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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Shanshan Guo, Donghong Zhao, Yue Zhu, Yongping Yu, Wenteng Chen & Guolin Zhang (2017): One-Pot Three-Component Protocol for the Synthesis of Substituted 2-Aminothiazoles, Synthetic Communications, DOI: 10.1080/00397911.2017.1350275

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1350275

One-Pot Three-Component Protocol for the Synthesis of Substituted 2-Aminothiazoles

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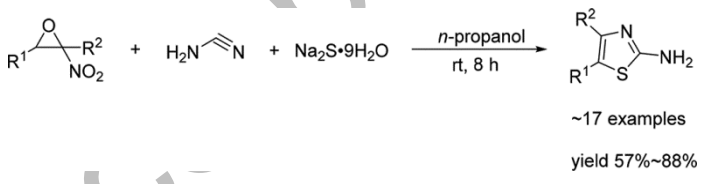
Abstract

Substituted 2-aminothiazoles have been synthesized from α-nitro-epoxides, cyanamide and sodium sulfide *via* a facile, three-component, and eco-friendly protocol with good to excellent yields. This reaction was achieved at room temperature without any additives. A possible mechanism has also been proposed.

Graphical Abstract



KEYWORDS: Multicomponent; 2-aminothiazoles; α-nitro-epoxides; cyanamide; sodium sulfide

INTRODUCTION

2-aminothiazole as one of the most important aza-heterocyles plays an important role in many complex natural products and pharmaceutical compounds, such as sulfathiazole (a common oral and topical antimicrobial), abafungin (a broad-spectrum antifungal agent) and dasatinib (a multi-BCR/Abl and Src family tyrosine kinase inhibitor for various Leukemias) (Figure 1). Moreover, 2-aminothiazoles have drawn much attention from medicinal chemists worldwide because of their broad biological activity, including antimicrobial [1], antiviral [2], antiprion [3], anti-inflammatory [4], anticancer [5], and so on.

In view of the importance of the 2-aminothiazoles, a great deal of attention has been given to its organic synthesis. Among them, the most prominent method to synthesize 2-aminothiazoles is Hantzsch cyclocondensation and its various improved methods [6], which involve condensation of a-haloketones with thiourea in the presence of various catalysts. Recently, one-pot protocol directly starting from ketones/aldehyde and thioureas has also been reported using halogenating reagent or catalysts [7]. Also, 2-aminothiazoles are also prepared *via* the reaction between isothiocyanates and oxime acetates or amine hydrochlorides [8]. Moreover, 2-aminothiazoles could be produced by treating styrenes with NBS *via* co-oxidant free, in situ formation of α-bromoketone in the presence of thiourea [9]. However, longer reaction time, harsh reaction conditions, the use of less environmentally friendly reagents, and expensive catalysts limited its utility. Therefore, it is desirable and challenging to develop a facile, eco-friendly approach for the synthesis of 2-aminothiazoles.

Herein we present a facile, multi-component, and eco-friendly protocol for the synthesis of 2-aminothiazoles with good to excellent yields from α-nitro-epoxides, cyanamide and sodium sulfide.

RESULTS AND DISCUSSION

Initially, α-nitro-epoxide **1d**, cyanamide **2** were selected as model reactants to optimize the reaction conditions (Table 1). We found that the formation of 2-aminothiazole **4d** with an acceptable yield (80%) in the presence of $Na_2S·9H_2O$ in *n*-propanol at room temperature (Table 1, entry 1). However, when using NaHS instead of $Na_2S·9H_2O$, the conversion of 4a was significantly decreased to 55% (Table 1, entry 2), so we selected $Na_2S·9H_2O$ as a sulfide reagent. Subsequent screening of reaction temperatures showed that the room temperature was the best (Table 1, entries 2 and 3). Further studies found that the solvent of the reaction had a significant impact on the efficiency for the formation of **4d**, and *n*-propanol was found superior to other aprotic and protic solvents (Table 1, entries 4–9). Furthermore, optimization of the different stoichiometric amount of $Na_2S·9H_2O$ showed that the conversion of 2-aminothiazole **4d** increased to 87% or 86%, respectively, when the amount of $Na_2S·9H_2O$ was risen to 3 or 4 equiv (Table 1, entries 11 and 12). However, there was no improved after reducing the amount of $Na_2S·9H_2O$ to 1 equiv (Table 1, entry 10). Besides, the screening of the stoichiometric amount of cyanamide (Table 1, entries 13–15) showed that the best conversion was obtained when using 3 equiv of cyanamide (Table 1, entry 14). On the basis of this initial

study, the optimal reactivity was obtained in *n*-propanol at room temperature when the mole ratio of α-nitro-epoxide, cyanamide and $Na_2S·9H_2O$ was 1:3:3 (Table 1, entry 14).

With the optimized reaction conditions in hand, we next investigated the generality and scope of the methodology for the synthesis of 2-aminothiazoles using a set of α-nitro-epoxides, which were readily prepared according to the literature [10] and the results were summarized in Table 2. When the electron-rich and -deficient benzene rings as the substituent R^1 (Table 2, **4a**-**4o,** except **4j** and **4k**), α-nitro-epoxides participated well to provide the corresponding 2-aminothiazoles in good to excellent yields. Generally, α-nitro-epoxides with electron-deficient groups at the R^1 position gave relatively poorer results (Table 2, **4a**, **4b** *vs* **4c**–**4e**; **4l** *vs* **4m**; **4n** *vs* **4o**). Additionally, the steric hindrance has a slightly effect on the reaction yields (Table 2, **4c** *vs* **4f**; **4d** *vs* **4g**, **4h**). However, when a heteroaryl group (Table 2, **4k**) or an alkyl group (Table 2, **4j**) was at the R^1 position, the yields of this reaction had a slightly decrease. Moreover, when using ethyl group (Table 2, **4l** and **4m**) or aryl group (Table 2, **4n** and **4o**) instead of methyl group at the R^2 position, the reaction can also afford the desired products. However, there was only trace or no desired product obtained when cyanamide was replaced with cyano substituted secondary amine or amide (Table 2, **4p** and **4q**).

The structures of 2-aminothiazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS (ESI). On the basis of the results above, we proposed the following possible mechanism for this reaction, as outlined in Scheme 1. In the case of sodium sulfide,

cyanamide **2** would undergo a nucleophilic attack to give intermediate **A** with a powerful nucleophilic center [11], which makes the α-nitro-epoxides **1** undergo a ring opening to afford intermediate **B** followed by the formation of intermediate **C** with the elimination of the nitro [12]. Then intramolecular nucleophilic attack of intermediate **C** would afford 2-aminothiazoles **3** with the elimination of water.

CONCLUSION

In summary, we have developed a facile, multi-component, and eco-friendly protocol for the one-pot synthesis of 2-aminothiazoles with good to excellent yields from α-nitro-epoxides, cyanamide and sodium sulfide. This reaction has the advantages of available starting materials, mild reaction conditions and no need for any additives. These features made this reaction as a widely used approach in medicinal chemistry.

EXPERIMENTAL SECTIONS

Purifications of reaction products were carried out by chromatography using silica gel (200 – 300 mesh). Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethyl-silane (TMS) served as internal standard ($\delta = 0$) and data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, Q = quartet, m = multiplet), and coupling constant (s) in Hertz. For ^{13}C NMR, TMS ($\delta = 0$) or DMSO ($\delta = 40.45$) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data was obtained using Agilent Technologies 6224 TOF LC/MS. Unless otherwise noted, all reagents were obtained

commercially and used without further purification The starting material α-nitro-epoxides **1a-1o** were prepared according to literature methods [10]. The starting material cyanamide and $Na_2S·9H_2O$ were commercially available, and **2p, 2q** were prepared according to literature methods [13].

General Procedure For The Synthesis Of 4

A mixture of α-nitro-epoxides **1** (0.5 mmol), cyanamide **2** (1.5 mmol), $Na_2S·9H_2O$ (1.5 mmol) was stirred in *n*-propanol 2 mL at room temperature for 8 h. After the completeness of the reaction, the reaction was diluted with water and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel to afford the desired product **4**.

4-methyl-5-(*p*-tolyl)thiazol-2-amine (**4a**): Yellow solid, 76.5 mg, yield 75%; mp: 147.4 – 148.6°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29 – 7.26 (m, 2H), 7.22 – 7.18 (m, 2H), 5.10 (s, 2H), 2.38 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.9, 143.0, 136.7, 129.8, 129.3, 128.7, 121.3, 21.2, 16.0; HRMS (ESI): m/z calcd for $C_{11}H_{12}N_2S$ $[M+H]^+$: 205.0799, found: 205.0797.

SUPPORTING INFORMATION

Supplemental data (full experimental procedures and characterization data) can be accessed on the publisher's website.

FUNDING

This project was supported from Zhejiang Provincial Natural Science Foundation of China (LY16H300001) to G. Zhang, National Natural Science Foundation of China (No. 81273356 and 81473074), National Science & Technology Major Projects for "Major New Drugs Innovation and Development" of China (2014ZX09304002-007) and Osteoporosis & Breast Cancer Research Center, USA to Y. Yu, National Natural Science Foundation of China (No. 81402778) to W. Chen.

REFERENCES

[1] (a) Brandt, A.; Cerquetti, M.; Corsi, G. B. *J. Med. Chem*. **1987**, *30*, 764–767; (b) Flanagan, M. E.; Brickner, S. J.; Lall, M.; Casavant, J.; Deschenes, L.; Finegan, S. M.; George, D. M.; Granskog, K.; Hardink, J. R.; Huband, M. D.; Hoang, T.; Lamb, L.; Marra, A.; Mitton-Fry, M.; Mueller, J. P.; Mullins, L. M.; Noe, M. C.; O'Donnell, J. P.; Pattavina, D.; Penzien, J. B.; Schuff, B. P.; Sun, J.; Whipple, D. A.; Young, J.; Gootz, T. D. *ACS Med. Chem. Lett*. **2011**, *2*, 385–390; (c) Karuvalam, R. P.; Haridas, K. R.; Nayak, S. K.; Row, T. N. G.; Rajeesh, P.; Rishikesan, R.; Kumari, N. S. *Eur. J. Med. Chem.* **2012**, *49*, 172–182; (d) Jagdale, B. S.; Adole, V. A. *IJPRS*, **2015**, *4*, 46–49; (e) Cui, S.; Addla, D.; Zhou, C. *J. Med. Chem.* **2016**, *59*, 4488–4510.

[2] Liu, R.; Huang, Z.; Murray, M. G.; Guo, X.; Liu, G. *J. Med. Chem*. **2011**, *54*, 5747–5768.

[3] (a) Ghaemmaghami, S.; May, B. C. H.; Renslo, A. R.; Prusiner, S. B. *J. Virol*. **2010**, *84*, 3408–3412; (b) Gallardo-Godoy, A.; Gever, J.; Fife, K. L.; Silber, B. M.; Prusiner, S. B.; Renslo, A. R. *J. Med. Chem.* **2011**, *54*, 1010–1021.

[4] (a) Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yarande, S.; Nivsarkar, M.; Padh, H.; Vasu, K. K.; Sudarsanam, V. *Eur. J. Med. Chem.* **2008**, *43*, 129–134; (b) Inamdar, G. S.; Pandya, A. N.; Thakar, H. M.; Sudarsanam, V.; Kachler, S.; Sabbadin, D.; Moro, S.; Klotz, K.-N.; Vasu, K. K. *Eur. J. Med. Chem*. **2013**, *63*, 924–934.

[5] (a) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cruz-Lopez, C.; Cara, C. L.; Basso, G.; Viola, G.; Khedr, M.; Balzarini, J.; Mahboobi, S.; Sellmer, A.; Brancale, A.; Hamel, E. *J. Med. Chem*. **2009,** *52*, 5551–5555; (b) Hitchin, J. R.; Blagg, J.; Burke, R.; Burns, S.; Cockerill, M. J.; Fairweather, E. E.; Hutton, C.; Jordan, A. M.; McAndrew, C.; Mirza, A.; Mould, D.; Thomson, G. J.; Waddell, I.; Ogilvie, D. J. *Med. Chem. Commun*. **2013**, *4*, 1513-1522.

[6] (a) Hantzsch, A.; Weber, J. H. *Chemische Berichte*, **1887**, *20*, 3118; (b) Ochiai, M.; Nishi, Y.; Hashimoto, S.; Tsuchimoto, Y.; Chen, D. W. *J. Org. Chem*. **2003**, *68*, 7887–7888; (c) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2006**, *47*, 5171–5172; (d) Donohoe, T. J.; Kabeshov, M. A.; Rathi, A. H.; I. Smith, E. D. *Org. Biomol. Chem.* **2012**, *10*, 1093-1101; (e) Facchinetti, V.; Avellar, M. M.; Nery, A. C. S.; Gomes, C. R. B.; Vasconcelos, T. R. A.; de Souza, M. V. N. *Synthesis*, **2016**, *48*, 437–440.

[7] (a) Karade, H.; Sathe, M.; Kaushik, M.P. *Catal. Commun.* **2007**, *8*, 741–746; (b) Zav'yalov, S. I.; Kravchenko, N. E.; Ezhova, G. I.; Kulikova, L. B.; Zavozin, A. G.; Dorofeeva, O. V. *Pharm. Chem. J.* **2007**, *41*, 105–108; (c) Yin, G.; Ma, J.; Shi, H.; Tao, Q. *Heterocycles*, **2012**, *85*, 1941–1948; (d) Jagdale, B. S.; Adole, V. A. *IJPRS*, **2015**, *4*, 46–49; (e) Zhao, J.; Xu, J.; Chen, J.; He, M.; Wang, X. *Tetrahedron*, **2015**, *71*, 539–543; (f) Sadeghi, M.; Safari, J.; Zarnegar, Z. *RSC Adv.*, **2016**, *6*, 64749–64755; (g) Ghodse, S. M.; Telvekar, V. N. *Tetrahedron Lett*. **2015**, *56*, 472–474.

[8] (a) Sasmal, P. K.; Chandrasekhar, A.; Sridhar, S.; Iqbal, J. *Tetrahedron*, **2008**, *64*, 11074–11080; (b) Tang, X.; Zhu, Z.; Qi, C.; Wu, W.; Jiang, H. *Org. Lett.* **2016**, *18*, 180−183.

[9] Shinde, M. H.; Kshirsagar, U. A. *Green Chem.* **2016**, *18*, 1455–1458.

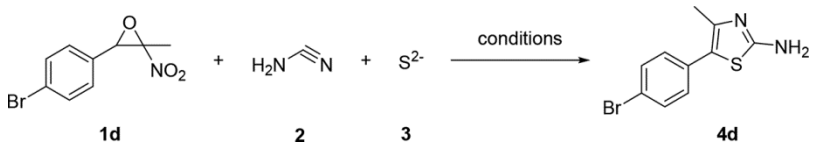
[10] (a) Karmarkar, S. N.; Kelkar, S. L.; Wadia, M. S. *Synthesis*, **1985**, *5*, 510–512; (b) Mikesell, P., Schwaebe, M., OiMare, M., Little, R. O. *Acta Chemica Scandinavica*, **1999**, *53*, 792−799; (c) Desai, U. V., Pore, D. M., Mane, R. B., Solabannavar, S. B., Wadgaonkar, P. P. *Synthetic Commun.* **2004**, 34, 19–24; (d) Greger, J. G., Yoon-Miller, S. J. P., Bechtold, N. R.; Flewelling, S. A.; MacDonald, J. P.; Downey, C. R.; Cohen, E. A.; Pelkey, E. T. *J. Org. Chem.* **2011**, *76*, 8203–8214; (e) Vidal-Albalat, A., Rodríguez, S., González, F. V. *Org. Lett.* **2014**, *16*, 1752−1755; (f) Zhao, D.; Guo, S.; Guo, X.; Zhang, G.; Yu, Y. *Tetrahedron*, **2016**, *72*, 5285−5289.

[11] (a) Courtier, A. J. U.S. Patent 2 521 778, **1950**; (b) Armitage, M. A.; Cashyap, M. M.; Saunders, D. *J Labelled. Compd. Rad.* **1986**, *23*, 343-354.

[12] (a) Ibrahim, M. M.; Grau, D.; Hampel, F.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2014**, *7*, 1401-1405; (b) Guo, X.; Chen W.; Chen, B.; Huang, W.; Qi, W.; Zhang, H.; Yu, Y. *Org. Lett*. **2015**, *17*, 1157–1159.

[13] (a) Kwon, K-H.; Serrano, C. M.; Koch, M.; Barrows, L. R.; Looper, R. E. *Org. Lett.* **2014**, *16*, 6048–6051; (b) Rassadin, V. A.; Boyarskiy, V. P.; Kukushkin, V. Y. *Org. Lett.* **2015**, *17*, 3502−3505.

Table 1. Optimization of reaction conditions [a]



1d 2 3 4d

Entry	S^{2-} (equiv)	Solvent	T/°C	Conversion [b]/%
1	$Na_2S·9H_2O$ (2)	*n*-propanol	rt	83 (80) [c]
2	NaHS (2)	*n*-propanol	rt	55
3	$Na_2S·9H_2O$ (2)	*n*-propanol	40	75
4	$Na_2S·9H_2O$ (2)	MeOH	rt	72
5	$Na_2S·9H_2O$ (2)	EtOH	rt	52
6	$Na_2S·9H_2O$ (2)	Acetone	rt	37
7	$Na_2S·9H_2O$ (2)	MeCN	rt	58
8	$Na_2S·9H_2O$ (2)	DMF	rt	20
9	$Na_2S·9H_2O$ (2)	DCE	rt	59
10	$Na_2S·9H_2O$ (1)	*n*-propanol	rt	77
11	$Na_2S·9H_2O$ (3)	*n*-propanol	rt	87 (84) [c]
12	$Na_2S·9H_2O$ (4)	*n*-propanol	rt	86 (84) [c]
13 [d]	$Na_2S·9H_2O$ (3)	*n*-propanol	rt	82 (78) [c]
14 [e]	**$Na_2S·9H_2O$ (3)**	***n*-propanol**	**rt**	**88 (86) [c]**
15 [f]	$Na_2S·9H_2O$ (3)	*n*-propanol	rt	87 (85) [c]

[a] Reaction conditions: α-nitro-epoxide (0.5 mmol, 1.0 equiv), cyanamide (2.5 mmol, 5.0 equiv), $Na_2S·9H_2O$/NaHS, 2 mL of solvent, 8 h, T/°C.

[b] Determined by LC-MS, based on the disappearance of the starting α-nitro-epoxide. The most efficient entry is highlighted in bold.

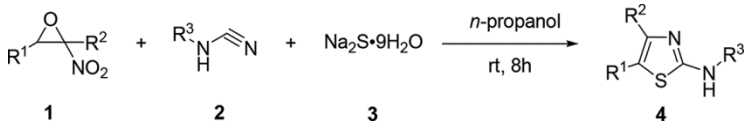
[c] Isolated yield.

[d] Reaction was performed using 2.0 equiv of cyanamide.

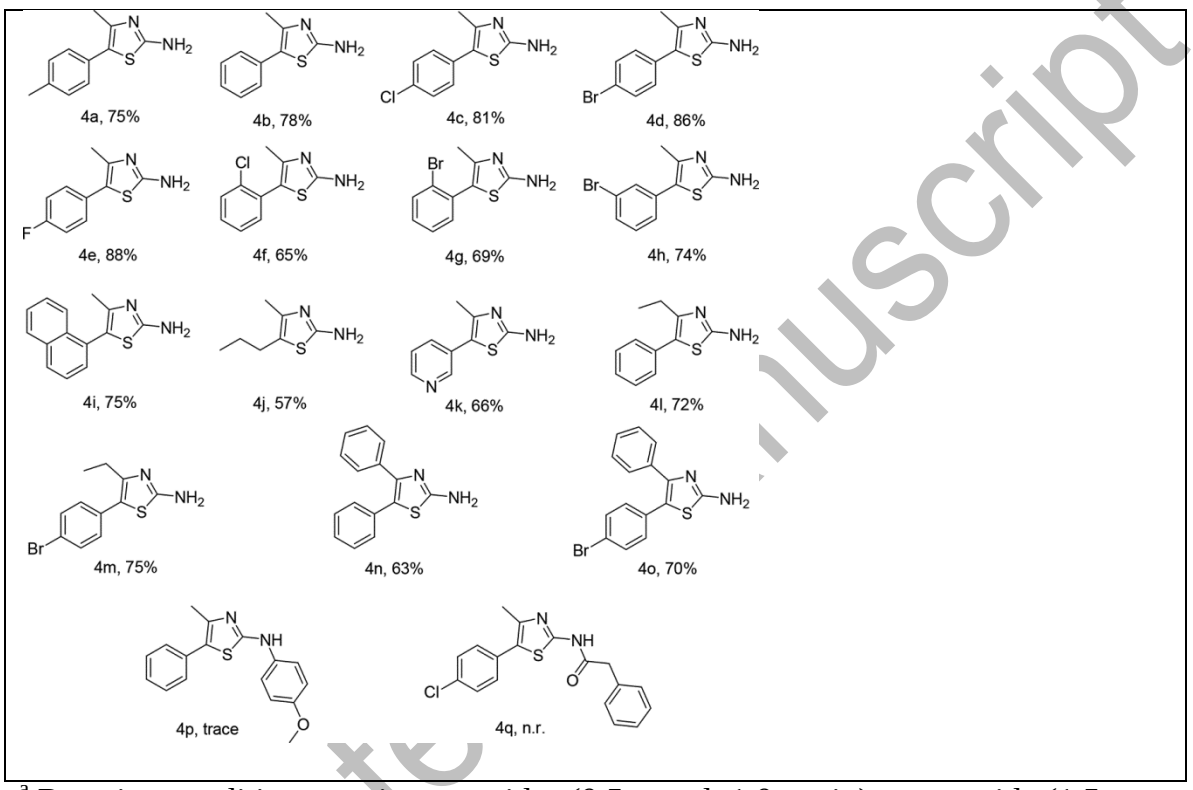
[e] Reaction was performed using 3.0 equiv of cyanamide.

[f] Reaction was performed using 4.0 equiv of cyanamide.

Table 2. Scope of the reaction of α-nitro-epoxides, cyanamide and $Na_2S·9H_2O$ under optimal conditions [a]



1 2 3 4



[a] Reaction conditions: α-nitro-epoxides (0.5 mmol, 1.0 equiv), cyanamide (1.5 mmol, 3.0 equiv), $Na_2S·9H_2O$ (1.5 mmol, 3.0 equiv), 2 mL of *n*-propanol, 8 h, rt. Isolated yield.

Scheme 1. Proposed mechanism for the synthesis of 2-aminothiazoles.

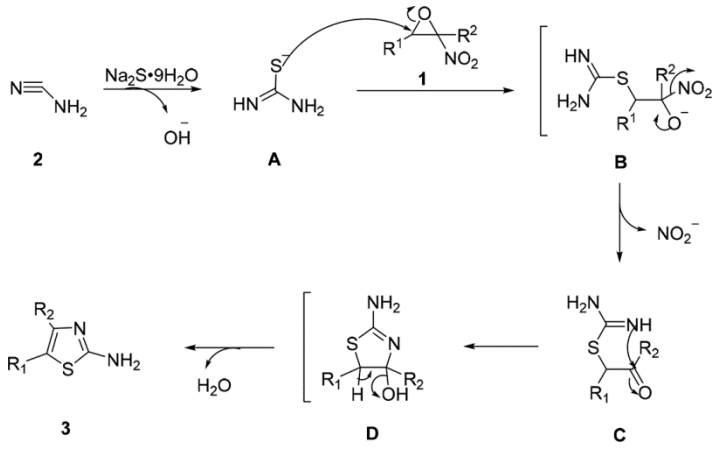
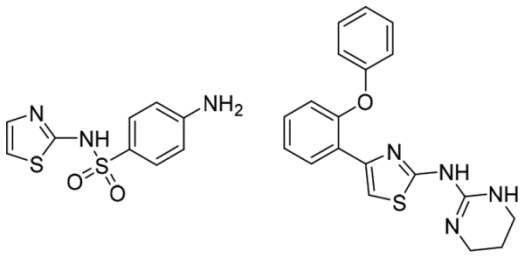
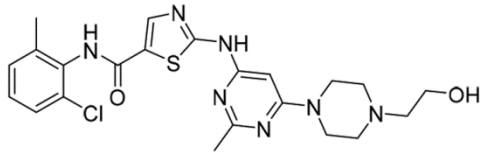


Figure 1. Some drugs incorporating the 2-aminothiazole moiety



Sulfathiazole
(Antimicrobial)

Abafungin
(Antifungal)



Dasatinib
(Antileukemic)