Sulfur-nitrogen heterocycles from the condensation of pyrazolones and 2-iminothiazolidin-4-ones with phenyl isothiocyanate

Emine Bagdatli, Senem Akkus, Cigdem Yolacan and Nüket Öcal*

Yildiz Technical University, Faculty of Arts and Sciences, Department of Chemistry, Davutpasa Campus, 34210 Istanbul, Turkey

The condensation of 2-pyrazolin-5-ones with phenyl isothiocyanate, followed by reaction of the resulting thiolate ions with chloroacetyl chloride, phenacyl bromide, oxalyl chloride, 1,4-dibromo-2,3-butanedione and ethyl chloroformate, resulted in cyclisation to S,N-heterocycles in all cases. 2-Iminothiazolidin-4-ones, with phenyl isothiocyanate and then chloroacetyl chloride or phenacyl bromide, similarly formed 2,4′-bi(thiazolidine)-derived products.

Keywords: phenyl isothiocyanate, 2-pyrazolin-5-ones, thiazolidines, thioanilides, 1,3-thiazepane-5,6-diones

Compounds carrying active hydrogen atoms can undergo condensations with aryl isothiocyanates to give intermediates that can be cyclised with suitable electrophiles to deliver N,S-heterocycles of pharmacological interest.[1] Metwally *et al*.[2] have reported on the sequential condensation of 2-pyrazolin-5-ones with phenyl isothiocyanates and cyclisation of the resulting thiocarbamoyl sodium salts with ethyl bromoacetate, chloroacetyl chloride, phenacyl bromide, ethyl chloroformate, diethyl α-bromomalonate, ethyl chloroformate, and ethyl β-bromopropanoate to give a variety of 4-, 5-, and 6-membered S,N-heterocycles. The thiazolidinones, thiazolines, thiazinones, and thiazetidinones so obtained exhibit pesticidal, anticonvulsant, nematocidal, herbicidal, antiviral, fungicidal, bactericidal, antiprotozal and hypoglycemic activity. The diversity of biological and physiological activity has been ascribed to the presence of the N–C–S unit in these compounds.[2a,b]

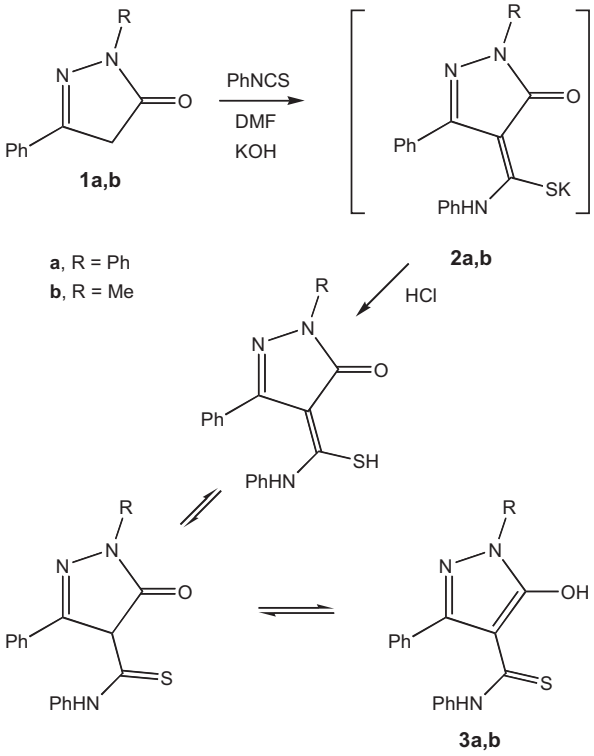
Previously we have reported on the syntheses of several thiazolidin-4-one derivatives having some biological activities.[3-6] Abdel-Megid has also reported some *p*-bis-(4-thiazolidinon-3-yl)phenylenes which were tested for their effect on cellobiase, produced by thermophilic fungi.[7] The biological significance of these classes of compound moved us to study the synthesis and physicochemical properties of some new thiazolidin-4-ones based on the cyclocondensations of 2-pyrazolin-5-ones with phenyl isothiocyanate and subsequent reactions with electrophiles such as oxalyl chloride and 1,4-dibromo-2,3-butanedione. Moreover, we have extended this cyclocondensation methodology to 2-*N*-alkyl and -arylimino-4-thiazolidinones which represent new systems with possible biological activity.

Results and discussion

In the first phase of our work, the starting materials, 1,3-diphenyl-1,4-dihydropyrazol-5-one (**1a**) and 1-methyl-3-phenyl-1,4-dihydropyrazol-5-one (**1b**), were prepared according to the literature procedures.[8] The reaction of compounds **1a** and **1b** with phenyl isothiocyanate and KOH in DMF afforded the intermediate non-isolable potassium salts **2a–b**. Quenching of the salts with HCl gave the corresponding thiocarbamoyl derivatives **3a–b** (Scheme 1).

Compounds **3a–b** exhibit tautomeric forms whose stabilisation depends on the influence of the substituents and the medium.[9] In the current study, compounds **3a** and **3b** were identified to be enols in $CDCl_3$ by spectroscopy. In the ^{1}H NMR spectra of compound **3a** and **3b,** two broad signals at 5.90 and ~ 7.20 ppm (OH) and 8.97 and 8.56 ppm (NH), respectively, were observed.

Reaction of phenacyl bromide with the salts **2a** and **2b** gave compounds **4a** and **4b** which were identified based on their



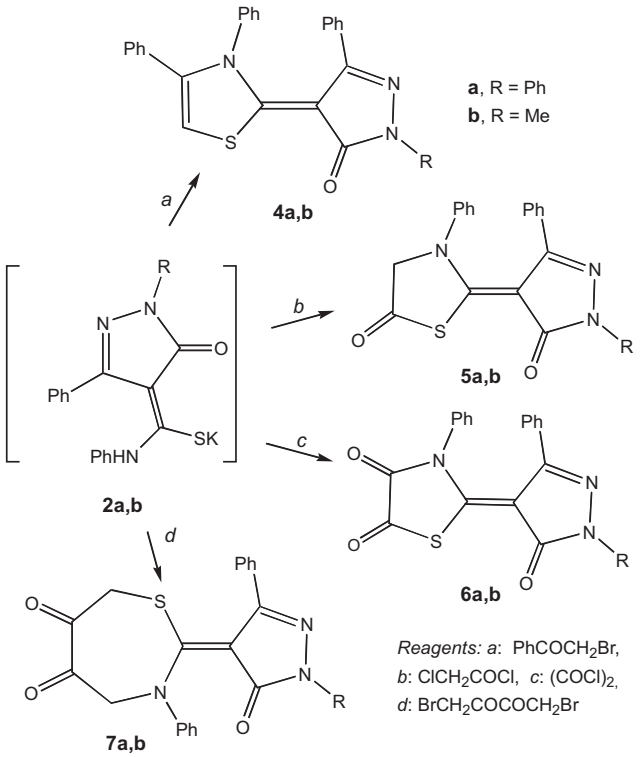
Scheme 1

spectral data. Further, The salts **2a** and **2b** were allowed to react with chloroacetyl chloride at low temperature to give compounds **5a** and **5b**. When compounds **1a** and **1b** were reacted with phenyl isothiocyanate in basic medium followed by cyclisation with oxalyl chloride, **6a** and **6b** were isolated, showing very similar NMR spectra, as expected. Similar cyclocondensations with 1,4-dibromo-2,3-butanedione gave compounds **7a** and **7b**. These products were characterised by FT-IR and NMR spectroscopy, as well as elemental analysis (Scheme 2).

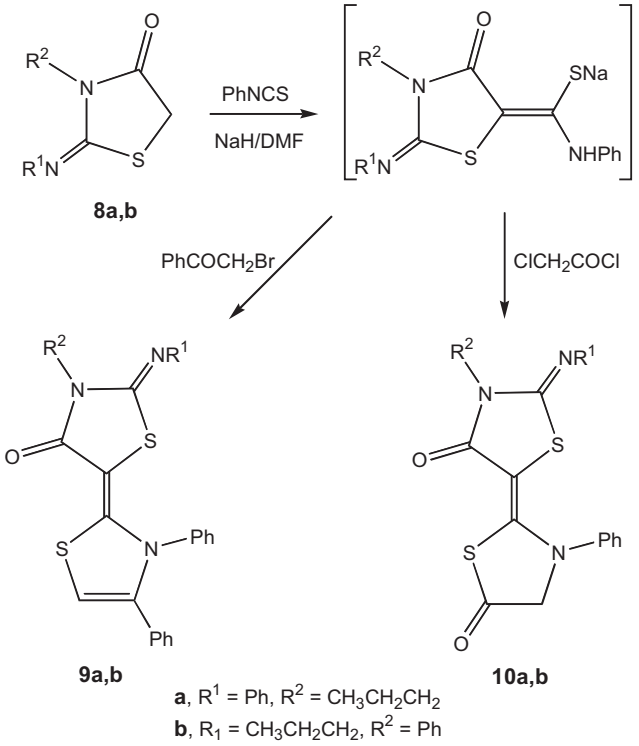
We extended the sequential thiocarbamoylation – cyclo-condensation using phenyl isothiocyanate and electrophiles such as phenacyl bromide, chloroacetyl chloride, applying it to 2-imino-4-thiazolidinones. 2-Phenylimino-3-propyl-4-thiazolidinone (**8a**) and 3-phenyl-2-propylimino-4-thiazolidinone (**8b**), were prepared according to published procedures.[10] The reactions of phenacyl bromide and chloroacetyl chloride with these compounds in basic medium afforded the bisthiazolidinones **9a–b** and **10a–b**, respectively (Scheme 3).

Our results have shown that the sequential condensation of phenyl isothiocyanate and cyclocondensation of the resulting thiocarbamoyl salts with α-halocarbonyl compounds with heterocycles containing active methylene groups is a useful

* Correspondent. E-mail: nocal@yildiz.edu.tr



Scheme 2



Scheme 3

reaction for the construction of novel heterocycles which may prove to be of pharmacological interest. Our studies on the application of these cyclocondensations to other heterocyclic C–H acids are ongoing and will be reported in due course.

Experimental

NMR spectra were recorded with $CDCl_3$ as solvent and TMS as internal reference, on a Bruker Digital FT-NMR Avance 400 MHz NMR spectrometer unless otherwise specified; alternatively, on an Varian Inova 500 MHz instrument. FT IR spectra were recorded (when solid, in KBr) on a Perkin-Elmer FT IR spectrometer. Most reactions were performed under dry nitrogen. Melting points were measured on a Gallenkamp melting point apparatus. Silica gel 60 (Merck) was used for column chromatography. TLC was conducted on standard conversion aluminum sheets pre-coated with 0.2 mm layer of silica gel. Elemental analyses were carried out with a Thermo Flash EA 1112 Series apparatus.

Preparation of thioanilides **3a,b**: *general procedure*
To a cold suspension of KOH (0.01 mol) in DMF (30 ml) was added compound **1a** or **1b** (0.01 mol) and phenyl isothiocyanate (0.01 mol). The mixture was stirred at room temperature overnight, then acidified with HCl (0.1 N). The solid products were filtered off, dried and purified by column chromatography.

5-Hydroxy-N,1,3-triphenyl-1H-pyrazole-4-carbothioamide (**3a**): n-Hexane/ethyl acetate 2 : 1; dark yellow solid (59%), m.p. 173°C. IR: ν_{max} 3436 (OH), 3282 (NH), 3169 (=C–H), 1595 (C=N) cm^{-1}. NMR (500/125 MHz): δ_H 5.90 (bs, 1H, OH), 6.92-6.94 (d, J = 8.0 Hz, 2H, aromatic), 7.03–7.05 (t, J = 7.0, 7.5 Hz, 1H, aromatic), 7.20–7.26 (m, 3H, aromatic), 7.31–7.40 (m, 7H, aromatic), 7.59–7.61 (d, J=8.5 Hz, 2H, aromatic), 8.97 (bs, 1H, NH); δ_C: 104.5 (C=C–OH), 146.2 (C=N), 158.7 (C=C–OH), 197.0 (C=S). Anal. Calc for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31; S, 8.63. Found: C, 70.89; H, 4.59; N, 11.39; S, 8.43%.

5-Hydroxy-1-methyl-N,3-diphenyl-1H-pyrazole-4-carbothioamide (**3b**): n-Hexane/ethyl acetate 1 : 2; yellow solid (56%), m.p. 126–128°C. IR: ν_{max} 3468 (OH), 3176 (NH), 3113 and 3023 (=C–H), 1586 (C=N) cm^{-1}. NMR: δ_H 3.76 (s, 3H, CH_3), 7.19–7.34 (m, 6H, aromatic and OH), 7.50–7.65 (m, 5H, aromatic), 8.56 (bs, 1H, NH) ppm; δ_C 33.5 (CH_3), 104.5 (C=C–OH), 148.0 (C=N), 158.2 (C=C–OH), 197.0 (C=S). Anal. Calc for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58; S, 10.36; Found: C, 65.82; H, 4.88; N, 13.50; S, 10.16%.

Synthesis of compounds **4a,b** *and* **7a,b**; *general procedure*
A solution of KOH (0.01 mol) in DMF was added to a stirred solution of compound **1a** or **1b** (0.01 mol) in DMF (30 ml) at 0–5°C under nitrogen. After 10 min stirring, phenyl isothiocyanate (0.01 mol) was added and the mixture was stirred for 10 h at 0°C. Phenacyl bromide (0.01 mol) or 1,4-dibromo-2,3-butanedione (0.01 mol) was added dropwise to the potassium salt of the intermediate within 20 min. The reaction mixture was stirred for an additional 30 min in the ice-bath and then stirred at room temperature overnight. The mixture was poured into crushed ice and the solid which separated was filtered by suction and dried at room temperature for a day. The residue was purified by column chromatography.

4-(3,4-Diphenylthiazol-2(3H)-ylidene)-1,3-diphenyl-1H-pyrazol-5(4H)-one (**4a**): n-Hexane/ethyl acetate 2 : 1; yellow solid (71%), m.p. 248–250°C. IR: ν_{max} 3115 and 3065 (=C–H), 1659 (C=O), 1596 (C=N) cm^{-1}. NMR: δ_H 6.93 (s, 1H, =CH), 7.17–7.25 (m, 2H, aromatic), 7.39–7.53 (m, 14H, aromatic), 7.88–7.91 (m, 2H, aromatic), 8.14–8.16 (d, J = 7.80 Hz, 2H, aromatic); δ_C 106.5 (C=C–C=O), 110.5 (Ph–C=C–S), 125.3 (Ph–C=C–S), 138.2 (C=C–C=O), 151.5 (C=N), 165.2 (C=O). Anal. Calc for $C_{30}H_{21}N_3OS$: C, 76.41; H, 4.49; N, 8.91; S, 6.80. Found: C, 76.25; H, 4.45; N, 8.80; S, 6.74%.

4-(3,4-Diphenylthiazol-2(3H)-ylidene)-1-methyl-3-phenyl-1H-pyrazol-5(4H)-one (**4b**): Yellow solid (82%), m.p. 224–226°C (from ethanol). IR: ν_{max} 3070 (=C–H), 1598 (C=O) cm^{-1}. NMR: δ_H 3.57 (s, 3H, CH_3), 6.88 (s, 1H, =CH), 7.35–7.49 (m, 13H, aromatic), 7.78–7.80 (m, 2H, aromatic); δ_C 36.5 (CH_3), 103.2 (C=C–C=O), 110.8 (Ph–C=C–S), 126.1 (Ph–C=C–S), 139.0 (C=C–C=O), 149.7 (C=N); 164.7 (C=O). Anal. Calc for $C_{25}H_{19}N_3OS$: C, 73.32; H, 4.68; N, 10.26; S, 7.82. Found: C, 73.12; H, 4.70; N, 10.34; S, 8.01%.

2-(5-Oxo-1,3-diphenyl-1H-pyrazol-4(5H)-ylidene)-3-phenyl-1,3-thiazepane-5,6-dione (**7a**): n-Hexane/ethyl acetate 1 : 3; yellow oil (68%). IR: ν_{max} 3060 (=C–H), 1742 (C=O), 1732 (C=O), 1622 (C=O), 1594 (C=N) cm^{-1}. NMR: δ_H 2.07 (s, 2H, CH_2), 3.15 (s, 2H, CH_2), 6.90–7.64 (m, 15H, aromatic); δ_C 32.7 (CH_2), 33.1 (CH_2), 104.7 (C=C–C=O), 137.3 (C=C–C=O), 147.5 (C=N), 164.4 (C=O), 198.7 (C=O). Anal. Calc for $C_{26}H_{19}N_3O_3S$: C, 68.86; H, 4.22; N, 9.27; S, 7.06. Found: C, 68.78; H, 4.26; N, 9.21; S, 7.00%.

2-(1-Methyl-5-oxo-3-phenyl-1H-pyrazol-4(5H)-ylidene)-3-phenyl-1,3-thiazepane-5,6-dione (**7b**): Yellow solid (77%), m.p. 89–91°C (from ethyl acetate). IR: ν_{max} 3061 (=C–H), 1747 (C=O), 1731 (C=O), 1607 (C=O), 1595 (C=N) cm^{-1}. NMR: δ_H 2.05 (s, 2H, CH_2), 3.13 (s, 2H, CH_2), 4.10 (s, 3H, CH_3), 6.89–7.20 (m, 10H, aromatic); δ_C 32.0 (CH_2), 32.1 (CH_2), 38.1 (CH_3), 101.3 (C=C–C=O), 138.6 (C=C–C=O), 148.0 (C=N), 166.3 (C=O), 199.2 (C=O). Anal. Calc

for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.74; S, 8.18. Found: C, 64.60; H, 4.40; N, 10.66; S, 8.10%.

Synthesis of compounds **5a,b** *and* **6a,b**; *general procedure*
Compound **1a** or **1b** (0.01 mol) and KOH (0.01 mol) were dissolved in DMF (30 ml) in a two necked flask. The solution became darker, and phenyl isothiocyanate (0.01 mol) was then added dropwise to the stirred mixture in an ice-bath under nitrogen. The solution was then stirred for 10 hours at room temperature. Chloroacetyl chloride (0.01 mol), or oxalyl chloride (0.01 mol) was added dropwise to the stirred solution through a syringe over a period of 20 min. The resulting solution was stirred for a further 5 h at the same temperature and then poured into crushed ice. The suspension was filtered and the filtrate was dried at room temperature for 24 h. The residue was purified by column chromatography.

4-(5-Oxo-3-phenylthiazolidin-2-ylidene)-1,3-diphenyl-1H-pyrazol-5(4H)-one (**5a**): n-Hexane/ethyl acetate 1:3. Yellow oil (51%). IR: ν_{max} 3067 (=C–H), 1735 (C=O), 1668 (C=O), 1594 (C=N) cm^{-1}. NMR: δ_H 3.96 (s, 2H, CH_2), 7.17–8.01 (m, 15H, aromatic); δ_C 33.2 (CH_2), 101.7 (C=C–C=O), 137.1 (C=C–C=O), 147.6 (C=N), 165.7 (C=O), 197.5 (C=O). Anal. Calc for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21; S, 7.78. Found: C, 70.25; H, 4.10; N, 10.11; S, 7.70%.

1-Methyl-4-(5-oxo-3-phenylthiazolidin-2-ylidene)-3-phenyl-1H-pyrazol-5(4H)-one (**5b**): n-Hexane/ethyl acetate 1:3; yellow solid (63%), m.p. 179–181°C. IR: ν_{max} 3057 (=C–H), 1735 (C=O), 1662 (C=O), 1593 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.41 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.61–7.18 (m, 10H, aromatic); δ_C 33.5 (CH_2), 101.5 (C=C–C=O), 137.2 (C=C–C=O), 148.6 (C=N), 165.9 (C=O), 198.1 (C=O). Anal. Calc for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03; S, 9.17. Found: C, 65.25; H, 4.31; N, 11.80; S, 9.02%.

2-(5-Oxo-1,3-diphenyl-1H-pyrazol-4(5H)-ylidene)-3-phenylthiazolidine-4,5-dione (**6a**): Ethyl acetate; cream-coloured solid (48%), m.p. 183–185°C. IR: ν_{max} 3059 (=C–H), 1678 (C=O), 1641 (C=O), 1622 (C=O), 1594 (C=N) cm^{-1}. NMR δ_H 7.00–7.64 (m, 15H, arom); δ_C 102.5 (C=C–C=O), 138.1 (C=C–C=O), 147.6 (C=N), 160.5 (C=O), 167.1 (C=O), 187.2 (C=O). Anal. Calc for $C_{24}H_{15}N_3O_3S$: C, 67.76; H, 3.53; N, 9.88; S, 7.52. Found: C, 67.65; H, 3.55; N, 9.81; S, 7.60%.

2-(1-Methyl-5-oxo-3-phenyl-1H-pyrazol-4(5H)-ylidene)-3-phenylthiazolidine-4,5-dione (**6b**): Cream-coloured solid (84%), m.p. 167–169°C (from CH_2Cl_2). IR: ν_{max} 3050, 3031 (=C–H), 1677 (C=O), 1637 (C=O), 1607 (C=O), 1592 (C=N) cm^{-1}. NMR δ_H 3.76 (s, 3H, CH_3), 7.07–7.43 (m, 5H, arom), 7.55–7.65 (m, 5H, arom); δ_C 33.3 (CH_3), 99.7 (C=C–C=O), 137.3 (C=C–C=O), 147.5 (C=N), 162.5 (C=O), 165.4 (C=O), 187.2 (C=O). Anal. Calc for $C_{19}H_{13}N_3O_3S$: C, 62.80; H, 3.61; N, 11.56; S, 8.81. Found: C, 63.01; H, 3.56; N, 11.48; S, 8.72%.

Synthesis of compounds **9a,b** *and* **10a,b**; *general procedure*
To a cold suspension of powdered sodium hydride (0.015 mol) in DMF (25 ml) was added **8a** (or **8b**) (0.01 mol) and phenyl isothiocyanate (0.01 mol). The mixture was stirred at room temperature overnight, then treated with phenacyl bromide or chloroacetyl chloride (0.01 mol). The solution was stirred at the same temperature for 6 h. The mixture was then poured into cold H_2O (100 ml) containing HCl (0.1 N, 2 ml). The solid products were filtered off and dried. The residues were purified by column chromatography.

5-(3,4-Diphenylthiazol-2(3H)-ylidene)-2-(phenylimino)-3-propylthiazolidin-4-one (**9a**): n-Hexane/ethyl acetate 2:1; yellow oil (34%). IR: ν_{max} 3058 (=C–H), 1654 (C=O), 1594 (C=N) cm^{-1}. NMR (500/125 MHz): δ_H 0.89–0.92 (t, J = 7.32 Hz, 3H, CH_3), 1.55–159 (m, 2H, CH_2), 3.22–3.26 (t, J = 6.84 Hz, 2H, N–CH_2), 6.90 (s, 1H, =CH), 6.97–7.78 (m, 15H, arom); δ_C 11.2 (CH_3), 20.4 ($CH_3CH_2CH_2$), 42.5 ($CH_3CH_2CH_2$), 112.5 (Ph–C=C–S), 118.9 (C=C–C=O), 133.7 (Ph–C=C–S), 138.2 (C=C–C=O), 149.5 (C=N), 166.1 (C=O). Anal. Calc for $C_{27}H_{23}N_3OS_2$: C, 69.05; H, 4.94; N, 8.95; S, 13.65. Found: C, 68.96; H, 4.96; N, 9.02; S, 13.75%.

5-(3,4-Diphenylthiazol-2(3H)-ylidene)-3-phenyl-2-(propylimino)thiazolidin-4-one (**9b**): n-Hexane/ethyl acetate 2:1; yellow oil (42%). IR: ν_{max} 3060 (=C–H), 1656 (C=O), 1594 (C=N) cm^{-1}. NMR (500/125 MHz): δ_H 0.87–0.91 (t, J = 7.32 Hz, 3H, CH_3), 1.54–157 (m, 2H, CH_2), 3.21–3.26 (t, J = 6.84 Hz, 2H, N–CH_2), 6.92 (s, 1H, =CH), 7.01–7.80 (m, 15H, arom); δ_C 13.0 (CH_3), 24.5 ($CH_3CH_2CH_2$), 55.5 ($CH_3CH_2CH_2$), 111.2 (Ph–C=C–S), 120.1 (C=C–C=O), 127.0 (Ph–C=C–S), 140.4 (C=C–C=O), 151.2 (C=N), 167.2 (C=O). Anal. Calc for $C_{27}H_{23}N_3OS_2$: C, 69.05; H, 4.94; N, 8.95; S, 13.65. Found: C, 68.94; H, 4.94; N, 8.98; S, 13.74%.

5-(5-Oxo-3-phenylthiazolidin-2-ylidene)-2-(phenylimino)-3-propylthiazolidin-4-one (**10a**): n-Hexane/ethyl acetate 3:1; orange solid (23%), m.p. 159–163°C. IR: ν_{max} 3054 (=C–H), 1726 (C=O), 1632 (C=O), 1593 (C=N) cm^{-1}. NMR (500/125 MHz): δ_H 0.89–0.91 (t, J = 7.32 Hz, 3H, CH_3), 1.56–160 (m, 2H, CH_2), 3.24–3.26 (t, J = 6.84 Hz, 2H, N–CH_2), 3.98 (s, 2H, CH_2), 7.28–7.48 (m, 10H, aromatic) ppm; ^{13}C NMR ($CDCl_3$) δ: 11.1 (CH_3), 20.4 ($CH_3CH_2CH_2$), 32.5 (CH_2), 44.5 ($CH_3CH_2CH_2$), 119.0 (C=C–C=O); 141.0 (C=C–C=O), 154.0 (C=N), 174.5 (C=O), 197.2 (C=O). Anal. Calc for $C_{21}H_{19}N_3O_2S_2$: C, 61.59; H, 4.68; N, 10.26; S, 15.65. Found: C, 61.76; H, 4.76; N, 10.03, S, 15.45%.

5-(5-Oxo-3-phenylthiazolidin-2-ylidene)-3-phenyl-2-(propylimino)thiazolidin-4-one (**10b**): n-Hexane/ethyl acetate = 3:1; orange oil (38%). IR: ν_{max} 3049 (=C–H), 1722 (C=O), 1638 (C=O), 1591 (C=N) cm^{-1}. NMR (500/125 MHz): δ_H 0.88–0.92 (t, J = 7.31 Hz, 3H, CH_3), 1.54–158 (m, 2H, CH_2), 3.23–3.26 (t, J = 6.83 Hz, 2H, N–CH_2), 3.98 (s, 2H, CH_2), 7.30–7.55 (m, 10H, aromatic); δ_C 12.9 (CH_3), 24.6 ($CH_3CH_2CH_2$), 33.7 (CH_2), 55.3 ($CH_3CH_2CH_2$), 120.5 (C=C–C=O); 139.2 (C=C–C=O), 152.5 (C=N), 174.5 (C=O), 198.1 (C=O). Anal. Calc for $C_{21}H_{19}N_3O_2S_2$: C, 61.59; H, 4.68; N, 10.26; S, 15.65; Found: C, 61.40; H, 4.60; N, 10.20; S, 15.55%.

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