

# Reaction of lithioamino anions with $\alpha$ -oxoketene dithioketals: an improved and a new general method for the synthesis of $\alpha$ -oxoketene *S,N*- and *N,N*-ketals

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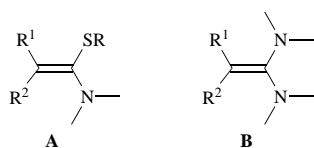
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A new method has been developed for the preparation of  $\alpha$ -oxoketene *S,N*- (**A**) and *N,N*-(**B**) ketals starting from  $\alpha$ -oxoketene dithioketals by employing mild conditions. Thus, lithioamino anions **2a–c**, **4** and **6** are treated with  $\alpha$ -oxoketene dithioketals **1** to afford the corresponding *S,N*-ketals **3a–j**, **5a–j**, **7a–e** and *N,N*-ketals **8a,b** in good yields. The scope and steric orientations of the reaction have been investigated.

Polarized ketene dithioketals have been recognised as useful building blocks in many synthetic operations.<sup>1</sup> They can further be converted into the corresponding *S,N*- (**A**) and *N,N*-(**B**)

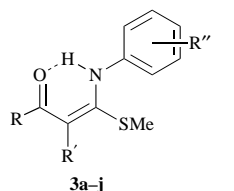
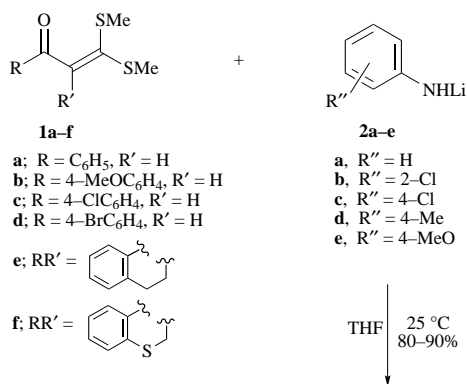


ketals making them important as precursors for a large variety of functionalized ketals. These *S,N*-ketals are considered as vinylogous amides if they are derived from ketones and as vinylogous amines if they are derived from other active methylene compounds. The ketene *S,N*- and *N,N*-ketals are quite stable and exhibit the properties shown by enamines. They undergo smooth nucleophilic displacement with various binucleophiles followed by intramolecular cyclization with the  $\alpha$ -oxo functionality. In addition to their reactivity as 1,3-electrophilic 3-carbon fragments, they differ from  $\alpha$ -oxoketene dithioketals in their enamine reactivity profile, providing C–C–N components in the product heterocycles. Based on this reactivity, a number of reactions have been reported from this and other laboratories for the construction of various heterocyclic ring systems, such as substituted pyrroles,<sup>2a,b</sup> quinoxalines,<sup>2a</sup> indoles,<sup>3</sup> pyridines,<sup>4</sup> pyridones,<sup>5</sup> imidazoles,<sup>6</sup> thiazoles,<sup>7</sup> pyrimidines,<sup>8</sup> etc. through the cyclocondensation of  $\alpha$ -oxoketene *S,N*-ketals with compounds having activated multiple (or heteromultiple) bonds. In continuation of these studies and in connection with a programme devoted to the preparation of substituted naphthyridines and pyrido[1,2-*a*]pyrimidines, the functionalized *S,N*-ketal derivatives of aminopyridines were needed. Attempts to prepare these *S,N*-ketals by the earlier reported procedures such as direct displacement,<sup>8,9</sup> aryl isothiocyanate method,<sup>10</sup> and thioamide and isothiourethane methods<sup>11,12</sup> were unsuccessful. In one of the papers<sup>8</sup> it was clearly mentioned that the less reactive  $\alpha$ -oxoketene dithioketals require more vigorous conditions and generally afford a mixture of *S,N*- and *N,N*-ketals which were often difficult to separate. Therefore an alternative convenient method for the preparation of *S,N*-ketals was always in demand. Nesmeianov and co-workers<sup>13</sup> isolated a series of compounds which they suggested were acylethylideneaminopyridines by the reaction of 2-aminopyridines with acylacetaldehyde acetals at 140 °C in sealed tubes overnight. However, these methods require not

only vigorous reaction conditions and longer reaction periods, but also result in relatively poor yields of the products. We now report a new method for the synthesis of *S,N*-ketals by reacting lithiated-amines with  $\alpha$ -oxo ketene *S,S*-ketals.

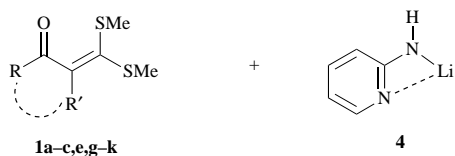
## Results and discussion

Our various trial experiments to prepare *S,N*-ketals **3a–j**, **5a–i** and **7a–e** by direct displacement of the methylthio group of  $\alpha$ -oxoketene dithioketals **1** either by refluxing in protic solvent or by heating at high temperature (~200 °C) without any solvent gave either starting materials or mixtures of *S,N*- and *N,N*-ketals which were often difficult to separate. However the lithiated amino salts prepared by deprotonation of the respective amines and aminoheterocycles with *n*-butyllithium underwent smooth displacement on the *S,S*-ketals to afford the corresponding *S,N*-ketals in high yield. Thus the lithioamino salt **2a** prepared by deprotonation of aniline with *n*-butyllithium at room temperature was treated with  $\alpha$ -oxoketene dithioketals **1a–f** to afford the corresponding *S,N*-ketals **3a–f** in 80–90% overall yield (Scheme 1). Similarly, the lithioamino salts **2b–e** prepared from the respective substituted anilines were also treated with the  $\alpha$ -oxoketene *S,S*-ketal **1a** under the same reaction conditions to afford the corresponding *S,N*-ketals **3g–j** in 80–84% overall yield. Surprisingly, the method was found to be good for the preparation of *S,N*-ketal derivatives of 2-amino- and 3-amino-pyridines (Schemes 2 and 3), which were unavailable by the earlier attempts. Reaction conditions are very mild and result in high overall yields. In view of the readily accessible starting materials and very easy manipulation of the reaction conditions, this method is a viable alternative to previously reported procedures. As a representative example, the corresponding 2-lithioamino salt **4** prepared by deprotonation of 2-aminopyridine with *n*-butyllithium underwent smooth displacement on the *S,S*-ketal **1a** at 0–25 °C to afford the corresponding *S,N*-ketal **5a** in 92% yield (Scheme 2). Similarly the other *S,N*-ketals **5b–h** derived from substituted acetophenones, 2-acetylfuran, 2-acetylthiophene, tetralone, etc. could also be prepared in overall high yields (80–93%) under identical conditions. The cinnamoylketene dithioketal **1k** was also similarly converted into the corresponding enaminone **5i**, in 85% yield. Next we examined the reactivity of 3-aminopyridines with  $\alpha$ -oxoketene dithioketals. The lithio salt of 3-aminopyridine was found to be stable at 45–50 °C and the displacement was found to be satisfactory at this temperature

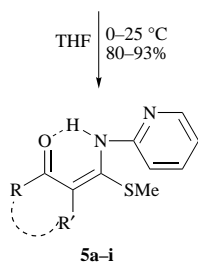


- a, R = C<sub>6</sub>H<sub>5</sub>, R' = R'' = H  
 b, R = 4-MeOC<sub>6</sub>H<sub>4</sub>, R' = R'' = H  
 c, R = 4-ClC<sub>6</sub>H<sub>4</sub>, R' = R'' = H  
 d, R = 4-BrC<sub>6</sub>H<sub>4</sub>, R' = R'' = H  
 e, RR' = , R'' = H  
 f, RR' = , R'' = H  
 g, R = C<sub>6</sub>H<sub>5</sub>, R' = H, R'' = 2-Cl  
 h, R = C<sub>6</sub>H<sub>5</sub>, R' = H, R'' = 4-Cl  
 i, R = C<sub>6</sub>H<sub>5</sub>, R' = H, R'' = 4-Me  
 j, R = C<sub>6</sub>H<sub>5</sub>, R' = H, R'' = 4-MeO

**Scheme 1**

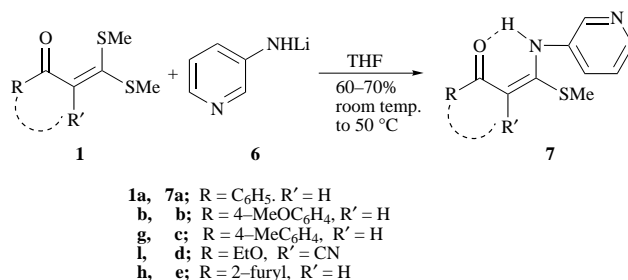


- 1a, 5a;** R = C<sub>6</sub>H<sub>5</sub>, R' = H  
**b, b;** R = 4-MeOC<sub>6</sub>H<sub>4</sub>, R' = H  
**c, c;** R = 4-ClC<sub>6</sub>H<sub>4</sub>, R' = H  
**g, d;** R = 4-MeC<sub>6</sub>H<sub>4</sub>, R' = H  
**h, e;** R = 2-furyl, R' = H  
**i, f;** R = 2-thienyl, R' = H  
 e, g; RR' =   
 j, h; RR' =   
 k, i; R = 4-MeOC<sub>6</sub>H<sub>4</sub>CH=CH, R' = H



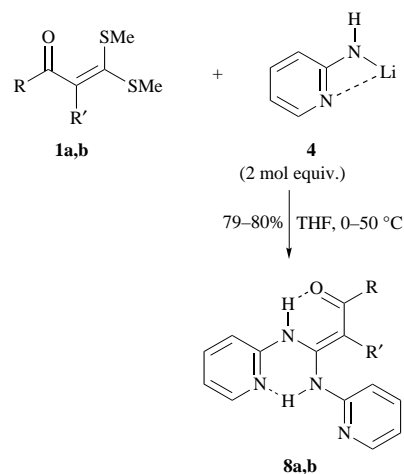
**Scheme 2**

rather than room temperature. Thus *S,N*-ketals **7a–e** were prepared in, overall, 60–70% yield by reaction of the lithiated 3-aminopyridine **6** with  $\alpha$ -oxoketene *S,S*-ketals **1a,b,g,l,h** (Scheme 3). *N,N*-Ketals of the respective amines were also obtained by refluxing the  $\alpha$ -oxoketene dithioketals with 2 mol equiv. quantities of the respective lithiated amines. Thus the hitherto unreported *N,N*-ketals **8a,b** were obtained in 79–80% overall



**Scheme 3**

yield by reaction of 2-lithioaminopyridine salt **4** (2.0 mol equiv.) with *S,S*-ketals **1a,b** (1.0 mol equiv.) (Scheme 4). Most



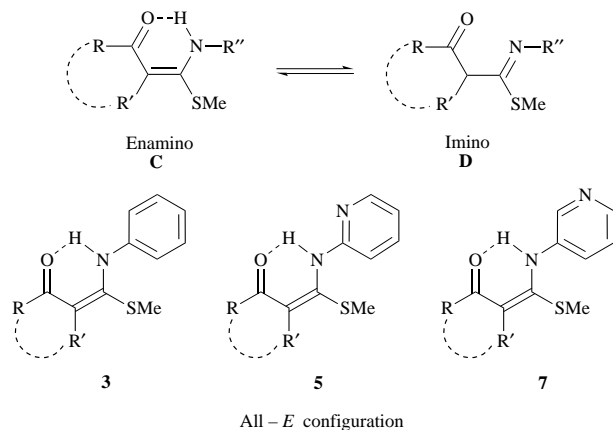
- 1, 8a;** R = C<sub>6</sub>H<sub>5</sub>, R' = H  
**b;** R = 4-MeOC<sub>6</sub>H<sub>4</sub>, R' = H

**Scheme 4**

of these *S,N*- and *N,N*-ketals are crystalline compounds which can be preserved at room temperature without any apparent decomposition.

All the *S,N*-ketals **3a–j**, **5a–i** and **7a–e** existed as only one stereoisomer, as evident from their sharp mps. The signals for SMe and vinylic protons appeared as sharp singlets in all cases, indicating the purity of their geometric isomerism. The geometry of the *S,N*-ketals thus formed were assigned the *E*-configuration on the basis of IR and NMR data. Polarized ketene *S,N*-ketals are known<sup>14</sup> to exist in tautomeric equilibrium between enamino **C** and imino **D** forms (Scheme 5) which can be easily distinguished with the help of IR and NMR spectroscopy. Spectral studies on  $\alpha$ -oxoketene *S,N*-ketals **3a–j** (Scheme 1), **5a–i** (Scheme 2) and **7a–e** (Scheme 3) prepared for the present investigation indicated that all of them exist in the enamino form **A** which supports the *E*-configuration. The IR spectra strongly indicate a hydrogen-bonded NH stretching vibration at 3330–3350 cm<sup>-1</sup>, suggesting its position with the intramolecularly associated hydrogen. The carbonyl stretching vibration in these compounds was merged with bands around and below 1600 cm<sup>-1</sup>, reflecting the characteristic conjugation effect of the amino group and strong intramolecular hydrogen bonding. <sup>1</sup>H NMR spectra of these *S,N*-ketals in deuteriochloroform showed a characteristic chelated NH proton far downfield near  $\delta$  13–15, assigned to the amino group which participated in a strong hydrogen bond with the oxygen of the carbonyl group (NH $\cdots$ O=C) in a six-membered, planar chelate (Scheme 5). A sharp singlet at  $\delta$  5.8–5.9 was typical for the vinylic protons of the acyclic *S,N*-ketals. The <sup>13</sup>C NMR spectrum always showed a signal far downfield near  $\delta$  186 assigned to the carbonyl carbon of the ketones. It is interesting to note that all the *S,N*-ketals were found to be exclusively in the *all-E*-configuration and the corresponding isomers were not

formed in any of the experiments. Apparently it appears that the strong intramolecular hydrogen bonding directs the overall configuration of the *S,N*-ketals (Scheme 5).



Scheme 5

In summary, we have described a new convenient method for the preparation of *S,N*- and *N,N*-ketals from readily accessible  $\alpha$ -oxoketene *S,S*-ketals. These *S,N*- and *N,N*-ketals are versatile intermediates because of the presence of several electrophilic and nucleophilic reactive sites which could be utilised in regioselective ring-closure strategies leading to novel heterocycles: these results will be described in our next paper.

## Experimental

Mps were determined on a Thomas Hoover (Capillary method) apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 297 and 983 spectrophotometers.  $^1\text{H}$  NMR (90 MHz) spectra were recorded on a Varian EM-390 spectrometer; high-resolution  $^1\text{H}$  NMR (300 MHz) and  $^{13}\text{C}$  NMR (75.5 MHz) spectra were recorded on a Bruker ACF-300 spectrometer with  $\text{SiMe}_4$  ( $\delta_{\text{C}}$  0.000) and  $\text{CDCl}_3$  ( $\delta_{\text{C}}$  77.00) as internal standards, respectively. *J*-Values are in Hz. Mass spectra were obtained on a JEOL JMS-D300 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid Analyser. All the  $\alpha$ -oxoketene dithioketals were reported<sup>15</sup> earlier and prepared accordingly.

### General procedure for the generation and reaction of 1-(lithio-amino)benzenes and substituted 1-(lithioamino)benzenes with $\alpha$ -oxoketene dithioketals: preparation of *S,N*-ketals 3a-j

To a stirred solution of aniline or a substituted aniline (10 mmol) in dry tetrahydrofuran (THF) (20 ml) was added *n*-butyllithium under a dry and inert atmosphere, over a period of 20 min at room temp. (25 °C). The reaction mixture was stirred for 30 min at the same temp. Lithiation was indicated by the appearance of a reddish brown colour. A solution of an oxoketene *S,S*-ketal (10 mmol) in dry THF (25 ml) was added. The contents were stirred at room temperature for 5–6 h. In the case of *S,N*-ketals 3e–g, after addition of oxoketene *S,S*-ketals the stirred reaction mixture was refluxed at 60 °C for 2–3 h to complete the reaction. Then it was brought to room temperature, worked up by being poured into saturated aq.  $\text{NH}_4\text{Cl}$  (100 ml), and extracted with chloroform (2  $\times$  50 ml) and the combined extracts were washed with water (2  $\times$  50 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give a crude product, which was purified by crystallization from chloroform–hexane or by passage through a column of silica gel with ethyl acetate–hexane (1:9) as eluent (3e–g). Analytical and spectral data of the hitherto unreported *S,N*-ketal 3h are given below.

**3-(2-Chloroanilino)-3-methylthio-1-phenylprop-2-en-1-one 3h.** Obtained as light yellow crystals (2.50 g, 82%), mp 110 °C (from chloroform–hexane);  $\nu_{\text{max}}$ (KBr)/ $\text{cm}^{-1}$  3320 (NH), 1603, 1592

and 1240;  $\delta_{\text{H}}$ (300 MHz;  $\text{CDCl}_3$ ) 2.38 (3 H, s,  $\text{SCH}_3$ ), 5.93 (1 H, s, vinylic), 7.15 (1 H, ddd, *J* 1.5, 6.6 and 8.9, 4-H), 7.23 (1 H, ddd, *J* 1.2, 6.6 and 8.7, 5-H), 7.39–7.45 (4 H, m, 6-H and ArH), 7.50 (2 H, m, ArH), 7.92 (1 H, dd, *J* 1.2 and 8.4, 3-H) and 13.47 (1 H, s, NH, exchanges  $\text{D}_2\text{O}$ );  $\delta_{\text{C}}$ (75.5 MHz;  $\text{CDCl}_3$ ) 14.77 ( $\text{SCH}_3$ ), 89.69 (=CH), 126.90 (C-6 anil), 127.1 (C-2' Ar), 127.46, 128.29 (C-3' Ar), 129.7 (C-4 anil), 130.0 (C-5 anil), 131.07 (C-3 anil), 135.77 (C-2 anil), 139.80 (C-1' Ar), 167.06 and 186.30 (C=O) [Found: C, 63.37; H, 4.5; N, 4.80.  $\text{C}_{16}\text{H}_{14}\text{ClNOS}$  (303.5) requires C, 63.26; H, 4.6; N, 4.6%].

### Generation of 2-(lithioamino)pyridine and its reaction with $\alpha$ -oxoketene dithioketals: general procedure for the preparation of ketal *S,N*-ketals 5a–i

To a stirred solution of 2-aminopyridine (0.94 g, 10 mmol) in anhydrous THF (20 ml) was added *n*-butyllithium (15 mmol) while the temperature was maintained at 0 °C. Lithiation was indicated by the appearance of a reddish brown colour. The reaction mixture was stirred at the same temperature for 30 min. A solution of oxoketene dithioketal (10 mmol) in dry THF (25 ml) was then added and the whole was stirred for 30–45 min (0 °C) and was then allowed to warm to room temp. The reaction mixture was further stirred at the same temperature for 1 h, worked up by being poured into saturated aq.  $\text{NH}_4\text{Cl}$  (50 ml) and extracted with chloroform (2  $\times$  50 ml), and the combined extracts were washed with water (2  $\times$  50 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give the crude product, which was purified by crystallization from chloroform–hexane (5a–f) or by passage through a silica gel column with ethyl acetate–hexane (1:9) as eluent (5g–i).

### 3-Methylthio-1-phenyl-3-(2-pyridylamino)prop-2-en-1-one 5a

Light yellow crystals (2.5 g, 92%), mp 90 °C (from chloroform–hexane);  $\nu_{\text{max}}$ (KBr)/ $\text{cm}^{-1}$  3496 and 3351 (NH), 1588, 1537 and 1244;  $\delta_{\text{H}}$ (300 MHz;  $\text{CDCl}_3$ ) 2.37 (3 H, s,  $\text{SCH}_3$ ), 5.93 (1 H, s, vinylic), 6.85 (1 H, m, 5-H pyridyl), 6.93 (1 H, d, *J* 9, 3-H pyridyl), 7.38–7.42 (3 H, m, ArH), 7.53 (1 H, ddd, *J* 1.5, 6.9 and 8.7, 4-H pyridyl), 7.86–7.89 (2 H, m, ArH), 8.27 (1 H, dt, *J* 1.5 and 6.6, 6-H pyridyl) and 14.64 (1 H, s, NH, exchanges  $\text{D}_2\text{O}$ );  $\delta_{\text{C}}$ (75.5 MHz;  $\text{CDCl}_3$ ) 15.9 ( $\text{SCH}_3$ ), 90.63 (=CH), 113.6, 118.0 (C-5 and -3 of pyridyl), 127.0, 128.5 and 131.4 (C-2', -3' and -4' of Ar), 137.6 (C-4 pyridyl), 139.8 (C-1' Ar), 146.6 (C-6 pyridyl), 152.2, 165.8 and 185.67 (C=O) [Found: C, 66.69; H, 5.15; N, 10.38.  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{OS}$  (270.1) requires C, 66.66; H, 5.18; N, 10.37%].

**1-(4-Methoxyphenyl)-3-methylthio-3-(2-pyridylamino)prop-2-en-1-one 5b.** Yellow crystals (2.80 g, 93%), mp 105 °C;  $\nu_{\text{max}}$ (KBr)/ $\text{cm}^{-1}$  3491, 3325 (NH), 1580, 1534 and 1238;  $\delta_{\text{H}}$ (300 MHz;  $\text{CDCl}_3$ ) 2.43 (3 H, s,  $\text{SCH}_3$ ), 3.82 (3 H, s,  $\text{OCH}_3$ ), 5.92 (1 H, s, vinylic), 6.91 (2 H, d, *J* 9, ArH), 6.93–6.98 (2 H, m, 6- and 3-H pyridyl), 7.59 (1 H, ddd, *J* 1.8, 7.8 and 8.7, 4-H pyridyl), 7.88–7.91 (2 H, d, *J* 9, ArH), 8.32 (1 H, dt, *J* 1.8 and 6.9, 6-H pyridyl) and 14.56 (1 H, s, NH, exchanges  $\text{D}_2\text{O}$ );  $\delta_{\text{C}}$ (75.5 MHz;  $\text{CDCl}_3$ ) 16.10 ( $\text{SCH}_3$ ), 55.3 ( $\text{OCH}_3$ ), 90.5 (=CH), 113.61 (C-2' Ar), 113.84 and 118.13 (C-5 and -3 pyridyl), 129.08 (C-3' Ar), 132.46 (C-1' Ar), 137.96 and 146.81 (C-4 and -6 pyridyl), 152.50, 162.19 (C-4' Ar) and 165.13 and 185.25 (C=O) [Found: C, 63.95; H, 5.29; N, 9.50.  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{OS}$  (300.1) requires C, 63.97; H, 5.33; N, 9.33%].

**1-(4-Chlorophenyl)-3-methylthio-3-(2-pyridylamino)prop-2-en-1-one 5c.** Bright yellow crystals (2.75 g, 90%), mp 116 °C (from chloroform–hexane);  $\nu_{\text{max}}$ (KBr)/ $\text{cm}^{-1}$  3498, 3347 (NH), 1579, 1538 and 1248;  $\delta_{\text{H}}$ (90 MHz;  $\text{CDCl}_3$ ) 2.38 (3 H, s,  $\text{SCH}_3$ ), 5.91 (1 H, s, vinylic), 6.91–7.10 (2 H, m, 5- and 3-H pyridyl), 7.49 (2 H, d, *J* 9, ArH), 7.59 (1 H, ddd, *J* 1.8, 7.9 and 8.7, 4-H pyridyl), 8.00 (2 H, d, *J* 9, ArH), 8.32 (1 H, dt, *J* 1.8 and 6.9, 6-H pyridyl) and 14.6 (1 H, s, NH);  $\delta_{\text{C}}$ (75 MHz;  $\text{CDCl}_3$ ) 15.6 ( $\text{SCH}_3$ ), 90.6 (=CH), 114.5, 118.5 (C-5 and -3 pyridyl), 128.5, 128.59 and 137.28 (C-2', -3' and -1' of Ar), 138.03 (C-4

pyridyl), 138.35 (C-4' Ar), 146.0 (C-6 pyridyl), 152.2, 166.58 and 184.52 (C=O) [Found: C, 59.13; H, 4.1; N, 9.10. C<sub>15</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub> (304.6) requires C, 59.06; H, 4.2; N, 9.12%].

**1-(4-Methylphenyl)-3-methylthio-3-(2-pyridylamino)prop-2-en-1-one 5d.** Yellow crystals (2.56 g, 90%), mp 110 °C (from chloroform–hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3487 and 3320 (NH), 1748, 1522, 1456 and 1250;  $\delta_{\text{H}}$ (90 MHz; CDCl<sub>3</sub>) 2.58 (3 H, s, CH<sub>3</sub>), 2.60 (3 H, s, SCH<sub>3</sub>), 5.94 (1 H, s, vinylic), 7.15 (1 H, m, 5-H pyridyl), 7.25 (1 H, d, *J* 9, 3-H pyridyl), 7.45 (2 H, d, *J* 8.9, ArH), 7.75 (1 H, ddd, *J* 1.3, 6.9 and 9.1, 4-H pyridyl), 8.05 (2 H, d, *J* 8.9, ArH), 8.51 (1 H, dt, *J* 1.3 and 6.9, 6-H pyridyl) and 14.95 (1 H, s, NH, exchanges D<sub>2</sub>O) [Found: C, 68.2; H, 5.3; N, 9.5. C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> (284.1) requires C, 67.60; H, 5.6; N, 9.75%].

**1-(2-Furyl)-3-methylthio-3-(2-pyridylamino)prop-2-en-1-one 5e.** Yellow crystals (2.3 g, 88%), mp 120 °C (from EtOAc–hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3460 and 3247 (NH), 1678, 1599 and 1230;  $\delta_{\text{H}}$ (300 MHz; CDCl<sub>3</sub>) 2.40 (3 H, s, SCH<sub>3</sub>), 5.92 (1 H, s, vinylic), 6.51 (1 H, dd, *J* 3 and 4.5, 4'-H furyl), 6.82 (1 H, m, 5-H pyridyl), 6.88 (1 H, d, *J* 9, 3-H pyridyl), 7.10 (1 H, d, *J* 4.5, 3'-H furyl), 7.48 (1 H, d, *J* 3, 5'-H furyl), 8.00 (1 H, ddd, *J* 1.2, 6.6 and 8.8, 4-H pyridyl), 8.30 (1 H, dt, *J* 1.2 and 6.9, 6-H pyridyl) and 14.80 (1 H, s, NH) [Found: C, 59.8; H, 4.70; N, 10.71. C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S (260.1) requires C, 59.99; H, 4.6; N, 10.76%].

**3-Methylthio-3-(2-pyridylamino)-1-(2-thienyl)prop-2-en-1-one 5f.** Light yellow crystals (217 g, 89%), mp 109 °C (from EtOAc–hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3386 and 3343 (NH), 1750, 1591 and 1281;  $\delta_{\text{H}}$ (300 MHz; CDCl<sub>3</sub>) 2.51 (3 H, s, SCH<sub>3</sub>), 5.91 (1 H, s, vinylic), 6.98 (1 H, m, 5-H pyridyl), 7.14 (1 H, dd, *J* 4.5 and 8, 4'-H thienyl), 7.25 (1 H, d, *J* 8.9, 3-H pyridyl), 7.60 (1 H, d, *J* 4.5, 3'-H thienyl), 7.75 (1 H, d, *J* 6.0, 5'-H thienyl), 7.80 (1 H, ddd, *J* 1.2, 6.6 and 8.7, 4-H pyridyl) and 8.50 (1 H, dt, *J* 1.2 and 6.9, 6-H pyridyl) [Found: C, 56.50; H, 4.2; N, 10.21. C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> (276) requires C, 56.52; H, 4.3; N, 10.4%].

**2-[Methylthio-(2-pyridylamino)methylene]-1-tetralone 5g.** Viscous yellow oil (2.6 g, 91%),  $\nu_{\max}$ (CCl<sub>4</sub>)/cm<sup>-1</sup> 3382, 1675, 1609, 1586 and 1236;  $\delta_{\text{H}}$ (90 MHz; CCl<sub>4</sub>) 2.15 (3 H, s, SCH<sub>3</sub>), 2.80–2.95 (4 H, m, 2 × CH<sub>2</sub>), 7.00 (1 H, ddd, *J* 1.5, 6.6 and 8.7, 5-H pyridyl), 7.20–7.31 (3 H, m, ArH), 7.40–7.50 (2 H, m, 3- and 4-H pyridyl), 8.09 (1 H, m, ArH), 8.43 (1 H, dd, *J* 1.5 and 8.9, 6-H pyridyl) and 13.1 (1 H, br s, NH, exchanges D<sub>2</sub>O) [Found: C, 68.50; H, 5.5; N, 9.3. C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S (296) requires C, 68.91; H, 5.4; N, 9.4%].

**6-Methoxy-2-[methylthio-(2-pyridylamino)methylene]-1-tetralone 5h.** Oil (2.50 g, 76.6%),  $\nu_{\max}$ (CCl<sub>4</sub>)/cm<sup>-1</sup> 3382, 3066, 1634, 1598, 1490 and 1270;  $\delta_{\text{H}}$ (90 MHz; CCl<sub>4</sub>) 2.67 (3 H, s, SCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 3.90–3.93 (4 H, m, 2 × CH<sub>2</sub>), 7.20 (1 H, ddd, *J* 1.2, 6.6 and 7.7, 5-H pyridyl), 7.31 (2 H, m, 3- and 4-H pyridyl), 7.40–7.45 (2 H, m, ArH), 7.89 (1 H, s, ArH), 8.55 (1 H, dd, *J* 1.2 and 9, 6-H pyridyl) and 13.00 (1 H, br s, NH) [Found: C, 65.5; H, 5.9; N, 8.40. C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S requires C, 66.25; H, 5.5; N, 8.5%].

**5-(4-Methoxyphenyl)-1-methylthio-1-(2-pyridylamino)penta-1,4-dien-3-one 5i.** Yellow crystals (2.77 g, 85%), mp 120 °C (from chloroform–hexane);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3414, 3370, 1606, 1545 and 1476;  $\delta_{\text{H}}$ (300 MHz; CDCl<sub>3</sub>) 2.41 (3 H, s, SCH<sub>3</sub>), 3.82 (3 H, s, OCH<sub>3</sub>), 5.43 (1 H, s, 2-H vinylic), 6.64 (1 H, d, *J* 15, 4-H), 6.8 (2 H, d, *J* 9, ArH), 6.92–6.97 (2 H, m, 3- and 4-H pyridyl), 7.5 (2 H, d, *J* 9, ArH), 7.56 (1 H, d, *J* 15, 5-H), 7.62 (1 H, ddd, *J* 1.5, 6.0 and 8.1, 5-H pyridyl), 8.32 (1 H, dd, *J* 1.5 and 9, 6-H pyridyl) and 14.7 (1 H, s, NH, exchanges D<sub>2</sub>O);  $\delta_{\text{C}}$ (75 MHz) 16.05 (SCH<sub>3</sub>), 55.26 (OCH<sub>3</sub>), 113.84, 114.1 (CH Ar), 118.13, 125.7 and 128.2 (CH Ar), 129.5, 137.9, 139.0, 146.7, 152.5, 160.8, 165.5 and 183.84 (C=O) [Found: C, 66.2; H, 5.5; N, 8.2. C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S (326) requires C, 66.5; H, 5.6; N, 8.4%].

#### Generation of 3-(lithioamino)pyridine and its reaction with $\alpha$ -oxoketene dithioketals: general procedure for the preparation of *S,N*-ketals 7a–e

To a stirred solution of 3-aminopyridine (1.41 g, 15 mmol) in dry THF (25 ml) was added *n*-butyllithium (15 mmol) under

nitrogen at room temp. The reaction mixture was heated at 45 °C for 30 min. Then it was brought to room temp. (25 °C) and a solution of *S,S*-ketal (10 mmol) in dry THF (25 ml) was added. The reaction mixture was further stirred for 5 h at ambient temp. It was then quenched with saturated aq. NH<sub>4</sub>Cl (50 ml) and extracted with chloroform (2 × 50 ml). The combined extracts were washed with water (2 × 50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to give a crude product, which was chromatographed on silica gel with ethyl acetate–hexane (2:8) as eluent.

**3-Methylthio-1-phenyl-3-(3-pyridylamino)prop-2-en-1-one 7a.** Low melting solid (2.00 g, 70%),  $\nu_{\max}$ (CCl<sub>4</sub>)/cm<sup>-1</sup> 3416, 3034, 1693, 1549 and 1256;  $\delta_{\text{H}}$ (90 MHz; CDCl<sub>3</sub>) 2.31 (3 H, s, SCH<sub>3</sub>), 5.91 (1 H, s, vinyl), 7.20–7.26 (1 H, m, 5-H pyridyl), 7.29–7.35 (1 H, m, 4-H pyridyl), 7.35–7.50 (3 H, m, ArH), 7.91–8.12 (2 H, m, ArH), 8.45 (1 H, dd, *J* 1.8 and 9.6, 6-H pyridyl), 8.62 (1 H, s, 2-H pyridyl) and 14.01 (1 H, NH, exchanges D<sub>2</sub>O) [Found: C, 66.65; H, 5.15; N, 10.31. C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S (270.1) requires C, 66.6; H, 5.1; N, 10.35%].

**1-(4-Methoxyphenyl)-3-methylthio-3-(3-pyridylamino)prop-2-en-1-one 7b.** Yellow crystals (2.1 g, 70%), mp 95 °C;  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3421, 3055, 1603, 1541 and 1246;  $\delta_{\text{H}}$ (90 MHz; CDCl<sub>3</sub>) 2.34 (3 H, s, SCH<sub>3</sub>), 3.75 (3 H, s, OCH<sub>3</sub>), 5.83 (1 H, s, vinylic), 6.84 (2 H, d, *J* 9, ArH), 7.19 (1 H, dd, *J* 6.6 and 9, 5-H pyridyl), 7.56 (1 H, dd, *J* 1.5 and 9, 4-H pyridyl), 7.81 (2 H, d, *J* 9, ArH), 8.35 (1 H, dd, *J* 1.5 and 8.5, 6-H pyridyl), 8.36 (1 H, s, 2-H pyridyl) and 13.44 (1 H, s, NH) [Found: C, 63.95; H, 5.30; N, 9.50. C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S (300.1) requires C, 63.97; H, 5.33; N, 9.33%].

**1-(4-Methylphenyl)-3-methylthio-3-(3-pyridylamino)prop-2-en-1-one 7c.** Low melting solid (1.95 g, 68%),  $\nu_{\max}$ (CCl<sub>4</sub>)/cm<sup>-1</sup> 3385, 3049, 1609, 1544 and 1184;  $\delta_{\text{H}}$ (90 MHz; CDCl<sub>3</sub>) 2.31 (3 H, s, CH<sub>3</sub>), 2.35 (3 H, s, SCH<sub>3</sub>), 5.81 (1 H, s, vinylic), 7.01 (2 H, d, *J* 9, ArH), 7.45–7.50 (2 H, m, 3- and 5-H pyridyl), 7.65 (2 H, d, *J* 9, ArH), 8.35 (1 H, dd, *J* 1.5 and 8, 6-H pyridyl), 8.56 (1 H, s, 2-H pyridyl) and 14.0 (1 H, NH) [Found: C, 67.50; H, 5.7; N, 9.75. C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S (284.1) requires C, 67.60; H, 5.61; N, 9.81%].

**Ethyl 2-cyano-3-methylthio-3-(3-pyridylamino)acrylate 7d.** Needles (2.40 g, 91.2%), mp 110 °C;  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3302, 2264 (C=N) 1670 and 1621;  $\delta_{\text{H}}$ (90 MHz; CDCl<sub>3</sub>) 1.30 (3 H, t, *J* 7, CH<sub>2</sub>CH<sub>3</sub>), 2.30 (3 H, s, SCH<sub>3</sub>), 4.36 (2 H, q, *J* 7, CH<sub>2</sub>CH<sub>3</sub>), 7.40 (dd, 1 H, *J* 6.6 and 9.6, 5-H pyridyl), 7.75 (1 H, d, *J* 8, 4-H pyridyl), 8.65 (2 H, m, s and d overlapped, 2- and 6-H pyridyl) and 12.10 (1 H, br s, NH) [Found: C, 54.66; H, 4.7; N, 16.10. C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S (263) requires C, 54.75; H, 4.9; N, 15.96%].

**1-(2-Furyl)-3-methylthio-3-(3-pyridylamino)prop-2-en-1-one 7e.** Yellow needles (1.65 g, 62%), mp 105 °C,  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3436, 3104, 1723, 1670 and 1017;  $\delta_{\text{H}}$ (90 MHz; CDCl<sub>3</sub>) 2.50 (3 H, s, SCH<sub>3</sub>), 5.91 (1 H, s, vinylic), 6.60 (1 H, d, *J* 4.5, 3'-H furyl), 7.30 (1 H, dd, *J* 4.5 and 5.5, 4'-H furyl), 7.50 (1 H, dd, *J*<sub>4,5</sub> 9 and *J*<sub>4,6</sub> 1.8, 4-H pyridyl), 7.52 (1 H, dd, *J*<sub>5,4</sub> 9 and *J*<sub>5,6</sub> 6, 5-H pyridyl), 7.70 (1 H, d, *J* 3, 5'-H furyl), 8.40 (1 H, dd, *J*<sub>6,5</sub> 6 and *J*<sub>6,4</sub> 1.8, 6-H pyridyl) and 8.60 (1 H, s, 2-H pyridyl) [Found: C, 59.8; H, 4.70; N, 10.71. C<sub>13</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub>S (260.1) requires C, 59.9; H, 4.6; N, 10.76%].

#### General procedure for the preparation of *N,N*-ketals 8a,b

To a stirred solution of 2-aminopyridine (1.88 g, 20 mmol) in anhydrous THF (25 ml), was added *n*-butyllithium (20 mmol) under a dry and inert atmosphere over a period of 20 min at room temperature (25 °C). After 30 min, a solution of  $\alpha$ -oxoketene dithioetal (10 mmol) in dry THF (25 ml) was added and stirring was continued for another 1 h at the same temperature. Then the reaction mixture was refluxed for 5 h at 60 °C (monitored by TLC). After cooling to room temp., the reaction mixture was quenched with saturated aq. NH<sub>4</sub>Cl (100 ml) and extracted with chloroform (2 × 50 ml) and the combined extracts were washed with water (2 × 50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a crude product, which was purified by

column chromatography (silica gel) with ethyl acetate–hexane (2:8) as eluent.

**1-Phenyl-3,3-bis-(2-pyridylamino)prop-2-en-1-one 8a.** Yellow crystals (2.50 g, 79%), mp 125 °C (from EtOAc–hexane);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3427, 1653, 1611, 1592 and 1545;  $\delta_{\text{H}}(90 \text{ MHz}; \text{CDCl}_3)$  6.95–7.35 (5 H, m, olefinic, ArH, and 5-H pyridyl), 7.50 (2 H, m, 3-H pyridyl), 7.65–8.10 (5 H, m, ArH, 2 × 4-H and 5-H), 8.40 (1 H, d, *J* 6.9, 6-H pyridyl), 8.60 (1 H, d, *J* 6.9, 6-H pyridyl), 13.30 (1 H, br s, NH) and 14.63 (1 H, br s, NH) [Found: C, 72.25; H, 5.09; N, 17.61.  $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}$  (316) requires C, 72.15; H, 5.06; N, 17.72%].

**1-(4-Methoxyphenyl)-3,3-bis-(2-pyridylamino)prop-2-en-1-one 8b.** Yellow crystals (2.80 g, 80.9%), mp 130 °C;  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3401, 1659, 1608, 1589 and 1532;  $\delta_{\text{H}}(\text{CDCl}_3)$  3.80 (3 H, s,  $\text{OCH}_3$ ), 6.90–7.30 (5 H, m, olefinic, ArH, 2 × 5-H pyridyl), 7.60 (4 H, m, 2 × 3-H and 2 × 4-H pyridyl), 8.00 (2 H, d, *J* 9, ArH), 8.25 (1 H, d, *J* 9, 6-H pyridyl), 8.55 (1 H, d, *J* 6.9, 6-H pyridyl), 13.20 (1 H, br s, NH) and 14.80 (1 H, br s, NH) [Found: C, 69.40; H, 5.12; N, 16.21.  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2$  (346) requires C, 69.36; H, 5.20; N, 16.18%].

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