

A SIMPLE CONSTRUCTION OF 2-PHENYLMINO-1,3-THIAZOLIDIN-4-ONES

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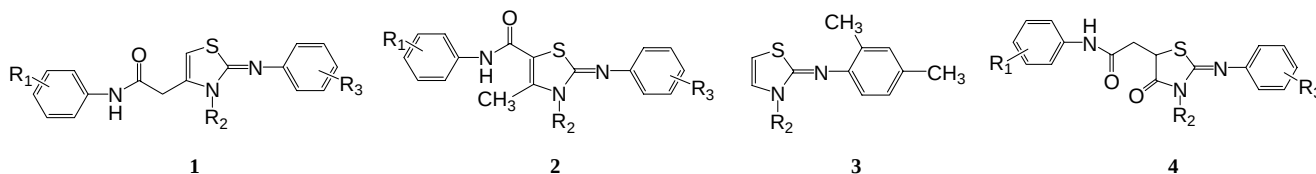
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Abstract - A new methodology for the construction of 2-phenylimino-1,3-thiazolidin-4-one skeleton is described. Reaction of maleic anhydride (**5a**) or maleimides (**5b**, **5c**) with thiourea (**6**) gave the corresponding 2-imino-1,3-thiazolidin-4-ones (**7**) and (**9**) respectively. The reaction proceeded with high yield in polar solvents. In non-polar solvents at high temperature, however, isothiocyanate (**8**) was formed as a by-product presumably by the pyrolysis of thiourea (**6**). The proposed mechanism of the reaction was discussed.

INTRODUCTION

Synthetic methods available for the construction of heterocyclic molecules can be used to effect a number of valuable synthetic transformation and much of the research in heterocyclic chemistry is concerned with the development of new methods for heterocyclic ring formation. There has been an increasing interest over the past several years in the chemistry of 2-iminothiazoline derivatives, primarily due to their remarkably broad spectrum of biological activity.¹ Examples of their biological activities are agrochemical herbicides,² insecticides,³ and fungicides.⁴ In the previous paper,⁵ we reported syntheses of 2-iminothiazolines (**1**) and (**2**), and the well known insecticide (**3**), which is effective against bee mite. It is clearly necessary to carry out structure-activity relationship studies of compound (**1**) to improve the potency and selectivity of these series of compounds as an effective fungicide. This report describes our preliminary effort toward the synthesis of new heterocyclic compounds of 1,3-thiazolidin-4-one derivative (**4**). Currently very few convenient syntheses of 1,3-thiazolidin-4-ones are available.⁶

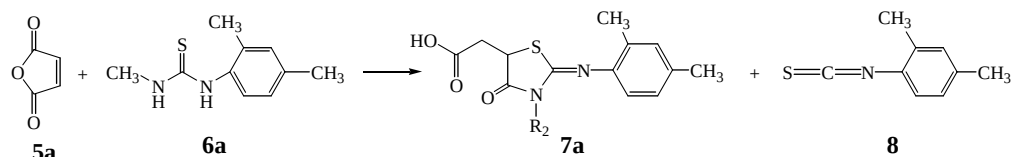


RESULTS AND DISCUSSION

To achieve the synthesis of target compounds we utilized the nucleophilic reactivity of sulfur in thiourea and electron-deficient character of olefin such as maleic anhydride (**5a**) or maleimides (**5b**, **5c**). Initially, maleic anhydride (**5a**) and substituted thiourea (**6a**) were chosen to evaluate the reactivity of both compounds (see Table 1). The starting **6a** was prepared by the reaction of methyl isothiocyanate with dimethylaniline.⁷ Reaction of **6a** with **5a** in refluxing methylene chloride for 14 h afforded the corresponding 1,3-thiazolidin-4-one-5-acetic acid (**7a**) in 53% yield (entry 1). With this initial data in hand we decided to investigate conditions under which this reaction proceeds. Thus, a number of solvents were examined. Table 1 shows the yields as a function of solvent and reaction time. For instance, reaction of **6a** with **5a** in CH₃CN at 82 °C gave **7a** in quantitative yield (entry 5), whereas in toluene the yield was

somewhat lower (entry 7, 92%). From Table 1 it is clear that CH₃CN is the solvent of choice. Additionally, the reaction proceeded smoothly in polar solvent (entries 5, 9). In contrast, the isothiocyanate (**8**) was formed as a by-product in non-polar solvent (entries 4, 6-8) by the decomposition of thiourea (**6a**), which was confirmed by independent reaction. Thus, pyrolysis of thiourea (**6a**) in refluxing toluene for 4 h resulted in isothiocyanate (**8**) in 68% yield.

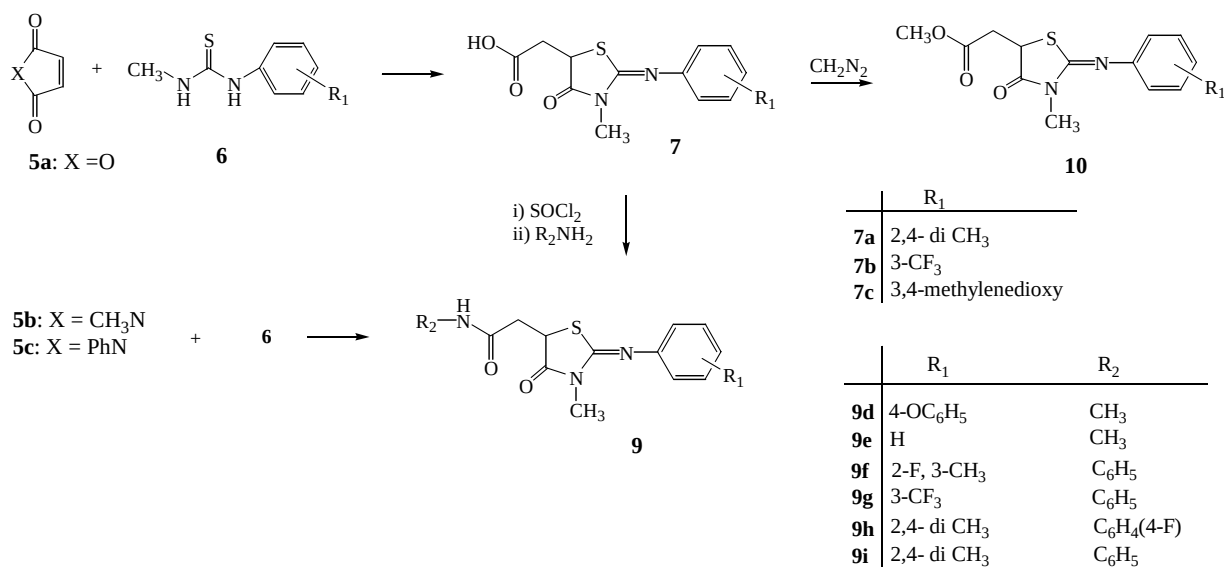
Table 1. Reaction of maleic anhydride (**5a**) with thiourea (**6a**) in various solvents



entry	solvent	temperature (°C)	reaction time(h)	product ratio (%) ^a		
				6a	7a	8
1	CH ₂ Cl ₂	40	14	47	53	0
2	acetone	56	20	27	73	0
3	C ₂ H ₅ OH	78	20	48	52	0
4	benzene	80	24	6	87	7
5	CH ₃ CN	82	24	0	100	0
6	1,4-dioxane	102	20	0	95	5
7	toluene	110	20	0	92	8
8	xylene	140	24	0	60	40
9	DMF	153	3	0	100	0

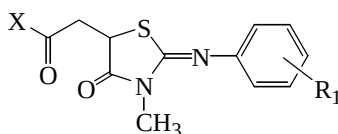
a: The yields were calculated by ¹H NMR spectra.

Next, we examined the reaction of various thioureas (**6**) with maleimides (**5b**) or (**5c**) to give the corresponding 1,3-thiazolidin-4-one acetamides (**9**), identical ¹H NMR spectra and TLC with those obtained from the compounds prepared by the chlorination of **7** followed by treatment of the corresponding amines respectively (see Scheme 1). As expected, treatment of the carboxylic acid (**7**) with diazomethane gave the corresponding methyl ester (**10**). Table 2 provides a list of various 2-imino-1,3-thiazolidin-4-ones that were prepared along with the yields, and melting points.



Scheme 1

Table 2. A list of 2-imino-1,3-thiazolidin-4-ones (**7**, **9**, and **10**) prepared, the yields, and melting points.



compounds	R ₁	X	solvent, reaction time	yield (%)	mp (°C)	methods *
7a	2,4-di CH ₃	OH	CH ₃ CN, 24 h	100	127-128	A
7b	3-CF ₃	OH	CH ₃ CN, 24 h	100	139	A
7c	3,4-methylenedioxy	OH	Toluene, 3 h	76	135-136	A
9d	4-OC ₆ H ₅	NHCH ₃	Toluene, 24 h	35	178-179	B
9e	H	NHCH ₃	CH ₃ CN, 24 h	43	180-181	B
9f	2-F, 3-CH ₃	NHC ₆ H ₅	CH ₃ CN, 24 h	76	148-151	C
9g	3-CF ₃	NHC ₆ H ₅	CH ₃ CN, 48 h	69	180-182	C
9h	2,4-di CH ₃	NHC ₆ H ₄ (4-F)		58	176-178	D
9i	2,4-di CH ₃	NHC ₆ H ₅		78	196-197	D
10a	2,4-di CH ₃	OCH ₃		99	Oil	E
10c	3,4-methylenedioxy	OCH ₃		73	115-116	E

* Method A: obtained by the reaction of **5a** with **6a**, **6b** or **6c**.

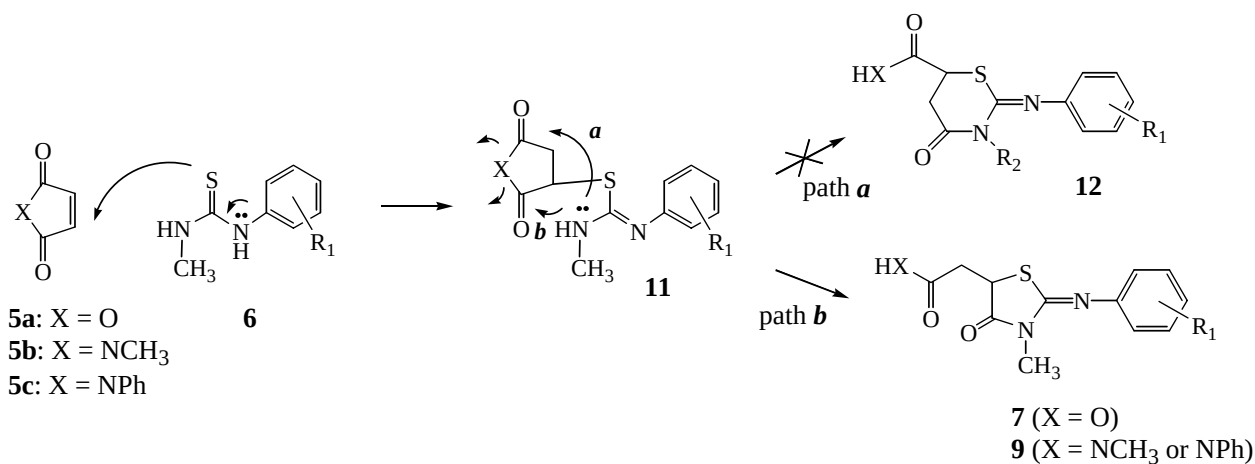
B: obtained by the reaction of **5b** with **6d** or **6e**.

C: obtained by the reaction of **5c** with **6f** or **6g**.

D: obtained by treatment of **7a** with thionyl chloride and then aniline derivative, respectively.

E: obtained by the reaction of **7a** or **7c** with diazomethane, respectively.

The mechanism of the reaction could be explained as follows. As shown in Scheme 2 nucleophilic 1,4-addition of the sulfur of thiourea (**6**) to maleic anhydride (**5a**) or maleimide (**5b**, **5c**) could afford iminosulfide (**11**). This unisolable intermediate (**11**) provides either 2-imino-1,3-thiazin-4-one (**12**) (path *a*) or 1,3-thiazolidin-4-one (**7**) or (**9**) (path *b*) as a result of an attack of the lone pair electron of the more basic



Scheme 2

methyl nitrogen on either carbonyl carbon. Since **12** was not the observed product, path **a** can be ruled out. All of these 1,3-thiazolidin-4-ones (**7**) or (**9**) were characterized by means of their spectral data and an X-Ray crystallographic analysis (see Figure 1 for 3,4-methylenedioxy analogue **10c**).⁸ Alternatively the more basic methyl nitrogen could attack the carbonyl carbon of maleic anhydride (**5a**) or maleimides (**5b**, **5c**) to form an amide and subsequent intramolecular 1,4-addition of the sulfur to the α , β -unsaturated carbonyl yield the same product (**7**) or (**9**).

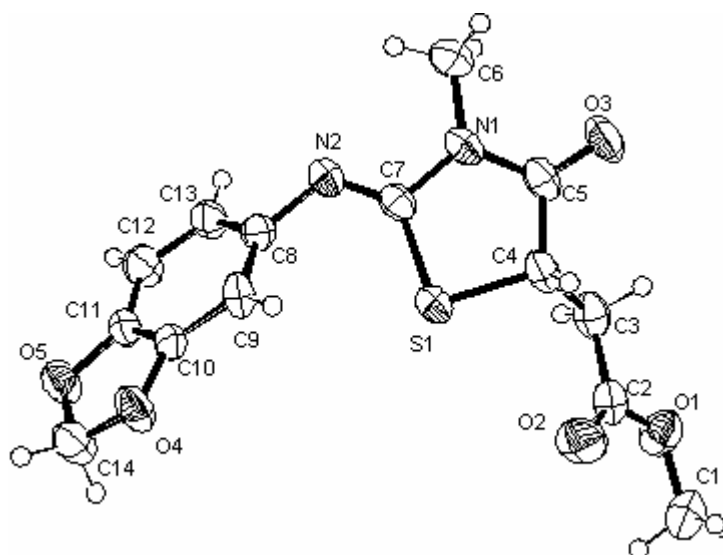


Figure 1. ORTEP plots of 3,4-methylenedioxy analogue (**10c**) with heteroatoms labeled.

EXPERIMENTAL SECTION

Melting points were determined on a Walden Precision Apparatus Electrothermal 9300 apparatus. All ¹H (300 MHz) and ¹³C NMR (78.5 MHz) spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shift (δ) are given in ppm and the coupling constants (*J*) in Hz. IR spectra were obtained on a Perkin-Elmer 16F-PC FT-IR and are reported in cm⁻¹. MS spectra were recorded on a Hewlett Packard 5890 series GC/MSD. Electron-impact high-resolution mass spectra (HRMS) were obtained on a JMS-700 Mass spectrometer high-resolution mass spectrometer at 70 eV.

Synthesis of 3-Methyl-2-(2,4-dimethylphenyl)imino-1,3-thiazolidin-4-one-5-acetic acid (**7a**) (**R**₁ = 2,4-di CH₃) (General Procedure)

A solution of maleic anhydride (**5a**) (0.98 g, 10 mmol) and thiourea (**6a**) (1.94 g, 10 mmol) in toluene (30 mL) was refluxed for 5 h. Evaporation of the solvent followed by crystallization from ethyl acetate and *n*-hexane gave **7a** as a yellow solid (2.69 g, 92 %).

mp 127-128 °C; ¹H NMR (CDCl₃) 2.11 and 2.30 (2s, 6H, 2 x CH₃), 2.89 (dd, 1H, *J* = 9.6, 17.9, methylene CH), 3.29 (dd, 1H, *J* = 3.5, 17.9, methylene CH), 3.34 (s, 3H, N-CH₃), 4.31 (dd, 1H, *J* = 3.5, 9.6, 5-CH), 6.77-7.02 (m, 3H, ArH), 10.01 (br s, 1H, COOH); ¹³C NMR 17.60, 20.95, 29.75, 37.67, 43.35, 119.73, 127.21, 129.56, 131.58, 134.45, 143.86, 153.90, 173.60, 175.17; IR (KBr) 2924, 1724, 1636, 1426, 1376, 1212; HRMS for C₁₄H₁₆N₂O₃S: Calcd 292.0881. Found, 292.0881; *Anal.* Calcd for C₁₄H₁₆N₂O₃S: C, 57.52, H, 5.52, N, 9.58, S, 10.97. Found, C, 57.4, H, 5.46, N, 9.47, S, 11.0.

3-Methyl-2-(3-trifluoromethylphenyl)imino-1,3-thiazolin-4-one-5-acetic acid (**7b**) (**R**₁ = 3-CF₃)

mp 139 °C; ¹H NMR (CDCl₃) 2.92 (dd, 1H, *J* = 9.9, 18.1, methylene CH), 3.45 (s, 3H, NCH₃), 3.36 (dd, 1H, *J* = 3.5, 18.1, methylene CH), 4.37 (dd, 1H, *J* = 3.5, 9.9, 5-CH), 5.69 (br s, 1H, COOH), 7.71-7.49 (m, 4H, ArH); IR (KBr) 2907, 1732, 1634, 1588, 1428, 1240, 1210; HRMS for C₁₃H₁₁N₂O₃F₃S: Calcd 332.0442. Found, 332.0439.

3-Methyl-2-[(3,4-methylenedioxy)phenyl]imino-1,3-thiazolin-4-one-5-acetic acid (7c) (R_1 = 3,4-methylenedioxy)

mp 135-136 °C; ^1H NMR (CDCl_3) 2.89 (dd, 1H, J = 9.8, 18.0, methylene CH), 3.31 (s, 3H, NCH_3), 3.33 (dd, 1H, J = 3.5, 18.0 Hz, methylene CH), 4.33 (dd, 1H, J = 3.5, 9.8, 5-CH), 5.96 (s, 2H, CH_2), 6.41 (d, 1H, J = 2.1, ArH), 6.44 (s, 1H, ArH), 6.77 (d, 2H, J = 2.1, ArH); IR (KBr) 3455, 1725, 1636, 1486, 1247, 1187, 1043 cm^{-1} ; *Anal.* Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$: C, 50.64, H, 3.92, N, 9.09, S, 10.40. Found, C, 50.7, H, 3.89, N, 8.96, S, 10.6.

3, *N*-Dimethyl-2-(4-phenoxyphenyl)imino-1,3-thiazolin-4-one-5-acetamide (9d) (R_1 = 4- OC_6H_5 , R_2 = CH_3)

mp 178-179 °C; ^1H NMR (CDCl_3) 2.64 (dd, 1H, J = 10.4, 15.5, methylene CH), 2.82 (d, 3H, J = 4.8, NCH_3), 3.20 (dd, 1H, J = 3.6, 15.5, methylene CH), 3.34 (s, 3H, 3- CH_3), 4.42 (dd, 1H, J = 3.6, 10.4, 5-CH), 5.50 (br s, 1H, NH), 6.95-7.36 (m, 9H, ArH); IR (KBr) 2937, 1722, 1634, 1488, 1240, 1210; HRMS for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$: Calcd 369.1147. Found, 369.1165; *Anal.* Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$: C, 61.77, H, 5.18, N, 11.37, S, 8.68. Found, C, 61.8, H, 5.15, N, 11.3, S, 8.71.

3, *N*-Dimethyl-2-phenylimino-1,3-thiazolin-4-one-5-acetamide (9e) (R_1 = H, R_2 = CH_3)

mp 180-181 °C; ^1H NMR (CDCl_3) 2.63 (dd, 1H, J = 10.2, 15.9, methylene CH), 2.81 (d, 3H, J = 4.8, NCH_3), 3.18 (dd, 1H, J = 3.6, 15.9, methylene CH), 3.34 (s, 3H, 3- CH_3), 4.02 (dd, 1H, J = 3.6, 10.2, 5-CH), 5.65 (br s, 1H, NH), 6.96-7.36 (m, 5H, ArH); IR (KBr) 2927, 1716, 1636, 1591, 1426, 1378; HRMS for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$: Calcd 277.0885. Found, 277.0880; *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$: C, 56.30, H, 5.45, N, 15.15, S, 11.56. Found, C, 56.3, H, 5.41, N, 15.0, S, 11.5.

3-Methyl-2-(2-fluoro-4-methylphenyl)imino-*N*-phenyl-1,3-thiazolin-4-one-5-acetamide (9f) (R_1 = 2-F, 3- CH_3 , R_2 = C_6H_5)

mp 148-151 °C; ^1H NMR (CDCl_3) 2.31 (s, 3H, CH_3), 2.83 (dd, 1H, J = 10.2, 16.2, methylene CH), 3.37 (s, 3H, 3- CH_3), 3.39 (dd, 1H, J = 3.6, 16.2, methylene CH), 4.49 (dd, 1H, J = 3.6, 10.2, 5-CH), 6.83-7.76 (m, 8H, ArH), 7.44 (br s, 1H, NH); IR (KBr) 2927, 1712, 1680, 1632, 1546, 1444, 1248; HRMS for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_2\text{FS}$: Calcd 371.1104. Found, 371.1097.

3-Methyl-2-(3-trifluoromethylphenyl)imino-*N*-phenyl-1,3-thiazolin-4-one-5-acetamide (9g) (R_1 = 3- CF_3 , R_2 = C_6H_5)

mp 180-182 °C; ^1H NMR (CDCl_3) 2.88 (dd, 1H, J = 10.7, 16.6, methylene CH), 3.33 (s, 3H, 3- CH_3), 3.44 (dd, 1H, J = 3.2, 16.6, methylene CH), 4.46 (dd, 1H, J = 3.2, 10.7, 5-CH), 7.02-7.54 (m, 9H, ArH), 9.77 (br s, 1H, NH); IR (KBr) 2957, 1710, 1670, 1634, 1544, 1338, 1308, 1110; HRMS for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_2\text{F}_3\text{S}$: Calcd 407.0915. Found, 407.0906.

Synthesis of Methyl 3-Methyl-2-[(3,4-(methylenedioxy)phenyl]imino-1,3-thiazolidin-4-one-5-acetate (10c) (R_1 = 3,4-methylenedioxy) (General Procedure)

A solution of 1,3-thiazolidin-4-one-5-acetic acid (7c) (616 mg, 2 mmol) (R_1 = 3,4-methylenedioxy) in methylene chloride (30 mL) cooled under the ice bath was added a solution of diazomethane dissolved in ether. Evaporation of the solvent followed by crystallization from ethyl acetate and *n*-hexane gave the corresponding methyl ester.

mp 115-116 °C; ^1H NMR (CDCl_3) 2.85 (dd, 1H, J = 9.9, 17.6, methylene CH), 3.27 (dd, 1H, J = 3.4, 17.6, methylene CH), 3.31 (s, 3H, 3- CH_3), 3.72 (s, 3H, OCH_3), 4.34 (dd, 1H, J = 3.4, 9.9 Hz, 5-CH), 5.97 (s, 2H, 3,4-methylenedioxy CH_2), 6.41-6.79 (m, 3H, ArH); IR (KBr) 2894, 1720(st), 1630(st), 1478, 1368, 1226, 1180, 1036; HRMS for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$: Calcd 322.0623. Found, 322.0620; *Anal.* Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$: C, 52.17, H, 4.38, N, 8.69, S, 9.95. Found, C, 52.3, H, 4.32, N, 8.64, S, 9.94.

Methyl 3-Methyl-2-(2,4-dimethylphenyl)imino-1,3-thiazolidin-4-one-5-acetate (10a) (R_1 = 2,4-di CH_3)

^1H NMR (CDCl_3) 2.13 and 2.30 (2s, 6H, 2 x CH_3), 2.85 (dd, 1H, J = 9.6, 17.5, methylene CH), 3.25 (dd,

1H, $J = 3.6$, 17.5, methylene CH), 3.35 (s, 3H, NCH₃), 3.69 (s, 3H, OCH₃), 4.33 (dd, 1H, $J = 3.6$, 9.6, 5-CH), 6.74-7.03 (m, 3H, ArH); ¹³C NMR δ 18.01, 27.31, 30.02, 38.07, 43.97, 52.68, 119.95, 127.46, 129.85, 131.82, 134.52, 144.50, 153.76, 170.84, 173.84; IR (KBr) 2967, 1734, 1636, 1426, 1370, 1208; HRMS for C₁₅H₁₈N₂O₃S: Calcd 306.1038. Found 306.1040.

Synthesis of 3-Methyl-2-(2,4-dimethylphenyl)imino-*N*-(4-fluorophenyl)-1,3-thiazolidin-4-one-5-acetamide (9h) (R₁ = 2,4-di CH₃, R₂ = C₆H₄(4-F)) (General Procedure)

A solution of 1,3-thiazolidine-4-one-5-acetic acid (**7a**) (R₁ = 2,4-di CH₃) (584 mg, 2 mmol) in benzene (15 mL) and thionyl chloride (0.16 mL, 2.2 mmol) was refluxed for 3 h. Evaporation of the solvent gave an light brown oily residue, which was dissolved in benzene (10 mL). To a reaction mixture cooled under ice bath was added sequentially 4-fluoroaniline (0.21 mL, 2.2 mmol) and triethylamine (0.31 mL 2.2 mmol). Stirring was continued for 20 h at rt. The reaction mixture was washed sequentially with 1N hydrochloric acid, aqueous saturated sodium bicarbonate solution, and then water. Drying (MgSO₄) and evaporation of the solvent gave an light brown oil (0.743 g). Crystallization from ethyl acetate and *n*-hexane afforded **9h** (R₁ = 2,4-di CH₃, R₂ = C₆H₄(4-F)) (0.447 g, 58 %) as a light yellow needle.

mp 176-178 °C; ¹H NMR (CDCl₃) 2.14 and 2.30 (2s, 6H, 2 x CH₃), 2.83 (dd, 1H, $J = 9.8$, 16.4, methylene CH), 3.34 (dd, 1H, $J = 3.8$, 16.4, methylene CH), 3.36 (s, 3H, NCH₃), 4.43 (dd, 1H, $J = 3.8$, 9.8, 5-CH), 6.74-7.44 (m, 7H, ArH), 7.65 (br s, 1H, NH); ¹³C NMR 18.25, 21.49, 30.27, 40.67, 44.48, 116.11, 116.41, 120.11, 122.46, 122.56, 127.74, 130.11, 132.12, 133.94, 133.98, 134.95, 144.42, 154.34, 158.48, 161.72, 167.93, 174.94; IR (KBr) 2927, 1719, 1702, 1636, 1559, 1438, 1378; HRMS for C₂₀H₂₀N₃O₂FS: Calcd 385.1260. Found 385.1257.

3-Methyl-2-(2,4-dimethylphenyl)imino-*N*-phenyl-1,3-thiazolidin-4-one-5-acetamide (9i) (R₁ = 2,4-di CH₃, R₂ = C₆H₅)

yield 78 %; mp 196-197 °C; R_f 0.42 (ethyl acetate : *n*-hexane = 1 : 4); ¹H NMR (CDCl₃): 2.14 and 2.30 (2s, 6H, 2 x CH₃), 2.84 (dd, 1H, $J = 9.7$, 16.2, methylene CH), 3.36 (dd, 1H, $J = 3.9$, 16.2, methylene CH), 3.38 (s, 3H, N-CH₃), 4.46 (dd, 1H, $J = 3.9$, 9.7, 5-CH), 6.75-7.49 (m, 8H, ArH), 7.63 (br s, 1H, NH); ¹³C NMR: 18.02, 21.28, 30.03, 40.07, 44.33, 119.93, 120.04, 125.07, 127.52, 129.42, 129.90, 131.89, 134.68, 137.79, 144.36, 154.12, 167.68, 174.74. IR (KBr) 2925, 1722, 1692, 1625, 1545, 1430, 1363; HRMS for C₂₀H₂₁N₃O₂S: Calcd 367.1354. Found 367.1351; *Anal.* Calcd for C₂₀H₂₁N₃O₂S: C, 65.37, H, 5.76, N, 11.44, S, 8.73. Found, C, 65.5, H, 5.75, N, 11.4, S, 8.66.

Pyrolysis of *N*-methyl-*N'*-(2,4-dimethylphenyl)thiourea (6a)

A solution of **6a** (0.5 g, 2.57 mmol) in toluene (25 mL) was refluxed for 4 h. Evaporation of the solvent gave white solid residue. Crystallization from ethyl acetate and petroleum ether afforded white solids (**8**) (0.289 g, 68%, $R_f = 0.47$ (ethyl acetate/*n*-hexane = 4/1)). mp 29-30 °C; ¹H NMR (CDCl₃): 2.30 and 2.34 (2s, 6H, 2 x CH₃), 6.94-7.09 (m, 3H, ArH); IR (KBr) 3445, 2917, 2088, 1780, 1646, 1386; MS, m/z 163 (M⁺); *Anal.* Calcd for C₉H₉NS: C, 66.22, H, 5.56, N, 8.58, S, 19.64. Found, C, 66.2, H, 5.52, N, 8.46, S, 19.7.

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8. The X-Ray analysis was performed with the 3,4-methylenedioxy analogue (**10c**) (see Scheme 1). The data were collected on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-Ray tube and a graphite crystal monochromator. Orthorhombic space group $P2_12_12_1$ (No. 19) with $a = 7.569(3)$, $b = 8.813(2)$, $c = 21.273(5)$, $V = 1419.0(4)$ Å³, $Z = 4$, $d_{\text{calc}} = 1.509$ gcm⁻³, $\mu = 0.255$ mm⁻¹. A total of 1138 independent absorption-corrected reflections were collected. The structure was solved using SHELXS86 and SHELXL93 programs. The resulting structural parameters were refined to convergence of $R_1 = 0.0398$ for 1138 independent reflections with $I > 2\sigma(I)$ using full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms.