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Novel isothiocyanate transposition in 2-alkyliminothiazoles: a simple solution for regiochemical problem

Dongyun Shin,* Jihoon Lee, Kee Dal Nam and Hoh-Gyu Hahn*

Life Sciences Research Division, Korea Institute of Science and Technology (KIST), 39-1 Hawolgok-dong, Seongbuk-gu, Seoul 136-791, Republic of Korea

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Abstract—Novel alkyl/aryl transposition in the reaction of 2-iminothiazoles with alkyl/aryl isothiocyanates was found out, and the reaction was very easy to handle and gave good to excellent chemical yields. Moreover, transposition reaction provided a simple but excellent solution for regiochemical problems in 2-iminothiazole synthesis.

2-Aminothiazole (**1**) and its isoform, 2-iminothiazole (**2**), are important classes of 5-membered heterocyclic compounds because of their wide utilities[1] (Fig. 1). They are not only seen as building blocks in natural products, but are also considered to be extraordinarily useful scaffolds, especially in combinatorial and medicinal chemistry.[2,3] Their inherent low toxicities and good pharmacokinetic profile for drug development make them one of the privileged structures in the realm of medicinal chemistry. With these reasons, there have been lots of reports on efficient and diversified syntheses of their derivatives and applications to specific drug targets.[3] In spite of a thorough investigation on the synthetic methods and applications of 2-aminothiazole,[4,5] less attention has been devoted to the chemistry of 2-iminothiazole, an isoform of *N*,*N*-dialkyl-2-aminothiazole.[6] 2-Iminothiazole also can be easily synthesized from α-halocarbonyls and *N*,*N*′-dialkylthiourea, and has an additional advantage over 2-aminothiazole that there are four derivatizable positions in it. Recently, we reported solution- and solid-phase syntheses of 2-akyl and aryl iminothiazoles from 4-chloroacetoanilides and dialkylthioureas, which were utilized in the establishment of diverse/focused chemical library of high quality.[7] But when unsymmetrical *N*,*N*′-dialkylthioureas were used, regiochemistry of the products was predetermined depending on the size of the substituents: a large group positioned at the imino nitrogen, which is general regiochemical trend in the type of reaction (Fig. 2).

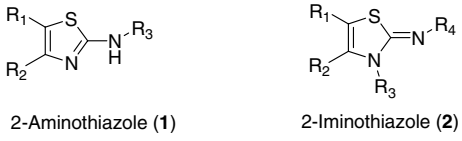

Figure 1. Structures of 2-aminothiazole and 2-iminothiazole.

In the course of studies on the functionalization of 2-iminothiazoles, we have found that the alkyl group attached at the imine nitrogen is substituted with that of alkyl isothiocyanate in mild conditions (Fig. 3). Herein, we disclose an unprecedent finding of alkyl/aryl transposition between 2-alkyliminothiazoline and alkyl/aryl isothiocyanate by rearrangement, more importantly, which gave an excellent solution for regiochemical problems in 2-iminothiazole formation.

2-Iminothiazole **3** was prepared by condensation of 3-chloro-2-butanone and *N*,*N*′-cyclohexylmethylthiourea. With this, the reaction condition of this transposition

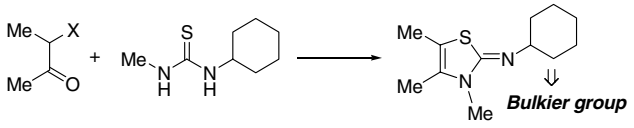

Figure 2. Regiochemical trend in the formation of 2-iminothiazole.

Keywords: 2-Iminothiazole; Isothiocyanate; Transposition; Regiochemistry.
* Corresponding authors. Tel.: +82 2 958 5143/5139; fax: +82 2 958 5189; e-mail addresses: dyshin21@kist.re.kr; hghahn@kist.re.kr

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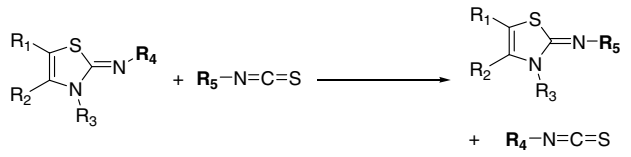


Figure 3. Novel isothiocyanate transposition of iminothiazole.

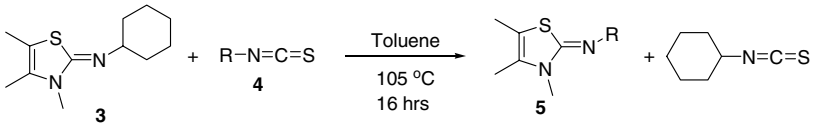
was carefully selected considering the reactivity of isothiocyanate and the reaction rate. After screening of solvents and temperature, toluene as a solvent showed optimal reaction rates and yields.[8] Therefore, all reactions were carried out under the condition of stirring in toluene for 16 h at 105 °C. Lower reaction temperature diminished the reaction rates. The transposition results are summarized in Table 1. As shown in entries 1–4, the substituted benzyl isothiocyanates afforded the rearranged products in almost quantitative yields regardless of the substituents on the phenyl ring. It seems that a mild electron-withdrawing effect of benzyl group makes the substituted benzyl isothiocyanates more reactive and prevents the transpositioned products from reverse transposition. But in case of alkyl isothiocyanate (entries 5–8) in which alkyl groups are considered to have electron donating effect, the desired products could be obtained just in moderate yields. Elevated amounts of alkyl isothiocyanates (5 equiv) and prolonged reaction times were needed for better chemical yields. However, the reaction did not complete. The above results imply that the reactivity of isothiocyanate transposition is very sensitive to the electronic properties of the substituents of isothiocyanate, and reverse transposition is possible. And phenyl isothiocyanate also worked in this transposition reaction (entry 9).

Scheme 1 illustrates the possible mechanism of this reaction. At first, imine nitrogen activated by nitrogen in the thiazole attacks the isothiocyanate, which generated formally thiazolinium ion **6**. Then, nitrogen is added to this thiazolinium ion, followed by rearrangement to release substituted product and cyclohexylisothiocyanate.

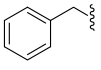
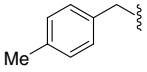
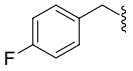
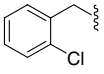
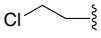
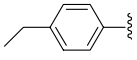
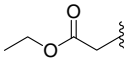
$$[\mathbf{7} \rightarrow \mathbf{8} \rightarrow \mathbf{5a}]$$

One of the major limitations in the generation of *N*,*N*′-dialkyliminothiazole scaffold-based chemical libraries for medicinal chemistry is that the regiochemistry of the two alkyl groups is predetermined depending on the steric and electronic properties. As mentioned above, when unsymmetrical *N*,*N*′-dialkylthioureas are

Table 1. Isothiocyanate transposition

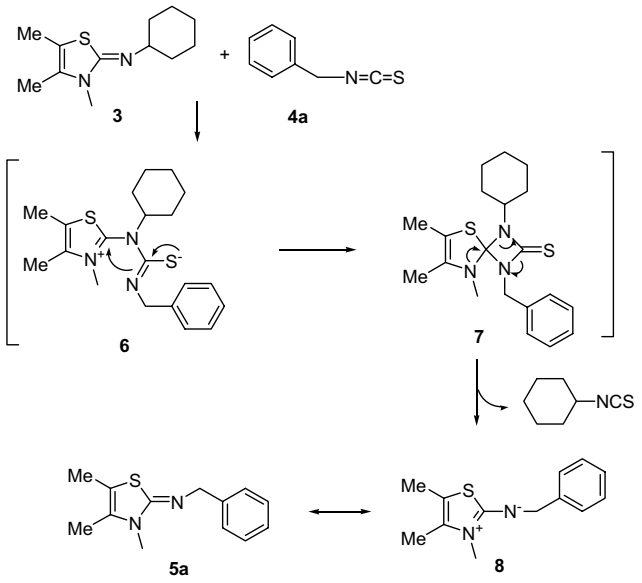


3 **4** **5**

Entry	4	R	Amount (equiv)	5, Yield[a] (%)
1	**4a**		3	**5a**, 90
2	**4b**		3	**5b**, 95
3	**4c**		3	**5c**, 93
4	**4d**		3	**5d**, 92
5	**4e**		5	**5e**, 64
6	**4f**		3	**5f**, 44
7	**4g**		5	**5g**, 47[b]
8	**4h**		5	**5h**, 51
9	**4i**		3	**5i**, 57
10	**4j**		3	**5j**, 99

[a] Isolated yields.

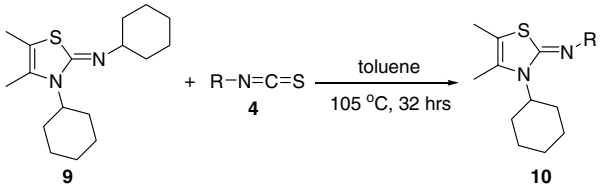
[b] The products were inseparable from starting material through normal SiO_2 TLC or column chromatography, and the yields were calculated by ^1H NMR ratio of starting material and products in the mixtures.

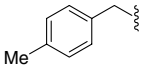
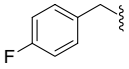
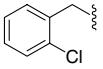
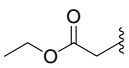


Scheme 1. Possible transposition mechanism.

used in this ring formation reaction, bulky alkyl groups take their positions at the imine nitrogen. So, we envisioned that this problem could be solved by applying our new transposition reaction. As a model substrate, we prepared *N*,*N*′-dicyclohexyl iminothiazoline **9** from symmetric bulky *N*,*N*′-dialkylthiourea and haloketone. Under the established reaction condition, transposition reactions were carried out with less bulkier alkyl isothiocyanates. As summarized in Table 2, the desired substituted iminothiazoles **10** with reverse regiochemistry were obtained in good to excellent yields, which showed the same reaction trend as the previous data. The substituted benzyl isothiocyanates could be obtained in nearly quantitative yields and the product was very stable, but it took longer reaction times in order to complete the reaction (reaction time; 32 h).

Table 2. Synthesis of reverse regiochemical product by isothiocyanate transposition



Entry	4	R	Amount (equiv)	9, Yield[a] (%)
1	**4a**		5	**10a**, 60
2	**4b**		5	**10b**, 89
3	**4c**		5	**10c**, 99
4	**4d**		5	**10d**, 99
5	**4e**		5	**10e**, 96
6	**4j**		5	**10j**, 87

[a] Isolated yields.

In conclusion, we found novel isothiocyanate transposition of *N*,*N*′-dialkyl-2-imino-1,3-thiazole. In this reaction, both alkyl and aryl isothiocyanates showed good reactivities. The main advantages of this reaction are that it is very easy to handle and deliver good chemical yields. Moreover, transposition reaction provided a simple but excellent solution for regiochemical problem in 2-iminothiazole synthesis from unsymmetrical *N*,*N*′-dialkylthioureas. The works on detailed scopes and limitations of this reaction including 2-iminothiazoles with various alkyl/aryl substituents are ongoing, and fruitful results will be reported in the near future.

Typical procedure. To a solution of iminothiazole **3** (110 mg, 0.491 mmol) in anhydrous toluene (2.5 mL) was added benzyl isothiocyanate **4a** (0.199 mL, 1.47 mmol). After stirring at 105 °C for 16 h, the reaction mixture was cooled and the solvent was evaporated in vacuo. The residues were purified by SiO_2 column chromatography to afford desired product **5a** (103 mg, 90%). Yellowish solid, mp = 76.5 °C ^{1}H NMR: 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: δ 159.08, 141.845, 130.76, 128.76, 128.02, 126.95, 101.33, 57.84, 31.45, 12.63, 11.92; IR (KBr, cm^{-1}): 1646.9, 1578.7, 1424.2, 1365.3, 1351.7, 727.0. 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]$^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.084.

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8. Detailed results will be provided in the following full paper.