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A three-component one-pot synthesis of 2-alkoxy-4-amino-*N*-arylthiazole-5-carboxamides

Hai-Long Zhao [a,b], Jie Zhou [a], Hong-Rui Song [b], Bai-Ling Xu [a,*]

[a] *Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation, Institute of Materia Medica Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China*
[b] *Department of Pharmacy Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China*

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ABSTRACT

A facile and efficient protocol was developed to access 2-alkoxy-4-amino-*N*-arylthiazole-5-carboxamides through a three-component one-pot reaction, which involved potassium methyl cyanimidodithiocarbonate, 2-halo-*N*-arylacetamides and alcohols. The easy availability and the broad structural diversity of substrates make the reaction useful for the construction of libraries in drug discovery.

1. Introduction

The thiazole ring system as a privileged structure was often explored in the drug discovery process [1–5], and a number of the marketed drugs contained a thiazole fragment [2,6,7]. So far, a great deal of diversified thiazole derivatives were produced and demonstrated a variety of biological activities such as cytotoxic, immunosuppressive and antifungal activities [1,8–10]. Pin1 (Protein interaction with NIMA1) is a peptidyl-prolyl *cis*/*trans* isomerase and inhibition of Pin1 is a potential therapeutic strategy for the treatment of cancer [11–15]. In our efforts to search for novel thiazoles as Pin1 inhibitors, the desired intermediate **3** was not obtained according to Scheme 1, while unexpectedly, 4-amino-2-ethoxy-*N*-(naphthalene-2-yl)thiazole-5-carboxamide (**4a**) was isolated in 54% yield. To our best knowledge, there were few 2-alkoxy-4-amino-*N*-arylthiazole-5-carboxamides reported in the literature [16,17]. Herein, we wish to present our detailed investigations on the synthesis of the title thiazole derivatives by a simple and efficient protocol.

2. Experimental

In this work, two different methods were developed to access the thiazole derivatives **4a**–**i** and **4k**–**r** as shown in Tables 1 and 2. The general procedure of method A was given as follows: A mixture of potassium methyl cyanimidodithiocarbonate **1** (1 equiv.) and 2-halo-*N*-arylacetamides **2** [18–20] (1 equiv.) was heated for 2–4 h using various alcohols (ROH) as reaction solvents. After that, 2 equivalents of triethylamine were added and the resulting reaction mixture was refluxed for further 4–8 h to furnish the desired molecules (**4a**–**d** and **4k**–**r**) in 41–84% yields. Method B: A mixture of compound **1** (1 equiv.) and 2-bromo-*N*-(naphthalen-2-yl)-acetamide **2a** (1 equiv.) in 2 mL of *tert*-butanol was loaded into the sealed reaction tube and irradiated by microwave for 15 min (power 60 W, temperature 120 °C, pressure 150 psi). And then, 10 equivalents of various alcohols as reactants and 2 equivalents of triethylamine were added. The resulting reaction mixture was irradiated by microwave at the same reaction conditions for 60–90 min to afford the corresponding final products (**4e**–**i**) in 24–48% yields.

3. Results and discussion

With an aim to explore the scope of this protocol, the substituent variations on the 2-position and 5-position of thiazoles were conducted by using a series of alcohols (Table 1, compounds **4a**–**j**) and aryl amines (Table 2, compounds **4k**–**r**), respectively. The chemical structures, synthetic methods and yields of all the obtained 2-alkoxy-4-amino-*N*-arylthiazole-5-carboxamides were summarized in Tables 1 and 2 [21].

As shown in Table 1, when the unbranched primary alcohols such as methanol, ethanol, *n*-propanol and *n*-butanol were tested

* Corresponding author.
E-mail address: xubl@imm.ac.cn (B.-L. Xu).

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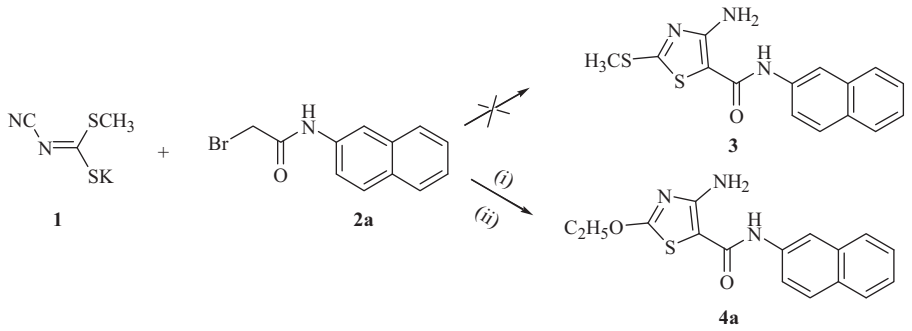


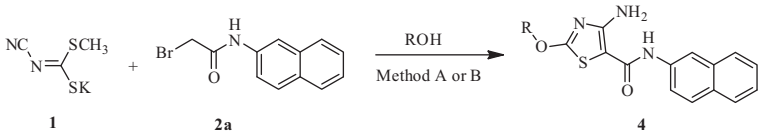
Scheme 1. Reagents and conditions: (i) ethanol, reflux, 1.5 h; (ii) Et_3N/ethanol, reflux, 4 h.

by functioning as both substrates and solvents in method A, the desired 2-alkoxy substituted thiazoles were obtained in moderate yields (46–62%). However, when the branched *iso*-propanol or *tert*-butanol were selected as a substrate, the desired compounds **4e** or **4j** was not found; on the contrary, *N*-(3-(naphthalen-2-yl)-4-oxothiazolidin-2-ylidene)cyanamide **6** as shown in Scheme 2 was isolated, probably due to the steric hindrance of *iso*-propanol and *tert*-butanol. To our delight, compound **4e** was obtained in 24% yield under microwave irradiation, although compound **4j** remained elusive in the reaction. Moreover, the initial attempt to introduce propargyloxy substituent onto the 2-position of thiazole scaffold *via* method A resulted in a sluggish reaction; but the desired product was generated in 42% yield when the reaction was promoted by microwave. In order to further diversify the alkoxy groups on the 2-poistion of thiazoles with different alcohols, method B was developed. In this method, 10 equivalents of various alcohols were used as substrates together with starting materials **1** and **2a**, and the reactions were carried out in *tert*-butanol as the reaction medium under microwave irradiation. According to this strategy, compounds **4f**–**i** bearing structural diversities were produced in moderate yields (42–48%).

Subsequently, a number of 2-halo-*N*-arylacetamides **2** as shown in Table 2 were examined to broaden the scope of this protocol. In the presence of 2 equivalents of triethylamine as a base, the three-component one-pot reaction of potassium methyl cyanimidodithiocarbonate **1**, 2-halo-*N*-arylacetamides **2** and ethanol underwent readily, and thus producing the desired trisubstituted thiazoles in moderate to good yields (41–84%). It was indicated that the reaction could well tolerate the variations of electron-poor (compounds **4l**–**n)** and electron-rich (compounds **4o**–**r**) aromatic groups (Ar).

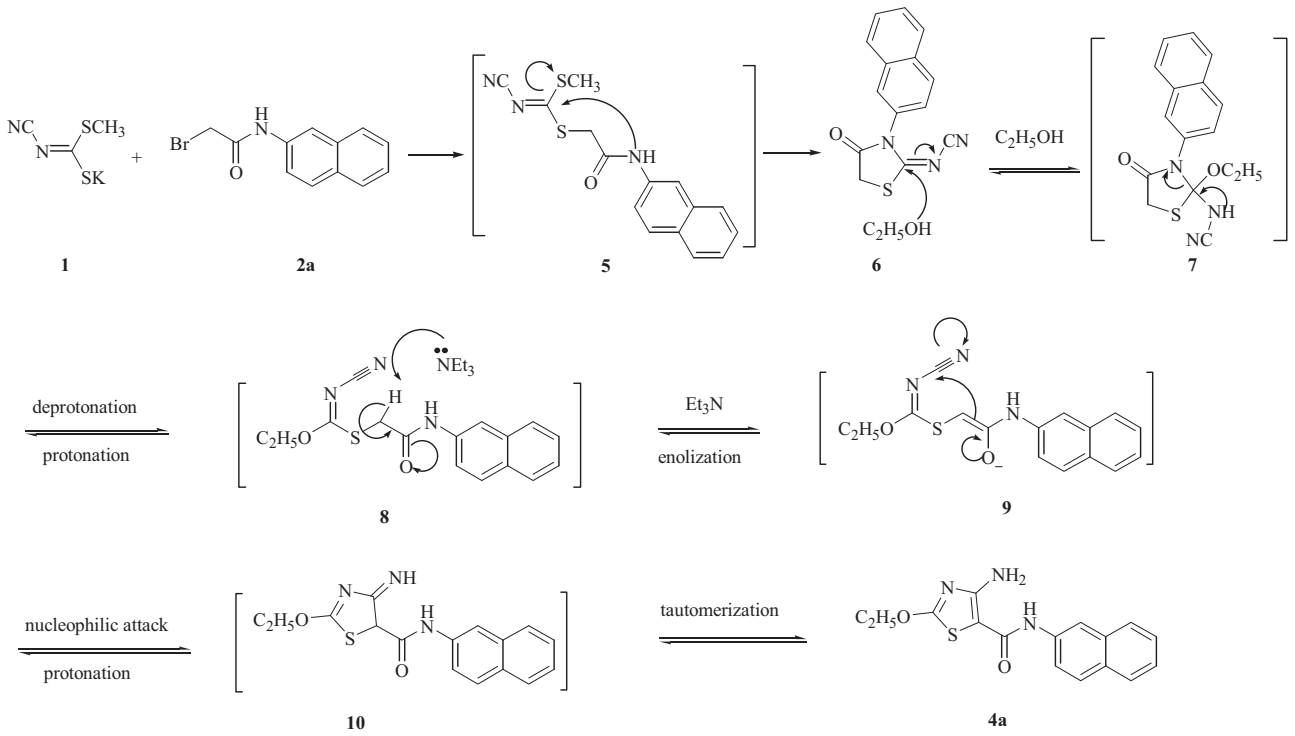
Preliminarily, the reaction mechanism for the formation of 2-alkoxy-4-amino-*N*-arylthiazole-5-carboxamides **4** was hypothesized using compound **4a** as an example as shown in Scheme 2. It was reported that the reaction of potassium methyl cyanimidodithiocarbonate **1** with 2-chloro-*N*-(naphthalen-2-yl)-acetamide **2a** could give rise to thiazolidone **6** [20] in ethanol in the absence of bases. And in this work, we isolated the intermediate **6** in 80% yield in ethanol and the intermediate **6** was heated at reflux in ethanol in the presence of triethylamine or NaH, and the desired compound **4a** was obtained in 60% and 65% yield, respectively. In order to further improve the yield of this reaction, the following attempts were conducted. When sodium ethoxide was used as the base for the preparation of **4a** with method A, the product **4a** was isolated in only 36% yield. While when KI (1 equiv.) was used with 2-bromo-*N*-*β*-naphthylacetamide **2a** or 2-iodo-*N*-*β*-naphthylacetamide **2j** was utilized to promote this reaction, the desired compound **4a** was obtained in comparable yield (57% and 52%

Table 1
Synthesis of 2-alkoxy-4-amino-*N*-(naphthalene-2-yl)thiazole-5-carboxamide derivatives.



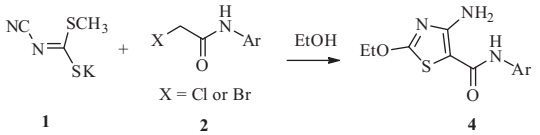
Product	R	Solvent	Method	Yield (%)[a]	Mp (°C)
4a	Et	Ethanol	Method A[b]	54	179–181
4b	Me	Methanol	Method A	62	216–218
4c	*n*-Pr	*n*-Propanol	Method A	46	95–97
4d	*n*-Bu	*n*-Butanol	Method A	55	93–94
4e	*i*-Pr	*iso*-Propanol	Method A	–[e]	
4e	*i*-Pr	*iso*-Propanol	Method B[c]	24	109–112
4f	Propargyl	*tert*-Butanol	Method A	–[d]	
4f	Propargyl	*tert*-Butanol	Method B	42	161–163
4g	Bn	*tert*-Butanol	Method B	45	145–147
4h	*i*-Bu	*tert*-Butanol	Method B	48	104–106
4i	$CH_3OCH_2CH_2$	*tert*-Butanol	Method B	45	187–189
4j	*t*-Bu	*tert*-Butanol	Method A	–[e]	
4j	*t*-Bu	*tert*-Butanol	Method B	–[e]	

[a] Isolated yields after silica gel column chromatography.
[b] Method A: (i) **1** (1 equiv.), **2a** (1 equiv.), refluxing 2–4 h; (ii) Et_3N (2 equiv.), refluxing 4–8 h; alcohols (ROH) as both substrates and solvents.
[c] Method B: (i) **1** (1 equiv.), **2a** (1 equiv.), microwave 15 min; (ii) Et_3N (2 equiv.), ROH (10 equiv.), microwave 60–90 min; *t*-BuOH as the solvent.
[d] The reaction was sluggish, and only a small amount of desired product was detected.
[e] Only compound **6** was formed, and no desired product was observed.



Scheme 2. A plausible mechanism proposed for the formation of 4-amino-2-ethoxy-*N*-(naphthalene-2-yl)thiazole-5-carboxamide (**4a**).

Table 2
Synthesis of 4-amino-2-ethoxy-*N*-arylthiazole-5-carboxamide derivatives *via* method A.[a]



Product	Ar	Yield (%)[b]	Mp (°C)
4k	Ph	84	137–139
4l	4-$CF_3C_6H_4$	41	186–188
4m	4-FC_6H_4	60	182–185
4n	4-$NO_2C_6H_4$	58	240–242
4o	4-$CH_3OC_6H_4$	44	210–212
4p	3-$CH_3C_6H_4$	58	141–143
4q	3,4-$(CH_3O)_2C_6H_3$	54	179–181
4r	4-Phenoxyphenyl	45	190–193

[a] Method A: (i) **1** (1 equiv.), **2** (1 equiv.), refluxing 2–4 h; (ii) Et_3N (2 equiv.), refluxing 4–8 h; ethanol as the substrate and solvent.
[b] Isolated yields after silica gel column chromatography.

yield, respectively), compared with the case where 2-bromo-*N*-β-naphthylacetamide **2a** was treated as a reactant. Based on these experimental results, a plausible mechanism for this three-component one-pot synthesis of trisubstituted thiazoles was suggested as illustrated in Scheme 2. The initial S_N2 substitution of thiolate **1** with 2-bromo-*N*-(naphthalen-2-yl)-acetamide and the subsequent intramolecular cyclization of intermediate **5** yielded thiazolidone **6**. Next, in the presence of triethylamine, ethanol attacks on the electrophilic carbon of *N*-cyanamide **6**, followed by the intramolecular ring opening of **7** to provide the key intermediate **8**. After deprotonation of **8** with Et_3N, the generated **9** underwent an intramolecular cyclization by attacking the present cyano group to afford **10**, which was tautomerized into the desired compound **4a** with the assistance of Et_3N.

4. Conclusion

An efficient and straightforward approach was developed for the construction of novel 2-alkoxy-4-amino-*N*-arylthiazole-5-carboxamide derivatives. It has been demonstrated that structurally diverse alcohols and 2-halo-*N*-arylacetamides, which were easily accessed by the reaction of 2-chloroacetyl chloride and arylamines, were well tolerated. Therefore, this three-component one-pot protocol could be used to build up a structurally diversified thiazole library for the drug discovery and development.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.12.005.

References

[1] N. Siddiqui, S.K. Arya, W. Ahsan, B. Azad, Diverse biological activities of thiazoles: a retrospect, Int. J. Drug Dev. Res. 3 (2011) 55–67.
[2] S.J. Kashyap, V.K. Garg, P.K. Sharma, et al., Thiazoles: having diverse biological activities, Med. Chem. Res. 21 (2012) 2123–2132.
[3] N. Siddiqui, M.F. Arshad, W. Ahsan, M.S. Alam, Thiazoles: a valuable insight into the recent advances and biological activities, Int. J. Pharm. Sci. Rev. Res. 1 (2009) 136–143.
[4] N.K. Shah, N.M. Shah, M.P. Patel, R.G. Patel, Synthesis, characterization and antimicrobial activity of some new biquinoline derivatives containing a thiazole moiety, Chin. Chem. Lett. 23 (2012) 454–457.
[5] C.B. Guo, Z.F. Cai, Z.R. Guo, et al., Design, synthesis and in vitro evaluation of thiazole derivatives of ibuprofen as cyclooxygenase-2 inhibitors, Chin. Chem. Lett. 17 (2006) 325–328.

[6] S.F. Cui, Y. Wang, J.S. Lu, G.L.V. Damu, C.H. Zhou, Recent advances in application of thiazole compounds, Sci. China: Chem. 42 (2012) 1105–1131.
[7] U. Galm, E. Wendt-Pienkowski, L.Y. Wang, et al., Comparative analysis of the biosynthetic gene clusters and pathways for three structurally related antitumor antibiotics bleomycin, tallysomycin and zorbamycin, J. Nat. Prod. 74 (2011) 526–536.
[8] J. Zhong, Muscarine, imidazole, oxazole, and thiazole alkaloids, Nat. Prod. Rep. 20 (2003) 584–605.
[9] S. Carradori, D. Secci, A. Bolasco, et al., Synthesis and cytotoxicity of novel (thiazol-2-yl)hydrazine derivatives as promising anti-Candida agents, Eur. J. Med. Chem. 65 (2013) 102–111.
[10] Y.J. Yang, Y.N. Yang, J.S. Jiang, et al., Synthesis and cytotoxic activity of heterocycle-substituted phthalimide derivatives, Chin. Chem. Lett. 21 (2010) 902–904.
[11] J.D. Moore, A. Potter, Pin1 inhibitors: pitfalls, progress and cellular pharmacology, Bioorg. Med. Chem. Lett. 23 (2013) 4283–4291.
[12] Y.Y. Xi, J. Jin, Y. Sun, et al., Design, synthesis and biological evaluation of novel diaryl ethers bearing a pyrimidine motif as human Pin1 inhibitors, Acta Pharm. Sin. 48 (2013) 1266–1272.
[13] C. Liu, J. Jin, L. Chen, et al., Synthesis and biological evaluation of novel human Pin1 inhibitors with benzophenone skeleton, Bioorg. Med. Chem. 20 (2012) 2992–2999.
[14] L.N. Zhu, J. Jin, C. Liu, et al., Synthesis and biological evaluation of novel quinazoline-derived human Pin1 inhibitors, Bioorg. Med. Chem. 19 (2011) 2797–2807.
[15] C.J. Zhang, Z.H. Zhang, B.L. Xu, Y.L. Wang, Recent advances in the study of Pinl and its inhibitors, Acta Pharm. Sin. 43 (2008) 9–17.
[16] T. Fuchigami, T. Nonaka, Facile synthesis of 5-acyl-4-amino-2-ethoxythiazoles from an [ethoxy(thiocarbonyl)]cyanamide salt and α-halo ketones, J. Org. Chem. 48 (1983) 3340–3341.
[17] T. Fuchigami, M.Y. Yeh, T. Nonaka, H.J. Tien, Studies of cyanamide derivatives. Part 109. A convenient method for preparation of 4-aminothiazole compounds from alkoxythiocarbonylcyanamide salts, Bull. Chem. Soc. Jpn. 56 (1983) 3851–3852.
[18] P. van der Peet, C.T. Gannon, I. Walker, et al., Use of click chemistry to define the substrate specificity of leishmania β-1,2-mannosyltransferases, ChemBioChem 7 (2006) 1384–1391.
[19] Y. Jin, Z.Y. Zhou, W. Tian, Q. Yu, Y.Q. Long, 4′-Alkoxyl substitution enhancing the anti-mitotic effect of 5-(3′,4′,5′-substituted)anilino-4-hydroxy-8-nitroquinazolines as a novel class of anti-microtubule agents, Bioorg. Med. Chem. Lett. 16 (2006) 5864–5869.
[20] D. Wobig, Thiazolderivate, III. Reaktionen von cyanimidodithiocarbonaten mit α-chloracetamiden, Liebigs Ann. Chem. 1977 (1977) 400–406.
[21] The synthetic procedure and structure identification for compounds **2a–j**, **4a–i** and **4k–r** are available in Supporting information. All synthesized final products were characterized by ^{1}H NMR, ^{13}C NMR and ESI-HRMS. For example, compound **4a**: light yellow solid; mp 179–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.77 (s, 1H), 8.27 (s, 1H), 7.79–7.89 (m, 3H), 7.58 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.1 Hz), 7.48 (t, 1H, J = 6.9 Hz), 7.38 (t, 1H, J = 7.2 Hz), 6.95 (brs, 2H), 4.14 (q, 2H, J = 6.9 Hz), 1.22 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.04, 163.47, 137.56, 133.60, 129.41, 128.73, 127.53, 127.02, 126.61, 124.44, 119.59, 113.80, 58.97, 14.65; HRMS (ESI) Calcd. for $C_{16}H_{16}N_3O_2S$ [M+H$^+$]: 314.0958; found: 314.0957.