Tetrahedron 67 (2011) 8343–8347

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# A facile and efficient synthesis of fully substituted pyridin-2(1*H*)-ones from α-oxoketene-*S*,*S*-acetals

Xiuyun Yang [a,*], Yanyan Cheng [a], Fei Zhao [c], Yunhui Li [a], Yuanli Ding [a], Yongjiu Liang [b], Fengjiao Gan [a], Dewen Dong [b,*]

[a] School of Chemistry and Environmental Engineering, Changchun University of Science and Technology, Changchun 130022, PR China
[b] Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, PR China
[c] Department of Chemistry, Nankai University, Tianjin 300071, PR China

ARTICLE INFO

*Article history:*
Received 7 June 2011
Received in revised form 23 August 2011
Accepted 23 August 2011
Available online 27 August 2011

ABSTRACT

A facile and efficient synthesis of fully substituted pyridin-2(1*H*)-ones has been developed by the reaction of readily available α-oxoketene-*S*,*S*-acetals with malononitrile in the presence of sodium methoxide in methanol under reflux.



## 1. Introduction

Pyridin-2(1*H*)-one motif makes up the core structure of numerous biologically active natural products and synthetic compounds, such as elfamycin and ilicolicin, that find a wide range of applications in pharmaceutical and agrochemical industry.[1,2] Pyridin-2(1*H*)-ones and their benzo-/hetero-fused analogues are very important in the area of natural product and pharmaceutical chemistry, and widely used as versatile intermediates in the synthesis of a variety of aza-heterocycles, such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[3,4] Extensive work has generated many approaches for the synthesis of pyridin-2(1*H*)-ones involving pyridinium salt chemistry,[5] Guareschi–Thorpe reaction,[6] Vilsmeier reaction,[7] hetero Diels–Alder reaction,[8] Dieckmann-type condensation,[9] and metal-mediated cycloaddition.[10] In addition, some notable methods starting from polarized ketene *S*,*S*- and *N*,*N*-acetals have been reported.[2d,11]

Over the past decades, the utility of α-oxoketene-*S*,*S*-acetals as versatile intermediates in organic synthesis has been recognized.[12] During the course of our studies, we successfully achieved the synthesis of β-lactams,[13] pyridines,[14] 2*H*-pyrans,[15] dihydropyranones,[16] tetronic acids,[17] and isothiazoles[18] from α-oxoketene-*S*,*S*-acetals, also developed novel strategies for the synthesis of highly substituted six-membered carbocycles[19] and heterocycles,[20] relying upon the utilization of α-alkenoyl ketene-*S*,*S*-acetals, as a five-carbon 1,5-bielectrophilic species in the formal [5+1] annulation with carbon, nitrogen, and sulfur nucleophiles, respectively.

In connection with our previous work and our continuing interest in the synthesis of valuable heterocycles, we examined the reaction of α-oxoketene-*S*,*S*-acetals **1** with malononitrile. As a result, we achieved one-pot synthesis of fully substituted pyridin-2(1*H*)-ones. Herein, we wish to report our results.

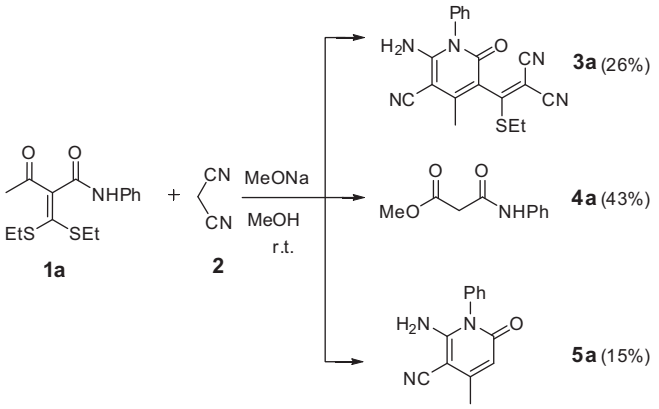
## 2. Results and discussion

The substrates, α-acyl, α-carbamoyl ketene-*S*,*S*-acetals **1**, were prepared from commercially available β-oxo amides in water in excellent yields following the procedure described in our previous work.[21] With a series of condensation adducts **1a**–**h** in hand, we selected 2-[bis(ethylthio) methylene]-3-oxo-*N*-phenylbutanamide **1a** as a model compound to examine its reaction behavior with malononitrile **2**. When **1a** and **2** (1.0 equiv) was subjected to sodium methoxide in methanol at room temperature for 5.0 h, the reaction could be completed as monitored by TLC (Table 1, entry 1). The resulting mixture was purified by silica column chromatography, and three main products were obtained, which were characterized as substituted pyridin-2(1*H*)-one **3a**, methyl 3-oxo-3-(phenylamino)propanoate **4a** and pyridin-2(1*H*)-one **5a**, respectively, on the basis of their spectral and analytical data (Scheme 1).

The optimization of the reaction conditions, including the ratio of malononitrile to **1a**, the base, reaction medium and temperature were then investigated and the results are summarized in Table 1. No reaction occurred when **1a** and **2** was treated with $K_2CO_3$ in DMF at room temperature (Table 1, entry 2). It was observed that the reaction of **1a** and **2** (2.0 equiv) proceeded smoothly in the presence of sodium methoxide (1.0 equiv) in methanol under reflux to afford **3a** in 67% yield (Table 1, entry 3). When the reaction was conducted with sodium ethoxide (1.0 equiv) in ethanol under

* Corresponding authors. Tel.: +86 431 85262190; fax: +86 431 85693057 (D.D.); tel.: +86 431 85582361; fax: +86 431 86804621 (X.Y.); e-mail addresses: yangxiuyun1@126.com (X. Yang), dwdong@ciac.jl.cn (D. Dong).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.08.066




**Scheme 1.** Reaction of α-oxoketene-*S*,*S*-acetal **1a** and malononitrile **2**.

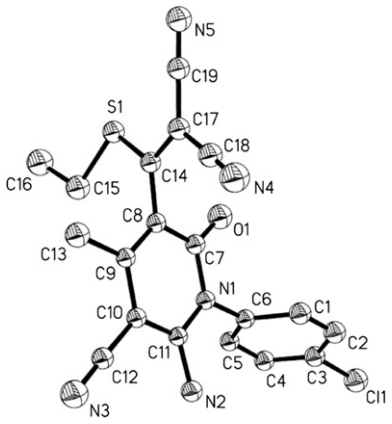
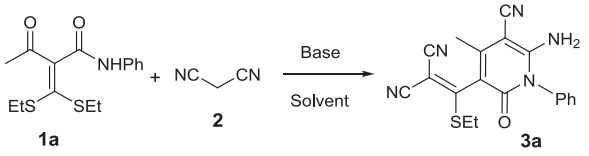



**Fig. 1.** The ORTEP drawing of **3h**.

reflux, **3a** was obtained in 64% yield (Table 1, entry 4). However, with sodium hydroxide as base in the reaction system, the yield of **3a** was decreased to 51% (Table 1, entry 5), whereas, product **4a** was obtained in 43% yield. The compound **4a** should be derived from nucleophilic vinylic substitution ($S_NV$)[22] and deacylation reactions of α-acyl, α-carbamoyl ketene-*S*,*S*-acetal **1a** as reported in our previous work.[23] The result also suggested that the side reaction might be attributed to the small amount of water within the reaction system, which was from solvent and/or the one generated from NaOH and methanol in situ. After a series of experiments, the optimized reaction conditions were obtained when **1a** and malononitrile (2.1 equiv) was performed in the presence of sodium methoxide (1.1 equiv) in absolute methanol under reflux, whereby the yield of **3a** reached 85% (Table 1, entry 6).

**Table 1**
Optimization of reaction conditions of **1a** with malononitrile **2**



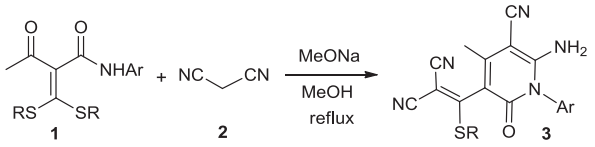

| Entry | Base (equiv) | Ratio **2** to **1a** | Solvent | Temp | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | MeONa (1.0) | 1.0:1.0 | MeOH | rt | 5.0 | 26 |
| 2 | $K_2CO_3$ (3.0) | 1.0:1.0 | DMF | rt | 5.0 | 0 |
| 3 | MeONa (1.0) | 2.0:1.0 | MeOH | Reflux | 4.0 | 67 |
| 4 | EtONa (1.0) | 2.0:1.0 | EtOH | Reflux | 4.0 | 64 |
| 5 | NaOH (1.0) | 2.0:1.0 | MeOH | Reflux | 4.0 | 51 |
| 6 | MeONa (1.1) | 2.1:1.0 | MeOH[b] | Reflux | 3.0 | 85 |

[a] Isolated yield for **3a**.
[b] Absolute MeOH was employed.

Under the optimized conditions as for the synthesis of **3a** in Table 1 (entry 6), a range of α-acyl, α-carbamoyl ketene-*S*,*S*-acetals **1b**–**h** bearing varied arylamide groups (Ar) and malononitrile was subjected to MeONa/MeOH, and the results are summarized in Table 2. The efficiency of the cyclization proved to be suitable for **1b**–**h** to give the corresponding substituted pyridin-2(1*H*)-ones **3** in good yields (Table 2, entries 2–9). It is worth mentioning that the structure of **3h** was elucidated by means of the X-ray single crystal analysis (Fig. 1), and further confirmed by its NMR spectra.

The versatility of this pyridin-2(1*H*)-one synthesis was further evaluated by performing α-acyl, α-carbamoyl ketene-*S*,*S*-acetals **1i**–**l** bearing varied alkylthio groups (SR) under the identical conditions (Table 2, entries 9–12). The results demonstrated the efficiency and synthetic interest of the cyclization reactions of **1** bearing variable arylamide and alkylthio groups with respect to

**Table 2**
Reactions of α-oxoketene-*S*,*S*-acetals **1** with malononitrile **2**[a]




| Entry | **1** | Ar | R | **3** | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | Ph | Et | **3a** | 85 |
| 2 | **1b** | 2-$MeOC_6H_4$ | Et | **3b** | 83 |
| 3 | **1c** | 2-$MeC_6H_4$ | Et | **3c** | 81 |
| 4 | **1d** | 2-$ClC_6H_4$ | Et | **3d** | 80 |
| 5 | **1e** | 2,4-$Me_2C_6H_3$ | Et | **3e** | 82 |
| 6 | **1f** | 4-$MeOC_6H_4$ | Et | **3f** | 76 |
| 7 | **1g** | 4-$MeC_6H_4$ | Et | **3g** | 83 |
| 8 | **1h** | 4-$ClC_6H_4$ | Et | **3h** | 78 |
| 9 | **1i** | Ph | Me | **3i** | 75 |
| 10 | **1j** | 2-$MeOC_6H_4$ | Me | **3j** | 82 |
| 11 | **1k** | Ph | Bn | **3k** | 74 |
| 12 | **1l** | 2-$MeOC_6H_4$ | Bn | **3l** | 77 |

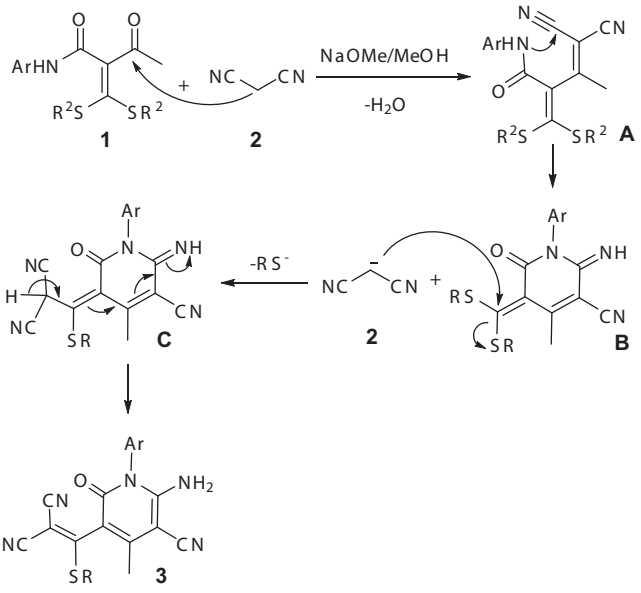
[a] Reagents and conditions: **1a** (2.0 mmol), malononitrile **2** (4.2 mmol), MeONa (2.2 mmol), absolute MeOH (10 mL), reflux, 3.0–4.0 h.
[b] Isolated yields.

basic conditions. Therefore, we provided a facile and efficient synthetic approach to fully substituted pyridin-2(1*H*)-ones of type **3**. It should be noted that the richness of the functionality, e.g., amino, cyano, and methylenemalononitrile moiety on the pyridin-2(1*H*)-one ring of **3**, may render them versatile as synthons in further synthetic transformations.

On the basis of the obtained results and our previous studies,[23] a plausible mechanism for the synthesis of substituted pyridin-2(1*H*)-ones **3** is presented in Scheme 2. In the presence of sodium methoxide, Knoevenagel condensation[24] between α-oxoketene-*S*,*S*-acetals **1** and malononitrile **2**[25] occurs to give intermediate **A**, which undergoes intramolecular cyclization reaction to afford intermediate **B**.[26] Tandem addition of the anion of malononitrile **2** to **B** and elimination of thiolate anion as a nucleophilic vinylic substitution ($S_NV$) process[22] leads to the formation of intermediate **C**, which finally furnishes the pyridin-2(1*H*)-one of type **3**.

## 3. Conclusion

In summary, we described a facile and efficient synthesis of fully substituted pyridin-2(1*H*)-ones **3** from readily available α-oxoketene-*S*,*S*-acetals **1** and malononitrile **2** in the presence of sodium methoxide in methanol under reflux, which involves consecutive Knoevenagel condensation, intramolecular cyclization, and



**Scheme 2.** Tentative mechanism of the reaction of α-oxoketene-*S*,*S*-acetals **1** with malononitrile **2**.

nucleophilic vinylic substitution ($S_NV$) reactions. This protocol is associated with readily available starting materials, mild conditions, good yields, and wide range of synthetic potential of the products.

## 4. Experimental

### 4.1. General information

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. $^1$H NMR and $^{13}$C NMR spectra were recorded at 300 MHz and 100 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm$^{-1}$. Petroleum ether (PE) used was the fraction boiling in the range 60–90 °C. Elemental analyses were carried out on a Perkin–Elmer PE-2400 analyzer.

### 4.2. Synthesis of substituted pyridin-2(1*H*)-ones 3

*4.2.1. Typical procedure for the preparation of **3** (with **3a** as an example).* To a solution of **1a** (0.62 g, 2.0 mmol) in methanol (15 mL) was added sodium methoxide (0.12 g, 2.2 mmol) under stirring at room temperature. To the mixture was added a solution of malononitrile (0.28 g, 4.2 mmol) in absolute methanol (10 mL) within 10 min. The mixture was heated and stirred under reflux for 3.0 h, then cooled down to room temperature. The resulting mixture was slowly poured into saturated aqueous NaCl (50 mL), and extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 2:1) to give **3a** as a yellow solid, yield: 85%.

### 4.3. Selected data for 3

*4.3.1. 2-Amino-5-[2,2-dicyano-1-(ethylthio)vinyl]-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile (**3a**).* Yellow solid; mp 236–238 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.17 (t, $J$=7.5 Hz, 3H), 2.2 (s, 3H), 2.8 (m, 2H), 7.23 (d, $J$=6.3, 1H), 7.32 (d, $J$=7.5 Hz, 1H), 7.47–7.60(m, 5H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=13.9, 18.4, 27.9, 73.7, 78.7, 107.2, 112.3, 112.7, 116.1, 128.5, 128.5 (2C), 129.7, 130.3 (2C), 133.8, 151.5, 156.2, 156.8, 181.1. IR (KBr, cm$^{-1}$): $\nu$=3420, 3328, 3220, 2970, 2218, 2198, 1660, 1662, 1522,1488, 723. Anal. Calcd for $C_{19}H_{15}N_5OS$: C, 63.14; H, 4.18; N, 19.38. Found: C, 63.34; H, 4.43; N, 19.20.

*4.3.2. 2-Amino-5-[2,2-dicyano-1-(ethylthio)vinyl]-1-(2-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3b**).* Yellow solid: mp 203–206 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.18 (t, $J$=7.5 Hz, 3H), 2.23 (s, 3H), 2.88 (m, 2H), 3.73(s, 3H), 7.1 (m, 1H), 7.23 (m, 2H), 7.49 (m, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=13.9, 18.4, 27.9, 55.7, 73.3, 78.8, 107.0, 113.0, 116.0, 121.4, 121.6, 121.7, 121.9, 129.8, 151.5, 154.4, 156.2, 181.1. IR (KBr, cm$^{-1}$): $\nu$=3420, 3324, 3215, 2221, 2202, 1660, 1623, 1527, 1499, 1462, 755. Anal. Calcd for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89. Found: C, 61.37; H, 4.40; N, 17.60.

*4.3.3. 2-Amino-5-[2,2-dicyano-1-(ethylthio)vinyl]-4-methyl-6-oxo-1-o-tolyl-1,6-dihydropyridine-3-carbonitrile(**3c**).* Yellow solid: mp 234–235 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.14–1.19 (m, 3H), 2.01 (s, 3H), 2.24 (s, 3H), 2.89 (m, 2H), 7.11–7.25 (m, 1H), 7.35–7.53 (m, 5H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=14.0, 16.4, 18.5, 27.9, 73.5, 79.0, 107.2, 116.1, 116.1, 127.9, 128.5, 130.0, 131.5, 132.6, 132.9, 135.5, 151.5, 155.8, 156.3, 181.0. IR (KBr, cm$^{-1}$): $\nu$=3405, 3312, 3216, 2206, 1670, 1626, 1577, 1527, 1460, 895, 739. Anal. Calcd for $C_{20}H_{17}N_5OS$: C, 63.98; H, 4.56; N, 18.65; S, 8.54. Found: C, 63.85; H, 4.97; N, 18.76.

*4.3.4. 2-Amino-1-(2-chlorophenyl)-5-[2,2-dicyano-1-(ethylthio)vinyl]-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3d**).* Yellow solid: mp 247–250 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.13–1.19 (m, 3H), 2.24 (d, 3H), 2.88 (m, 2H), 7.46–7.58 (m, 3H), 7.68–7.72 (m, 2H), 7.81 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=14.0, 18.4, 27.9, 73.6, 79.0, 107.0, 112.3, 112.6, 116.0, 129.3, 130.7, 131.0, 131.2, 131.5, 131.7, 151.9, 152.4, 156.0, 180.6. IR (KBr, cm$^{-1}$): $\nu$=3405, 3315, 3220, 2208, 1675, 1628, 1574, 1532, 1476, 748. Anal. Calcd for $C_{19}H_{14}ClN_5OS$: C, 57.65; H, 3.56; Cl, 8.96; N, 17.69. Found: C, 57.56; H, 3.65; Cl, 8.70; N, 17.55.

*4.3.5. 2-Amino-5-[2,2-dicyano-1-(ethylthio)vinyl]-1-(2,4-di-methylphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3e**).* Yellow solid: mp 207–210 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.13–1.19 (m, 3H), 1.96 (s, 3H), 2.2 (s, 3H), 2.34 (s, 3H), 2.88 (m, 2H), 6.98–7.11 (m, 1H) 7.18 (d, $J$=8.1 Hz, 1H), 7.24 (s, 1H), 7.43 (s, 1H), 7.50 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=14.0, 16.3, 18.3, 20.7, 27.9, 73.4, 79.0, 107.2, 112.3, 112.6, 116.1, 128.4, 128.6, 130.2, 132.2, 135.1, 139.4, 151.4, 155.8, 156.4, 181.1. IR (KBr, cm$^{-1}$): $\nu$=3445, 3335, 3203, 2218, 2202, 1664, 1614, 1591, 1525, 1496, 893, 823, 772, 694. Anal. Calcd for $C_{21}H_{19}N_5OS$: C, 64.76; H, 4.92; N, 17.98. Found: C, 64.80; H, 4.80; N, 17.75.

*4.3.6. 2-Amino-5-[2,2-dicyano-1-(ethylthio)vinyl]-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3f**).* Yellow solid: mp 212–214 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.13–1.18 (m, 3H), 2.21 (s, 3H), 2.88 (m, 2H), 3.81 (s, 3H), 7.08–7.25 (m, 5H), 7.46 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=13.9, 18.4, 27.9, 55.4, 73.6, 78.7, 107.1, 112.3, 112.7, 115.4, 115.6, 116.1, 126.1, 129.6, 129.7, 151.3, 156.5, 157.0, 1601.0, 181.2. IR (KBr, cm$^{-1}$): $\nu$=3380, 3307, 3208, 2208, 1712, 1655, 1612, 1581, 1509, 828. Anal. Calcd for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89. Found: C, 61.35; H, 4.22; N, 17.70.

*4.3.7. 2-Amino-5-[2,2-dicyano-1-(ethylthio)vinyl]-4-methyl-6-oxo-1-p-tolyl-1,6-dihydropyridine-3-carbonitrile (**3g**).* Yellow solid: mp

226–227 °C. H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.16 (t, $J$=7.5 Hz, 3H), 2.22 (s, 3H), 2.38 (s, 3H), 2.88 (m, 2H), 7.09 (d, $J$=8.4 Hz, 1H), 7.18 (d, $J$=7.5 Hz, 1H), 7.32–7.43 (m, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=13.9, 18.4, 20.8, 27.9, 73.7, 78.5, 107.2, 112.3, 112.7, 116.1, 128.5, 128.2, 128.4, 130.6, 130.8, 131.1, 132.2, 139.2, 151.4, 156.3, 156.8, 181.8. IR (KBr, cm$^{-1}$): $\nu$=3423, 3328, 3216, 2223, 2205, 1661, 1624, 1582, 1527, 841. Anal. Calcd for $C_{20}H_{17}N_5OS$: C, 63.98; H, 4.56; N, 18.65. Found: C, 63.88; H, 4.55; N, 18.70.

*4.3.8. 2-Amino-1-(4-chlorophenyl)-5-[2,2-dicyano-1-(ethyl-thio)vinyl]-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3h**).* Yellow solid: mp 264–267 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.16 (t, $J$=7.5 Hz, 3H), 2.23 (s, 3H), 2.88 (m, 2H), 7.26–7.30 (m, 1H), 7.37–7.41 (m, 1H), 7.57–7.64 (m, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=14.0, 18.4, 27.9, 73.8, 78.8, 107.0, 112.7, 116.1, 130.1, 130.4, 130.6, 130.7, 130.8, 132.8, 134.5, 151.7, 156.2, 156.7, 180.9. IR (KBr, cm$^{-1}$): $\nu$=3454, 3416, 3323, 3225, 2226, 2205, 1668, 1626, 1513, 1491, 752. Anal. Calcd for $C_{19}H_{14}ClN_5OS$: C, 57.65; H, 3.56; N, 17.69. Found: C, 57.53; H, 3.44; N, 17.60.

CCDC-805824 (**3h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223 336 033; or email: deposit@ccdc.cam.ac.uk.

*4.3.9. 2-Amino-5-[2,2-dicyano-1-(methylthio)vinyl]-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile (**3i**).* Yellow solid: mp 260–262 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=2.23 (s, 3H), 2.40 (s, 3H), 7.22–7.25 (m, 2H), 7.33–7.36 (m, 1H), 7.46 (s, 1H), 7.53–7.55 (m, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=15.8, 18.4, 73.8, 78.4, 107.2, 112.3, 112.8, 128.6, 128.7, 129.3, 129.8, 130.0, 130.3, 133.8, 156.2, 156.6, 182.3; IR (KBr, cm$^{-1}$): $\nu$=3420, 3324, 3219, 2207, 1666, 1624, 1600, 1576, 1498, 761. Anal. Calcd for $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16. Found: C, 62.04; H, 3.83; N, 19.98.

*4.3.10. 2-Amino-5-[2,2-dicyano-1-(methylthio)vinyl]-1-(2-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3j**).* Yellow solid: mp 267–269 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=2.21 (s, 3H), 2.36 (s, 3H), 3.72 (s, 3H), 7.08–7.13 (m, 1H), 7.21–7.28 (m, 2H), 7.45–7.47 (m, 1H), 7.51 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=15.3, 18.2, 55.7, 73.4, 78.3, 107.0, 112.8, 113.2, 116.1, 121.4, 121.6, 121.7, 121.9, 129.8, 131.5, 151.6, 154.4, 156.2, 182.4. IR (KBr, cm$^{-1}$): $\nu$=3414, 3311, 3216, 3164, 2219, 2200, 1669, 1623, 1578, 1526, 1489, 761. Anal. Calcd for $C_{19}H_{15}N_5O_2S$: C, 60.46; H, 4.01; N, 18.56. Found: C, 60.33; H, 4.21; N, 18.65.

*4.3.11. 2-Amino-5-[1-(benzylthio)-2,2-dicyanovinyl]-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile (**3k**).* Yellow solid: mp 240–242 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=2.17 (s, 3H), 4.12 (s, 2H), 6.7 (s, 1H), 7.22–7.25 (m, 3H), 7.32–7.34 (m, 3H), 7.49–7.55 (m, 5H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=20.3, 37.2, 71.2, 81.3, 107.0, 115.1, 115.9, 116.3, 128.5, 128.7, 128.9, 129.0, 129.1, 129.3, 129.7, 129.8, 130.0, 130.3, 133.8, 134.7, 155.8, 158.1, 158.8, 180.4. IR (KBr, cm$^{-1}$): $\nu$=3344, 3202, 2204, 1657, 1629, 1572, 1537, 1494, 1553, 753. Anal. Calcd for $C_{23}H_{16}N_5OS$: C, 67.30; H, 3.93; N, 17.06. Found: C, 67.46; H, 3.85; N, 17.21.

*4.3.12. 2-Amino-5-[1-(benzylthio)-2,2-dicyanovinyl]-1-(2-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**3l**).* Yellow solid: mp 230–232 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$=1.56 (s, 3H), 3.77 (s, 3H), 4.22 (s, 2H), 7.12–7.16 (m, 2H), 7.20–7.25 (m, 2H), 7.29–7.32 (m, 5H), 7.53–7.55 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$=18.1, 36.6, 55.9, 73.7, 78.4, 107.2, 112.5, 115.8, 121.9, 127.5, 127.6, 128.4, 128.5, 128.8, 128.9, 129.8, 129.9, 131.5, 131.6, 136.1, 152.6, 154.6, 156.2, 180.9. IR (KBr, cm$^{-1}$): $\nu$=3413, 3321, 3219, 2215, 1663, 1619, 1574, 1527, 1496, 750. Anal. Calcd for $C_{25}H_{19}N_5O_2S$: C, 66.21; H, 4.22; N, 15.44. Found: C, 66.53; H, 4.31; N, 15.75.

## Acknowledgements

Financial support of this research by the National Natural Science Foundation of China (20872136) and Department of Science and Technology of Jilin Province (20090535 and 201105051) is greatly acknowledged.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.066.

## References and notes

1. (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, NY, 1981; Vol. 5, pp 1–54; (b) Nagarajan, M.; Xiao, X.; Anotony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 5712; (c) Li, Q.; Mitscher, L. A.; Shen, L. L. *Med. Res. Rev.* **2000**, *20*, 231; (d) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 167–243; (e) Jones, G. Pyridines and their benzo derivatives: synthesis In *Comprehensive Heterocyclic Chemistry*; Boulton, A., McKillop, A., Eds.; Pergamon: Oxford, 1984; Chapter 2.08, pp 395–510.
2. (a) José, L. M.; Karina, M.; Cecilia, J.; Rafael, C. P. *ChemMedChem* **2007**, *2*, 1141; (b) Jayasinghe, L.; Abbas, H. K.; Jacob, M. R.; Herath, W.; Nanayakkara, N. P. D. *J. Nat. Prod.* **2006**, *69*, 439; (c) Liang, F.; Cheng, X.; Liu, J.; Liu, Q. *Chem. Commun.* **2009**, 3636; (d) Schirok, H.; Alonso-Alija, C.; Benet-Buchholz, J.; Göller, A. H.; Grosser, R.; Michels, M.; Paulsen, H. *J. Org. Chem.* **2005**, *70*, 9463.
3. (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757; (b) Angibaud, P. R.; Venet, M. G.; Filliers, W.; Broeckx, R.; Ligny, Y. A.; Muller, P.; Poncelet, V. S.; End, D. W. *Eur. J. Org. Chem.* **2004**, 479.
4. (a) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691; (b) Cox, R. J.; Ohagan, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2537.
5. (a) Decker, H. *Chem. Ber.* **1892**, *25*, 443; (b) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623; (c) Du, W. *Tetrahedron* **2003**, *59*, 8649; (d) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607.
6. (a) Baron, H.; Remfry, F. G. P.; Thorpe, J. F. *J. Chem. Soc.* **1904**, *85*, 1726; (b) Aggarwal, V.; Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 214; (c) Gibson, K. R.; Hitzel, L.; Mortishire-Smith, R. J.; Gerhard, U.; Jelley, R. A.; Reeve, A. J.; Rowley, M.; Nadin, A.; Owens, A. P. *J. Org. Chem.* **2002**, *67*, 9354.
7. (a) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345; (b) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593; (c) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504.
8. (a) Robin, A.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Tetrahedron Lett.* **2004**, *45*, 9557; (b) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428.
9. Chung, K. H.; Cho, K. Y.; Asami, Y.; Takahashi, N.; Yoshida, S. *Heterocycles* **1991**, *32*, 99.
10. (a) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787; (b) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117; (c) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368; (d) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648.
11. (a) Anabha, E. R.; Asokan, C. V. *Synthesis* **2006**, 151; (b) Chakrabarti, S.; Panda, K.; Misara, N. C.; Ila, H.; Junjappa, H. *Synlett* **2005**, 1437; (c) Mahata, P. K.; Syam, U. K.; Kumar Sriram, V.; Ila, H.; Junjappa, H. *Tetrahedron* **2003**, *59*, 2631; (d) Schirok, H.; Alonso-Alija, C.; Michels, M. *Synthesis* **2005**, 3085; (e) Chen, L.; Zhao, Y.; Liu, Q.; Cheng, C.; Piao, C. *J. Org. Chem.* **2007**, *72*, 9259.
12. For reviews on the synthesis and application of α-oxoketene-*S*,*S*-acetals, see: (a) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029; (b) Tominaga, Y. *J. Heterocycl. Chem.* **1989**, *46*, 143; (c) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423; (d) Kolb, M. *Synthesis* **1990**, 171; (e) Junjappa, H.; Ila, H. *Phosphorous, Sulfur Silicon* **1994**, *95*, 35; (f) Junjappa, H.; Ila, H.; Mohanta, P. K. In *Progress in Heterocyclic Chemistry*; Gribble, G. H., Gilchrist, L. T., Eds.; Pergamon: Oxford, 2001; Vol. 13; Chapter 1, pp 1–24.
13. Yang, Y.; Xiang, D.; Zhao, X.; Liang, Y.; Huang, J.; Dong, D. *Tetrahedron* **2008**, *64*, 4959.
14. Sun, S.; Liu, Y.; Liu, Q.; Zhao, Y.; Dong, D. *Synlett* **2004**, 1731.
15. Liu, Y.; Dong, D.; Liu, Q.; Qi, Y.; Wang, Z. *Org. Biomol. Chem.* **2004**, *2*, 28.
16. Ouyang, Y.; Huang, J.; Pan, W.; Liang, Y.; Yang, Y.; Dong, D. *Eur. J. Org. Chem.* **2009**, 2003.
17. Bi, X.; Liu, Q.; Sun, S.; Liu, J.; Pan, W.; Zhao, L.; Dong, D. *Synlett* **2005**, 49.
18. Huang, J.; Lu, Y.; Qiu, B.; Liang, Y.; Li, N.; Dong, D. *Synthesis* **2007**, 2791.
19. Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578.
20. (a) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580; (b) Bi, X.; Dong, D.; Li, Y.; Liu, Q.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 10886; (c) Pan, W.; Dong, D.; Ouyang, Y.; Wu, R.; Yang, Y.; Liu, Q. *Synthesis* **2007**, 2115.
21. Ouyang, Y.; Dong, D.; Yu, H.; Liang, Y.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 206.

22. (a) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017; (b) Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 2719; (c) Baldwin, J. E.; Adlington, R. M.; Aurelia, C.; Nageswara Rao, I.; Marquez, R.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 2125; (d) Bernasconi, C. F.; Brown, S. D.; Ali, M.; Rappoport, Z.; Yamataka, H.; Salim, H. *J. Org. Chem.* **2006**, *71*, 4795.
23. (a) Dong, D.; Yu, H.; Ouyang, Y.; Liu, Q.; Bi, X.; Lu, Y. *Synlett* **2006**, 283; (b) Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4535; (c) Yu, H.; Liu, Q.; Yin, Y.; Fang, Q.; Zhang, J.; Dong, D. *Synlett* **2004**, 999; (d) Liu, Q.; Che, G.; Yu, H.; Liu, Y.; Zhang, J.; Zhang, Q.; Dong, D. *J. Org. Chem.* **2003**, *68*, 9148.
24. Jones, G. In *The Knoevenagel Condensation*; Adams, R., Ed.; Organic Reactions; John Wiley: New York, N Y, 1967; Vol. 15, pp 204–599.
25. For the reactions of malononitrile, see: (a) Freeman, F. *Chem. Rev.* **1969**, *69*, 591; (b) Freeman, F. *Chem. Rev.* **1980**, *80*, 329.
26. (a) Liang, F.; Cheng, X.; Liu, J.; Liu, Q. *Chem. Commun.* **2009**, 3636; (b) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033.