Recent progress in the synthesis of thiazolo[3,2-a]pyrimidine compounds

F Y Wu, Y Luo and C B Hu

School of Materials and Chemical Engineering, Chongqing University of Arts and Sciences, Chongqing 402160, China

1 E-mail: bch1002@126.com

Abstract. In this paper, the progress in the synthesis of thiazolo[3,2-a]pyrimidine compounds in the field of medicine and pesticide were reviewed. The main synthetic routes include: (i) synthesis of thiazolo[3,2-a]pyrimidines, spiro thiazolo[3,2-a]pyrimidines and pyrazolo[3,4-d]thiazolo[3,2-a]pyrimidines by multicomponent reactions (MCRs). (ii) synthesis of thiazolo[3,2-a]pyrimidines by condensation of pyrimidine-2-thiones, which were obtained by Biginelli reaction between aromatic aldehydes and thiourea, with substituted 2-bromo-1-phenylethanone or chloroacetic acid. (iii) synthesis of pyrido[4,3-d]thiazolo[3,2-a]pyrimidinones via Pictet–Spengler reaction. (iv) synthesis of pyrido[4,3-d]thiazolo[3,2-a]pyrimidine by reacting 2-aminothiazole with the α, β-unsaturated ketones.

1. Introduction

Systems including fused thiazole and pyrimidine units play important role in organisms because they have good biological potentials. The thiazolo[3,2-a]pyrimidine moiety as an kind of the most important structures, have been shown to display a great diversity of biological activities, including anti-inflammatory [1], antihypertensive [2], psychopharmacological [3], antimicrobial [4], antinociceptive [5], antibacterial [6], antitumor [7] and anti-HSV-1 [8]. They can act as calcium antagonists [9], diacylglycerol (DG) kinase inhibitors [10], HIV-1 reverse transcriptase inhibitors [11], group 2 metabotropic glutamate receptor antagonists [12], and some thiazolo[3,2-a]pyrimidines have been reported as new acetylcholinesterase (AChE) inhibitors and CDC25B phosphatase inhibitors, used to treat Alzheimer’s disease [13], cancer [14]. At present, the thiazolo[3,2-a]pyrimidine skeleton has been widely used as the core of the drug, which represents ritanserin and setoperone [15]. Therefore, the synthesis of thiazolo[3,2-a]pyrimidine compounds have been attracted wide attention of the chemical workers.

In the past decade, variety methods have been reported for the synthesis of thiazolo[3,2-a]pyrimidine derivatives. The main synthetic routes include: (i) synthesis of thiazolo[3,2-a]pyrimidines, spiro thiazolo[3,2-a]pyrimidines and pyrazolo[3,4-d]thiazolo[3,2-a]pyrimidines by multicomponent reactions (MCRs). (ii) synthesis of thiazolo[3,2-a]pyrimidines by condensation of pyrimidine-2-thiones, which were obtained by Biginelli reaction between aromatic aldehydes and thiourea, with substituted 2-bromo-1-phenylethanone or chloroacetic acid. (iii) synthesis of pyrido[4,3-d]thiazolo[3,2-a]pyrimidinones via Pictet–Spengler reaction. (iv) synthesis of pyrido[4,3-d]thiazolo[3,2-a]pyrimidine by reacting 2-aminothiazole with the α, β-unsaturated ketones.
2. Synthesis of thiazolo[3,2-a]pyrimidines by Multicomponent Reactions (MCRs)

Multicomponent reactions (MCRs) have become as one of the most efficient strategies for the assembly of complex structural frameworks through the combination of two or more distinct reactions into a one-pot transformation. The strategy is well suited for building complex molecules from readily available starting materials without the need for isolation and purification of intermediates, minimization of waste, labor, time, and cost, provides an eco-friendly protocol [16].

Adib et al. reported a one-pot three-component reaction for the synthesis of 5H-thiazolo[3,2-a]pyrimidines 1 with dialkyl acetylene-dicarboxylates, isocyanides and ethyl 2-oxo-2-(1,3-thiazol-2-ylamino)acetates as raw materials in 2007. The reaction was completed spontaneously in CH$_2$Cl$_2$ at room temperature within 24 h, and the yield could reach up to 90% [17].

\[
\text{R-N} = \text{C} + \text{R'O}_2\text{CH}_2\text{CO}_2\text{R'}^+ + \text{S} \xrightarrow{\text{CH}_2\text{Cl}_2,\text{r.t.}, 24\text{h}} \text{NCOCO}_2\text{Et} \xrightarrow{83-90\%} \text{1}
\]

**Scheme 1.** Synthesis of 5H-thiazolo[3,2-a]pyrimidines.

In 2012, Esmaeili et al. presented new polysubstituted 3-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine compounds 2, which was synthesized by the reaction of dialkyl acetylenedicarboxylates, isocyanides and 2-imino-1,3-thiazolidin-4-one via MCRs[18].

\[
\text{R}_1\text{N} = \text{C} + \text{R}_2\text{O}_2\text{CH}_2\text{CO}_2\text{R}_2^+ + \text{S} \xrightarrow{\text{CH}_2\text{Cl}_2,\text{r.t.}} \text{NH} \xrightarrow{70-87\%} \text{2}
\]

**Scheme 2.** Synthesis of 3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine compounds.

Then a new series of spiro[indole-3,6'-pyrano[2,3-d]][1,3]thiazolo[3,2-a]pyrimidine derivatives 3 were synthesized with the reaction of malononitrile, isatin, in the presence of diisopropylethylamine via MCRs by Esmaeili et al., too. This reaction could be completed in 14 to 40 minutes, with a yield of 89-95%, and this new spiro-system was expected to good biological activity because it contains pyranothiazolopyrimidine and oxindole scaffolds[19].

\[
\xrightarrow{\text{DIEA, EtOH, Reflux, 14-40min}} \xrightarrow{\text{88-95\%}} \text{3}
\]

**Scheme 3.** Synthesis of spiro[indole-3,6'-pyrano[2,3-d]][1,3]thiazolo[3,2-a]pyrimidine derivatives.

In 2016, a new multicomponent reaction strategy for the facile synthesis of densely functionalized pyrazolo[3,4-d]-thiazolo[3,2-a]pyrimidines 4 with easily obtained α-thiocyanate ketones, aryl aldehydes, and pyrazol-5-amines as raw materials was established by Jiang et al. The reaction could be
completed within 20-30 minutes, with a yield of 56-82% in HOAc under microwave irradiation. The remarkable feature of the developed process was that it had been enabled cascade-type formation of C-N and C-C bonds through successive nucleophilic addition/5-exo-trig cyclization/6-endo-trig cyclization steps, this represented a new bicyclization strategy for the construction of N,S-containing heterocycles [20]. The compounds exhibit xanthine oxidase inhibitory activity because it incorporating both the thiazolo[3,2-a]pyrimidine and pyrazole motifs [21].

Scheme 4. Synthesis of densely functionalized pyrazolo[3,4-d]-thiazolo[3,2-a]pyrimidines.

3. Synthesis of thiazolo[3,2-a]pyrimidines by condensation of pyrimidine-2-thiones, which were obtained by Biginelli reaction between aromatic aldehydes and thiourea, with substituted 2-bromo-1-phenylethanone or chloroacetic acid

Pyrimidine-2-thione is a kind of important Biginelli reaction products, because of its various pharmacological activities. In recent years, pyrimidine-2-thiones have received the widespread attention and research, and more and more thiazolo[3,2-a]pyrimidines were synthesized with pyrimidine-2-thiones as the raw materials. In 2014, eight 5H-thiazolo[3,2-a]pyrimidine derivatives 5 were synthesized with Hantzsch condensation of pyrimidine-2-thione, which was obtained by the Biginelli reaction between aromatic aldehydes and thiourea, with substituted 2-bromo-1-phenylethanone by Jia et al. The antitumor activities were evaluated against MCF-7, A549 and HT-29 in vitro by MTT assay, and the results showed that antitumor activity of compound 5c on HT-29 cells were similar to control drug [22].

Scheme 5. Synthesis of 5H-thiazolo[3,2-a]pyrimidine derivatives.

Wang et al. synthesized five new thiazolo[3,2-a]pyrimidine derivatives 6 containing pyrazole group by Knoevenagel reactions of 4-(5-chloro-3-methyl-1-phenyl-4-pyrazolyl)-3, 4-dihydropyrimidine-2(1H)-thione which was prepared by Vilsmeier-Haack and Biginelli reaction using 3-methyl-1-phenyl-2-pyrazolin-5-one as the raw materials with arylaldehyde. The in-vitro anticanceractivities of the new thiazolo[3,2-a]pyrimidines against human prostate cancer PC-3 cells
were tested by MTT assay, and the results showed that 6a-6e exhibited certain anticancer activities and 6a exhibited the strongest anticancer activities with IC₅₀ of 44.45 μM [23].

![Scheme 6. Synthesis of thiazolo[3, 2-a]pyrimidines derivatives using 3-methyl-1-phenyl-2-pyrazolin-5-one as the raw materials.](image)

Then, nine novel thiazolo[3,2-a]pyrimidine derivatives with pyrazole substituent 7 were synthesized from substituted phenylhydrazines via Vilsmeier-Haack, Biginelli and Knoevenagel reactions. The antiproliferative activities of target compounds against human prostate cancer PC-3 and human hepatoma HepG2 cell lines were evaluated by methyl thiazolyl tetrazolium (MTT) assay. The results displayed that several compounds showed moderate to potent antitumor activity [24].

![Scheme 7. Synthesis of thiazolo[3, 2-a]pyrimidine derivatives using substituted phenylhydrazines as the starting material.](image)

4. **Synthesis of pyridothieno-fused thiazolo[3,2-a]pyrimidinones via Pictet-Spengler reaction**

The Pictet–Spengler reaction [25] is a kind of the most excellent strategies for C–C bond formation obtained considerable important for the synthesis of variety products and novel heterocycles of biological interest in synthetic organic chemistry [26], because of its outstanding functional group tolerance, stereo- and regio-selectivity. Wang et al. reported an effective method for the synthesis of pharmacologically excellent, functionalized fused pyrido[3”, 2”: 4’, 5’]thieno[3’, 2’: 2, 3]pyrido[4,5-d][1,3]thiazolo[3,2-a]pyrimidine-4-one derivatives 8 via Pictet–Spengler reaction between 2-(3-aminothieno[2,3-b]pyridin-2-yl)thiazolo[3,2-a]pyrimidin-5-one and aromatic aldehydes with NH₂SO₃H as the catalysis. 2-(3-Aminothieno[2,3-b]pyridin-2-yl)thiazolo[3,2-a]pyrimidin-5-ones were obtained by the condensation of 7-(chloromethyl)-5H-thiazolo[3,2-a]pyrimidin-5-one with 3-cyanopyridine-2-thione via Thorpe–Ziegler isomerization [27]. The advantages of this method were of easy available starting materials, mild reaction conditions, simple product isolation and good yields.
5. Synthesis of pyrido[4,3-d]thiazolo[3,2-a]pyrimidine by reacting 2-aminothiazole with the α, β-unsaturated ketones

Pyrido[4,3-d]thiazolo[3,2-a]pyrimidines 9 were designed and synthesized by reacting 2-aminothiazole with the α, β-unsaturated ketones which obtained by reacting N-ethyl-piperidone with various benzaldehyde analogues in ethanolic solution of sodium hydroxide. The in-vitro antitumor activity of the obtained compounds were evaluated at the National Cancer Institute (NCI) 60 cell lines panel assay. Some of the synthesized pyrido[4,3-d]thiazolo[3,2-a]pyrimidines showed outstanding broad-spectrum antitumor activity and could be considered as a useful template for future development to obtain more potent antitumor agent(s) [28].

6. Summary

As was mentioned above, the synthesis methods of thiazolo[3,2-a]pyrimidine compounds were numerous. Over the course of the study, the original synthesis of thiazolo[3,2-a]pyrimidines by condensation of pyrimidine-2-thiones, which were obtained by Biginelli reaction between aromatic aldehydes and thiourea, with substituted 2-bromo-1-phenylethanone reaction was improved and the new MCRs were constantly discovered. At the same time, many new thiazolo[3,2-a]pyrimidine compounds with high activity and high selectivity could be developed as medicine or pesticides. At present, the synthesis and research of thiazolo[3,2-a]pyrimidine compounds have attracted wide attention from the chemical industry at home and abroad. It is believed that in the near future, thiazolo[3,2-a]pyrimidine compounds will play an important role in the field of organic synthesis research and related applications.

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References

[1] Tozkoparan B, Ertan M, Kelicen P and Demirdamar R 1999 *Il Farmaco* **54** 588–93
[2] Jeanneau-Nicolle E, Benoit-Guyod M, Namil A and Leclerc G 1992 *Eur. J. Med. Chem.* **27** 115-20
[3] Van Laar M, Volkerts E and Verbatim M 2001 *Psychopharmacology* **154** 189-97
[4] Sayed H H, Shamroukh A H and Rashad A E 2006 *Acta Pharm.* **56** 231-44
[5] Alam O, Khan S A, Siddiqui N and Ahsan W 2010 *Med. Chem. Res.* **19** 1245-58
[6] Coburn R A and Glennon R A 1973 *J. Pharm. Sci.* **62** 1785-89
[7] Abu-Hashem A A, Youssif M M and Hussein H A R 2011 *J. Chin. Chem. Soc.* **58** 41-48
[8] Mohamed S F, Flefel E M, Amr A and Abd El-Shafy D N 2010 *Eur. J. Med. Chem.* **45** 1494-1501
[9] Balkan A, Uma S, Ertan M and Wiegrebe W 1992 *Pharmazie* **47** 687-88
[10] Nobe K, Miyatake M, Nobe H, Sakai Y, Takashima J and Momose K 2004 *Br. J. Pharmacol.* **143** 166-78
[11] Proudfoot J R 1998 *Expert Opin. Ther. Pat.* **8** 971-82
[12] Wichmann J, Adam G, Kolczewski S, Mutel V and Woltering T 1999 *Bioorg. Med. Chem. Lett.* **9** 1573-76
[13] Zhi H, Chen L, Zhang L, Liu S, Wan D C C, Lin H and Hu C 2008 *ARKIVOC* **xiii** 266-78
[14] Kolb S, Mondésert O, Goddard M, Jullien D, Villoutreix B O, Ducommun B, Garbay C and Braud E 2009 *ChemMedChem* **4** 633-48
[15] Cornish J W, Maiani I, Fudala P J, Ehrman R N, Robbins S J and O’Brien C P 2001 *Drug Alcohol Depend.* **61** 183-89
[16] a)Dömling A, Wang W and Wang K 2012 *Chem. Rev.* **112** 3083-3135; b)Zhu J P and Bienaymé H 2004 *Multicomponent Reactions* (Weinheim Wiley-VCH)
[17] Adib M, Nosrati M, Mahdavi M, Zhu L G and Mirzaei P 2007 *Synlett.* **17** 2703-06
[18] Esmaili A A, Zangouei M, Fakhari A R and Habibi A 2012 *Tetrahedron Lett.* **53** 1351-53
[19] Esmaili A A, Amini-Ghalandarabad S, Mesbah F, Tasnim M, Izadyar M, Fakhari A R and Salimi A R 2015 *Tetrahedron* **71** 2458-62
[20] Hao W J, Zhou P, Wu F Y, Jiang B, Tu S J and Li G 2016 *Eur. J. Org. Chem.* **11** 1968-71
[21] Khobragade C N, Bodade R G, Dawane B S, Konda S G and Khandare N T 2010 *J. Enzyme Inhib. Med. Chem.* **25** 615-21
[22] Wang C H, Jia Y H and Cai D 2014 *Chemistry* **77** 174-77
[23] Wang J, Lin Y, Zhu X L, Nie J, Zhang L and Yao Q Z 2015 *Chinese J. Synth. Chem.* **23** 580-83
[24] Zhang L, Lin Y, Wang J, Zhu X L, Yao Q L and Yao Q Z 2015 *Chin. J. Org. Chem.* **35** 497-504
[25] Pictet A, Spengler T T 1911 *Ber. Dtsch. Chem. Ges.* **44** 2030-36.
[26] (a) Youn S W 2006 *Org. Prep. Proced. Int.* **38** 505–91; (b) Kundu B, Agarwal P K, Sharma S K 2012 *Curr. Org. Synth.* **9** 357-76
[27] Wang D L, Wang D, Yan L, Pan G Y and Yang J N 2016 *Chin. Chem. Lett.* **27** 953-56
[28] Al-Omary F A M, Hassan G S, El-Messery S M and El-Subbagh H I 2012 *Eur. J. Med. Chem.* **47** 65-72