Tetrahedron 64 (2008) 11074–11080

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Novel one-step method for the conversion of isothiocyanates to 2-alkyl(aryl)aminothiazoles☆

Pradip K. Sasmal *, A. Chandrasekhar, S. Sridhar, Javed Iqbal

*Discovery Research, Dr. Reddy's Laboratories Ltd., Miyapur, Hyderabad 500 049, AP, India*

ARTICLE INFO

*Article history:*
Received 23 April 2008
Received in revised form
22 September 2008
Accepted 25 September 2008
Available online 7 October 2008

*Keywords:*
Thiazoles
Intramolecular thia-Michael reaction
Isothiocyanates
Thiazolylmethylphosphonates

ABSTRACT

2-Aminothiazole derivatives are widely used structural motifs in medicinal chemistry due to their broad application in drug development. Herein we demonstrate a novel one-step method for the synthesis of 2-aminothiazole derivatives from the corresponding isothiocyanates via thiourea formation followed by cycloisomerisation in an intramolecular thia-Michael fashion. This method is very mild, simple and highly efficient and versatile enough to accommodate various amino substitutions at the C2 position of thiazoles. This methodology is equally well applicable to synthesise various 2-substituted amino-5-thiazolylmethylphosphonate derivatives.



## 1. Introduction

Thiazole derivatives are the prominent players in the pharmaceutical research as they possess several biological properties.[1–8] Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active natural products. Typically, 2-aminothiazole derivatives are well known common motifs in medicinal chemistry due to their broad application in drug development for the treatment of allergies,[9] hypertension,[10] inflammation[11] and bacterial infections.[12] 2-Aminothiazole derivatives have also shown high affinity for the NPY5 (neuropeptide Y5) receptor for the treatment of eating disorders such as obesity and hyperphagia.[13] Besides, aminothiazoles are reported to be CDK (cyclin dependent kinase) inhibitors[14] for the treatment of cancer and 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1) inhibitors[15] for the treatment of metabolic disorders. Generally, 2-aminothiazoles are prepared by the Hantzsch method[16–18] (condensation of α-halo ketones with monosubstituted thioureas) or by modified Hantzsch methodologies such as the one reported by Ochiai's group, which used mild reaction conditions to generate 2-aminothiazoles via the reaction of in situ generated α-$\lambda^3$-iodanyl ketones with thioureas.[19] Aminothiazoles are also prepared by the reaction of α-thiocyanato carbonyl compounds with aromatic or aliphatic amine hydrochlorides.[20–23] Recently, Kodomari's group has reported the synthesis of 2-aminothiazoles from α-bromo ketones using the supported reagents $KSCN/SiO_2–RNH_3OAc/Al_2O_3$.[24] Despite these procedures, novel and widely applicable methods for the synthesis of 2-aminothiazole derivatives are still in demand.

## 2. Results and discussion

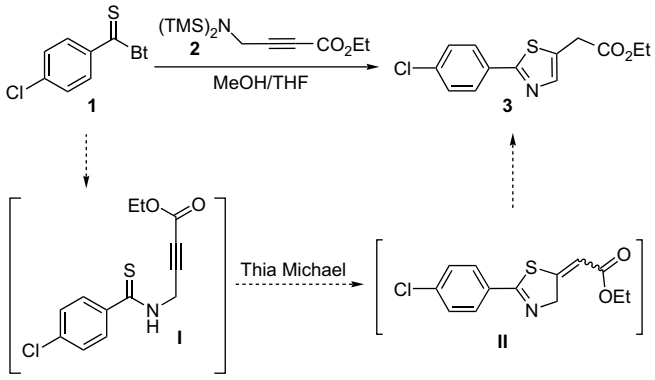
Recently, we disclosed an intramolecular thia-Michael strategy[25] for the synthesis of thiazole derivatives. As, for example, 1-thiobenzoylbenzotriazole **1** was converted to thiazole derivative **3** (Scheme 1) by its treatment with ethyl 4-*N*,*N*-bis(trimethylsilyl)aminobut-2-ynoate **2**[26] in the presence of MeOH in THF without requiring any base for the final cyclisation.

When this protocol (condition A, Scheme 2) was applied to 1-thiocarbamoylbenzotriazole **4**[27] the expected 2-aminothiazole **6** was not obtained. After several experiments we realised that N-desilylation of **2** using 10 equiv of MeOH in THF is very sluggish in the presence of triethylamine (condition B), whereas unlike thioamide (example **3**) base is required for the intramolecular cyclisation of thiourea to aminothiazole derivatives. A combination of triethylamine and methanol as solvent could balance N-desilylation of **2** followed by thiourea formation and cyclisation/aromatisation to produce compound **6** from **4** in 48% yield (condition C). Treatment of **4** with the HCl salt of ethyl 3-aminoprop-1-yn-1-carboxylate **8a**[28] (Scheme 3) in the presence of $Et_3N$ in THF afforded the desired aminothiazole derivative **6** in 81% isolated yield (condition D). Conversion of **4** to **6** under various reaction conditions as mentioned in Scheme 2 has been summarised in Table 1. None of

☆ DRL Publication No. 671.

* Corresponding author. Tel.: +91 40 2304 5439; fax: +91 40 2304 5438.
*E-mail address:* sasmalpk@yahoo.co.in (P.K. Sasmal).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.09.074



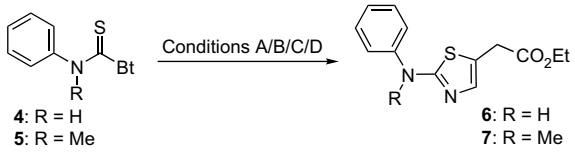

**Scheme 1.** Synthesis of thiazole **3** from **1**.

these above conditions including condition D produced compound **7** from **5**.[27] These results demonstrate that benzotriazole carbothioamide system is converted to the thiourea derivatives not through direct replacement of Bt group rather through the intermediacy of the corresponding isothiocyanate[29] and in the presence of base, formation of isothiocyanate is possible only for compound **4**, not for compound **5**.

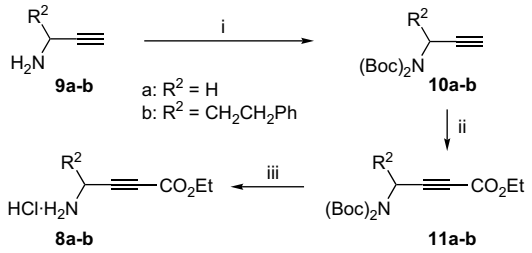
These observations encouraged us to develop a direct method for the conversion of isothiocyanates to 2-aminothiazole derivatives and in that case this protocol will be the shortest possible route to synthesise this class of compounds.

To test our hypothesis, we initially prepared amine hydrochlorides **8** as summarised in Scheme 3. For the synthesis of **8a**, commercially available propargylamine (**9a**) was first protected as its Di-Boc derivative **10a** by the treatment with excess $Boc_2O$ in MeCN in the presence of DMAP in 95% yield. Compound **10a** was then subjected to C-alkylation with ethyl chloroformate in the presence of LDA as base to afford ethyl propiolate derivative **11a** in 70% yield. Deprotection of *N*-Boc with ethereal HCl furnished the corresponding amine salt **8a** in 80% yield for subsequent studies. Following a similar protocol, 5-phenylpent-1-yn-3-amine (**9b**)[30] was converted to the desired amine partner **8b** in 45% overall yield. Both **8a** and **8b** can be stored for several months in the refrigerator without exposing to moisture but, they are highly hygroscopic and unstable in solution ($H_2O$ and DMSO) as they are partially converted to their corresponding vinyl chlorides by the Michael addition of internal HCl to the propiolate system.[31]

Initially, *p*-chlorophenyl isothiocyanate (**12a**)[32] was reacted with amine **8a** in THF in the presence of triethylamine at room temperature and according to our expectation we obtained the corresponding product ethyl 2-(2-(4-chlorophenylamino)thiazol-5-yl)acetate in 82% yield (entry 1, Table 2). Though, in the literature, the synthesis of 2-amino-4-thiazolyl acetate derivatives is well documented, synthesis of 2-amino-5-thiazolyl acetate derivatives is poorly addressed.[14,33–35] Encouraged by our experimental result, amine **8a** was reacted with various isothiocyanates and in all the cases, reactions were smooth and the corresponding thiazole derivatives were obtained in good to excellent yields. The results of




**Scheme 2.** Reaction conditions, A: **2** (1.5 equiv), THF, MeOH (10 equiv), rt, 24 h; B: **2** (1.5 equiv), THF, $Et_3N$ (3.0 equiv), MeOH (10 equiv), rt, 24 h; C: **2** (1.5 equiv), MeOH, $Et_3N$ (3.0 equiv), rt, 24 h; D: **8a** (1.5 equiv), THF, $Et_3N$ (3.0 equiv), rt, 12 h.




**Scheme 3.** Reagents and conditions: (i) $(Boc)_2O$ (2.5 equiv), DMAP (1.0 equiv), MeCN, rt, 12 h; (ii) LDA (1.5 equiv), ethyl chloroformate (1.5 equiv), ether, −78 °C (1 h) then −30 °C, 4 h; (iii) dry HCl, ether, 0 °C, 5 h.

these cyclisation reactions are summarised in Table 2. Amine **8b** also behaved in a similar fashion giving high yield of 2,4,5-trisubstituted thiazole derivatives (entries 13 and 14). Both alcoholic functionality (entry 10) and ester group (entries 3 and 14) were well tolerated in this process.

We next investigated the application of this methodology to synthesise various 2-substituted amino-5-thiazolylmethylphosphonate derivatives from the corresponding isothiocyanates and propynylphosphonates as these thiazole appended phosphonates will serve as suitable intermediates for further C–C bond forming reactions. Towards this purpose, we made the HCl salt of diethyl 3-aminoprop-1-ynylphosphonate (**28a**)[36] and diethyl 3-amino-5-phenylpent-1-ynylphosphonate (**28b**)[36] following Scheme 4.

Treatment of **12a** with amine salt **28a** led to the smooth formation of the desired compound **29** in 88% yield (Table 3). The characteristic $^1H$ NMR signal at $\delta$ 7.07 as doublet with coupling constant $^4J_{HP}$ 4.3 Hz and the $^{13}C$ NMR signal at $\delta$ 25.3 as doublet with coupling constant $^1J_{CP}$ 145.3 Hz confirmed the formation of thiazolylmethylphosphonate derivative. Reaction of various isothiocyanates with the amino counter parts **28a**-**b** ended up with good to excellent yields of the corresponding thiazolylmethylphosphonate derivatives and the results are summarised in Table 3. According to our knowledge, the synthesis of 2-substituted amino-5-thiazolylmethylphosphonate derivatives has not been reported in the literature.[37]

## 3. Conclusion

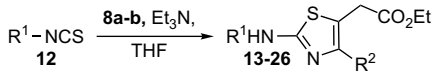
In conclusion, we have demonstrated a novel method for the synthesis of 2-aminothiazole derivatives in one-step from the corresponding isothiocyanates via thiourea formation followed by cycloisomerisation in an intramolecular thia-Michael fashion. The beauty of this method lies in the fact that it is very mild, simple and highly efficient. This method may find wide application for the laboratory-scale and combinatorial synthesis of 2,4-disubstituted and 2,4,5-trisubstituted thiazole libraries. Especially, thiazole appended phosphonates could be utilised as suitable intermediates for further C–C bond forming reactions.

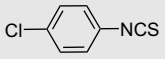
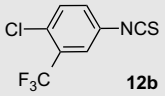
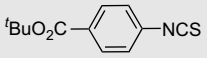
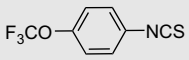
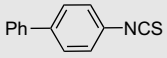
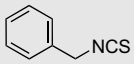
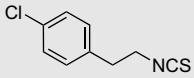
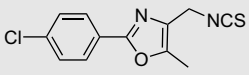
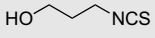
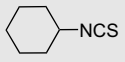
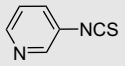
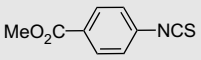
**Table 1**
Conversion of **4** and **5** to **6** and **7**, respectively

| Reaction condition | Yield (%)[a] | |
|---|---|---|
| | **6** | **7** |
| A | NR[b] | NR |
| B | 8 | NR |
| C | 45 | NR |
| D | 81 | NR |

[a] Isolated yield.
[b] NR=no reaction.

**Table 2**
Synthesis of thiazole derivatives

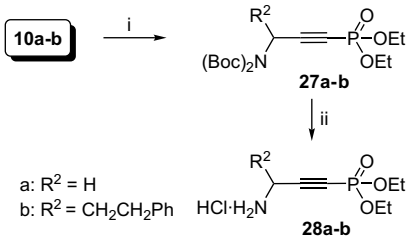



| Entry | Isothiocyanate | Amine | Product (% yield) |
|---|---|---|---|
| 1 |  **12a** | **8a** | **13** (82) |
| 2 |  **12b** | **8a** | **14** (81) |
| 3 |  **12c** | **8a** | **15** (81) |
| 4 |  **12d** | **8a** | **16** (75) |
| 5 |  **12e** | **8a** | **17** (88) |
| 6 |  **12f** | **8a** | **18** (75) |
| 7 |  **12g** | **8a** | **19** (65) |
| 8 |  **12h** | **8a** | **20** (71) |
| 9 |  **12i** | **8a** | **21** (93) |
| 10 |  **12j** | **8a** | **22** (70) |
| 11 |  **12k** | **8a** | **23** (86) |
| 12 |  **12l** | **8a** | **24** (72) |
| 13 | **12a** | **8b** | **25** (82) |
| 14 |  **12m** | **8b** | **26** (83) |

## 4. Experimental

### 4.1. General

All reactions were carried out under inert atmosphere. All solvents were distilled prior to use. Anhydrous solvents were distilled by following standard protocols. Low temperature baths were ice/water (0 °C) and $CO_2$(s)/acetone (−78 °C). Reaction temperatures refer to that of the bath. Melting points (mp) were recorded with Buchi Melting Point B-540 instrument and are uncorrected. IR spectra were recorded either neat or as KBr pallet with a Shimadzu IR-Prestige-21 instrument and only diagnostic and/or intense peaks




**Scheme 4.** Reagents and conditions: (i) LDA (1.5 equiv), diethyl chlorophosphate (1.5 equiv), ether, −78 °C, 1 h, then −30 °C, 4 h; (ii) dry HCl, ether, 0 °C, 5 h.

are reported. Mass spectra were recorded with PE Sciex model API 3000 instrument. HRMS spectra were with Waters LCT Premier XE (Micromass Oa-TOF) instrument. $^1$H NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ with either Varian Gemini 200 MHz or Varian Mercury Plus 400 MHz instruments. $^{13}$C NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ at 50 MHz with Varian Gemini 200 MHz instrument. Signals due to the solvent ($^{13}$C NMR) or residual protonated solvent ($^1$H NMR) served as the internal standard. The $^1$H NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants ($J$) corresponds to the order of the multiplicity assignment. Unless otherwise noted, all '$J$' refers to $^3J_{HH}$ coupling constant. All reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR.

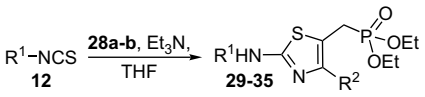
### 4.2. Di-*tert*-butyl prop-2-ynylimidodicarbonate (10a)

To a solution of propargylamine (5.0 g, 90.90 mmol) in acetonitrile (50 mL) was added di-*tert*-butyldicarbonate (49.6 g, 227.27 mmol) followed by DMAP (11.1 g, 90.90 mmol). The reaction mixture was stirred at room temperature for 16 h and then diluted with ethyl acetate (300 mL). The organic layer was washed successively with water and brine and dried over anhydrous $Na_2SO_4$. Concentration and purification over silica gel (100–200 mesh) using 10% ethyl acetate in petroleum ether as eluent afforded **10a** (22 g, 95% yield) as an oil. $R_f$=0.56 (10% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.35 (d, $J$=2.5 Hz, 2H), 2.18 (t, $J$=2.5 Hz, 1H), 1.53 (s, 18H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 151.0, 82.2, 79.1, 70.2, 35.2, 27.4; IR (neat): 2980, 1794, 1751, 1369, 1231, 1150 cm$^{-1}$; MS (ES): $m/z$ 256.1 (M+1); HRMS $m/z$ found 278.1380, calcd for $C_{13}H_{21}NO_4Na$ 278.1368.

### 4.3. Di-*tert*-butyl 5-phenylpent-1-yn-3-ylimidodicarbonate (10b)

Following a similar procedure as mentioned in **10a**, compound **10b** was obtained in 85% yield as an oil. $R_f$=0.62 (10% ethyl acetate

**Table 3**
Synthesis of thiazole derivatives




| Entry | Isothiocyanate | Amine | Product (% yield) |
|---|---|---|---|
| 1 | **12a** | **28a** | **29** (88) |
| 2 | **12f** | **28a** | **30** (66) |
| 3 | **12i** | **28a** | **31** (63) |
| 4 | **12l** | **28a** | **32** (70) |
| 5 | **12m** | **28a** | **33** (81) |
| 6 | **12a** | **28b** | **34** (82) |
| 7 | **12m** | **28b** | **35** (85) |

in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.31–7.27 (m, 2H), 7.21–7.17 (m, 3H), 4.84–4.80 (m, 1H), 3.33–3.32 (m, 1H), 2.67–2.55 (m, 2H), 2.22–2.06 (m, 2H), 1.44 (s, 18H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 151.9, 140.7, 128.3, 125.9, 82.8, 81.7, 71.7, 47.6, 35.8, 32.4, 27.9; IR (neat): 2980, 2934, 1746, 1705, 1369, 1140 cm$^{-1}$; MS (ES): $m/z$ 360.3 (M+1); HRMS $m/z$ found 398.1734, calcd for $C_{21}H_{29}NO_4K$ 398.1734.

### 4.4. Ethyl 4-(bis(*tert*-butoxycarbonyl)amino)but-2-ynoate (11a)

A solution of diisopropyl amine (6.6 mL, 47.06 mmol) in diethylether (20 mL) was cooled to −78 °C and to it was added $^n$BuLi (1.6 M in hexane, 18.8 mL, 47.06 mmol) drop wise and stirred at 0 °C for 1 h. Then the reaction mixture was cooled to −78 °C and a solution of **10a** (8.0 g, 31.37 mmol) in diethylether (80 mL) was added drop wise and continued stirring for additional 1 h. Then ethyl chloroformate (4.5 mL, 47.06 mmol) was added drop wise and stirred for 1 h at the same temperature. The reaction mixture was warmed up to −30 °C over a period of 3 h and then quenched by the addition of saturated sodium sulfate solution followed by water and stirred at room temperature for 30 min. The organic layer was separated, washed successively with water, brine and dried over anhydrous $Na_2SO_4$. Concentration and purification over silica gel (100–200 mesh) using 10% ethyl acetate in petroleum ether as eluent afforded **11a** (7.2 g, 70% yield) as an oil. $R_f$=0.52 (10% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.50 (s, 2H), 4.22 (q, $J$=7.0 Hz, 2H), 1.53 (s, 18H), 1.30 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 153.0, 151.0, 83.4, 74.4, 70.7, 61.8, 35.6, 27.9, 13.9; IR (neat): 2982, 2936, 2239, 1717, 1369, 1250, 1148 cm$^{-1}$; MS (ES): $m/z$ 350.1 (M+1); HRMS $m/z$ found 350.1580, calcd for $C_{16}H_{25}NO_6Na$ 350.1580.

### 4.5. Ethyl 4-(bis(*tert*-butoxycarbonyl)amino)-6-phenylhex-2-ynoate (11b)

Following a similar procedure as mentioned in **11a**, compound **11b** was obtained in 72% yield as an oil. $R_f$=0.57 (10% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.31–7.28 (m, 2H), 7.22–7.18 (m, 3H), 5.08 (t, $J$=7.8 Hz, 1H), 4.18 (q, $J$=7.2 Hz, 2H), 2.66–2.52 (m, 2H), 2.26–2.15 (m, 2H), 1.45 (s, 18H), 1.22 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 153.3, 151.4, 140.3, 128.5, 128.3, 126.2, 85.5, 83.4, 75.7, 61.9, 47.4, 35.4, 32.3, 28.0, 14.0; IR (neat): 2980, 2241, 1748, 1715, 1369, 1248, 1138 cm$^{-1}$; MS (ES): $m/z$ 432.3 (M+1); HRMS $m/z$ found 454.2265, calcd for $C_{24}H_{33}NO_6Na$ 454.2206.

### 4.6. Ethyl 4-aminobut-2-ynoate hydrochloride (8a)

To an ice-cooled ethereal HCl solution (40 mL) was added **11a** (4 g, 12.23 mmol) and stirred at room temperature for 1 h. Separated solid was filtered, washed with ether and dried under vacuum to afford **8a** (1.6 g, 80% yield) as an off white solid (highly hygroscopic). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.82 (br s, 3H), 4.22 (q, $J$=7.2 Hz, 2H), 3.98 (s, 2H), 1.23 (t, $J$=7.2 Hz, 3H); IR (neat): 3200–2800 (br), 2984, 2253, 1721, 1369, 1258, 748 cm$^{-1}$. MS (ES): $m/z$ 127.9; HRMS $m/z$ found 128.0711, calcd for $C_6H_{10}NO_2$ 128.0712.

### 4.7. Ethyl 4-amino-6-phenylhex-2-ynoate hydrochloride (8b)

Following a similar procedure as mentioned in **8a**, compound **8b** was obtained in 74% yield. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.95 (br s, 3H), 7.34–7.28 (m, 2H), 7.27–7.16 (m, 3H), 4.33–4.30 (m, 1H), 4.20 (q, $J$=7.1 Hz, 2H), 2.83–2.52 (m, 2H), 2.25–1.98 (m, 2H), 1.24 (t, $J$=7.1 Hz, 3H); IR (neat): 3200–2800, 2932, 1726, 1699, 1499, 1223, 1192 cm$^{-1}$. MS (ES): $m/z$ 232.3; HRMS $m/z$ found 232.1328, calcd for $C_{14}H_{18}NO_2$ 232.1338.

### 4.8. Di-*tert*-butyl 3-(diethoxyphosphoryl)prop-2-ynylimidodicarbonate (27a)

To a solution of diisopropyl amine (6.6 mL, 47.06 mmol) in diethylether (20 mL) was added $^n$BuLi (1.6 M in hexane, 18.8 mL, 47.06 mmol) drop wise at −78 °C. The reaction mixture was placed in an ice water bath and stirred at 0 °C for 1 h. Then the reaction mixture was cooled to −78 °C and a solution of **10a** (8.0 g, 31.37 mmol) in diethylether (80 mL) was added drop wise and continued stirring for additional 1 h. Then was added diethyl chlorophosphate (6.8 mL, 47.06 mmol) drop wise and continued stirring at −78 °C for 1 h. The reaction mixture was allowed to warm up to −30 °C over a period of 3 h and quenched with saturated sodium sulfate solution followed by water and stirred at room temperature for 30 min. The organic layer was separated, washed successively with water, brine and dried over anhydrous $Na_2SO_4$ and rotary evaporated. The residue was purified on silica gel (100–200 mesh) using 10% ethyl acetate in petroleum ether as eluent to afford **27a** (9.8 g, 80% yield) as an oil. $R_f$=0.48 (10% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.47 (d, $^4J_{HP}$=3.8 Hz, 2H), 4.07–4.03 (m, 4H), 1.46 (s, 18H), 1.26 (t, $J$=6.9 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 150.9, 96.5 (d, $^2J_{CP}$=50.7 Hz), 83.5, 74.3 (d, $^1J_{CP}$=294.8 Hz), 63.0 (d, $^2J_{CP}$=5.3 Hz), 35.9 (d, $^3J_{CP}$=4.2 Hz), 27.8, 15.9 (d, $^3J_{CP}$=7.9 Hz); IR (neat): 2982, 2214, 1755, 1728, 1369, 1261, 1148 cm$^{-1}$; MS (ES): $m/z$ 409.3 (M+1); HRMS $m/z$ found 414.1672, calcd for $C_{13}H_{14}N_2O_2SCl$ 414.1658.

### 4.9. Di-*tert*-butyl 1-(diethoxyphosphoryl)-5-phenylpent-1-yn-3-ylimidodicarbonate (27b)

Following a similar procedure as mentioned in **27a**, compound **27b** was obtained in 60% yield as an oil. $R_f$=0.58 (10% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.32–7.28 (m, 2H), 7.22–7.18 (m, 3H), 5.09–5.04 (m, 1H), 4.10–4.02 (m, 4H), 2.67–2.52 (m, 2H), 2.34–2.10 (m, 2H), 1.45 (s, 18H), 1.27 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 151.3, 140.1, 128.4, 128.2, 126.2, 98.5 (d, $^2J_{CP}$=50.7 Hz), 83.5, 80.0 (d, $^1J_{CP}$=293.3 Hz), 63.1 (d, $^2J_{CP}$=5.3 Hz), 47.6 (d, $^3J_{CP}$=4.2 Hz), 35.1, 32.2, 27.9, 16.0 (d, $^3J_{CP}$=7.2 Hz); IR (neat): 2982, 2208, 1746, 1709, 1369, 1263, 1140, 1026 cm$^{-1}$; MS (ES): $m/z$ 513.4 (M+1); HRMS $m/z$ found 518.2292, calcd for $C_{25}H_{38}NO_7NaP$ 518.2284.

### 4.10. Diethyl 3-aminoprop-1-ynylphosphonate hydrochloride (28a)

Following a similar procedure as mentioned in **8a**, **28a** was obtained in 90% yield. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.74 (br s, 3H), 4.18–3.90 (m, 6H), 1.29 (t, $J$=6.8 Hz, 6H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 93.9 (d, $^2J_{CP}$=50.0 Hz), 75.8 (d, $^1J_{CP}$=287.3 Hz), 63.2 (d, $^2J_{CP}$=5.7 Hz), 28.3 (d, $^3J_{CP}$=4.6 Hz), 15.9 (d, $^3J_{CP}$=7.2 Hz); IR (neat): 3418, 2984, 1620, 1396, 1240, 1022 cm$^{-1}$. MS (ES): $m/z$ 192.1; HRMS $m/z$ found 192.0781, calcd for $C_7H_{15}NO_3P$ 192.0790.

### 4.11. Diethyl 3-amino-5-phenylpent-1-ynylphosphonate hydrochloride (28b)

Following a similar procedure as mentioned in **8a**, **28b** was obtained in 80% yield. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.94 (br s, 3H), 7.35–7.31 (m, 2H), 7.25–7.21 (m, 3H), 4.31–4.17 (m, 1H), 4.16–4.12 (m, 4H), 2.82–2.68 (m, 2H), 2.22–2.11 (m, 1H), 2.10–2.04 (m, 1H), 1.31 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 139.8, 128.5, 128.1, 126.3, 95.5 (d, $^2J_{CP}$=48.4 Hz), 76.6 (d, $^1J_{CP}$=284.2 Hz), 63.3 (d, $^2J_{CP}$=5.7 Hz), 41.5 (d, $^3J_{CP}$=4.2 Hz), 33.6, 30.8, 15.9 (d, $^3J_{CP}$=6.8 Hz); IR

(neat): 3399, 3026–2629 (br), 2214, 1722, 1603, 1371, 1240, 1022 $cm^{-1}$. MS (ES): *m*/*z* 296.1; HRMS *m*/*z* found 296.1407, calcd for $C_{15}H_{23}NO_3P$ 296.1416.

### 4.12. General procedure for thiazole formation

The isothiocyanate (1.0 mmol) was dissolved in THF (0.2 M) under an inert atmosphere. To the solution at room temperature was added amine salt (1.5 equiv) followed by $Et_3N$ (3.0 equiv). The reaction mixture was stirred for 12 h (24 h, for the phosphonate derivatives) and by this time, both starting material and the intermediate thiourea were disappeared, as checked by TLC. The reaction mixture was diluted with ethyl acetate and the organic layer was successively washed with water and brine and dried ($Na_2SO_4$). Concentration and chromatographic purification afforded the desired thiazole derivatives.

### 4.13. Ethyl 2-(2-(4-chlorophenylamino)thiazol-5-yl)-acetate (13)

$R_f$=0.62 (40% ethyl acetate in petroleum ether); mp 111–113 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.20 (br s, 1H), 7.63 (d, *J*=8.8 Hz, 2H), 7.32 (d, *J*=8.8 Hz, 2H), 7.07 (s, 1H), 4.12 (q, *J*=7.1 Hz, 2H), 3.80 (s, 2H), 1.20 (t, *J*=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.0, 163.1, 140.0, 137.3, 128.6, 124.1, 118.9, 118.1, 60.6, 31.9, 14.0; IR (KBr): 3446–2771 (br), 3246, 3190, 2980, 1736, 1614, 1495, 1186, 1165 $cm^{-1}$; MS (ES): *m*/*z* 296.7 (M+1); HRMS *m*/*z* found 297.0449, calcd for $C_{13}H_{14}N_2O_2SCl$ 297.0465.

### 4.14. Ethyl 2-(2-(4-chloro-2-(trifluoromethyl)phenyl-amino)thiazol-5-yl)acetate (14)

$R_f$=0.70 (40% ethyl acetate in petroleum ether); mp 68–70 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.56 (br s, 1H), 8.23 (d, *J*=2.9 Hz, 1H), 7.82 (dd, *J*=2.7 & 9.0 Hz, 1H), 7.60 (d, *J*=8.8 Hz, 1H), 7.14 (s, 1H), 4.12 (q, *J*=7.1 Hz, 2H), 3.83 (d, $^4J_{HH}$=1.0 Hz, 2H), 1.21 (t, *J*=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 169.9, 162.6, 140.3, 137.4, 131.9, 125.9 (q, $^1J_{CF}$=30.5 Hz), 121.2, 119.8, 115.0, 114.9, 60.6, 31.8, 13.9; IR (KBr): 3248, 2920, 1734, 1570, 1337, 1180, 1134, 1028 $cm^{-1}$; MS (ES): *m*/*z* 364.9 (M+1); HRMS *m*/*z* found 365.0344, calcd for $C_{14}H_{13}N_2O_2F_3SCl$ 365.0338.

### 4.15. *tert*-Butyl 4-(5-(2-ethoxy-2-oxoethyl)thiazol-2-ylamino)benzoate (15)

$R_f$=0.52 (40% ethyl acetate in petroleum ether); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 10.49 (br s, 1H), 7.83 (d, *J*=8.9 Hz, 2H), 7.68 (d, 8.9 Hz, 2H), 7.13 (s, 1H), 4.11 (q, *J*=7.1 Hz, 2H), 3.84 (s, 2H), 1.53 (s, 9H), 1.20 (t, *J*=7.1 Hz, 3H); IR (neat): 3329, 2978, 1738, 1705, 1605, 1292, 1159, 1115 $cm^{-1}$; MS (ES): *m*/*z* 363.2 (M+1).

### 4.16. Ethyl 2-(2-(4-(trifluoromethoxy)phenylamino)thiazol-5-yl)acetate (16)

$R_f$=0.64 (40% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.26 (br s, 1H), 7.70 (d, *J*=9.0 Hz, 2H), 7.28 (d, *J*=9.0 Hz, 2H), 7.07 (s, 1H), 4.11 (q, *J*=7.1 Hz, 2H), 3.81 (s, 2H), 1.21 (t, *J*=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.0, 163.2, 141.7, 141.7, 140.3, 137.3, 121.7, 119.0, 117.7, 60.6, 31.9, 14.0; IR (neat): 3244, 3206, 2957, 1740, 1225, 1667 $cm^{-1}$; MS (ES): *m*/*z* 347 (M+1); HRMS *m*/*z* found 347.0674, calcd for $C_{14}H_{14}N_2O_3F_3S$ 347.0677.

### 4.17. Ethyl 2-(2-(biphenyl-4-ylamino)thiazol-5-yl)acetate (17)

$R_f$=0.55 (40% ethyl acetate in petroleum ether); mp 146–148 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.18 (br s, 1H), 7.69 (d, *J*=8.6 Hz, 2H), 7.64–7.60 (m, 4H), 7.45–7.41 (m, 2H), 7.32–7.30 (m, H), 7.08 (s, 1H), 4.12 (q, *J*=7.1 Hz, 2H), 3.81 (s, 2H), 1.21 (t, *J*=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.1, 163.4, 140.7, 139.9, 137.5, 132.6, 128.8, 127.0, 126.6, 125.9, 118.6, 117.1, 60.6, 31.9, 14.0; IR (KBr): 3300–2600 (br), 3244, 2940, 1740, 1609, 1558, 1456, 1439, 1161 $cm^{-1}$; MS (ES): *m*/*z* 339 (M+1); HRMS *m*/*z* found 339.1174, calcd for $C_{19}H_{19}N_2O_2S$ 339.1167.

### 4.18. Ethyl 2-(2-(benzylamino)thiazol-5-yl)acetate (18)

$R_f$=0.48 (40% ethyl acetate in petroleum ether); mp 86–88 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.93 (t, *J*=5.9 Hz, 1H), 7.34–7.29 (m, 4H), 7.27–7.21 (m, 1H), 6.80 (s, 1H), 4.40 (d, *J*=5.9 Hz, 2H), 4.07 (q, *J*=7.0 Hz, 2H), 3.66 (s, 2H), 1.18 (t, *J*=7.0 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.2, 168.7, 139.2, 137.2, 128.1, 127.3, 126.7, 116.2, 60.4, 47.4, 32.1, 14.0; IR (KBr): 3180, 2984, 1738, 1578, 1173, 1208 $cm^{-1}$; MS (ES): *m*/*z* 276.7 (M+1); HRMS *m*/*z* found 277.1016, calcd for $C14H_{17}N_2O_2S$ 277.1011.

### 4.19. Ethyl 2-(2-(4-chlorophenethylamino)thiazol-5-yl)acetate (19)

$R_f$=0.12 (40% ethyl acetate in petroleum ether); mp 88–90 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.28 (d, *J*=8.5 Hz, 2H), 7.15 (d, *J*=8.5 Hz, 2H), 6.90 (t, $^4J_{HH}$=1.1 Hz, 1H), 4.95 (br s, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.65 (d, $^4J_{HH}$=1.1 Hz, 2H), 3.55–3.48 (m, 2H), 2.92 (t, *J*=7.0 Hz, 2H), 1.28 (t, *J*=7.1 Hz, 3H); IR (KBr): 3204, 2994, 1746, 1557, 1146 $cm^{-1}$; MS (ES): *m*/*z* 325.1 (M+1).

### 4.20. Ethyl 2-(2-((2-(4-chlorophenyl)-5-methyloxazol-4-yl)methylamino)thiazol-5-yl)acetate (20)

$R_f$=0.24 (40% ethyl acetate in petroleum ether); mp 146–148 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.91 (d, *J*=8.8 Hz, 2H), 7.83 (t, *J*=5.4 Hz, 1H), 7.57 (d, *J*=8.8 Hz, 2H), 6.83 (s, 1H), 4.28 (d, *J*=5.4 Hz, 2H), 4.07 (q, *J*=7.0 Hz, 2H), 3.67 (s, 2H), 2.41 (s, 3H), 1.18 (t, *J*=7.0 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.1, 168.1, 157.4, 145.9, 137.1, 134.7, 133.4, 129.1, 127.1, 125.7, 116.4, 60.4, 38.2, 32.1, 14.0, 10.1; IR (KBr): 3165.2, 2974, 1738, 1570, 1369, 1184, 1092 $cm^{-1}$ MS (ES): *m*/*z* 392.0 (M+1); HRMS *m*/*z* found 392.0835, calcd for $C_{18}H_{19}N_3O_3SCl$ 392.0836.

### 4.21. Ethyl 2-(2-(isopropylamino)thiazol-5-yl)acetate (21)

$R_f$=0.45 (40% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.27 (d, *J*=7.3 Hz, 1H), 6.78 (s, 1H), 4.11 (q, *J*=7.0 Hz, 2H), 3.76–3.68 (m, 1H), 3.65 (s, 2H), 1.19 (t, *J*=7.0 Hz, 3H), 1.14 (d, *J*=6.3 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.1, 168.0, 137.3, 115.4, 60.4, 45.8, 32.2, 22.3, 14.0; IR (neat): 3369.6, 2972, 1736, 1537, 1171 $cm^{-1}$; MS (ES): *m*/*z* 229 (M+1); HRMS *m*/*z* found 229.1006, calcd for $C_{10}H_{17}N_2O_2S$ 229.1011.

### 4.22. Ethyl 2-(2-(3-hydroxypropylamino)thiazol-5-yl)-acetate (22)

$R_f$=0.23 (60% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.37 (t, *J*=5.3 Hz, 1H), 6.79 (s, 1H), 4.55–4.44 (br s, 1H), 4.08 (q, *J*=7.1 Hz, 2H), 3.66 (d, $^4J_{HH}$=0.9 Hz, 2H), 3.45 (t, *J*=6.3 Hz, 2H), 3.24–3.19 (m, 2H), 1.70–1.64 (m, 2H), 1.19 (t, *J*=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.8, 170.5, 136.6, 116.4, 61.2, 59.3, 42.4, 32.8, 32.1, 14.0; IR (neat): 3291, 1732, 1545, 1369, 1153 $cm^{-1}$; MS (ES): *m*/*z* 245.5 (M+1). HRMS *m*/*z* found 245.0958, calcd for $C_{10}H_{17}N_2O_3S$ 245.0960.

### 4.23. Ethyl 2-(2-(cyclohexylamino)thiazol-5-yl)acetate (23)

$R_f$=0.42 (40% ethyl acetate in petroleum ether); mp 103–104 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.32 (d, $J$=7.3 Hz, 1H), 6.76 (s, 1H), 4.08 (q, $J$=7.9 Hz, 2H), 3.64 (d, $^4J_{HH}$=1.0 Hz, 2H), 3.42–3.38 (m, 1H), 1.92–1.89 (m, 2H), 1.71–1.67 (m, 2H), 1.57–1.54 (m, 2H), 1.19 (t, $J$=7.9 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.2, 167.9, 137.1, 115.3, 60.4, 52.9, 32.3, 32.1, 25.3, 24.4, 14.0; IR (neat): 3370, 3200, 2930, 1736, 1529, 1177, 1161, 1130 cm$^{-1}$; MS (ES): $m/z$ 269.8 (M+1); HRMS $m/z$ found 269.1331, calcd for $C_{13}H_{21}N_2O_2S$ 269.1324.

### 4.24. Ethyl 2-(2-(pyridin-3-ylamino)thiazol-5-yl)acetate (24)

$R_f$=0.12 (40% ethyl acetate in petroleum ether); mp 131–132 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.30 (br s, 1H), 8.72 (d, $J$=2.0 Hz, 1H), 8.16–8.13 (m, 2H), 7.33–7.29 (m, 1H), 7.10 (s, 1H), 4.12 (q, $J$=7.1 Hz, 2H), 3.82 (s, 2H), 1.18 (t, $J$=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.0, 163.0, 141.6, 138.6, 137.8, 137.4, 123.6, 123.1, 119.4, 60.6, 31.9, 14.0; IR (neat): 3277, 3200, 2992, 2745, 1732, 1541, 1518, 1429, 1180 cm$^{-1}$; MS (ES): $m/z$ 263.7 (M+1); HRMS $m/z$ found 264.0796, calcd for $C_{12}H_{14}N_3O_2S$ 264.0807.

### 4.25. Ethyl 2-(2-(4-chlorophenylamino)-4-phenethylthiazol-5-yl)acetate (25)

$R_f$=0.63 (30% ethyl acetate in petroleum ether); mp 186–188 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.44 (br s, 1H), 7.56 (d, $J$=7.9 Hz, 2H), 7.29 (d, $J$=7.9 Hz, 2H), 7.27–7.18 (m, 5H), 3.86 (q, $J$=7.1 Hz, 2H), 3.34 (s, 2H), 2.87–2.83 (m, 2H), 2.75–2.71 (m, 2H), 1.00 (t, $J$=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 168.5, 161.0, 140.1, 135.4, 134.1, 130.0, 129.7, 128.5, 128.4, 127.1, 126.4, 120.2, 61.4, 35.3, 29.4, 26.3, 14.0; IR (KBr): 3335, 2907, 1707, 1493, 1474, 1368, 1215, 700 cm$^{-1}$; MS (ES): $m/z$ 401.2 (M+1); HRMS $m/z$ found 401.1096, calcd for $C_{21}H_{22}N_2O_2SCl$ 401.1091.

### 4.26. Methyl 4-(5-(2-ethoxy-2-oxoethyl)-4-phenethylthiazol-2-ylamino)benzoate (26)

$R_f$=0.60 (40% ethyl acetate in petroleum ether); mp 160–162 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.49 (br s, 1H), 8.05 (d, $J$=8.6 Hz, 2H), 7.39 (d, $J$=8.6 Hz, 2H), 7.32–7.29 (m, 2H), 7.24–7.19 (m, 2H), 3.89 (s, 3H), 3.83 (q, $J$=7.1 Hz, 2H), 3.36 (s, 2H), 2.87–2.84 (m, 2H), 2.76–2.72 (m, 2H), 0.96 (t, $J$=7.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 168.5, 166.0, 160.9, 140.1, 139.6, 130.9, 130.7, 128.8, 128.5, 128.4, 127.4, 126.4, 120.0, 61.4, 52.4, 35.3, 29.4, 26.3, 14.0; IR (KBr): 3067, 2934, 1724, 1479, 1288, 1182 cm$^{-1}$; MS (ES): $m/z$ 425.2 (M+1); HRMS $m/z$ found 425.1531, calcd for $C_{23}H_{25}N_2O_4S$ 425.1535.

### 4.27. Diethyl (2-(4-chlorophenylamino)thiazol-5-yl)-methylphosphonate (29)

$R_f$=0.14 (60% ethyl acetate in petroleum ether); mp 177–179 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.22 (br s, 1H), 7.61 (d, $J$=9.2 Hz, 2H), 7.34 (d, $J$=9.2 Hz, 2H), 7.07 (d, $^4J_{HP}$=4.3 Hz, 1H), 4.07–4.02 (m, 4H), 3.38 (dd, $^4J_{HH}$=0.8 Hz, $^2J_{HP}$=20.0 Hz, 2H), 1.24 (t, $J$=7.1 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 164.5 (d, $^4J_{CP}$=1.9 Hz), 139.2, 137.7 (d, $^3J_{CP}$=11.0 Hz), 129.2, 127.2, 119.1, 115.7 (d, $^2J_{CP}$=11.0 Hz), 62.6 (d, $^2J_{CP}$=6.4 Hz), 25.3 (d, $^1J_{CP}$=145.3 Hz), 16.4 (d, $^3J_{CP}$=5.7 Hz); IR (KBr): 3265, 3101, 3069, 1612, 1541, 1522, 1242, 1034 cm$^{-1}$; MS (ES): $m/z$ 361.0 (M+1); HRMS $m/z$ found 361.0560, calcd for $C_{14}H_{19}N_2O_3PSCl$ 361.0543.

### 4.28. Diethyl (2-(benzylamino)thiazol-5-yl)-methylphosphonate (30)

$R_f$=0.42 (40% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.90 (t, $J$=5.8 Hz, 1H), 7.34–7.26 (m, 3H), 7.25–7.21 (m, 2H), 6.78 (d, $^4J_{HP}$=4.6 Hz, 1H), 4.39 (d, $J$=5.9 Hz, 2H), 4.00–3.93 (m, 4H), 3.21 (dd, $^4J_{HH}$=0.9, $^2J_{HP}$=20.0 Hz, 2H), 1.19 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.2, 139.1, 137.4 (d, $^3J_{CP}$=3.8 Hz), 128.5, 127.5, 127.4, 113.7 (d, $^2J_{CP}$=11.0 Hz), 62.3 (d, $^2J_{CP}$=6.5 Hz), 49.6, 25.1 (d, $^1J_{CP}$=145.3 Hz), 16.3 (d, $^3J_{CP}$=6.1 Hz); IR (neat): 3267, 2981, 2930, 1667, 1537, 1236, 1024 cm$^{-1}$; MS (ES): $m/z$ 341.2 (M+1); HRMS $m/z$ found 341.1075, calcd for $C_{15}H_{22}N_2O_3PS$ 341.1089.

### 4.29. Diethyl (2-(isopropylamino)thiazol-5-yl)-methylphosphonate (31)

$R_f$=0.40 (40% ethyl acetate in petroleum ether); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.24 (d, $J$=7.3 Hz, 1H), 6.77 (d, $^4J_{HP}$=4.3 Hz, 1H), 4.02–3.95 (m, 4H), 3.74–3.69 (m, 1H), 3.21 (d, $^2J_{HP}$=20.0 Hz, H), 1.21 (t, $J$=7.1 Hz, 6H), 1.14 (d, $J$=6.5 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 169.6, 136.9 (d, $^2J_{CP}$=11.0 Hz), 113.2 (d, $^2J_{CP}$=11.0 Hz), 62.3 (d, $^2J_{CP}$=6.8 Hz), 47.9, 25.2 (d, $^1J_{CP}$=145.3 Hz), 22.6, 16.3 (d, $^3J_{CP}$=5.7 Hz); IR (neat): 3266, 2967, 2932, 2874, 1726, 1531, 1261, 1026 cm$^{-1}$; HRMS $m/z$ found 293.1088, calcd for $C_{11}H_{22}N_2O_3PS$ 293.1089.

### 4.30. Diethyl (2-(pyridin-3-ylamino)thiazol-5-yl)-methylphosphonate (32)

$R_f$=0.15 (80% ethyl acetate in petroleum ether); mp 120–122 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.30 (br s, 1H), 8.73 (d, $J$=2.2 Hz, 1H), 8.16–8.13 (m, 2H), 7.34–7.31 (m, 1H), 7.08 (d, $^4J_{HP}$=4.3 Hz, 1H), 4.05–3.98 (m, 4H), 3.37 (d, $^2J_{HP}$=20.1 Hz, 2H), 1.23 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 164.1 (d, $^4J_{CP}$=1.9 Hz), 142.0, 139.1, 138.1, 137.9 (d, $^3J_{CP}$=11.4 Hz), 124.3, 123.8, 116.2 (d, $^2J_{CP}$=11.3 Hz), 62.7 (d, $^2J_{CP}$=7.2 Hz), 25.2 (d, $^1J_{CP}$=145.4 Hz), 16.3 (d, $^3J_{CP}$=5.7 Hz); IR (KBr): 3252, 3181, 3053, 3015, 2988, 2903, 1614, 1543, 1522, 1422, 1223, 1024 cm$^{-1}$; MS (ES): $m/z$ 328.1 (M+1); HRMS $m/z$ found 328.0883, calcd for $C_{13}H_{19}N_3O_3SP$ 328.0885.

### 4.31. Methyl 4-(5-((diethoxyphosphoryl)methyl)thiazol-2-ylamino)benzoate (33)

$R_f$=0.44 (60% ethyl acetate in petroleum ether); mp 177–179 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.51 (br s, 1H), 7.89 (d, $J$=8.9 Hz, 2H), 7.70 (d, $J$=8.9 Hz, 2H), 7.13 (d, $^4J_{HP}$=4.3 Hz, 1H), 4.05–3.98 (m, 4H), 3.81 (s, 3H), 3.39 (dd, $^4J_{HH}$=0.8 Hz, $^2J_{HP}$=20.0 Hz, 2H), 1.23 (t, $J$=7.1 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 166.8, 163.7 (d, $^4J_{CP}$=2.3 Hz), 144.8, 137.8 (d, $^3J_{CP}$=11.0 Hz), 131.1, 122.8, 116.5 (d, $^2J_{CP}$=11.0 Hz), 116.0, 62.7 (d, $^2J_{CP}$=6.8 Hz), 51.8, 25.2 (d, $^1J_{CP}$=145.3 Hz), 16.3 (d, $^3J_{CP}$=5.7 Hz); IR (KBr): 3267, 3069, 1715, 1607, 1518, 1283, 1229 cm$^{-1}$; MS (ES): $m/z$ 385.3 (M+1); HRMS $m/z$ found 385.0968, calcd for $C_{16}H_{22}N_2O_5PS$ 385.0987.

### 4.32. Diethyl (2-(4-chlorophenylamino)-4-phenethylthiazol-5-yl)methylphosphonate (34)

$R_f$=0.18 (60% ethyl acetate in petroleum ether); mp 88–90 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.12 (br s, 1H), 7.60 (d, $J$=9.0 Hz, 2H), 7.32 (d, $J$=9.0 Hz, 2H), 7.30–7.23 (m, 4H), 7.20–7.16 (m, 1H), 4.02–3.94 (m, 4H), 3.15 (d, $^2J_{HP}$=20.1 Hz, 2H), 2.95–2.91 (m, 2H), 2.82–2.78 (m, 2H), 1.20 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 162.2, 149.3 (d, $^4J_{CP}$=11.3 Hz), 141.6, 139.3, 129.1, 128.4, 128.3, 127.0, 125.9, 119.0, 109.2 (d, $^2J_{CP}$=11.4 Hz), 62.5 (d, $^2J_{CP}$=6.8 Hz), 35.4 (d, $^4J_{CP}$=2.6 Hz), 31.1, 24.3 (d, $^1J_{CP}$=145.3 Hz), 16.4 (d, $^3J_{CP}$=5.7 Hz); IR

(KBr): 3264, 3067, 1616, 1531, 1491, 1314, 1229 $cm^{-1}$; MS (ES): *m*/*z* 465.1 (M+1); HRMS *m*/*z* found 465.1164, calcd for $C_{22}H_{27}N_2O_3PSCl$ 465.1169.

### 4.33. Methyl 4-(5-((diethoxyphosphoryl)methyl)-4-phenethylthiazol-2-ylamino)benzoate (35)

$R_f$=0.50 (50% ethyl acetate in petroleum ether); mp 168–170 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.45 (br s, 1H), 7.89 (d, $J$=9.0 Hz, 2H), 7.68 (d, $J$=9.0 Hz, 2H), 7.30–7.24 (m, 4H), 7.20–7.16 (m, 1H), 3.99 (dq, $^3J_{HH}$=7.0 Hz, $^3J_{HP}$=14.0 Hz, 4H), 3.81 (s, 3H), 3.19 (d, $^2J_{HP}$=20.0 Hz, 2H), 2.97–2.94 (m, 2H), 2.86–2.82 (m, 2H), 1.21 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 166.8, 161.0 (d, $^3J_{CP}$=2.2 Hz), 149.4 (d, $^4J_{CP}$=11.3 Hz), 145.1, 141.5, 130.9, 128.3, 128.2, 125.8, 122.2, 115.9, 109.7 (d, $^2J_{CP}$=11.7 Hz), 62.5 (d, $^2J_{CP}$=7.2 Hz), 51.7, 35.2 (d, $^4J_{CP}$=2.3 Hz), 31.0, 24.1 (d, $^1J_{CP}$=145.3 Hz), 16.3 (d, $^3J_{CP}$=5.7 Hz); IR (KBr): 3264, 3075, 1715, 1605, 1524, 1433, 1281, 1254, 1175, 1028 $cm^{-1}$; MS (ES): *m*/*z* 489.3 (M+1); HRMS *m*/*z* found 489.1618, calcd for $C_{24}H_{30}N_2O_5PS$ 489.1613.


## Acknowledgements

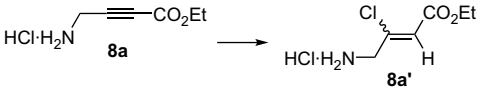
We thank Dr. Reddy's Laboratories Ltd. for the support and encouragement. Help from the analytical department in the form of spectral data is also appreciated.


## Supplementary data

$^1$H NMR and $^{13}$C NMR spectra of compounds **13**, **20**, **22**, **25**, **26**, **28b**, **32**, **33**, **34** and **35** are available as Supplementary data (20 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.074.

## References and notes


1. Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, NY, 1984; Vol. 6, pp 235–332.
2. Miwatashi, S.; Arikawa, Y.; Kotani, E.; Miyamoto, M.; Naruo, K.-I.; Kimura, H.; Tanaka, T.; Asahi, S.; Ohkawa, S. *J. Med. Chem.* **2005**, *48*, 5966.
3. Papadopoulou, C.; Geronikaki, A.; Hadjipavlou-Litina, D. *IL Farmaco* **2005**, *60*, 969 and references cited therein.
4. Kumar, Y.; Green, R.; Borysko, K. Z.; Wise, D. S.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem.* **1993**, *36*, 3843.
5. Ei-Subbagh, H. I.; Al-Obaid, A. M. *Eur. J. Med. Chem.* **1996**, *31*, 1017.
6. Pereira, R.; Gaudon, C.; Iglesias, B.; Germain, P.; Gronemeyer, H.; de Lera, A. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 49.
7. Tsuruni, Y.; Ueda, H.; Hayashi, K.; Takase, S.; Nishikawa, M.; Kiyoto, S.; Okuhara, M. *J. Antibiot.* **1995**, *48*, 1066.
8. Wang, W.-L.; Yao, D.-Y.; Gu, M.; Fan, M.-Z.; Li, J.-Y.; Xing, Y.-C.; Nan, F.-J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5284.
9. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.
10. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. J. J.; Connoly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batly, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562.
11. Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719.
12. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.
13. Nettekoven, M.; Guba, W.; Neidhart, W.; Mattei, P.; Pflieger, P.; Roche, O.; Taylor, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1409.
14. Mortlock, A. PCT Int. Appl. 2004, WO2004058752.
15. Nilsson, C.; Dreifeldt, C. PCT Int. Appl. 2004, WO2004112782.
16. Hantzsch, A.; Weber, J. H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118.
17. Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473.
18. Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193.
19. Ochiai, M.; Nishi, Y.; Hashimoto, S.; Tsuchimoto, Y.; Chen, D.-W. *J. Org. Chem.* **2003**, *68*, 7887 and references cited therein.
20. Baily, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409.
21. Kearney, P. C.; Fernandez, M. *J. Org. Chem.* **1998**, *63*, 196.
22. Rudolp, J. *Tetrahedron* **2000**, *56*, 3161.
23. Schantl, J. G.; Lagoja, I. M. *Synth. Commun.* **1998**, *28*, 1451.
24. Kodomari, M.; Aoyama, T.; Suzuki, Y. *Tetrahedron Lett.* **2002**, *43*, 1717.
25. Sasmal, P. K.; Sridhar, S.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 8661.
26. Corriu, R. J. P.; Bolin, G.; Iqbal, J.; Moreau, J. J. E.; Vernhel, C. *Tetrahedron* **1993**, *49*, 4603.
27. Katritzky, A. R.; Ledoux, S.; Witek, R. M.; Nair, S. K. *J. Org. Chem.* **2004**, *69*, 2976.
28. Maclnnes, I.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1077.
29. This observation was also reported by Katritzky's group; see Ref. 27.
30. Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593.
31. In DMSO-$d_6$ solution of **8a**, the appearance of $^1$H NMR signal at $\delta$ 6.65 and 3.90 and $^{13}$C NMR signal at $\delta$ 120.2 (=CH) indicated that most probably **8a** partially and predominantly converted to **8a′**. This conversion took place slowly in dilute solution whereas increased with time and concentration. In DMSO-$d_6$ (0.01 M concentration), **8a/8a′** after 5 min, 10.6:1; after 5 h, 3.3:1; after 1 day, 2.9:1 and after 7 days, 1.5:1. When the concentration was 0.1 M in DMSO-$d_6$, **8a/8a′** was 1.8:1 after 5 min.




32. Isothiocyanates are either commercially available or were prepared from the corresponding amines by the treatment of thiophosgene in dichloromethane in the presence of pyridine.
33. Westphal, G.; Wasicki, H. *Z. Chem.* **1968**, *8*, 337.
34. Sawhney, S. N.; Dhindsa, G. S.; Singh, S. P. *Indian J. Chem., Sect. B* **1983**, *22*, 1044.
35. Reddy, G. J.; Rao, K. S.; Jayaveera, K. N.; Sailaja, S.; Reddanna, P.; Reddy, D. B. *Indian J. Chem., Sect. B* **2006**, *45*, 2143.
36. Unlike their ester counter parts **8a** and **8b**, the solution stability of phosphonate salts **28a** and **28b** were longer enough to record their both $^1$H and $^{13}$C NMR spectra.
37. The synthesis of diisopropyl(2-amino-4-methylthiazol-5-yl)methylphosphonate was reported, see: Penz, G.; Zbiral, E. *Chem. Ber.* **1985**, *118*, 4131.