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Solvent-free synthesis of functionalized 2,3-dihydrothiazoles from isothiocyanates, primary alkylamines, and 2-chloro-1,3-dicarbonyl compounds

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A simple one-pot synthesis of 3-alkyl-4-methyl-2-phenylimino-2,3-dihydrothiazoles from the reaction of phenylisothiocyanate, primary alkylamines and 2-chloro-1,3-dicarbonyl compounds under solvent-free conditions is described.

Keywords: 2,3-dihydrothiazole; isothiocyanate; primary alkylamine, 1,3-dicarbonyl compound; solvent-free

1. Introduction

Thiazoles and their derivatives exhibit various biological activities such as antiviral, antimicrobial, anti-inflammatory, and antituberculosis (*1–3*). The thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto-acids (*4*). Some thiazolines show interesting anti-HIV or anticancer activities and can inhibit cell division (*5*). In view of the importance of thiazoles, several methods for their synthesis have been developed. The most widely used method is the Hantzsch synthesis (*6–8*) involving the reaction of α-halocarbonyl compounds with thioureas or thioamides. Recently, a synthesis of thiazol-2-imine derivative from benzoylphenylthioureas and the *in situ* generated α-bromoketones obtained by the reaction of enolizable ketones with 1,10-(ethane-1,2-diyl)dipyridinium bistribromide has been reported (*9, 10*).

As part of our current studies on the synthesis of sulfur-containing organic compounds (*11–14*), we describe an efficient method for the synthesis of functionalized 2,3-dihydrothiazoles under solvent-free conditions. This new catalyst-free and one-pot synthetic method seems facile; work-up procedure is easy and gives pure target compounds containing several potential centers for further modification.

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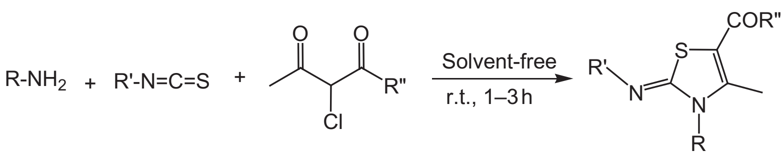
2. Results and discussion

The reaction of primary alkylamines **1** with isothiocyanates **2** in the presence of α-chlorocarbonyl compounds **3** proceeds smoothly at room temperature to produce 3-alkyl-4-methyl-2-arylimino-2,3-dihydrothiazoles **4a**–**4t** in good yields after purification (Scheme 1). In this procedure, we have modified the Hantzsch method for thiazole synthesis *via* the reaction of unsymmetrical thioureas (**5**, see Scheme 2) with α-chlorocarbonyl compounds. Thus, various thiourea derivatives were prepared from **1** and **2**. Functionalized 2,3-dihydrothiazoles **4** were obtained from the reaction of these thioureas with **3**. The structures of compounds **4a**–**4k** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed nine signals for methyl ($\delta = 1.28$ and 2.54 ppm), methoxy ($\delta = 3.82$ ppm), and methylene ($\delta = 4.22$ and 5.21 ppm) protons along with signals ($\delta = 6.89$–7.37 ppm) for the aromatic protons. The imino and carbonyl resonances in the ^{13}C NMR spectrum of **4a** appear at 159.5 and 162.4 ppm, respectively. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 382$. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**4k** were similar to those of **4a** except for the side chains, which exhibited characteristic resonances in the appropriate regions of the spectrum.

Mechanistically, the reaction starts with the formation of unsymmetrical thiourea derivative **5** from primary alkylamines and phenyl isothiocyanates. Subsequent nucleophilic alkylation of **5** with α-chloroketones **3** yields intermediate **6**. This intermediate undergoes HCl elimination and

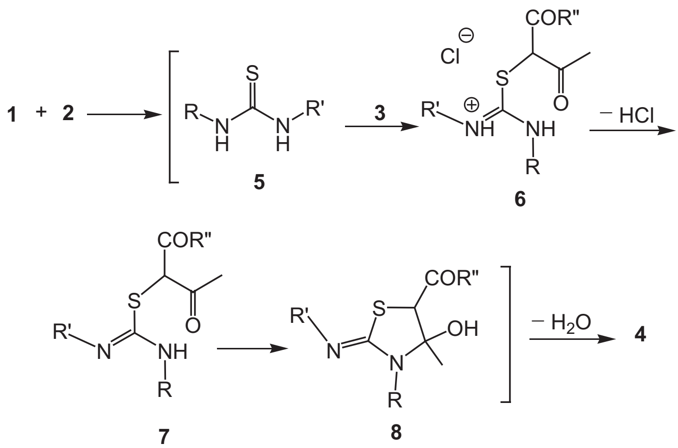


1 **2** **3** **4**

1, 2, 3, 4	R	R'	R"	Yield (%) of **4**
a	4-MeOC$_6$H$_4$CH$_2$	Ph	OEt	81
b	4-ClC$_6$H$_4$CH$_2$	Ph	OEt	90
c	2-ClC$_6$H$_4$CH$_2$	Ph	OEt	83
d	4-MeC$_6$H$_4$CH$_2$	Ph	OEt	93
e	Bn	Ph	OEt	87
f	^{n}Bu	Ph	OEt	91
g	^{n}Pr	Ph	OEt	85
h	Et	Ph	OEt	83
i	Bn	Ph	Me	75
j	^{n}Bu	Ph	Me	92
k	cyclohexyl	Ph	Me	99
l	Bn	PhCO	Me	85
m	Et	PhCO	OMe	90
n	^{n}Bu	PhCO	OMe	95
o	cyclohexyl	PhCO	OMe	90
p	Bn	PhCO	OMe	87
q	PhCH(CH$_3$)NH$_2$	PhCO	OMe	85
r	2-furfuryl	PhCO	OMe	90
s	^{n}Bu	2-FC$_6$H$_4$CO	OMe	86
t	Bn	2-FC$_6$H$_4$CO	OMe	80

Scheme 1. The three-component one-pot synthesis of 2,3-dihydrothiazoles **4**.

subsequent intramolecular cyclization reaction to form the heterocyclic intermediate **8**, which generates **4** by elimination of water (Scheme 2).



Scheme 2. Plausible mechanism for the formation of 2,3-dihydrothiazoles **4**.

3. Conclusions

We have described a convenient route to functionalized 3-alkyl-4-methyl-2-phenylimino-2,3-dihydrothiazoles from primary alkylamines and phenylisothiocyanate in the presence of α-chloroketones. The advantage of the present procedure is that the reaction is performed under solvent-free conditions by simply mixing the starting materials. The procedure described here also provides an efficient one-pot methodology for the preparation of functionalized 2,3-dihydrothiazoles.

4. Experimental

4.1. *General*

Primary alkylamines **1**, isothiocyanates **2**, and α-halocarbonyl compounds **3** were obtained from Fluka and were used without further purification; IR spectra: Shimadzu IR-460 spectrometer; ^{1}H- and ^{13}C-NMR spectra: Bruker DRX-300AVANC instrument in $CDCl_3$ at 300 and 75 MHz, respectively, δ in ppm, and J in Hz; EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer in m/z. Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer.

4.2. *General procedure for the preparation of compounds 4*

A mixture of 0.27 g of **2** (2 mmol) and the primary alkylamine **1** (2 mmol) was stirred at r.t. for 20 min. Then, α-halocarbonyl **3** (2 mmol) was added to the reaction mixture and stirred at r.t. After completion of the reaction [1–3 h; TLC (AcOEt/hexane 2:1)], the reaction mixture was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/AcOEt 4:1)].

4.2.1. *Ethyl 3-(4-methoxybenzyl)-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4a**)*

Dark yellow oil, yield: 0.61 g (81%). IR (KBr): 1690 (C=O), (C=N)cm^{-1}. ^{1}H NMR: 1.28 (3H, t, ^{3}J = 7.1 Hz, Me), 2.54 (3H, s, Me), 3.82 (3H, s, MeO), 4.22 (2H, q, ^{3}J = 7.1 Hz, CH_2O), 5.21 (2H, s, CH_2), 6.89 (2H, d, ^{3}J = 8.0 Hz, 2CH), 7.08 (2H, d, ^{3}J = 8.0 Hz, 2CH), 7.09 (1H, d, ^{3}J = 8.0 Hz, CH), 7.27 (2H, d, ^{3}J = 8.0 Hz, 2CH), 7.37 (2H, t, ^{3}J = 8.0 Hz, 2CH). ^{13}C NMR: 13.7 (Me), 14.7 (Me), 47.2 (CH_2), 55.7 (MeO), 61.1 (CH_2O), 100.1 (C), 114.6 (2CH), 121.7 (CH), 123.9 (2CH), 128.6 (2CH), 129.9 (2CH), 147.4 (C), 150.9 (C), 156.1 (C), 158.1 (C), 159.5 (C=N), 162.4 (C=O). EI-MS: m/z (%) = 382 (M^+, 56), 290 (8), 233 (8), 197 (49), 121 (100), 103 (7), 91 (11), 77 (22). Anal. Calcd for $C_{21}H_{22}N_2O_3S$ (382.47): C, 65.95%; H, 5.80%; N, 7.32%; found: C, 65.73%; H, 5.93%; N, 7.42%.

4.2.2. *Ethyl 3-(4-chlorobenzyl)-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4b**)*

Dark yellow oil, yield: 0.69 g (90%). IR (KBr): 1694 (C=O), 1610 (C=N)cm^{-1}. ^{1}H NMR: 1.29 (3H, t, ^{3}J = 7.1 Hz, Me), 2.51 (3H, s, Me), 4.22 (2H, q, ^{3}J = 7.1 Hz, CH_2O), 5.23 (2H, s, CH_2), 7.04–7.12 (3H, m, 3CH), 7.21–7.32 (4H, m, 4CH), 7.38–7.46 (2H, m, 2CH). ^{13}C NMR: 13.6 (Me), 14.7 (Me), 49.1 (CH_2), 61.2 (CH_2O), 99.8 (C), 121.6 (CH), 124.1 (2CH), 125.8 (2CH), 128.1 (2CH), 128.5 (2CH), 129.1 (C), 129.4 (C), 129.9 (C), 130.8 (C), 156.1 (C=N), 165.6 (C=O). EI-MS: m/z (%) = 388 (M^++2, 14), 386 (M^+, 43), 203 (12), 201 (38), 127 (33), 125 (100), 77 (22). Anal. Calcd for $C_{20}H_{19}ClN_2O_2S$ (386.89): C, 62.09%; H, 4.95%; N, 7.24%; found: C, 62.43%; H, 5.13%; N, 7.32%.

4.2.3. *Ethyl 3-(2-chlorobenzyl)-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4c**)*

Dark yellow oil, yield: 0.64 g (83%). IR (KBr): 1701 (C=O), 1614 (C=N) cm^{-1}. ^{1}H NMR: 1.31 (3H, t, ^{3}J = 7.0 Hz, Me), 2.47 (3H, s, Me), 4.24 (2H, q, ^{3}J = 7.0 Hz, CH_2O), 5.36 (2H, s, CH_2), 7.03–7.11 (5H, m, 5CH), 7.32–7.42 (4H, m, 4CH). ^{13}C NMR: 13.3 (Me), 14.9 (Me), 45.7 (CH_2), 61.2 (CH_2O), 100.6 (C), 121.6 (CH), 124.1 (2CH), 127.2 (CH), 127.7 (CH), 128.6 (2CH), 129.9 (CH), 130.1 (CH), 132.8 (C), 133.7 (C), 146.9 (C), 150.7 (C), 157.6 (C=N), 162.4 (C=O). EI-MS: m/z (%) = 388 (M^++2, 16), 386 (M^+, 48), 203 (11), 201 (33), 127 (33), 125 (100), 77 (22). Anal. Calcd for $C_{20}H_{19}ClN_2O_2S$ (386.90): C, 62.09%; H, 4.95%; N, 7.24%; found: C, 62.33%; H, 5.08%; N, 7.30%.

4.2.4. *Ethyl 4-methyl-3-(4-methylbenzyl)-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4d**)*

Dark yellow oil, yield: 0.68 g (93%). IR (KBr): 1701 (C=O), 1613 (C=N) cm^{-1}. ^{1}H NMR: 1.29 (3H, t, ^{3}J = 7.1 Hz, Me), 2.36 (3H, s, Me), 2.52 (3H, s, Me), 4.22 (2H, q, ^{3}J = 7.1 Hz, CH_2O), 5.24 (2H, s, CH_2), 7.07–7.12 (3H, m, 3CH), 7.16–7.19 (4H, m, 4CH), 7.34–7.39 (2H, m, 2CH).^{13}C NMR: 13.6 (Me), 14.7 (Me), 21.5 (Me), 47.5 (CH_2), 61.1 (CH_2O), 100.1 (C), 121.7 (CH), 123.9 (2CH), 127.1 (4CH), 129.9 (2CH), 133.6 (C), 137.7 (C), 147.5 (C), 150.9 (C), 158.1 (C=N), 162.5 (C=O). EI-MS: m/z (%) = 366 (M^+, 55), 274 (12), 233 (10), 181 (95), 105 (100), 102 (20), 77 (16). Anal. Calcd for $C_{21}H_{22}N_2O_2S$ (366.48): C, 68.82%; H, 6.05%; N, 7.64%; found: C, 68.49%; H, 6.13%; N, 7.72%.

4.2.5. *Ethyl 3-benzyl-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4e**)*

Dark yellow oil, yield: 0.61 g (87%); IR (KBr): 1702 (C=O), 1613 (C=N) cm^{-1}; ^{1}H NMR: 1.29 (3H, t, $^{3}J = 7.0$ Hz, Me), 2.52 (3H, s, Me), 4.22 (2H, q, $^{3}J = 7.0$ Hz, CH_2O), 5.28 (2H, s, CH_2), 7.06–7.09 (5H, m, 5CH), 7.32–7.39 (5H, m, 5CH). ^{13}C NMR: 13.6 (Me), 14.7 (Me), 47.7 (CH_2), 61.1 (CH_2O), 100.2 (C), 121.7 (CH), 124.1 (2CH), 127.2 (CH), 128.1 (2CH), 129.3 (2CH), 129.9 (2CH), 136.6 (C), 147.3 (C), 150.9 (C), 158.1 (C=N), 162.4 (C=O). EI-MS: m/z (%) = 352 (M^+, 31), 167 (76), 91 (100), 77 (16). Anal. Calcd for $C_{20}H_{20}N_2O_2S$ (352.45): C, 68.16%; H, 5.72%; N, 7.95%; found: C, 68.01%; H, 5.65%; N, 7.92%.

4.2.6. *Ethyl 3-butyl-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4f**)*

Dark yellow oil, yield: 0.65 g (87%). IR (KBr): 1699 (C=O), 1612 (C=N) cm^{-1}. ^{1}H NMR: 1.01 (3H, t, $^{3}J = 6.8$ Hz, Me), 1.28 (3H, t, $^{3}J = 7.1$ Hz, Me), 1.44 (2H, m, $^{3}J = 6.8$ Hz, CH_2), 1.76 (2H, m, $^{3}J = 6.8$ Hz, CH_2), 2.61 (3H, s, Me), 3.96 (2H, t, $^{3}J = 6.8$ Hz, CH_2), 4.21 (2H, q, $^{3}J = 7.1$ Hz, CH_2O), 7.04–7.11 (3H, m, 3CH), 7.34–7.38 (2H, m, 2CH). ^{13}C NMR: 13.4 (Me), 14.2 (Me), 14.8 (Me), 20.5 (CH_2), 30.7 (CH_2), 44.7 (CH_2), 60.9 (CH_2O), 99.9 (C), 121.7 (CH), 123.9 (2CH), 129.9 (2CH), 136.6 (C), 147.2 (C), 151.4 (C=N), 162.6 (C=O). EI-MS: m/z (%) = 318 (M^+, 100), 303 (10), 262 (39), 226 (19), 189 (15), 91 (10), 41 (17). Anal. Calcd for $C_{17}H_{22}N_2O_2S$ (318.43): C, 64.12%; H, 6.96%; N, 8.80%; found: C, 64.55%; H, 6.91%; N, 8.92%.

4.2.7. *Ethyl 4-methyl-2-(phenylimino)-3-propyl-2,3-dihydrothiazole-5-carboxylate (**4g**)*

Dark yellow oil, yield: 0.51 g (85%). IR (KBr): 1718 (C=O), 1620 (C=N) cm^{-1}. ^{1}H NMR: 0.93 (3H, t, $^{3}J = 7.0$ Hz, Me), 1.36 (3H, t, $^{3}J = 7.1$ Hz, Me), 1.68 (2H, m, $^{3}J = 7.0$ Hz, CH_2), 2.54 (3H, s, Me), 3.46 (2H, t, $^{3}J = 7.0$ Hz, CH_2), 4.22 (2H, q, $^{3}J = 7.1$ Hz, CH_2O), 6.83–6.88 (3H, m, 3CH), 7.36–7.42 (2H, m, 2CH). ^{13}C NMR: 11.8 (Me), 12.5 (Me), 14.6 (Me), 22.2 (CH_2), 52.5 (CH_2), 61.8 (CH_2O), 100.3 (C), 121.2 (CH), 128.9 (2CH), 130.1 (2CH), 136.4 (C), 146.9 (C), 152.8 (C=N), 163.1 (C=O). EI-MS: m/z (%) = 304 (M^+, 100), 119 (55), 185 (34), 77 (16). Anal. Calcd for $C_{16}H_{20}N_2O_2S$ (304.41): C, 63.13%; H, 6.62%; N, 9.20%; found: C, 63.44%; H, 6.81%; N, 9.37%.

4.2.8. *Ethyl 3-ethyl-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-carboxylate (**4h**)*

Dark yellow oil, yield: 0.48 g (83%). IR (KBr): 1699 (C=O), 1612 (C=N) cm^{-1}. ^{1}H NMR: 1.28 (3H, t, $^{3}J = 7.1$ Hz, Me), 1.37 (3H, t, $^{3}J = 7.1$ Hz, Me), 2.62 (3H, s, Me), 4.04 (2H, q, $^{3}J = 7.1$ Hz, CH_2), 4.21 (2H, q, $^{3}J = 7.1$ Hz, CH_2O), 7.05–7.11 (3H, m, 3CH), 7.34–7.39 (2H, m, 2CH). ^{13}C NMR 13.2 (Me), 13.8 (Me), 14.8 (Me), 39.9 (CH_2), 61.1 (CH_2O), 99.8 (C), 121.7 (CH), 123.9 (2CH), 129.9 (2CH), 146.8 (C), 151.3 (C), 157.5 (C=N), 162.5 (C=O). EI-MS: m/z (%) = 290 (M^+, 100), 262 (12), 186 (34), 114 (17), 105 (55), 77 (14), 70 (18), 42 (31). Anal. Calcd for $C_{15}H_{18}N_2O_2S$ (290.38): C, 62.04%; H, 6.25%; N, 9.65%; found: C, 62.07%; H, 6.16%; N, 9.79%.

4.2.9. *1-(3-Benzyl-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-yl)ethanone (**4i**)*

Dark yellow oil, yield: 0.48 g (75%), IR (KBr): 1775 (C=O), 1633 (C=N) cm^{-1}. ^{1}H NMR: 2.29 (3H, s, Me), 2.54 (3H, s, Me), 5.31 (2H, s, CH_2), 7.07–7.11 (5H, m, 5CH), 7.28–7.41 (5H, m, 5CH). ^{13}C NMR: 14.3 (Me), 30.5 (Me), 47.9 (CH_2), 110.8 (C), 121.7 (2CH), 124.4 (CH), 127.0 (2CH), 128.1 (CH), 129.3 (2CH), 129.9 (2CH), 136.1 (C), 146.5 (C), 150.8 (C), 158.3 (C=N), 189.6 (C=O). EI-MS: m/z (%) = 322 (M^+, 55), 168 (69), 91 (100), 77 (26). Anal. Calcd for $C_{19}H_{18}N_2OS$ (322.42): C, 70.78%; H, 5.63%; N, 8.69%; found: C, 70.93%; H, 5.83%; N, 8.82%.

4.2.10. *1-(3-Butyl-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-yl)ethanone (**4j**)*

Dark yellow oil, yield: 0.52 g (92%). IR (KBr): 1771 (C=O), 1622 (C=N) cm^{-1}. ^1H NMR: 1.01 (3H, t, $^3J = 7.0$ Hz, Me), 1.44–1.48 (2H, m, CH_2), 1.76–1.79 (2H, m, CH_2), 2.26 (3H, s, Me) 2.63 (3H, s, Me), 3.99 (2H, t, $^3J = 7.0$ Hz, CH_2N), 7.07 (2H, d, $^3J = 7.3$ Hz, 2CH), 7.10 (1H, t, $^3J = 7.3$ Hz, CH), 7.36–7.39 (2H, m, 2CH). ^{13}C NMR: 14.1 (Me), 14.2 (CH_2), 20.4 (Me), 30.5 (CH_2), 30.6 (Me), 44.8(CH_2), 109.9(C), 121.7 (2CH), 122.1 (C), 124.2 (C), 129.6 (CH), 129.9 (2CH), 146.5 (C=N), 189.6 (C=O). EI-MS: m/z (%) = 288 (M^+, 100), 133 (53), 135 (29), 77 (17). Anal. Calcd for $C_{16}H_{20}N_2OS$ (288.41): C, 66.63%; H, 6.99%; N, 9.71%; found: C, 66.97%; H, 6.72%; N, 9.82%.

4.2.11. *1-(3-Cycloexyl-4-methyl-2-(phenylimino)-2,3-dihydrothiazole-5-yl)ethanone (**4k**)*

Dark yellow oil, yield: 0.55 g (89%). IR (KBr): 1769 (C=O), 1629 (C=N) cm^{-1}. ^1H NMR: 1.21–2.20 (10H, m, $5CH_2$), 2.23 (3H, s, Me), 2.65 (3H, s, Me), 4.21 (1H, m, CH), 7.01 (2H, d, $^3J = 7.4$ Hz, 2CH), 7.10 (1H, t, $^3J = 7.4$ Hz, CH), 7.35–7.39 (2H, m, 2CH). ^{13}C NMR: 14.9 (Me), 25.5 (CH_2), 26.7 ($2CH_2$), 29.2 (Me), 30.8 ($2CH_2$), 58.6 (CH), 109.5(C), 121.5 (2CH), 124.0 (C), 130.0 (CH), 130.1 (2CH), 147.2 (C), 151.5 (C=N), 189.8 (C=O). EI-MS: m/z (%) = 314 (M^+, 100), 159 (53), 155 (33), 77 (36). Anal. Calcd for $C_{18}H_{22}N_2OS$ (314.45): C, 68.75%; H, 7.05%; N, 8.91%; found: C, 68.43%; H, 7.33%; N, 9.12%.

4.2.12. *N-(5-Acetyl-3-benzyl-4-methylthiazole-2(3H)-yliden)benzamide (**4l**)*

White powder, yield: 0.30 g (85%), mp: 132–134°C. IR (KBr): 1685 (C=O), 1617 (C=N) cm^{-1}. ^1H NMR: 2.52 (3H, s, Me), 2.68 (3H, s, Me), 5.68 (1H, s, CH_2), 7.29–7.39 (5H, m, 5CH), 7.42–7.53 (3H, m, 3CH), 8.30–8.33 (2H, m, 2CH). ^{13}C NMR: 13.3 (Me), 27.4 (Me), 49.9 (CH_2N), 128.5 (2CH), 128.6 (2CH), 129.5 (2CH), 129.8 (2CH), 130.4 (CH), 131.6 (C), 132.7 (CH), 136.5 (C), 137.4 (C), 141.8 (C), 162.8 (C=N), 175.5 (C=O), 189.3 (C=O). EI-MS: m/z (%) = 350 (M^+, 46), 269 (16), 239 (23), 207 (34), 105 (100), 91 (13), 77 (20). Anal. Calcd for $C_{20}H_{18}N_2O_2S$ (350.11): C, 68.55%, H, 5.18%, N, 7.99%; found: C, 68.83%, H, 5.30%, N, 8.08%.

4.2.13. *Methyl 2-(benzoylimino)-3-ethyl-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4m**)*

White powder, yield: 0.27 g (90%), mp: 138–140°C. IR (KBr): 1689 (C=O), 1597 (C=N) cm^{-1}. ^1H NMR: $\delta = 1.46$ (3H, t, $^3J_{HH} = 7.1$ Hz, Me), 2.76 (3H, s, Me), 3.88 (3H, s, MeO), 4.40 (2H, q, $^3J_{HH} = 7.1$ Hz, CH_2N), 7.43–7.55 (3H, m, 3CH), 8.35–8.35 (m, 2CH). ^{13}C NMR: $\delta = 12.8$ (Me), 14.0 (Me), 42.0 (CH_2N), 52.4 (MeO), 108.2 (C), 128.4 (2CH), 129.7 (2CH), 132.1 (CH), 137.0 (C), 144.1 (C), 162.9 (C=N), 168.0 (C=O), 175.6 (C=O). EI-MS: m/z (%) = 304 (M^+, 9), 275 (35), 245 (26), 193 (17), 105 (100), 77 (45), 42 (8). Anal. Calcd for $C_{15}H_{16}N_2O_3S$ (304.09): C, 59.19%, H, 5.30%, N, 9.20%; found: C, 59.28%, H, 5.24%, N, 9.24%.

4.2.14. *Methyl 2-(benzoylimino)-3-butyl-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4n**)*

White powder, yield: 0.31 g (95%), mp: 141–143°C. IR (KBr): 1710 (C=O), 1601 (C=N) cm^{-1}. ^1H NMR: $\delta = 1.04$ (3H, t, $^3J_{HH} = 7.3$ Hz, Me), 1.51(2H, sextet, $^3J_{HH} = 7.5$ Hz, CH_2), 1.86 (3H, qui,$^3J_{HH}$ = 7.5 Hz, CH_2), 2.76 (3H, s, Me), 3.88 (3H, s, MeO), 4.34 (2H, q, $^3J_{HH}$ = 7.8 Hz, CH_2O), 7.44–7.55 (3H, m, 3CH), 8.32–8.35 (2H, m, 2CH). ^{13}C NMR: 13.0 (Me), 14.1 (Me), 20.5 (CH_2), 30.9 (CH_2), 46.7 (CH_2N), 52.4 (MeO), 110.2 (C), 128.5 (2CH), 129.7 (2CH), 132.1 (CH), 137.0 (C), 144.4 (C), 163.0 (C=N), 168.0 (C=O), 175.1 (C=O). EI-MS: m/z (%) = 332 (M^+, 5), 264 (42), 222 (27), 164 (18), 105 (100), 77 (42), 72 (9), 59 (15). Anal. Calcd for $C_{17}H_{20}N_2O_3S$ (332.42): C, 61.42%, H, 6.06%, N, 8.43%; found: C, 61.35%, H, 6.12%, N, 8.38%.

4.2.15. *Methyl 2-(benzoylimino)-3-cyclohexyl-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4o**)*

White powder, yield: 0.32 g (90%), mp: 154–156°C. IR (KBr): 1718 (C=O), 1620 (C=N) cm^{-1}. ^1H NMR: δ = 1.43–1.61 (4H, m, $2CH_2$), 1.80–1.99 (4H, m, $2CH_2$), 2.77 (3H, s, Me), 3.87 (3H, s, MeO), 4.45 (2H, m, CH_2N), 7.49–7.57 (3H, m, 3CH), 8.29–8.32 (2H, m, 2CH). ^{13}C NMR: 12.8 (Me), 24.1 ($2CH_2$), 25.8 (CH_2), 26.3 ($2CH_2$), 51.8 (MeO), 60.6 (CH_2N), 109.2 (C), 128.6 (2CH), 129.3 (2CH), 132.0 (CH), 137.4 (C), 145.7 (C), 162.5 (C=N), 167.5 (C=O), 175.7 (C=O). EI-MS: m/z (%) = 358 (M^+, 11), 276 (55), 248 (22), 199 (8), 105 (100), 77 (37), 59 (8). Anal. Calcd for $C_{19}H_{22}N_2O_3S$ (358.14): C, 63.66%, H, 6.19%, N, 7.82%; found: C, 63.42%, H, 6.15%, N, 7.93%.

4.2.16. *Methyl 2-(benzoylimino)-3-benzyl-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4p**)*

White powder, yield: 0.32 g (87%), mp: 148–150°C. IR (KBr): 1712 (C=O), 1618 (C=N) cm^{-1}. ^1H NMR: 2.66 (3H, s, Me), 3.88 (3H, s, MeO), 5.66 (2H, s, CH_2), 7.30–7.41 (1H, m, 5CH), 7.43–7.51 (3H, m, 3CH), 8.30–8.32 (2H, m, 2CH). ^{13}C NMR: 13.3 (Me), 49.9 (CH_2N), 52.5 (MeO), 100.3 (C), 127.3 (CH), 128.5 (2CH), 128.6 (CH), 129.5 (2CH), 129.8 (2CH), 132.2 (CH), 135.6 (C), 136.7 (C), 144.8 (C), 162.8 (C=N), 168.9 (C=O), 175.3 (C=O). EI-MS: m/z (%) = 358 (M^+, 18), 267 (34), 298 (25), 255 (10), 105 (100), 77 (46), 59 (13). Anal. Calcd for $C_{20}H_{18}N_2O_3S$ (366.43): C, 65.55%, H, 4.95%, N, 7.64%; found: C, 65.33%, H, 5.04%, N, 7.75%.

4.2.17. *Methyl 2-(benzoylimino)-4-methyl-3-(1-phenylethyl)-1,3-thiazole-5-carboxylate (**4q**)*

White powder, yield: 0.32 g (85%), mp: 183–185°C. IR (KBr): 1698 (C=O), 1614 (C=N) cm^{-1}. ^1H NMR: 2.14 (3H, d, ^3J = 7.2 Hz, Me), 2.61 (1H, q, ^3J = 7.2 Hz, CH_2), 2.83 (3H, s, Me), 3.88 (3H, s, MeO), 5.66 (2H, s, CH_2), 7.31–7.42 (5H, m, 5CH), 7.44–7.53 (3H, m, 3CH), 8.15–8.18 (2H, m, 2CH). ^{13}C NMR: 13.9 (Me), 16.6 (Me), 51.9 (MeO), 56.2 (CH_2N), 109.8 (C), 126.5 (2CH), 127.8 (CH), 128.4 (CH), 129.1 (2CH), 129.5 (2CH), 132.1 (CH), 137.1 (C), 140.1 (C), 145.7 (C), 162.4 (C=N), 168.1 (C=O), 174.2 (C=O). EI-MS: m/z (%) = 380 (M^+, 19), 321 (8), 275 (35), 269 (22), 105 (100), 77 (29), 59 (17). Anal. Calcd for $C_{21}H_{20}N_2O_3S$ (380.12): C, 66.29%, H, 5.30%, N, 7.36%; found: C, 66.48%, H, 5.21%, N, 7.47%.

4.2.18. *Methyl2-(benzoylimino)-3-(furan-2-ylmethyl)-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4r**)*

White powder, yield: 0.32 g (90%), mp: 149–151°C. IR (KBr): 1699 (C=O), 1608 (C=N) cm^{-1}. ^1H NMR: 2.89 (3H, s, Me), 3.88 (3H, s, MeO), 5.56 (2H, s, CH_2), 6.34–6.36 (1H, m, CH), 6.50–6.51 (1H, m, CH), 7.37–7.38 (1H, m, CH), 7.46–7.55 (3H, m, 3CH), 8.36–8.38 (2H, m, 2CH). ^{13}C NMR: 13.2 (Me), 42.7 (CH_2N), 52.5 (MeO), 109.0 (C), 110.3 (CH), 111.2 (CH), 128.5 (2CH), 129.8 (2CH), 132.3 (CH), 136.8 (C), 143.1 (CH), 144.5 (C), 148.6 (C), 162.9 (C=N), 168.5 (C=O), 175.0 (C=O). EI-MS: m/z (%) = 356 (M^+, 10), 297 (23), 274 (17), 246 (28), 105 (100), 77 (17), 59 (10). Anal. Calcd for $C_{18}H_{16}N_2O_4S$ (356. 40): C, 60.66%, H, 4.53%, N, 7.86%; found: C, 60.35%, H, 4.59%, N, 7.98%.

4.2.19. *Methyl 3-butyl-2-(2-fluorobenzoylimino)-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4s**)*

White crystal, yield: 0.28 g (86%), mp: 157–159°C. IR (KBr): 1709 (C=O), 1620 (C=N) cm^{-1}. ^{1}H NMR: $\delta = 1.01$ (3H, t, $^3J_{HH} = 7.3$ Hz, Me), 1.47 (2H, sextet, $^3J_{HH} = 7.4$ Hz, CH_2), 1.81 (2H, qui, $^3J_{HH} = 7.5$ Hz, CH_2), 2.74 (3H, s, Me), 3.87 (3H, s, MeO), 4.30 (2H, q, $^3J_{HH} = 7.6$ Hz, CH_2O), 7.10–7.23 (2H, m, 2CH), 7.46–7.49 (1H, m, 1CH), 8.15–8.20 (1H, m, CH). ^{13}C NMR: 13.0 (Me), 14.1 (Me), 20.5 (CH_2), 30.9 (CH_2), 46.7 (CH_2N), 52.4 (MeO), 110.3 (C), 117.2 (d, $^2J_{CF} = 22.7$, CH), 124.0 (d, $^4J_{CF} = 3.8$, CH), 125.5 (d, $^3J_{CF} = 8.4$, C), 132.5 (d, $^2J_{CF} = 20.7$, CH) , 133.3 (d, $^3J_{CF} = 8.8$, CH), 144.5 (C), 162.6 (d, $^1J_{CF} = 257.0$, C–F), 162.9 (C=N), 164.3 (C=N), 167.8 (C=O), 173.0 (d, $^3J_{CF} = 4.3$, C=O). EI-MS: m/z (%) = 350 (M^+, 15), 292 (25), 222 (21), 123 (100), 105 (46), 77 (17), 72 (8), 59 (12). Anal. Calcd for $C_{17}H_{19}FN_2O_3S$ (350. 41): C, 58.27%, H, 5.47%, N, 7.99%; found: C, 58.16%, H, 5.59%, N, 8.18%.

4.2.20. *Methyl 3-benzyl-2-(2-fluorobenzoylimino)-4-methyl-2,3-dihydrothiazole-5-carboxylate (**4t**)*

White powder, yield: 0.31 g (80%), mp: 140–142°C. IR (KBr): 1701 (C=O), 1613 (C=N) cm^{-1}. ^{1}H NMR: 2.70 (3H, s, Me), 3.88 (3H, s, MeO), 5.77 (2H, s, CH_2), 7.15–7.27 (2H, m, 2CH), 7.30–7.42 (5H, m, 5CH), 7.52–7.55 (1H, m, CH), 8.11–8.16 (1H, m, CH). ^{13}C NMR: 12.5 (Me), 49.6 (CH_2N), 52.0 (MeO), 109.6 (C), 117.3 (d, $^2J_{CF} = 21.7$, CH), 123.5 (d, $^2J_{CF} = 20.1$, C), 124.1 (d, $^4J_{CF} = 3.9$, CH), 127.2 (2CH), 128.2 (CH), 129.5 (2CH), 130.4 (C), 133.5 (d, $^3J_{CF} = 12.0$, CH), 135.2 (d, $^3J_{CF} = 10.8$, CH), 145.6 (C), 162.3 (C=N), 164.9 (d, $^1J_{CF} = 264.0$, C–F), 172.5 (C=O), 176.9 (d, $^3J_{CF} = 4.5$, C=O). EI-MS: m/z (%) = 384 (M^+, 21), 293 (34), 255 (18), 225 (10), 123 (100), 105 (72), 77 (37), 59 (8). Anal. Calcd for $C_{20}H_{17}FN_2O_3S$ (384.09): C, 62.49%, H, 4.46%, N, 7.29%; found: C, 62.75%, H, 4.49%, N, 7.38%.

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