Chinese Chemical Letters 27 (2016) 953–956

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Original article

An efficient synthesis of novel pyridothieno-fused thiazolo[3,2-*a*]pyrimidinones *via* Pictet–Spengler reaction

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ARTICLE INFO

Article history:
Received 8 December 2015
Received in revised form 8 January 2016
Accepted 2 February 2016
Available online 28 February 2016

Keywords:
7-Chloromethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one
3-Cyanopyridine-2-thione
Pyrido[3″,2″:4′,5′]thieno[3′,2′:2,3]pyrido [4,5:*d*] [1,3]Thiazolo[3,2-*a*]pyrimidine-4-one
Thorpe–Ziegler reaction
Pictet–Spengler reaction

ABSTRACT

An efficient method for the synthesis of novel pyrido[3″,2″:4′,5′]thieno[3′,2′:2,3]pyrido [4,5:*d*][1,3]thiazolo[3,2-*a*]pyrimidine-4-one derivatives (**5**) has been developed using a Pictet–Spengler reaction between 2-(3-aminothieno[2,3-*b*]pyridin-2-yl)thiazolo[3,2-*a*] pyrimidin-5-one (**3**), which could be obtained from the condensation of 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**1**) with 3-cyanopyridine-2-thione (**2**) *via* Thorpe–Ziegler isomerization, and aromatic aldehydes under NH_2SO_3H as catalysis in good yields.

1. Introduction

Functionalized heterocyclic building blocks are of great importance in both medicinal and synthetic chemistry and development of new efficient synthetic methodologies for these scaffolds remains a great challenge in modern organic synthesis [1]. It is well known that several drugs exploit heterocyclic systems and are often nitrogen-containing with both five- and six-membered rings.

For example, some derivatives of thiazolo[3,2-*a*]pyrimidines are known to exhibit versatile biological activity, which include anticancer [2], antitumor [3], antiinfl ammatory [4], antinociceptive [5], antiviral [6], and antibiofilm properties [7]. Owing to these remarkably broad pharmacological properties, a variety of synthetic methods have been reported for the preparation of thiazolo[3,2-*a*] pyrimidinone derivatives [6–10].

In addition, thienopyridine [11] and their annulated with heterocycles [12] have attracted widespread interest owing to their presence in natural products, and their biological and pharmacological activities.

The Pictet–Spengler reaction [13] has become one of the most prominent strategies for carbon–carbon bond formation in synthetic organic chemistry with excellent functional group tolerance, regio- and stereo-selectivity. From this perspective, the modified Pictet–Spengler reactions are attained considerable important for the synthesis of various products and novel heterocycles of biological interest [14].

In view of the above observations and continuing our previous works on develop new methodologies for the preparation of fused heterocyclic compounds [15], herein we report the synthesis of some new condensed heterocyclic systems: pyrido[3″,2″:4′,5′] thieno [3′,2′:2,3]pyrido[4,5:*d*][1,3]thiazolo[3,2-*a*]pyrimidine-4-one derivatives by the application of Pictet–Spengler reaction (Scheme 1).

2. Experimental

2.1. Preparation of 2-(3-aminothieno[2,3-b]pyridin-2-yl)thiazolo [3,2-a]pyrimidin-5-one (*3*)

To a solution of 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **1** [16] (20.0 mmol) in DMF (25 mL) was added 3-cyanopyridine-2-thione **2** (4.11 g, 30.0 mmol) and anhydrous potassium carbonate (5.52 g, 40.0 mmol). The mixture was heated at 80 °C for 4 h. After cooling to room temperature, water (50 mL)

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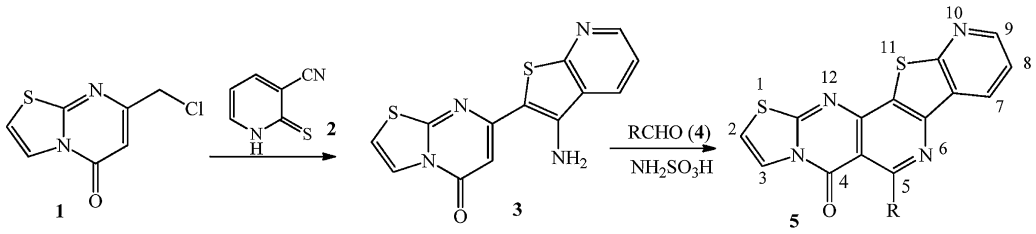
http://dx.doi.org/10.1016/j.cclet.2016.02.007



Scheme 1. Syntheses of fused thiazolopyrimidines.

was added and stirred for 20 min. The solid was filtered and recrystallized from HOAc to give **3** in 83% yield. Mp > 300 °C. IR (KBr, cm^{-1}): ν 34265 (NH), 3356 (NH), 1686 (C=O). ^1H NMR (400 MHz, DMSO-d_6): δ 6.05 (s, 1H), 7.43–7.48 (m, 3H), 7.50 (d, 1H, J = 4.8 Hz), 8.01 (d, 1H, J = 4.8 Hz), 8.49 (d, 1H, J = 7.6 Hz), 8.61 (d, 1H, J = 8.0 Hz). Anal. Calcd. for $C_{13}H_8N_4OS_2$: C 51.98, H 2.68, N 18.65. Found: C 52.05, H 2.76, N 18.73.

2.2. Preparation of pyrido[3″,2″:4′,5′]thieno[3′,2′:2,3]pyrido-[4,5:d][1,3]thiazolo[3,2-a]pyrimidine-4-one derivatives

A mixture of 2-(3-aminothieno[2,3-*b*]pyridin-2-yl)thiazolo[3,2-*a*]pyrimidin-5-one **3** (1.0 mmol), aromatic aldehyde **4** (1.0 mmol) and sulfamic acid (SA) (10 mg, 0.1 mmol) in DMF (15 mL) was heated for 7–16 h at 100 °C. After the completion of the reaction judged by TLC analysis, the reaction mixture was cooled to room temperature. Water (50 mL) was added and the mixture was stirred for 30 min. The solid was filtered and recrystallized from DMF to afford the corresponding products (**5a–l**) [17].

3. Results and discussion

In this study, the key intermediate amine 2-(3-aminothieno[2,3-*b*]pyridin-2-yl)thiazolo[3,2-*a*]pyrimidin-5-one **3** was obtained by the condensation of 7-(chloromethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **1** with 3-cyanopyridine-2-thione **2** *via* Thorpe–Ziegler isomerization [18] in good yield. Its structure was determined from the spectral data as well as elemental analysis.

In an initial endeavor, we selected benzaldehyde **4a** as a model aldehyde to react with an equimolar of the intermediate amine **3a** for the preparation of pyrido[3″,2″:4′,5′]thieno[3′,2′:2,3]pyrido-[4,5:*d*][1,3]thiazolo[3,2-*a*]pyrimidine-4-one **5a** and investigated the optimal reaction conditions. The effects of solvents, catalysts and temperature were evaluated for this reaction, and the results are summarized in Table 1. It was found that the reaction could not proceed in DMF under catalyst-free conditions (entry 1). Later, the reaction was performed in the presence of catalytic amounts of sulfamic acid (H_2NSO_3H, SA, 10 mol%), in the presence of different solvents, moderate yields of the product were obtained (entries 2–5). Notably, DMF was found to be the best solvent providing 74% of the product with in 10 h (entry 5). After obtaining the desired product in good yields, the amount of SA and the temperature required for this reaction were evaluated. The reaction was performed using 15 mol%, 20 mol%, and 30 mol% of sulfamic acid in DMF at 100 °C. It was found that while increasing the amount of SA, the yields increased from 86% to 85%, and 80%, respectively (entries 6–8). Later the reaction was conducted at different temperatures, it was observed that while increasing the temperatures from 110 to 120, and 130 °C. The yields also increased from 84% to 82%, and 78%, respectively (entries 9–11). In addition, several other acids were then evaluated for their catalytic efficiency in this reaction. The results indicated that SA provided a superior catalytic effect to *p*-TsOH, TFA, and H_2SO_4 (entries 12–14). Therefore, it could be concluded that 15 mol% of sulfamic acid in DMF at 100 °C are optimum conditions for this transformation.

Under the optimized conditions, a wide range of aromatic aldehydes **4** underwent this one-pot condensation with of 2-(3-aminothieno[2,3-*b*]pyridin-2-yl)thiazolo[3,2-*a*]pyrimidin-5-one **3** to give the corresponding fused thiazolo[3,2-*a*]pyrimidinones **5**.

As shown in Table 2, this protocol could be applied not only to the aromatic aldehydes with either electron with drawing groups (such as halide groups) or electrondonating groups (such as alkyl, hydroxy groups), but also to heterocyclic aldehydes. Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction. Furthermore, when an alphatic aldehyde was treated with **3**, the desired products **5m** and **5n** were also obtained in 57% and 60%, respectively (entries 13, 14).

All the products were characterized by IR, ^1H NMR, ^{13}C NMR and elemental analysis. And all the data are consistent with the proposed structures.

Table 1
Optimization of reaction conditions on the synthesis of pyrido[3″,2″:4′,5′]thieno[3′,2′:2,3]pyrido [4,5:*d*][1,3]thiazolo[3,2-*a*]pyrimidine-4-one **5a**[a].

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	–	DMF	100	24	0
2	SA (10)	CH_3CN	80	18	42
3	SA (10)	HOAc	100	13	68
4	SA (10)	Toluene	100	16	47
5	SA (10)	DMF	100	10	74
6	SA (15)	DMF	100	7	86
7	SA (20)	DMF	100	7	85
8	SA (30)	DMF	100	6	80
9	SA (15)	DMF	110	7	84
10	SA (15)	DMF	120	6	82
11	SA (15)	DMF	130	6	78
12	*p*-TsOH (15)	HOAc	120	14	73
13	TFA (15)	DMF	100	12	80
14	H_2SO_4 (15)	DMF	100	13	68

[a] Reaction conditions: **3a** (1.0 mmol), benzaldehyde (**4a**, 1.0 mmol), solvent (20 mL).

Table 2
Synthesis of fused thiazolo[3,2-*a*]pyrimidinones **5**.

Entry	Products	*R*′	Time (h)[a]	Yield (%)[b]
1	**5a**	C_6H_5	10	86
2	**5b**	4-MeC_6H_4	9	84
3	**5c**	2-$MeOC_6H_4$	11	78
4	**5d**	3-$MeOC_6H_4$	8	80
5	**5e**	4-$MeOC_6H_4$	8	85
6	**5f**	3,4-$(MeO)_2C_6H_3$	7	85
7	**5g**	4-HOC_6H_4	10	82
8	**5h**	4-ClC_6H_4	12	80
9	**5i**	4-FC_6H_4	12	78
10	**5j**	4-$NO_2C_6H_4$	15	75
11	**5k**	2-Furyl	10	78
12	**5l**	2-Thienyl	12	75
13	**5m**	*n*-Pr	16	57
14	**5n**	*n*-Bu	16	60

[a] Reaction progress monitored by TLC.
[b] Isolated yield.