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*NOTE*

# Novel Synthesis of 3-(Substituted phenyl)-2-[(substituted benzoyl)imino]-1,3-thiazolidine-4-one Derivatives from Substituted Thiourea

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In this work, we proposed the synthesis of several new derivatives of 3-(substituted phenyl)-2-[(substituted benzoyl)imino]-1,3-thiazolidine-4-one by using substituted thiourea and chloroacetic acid. The structure of compounds were confirmed with IR, $^1$H NMR and $^{13}$C NMR spectroscopy.

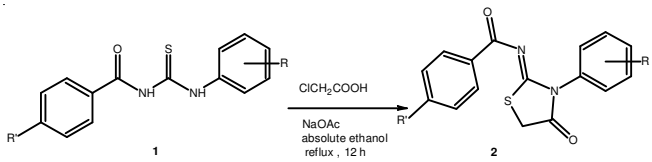
**Key Words: Thiazolidin, Thiazolidin-4-one, Substituted thiourea, Chloroacetic acid.**

Small ring heterocycles containing nitrogen and sulfur have been under investigation for a long time because of their important medicinal properties. Among the wide range of heterocycles explored to develop pharmaceutically important molecules, thiazolidins have played an important role in medicinal chemistry. A survey of literature has shown that compounds having thiazole nucleus possess a broad range of biological activities such as antiinflammatory, antibacterial, antifungal. Among these type of molecules, thiazolidines have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, tituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, antiinflammatory and analgesic properties[1-8]. Recently reported some of work on the synthesis, transformations and wide rang biological properties of various thiazolidines molecules[9-16]. In this study we report the synthesis of some new 3-(substituted phenyl)-2-[(substituted benzoyl)imino]-1,3-thiazolidine-4-one derivatives.

The melting points were taken on an electrothermal capillary melting point apparatus and are uncorrected. Thin-layer chromatographies were performed using HF254 fluorescent silica gel plates (Merck), which were examined under UV 254 and 365 nm light. Silica gel (230-400 mesh) was used for flash chromatography separations. Infrared spectra (ν/cm$^{-1}$) were recorded on Shimadzu IR-470, using KBr disks $^1$H and $^{13}$C NMR spectra were recorded on DRX-500 MHz NMR spectrometer at 293 K in $CDCl_3$. $^1$H and $^{13}$C NMR spectra were recorded on DRX-500 MHz NMR spectrometer at 293 K in $CDCl_3$. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS.

**Preparation of 3-(substituted phenyl)-2-[(substituted benzoyl)imino]-1,3-thiazolidine-4-one derivatives:** A mixture of thiourea (10 mmol), chloroacetic acid (10 mmol) and anhydrous sodium acetate in absolute ethanol was refluxed for 12 h. Excess of solvent was distilled off and the reaction mixture was poured on crushed ice. The solid obtained was filtered, washed with water and recrystallized from ethanol 96 %.

As part of our current studies on the development of new routes in heterocyclic synthesis, we wish to report a convenient strategy for synthesizing 3-(substituted phenyl)-2-[(substituted benzoyl)imino]-1,3-thiazolidine-4-one (**2**) form the reaction of 1-aryl-3-arylcarbonylthioureas (**1**) with chloroacetic acid in good yields[17] (**Scheme-I**).

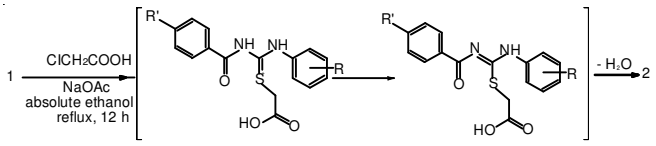



| Entry | R | R' | Yield (%) | m.p. (ºC) |
|---|---|---|---|---|
| **2a** | *o*-Methyl | Cl | 75 | 170-171 |
| **2b** | *p*-Methyl | Cl | 76 | 191-192 |
| **2c** | *p*-Ethyl | Cl | 72 | 219-220 |
| **2d** | *o*-Methyl | Me | 70 | 172-173 |
| **2e** | *p*-Methyl | Me | 75 | 232-233 |
| **2f** | *p*-Ethyl | Me | 73 | 217-218 |

**Scheme-I**

Compounds **2** results form the initial conjugate addition of the sulfur atom to the chloroacetic acid. Then, the acid group

of intermediate is attacked by the amino moiety to yield 2 by elimination of $H_2O$ (**Scheme-II**).




**Scheme-II**

**(2*Z*)-3-(2-Methylphenyl)-2-[(4-chlorobenzoyl)imino]-1,3-thiazolidine-4-one(2a):** Yellow crystals, yield: (75%), m.p. 170-171 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3078 (arom. CH *str.*); 2936 (aliph. C-H *str.*) 1731, 1647 (C=O *str.*); 1593 (C=N *str.*). $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 2.21 (3H, s, $CH_3$); 4.05 (2H, s, $CH_2$); 7.20 (H, d, *J* = 6.4, CH); 7.33 (2H, d, *J* = 4.8, 2CH); 7.38 -7.48 (3H, m, 3CH); 7.88 (2H, d, *J* = 4.8, 2CH). $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 17.6 ($CH_3$); 33.2 ($CH_2$); 127.1 (CH); 128.0 (CH); 128.6 (2CH); 129.9 (CH); 131.1 (CH); 131.4 (2CH); 133.4 (C); 133.9 (C); 135.6 (C); 139.5 (C); 172.0 (C=N); 172.3 (C=O); 176.4 (C=O).

**(2*Z*)-3-(4-Methylphenyl)-2-[4-chlorobenzoyl)imino]-1,3-thiazolidine-4-one(2b):** Yellow crystals, yield: (76 %), m.p. 191-192 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1742, 1640 (C=O *str.*); 1590 (C=N *str.*). $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 2.48 (3H, s, $CH_3$); 4.10 (2H, s, $CH_2$); 7.23 (2H, d, *J* = 4.8, 2CH); 7.35 (2H, d, *J* = 4.8, 2CH); 7.37 (2H, d, *J* = 2.0, 2CH); 7.95 (2H, d, *J* = 4.8, 2CH). $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 21.3 ($CH_3$); 33.2 ($CH_2$); 127.3 (2CH); 128.6 (2CH); 129.9 (2CH); 131.4 (2CH); 131.9 (C); 133.5 (C); 139.4 (C); 139.5 (C); 172.5 (C=N); 172.9 (C=O); 176.4 (C=O).

**(2*Z*)-3-(4-Ethylchlorophenyl)-2-[(4-chlorobenzoyl) imino]-1,3-thiazolidine-4-one (2c):** White crystal, yield: (72 %), m.p. 219-220 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1740, 1650 (C=O *str.*); 1591 (C=N *str.*). $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.33 (3H, t, *J* = 7.6, $CH_3$); 2.79 (2H, q, *J* = 7.6, $CH_2$); 4.02 (2H, s, $CH_2$), 7.26 (2H, d, *J* = 4.8, 2CH); 7.35 (2H, d, *J* = 4.8, 2CH); 7.38 (2H, d, *J* = 4.8, 2CH); 7.96 (2H, d, *J* = 4.8, 2CH). $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 ($CH_3$); 28.6 ($CH_2$); 33.2 ($CH_2$); 127.4 (2CH); 128.6 (2CH); 128.7 (2CH); 131.4 (2CH); 132.1 (C); 133.5 (C); 139.5 (C); 145.5 (C); 172.4 (C=N); 172.9 (C=O); 176.4 (C=O).

**(2*Z*)-3-(2-methylphenyl)-2-[4-methylbenzoyl)imino]-1,3-thiazolidine-4-one (2d):** Yellow crystals, yield: (70 %), m.p. 172-173 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1751, 1640 (C=O *str.*); 1592 (C=N *str.*). $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 2.21 (3H, s, $CH_3$); 2.38 (3H, s, $CH_3$); 4.03 (2H, s, $CH_2$); 7.16 (2H, d, *J* = 8.0, 2CH); 7.21 (H, d, *J* = 7.6, CH); 7.37-7.45 (3H, m, 3CH); 7.85 (2H, d, *J* = 8.0, 2CH). $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 17.6 ($CH_3$); 21.7 ($CH_3$); 33.2 ($CH_2$); 127.0 (CH); 128.1 (CH); 129.0 (2CH); 129.7 (CH); 130.1 (2CH); 131.1 (CH); 132.4 (C); 134.1 (C); 135.7 (C); 144.0 (C); 171.2 (C=N); 172.2 (C=O); 177.3 (C=O).

**(2*Z*)-3-(4-methylphenyl)-2-[4-methylbenzoyl)imino]-1,3-thiazolidine-4-one (2e):** Yellow crystals, yield: (75 %), m.p. 232-223 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1739, 1640 (C=O *str.*); 1593 (C=N *str.*). $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 2.38 (3H, s, $CH_3$); 2.47 (3H, s, $CH_3$); 3.99 (2H, s, $CH_2$); 7.19 (2H, d, *J* = 8.0, 2CH); 7.24 (2H, d, *J* = 4.8, 2CH); 7.37 (2H, d, *J* = 8.0, 2CH); 7.91 (2H, d, *J* = 8.0, 2CH). $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 21.4 ($CH_3$); 21.7 ($CH_3$); 33.2 ($CH_2$); 127.4 (2CH); 129.0 (2CH); 129.9 (2CH); 130.1 (2CH); 132.1 (C); 132.4 (C); 139.2 (C); 144.0 (C); 171.7 (C=N); 172.6 (C=O); 177.3 (C=O).

**(2*Z*)-3-(4-Ethylchlorophenyl)-2-[(4-chlorobenzoyl) imino]-1,3-thiazolidine-4-one (2f):** White crystals, yield: (73 %), m.p. 217-218 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1743, 1635 (C=O *str.*); 1591 (C=N *str.*). $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.33 (3H, t, *J* = 7.6, $CH_3$); 2.39 (3H, s, $CH_3$); 2.78 (2H, q, *J* = 7.6, $CH_2$); 4.02 (2H, s, $CH_2$); 7.19 (2H, d, *J* = 8.0, 2CH); 7.28 (2H, d, *J* = 6.4, 2CH); 7.40 (2H, d, *J* = 4.8, 2CH); 7.92 (2H, d, *J* = 4.8, 2CH). $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 ($CH_3$); 21.7 ($CH_3$); 28.6 ($CH_2$); 33.2 ($CH_2$); 127.4 (2CH); 128.6 (2CH); 129.0 (2CH); 130.1 (2CH); 132.2 (C); 132.4 (C); 143.9 (C); 145.3 (C); 171.6 (C=N); 172.6 (C=O); 177.3 (C=O).

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