Tetrahedron 66 (2010) 5707–5713

Contents lists available at ScienceDirect

Tetrahedron

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

Intermolecular alkyl/aryl exchange of 2-iminothiazoles with isothiocyanates and isocyanates: scopes and limitations

Dongyun Shin *, Jihoon Lee, Hoh-Gyu Hahn

Life/Health Division, Korea Institute of Science and Technology, 39-1 Hawolgok-dong, Seongbuk-gu, Seoul 136-791, Republic of Korea

ARTICLE INFO

Article history:
Received 19 March 2010
Received in revised form 3 May 2010
Accepted 4 May 2010
Available online 10 May 2010

Keywords:
Synthesis
Medicinal
Iminothiazole
Thiazole
Isothiocyanate
Isocyanate

ABSTRACT

2-Iminothiazole, an isoform of 2-aminothiazole, is a scaffold of synthetic and medicinal significance. We have reported an efficient method by which alkyl group of 2-alkyliminothiazoles is changed into other alkyl groups by isothiocyanates. In this article, a detailed mechanistic aspect, and the scopes and limitations were disclosed. All the reactions were carried out in toluene at 105 °C without any additive. The reaction is a reversible process and the equilibrium is determined by the reactivity of both reactants, in which the more electron-withdrawing alkyl or aryl groups at the 2-imino group or isothiocyanate showed higher reactivities. With this simple method, we effectively altered the alkyl group attached on the imine nitrogen. A synthetic problem in 2-iminothiazole chemistry, synthesis of amino acid-derived 2-iminothiazole was solved in a very simple manner. Using suitably designed 2-iminothiazole substrate, the electrophilic reactivity of various isothiocyanates could be empirically compared by this exchange reaction. Moreover, successful exchange reaction using isocyanates instead of isothiocyanates broadened the utility of this reaction.

1. Introduction

Five-membered heterocycles are not only found in numerous natural products, but also are widely used as valuable scaffolds in medicinal chemistry and combinatorial chemistry.[1] Among them, 2-iminothiazole (**1**), isoform of 2-aminothiazole, is considered to be the privileged structures for the drug discovery due to its inherent low toxicities and good pharmacokinetic profiles, and their chemical diversity in substituents makes them very frequently utilized as a core scaffold in the construction of chemical library as well (Fig. 1).[2,3]

2-Iminothiazole is generally prepared by the single step reaction of thioureas and α-halocarbonyls, where thioureas should be disubstituted at both of the nitrogens. Unless substituents at the two nitrogen are identical, there are two possible regiomers. The general tendency of regiochemistry in the synthesis of 2-iminothiazole is that the smaller substituent positions at the 3-nitrogen and the bulkier one at the 2-imino nitrogen under neutral conditions, though acidity of reaction solvent can lead to the regiomeric mixtures.[4,5]

Recently, novel finding of the aryl/alkyl exchange reaction between 2-iminothiazole and isothiocyanate was reported by us, which describes that alkyl or aryl group at the 2-imino nitrogen of 2-iminothiazole is exchanged with R_2 in the isothiocyanate under thermal condition (Fig. 2).[6] Herein, we would present the scope and limitation of our novel finding on this exchange. With this new exchange reaction, a synthetic problem in 2-iminothiazole chemistry, synthesis of amino acid-derived 2-iminothiazole was solved in simple manner. Successful exchange reaction using isocyanates instead of isothiocyanate is also addressed.

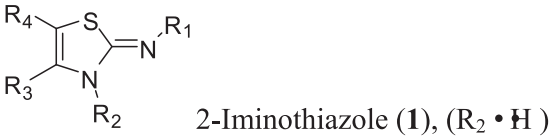


Figure 1. Structure of 2-iminothiazole.

Figure 2. Intermolecular alkyl/aryl exchange of 2-Iminothiazoles with Isothiocyanates.

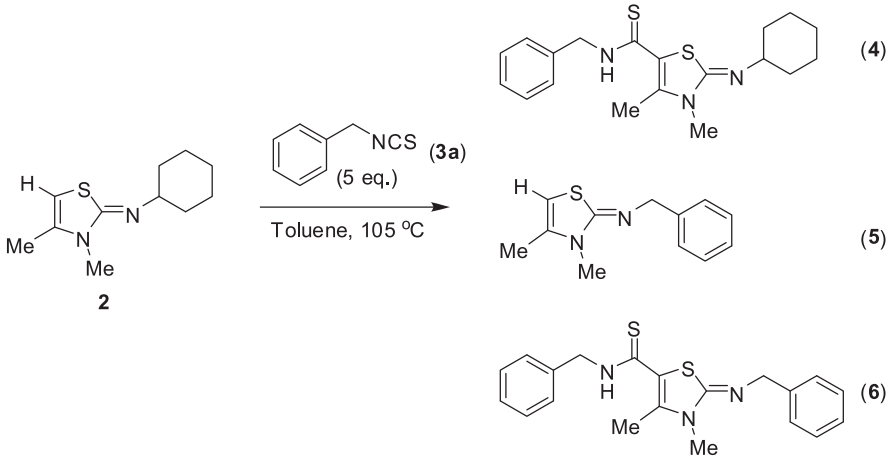
* Corresponding author. Tel.: +82 958 5143; fax: +82 958 5189; e-mail address: dyshin21@kist.re.kr (D. Shin).

0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.05.015

2. Results and discussion

2.1. Initial observation of novel exchange reaction

Initially, we focused our efforts on the expansion of our 2-iminothiazole chemistry to functionalize the 5-position in 2-iminothiazole. We assumed that the 5-position in 2-iminothiazole might be chemically activated due to its characteristics of an enamine. Therefore, we envisioned that 5-position could be alkylated by electrophiles with suitable reactivities. With structural features in mind, testing material, 2-cyclohexylimino-3,4-dimethylthizoline (**2**), was readily prepared by the condensation of 1-chloroacetone and 2-*N*-cyclohexyl-3-*N*′-methylthiourea, which was subjected to thiocarbamoylation with benzylisothiocyanate (**3a**) in toluene at 105 °C. Through this experiment, we could isolate one major and two minor products, along with a small amount of substrate. By ^{1}H NMR spectrum analysis and other spectra data, their structures were able to be characterized, as shown in Scheme 1. One minor compound proved to be the expected 2-iminothiazole **4**, which was the electrophilically substituted one at 5-carbon in 2-iminothiazole by one molecule of isothiocyanate. However, the major product was the completely unexpected 2-benzyliminothiazole **5**, in which the cyclohexyl group was substituted with the benzyl group, which is originated from benzylisothiocyanate (**3a**). Another minor product was 2-benzyliminothiazole **6**, which underwent additional electrophilic substitution at C-5 after a substitution of cyclohexyl with benzyl at 2-imino position. From those results, in accordance with our expectation, 5-carbon of 2-iminothiazole showed moderate reactivity toward isothiocyanate to afford 5-substituted 2-iminothiazole (**2**→**4**). More importantly, a new alkyl exchange reaction between 2-alkyliminothiazole and alkylisothiocyanate (**3**→**5**) was found, where the 2-nitrogen of 2-iminothiazole exhibited unforeseen nucleophilicity toward the isothiocyanate electrophile.



Scheme 1. The reaction of alkyliminothiazoles with Benzylisothiocyanate.

2.2. Possible mechanism of isothiocyanate transposition

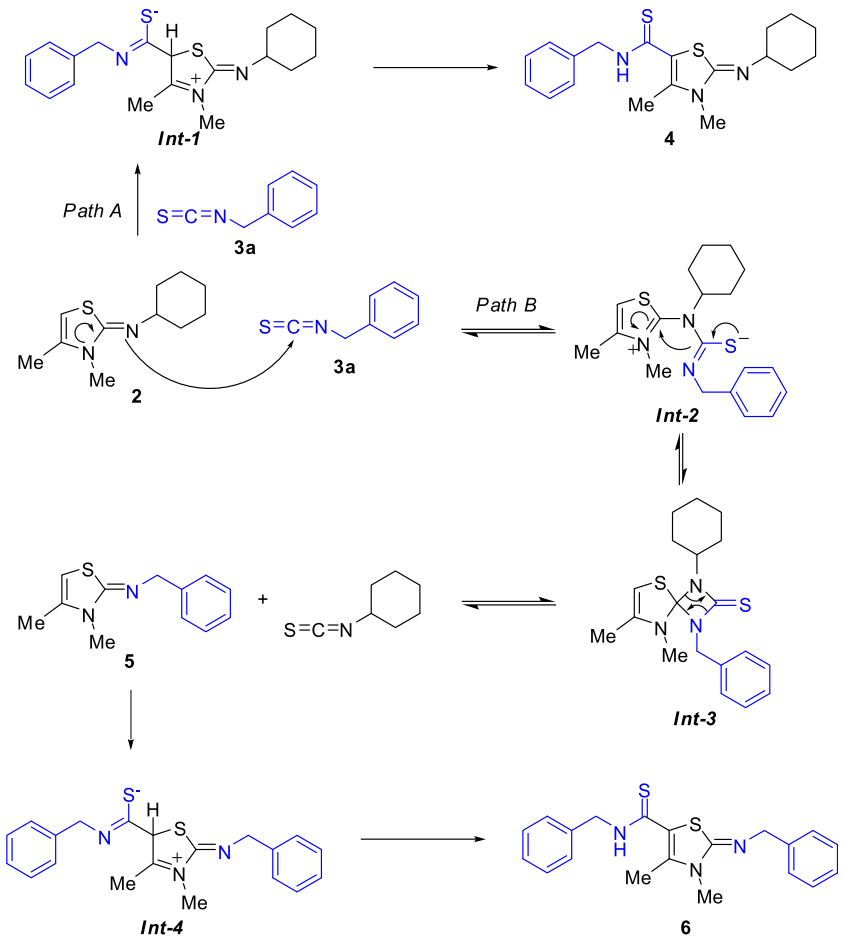
A possible mechanism is illustrated in Scheme 2. Path A, leading to only C-5 substituted compound **4**, proceeded through direct alkylation (*Int*-**1**) of enamine by isothiocyanate, followed by re-aromatization-type isomerization. In **P**ath B, all the steps from substrate **2** to compound **5** are thought to be reversible, and the force driving the process to completion is the difference of relative reactivity of two imino nitrogens (**2** and **5**), and alkylisothiocyanates (**3a**) and cyclohexylisothiocyanate. Larger electron-withdrawing effect of benzyl group than cyclohexyl, makes benzylisothiocyanate (**3a**) more reactive (**2**→*Int*-**2**), and the resulting benzyl 2-iminothiazole **5**, less reactive toward the first addition step of cyclohexylisothiocyanate in this exchange (**5**→*Int*-**3**). While we presented the stepwise process for the four-membered intermediate *Int*-3 from *Int*-**2**, direct [2+2]-cycloaddition mechanism is also possible. C-5 substituted product **6** was generated by the introduction of additional benzylisothiocyanate (**3a**). Cyclohexylisothiocyanate was detected in reaction mixture by GC–MS. It is obvious that this exchange reaction is highly affected by the reactivity of alkylisothicyanate and the rearrangement process is faster than C-5 alkylation of thiazole (vide infra).

2.3. Reaction scopes and limitations

In previous communication,[6] we revealed our initial results on this chemistry, which include optimization of reaction conditions (solvents, temperature, and reaction time) and brief reaction tendency using 2-cyclohexy-4,5-dimethyl-3-*N*-methyliminothiazole, where the 5-position is substituted with methyl group in order to block 5-acylation occurring in the reaction with alkylisothiocyanate. Toluene as a solvent, 13 h as reaction time, and 105 °C as reaction temperature was selected as an optimal condition.

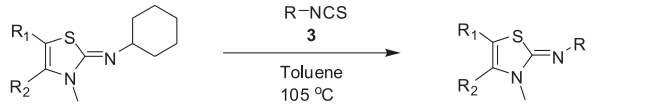
In order to broaden the utility of this method, we devised more complex substrates, such as 4-phenyl-5-methyl iminothiazole **7**, 4-methoxycarbonylmethyl-5-phenyl iminothiazole **8**, and 4-phenyl-5-phenyl iminothiazole **9**, which are C-4 and C5-derivatized thiazoles instead of methyl group. The substrates can be simply prepared by the established method in high yield. The exchange reaction was carried out with two different isothiocyanates **3a** and **3b**. As depicted in Table 1, all chemical yields were good to excellent though the reaction time was slightly longer than before. (entries 1–6). The 2-iminothiazole **8** possessing methoxycarbonylmethyl at C-4, which has mild electron-withdrawing effect, was less reactive than other substrates **7** and **9**. Though any significant side reactions were not observed in the reaction of **8**, a small portion of starting material was not completely consumed (entries 2 and 5).

It was expected that the relative reactivities of alkyl/aryl isothiocyanates could be revealed by the chemical yields of this reaction (Table 2). For this purpose, two model substrates, 2-(2,4-dimethoxy)phenyliminothiazole **13** and 2-phenyliminothiazole **14** were prepared. Based on the previous results, substrate **13** was expected to have higher reactivity to this exchange than substrate **14** due to its electron-rich characteristic of phenyl group. Entries 1–4 presents the chemical yields of exchange reaction of four benzyl and substituted benzylisothiocyanates. Among them, *p*-Fluorobenzylisothiocyanate showed the highest reactivity (87%),



Scheme 2. A plausible mechanism.

Table 1
Alkyl exchange of diversified 2-cyclohexyliminothiazoles with benzylisothiocyanate and ethyl isothiocyanatoacetate



7 $R_1 = CH_3$, $R_2 = C_6H_5$
8 $R_1 = CH_3$, $R_2 = CH_2CO_2CH_3$
9 $R_1 = R_2 = C_6H_5$

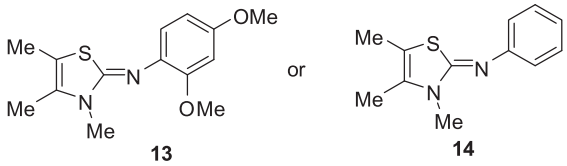
10 $R_1 = CH_3$, $R_2 = C_6H_5$
11 $R_1 = CH_3$, $R_2 = CH_2CO_2CH_3$
12 $R_1 = R_2 = C_6H_5$

Entry[a]	Thiazole	R	Product	Yield[b] (%)
1	**7**	Benzyl (**3a**)	**10a**	92
2	**8**		**11a**	65
3	**9**		**12a**	98
4	**7**	EtO_2CCH_2 (**3b**)	**10b**	92
5	**8**		**11b**	73
6	**9**		**12b**	99

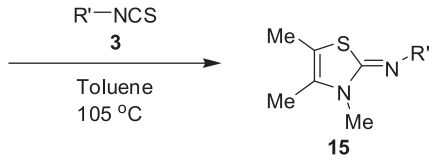
[a] In all reactions, 3 equiv of isothiocyanates **3** were used, and the reactions were conducted for 13 h.
[b] Purified yields after silica gel chromatography.

and the order of yields was *p*-chlorobenzylisothiocyanate (75%), benzylisothiocyanate (65%) *p*-methylbenzylisothiocyanate (35%). And, in accordance with our assumption, the 4-ethylphenylisothiocyanate (**3h**), which is considered to have its reactivity between the 2,4-dimethoxyphenylisothiocyanate **13** and phenylisothiocyanate **14**, showed great reactivity differences toward two 2-iminothiazole substrates. (90% in **13**, 0% in **14**, respectively) In the case of 2-(2,4-dimethoxy)phenyliminothiazole

Table 2
Comparison of relative reactivities of various isothiocyanates by chemical yields



13 or **14**



15

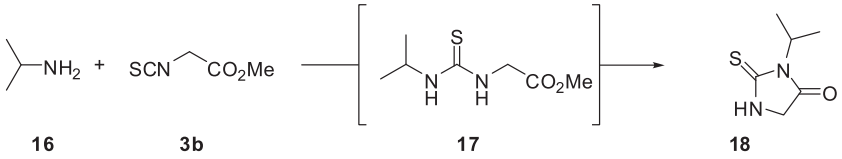
Entry[a]	Substrate	**3** (R′)	Product	Yield[b] (%)
1	**13**	**3a** ($C_6H_5CH_2$)	**15a**	67
2	**13**	**3c** (*p*-Me–$C_6H_4CH_2$)	**15c**	35
3	**13**	**3d** (*p*-F–$C_6H_4CH_2$)	**15d**	87
4	**13**	**3e** (*o*-Cl–$C_6H_4CH_2$)	**15e**	75
5	**13**	**3f** (Methyl)	**15f**	10
6	**13**	**3g** ($ClCH_2CH_2$)	**15g**	55
7	**13**	**3h** (Isopropyl)	**15h**	23
8	**13**	**3i** (4-Et–C_6H_4)	**15i**	90
9	**14**	**3i** (4-Et–C_6H_4)	**15i**	NR[c]

[a] In all reactions, 3 equiv of isothiocyanates **3** were used, and the reactions were conducted for 20 h.
[b] Purified yields after silica gel chromatography.
[c] No reaction.

13, the isolated yield was 90%, while any isolable product was not obtained for 2-phenyliminothiazole **14** (Table 2, entries 7 and 8). Alkylisothiocyanates **3f**–**h** revealed low reactivity toward this exchange reaction. Those results imply that this reaction can give an empirical comparison of the relative reactivity of isothiocyanates using suitable 2-iminothiazole substrate. This result further supports that the electronic effect is very important in this reaction.

Next, we turned our attention toward applying our novel method in solving some synthetic problems in thiourea preparation in 2-iminothiazole chemistry. Since amino acids are common precursor or building block in medicinal chemistry, amino acid-derived thiourea, therefore, can be used as a useful reagent for 2-iminothiazole synthesis.

The amino acid-derived 2-iminothizole is expected to be obtained by the reaction of α-haloketone with amino acid-derived thiourea; however, as illustrated in Scheme 3, when amine reacts with amino acid-derived isothiocyanate for the synthesis of thiourea, the reaction doesn't stop at thiourea **17**, but proceeds to cyclization to the 2-thioxoimidazolidin-4-one **20**.[7] It is not easy to prepare the various amino acid-derived thioureas, and as a consequence, amino acid-derived 2-iminothiazole cannot be readily synthesized. Our new exchange method can provide a solution for this problem.



Scheme 3. Reaction of amine and amino acid-derived isothiocyanate with amine.

As shown in Table 1, entries 4–6, ethyl 2-isothiocyanatoacetate derived from glycine exhibited an excellent reactivity toward this exchange reaction. This result can easily be explainable because methoxycarbonylmethyl group has an electron-withdrawing effect on the isothiocyanate moiety. With commercially available amino acid-derived isothiocyanate **3j**, **3k**, and **3l**, the exchange reactions were carried out under the same conditions as above. In accordance with our expectation, all reactions were successful with good to excellent yields, as summarized in Table 3. The reaction tendency shows that smaller (**3j**) and more electropositive (**3l**) isothiocyanate give higher yields. And also, all the products of this exchange reaction using chiral amino acid-derived isothiocyanates were optically active.

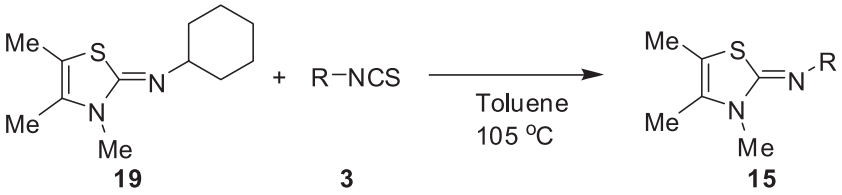
2.4. Exchange reaction using isocyanate

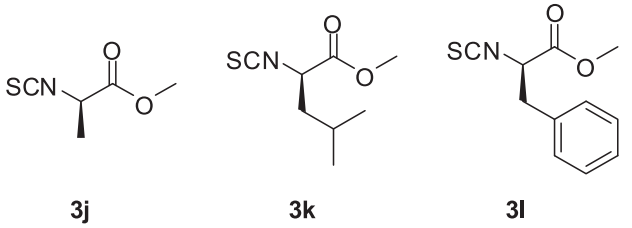
Isocyanates are common alternatives for isothiocyanates in medicinal chemistry. Both species usually show similar reactivity toward nucleophiles. Therefore, we envisioned that isocyanates would participate in this exchange reaction. We carried out reactions with several isocyanates under the same conditions as the isothiocyanate reaction (Table 4). As shown in entries 1–4, alkyl exchanges of 2-cyclohexyliminothiazole with alkylisocyanates **19** were successful, and desired products were obtained in high yields without any side reactions. It is noteworthy that chloroethylimino compound **15g** was gained from 2-chloroethylisocyanate (**20g**) in much higher yield (88%) than from the chloroethylisothicyanate. However, the reaction with phenyl isocyanate delivered only indefinable products (entry 5).

3. Conclusion

We found a new reactivity-driven isothiocyanate exchange of 2-iminothiazole. Through our experiments, the reaction tendency that electronic effect of substrates and alkylisothiocyanates is the most significant factor in this reaction, and reaction scopes were

Table 3
Application of alkyl exchange to the reactions with isothiocyanates derived from amino acids

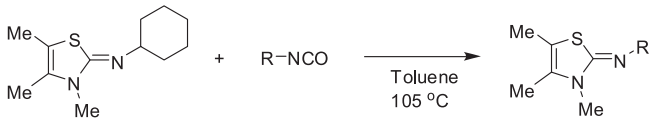




Entry[a]	3	Reaction time	Product	Yield[b] (%)
1	**3j**	20 h	**15j**	70
2	**3k**	20 h	**15k**	66
3	**3l**	20 h	**15l**	88

[a] In all reactions, 3 equiv of isothiocyanates **3** were used.
[b] Purification yield after silica gel chromatography.

Table 4
Alkyl exchange reaction of 2-iminothiazole with alkylisocyanates



Entry[a]	20	R	Product	Yield[b] (%)
1	**20a**	$C_6H_5CH_2$	**15a**	83
2	**20b**	EtO_2CCH_2	**15b**	99
3	**20e**	*o*-Cl–$C_6H_4CH_2$	**15e**	88
4	**20g**	2-chloroethyl	**15g**	95
5	**20o**	Phenyl	**NR**	—

[a] In all reactions, 3 equiv of isocyanates **20** were used, and the reaction time was 13 h.
[b] Purified yields after silica gel chromatography.

disclosed. And also, we were able to establish reaction mechanism, in which all the exchange processes are thought to be reversible. Synthetic problem in 2-iminothiazole chemistry, synthesis of amino acid-derived 2-iminothiazole, was solved by using this exchange reaction, where it was unnecessary to prepare the amino acid-derived thioureas. We showed an empirical method of comparing the relative reactivities of isothiocyanates. Moreover, successful exchange reaction using isocyanates broadened the utility of this reaction. Our current efforts are ongoing to apply this method to solid-phase synthesis of more diversified 2-iminothiazoles.

4. Experimental section

4.1. General

All Isothiocyanates and isocyanates reaction with 2-alkyl/aryl iminothiazoles was performed a following reaction procedure. The equivalent of Isothiocyanates and isocyanates and the reaction time are presented in the text or tables.

4.2. General information

All reactions were carried out using oven-dried glassware, and all solvents and commercially available chemicals were used without additional purification. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plate (silica gel 60 GF_{245}, 0.25 mm) were used. For flash column chromatography, Merck Kieselgel 60 (70–230 mesh) was used. Yields refer to purified and spectroscopically pure compounds. All melting points were measured in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Fourier Transform Infrared Spectrometer and were reported as wavenumbers (ν, cm^{-1}). Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were measured on 300 MHz spectrometer operating 300 MHz for ^1H nuclei and 75 MHz for ^{13}C, using DMSO-d_6 or $CDCl_3$ as solvents, and their spectra were reported in parts per million relative to DMSO (δ 2.50) or $CHCl_3$ (δ 7.24) for ^1H NMR and relative to the central DMSO-d_6 (δ 39.51) or $CDCl_3$ (δ 77.23) resonance for ^{13}C NMR. ^1H NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; dq, doublet of quartets; t, triplet; m, multiplet; br s, broad singlet), and coupling constants (J) in ^1H NMR are in hertz.

4.3. General procedure

To a solution of iminothiazole (1 equiv) in anhydrous toluene (0.3 M) was added isothiocyanate or isocyanate (3 equiv or the designated time in the text). After stirring at 105 °C for 13 h (or the designated time in the text), the reaction mixture was cooled and the solvent was evaporated in vacuo. The residues were purified by SiO_2 column chromatography to afford a desired product.

*4.3.1. N-(3,5-Dimethyl-4-phenylthiazol-2(3H)-ylidene)(phenyl) methanamine (**10a**).* Yield: 92%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 7.52–7.46 (m, 5H), 7.41–7.36 (m, 2H), 7.33–7.28 (m, 3H), 4.47 (s, 2H), 3.22 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 141.0, 135.5, 131.0, 130.3, 129.1, 129.0, 128.6, 128.0, 126.9, 106.5, 58.1, 33.6, 13.1; IR (KBr, cm^{-1}): 2920, 1598, 1497, 1367, 1293, 1120, 701. Mass (FAB^+): *m*/*z* 295 $[M+H]^+$; HRMS calculated for $C_{18}H_{19}N_2S$: 295.1269; found:$C_{18}H_{19}N_2S$:295.1262 $[M+H]^+$.

*4.3.2. Ethyl 2-(2-(benzylimino)-2,3-dihydro-3,5-dimethylthiazol-4-yl)acetate (**11a**).* Yield: 65%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 7.45–7.43 (m, 2H), 7.37–7.32 (m, 2H), 7.28–7.25 (m, 1H), 4.37 (s, 2H), 3.76 (s, 3H), 3.49 (s, 2H), 3.38 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 160.2, 140.9, 128.5, 127.9, 126.8, 126.7, 107.3, 57.9, 52.8, 31.8, 31.6, 12.6; IR (KBr, cm^{-1}): 2922, 1740, 1611, 1433, 1337, 1170, 721. Mass (FAB^+): *m*/*z* 305 $[M+H]^+$.

*4.3.3. N-(3-Methyl-4,5-diphenylthiazol-2(3H)-ylidene)(phenyl)methanamine (**12a**).* Yield: 98%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 7.58–7.56 (m, 2H), 7.51–7.48 (m, 3H), 7.45–7.41 (m, 2H), 7.38–7.35 (m, 2H), 7.32–7.30 (m, 1H), 7.19–7.15 (m, 3H), 7.09–7.06 (m, 2H), 4.55 (s, 2H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 141.1, 135.8, 133.0, 131.8, 130.7, 129.6, 129.5, 128.6, 128.0, 128.0, 126.9, 126.8, 110.9, 58.4, 33.1; IR (KBr, cm^{-1}) 3430, 2905, 1623, 1418, 1360, 726. Mass (FAB^+): *m*/*z* 357 $[M+H]^+$; HRMS calculated for $C_{23}H_{21}N_2S$: 357.1425; found:$C_{23}H_{21}N_2S$: 357.1427 $[M+H]^+$.

*4.3.4. Ethyl 2-(3,5-dimethyl-4-phenylthiazol-2(3H)-ylideneamino) acetate (**10b**).* Yield: 92%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 7.47–7.39 (m, 3H), 7.23–7.20 (m, 2H), 4.21 (q, J=6.9 Hz, 2H), 3.97 (s, 2H), 3.10 (s, 3H), 1.95 (s, 3H), 1.27 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 162.6, 135.6, 130.8, 130.2, 129.1, 120.0, 106.5, 61.0, 55.9, 33.4, 14.5, 13.0; IR (KBr, cm^{-1}): 2915, 1750, 1634, 1603, 1330, 1183. Mass (FAB^+): *m*/*z* 291 $[M+H]^+$; HRMS calculated for $C_{15}H_{19}N_2O_2S$: 291.1167; found: $C_{15}H_{19}N_2O_2S$: 291.1162 $[M+H]^+$.

*4.3.5. Ethyl 2-(2-(ethoxycarbomethylimino)-2,3-dihydro-3,5-dimethylthiazol-4-yl)acetate (**11b**).* Yield: 73%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 4.13 (q, J=7.2 Hz, 2H), 3.84 (s, 2H), 3.64 (s, 3H), 3.38 (s, 2H), 3.23 (s, 3H), 2.02 (s, 3H), 1.20 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 169.4, 162.0, 126.8, 107.3, 61.0, 55.8, 52.8, 31.6, 31.6, 14.5, 12.5; IR (KBr, cm^{-1}): 2980, 1749, 1733, 1606, 1416, 1260, 1181. Mass (FAB^+): *m*/*z* 300 $[M+H]^+$.

*4.3.6. Ethyl 2-(3-methyl-4,5-diphenylthiazol-2(3H)-ylideneamino) acetate (**12b**).* Yield: 99%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 7.44–7.41 (m, 3H), 7.29–7.26 (m, 2H), 7.15–7.08 (m, 3H), 7.01–7.6.98 (m, 2H), 4.27 (q, J=6.9 Hz, 2H), 4.09 (s, 2H), 3.19 (s, 3H), 1.33 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 161.5, 135.8, 132.6, 131.5, 130.6, 129.6, 129.4, 128.6, 128.0, 126.9, 111.2, 61.1, 56.0, 33.1, 14.6; IR (KBr, cm^{-1}): 2815, 1747, 1615, 1594, 1417, 1361, 1174. Mass (FAB^+): *m*/*z* 353 $[M+H]^+$; HRMS calculated for $C_{20}H_{21}N_2O_2S$: 353.1324; found: $C_{20}H_{21}N_2O_2S$: 353.1315 $[M+H]^+$.

*4.3.7. Phenyl-N-(3,4,5-trimethylthiazol-2(3H)-ylidene)methanamine (**15a**).* Yield: 67% from **13**; 83% from **19**, yellowish solid, mp: 76–77 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.35–7.27 (m, 4H), 7.22–7.17 (m, 1H), 4.15 (s, 2H), 3.21 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.1, 141.8, 130.8, 128.8, 128.0, 126.9,

101.3, 57.8, 31.5, 12.6, 11.9; IR (KBr, cm^{-1}): 2922, 1646, 1578, 1424, 1365, 1351, 727. Mass (FAB^+): *m/z* 233 $[M+H]^+$; HRMS calculated for $C_{13}H_{17}N_2S$: 233.1112; found: $C_{13}H_{17}N_2S$: 233.1119 $[M+H]^+$.

*4.3.8. Ethyl 2-(3,4,5-trimethylthiazol-2(3H)-ylideneamino)acetate (**15b**).* Yield: 99%, yellowish solid, mp: 44–45 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 4.16 (q, *J*=7.2 Hz, 2H), 3.88 (s, 2H), 3.27 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 162.9, 130.0, 103.2, 61.0, 55.6, 31.5, 14.5, 12.4, 11.9; IR (KBr, cm^{-1}): 1917, 1750, 1605, 1403, 1193, 1030. Mass (FAB^+): *m/z* 229 $[M+H]^+$; HRMS calculated for $C_{10}H_{17}N_2O_2S$: 229.1011; found: $C_{10}H_{17}N_2O_2S$:229.1006 $[M+H]^+$.

*4.3.9. p-Tolyl-N-(3,4,5-trimethylthiazol-2(3H)-ylidene)methanamine (**15c**).* Yield: 35%, yellowish solid, mp: 80–81 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.21–7.18 (d, *J*=8.1 Hz, 2H), 7.10–7.07 (d, *J*=8.1 Hz, 2H), 4.11 (s, 2H), 3.02 (s, 3H), 2.26 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.2, 138.6, 135.9, 130.8, 129.3, 128.0, 101.7, 57.4, 21.40, 12.6, 11.9; IR (KBr, cm^{-1}): 2919, 1607, 1418, 1359, 797. Mass (FAB^+): *m/z* 247 $[M+H]^+$; HRMS calculated for $C_{14}H_{19}N_2S$: 247.1269; found: $C_{14}H_{19}N_2S$: 247.1272 $[M+H]^+$.

*4.3.10. 4-Fluorophenyl-N-(3,4,5-trimethylthiazol-2(3H)-ylidene) methanamine (**15d**).* Yield: 87%, yellowish solid, mp: 90–91 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.38–7.33 (m, 2H), 7.10–7.07 (m, 2H), 4.12 (s, 2H), 3.20 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9 (d, *J*=239 Hz), 137.2 (d, *J*=3 Hz), 130.1, 129.97 (d, *J*=8 Hz), 114.7 (d, *J*=21 Hz), 100.4, 56.1, 30.7, 11.9, 11.15; IR (KBr, cm^{-1}): 2920, 1598, 1507, 1408, 1222, 857. Mass (FAB^+): *m/z* 251 $[M+H]^+$; HRMS calculated for $C_{13}H_{16}N_2SF$: 251.1018; found: $C_{13}H_{16}N_2SF$: 251.1016 $[M+H]^+$.

*4.3.11. 2-Chlorophenyl-N-(3,4,5-trimethylthiazol-2(3H)-ylidene) methanamine (**15e**).* Yield: 75% from **13**; 88% from **19**, yellowish solid, mp: 88–89 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.61–7.58 (m, 1H), 7.42–7.39 (m, 1H), 7.34–7.32 (m, 2H), 4.18 (s, 1H), 3.26 (s, 3H), 2.04–2.03 (d, 1.5, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.8, 138.9, 132.8, 130.9, 129.8, 129.5, 128.7, 127.7, 101.7, 55.2, 31.5, 12.58, 11.9; IR (KBr, cm^{-1}): 2922, 1602, 1417, 1351, 1050, 747. Mass (FAB^+): *m/z* 267 $[M+H]^+$; HRMS calculated for $C_{13}H_{16}N_2SCl$: 267.0723; found: $C_{13}H_{16}N_2SCl$: 267.0715 $[M+H]^+$.

*4.3.12. N-(3,4,5-Trimethylthiazol-2(3H)-ylidene)methanamine (**15f**).* Yield: 10%, yellowish oil; ^1H NMR (300 MHz, DMSO-d_6): δ 3.11 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 135.0, 111.8, 34.4, 33.6, 12.1, 11.8; IR (KBr, cm^{-1}): 2981, 2833, 1617, 1404. Mass (FAB^+): *m/z* 157 $[M+H]^+$; HRMS calculated for $C_7H_{13}N_2S$: 157.0799; found: $C_7H_{13}N_2S$: 157.0796 $[M+H]^+$.

*4.3.13. 2-Chloro-N-(3,4,5-trimethylthiazol-2(3H)-ylidene)ethanamine (**15g**).* Yield: 55% from **13**; 95% from **19**, yellowish solid, mp: 100–102 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (t, *J*=6.9 Hz, 2H), 3.75–3.70 (2H, *J*=6.9 Hz, 2H), 3.45–3.41 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 130.0, 103.7, 56.0, 44.5, 31.8, 12.4, 11.9; IR (KBr, cm^{-1}): 2920, 1599, 1353, 1241, 752. Mass (FAB^+): *m/z* 205 $[M+H]^+$; HRMS calculated for $C_8H_{14}N_2SCl$: 205.0566; found: $C_8H_{14}N_2SCl$: 205.0561 $[M+H]^+$.

*4.3.14. N-(3,4,5-Trimethylthiazol-2(3H)-ylidene)propan-2-amine (**15h**).* Yield: 23%, yellowish oil; ^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.42 (m, 1H), 2.15 (d, *J*=0.9 Hz, 3H), 2.09 (d, *J*=0.9 Hz, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 133.4, 111.4, 53.7, 35.9, 21.7, 12.3, 11.9; IR (KBr, cm^{-1}): 2842, 1597, 1374, 1154, 719. Mass (FAB^+): *m/z* 185 $[M+H]^+$; HRMS calculated for $C_9H_{17}N_2S$: 185.1112; found: $C_9H_{17}N_2S$: 185.1111 $[M+H]^+$.

*4.3.15. 4-Ethyl-N-(3,4,5-trimethylthiazol-2(3H)-ylidene)benzenamine (**15i**).* Yield: 90%, yellowish solid, mp: 82–83 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.09 (d, *J*=8.4 Hz, 2H), 6.83 (d, *J*=8.4 Hz, 2H), 3.29 (s, 3H), 2.51 (q, *J*=7.5 Hz, 2H), 2.04 (s, 3H), 2.00 (s, 3H), 1.18–1.13 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.4, 150.1, 138.0, 130.4, 129.2, 121.7, 101.7, 31.9, 28.3, 13.5, 12.35, 12.0; IR (KBr, cm^{-1}): 1961, 1591, 1504, 1333, 838. Mass (FAB^+): *m/z* 247 $[M+H]^+$; HRMS calculated for $C_{14}H_{19}N_2S$: 247.1269; found: $C_{14}H_{19}N_2S$: 247.1272 $[M+H]^+$.

*4.3.16. Methyl 2-(3,4,5-trimethylthiazol-2(3H)-ylideneamino)propanoate (**15j**).* Yield: 70%, yellowish oil; ^1H NMR (300 MHz, $CDCl_3$): δ 3.75–3.68 (m, 1H), 3.68 (s, 3H), 3.28 (s, 3H), 2.02 (d, *J*=0.9 Hz, 3H), 1.96 (d, *J*=0.9 Hz, 3H), 1.45 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 161.3, 129.6, 102.6, 62.4, 52.2, 31.6, 19.5, 12.4, 11.8; IR (KBr, cm^{-1}): 2947, 1742, 1588, 1324, 1136. Mass (FAB^+): *m/z* 229 $[M+H]^+$; HRMS calculated for $C_{10}H_{17}N_2O_2S$: 229.1011; found: $C_{10}H_{17}N_2O_2S$: 229.1015 $[M+H]^+$.

*4.3.17. Methyl 2-(3,4,5-trimethylthiazol-2(3H)-ylideneamino)-4-methylpentanoate (**15k**).* Yield: 66%, yellowish oil; ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.65–3.60 (m, 1H), 3.27 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.78–1.66 (m, 3H), 0.88 (dd, *J*=21.9, 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 161.2, 129.5, 102.4, 65.9, 52.0, 43.4, 31.6, 25.1, 23.4, 22.2, 12.4, 11.8; IR (KBr, cm^{-1}): 2953, 1745, 1600, 1349, 1143. Mass (FAB^+): *m/z* 271 $[M+H]^+$; HRMS calculated for $C_{13}H_{23}N_2O_2S$: 271.1480; found: $C_{13}H_{23}N_2O_2S$: 271.1487 $[M+H]^+$.

*4.3.18. Methyl 2-(3,4,5-trimethylthiazol-2(3H)-ylideneamino)-3-phenylpropanoate (**15l**).* Yield: 88%; ^1H NMR (300 MHz, DMSO-d_6): δ 7.29–7.21 (m, 5H), 3.66–3.60 (m, 1H), 3.53 (s, 3H), 3.11 (s, 3H), 3.11–3.04 (m, 1H), 2.92–2.85 (m, 1H), 1.96 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 160.7, 139.0, 130.7, 129.9, 128.8, 126.9, 101.7, 69.4, 52.2, 40.4, 31.5, 12.4, 11.9; IR (KBr, cm^{-1}): 2922, 1745, 1589, 1416, 1207, 704. Mass (FAB^+): *m/z* 305 $[M+H]^+$; HRMS calculated for: $C_{16}H_{21}N_2O_2S$: 305.1324; found: $C_{16}H_{21}N_2O_2S$: 305.1329 $[M+H]^+$.

Acknowledgements

This work is supported by Korea Institute of Science and Technology (KIST).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.015. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Recent reviews on five-membered heterocycles in chemical synthesis and natural product: (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382; (b) Huffman, J.; Padgett, L. *Curr. Med. Chem.* **2005**, *12*, 1395; (c) Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. *Mar. Drugs* **2009**, *7*, 705; (d) Zhang, J.; Polishchuk, E.; Chen, J.; Ciufolini, M. *J. Org. Chem.* **2009**, *74*, 9140; (e) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095.
2. Dondoni, A.; Merino, P. *Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, 1996; Vol. 3, Chapter 3.06.
3. Examples of iminothiazole and 2-aminothiazole in chemical library and medicinal chemistry; (a) Samimi, H.; Mamaghani, M.; Tabatabaeian, K. *Heterocycles* **2008**, *75*, 2825; (b) Mang, S.; Jakupovic, S.; Schunk, H.; Ambrosi, O.; Jakupovic, J. *J. Comb. Chem.* **2006**, *8*, 268; (c) Lin, R.; Connolly, P.; Huang, S.; Wetter, S.; Lu, Y.; Murray, W.;

Emanuel, S.; Gruninger, R.; Fuentes-Pesquera, A.; Rugg, C.; Middleton, S.; Jolliffe, L. *J. Med. Chem.* **2005**, *48*, 4208; (d) Borzilleri, R.; Bhide, R. S.; Barrish, J. C.; D'Arienzo, C. J.; Derbin, G. M.; Fargnoli, J.; Hunt, J. T.; Jeyaseelan, R. , Sr.; Kamath, A.; Kukral, D.; Marathe, P.; Mortillo, S.; Qian, L.; Tokarski, J. S.; Wautlet, B. S.; Zheng, X.; Lombardo, L. *J. Med. Chem.* **2006**, *49*, 3766; (e) Furet, P.; Bold, G.; Meyer, T.; Roesel, J.; Guagnano, V. *J. Med. Chem.* **2006**, *49*, 4451; (f) Arcadi, A.; Attanasi, O.; Giorgi, G.; Filippone, P.; Rossi, E.; Santeusanio, S. *Tetrahedron Lett.* **2003**, *44*, 8391.

4. Bramley, S. E.; Dupplin, V.; Goberdhan, D. G. C.; Meakins, G. D. *J. Chem. Soc. Perkin Trans. 1* **1987**, 639.
5. (a) Bae, S.; Hahn, H.; Nam, K. *J. Comb. Chem.* **2005**, *7*, 7; (b) Bae, S.; Hahn, H.; Nam, K. *J. Comb. Chem.* **2005**, *7*, 826; (c) Hahn, H.; Shin, S.; Mah, H. *J. Kor. Chem. Soc.* **2001**, *45*, 612.
6. Shin, D.; Lee, J.; Nam, K.; Hahn, H. *Tetrahedron Lett.* **2007**, *48*, 3089.
7. (a) Ciez, D.; Kalinowska-Tluscik, J.; Peyrat, S.; Touko, E.; Trzewik, B.; Zwolinski, K. *Synthesis* **2008**, *20*, 3261; (b) Muccioli, G.; Fazio, N.; Scriba, G.; Poppitz, W.; Cannata, F.; Poupaert, J.; Wouters, J.; Lambert, D. *J. Med. Chem.* **2006**, *49*, 417; (c) Fuentes, J.; Salameh, B.; Angeles, P.; Fernandez, C.; Francisco, J.; Gasch, C. *Tetrahedron* **2006**, *62*, 97.