild conditions and high yields, this novel approach is actually involved in sequential aldol condensation and acid-catalyzed intramolecular oxa-pyridylethylation reaction.

Acknowledgment

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Table 2 One-Pot Synthesis of Tetronic Acid Derivatives **10**

Product	R	R	Substrate **2**	Temp (°C)	Time (h)	Yield (%)[a]
10a	-$(CH_2)_2$-		**2a**	r.t.	2.0	90
10b	-$(CH_2)_3$-		**2a**	r.t.	2.0	92
10c	-$(CH_2)_4$-		**2a**	r.t.	2.5	89
10d[b]	Me	Me	**2a**	r.t.	3.0	85
10e[c]	H	H	**2a**	80	4.0	71
10f	$HO(CH_2)_2$-	$HO(CH_2)_2$-	**2a**	r.t.	1.5	90
10g	-$(CH_2)_2$-		**2b**	r.t.	3.5	83
10h[c]	H	H	**2b**	80	5.0	67
10i	$HO(CH_2)_2$-	$HO(CH_2)_2$-	**2b**	r.t.	3.0	85

[a] Isolated yields.
[b] Methylamine (aq, 30%) was used.
[c] NH_3 (aq, 27%) was employed and the reaction mixture was heated to 80 °C after ammonia was added.

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(11) **General Procedure for the Preparation of 3 (3a as example)**.
To a solution of α-acetyl-α-ethoxylcarbonyl ketene cyclic dithioacetal **1a** (2.32 g, 10 mmol) and 4-pyridine carboxaldehyde **2a** (1.28 g, 12 mmol) in 30 mL EtOH–H_2O (2:1, v/v), NaOH (0.8 g, 20 mmol) was added. After stirring at r.t. for 0.5 h, the mixture was acidified with aq HCl (1 N) to adjust the pH value to 5 and was stirred for another 0.5 h. The resulting mixture was poured into cold sat. aq $NaHCO_3$ and was stirred for 10 min. A yellowish solid was filtered and washed with H_2O (3 × 30 mL). The crude product was purified by column chromatography over silica gel using acetone–Et_2O (2:1, v/v) as eluent to give product **3a** (2.80 g, 95%) as a white crystal.

3-(1,3-Dithiolan-2-ylidene)-5-(pyridin-4-ylmethyl)furan-2,4(3*H*,5*H*)-dione (3a): white crystal; mp 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 (dd, *J* = 8.0, 16.0 Hz, 1 H), 3.29 (dd, *J* = 4.0, 16.0 Hz, 1 H), 3.57–3.65 (m, 4 H), 4.89 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 8.50 (d, *J* = 4.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.5, 186.1, 168.0, 149.9 (2 C), 144.5, 124.9 (2 C), 106.3, 82.2, 38.7, 37.9, 36.8. IR (KBr): 1739, 1680, 1601, 1486, 1195, 1074, 828 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_3S_2$: C, 53.22; H, 3.78; N, 4.77; found: C, 53.46; H, 3.95; N, 4.98. Selected crystal data for **3a**: colorless plate orthorhombic space group P2 (1)2(1)2(1), *a* = 4.9141 (3), *b* = 10.8597 (6), *c* = 24.4537 (15) Å, *V* = 1304.99 (13) Å^3, *β* = 90°, *Z* = 4, D_c = 1.493 g cm^{-3}, *μ* (Cu-$K_α$) = 1.40 cm^{-1}.

3-(1,3-Dithiolan-2-ylidene)-5-(pyridin-4-yl-monodeuterated methyl) Furan-2,4(3*H*,5*H*)-dione (3a-D): white solid; mp 194–196 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.03 (d, *J* = 7.0 Hz, 0.5 H), 3.27 (d, *J* = 3.5 Hz, 0.5 H), 3.57–3.66 (m, 4 H), 4.88 (dd, *J* = 3.5, 7.0 Hz, 1 H), 7.20 (d, *J* = 4.5 Hz, 2 H), 8.51 (d, *J* = 4.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.9, 186.0, 168.2, 150.1 (2 C), 144.8, 125.0 (2 C), 106.9, 82.4, 38.5, 38.1. IR (KBr): 1741, 1679, 1601, 1488, 1191, 1074, 1029, 791 cm^{-1}. MS (ESI): *m/z* (%) = 295 (100) $[M + 1]^+$.

3-(1,3-Dithian-2-ylidene)-5-(pyridin-4-ylmethyl)furan-2,4(3*H*,5*H*)-dione (3b): white solid; mp 199–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32–2.36 (m, 2 H), 2.97 (dd, *J* = 7.2, 14.7 Hz, 1 H), 3.11–3.13 (m, 4 H), 3.24 (dd, *J* = 3.6, 14.7 Hz, 1 H), 4.75 (dd, *J* = 3.6, 7.2 Hz, 1 H), 7.18 (d, *J* = 5.7 Hz, 2 H), 8.49 (d, *J* = 5.7 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5, 184.0, 167.5, 149.8 (2 C), 144.3, 124.8 (2 C), 108.7, 81.0, 36.7, 30.9, 28.5, 28.4, 21.1. IR (KBr): 1733, 1669, 1433, 1173, 1074, 818 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.48; H, 4.38; N, 4.75.

3-(1,3-Dithiolan-2-ylidene)-5-(pyridin-2-ylmethyl)furan-2,4(3*H*,5*H*)-dione (3c): white solid; mp 182–184 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14 (dd, *J* = 8.0, 16.0 Hz,

1 H), 3.50 (dd, *J* = 4.0, 16.0 Hz, 1 H), 3.59–3.65 (m, 4 H), 5.20 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.14–7.17 (m, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.59–7.64 (m, 1 H), 8.52 (d, *J* = 4.4 Hz, 1 H). IR (KBr): 1736, 1678, 1591, 1492, 1436, 1196, 1071, 779 cm^{-1}. MS (ESI): *m/z* (%) = 294 (100) $[M + 1]^+$. Anal. Calcd for $C_{13}H_{11}NO_3S_2$: C, 53.22; H, 3.78; N, 4.77. Found: C, 53.41; H, 3.94; N, 4.96.

3-(1,3-Dithian-2-ylidene)-5-(pyridin-2-ylmethyl)furan-2,4(3*H*,5*H*)-dione (3d): white solid; mp 171–173 °C. ^{1}H NMR (600 MHz, $CHCl_3$): δ = 2.36–2.40 (m, 2 H), 3.09 (dd, *J* = 9.0, 14.4 Hz, 1 H), 3.13–3.16 (m, 4 H), 3.46 (dd, *J* = 3.6, 14.4 Hz, 1 H), 5.08 (dd, *J* = 3.6, 9.0 Hz, 1 H), 7.14–7.16 (m, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.60–7.63 (m, 1 H), 8.53 (d, *J* = 4.8 Hz, 1 H). IR (KBr): 1727, 1664, 1433, 1421, 1175, 1079 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.85; H, 4.06; N, 4.78.

3-(1,3-Dithiolan-2-ylidene)-5-(quinolin-2-ylmethyl)furan-2,4(3*H*,5*H*)-dione (3e): white solid; mp 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (dd, *J* = 7.8, 15.6 Hz, 1 H), 3.57–3.66 (m, 4 H), 3.68 (dd, *J* = 3.9, 15.6 Hz, 1 H), 5.28 (dd, *J* = 3.9, 7.8 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.45–7.50 (m, 1 H), 7.62–7.67 (m, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H). IR (KBr): 1740, 1675, 1501, 1428, 1197, 1074, 1008 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_3S_2$: C, 59.46; H, 3.82; N, 4.08. Found: C, 59.71; H, 4.08; N, 3.82.

3-(1,3-Dithian-2-ylidene)-5-(quinolin-2-ylmethyl)furan-2,4(3*H*,5*H*)-dione (3f): white solid; mp 194–196 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34–2.36 (m, 2 H), 3.10–3.13 (m, 4 H), 3.37 (dd, *J* = 8.0, 15.5 Hz, 1 H), 3.64 (dd, *J* = 4.0, 15.5 Hz, 1 H), 5.15 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.31–7.33 (m, 1 H), 7.46–7.49 (m, 1 H), 7.64–7.67 (m, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H). IR (KBr): 1733, 1670, 1599, 1436, 1173, 1079 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_3S_2$: C, 60.48; H, 4.23; N, 3.92. Found: C, 60.69; H, 4.05; N, 4.08.

(*E*)-2-(1,3-Dithiolan-2-ylidene)-3-oxo-5-(pyridin-3-yl)-pent-4-enoic Acid (4g): yellowish solid; mp 186–188 °C. ^{1}H NMR (500 MHz, DMSO): δ = 3.38–3.41 (m, 4 H), 7.42–7.45 (m, 1 H), 7.46 (d, *J* = 16.0 Hz, 1 H), 7.52 (d, *J* = 16.0 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.56 (d, *J* = 4.5 Hz, 1 H), 8.83 (s, 1 H). IR (KBr): 3419, 1683, 1642, 1586, 1419, 1206, 733 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_3S_2$: C, 53.22; H, 3.78; N, 4.77. Found: C, 53.02; H, 3.91; N, 4.58.

(*E*)-2-(1,3-Dithiolan-2-ylidene)-5-(4-nitrophenyl)-3-oxo-pent-4-enoic Acid (4h): yellowish solid; mp 188–189 °C. ^{1}H NMR (500 MHz, DMSO): δ = 3.44–3.60 (m, 4 H), 7.52 (d, *J* = 16.0 Hz, 1 H), 7.58 (d, *J* = 16.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 2 H), 8.25 (d, *J* = 8.0 Hz, 2 H). IR (KBr): 3445, 1634, 1599, 1510, 1416, 1343, 1205, 731 cm^{-1}; known compound, see ref.[10]

(*E*)-2-(1,3-Dithiolan-2-ylidene)-5-(2-nitrophenyl)-3-oxo-pent-4-enoic Acid (4i): yellowish solid; mp 191–193 °C. ^{1}H NMR (500 MHz, DMSO): δ = 3.39–3.45 (m, 4 H), 7.34 (d, *J* = 15.0 Hz, 1 H), 7.64–7.67 (m, 1 H), 7.74 (d, *J* = 15.0 Hz, 1 H), 7.77–7.86 (m, 1 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H). IR (KBr): 2929, 1654, 1628, 1578, 1525, 1428, 1391, 1342, 1274, 1207, 727 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NO_5S_2$: C, 49.84; H, 3.29; N, 4.15. Found: C, 50.11; H, 3.34; N, 4.28.

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(26) **General Procedure for the Preparation of 10 (10e as example).**

To a solution of **1a** (2.32 g, 10 mmol) and **2a** (1.28 g, 12 mmol) in 30 mL EtOH–H_2O (2:1, v/v), NaOH (0.8 g, 20 mmol) was added. After stirring at r.t. for 0.5 h, the mixture was acidified with aq HCl (1 N) to adjust the pH value to 5 and was stirred for another 0.5 h till the lactonization reaction was completed (monitored by TLC). Then, aq NH_4OH (6 mL, 27%) was added and the reaction mixture was heated to 80 ºC. After stirring for 3 h, the mixture was allowed to cool down to r.t. and poured into cold aq NH_4Cl. A yellowish solid precipitated from the system, which was filtered and washed with H_2O (3 × 30 mL). The crude product was purified by column chromatography over silica gel using acetone–Et_2O (5:1, v/v) as eluent to give product **10e** as a white solid (1.65 g, 71%).

3-(Imidazolidin-2-ylidene)-5-(pyridin-4-ylmethyl)furan-2,4(3*H*,5*H*)-dione (10a): white solid; decomposition point 241–243 °C.^{1}H NMR (400 MHz, DMSO): δ = 2.80 (dd, *J* = 8.0, 14.4 Hz, 1 H), 2.33 (dd, *J* = 4.0, 14.4 Hz, 1 H), 3.57 (br s, 4 H), 4.74 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.26 (d, *J* = 6.0 Hz, 2 H), 8.45 (d, *J* = 6.0 Hz, 2 H). IR (KBr): 3334, 1734, 1647, 1601, 1447, 1058, 1000 cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.47; H, 4.82; N, 16.43.

5-(Pyridin-4-ylmethyl)-3-(tetrahydropyrimidin-2(1*H*)-ylidene)furan-2,4(3*H*,5*H*)-dione (10b): white solid; mp 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01–2.07 (m, 2 H), 2.95 (dd, *J* = 8.0, 16.0 Hz, 1 H), 3.25 (dd, *J* = 4.0, 16.0 Hz, 1 H), 3.42 (br s, 4 H), 4.70 (dd, *J* = 4.0, 8.0 Hz, 1 H), 7.22 (d, *J* = 4.0 Hz, 2 H), 7.87 (br s, 1 H), 8.50 (d, *J* = 4.0 Hz, 2 H), 8.60 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO): δ = 192.8,

173.1, 154.7, 149.2 (2 C), 145.9, 124.7 (2 C), 79.7, 37.6 (2 C), 36.2, 19.0. IR (KBr): 3325, 3279, 1710, 1634, 1602, 1464, 1417, 1151, 1007 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.77; H, 4.38; N, 4.55. MS (ESI): *m/z* (%) = 569 (100) $[2 M + 23]^+$.

3-(1,3-Diazepan-2-ylidene)-5-(pyridin-4-ylmethyl)furan-2,4(3*H*,5*H*)-dione (10c): white solid; mp 193–194 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.91 (br s, 4 H), 2.93 (dd, *J* = 7.2, 14.4 Hz, 1 H), 3.25 (dd, *J* = 3.6, 14.4 Hz, 1 H), 3.47 (br s, 4 H), 4.69 (dd, *J* = 3.6, 7.2 Hz, 1 H), 7.23 (d, *J* = 5.6 Hz, 2 H), 8.27 (br s, 1 H), 8.50 (d, *J* = 5.6 Hz, 2 H), 9.05 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO): δ = 193.9, 174.5, 163.1, 149.6 (2 C), 145.1, 124.8 (2 C), 82.2, 80.08, 44.4 (2 C), 36.6, 27.0 (2 C). IR (KBr): 3269, 1709, 1635, 1467, 1062, 993 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_3S_2$: C, 56.05; H, 4.70; N, 4.36. Found: C, 56.25; H, 4.81; N, 4.33. MS (ESI): *m/z* (%) = 596 (100) $[2 M + 23]^+$.

3-[Bis(methylamino)methylene]-5-(pyridin-4-ylmethyl)furan-2,4-(3*H*,5*H*)-dione (10d): white solid; mp 151–153 °C. ^1H NMR (500 MHz, DMSO): δ = 2.79 (dd, *J* = 7.5, 14.0 Hz, 1 H), 3.12 (dd, *J* = 3.5, 14.0 Hz, 1 H), 3.00 (br s, 6 H), 4.70 (br s, 1 H), 7.25 (d, *J* = 6.0 Hz, 2 H), 8.26 (br s, 2 H), 8.44 (d, *J* = 6.0 Hz, 2 H). IR (KBr): 3252, 1713, 1641, 1601, 1465, 1070, 811, 787 cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.91; H, 5.98; N, 16.29.

3-(Diaminomethylene)-5-(pyridin-4-ylmethyl)furan-2,4-(3*H*,5*H*)-dione (10e): white solid; mp 196–198 °C. ^1H NMR (500 MHz, DMSO): δ = 2.74 (dd, *J* = 3.5, 14.5 Hz, 1 H), 3.10 (dd, *J* = 7.5, 14.5 Hz, 1 H), 4.43 (dd, *J* = 3.5, 7.5 Hz, 1 H), 7.08 (br s, 1 H), 7.17 (br s, 1 H), 7.27 (d, *J* = 5.5 Hz, 2 H), 7.90 (d, *J* = 5.0 Hz, 1 H), 8.45 (d, *J* = 5.5 Hz, 2 H), 9.66 (d, *J* = 5.0 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO): 192.3, 189.7, 173.4, 149.0 (2 C), 146.9, 124.8 (2 C), 93.6, 77.5, 37.0. IR (KBr): 3268, 3132, 1700, 1592, 1463, 1049, 834 cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.42; H, 4.90; N, 18.23.

3-[Bis(2-hydroxyethylamino)methylene]-5-(pyridin-4-ylmethyl)furan-2,4(3*H*,5*H*)-dione (10f): white solid; mp 157–158 °C. ^1H NMR (500 MHz, DMSO): δ = 2.78 (dd, *J* = 8.5, 14.5 Hz, 1 H), 3.14 (dd, *J* = 2.5, 14.5 Hz, 1 H), 3.54–3.56 (m, 8 H), 4.75 (dd, *J* = 2.5, 8.5 Hz, 1 H), 5.07 (br s, 2 H), 7.26 (d, *J* = 5.0 Hz, 2 H), 8.45 (d, *J* = 5.0 Hz, 2 H), 8.55 (br s, 2 H). IR (KBr): 3334, 1709, 1648, 1560, 1466, 1210, 1009 cm^{-1}. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.17; H, 6.01; N, 13.05.

3-(Imidazolidin-2-ylidene)-5-(pyridin-2-ylmethyl)furan-2,4(3*H*,5*H*)-dione (10g): white solid; decomposition point 240–241 °C. ^1H NMR (400 MHz, DMSO): δ = 2.85 (dd, *J* = 9.6, 14.4 Hz, 1 H), 3.25 (dd, *J* = 3.2, 14.4 Hz, 1 H), 3.59 (br s, 4 H), 4.85 (dd, *J* = 3.2, 9.6 Hz, 1 H), 7.26–7.29 (m, 1 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.73–7.78 (m, 1 H), 8.29 (br s, 2 H), 8.52 (d, *J* = 4.4 Hz, 1 H). IR (KBr): 3316, 1716, 1646, 1615, 1448, 1061, 785, 630 cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.55; H, 4.79; N, 16.34. Selected crystal data: monoclinic, P2 (1)/c, *a* = 5.1342 (2), *b* = 25.5679 (14), *c* = 11.3206 (9) Å, *V* = 1478.32 (15) $Å^3$, β = 95.853 (3)°, *Z* = 4, D_c = 1.435 g cm^{-3}, μ (Cu-K_α) = 1.40 cm^{-1}.

3-(Diaminomethylene)-5-(pyridin-2-ylmethyl)furan-2,4-(3*H*,5*H*)-dione (10h): white solid; mp 198–200 °C. ^1H NMR (400 MHz, DMSO): δ = 2.84 (dd, *J* = 9.6, 14.8 Hz, 1 H), 3.24 (dd, *J* = 3.2, 14.8 Hz, 1 H), 4.86 (dd, *J* = 3.2, 9.6 Hz, 1 H), 7.22–7.25 (m, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.60 (s, 2 H), 7.71–7.73 (m, 1 H), 7.74 (br s, 2 H), 8.50 (d, *J* = 4.4 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO): δ = 193.1, 189.6, 174.0, 157.8, 148.7, 136.6, 123.7, 93.3, 78.1, 40.5. IR (KBr): 3282, 3140, 1699, 1631, 1596, 1456, 1061, 1012, 759 cm^{-1}. MS (ESI): *m/z* (%) = 234 (100) $[M + 1]^+$. Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.39; H, 4.89; N, 18.25.

3-[Bis(2-hydroxyethylamino)methylene]-5-(pyridin-2-ylmethyl)furan-2,4(3*H*,5*H*)-dione (10i): white solid; mp 158–159 °C. ^1H NMR (400 MHz, DMSO): δ = 2.82 (dd, *J* = 10.0, 14.8 Hz, 1 H), 3.25 (dd, *J* = 2.4, 14.8 Hz, 1 H), 3.57 (br s, 8 H), 4.86 (dd, *J* = 2.4, 10.0 Hz, 1 H), 5.07 (br s, 2 H), 7.23–7.26 (m, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.70–7.74 (m, 1 H), 8.51 (d, *J* = 4.0 Hz, 1 H), 8.62 (br s, 2 H). IR (KBr): 3340, 1710, 1655, 1559, 1465, 1196, 1070 cm^{-1}. MS (ESI): *m/z* (%) = 322 (100) $[M + 1]^+$. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.20; H, 6.07; N, 13.13.