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A facile and one-pot synthesis of Dihydrothiazole-4-carboxylates under mild, solvent- and catalyst-free conditions

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Abstract: Ethyl 2-(alkylimino)-3-phenyl-2,3-dihydrothiazole-4-carboxylates and Diethyl 3,3'-(1,4-phenylene)-bis-[2-(alkylimino)-2,3-dihydrothiazole-4-carboxylates] derivatives were produced from the three-component reaction between primary alkylamines and phenyl isothio cyanate (and also 1,4-phenylene diisothiocyanate) in the presence of ethyl bromopyruvate. The reactions were performed under mild, solvent- and catalyst free conditions at room temperature and led to the desired products in good to high yields.

Keywords: Solvent-free conditions, Catalyst-free conditions, Three-component reaction, One-pot synthesis, Neutral reaction conditions.

Introduction

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences which provide a maximum of structural complexity and diversity with just a minimum number of synthetic steps to assemble compounds with interesting properties [1]. According to Corey molecular size, element and functional group content, cyclic connectivity, stereocenter content, chemical reactivity, and structural instability all contribute to molecular complexity [2].

In this area, multicomponent reactions (MCRs) have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economical and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, as well as the very large number of accessible compounds are among the described advantages of MCRs [3]. Thus, they are amenable to automation for combinatorial synthesis [4]. In the field of the development of the drugs, Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities [5,6]. They recently have found application in drug development for the treatment of allergies [7], hypertension [8], inflammation [9], schizophrenia [10], bacterial [11], HIV infections [12], hypnotics [13] and more recently for the treatment of pain [14], as fibrinogen receptor antagonists with anti thrombotic activity [15] and as new inhibitors of bacterial DNA gyrase B [16]. In view of the importance of thiazoles and their derivatives, several methods have been developed for their synthesis. The most widely used method is Hantzsch synthesis involving the reaction of α-halocarbonyl compounds with thioureas or thioamides [17-19]. Moreover, the synthesis of thiazol-2-imine derivatives from benzoyl phenylthioureas and *in situ* generated α-bromoketones obtained by the reaction of enolizable ketones with 1,10-(ethane-1,2-diyl)dipyridinium bistribromide has been reported [20, 21]. Thiazole derivatives were also synthesized by using catalysts such as ammonium 12-molybdo phosphate [22], cyclodextrin [23], iodine [24a], and silica chloride

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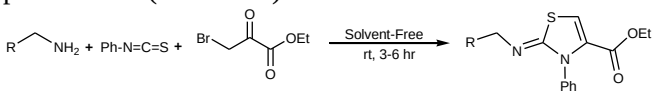
[24b] in organic solvents such as 1-methyl-2-pyrrolidinone [25], and with the use of microwave irradiation [26]. Recently, some new thiazole derivatives were synthesized without catalyst by intramolecular thia-Michael strategy [27] or by using starting materials such as Dibenzobarralene [28],1-Chloro-3,4-dihydronaphthalene-2-carboxaldehyde [29], and 2,3,5-Trichlorobenzaldehyde [30]. However, in spite of their efficiency and potential utility, many of these methods suffer from drawbacks, such as harsh reaction conditions, cumbersome product isolation procedures, and expensive catalysts or starting materials.

As a part of our current studies, on the synthesis of sulfur-containing organic compounds [31-36], in this article, we describe an efficient method for the synthesis of 2,3-dihydrothiazole-4-carboxylates under solvent-free conditions. This catalyst-free and one-pot synthetic method is facile with an easy workup procedure that gives the pure target compounds containing several potential centers for further modification.

Results and discussion

In order to find a synthetic rout for the synthesis of Ethyl 2-(alkylimino)-3-phenyl-2,3-dihydrothiazole-4-carboxylates and Diethyl 3,3'-(1,4-phenylene)-bis-[2-(alkylimino)-2,3-dihydro thiazole-4-carboxylates] derivatives, we focused our attention on a one-pot multicomponent reaction between alkylamines **1**, phenylisothiocianate **2** or 1,4-phenylene diisothiocyanate **9** and ethyl bromopyruvate **3**.

The reactions of alkylamines **1** and phenyl isothiocyanate **2** in the presence of ethyl bromopyru vate **3** proceed smoothly at room temperature to produce Ethyl 2-(alkylimino)-3-phenyl-2,3-di hydrothiazole-4-carboxylates **4a-4j** in good yields after purification (Scheme **1**).



1, 4	R	Time (hr)	Yield (%)
a	4-MeO-C_6H_4	3	86
b	4-Cl-C_6H_4	4.5	81
c	2-Cl-C_6H_4	6	86
d	4-Me-C_6H_4	3.5	83
e	2-MeO-C_6H_4	5	80
f	C_6H_5	4.5	87
g	4-F-C_6H_4	5	90
h	Me	5	73
i	Et	5	81
j	^{n}Pr	5	80

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

The structures of compounds **4a-4j** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed eight signals for methyl (δ = 1.34 ppm), methoxy (δ = 3.83 ppm), methylene groups (δ = 4.30 ppm for OCH_2 and δ = 5.58 ppm for CH_2N) protons, and olefinic CH (δ = 6.96 ppm) along with signals (δ = 6.90, 7.09-7.14, and 7.38-7.44 ppm) for the nine aromatic protons. The ^{13}C NMR spectrum of **4a** showed 16 signals for methyl (δ = 14.18 ppm), methylene groups (δ = 47.63 ppm for CH_2N and δ = 61.43 ppm for CH_2O), and methoxy (δ = 55.25 ppm) carbons along with signals (δ = 111.50-158.46 ppm) for the two olefinic and twelve aromatic carbons that are in agreement with the proposed structure. In addition, ^{13}C NMR peaks in the spectrum of **4a** at 158.61 and 158.86 ppm are diagnostic for imino and carbonyl groups, respectively. Partial assignments of these resonances are given in the experimental section.

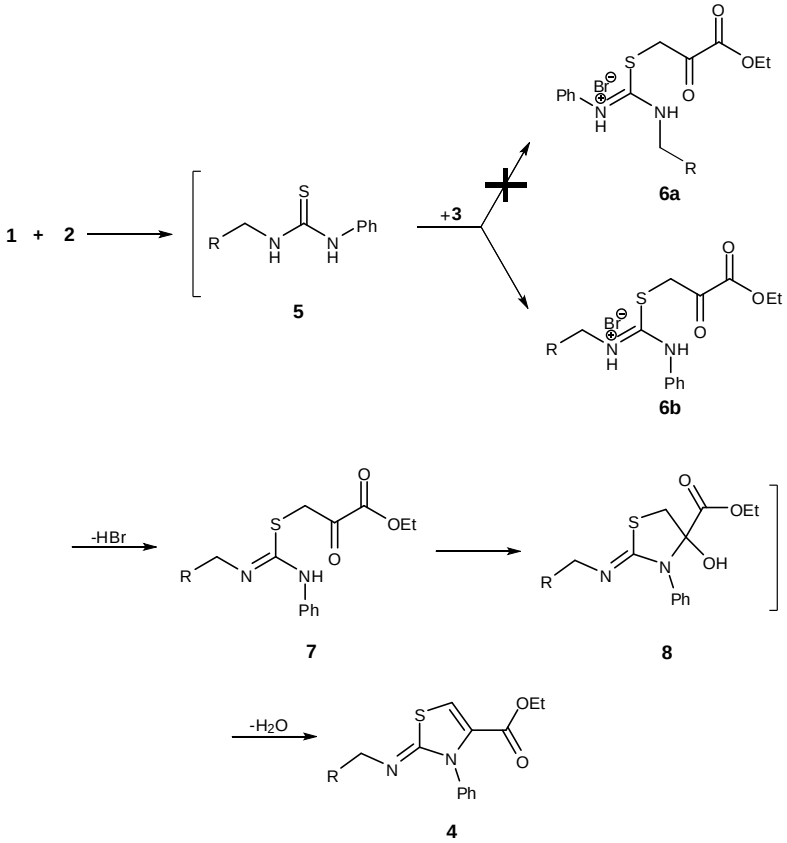
A plausible mechanism for this reaction is given in Scheme **2** and is initiated by reaction of the primary alkylamine and phenyl isothiocyanate to give the unsymmetrical thiourea derivatives **5.**

Subsequent regioselective nucleophilic alkylation of **5** with ethyl bromopyruvate **3** yields intermediate **6b**. Considering the higher nucleophilic power of nitrogen in CH_2-NH as compared with that of Ph-NH it is more reasonable for the initial electron transfer on sulfur for alkylation of **5** to be conducted *via* CH_2-NH. Furthermore, considering the higher electrophilic properties of the carbon atom in C-Br compared with that of carbonyl group and the softness of sulfur and CH_2 it seems that the alkylation of intermediate **5** is more reasonable to occur in a regioselective manner *via* initial attack of sulfur on CH_2-Br of compound **3**. Therefore, the intermediate **6a** can not be formed at this stage of the proposed mechanism and the reaction leads to the formation of intermediate **6b**. This intermediate undergoes HBr elimination and subsequent intramolecular cyclization to form the heterocyclic intermediate **8**, which generates **4** by elimination of water.

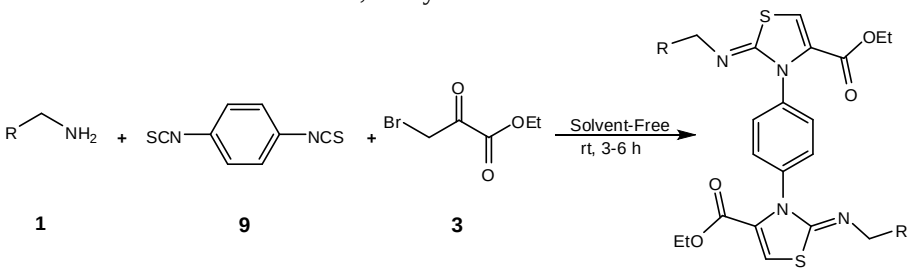
The same plausible mechanism is repeated for the preparation of second five-membered ring compounds category **10** (Scheme **3**).

When the reaction was carried out using one equivalent of 1,4-phenylene diisothiocyanate **9** and two equivalents of alkylamine **1** in the presence of two equivalents of ethyl bromopyruvate **3**, Diethyl 3,3'-

(1,4-phenylene)-bis-[2-(alkylimino)-2,3-dihydro thiazole-4-carboxylates] **10a-10e** were obtained in good yields after purification (Scheme **3**).



Scheme 2: Plausible mechanism for the formation of 2,3-dihydrothiazoles **4** and **10**.



1, 10	R	Time (hr)	Yield (%)
a	4-MeO-C_6H_4	3	91
b	4-Cl-C_6H_4	5	89
c	2-Cl-C_6H_4	6	80
d	4-Me-C_6H_4	4.5	93
e	C_6H_5	5	85

Scheme 3: The three-component one-pot synthesis of 2,3-dihydrothiazoles **10**.

Conclusion

We have reported a convenient transformation from the reaction between phenyl isothiocyanate (and also 1,4-phenylene diisothiocyanate) and primary alkyl amines in the presence of ethyl bromopyruvate, which affords Ethyl 2-(alkylimino)-3-phenyl-2,3-dihydro thiazole-4-carboxylates and Diethyl 3,3'-(1,4-phenylene)-bis-[2-(alkylimino)-2,3-dihydrothiazole-4-carboxylates].

The present method has several advantages such as the lack of need for a solvent and catalyst, good yields,

short reaction times, the substances can be mixed without any activation or modification, simple experimental work-up procedure, and neutral reaction conditions performed at room temperature by simple mixing of the starting materials. The procedure described here provides an efficient one-pot methodology for the preparation of functionalized 2,3-dihydro thiazoles. The 2,3-dihydrothiazoles **4** and **10** can be considered as potentially useful synthetic intermediates.

Experimental

Chemical and instrumentation:

Amines **1**, isothiocyanates **2** and **9**, and ethyl bromopyruvate **3** were obtained from Fluka and Merck and were used without further purification; m.p.: Electrothermal 9100 apparatus; IR spectra: Shimadzu IR-460 spectrometer with solid cell (for compundes **10**) and liquid cell (for compounds **4**) of KBr; ^{1}H and ^{13}C NMR spectra: Bruker DRX-400 AVANC instrument; in $CDCl_3$ at 400.13 MHz and 100.61 MHz, respectively, δ in ppm, and J in Hz; Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer. The analyses data were in agreement with the proposed structures.

General procedure for the preparation of compounds 4a-4j:

A mixture of 0.271 g of phenyl isothiocyanate **2** (2 mmoles) and the primary alkylamine **1** (2 mmoles) was stirred at room temperature for 45 min. Then, ethyl bromopyruvate **3** (2 mmoles) was added dropwise to the reaction mixture and stirred at room temperature. After completion of the reaction [3-6 h; TLC (*n*-hexane /AcOEt 3:1)], the reaction mixture was purified by column chromatography [silica gel (230-240 mesh; Merck), *n*-hexane/AcOEt 4:1)] to afford the pure title compounds.

Ethyl 2-(4-methoxybenzylimino)-3-phenyl-2,3-dihydrothiazole-4-carboxylate (4a):

Yellow oil; Yield: 0.32 g (86 %); IR (liquid cell of KBr): $\bar{\nu}$ = 3050 (CH arom), 2980 (CH aliph), 1710 (C=O), 1610, 1580 (C=C), 1240 (C=N) cm^{-1}; ^{1}H NMR: δ = 1.34 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.83 (3H, s, OCH_3), 4.30 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.58 (2H, s, NCH_2), 6.90 (2H, d, $^3J_{HH}$= 8.4 Hz, 2 CH), 6.96 (1H, s, CH), 7.09- 7.14 (3H, m, 3 CH), 7.38-7.44 (4H, m, 4 CH) ppm; ^{13}C NMR: δ =14.18 (CH_3), 47.63 (NCH_2), 55.25 (OCH_3), 61.43 (OCH_2), 111.5 (CH), 113.77 (2 CH), 121.38 (CH), 123.4 (2 CH), 129.3 (2 CH), 129.6 (2 CH), 129.9 (C), 130.2 (C), 151.26 (C), 158.46 (C), 158.61 (C=N), 158.86 (C=O) ppm; *Anal*. Calcd for $C_{20}H_{20}N_2O_3S$ (368.45): C, 65.19; H, 5.47; N, 7.6. Found: C, 65.22; H 5.40; N, 7.55 %.

Ethyl 2-(4-chlorobenzylimino)-3-phenyl-2,3-dihydro thiazole-4-carboxylate (4b):

Dark yellow oil; Yield: 0.30 g (81 %); IR (liquid cell of KBr): $\bar{\nu}$ = 3060 (CH arom), 2950 (CH aliph), 1718 (C=O), 1615, 1583 (C=C), 1260 (C=N) cm^{-1}; ^{1}H NMR: δ =1.33 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.28 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.57 (2H, s, NCH_2), 6.99 (1H, s, CH), 7.04 (2H, d, $^3J_{HH}$= 7.6 Hz, 2 CH), 7.10 (2H, t, $^3J_{HH}$= 7.6 Hz, 2 CH), 7.31 (2H, d, $^3J_{HH}$= 7.5 Hz, 2 CH), 7.36-7.39 (3H, m, 3 CH) ppm; ^{13}C NMR: δ =14.13 (CH_3), 47.67 (NCH_2), 61.52 (OCH_2), 111.74 (CH), 121.28 (CH), 123.54 (2 CH), 128.53 (2 CH), 129.14 (2 CH), 129.59 (2 CH), 129.64 (C), 132.98 (C), 136.46 (C), 150.95 (C), 158.32 (C=N), 158.36 (C=O) ppm; *Anal*. Calcd for $C_{19}H_{17}ClN_2O_2S$ (372.87): C, 61.20; H, 4.59; N, 7.51. Found: C, 61.17; H 4.63; N, 7.48 %.

Ethyl 2-(2-chlorobenzylimino)-3-phenyl-2,3-dihydro thiazole-4-carboxylate (4c):

Dark yellow oil; Yield: 0.32 g (86 %); IR (liquid cell of KBr): $\bar{\nu}$ = 3045 (CH arom), 2970 (CH aliph), 1718 (C=O), 1618, 1582 (C=C), 1280 (C=N) cm^{-1}; ^{1}H NMR: δ = 1.25 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.22 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.66 (2H, s, NCH_2), 6.97 (1H, s, CH), 7.02 (2H, d, $^3J_{HH}$= 8.4 Hz, 2 CH), 7.09 (1H, d, $^3J_{HH}$= 8.3 Hz, CH), 7.20-7.26 (2H, m, 2 CH), 7.29 (1H, s, CH), 7.35 (2H, t, $^3J_{HH}$= 8.4 Hz, 2 CH), 7.40-7.42 (1H, m, CH) ppm; ^{13}C NMR: δ =13.97 (CH_3), 47.18 (NCH_2), 61.55 (OCH_2), 111.52 (CH), 121.30 (CH), 123.55 (2 CH), 126.47 (CH), 126.79 (CH), 127.97 (CH), 129.50 (2 CH), 129.57 (CH), 130.12 (C), 132.43 (C), 135.21 (C), 150.92 (C), 158.06 (C=N), 158.12 (C=O) ppm; *Anal*. Calcd for $C_{19}H_{17}ClN_2O_2S$ (372.87): C, 61.20; H, 4.59; N, 7.51. Found: C, 61.17; H 4.63; N, 7.48 %.

Ethyl 2-(4-methylbenzylimino)-3-phenyl-2,3-dihydro thiazole-4-carboxylate (4d):

Yellow oil; Yield: 0.29 g (83 %); IR (liquid cell of KBr): $\bar{\nu}$ = 3058 (CH arom), 2988 (CH aliph), 1720 (C=O), 1620, 1586 (C=C), 1275 (C=N) cm^{-1}; ^{1}H NMR: δ =1.32 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.36 (3H, s, CH_3), 4.27 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.58 (2H, s, NCH_2), 6.96 (1H, s, CH), 7.09 (3H, t, $^3J_{HH}$= 7.9 Hz, 3 CH), 7.15 (2H, d, $^3J_{HH}$= 8.00 Hz, 2 CH), 7.31 (2H, s, 2 CH),

7.37 (2H, t, $^3J_{HH}$= 8.00Hz, 2 CH) ppm; ^{13}C NMR: δ =14.12 (CH_3), 21.16 (CH_3), 47.95 (NCH_2), 61.39 (OCH_2), 111.4 (CH), 121.36 (CH), 123.37 (2 CH), 121.61 (4 CH), 129.08 (2 CH), 129.59 (C), 134.93 (C), 136.78 (C), 151.23 (C), 158.4 (C=N), 158.6 (C=O) ppm; *Anal*. Calcd for $C_{20}H_{20}N_2O_2S$ (352.45): C, 68.15; H, 5.72; N, 7.95. Found: C, 68.20; H 5.68; N, 7.91 %.

Ethyl 2-(2-methoxybenzylimino)-3-phenyl-2,3-dihydro thiazole-4-carboxylate (4e):

Yellow oil; Yield: 0.30 g (80 %); IR (liquid cell of KBr): $\overline{\nu}$ = 3095 (CH arom), 2990 (CH aliph), 1710 (C=O), 1610, 1579 (C=C), 1243 (C=N) cm^{-1}; ^{1}H NMR: δ = 1.29 (3H, t, $^3J_{HH}$ =7.2 Hz, CH_3), 3.86 (3H, s, OCH_3), 4.25 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.56 (2H, s, NCH_2), 6.88 (2H, d, $^3J_{HH}$= 8.00 Hz, 2 CH), 6.94 (1H, s, CH), 6.98 (1H, d, $^3J_{HH}$= 8.00 Hz, CH), 7.07 (2H, t, $^3J_{HH}$= 8.00 Hz, 2 CH), 7.25 (3H, t, $^3J_{HH}$= 7.9 Hz, 3 CH), 7.33 (1H, t, $^3J_{HH}$= 7.9 Hz, CH) ppm; ^{13}C NMR: δ = 14.04 (CH_3), 47.91(NCH_2), 55.24 (OCH_3), 61.34 (OCH_2), 110.12 (CH), 110.37 (CH), 120.21 (CH), 121.38 (CH), 123.31 (2 CH), 125.52 (C), 127.71 (CH), 128.07 (2 CH), 129.51 (CH), 130.96 (C), 136.86 (C), 151.23 (C), 157.10 (C=N), 158.52 (C=O) ppm; *Anal*. Calcd for $C_{20}H_{20}N_2O_3S$ (368.45): C, 65.19; H, 5.47; N, 7.6. Found: C, 65.22; H 5.40; N, 7.55 %.

Ethyl 2-(benzylimino)-3-phenyl-2,3-dihydrothiazole-4-carboxylate (4f):

Dark yellow oil; Yield: 0.28 g (87 %); IR (liquid cell of KBr): $\overline{\nu}$ = 3055 (CH arom), 2998 (CH aliph), 1717 (C=O), 1617, 1583 (C=C), 1258 (C=N) cm^{-1}; ^{1}H NMR: δ = 1.33 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.28 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.67 (2H, s, NCH_2), 6.99 (1H, s, CH), 7.09-7.15 (3H, m, 3 CH), 7.32 (1H, d, $^3J_{HH}$= 7.2 Hz, CH), 7.37-7.46 (6H, m, 6 CH) ppm; ^{13}C NMR: δ = 14.15 (CH_3), 48.30 (NCH_2), 61.45 (OCH_2), 111.51 (CH), 121.39 (CH), 123.46 (2 CH), 127.22 (CH), 127.57 (2 CH), 128.45 (2 CH), 129.65 (2 CH), 129.95 (C), 138.01 (C), 151.21 (C), 158.39 (C=N), 158.56 (C=O) ppm; *Anal*. Calcd for $C_{19}H_{18}N_2O_2S$ (338.42): C, 67.43; H, 5.36; N, 8.28. Found: C, 67.40; H 5.39; N, 8.23 %.

Ethyl 2-(4-fluorobenzylimino)-3-phenyl-2,3-dihydro thiazole-4-carboxylate (4g):

Dark yellow oil; Yield: 0.32 g (90 %); IR (liquid cell of KBr): $\overline{\nu}$ =3045 (CH arom), 2900 (CH aliph), 1712 (C=O), 1619, 1581 (C=C), 1260 (C=N) cm^{-1}; ^{1}H NMR: δ = 1.33 (3H, t, $^3J_{HH}$ = 6.8 Hz, CH_3), 4.28 (2H, q, $^3J_{HH}$ = 6.8 Hz, OCH_2), 5.57 (2H, s, NCH_2), 6.98 (1H, s, CH), 7.00-7.05 (3H, m, 3 CH), 7.10 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.35-7.44 (4H, m, 4 CH) ppm; ^{13}C NMR: δ = 14.12 (CH_3), 47.55 (NCH_2), 61.48 (OCH_2), 111.67 (CH), 115.29 (2 CH), 121.29 (CH), 123.5 (2 CH), 129.51 (2 CH), 129.59 (2 CH), 129.63(C), 134.24 (C), 135.21(C), 151.21 (C), 159.93 (C=N), 160.11 (C=O) ppm; *Anal*. Calcd for $C_{19}H_{17}FN_2O_2S$ (356.42): C, 64.02; H, 4.81; N, 7.86. Found: C, 64.08; H 4.86; N, 7.90 %.

Ethyl 2-(ethylimino)-3-phenyl-2,3-dihydrothiazole-4-carboxylate (4h):

Yellow oil; Yield: 0.2 g (73 %); IR (liquid cell of KBr): $\overline{\nu}$ = 3048 (CH arom), 2986 (CH aliph), 1718 (C=O), 1616, 1580 (C=C), 1263 (C=N) cm^{-1}; ^{1}H NMR: δ =1.38 (6H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_3), 4.28- 4.41 (4H, m, NCH_2, OCH_2), 6.94 (1H, s, CH), 7.05 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2 CH), 7.08 (1H, t, $^3J_{HH}$ = 8.3 Hz, CH), 7.36 (2H, t, $^3J_{HH}$ = 8.4 Hz, 2 CH) ppm; ^{13}C NMR: δ =13.97 (CH_3), 14.18 (CH_3), 41.11(NCH_2), 61.37 (OCH_2), 111.04 (CH), 121.47 (CH), 123.3 (2CH), 129.6 (2CH), 130.00(C), 151.56 (C), 158.26 (C=N), 158.39 (C=O) ppm; *Anal*. Calcd for $C_{14}H_{16}N_2O_2S$ (276.36): C, 60.84; H, 5.84; N, 10.14. Found: C, 60.80; H 5.89; N, 10.20 %.

Ethyl 2-(n-propylimino)-3-phenyl-2,3-dihydrothiazole-4-carboxylate (4i):

Yellow oil; Yield: 0.23 g (81 %); IR (liquid cell of KBr): $\overline{\nu}$ = 3051 (CH arom), 2950 (CH aliph), 1725 (C=O), 1620, 1585 (C=C), 1245 (C=N) cm^{-1}; ^{1}H NMR: δ =1.00 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.39 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.81 (2H, six, $^3J_{HH}$ = 7.3 Hz, CH_2), 4.27-4.36 (4H, m, NCH_2, OCH_2), 6.94 (1H, s, CH), 7.03 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.08 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.36 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2 CH) ppm; ^{13}C NMR: δ =11.13 (CH_3), 14.19 (CH_3), 22.04 (CH_2), 47.14 (NCH_2), 61.35 (OCH_2), 110.98 (CH), 121.44 (CH), 123.28 (2 CH), 129.61 (2 CH), 130.2 (C), 151.62 (C), 158.46 (C=N), 158.53 (C=O) ppm; *Anal*. Calcd for $C_{15}H_{18}N_2O_2S$ (290.38): C, 62.04; H, 6.25; N, 9.65. Found: C, 62.1; H 6.20; N, 9.7 %.

Ethyl 2-(n-butylimino)-3-phenyl-2,3-dihydr othiazole-4-carboxylate (4j):

Yellow oil; Yield: 0.24 g (80 %); IR (liquid cell of KBr): $\overline{\nu}$ = 3105 (CH arom), 2955 (CH aliph), 1719 (C=O), 1612, 1581 (C=C), 1284 (C=N) cm^{-1}; ^{1}H NMR: δ =1.01 (3H, t, $^3J_{HH}$ = 8.0 Hz, CH_3), 1.39 (3H, t, $^3J_{HH}$ = 6.8 Hz, CH_3), 1.44 (2H, six, $^3J_{HH}$ = 8.0 Hz, CH_2), 1.77 (2H, qui, $^3J_{HH}$ = 7.9 Hz, CH_2), 4.12 (2H, t, $^3J_{HH}$ = 7.9

Hz, NCH_2), 4.34 (2H, q, $^3J_{HH}$ = 6.8 Hz, OCH_2), 6.94 (1H, s, CH), 7.04 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.08 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.37(2H, t, $^3J_{HH}$ = 7.6 Hz, 2 CH) ppm; ^{13}C NMR: δ = 13.94 (CH_3), 14.2 (CH_3), 19.99 (CH_2), 30.96 (CH_2), 45.54 (NCH_2), 61.35 (OCH_2), 111.0 (CH), 121.44 (CH), 123.25 (2 CH), 129.6 (2 CH), 130.16 (C), 151.61 (C), 158.41 (C=N), 158.44 (C=O) ppm; *Anal*. Calcd for $C_{16}H_{20}N_2O_2S$ (304.41): C, 63.12; H, 6.62; N, 9.20. Found: C, 63.09; H 6.59; N, 9.29 %.

General procedure for the preparation of compounds 10a-10e:

A mixture of 0.385 g of 1,4-phenylene diisothiocyanate **9** (2 mmoles) and the primary alkyl amine **1** (4 mmoles) was stirred at room temperature for 60 min. Then, ethyl bromopyruvate **3** (4 mmoles) was added dropwise to the reaction mixture and stirred at room temperature. After completion of the reaction [3-6 h; TLC (*n*-hexane /AcOEt 3:1)], the reaction mixture was purified by column chromatography [silica gel (230-240 mesh; Merck), *n*-hexane/AcOEt 4:1)] to afford the pure title compounds.

Diethyl 3,3'-(1,4-phenylene)-bis-[2-(4-methoxybenzyl imino)-2,3-dihydrothiazole-4-carboxylate] (10a):

Yellow powder; yield: 0.61 g (91%); mp 228-230 °C; IR (KBr): $\overline{\nu}$ = 3028 (CH arom), 2955 (CH aliph), 1722 (2 C=O), 1612, 1581 (C=C), 1289 (2 C=N) cm^{-1}; ^{1}H NMR: δ =1.32 (6H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_3), 3.81 (6H, s, 2 OCH_3), 4.28 (4H, q, $^3J_{HH}$ = 7.2 Hz, 2 OCH_2), 5.56 (4H, s, 2 NCH_2), 6.87 (4H, d, $^3J_{HH}$= 8.4 Hz, 4 CH), 6.96 (2H, s, 2 CH), 7.18 (4H, d, $^3J_{HH}$= 8.4 Hz, 4 CH), 7.52 (4H, s, C_6H_4) ppm; ^{13}C NMR: δ =14.2 (2 CH_3), 47.43 (2 NCH_2), 53.2 (2 OCH_3), 60.88 (2 OCH_2), 111.46 (2 CH), 114.2 (4 CH), 128.8 (4 CH), 129.10 (4 CH of C_6H_4), 131.1 (2C), 131.5 (2C), 151.68 (2C), 158.55 (2C), 158.68 (2 C=N), 158.92 (2 C=O) ppm; *Anal*. Calcd for $C_{34}H_{34}N_4O_6S_2$ (658.77): C, 61.98; H, 5.2; N, 8.5. Found: C, 61.9; H 5.31; N, 8.59 %.

Diethyl 3,3'-(1,4-phenylene)-bis-[2-(4-chlorobenzyl imino)-2,3-dihydrothiazole-4 carboxylate] (10b):

Yellow powder; yield: 0.59 g (89%); mp 250-253 °C; IR (KBr): $\overline{\nu}$ = 3061 (CH arom), 2987 (CH aliph), 1728 (2 C=O), 1615, 1580 (C=C), 1281 (2 C=N) cm^{-1}; ^{1}H NMR: δ =1.29 (6H, t, $^3J_{HH}$= 7.1 Hz, 2 CH_3), 4.22 (4H, q, $^3J_{HH}$= 7.1 Hz, 2 OCH_2), 5.23 (4H, s, 2 NCH_2), 6.92 (2H, s, 2 CH), 7.23 (4H, d, $^3J_{HH}$= 7.5 Hz, 4 CH), 7.45 (4H, d, $^3J_{HH}$= 7.4 Hz, 4 CH), 7.55 (4H, s, C_6H_4) ppm; ^{13}C NMR: δ =14.4 (2 CH_3), 45.51 (2 NCH_2), 61.4 (2 OCH_2), 110.98 (2 CH), 128.33 (4 CH), 128.82 (4 CH of C_6H_4), 130.48 (4 CH), 131.2 (2C), 131.84 (2C), 137.21 (2C), 151.26 (2C), 157.82 (2 C=N), 158.23 (2 C=O) ppm; *Anal*. Calcd for $C_{32}H_{28}Cl_2N_4O_4S_2$ (667.61): C, 57.57; H, 4.23; N, 8.4. Found: C, 57.61; H 4.31; N, 8.32 %.

Diethyl 3,3'-(1,4-phenylene)-bis-[2-(2-chlorobenzyl imino)-2,3-dihydrothiazole-4-carboxylate] (10c):

Yellow powder; yield: 0.53 g (80%); mp 244-246 °C; IR (KBr): $\overline{\nu}$ = 3055 (CH arom), 2976 (CH aliph), 1725 (2 C=O), 1610, 1579 (C=C), 1246 (2 C=N) cm^{-1}; ^{1}H NMR: δ =1.23 (6H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_3), 4.26 (4H, q, $^3J_{HH}$ = 7.2 Hz, 2 OCH_2), 5.41 (4H, s, 2 NCH_2), 6.86 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.01 (2H, s, 2 CH), 7.23-7.36 (4H, m, 4 CH), 7.57 (2H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.62 (4H, s, C_6H_4) ppm; ^{13}C NMR: δ =14.7 (2 CH_3), 48.31 (2 NCH_2), 60.88 (2 OCH_2), 110.95 (2 CH), 126.31 (2 CH), 126.82 (2 CH), 127.58 (2 CH), 129.30 (4 CH of C_6H_4), 129.76 (2 CH), 131.15 (2C), 133.58 (2C), 135.44 (2C), 151.85 (2C), 157.93 (2 C=N), 158.26 (2 C=O) ppm; *Anal*. Calcd for $C_{32}H_{28}Cl_2N_4O_4S_2$ (667.61): C, 57.57; H, 4.23; N, 8.4. Found: C, 57.61; H 4.31; N, 8.32 %.

Diethyl 3,3'-(1,4-phenylene)-bis-[2-(4-methylbenzyl imino)-2,3-dihydrothiazole-4-carboxylate] (10d):

Yellow powder; yield: 0.58 g (93%); mp 202-204 °C; IR (KBr): $\overline{\nu}$ =3080 (CH arom), 2995 (CH aliph), 1718 (2 C=O), 1618, 1575 (C=C), 1240 (2 C=N) cm^{-1}; ^{1}H NMR: δ =1.29 (6H, t, $^3J_{HH}$= 7.2 Hz, 2 CH_3), 2.52 (6H, s, 2 CH_3), 4.31 (4H, q, $^3J_{HH}$= 7.1 Hz, 2 OCH_2), 5.24 (4H, s, 2 NCH_2), 6.89 (2H, s, 2 CH), 7.12 (4H, d, $^3J_{HH}$ = 7.5 Hz, 4 CH), 7.18 (4H, d, $^3J_{HH}$ = 7.5 Hz, 4 CH), 7.58 (4H, s, C_6H_4) ppm; ^{13}C NMR: δ =13.35 (2 CH_3), 14.61 (2 CH_3), 48.12 (2 NCH_2), 60.58 (2 OCH_2), 110.79 (2 CH), 127.56 (4 CH), 129.28 (4 CH), 129.38 (4 CH of C_6H_4), 131.6 (2C), 135.58 (2C), 137.73 (2C), 151.63 (2C), 158.92 (2 C=N), 159.12 (2 C=O) ppm; *Anal*. Calcd for $C_{34}H_{34}N_4O_4S_2$ (627.77): C, 65.05; H, 5.46; N, 8.93. Found: C, 65.11; H 5.5; N, 8.86 %.

Diethyl 3,3'-(1,4-phenylene)-bis-[2-(benzylimino)-2,3-dihydrothiazole-4-carboxylates] (10e):

Yellow powder; yield: 0.51 g (85%); mp 179-181 °C; IR (KBr): $\overline{\nu}$ = 3073 (CH arom), 2980 (CH aliph), 1726 (2 C=O), 1611, 1572 (C=C), 1244 (2 C=N) cm^{-1}; ^{1}H NMR: δ =1.31 (6H, t, $^3J_{HH}$ =7.2 Hz, 2 CH_3), 4.28 (4H, q, $^3J_{HH}$= 7.1 Hz, 2 OCH_2), 5.39 (4H, s, 2 NCH_2), 6.95 (2H, s, 2 CH), 7.04-7.11 (10 H, m, 10 CH), 7.51

(4H, s, C_6H_4) ppm; ^{13}C NMR: δ=13.5 (2 CH_3), 47.7 (2 NCH_2), 61.08 (2 OCH_2), 111.35 (2 CH), 121.7 (2 CH), 124.16 (4 CH), 128.32 (4 CH), 129.42 (4 CH of C_6H_4), 136.6 (2C), 138.4 (2C), 150.94 (2C), 158.1 (2 C=N), 162.4 (2 C=O) ppm; *Anal*. Calcd for $C_{32}H_{30}N_4O_4S_2$ (598.72): C, 64.19; H, 5.05; N, 9.36. Found: C, 64.22; H 5.12; N, 9.5 %.

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References

[1] (a) Schreiber, S. L. *Science* **2000**, 287, 1964; (b) Do¨mling, A. *Curr. Opin. Chem. Biol*. **2002**, *6*, 303.
[2] Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis. Wiley: New York*, **1995,** 2.
[3] (a) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind*. **1997**, 765-769; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259.
[4] (a) Weber, L.; Illgen, K.; Almstetter, M. *Synlett*. **1999**, 366; (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J*. **2000**, 6, 3321.
[5] Quiroga , J.; Hernandez, P.; Insuassy, B. R.; Abonia, R.; Cobo, J.; Sanchez, A.; Nogueras, M.; Low, J. N. *J. Chem. Soc. Perkin Trans.1*. **2002**, 555.
[6] Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem*. **2002**, *45*, 744.
[7] Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem*. **1983**, *26*, 1158.
[8] Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor Jr., D. G.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem*. **1992**, *35*, 2562.
[9] Sharma, P. K.; Sawnhney, S. N.; Gupta, A.; Singh, G. B.; Bani, S. *Indian J. Chem*. **1998**, *37B*, 376.
[10] Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem*. **1990**, *33*, 311.
[11] Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1601.
[12] Bell, F. W.; Cantrell, A. S.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin Jr., J. M.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *J. Med. Chem*. **1995**, *38*, 4929.
[13] Ergenc, N.; Capan, G.; Gu¨ nay, N. S.; O¨ zkirimli, S.; Gu¨ ngor, M.; O¨ zbey, S.; Kendi, E. *Arch. Pharm. Pharm, Med. Chem*. **1999**, *332*, 343.
[14] Carter, J. S.; Kramer, S.; Talley, J. J.; Penning, T.; Collins, P.; Graneto, M. J.; Seibert, K.; Koboldt, C.; Masferrer, J.; Zweifel, B. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1171.
[15] Badorc, A.; Bordes, M. F.; De Cointet, P.; Savi, P.; Bernat, A.; Lale, A.; Petitou, M.; Maffrand, J. P.; Herbert, J. M. *J. Med. Chem*. **1997**, *40*, 3393.
[16] Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F. U.; *J. Med., Chem*. **2001**, *44*, 619.
[17] Hantzsch, A.;Weber, J. H. *Ber. Dtsch. Chem. Ges*. **1887,** *20*, 3118.
[18] Aguilar, E.; Meyers, A. I. *Tetrahedron Lett*. **1994**, *35*, 2473.
[19] Varma, R.S. *Pure. Appl. Chem*. **2001**, *73*, 193.
[20] Singh, C.B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397.
[21] Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron.* **2008**, *64*, 1931.
[22] Das, B.; Saidi Reddy, V.; Ramu, R. *J. Mol. Catal. A: Chem*. **2006**, *252*, 235.
[23] Narender, M.; Somi Reddy, M.; Sridhar, R.; Nageswar, Y. V. D.; Rama Rao, K. *Tetrahedron Lett*. **2005**, *46*, 5953.
[24] (a) Siddiqui, H. L.; Iqbal, A.; Ahmed, S.; Weaver, G. *Molecules*. **2006**, *11*, 206; (b) Karade, H.; sathe, M.; Kaushik, M. P. *Catal. Commun*. **2007**, *8*, 741.
[25] Garcia-Egido, E.; Wong, S. Y. F.; Warrington, B. H. *Lab. Chip*. **2002**, *2*, 31.
[26] George, W. K.; Arjun, R. M. *Tetrahedron Lett*. **2006**, *47*, 5171.
[27] Sasmal, P.K.; Sridhar, S.; Iqbal, J. *Tetrahedron Lett*. **2006**, *47*, 8661.
[28] Khalil, A. M.; Berghot, M. A.; Gouda, M. A. *Eur. J. Med. Chem* . **2009**, *44*, 4434.
[29] Bondock, S.; Khalifa,W.; Fadda, A. A. *Eur. J. Med. Chem* . **2007**, *42*, 948.
[30] Karegoudar, P.; Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem* . **2008**, *43*, 261.
[31] Yavari, I.; Hajinasiri, R.; Sayyed-Alangi, S. Z.; Iravani, N. *Monatsh. Chem*. **2008**, *139*, 1029.
[32] Yavari, I.; Sayyed-Alangi, S. Z.; Sabbaghan, M.; Hajinasiri, R.; Iravani. N. *Monatsh. Chem*. **2008**, *139*, 1025.
[33] Yavari, I.; Iravani. N.; Sayyed-Alangi, S. Z.; Hajinasiri, R. *Monatsh. Chem*. **2009**, *140*, 1199.
[34] Yavari, I.; Hajinasiri, R.; Sayyed-Alangi, S. Z.; Iravani, N. *J. Iran. Chem. Soc*. **2009**, *6*, 705.
[35] Iravani, N.; Karami, B.; Asadimoghaddam, F.; Monfared, M.; Karami, N. *J. Sulfur. Chem*. **2012**, *33*, 279.
[36] Iravani, N.; Albadi, J.; Varnaseri, S.; Jaberi, Z.; Karami, N.; Khadamati, M. *J. Chin. Chem. Soc*. **2012**, *59*, 1567.