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**EFFICIENT 2-AMINO-2-THIAZOLIN-4-ONES OR 2-IMINOTHIAZOLIDIN-4-ONES FORMATION FROM THIOUREAS AND MALEIMIDES UNDER SOLVENT-FREE CONDITIONS**

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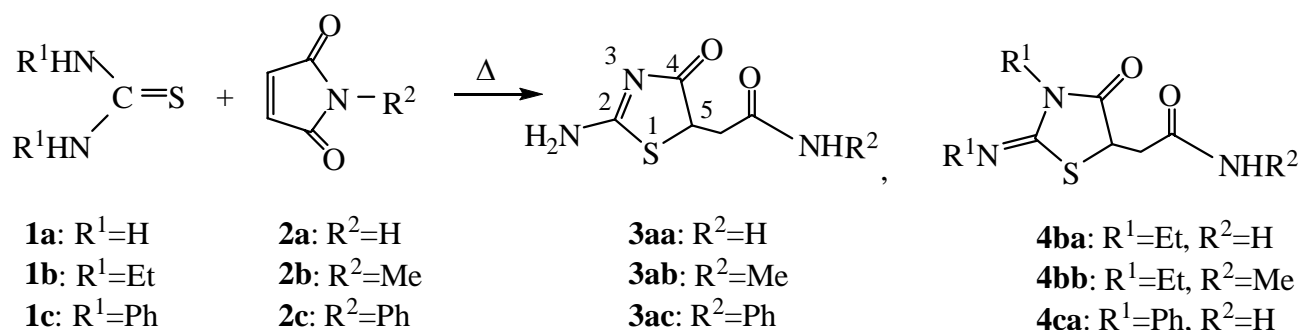
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**Abstract** – A facile method for the construction of 2-thiazolin-4-one or thiazolidin-4-one structure is described. Condensation reactions of thiourea (**1a**) and maleimides (**2**) under solvent-free conditions gave 2-amino-2-thiazolin-4-ones (**3**) *via* Michael-type reaction, while similar reactions of *N*-substituted thioureas (**1b-d**) with **2** afforded 2-iminothiazolidin-4-ones (**4**). Since the solvent-free reactions of **1** with **2a** afforded **3** in good yields, the synthetic method was found to be effective from the viewpoint of green chemistry.

2-Thiazoline and thiazolidine derivatives have been reported to exhibit pharmacological and biological activities, respectively. For example some 2-thiazoline derivatives present interesting anti-HIV<sup>1</sup> and

anti-cancer<sup>2</sup> activities, while thiazolidine derivatives show insecticidal<sup>3</sup> and fungisidal<sup>4</sup> activities. The classical synthesis of these compounds has been carried out in solution reactions between thioureas and maleimides or maleic anhydride, and so on<sup>5</sup> except microwave-assisted solvent-free synthesis.<sup>6</sup> In continuation of our studies related to the development of the solid-state organic synthesis,<sup>7</sup> we report here a simple and efficient synthetic method for 2-amino-2-thiazolin-4-ones or 2-iminothiazolidin-4-ones under solvent-free conditions.

A mixture of crystals of **1a** (0.20 mmol) and *N*-methylmaleimide (**2b**) (0.20 mmol) in a mortar was ground for 10 min with a pestle. The powder was kept at 60 °C in the glass-tube oven for 24 h. The reaction mixture was washed with acetone and filtered to give **3ab** in 59% yield (Scheme 1). Similar reaction of *N, N'*-diphenylthiourea (**1c**) (0.20 mmol) with maleimide (**2a**) (0.20 mmol) afforded **4ca** in 77% yield. The results of the similar reactions of **1a-d** with **2a-c** were summarized in Table 1. Since



Scheme 1

products **3ab** and **4ca** were recrystallized from ethanol to give single crystals, the structures of **3ab** (Figure 1)<sup>8</sup> and **4ca** (Figure 2)<sup>9</sup> were established by X-Ray crystallographic analyses as 2-amino-2-thiazolin-4-one-5-*N*-methylacetamide and (*Z*)-2-(*N*-phenylimino)-3-phenylthiazolidin-4-on-5-acetamide, respectively. It was found that the pairs of **3ab** were linked together to form planar tricyclic dimers by pairs of intermolecular hydrogen bonds between amino proton and nitrogen in the 2-thiazoline ring with H···N distance of 2.12 Å (Figure 3). The assignment of the same structures (**3** and **4**) to other 2-thiazolin-4-ones and thiazolidin-4-ones were based on their <sup>1</sup>H NMR, IR and MS spectra that were analogous to those of **3ab** and **4ca**.<sup>10</sup> Since intermolecular hydrogen bonds were found in **3ab** as

mentioned above the chemical shifts of the amino protons at the 2-thiazoline ring were observed at lower-field ( $\delta$  8.69 and 8.90), whose chemical shifts also appeared to **3aa** and **3ac**. On the other hand, the amino protons of amido group for **4ca** were observed at higher-field ( $\delta$  7.46 and 7.54). Similar chemical shifts were also observed to **4ba** and **4bb**.

Table 1 Reactions of Thioureas (**1**) with Maleimides (**2**) in the Solid State<sup>a</sup> and in Solution.<sup>b</sup>

| thiourea  | maleimide | yield(%) <sup>c</sup> in the solid state            |                                     | yield(%) <sup>c</sup> in solution                    |   |
|-----------|-----------|---|-------------------------------------|--|---|
|           |           | <b>3</b> or <b>4</b>                                | recovered <b>2</b>                  | <b>3</b> or <b>4</b>                                 | recovered <b>2</b>                                  |
| <b>1a</b> | <b>2a</b> | 95 ( <b>3aa</b> )                                   | 5                                   | 96 ( <b>3aa</b> )                                    | 2   |
|           |           | 15 ( <b>3aa</b> ) <sup>d</sup>                      | 85 <sup>d</sup>                     | 100 ( <b>3aa</b> ) <sup>e</sup>                      | 0 <sup>e</sup>                                      |
|           | <b>2b</b> | 59 ( <b>3ab</b> )<br>0 <sup>d</sup>                 | 41<br>100 <sup>d</sup>              | 98 ( <b>3ab</b> )<br>100 ( <b>3ab</b> ) <sup>e</sup> | 2<br>0 <sup>e</sup>                                 |
| <b>1b</b> | <b>2a</b> | 26 ( <b>3ac</b> )<br>0 <sup>d</sup>                 | 74<br>100 <sup>d</sup>              | 97 ( <b>3ac</b> )<br>99 ( <b>3ac</b> ) <sup>e</sup>  | 1<br>1 <sup>e</sup>                                 |
|           |           | <b>2b</b>   | 51 ( <b>4ba</b> )<br>0 <sup>d</sup> | 49<br>100 <sup>d</sup>                               | 98 ( <b>4ba</b> )<br>93 ( <b>4bb</b> ) <sup>e</sup> |
| <b>1c</b> | <b>2a</b> | 95 ( <b>4ba</b> )<br>30 ( <b>4ba</b> ) <sup>d</sup> | 5<br>70 <sup>d</sup>                | 94 ( <b>4ba</b> )<br>86 ( <b>4ba</b> ) <sup>e</sup>  | 6<br>14 <sup>e</sup>                                |
|           |           | <b>2b</b>   | 51 ( <b>4bb</b> )<br>0 <sup>d</sup> | 49<br>100 <sup>d</sup>                               | 98 ( <b>4bb</b> )<br>93 ( <b>4bb</b> ) <sup>e</sup> |
| <b>1c</b> | <b>2a</b> | 77 ( <b>4ca</b> )<br>0 <sup>d</sup>                 | 23<br>100 <sup>d</sup>              | 98 ( <b>4ca</b> )<br>35 ( <b>4ca</b> ) <sup>e</sup>  | 2<br>65 <sup>e</sup>                                |

<sup>a</sup>Equimolar mixture of **1** and **2** was heated at 60 °C for 24 h. <sup>b</sup>Equimolar ethanol solution (0.1 M) of **1** and **2** was heated at 60 °C for 24 h. <sup>c</sup>Estimated from NMR analyses based on total integral between **2** and **3** (or **4**). <sup>d</sup>Equimolar mixture of **1** and **2** was left at room temperature for 7d. <sup>e</sup>Equimolar ethanol solution (0.1 M) of **1** and **2** was left at room temperature for 7d.

Since the solvent-free reactions of **1a-c** with **2a** (60 °C, 24h) afforded **3aa**, **3ab**, and **3ac** in good yields (Table 1), the synthetic method was found to be effective from the viewpoint of green

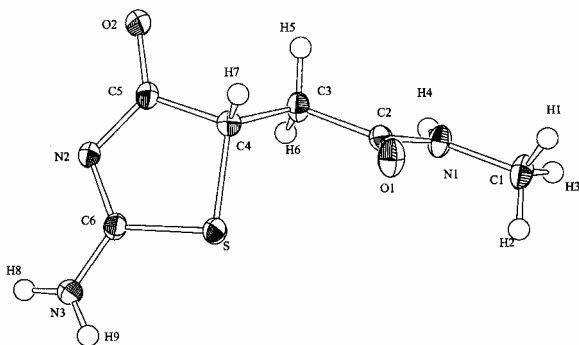


Figure 1 ORTEP drawing of **3ab**.

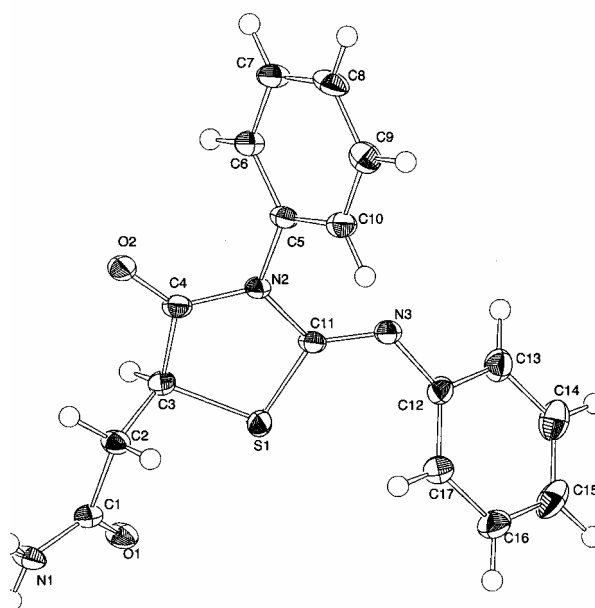


Figure 2 ORTEP drawing of **4ca**.

chemistry. It was inferred that the molecular packings between **1a-c** and **2a** were similar structures to 1:1 complex crystals between 2-pyrones and maleimide using non-covalent interactions which had given highly selective [2+2] cycloadducts quantitatively by photoirradiation in the solid state.<sup>7</sup> The decrease in reactivity of **1a** with **2b** or **2c** compared to that of **1a** with **2a** in the solid state was estimated to be caused by the lack of additional intermolecular hydrogen bond like N-H (**2a**)...O=C observed in the 1:1 complex crystals between 2-pyrones and **2a**. The reaction mechanism was considered to proceed via Michael addition of the sulfur of **1** to **2** to afford **4** which tautomerized to give **3** in the case of **1a** ( $R^1 = H$ ) (Scheme 2).

It was estimated that the activation energies of the reactions between **1a** and **2a-c** were relatively lower than the similar Michael addition containing hetero atom because the reactions in ethanol proceeded to give **3aa**, **3ab**, and **3ac** quantitatively at 60 °C and even at room temperature.

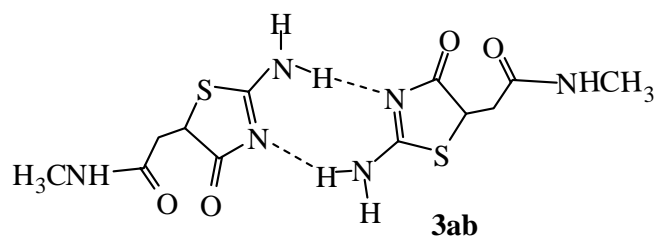
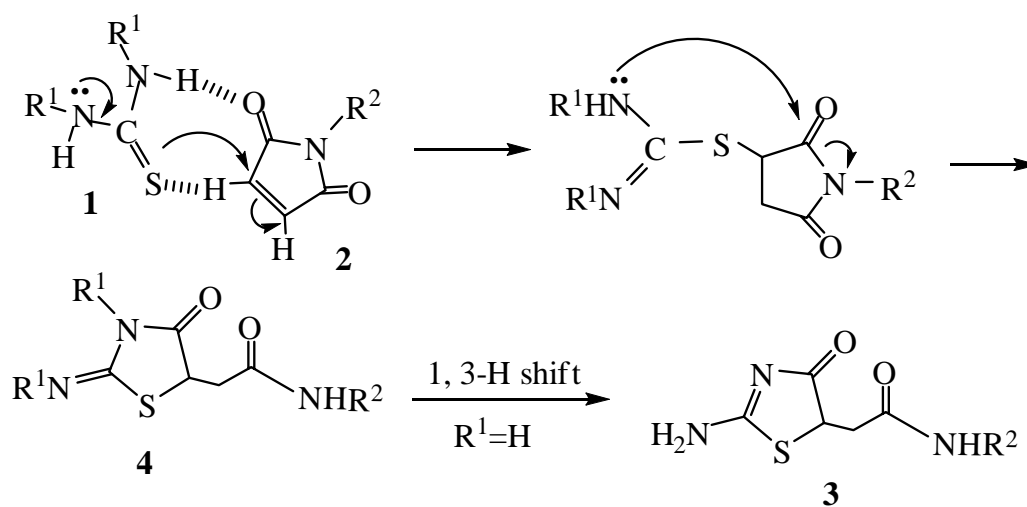


Figure 3 Intermolecular hydrogen bonds in **3ab**.



Scheme 2

## REFERENCES AND NOTES

1. G. Pattenden, B. Mulqueen, and J. Falek, *Tetrahedron Lett.*, 1994, **35**, 5705.

2. G. Pattenden, C. Boden, and T. Ye, *Synlett*, **1995**, 417.
3. A. Hirashima, H. Tarui, E. Taniguchi, and M. Eto, *Pestic. Biochem. Physiol.*, 1994, **50**, 83.
4. H. Naumann, H. Dehne, C. Fieseler, K. Goetzschel, M. Pallas, D. Schoenfelder, W. Mueller, W. Kochmann, K. Naumann, and W. Steinke, Ger. (East) DD 241,844, **1987** (*Chem. Abstr.*, 1987, **107**, 91901m).
5. D. H. Marrian, *J. Chem. Soc.*, **1949**, 1797; V. Balasubramaniyan, P. Balasubramaniyan, and M. J. Wani, *Proc. Acad. Sci. (Chem. Sci.)*, 1991, **103**, 621 and references cited therein; H.-G. Hahn, K. D. Nam, and H. Mah, *Heterocycles*, 2001, **55**, 1283; M. D'hooghe and N. De Kimpe, *Tetrahedron*, 2006, **62**, 513.
6. S. Kasmi, J. Hamelin, and H. Benhaoua, *Tetrahedron Lett.*, 1998, **39**, 8093.
7. T. Obata, T. Shimo, M. Yasutake, T. Shinmyozu, M. Kawaminami, R. Yoshida, and K. Somekawa, *Tetrahedron*, 2001, **57**, 1531; T. Shimo, T. Uezono, T. Obata, M. Yasutake, T. Shinmyozu, and K. Somekawa, *Tetrahedron*, 2002, **58**, 6111; T. Shimo, R. Yamaguchi, Y. Odo, and K. Somekawa, *Heterocycles*, 2004, **63**, 1541; W. Wang, T. Shimo, T. Shinmyozu, T. Iwanaga, and K. Somekawa, *Heterocycles*, 2006, **68**, 1381.
8. X-Ray crystal data for **3ab** (C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>S); T=113 K, Mo-K $\alpha$  (Rigaku RAXSIS-RAPID imaging plate diffractometer,  $\lambda$ =0.71069 Å), crystal dimensions 0.48 x 0.40 x 0.20 mm<sup>3</sup> (a colorless block crystal), a=14.1282 (4), b=4.6976 (2), c=15.6902 (4) Å,  $\beta$ = 108.567 (1)°, monoclinic, space group P2<sub>1</sub>/c (#14), Z=4,  $\mu_{\text{MoK}\alpha}$ =2.96 cm<sup>-1</sup>, Mr=187.22, V=987.15 (5) Å<sup>3</sup>, anode power 50 KV x 32 mA,  $\rho_{\text{calc}}$ =1.260 g/cm<sup>3</sup>,  $2\theta_{\text{max}}$ =55.0°, F (000)=392.00. 9060 reflections measured, 1860 observed (I > 3.00 $\sigma$ (I)), number of parameters 162. The structure was solved by direct method and was refined on SIR 92.<sup>10</sup> Data were corrected for Lorentz polarizations. The data/parameter ratio was 11.48. R=0.026, R<sub>w</sub>=0.037, GOF=1.25, max/min residual density +0.26/-0.17 eÅ<sup>-3</sup>. **4ca** (C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S); T=123K, crystal dimensions 0.17 x 0.04 x 0.41 mm<sup>3</sup> (a colorless platelet crystal), a=4.6757 (8), b=9.502 (2), c=34.392 (6) Å,  $\beta$ =90.117 (7)°, monoclinic, space group P2<sub>1</sub>/c (#14), Z=4,  $\mu_{\text{MoK}\alpha}$ =2.25 cm<sup>-1</sup>, Mr=325.38, V=1527 (1) Å<sup>3</sup>,  $\rho_{\text{calc}}$ =1.414 g/cm<sup>3</sup>, F (000)=680.00. 25391 reflections measured, 3486 observed (All,

$2\sigma < 54.97^\circ$ ), number of parameters 208. The structure was solved by direct method and was refined on SIR 97.<sup>11</sup> The data/parameter ratio was 16.76.  $R=0.072$ ,  $R_w=0.146$ ,  $GOF=1.39$ , max/min residual density  $+0.57/-0.62 \text{ e}\text{\AA}^{-3}$ . All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

9. All the new compounds gave the correct analytical and MS data. Selected spectral data are given below.

**3aa**: mp 244-245 °C;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  2.37 (1H, dd,  $J=16.0, 11.6$  Hz), 2.98 (1H, dd,  $J=16.0, 3.2$  Hz), 4.24 (1H, dd,  $J=11.6, 3.2$  Hz), 7.00, 7.48 (each 1H, s), 8.72, 8.94 (each 1H, s). IR (KBr) 3440, 3350, 3200, 1718, 1680, 1650  $\text{cm}^{-1}$ . **3ab**: mp 219-220 °C;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  2.35 (1H, dd,  $J=16.0, 11.6$  Hz), 2.55 (3H, d,  $J=4.4$  Hz), 2.94 (1H, dd,  $J=16.0, 3.2$  Hz), 4.23 (1H, dd,  $J=11.6, 3.2$  Hz), 7.91 (1H, s), 8.69, 8.90 (each 1H, s). IR (KBr) 3310, 1675, 1635  $\text{cm}^{-1}$ . **3ac**: mp 257-259 °C;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  2.69 (1H, dd,  $J=16.4, 11.0$  Hz), 3.26 (1H, dd,  $J=16.4, 3.4$  Hz), 4.39 (1H, dd,  $J=11.4, 3.4$  Hz), 7.05 (1H, Ph), 7.30, 7.48 (each 2H, Ph), 8.79, 9.00 (each 1H, s), 10.12 (1H, s). IR (KBr) 3280, 3210, 1670  $\text{cm}^{-1}$ . **4ba**: mp 186- 187 °C;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  1.06, 1.15 (each 3H, t,  $J=7.0$  Hz), 2.56 (1H, dd,  $J=16.4, 10.0$  Hz), 2.98 (1H, dd,  $J=16.4, 3.6$  Hz), 3.22, 3.61 (each 2H, q,  $J=7.0$  Hz), 4.36 (1H, dd,  $J=10.0, 3.6$  Hz), 7.05, 7.49 (each 1H, s). IR (KBr) 3380, 1710, 1670  $\text{cm}^{-1}$ . **4bb**: mp 137-140 °C;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  1.05, 1.16 (each 3H, t,  $J=7.2$  Hz), 2.55 (3H, d,  $J=3.6$  Hz), 2.56 (1H, dd,  $J=16.0, 10.0$  Hz), 2.97 (1H, dd,  $J=16.0, 3.2$  Hz), 3.22, 3.53 (each 2H, q,  $J=7.2$  Hz), 4.40 (1H, dd,  $J=10.0, 3.2$  Hz), 7.96 (1H, s). IR (KBr) 3330, 1700, 1640  $\text{cm}^{-1}$ . **4ca**: mp 233-236 °C;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  2.85 (1H, dd,  $J=16.6, 10.0$  Hz), 3.05 (1H, dd,  $J=16.6, 3.2$  Hz), 4.55 (1H, dd,  $J=10.0, 3.2$  Hz), 6.85, 7.09, 7.32, 7.42, 7.51 (each 2H, Ph), 7.46, 7.54 (each 1H). IR (KBr) 3420, 3170, 1705, 1660, 1635  $\text{cm}^{-1}$ .

10. A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi, and G. Polidori, *J. Appl. Cryst.*, 1994, **27**, 435.

11. A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, and A. G. G. Moliterni, G. Polidori, and R. Spagna, *J. Appl. Cryst.*, 1999, **32**, 115.