Tetrahedron 72 (2016) 8610–8616

Contents lists available at ScienceDirect

Tetrahedron

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

An efficient method for the construction of 2-Aminothiazolo[5,4-*c*] pyridines via $K_3[Fe(CN)_6]$ oxidized SP^2 C–H Functionalization

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ARTICLE INFO

Article history:
Received 11 September 2016
Received in revised form
9 November 2016
Accepted 14 November 2016
Available online 15 November 2016

Keywords:
Pyridylthioureas
Thiazolo[5,4-*c*]pyridines
$K_3[Fe(CN)_6]$
Oxidative cyclization
Free-radical

ABSTRACT

A practical approach to synthesize 2-aminothiazolo[5,4-*c*]pyridines from simple asymmetric pyridylthioureas was achieved by utilizing $K_3[Fe(CN)_6]$ as the oxidant. These reactions went through an intramolecular oxidation and finally led to the formation of C–S bond. Furthermore, the possible oxidative cyclization mechanism was also explored by the addition of radical scavengers, which showed that the oxidative cyclization was promoted via a free radical mechanism.

1. Introduction

Thiazole is one of the most important heterocyclic structures. It widely exits in heterocyclic compounds.[1] As one of its derivatives, thiazolopyridine has attracted a great deal of attentions due to their broad range of biological activities and pharmaceutical properties.[2–4] For example, Edoxaban (**A**) which contains a tetrahydrothiazolo[5,4-*c*]pyridine ring was expected to be used as an orally effective anticoagulant drug.[2] A series of thiazolopyridine compounds (**B**) are good candidates as TYK2 kinase inhibitors.[3] The derivatives of thiazolo[5,4-*b*]quinoline (**C**) was described as a new type of potential antitumor agents.[4] (Fig. 1).

Surprisingly, so far only a few synthetic methods of constructing thiazolopyridine have been reported.[1c,5] The methods are either based on the condensation of *ortho*-aminopyridinethiols with carboxylic acids or aldehydes[6]; or Hugershoff reaction, in which the benzothiourea can be oxidated with liquid bromine or an alternative electrophilic bromine source to form the benzothiazole ring.[7] Recently, some new methods have been reported, such as transition-metal-catalyzed cyclization of *ortho*-aminochloropyridine with additional sulfur sources as coupling partners[8] or transition-metal-catalyzed direct C–H functionalization/cyclization of pyridinylthioamide.[9] However, these approaches suffer from difficulties in the preparation of starting materials, harsh reaction conditions and the use of precious metal catalyst. Therefore, a highly efficient, mild and low-cost protocol for the synthesis of thiazolopyridine would be quite desirable. It is noteworthy that the Jacobson reaction has been widely used in preparation of many benzothiazole compounds.[10] Therefore, we anticipate that the direct intramolecular oxidation between pyridine and thiourea may probably occur and finally lead to the formation of C–S bond via C–H functionalization. This method would be an attractive approach to synthesize thiazolo[5,4-*c*]pyridine compounds. In this research, we presented a convenient two-step procedure for the synthesis of the thiazolo[5,4-*c*]pyridine nuclei from commercially available starting material 4-aminopyridine in mild reaction conditions.

2. Results and discussion

Our initial purpose was to obtain the thiazolo[5,4-*c*]pyridine compounds and their derivatives which could be potentially used as lead compounds. In our previous work about the reaction conditions of Jacobson reaction, we found that when the substituents on benzene were electron-withdrawing groups, the benzothiazole products were always obtained in high yield. In fact the reaction

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http://dx.doi.org/10.1016/j.tet.2016.11.032
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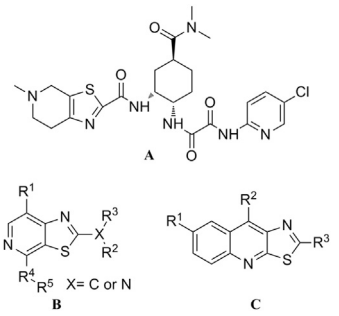
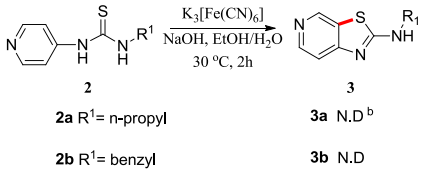


Fig. 1. Structure of bioactive thiazolopyridine derivatives.

sites tend to be in the electron rich position, but the electron rich substrate may produce more byproducts and finally decrease the yield. Since the pyridine ring is relatively electron deficient, we believe similar reactions as Jacobson reaction would occur in a good yield. The starting material pyridylthiourea was prepared by reacting 4-aminopyridine with *1,1'*-thiocarbonyldimidazole and secondary amine in sequence. In this study, oxidative cyclization of pyridylthiourea with aqueous potassium ferricyanide as the oxidant resulted in a number of intriguing thiazolo[5,4-*c*]pyridine compounds in up to 85% yield.

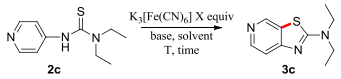
The first attempt was carried out to generate the target **3a** and **3b** by oxidizing corresponding pyridylthioureas **2a** and **2b** in one step (Scheme 1). Unfortunately, no expected products were observed under such condition, and this result was consistent with Jan Bergman's works in 2003.[1g] We found that there are two active protons in **2a** or **2b**. These protons may play a role in inhibiting the cyclization. To test our hypothesis, we decided to replace the primary amine with the secondary amine in the pyridylthiourea.

Therefore, compound **2c** was synthesized to be our model substrate (Table 1, enties 1–20). Its oxidative cyclization reaction was tested under standard oxidative condition utilizing $K_3[Fe(CN)_6]$ as the oxidant. To our delight, this cyclization successfully occurred at 30 °C and gave the desired product **3c** in a yield of 80% determined by HPLC (Table 1, entry 1). To investigate this oxidative cyclization reaction, an evaluation of different reaction conditions has been developed. When the oxidative cyclization reaction was conducted in various solvents, the cyclized product **3c** was also able to be successfully obtained (Table 1, entries 2–10). We also found that when the solvent was a mixture of EtOH and H_2O in a ratio of 1:1, it generate the best result (Table 1, entry 1). In the same time, we noticed this transformation will be completed in 2 h (Table 1, entries 11, 12). Then a screening of different bases were conducted under the same condition, the results indicated that it had the highest yield when NaOH was used as the base (Table 1, entries 13–17). Finally, the usage amount of oxidant was investigated, We gradually increased the equivalent of $K_3[Fe(CN)_6]$ in this reaction, the substrate was almost transformed to the ring-closure products when 4 equivalents of $K_3[Fe(CN)_6]$ were used (Table 1, entries 18–20). Therefore, we finally chose to use 4 equivalents of



Scheme 1. The substrate contains two active protons[a]. [a] General reaction conditions: 0.1 mmol of **2**; 2 equivalents of potassium ferricyanide; 2 equiv of base; 2.0 mL of EtOH. and 2.0 mL of water, 30 °C, 2 h, Air. [b] No detected.

Table 1
Optimization of the reaction conditions[a].



Entry	Solvent	X	Base	Time(h)	Yield(%)[b]
1	EtOH/H_2O	2	K_2CO_3	2	80
2	Acetone/H_2O	2	K_2CO_3	2	61
3	DMF/H_2O	2	K_2CO_3	2	55
4	DMSO/H_2O	2	K_2CO_3	2	12
5	THF/H_2O	2	K_2CO_3	2	55
6	CH_3CN/H_2O	2	K_2CO_3	2	51
7	EtOH	2	K_2CO_3	2	4
8	H_2O	2	K_2CO_3	2	69
9	EtOH/H_2O	2	K_2CO_3	2	50[c]
10	EtOH/H_2O	2	K_2CO_3	2	58[d]
11	EtOH/H_2O	2	K_2CO_3	0.5	75
12	EtOH/H_2O	2	K_2CO_3	1	79
13	EtOH/H_2O	2	NaOH	2	82
14	EtOH/H_2O	2	KOH	2	77
15	EtOH/H_2O	2	LiOH·H_2O	2	73
16	EtOH/H_2O	2	Na_2CO_3	2	61
17	EtOH/H_2O	2	$KHCO_3$	2	35
18	EtOH/H_2O	1	NaOH	2	45
19	EtOH/H_2O	3	NaOH	2	96
20	EtOH/H_2O	4	NaOH	2	97

[a] Reaction conditions unless otherwise specified: 0.1 mmol of **2c**; 2 equivalents of oxidant; 2 equivalents of base; 2.0 mL of EtOH and 2.0 mL of H_2O; 30 °C; N_2 atmosphere.
[b] Determined by HPLC.
[c] 1.0 mL of EtOH and 3.0 mL of water as the solvent.
[d] 3.0 mL of EtOH and 1.0 mL of water as the solvent.

$K_3[Fe(CN)_6]$ and 2 equivalents of NaOH at 30 °C in EtOH/H_2O as the optimal reaction condition (Table 1, entry 20).

In order to extend the substrate scope of oxidative cyclization, a series of pyridylthiourea compounds were synthesized in the same reaction conditions and were then oxidized to provide the corresponding *N,N*-disubstitutedthiazolo[5,4-*c*]pyridin-2-amine derivatives. We found that these reactions were suitable for alkyl secondary amine and both of steric hindrance and chain length didn't show any disadvantageous influence on the final products **3c**-**3f** (Table 2, entries 1–4). Furthermore, we replaced the secondary amine group with nitrogen-heterocyclic structures, such as piperidine, morpholine, N-methylpiperazine and 1-boc-piperazine. The desired products were obtained in moderate yields **3g**-**3j** (Table 2, entries 5–8). However, when the aromatic secondary amine such as monomethylaniline was adopted into substrate **2k**, compound **3k'** instead of the desired compound **3k** was obtained with up to 84% isolated yield (Table 2, entry 9). This result might be due to the fact that the active sulfur radical would prefer to attack the more electron-rich benzene rather than pyridine. To the contrary of **2k**, when **2l** was used as starting material, the desired product **3l** was obtained with the yield up to 73% (Table 2, entry 10). In addition, the ring-closure products were also afforded smoothly with moderate yields when the substrates **2m**-**2o** contained electron-withdrawing groups such as amide, cyano and nitro (Table 2, entries 11–13).

The methodology also exhibited a broad substrate scope and diversity. The pyridine ring bearing electron-withdrawing or electron–donating groups all well tolerated the reaction conditions and produced the target compounds in moderate to good yields. The effect of the substituents on pyridine ring was investigated (Table 3, entries 1–7). In this context, a particularly appealing feature of the oxidative system is the synthesis of 7-halothiazolo[5,4-*c*]pyridines without affecting the *ortho*-halide group. Halo substituents **3p**-**3r**