Tetrahedron 73 (2017) 5194–5199

Contents lists available at ScienceDirect

Tetrahedron

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

Elemental sulfur mediated cyclization via redox strategy: Synthesis of benzothiazoles from *o*-chloronitrobenzenes and benzyl chlorides

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ARTICLE INFO

Article history:
Received 26 May 2017
Received in revised form
4 July 2017
Accepted 8 July 2017
Available online 10 July 2017

Keywords:
Benzothiazoles
Benzyl chlorides
Elemental sulfur
Cyclization
Redox strategy

ABSTRACT

A novel metal-free synthesis of 2-substituted benzothiazoles from easily available *o*-chloronitrobenzenes and benzyl chlorides using elemental sulfur as traceless oxidizing agent has been developed. The protocol provides a simple, efficient, and atom-economic way to access to benzothiazoles in moderate to excellent yields. And the approach exhibited good functional group tolerance.

1. Introduction

2-Substituted benzothiazole derivatives represent an important class of heterocyclic compounds which play essential roles as key blocks in the synthesis of a variety of drugs such as antitumoral, antimicrobial, anti-inflammatory and anticonvulsant agents.[1,2] Thus, there are numerous efforts aimed at developing efficient methods for rapid construction of benzothiazoles.

The conventional wisdom approaches for the synthesis of these compounds typically rely on the condensation of 2-aminothiophenols with aldehydes[3] or carboxylic acids[4] under oxidative conditions, the oxidative cross-coupling of benzothiazoles and phenylacetic acids[5] or intramolecularcyclization of 2-haloanilides catalyzed by transition metal.[6] However, these reactions are suffering from difficulties in preparation of starting materials, application of excess added agents, and harsh reaction conditions. To overcome these limitations, it is crucial to make a valid and practical protocol for the construction of C–C and C–S bonds in a direct step- and atom-economical approach.[7] To the best of our knowledge, the strategy for the redox reactions has become a powerful tool to synthesize heterocyclic compounds, as it is highlighted by the direct product formation without an added agent such as oxidant, reductant, acid or base.[8] Recently, our group disclosed a green and novel synthesis of 2-substituted benzothiazoles from 2-chloronitrobenzenes and aliphatic amines via elemental sulfur mediated redox cyclization in the absence of external oxidant or reductant (Scheme 1a).[9a] And meanwhile, Nguyue group also illuminated an analogical methodology.[9b] A decarboxylative redox reaction using *o*-chloronitroarenes, arylacetic acids and elemental sulfur as substrates under solvent- and catalyst-free conditions has been developed by Guntreddi group (Scheme 1b).[10] Thus it can be seen that elemental sulfur which is readily available, nontoxic, and stable under ambient conditions plays a vital role in redox reactions as oxidant and reductant due to its valence states diversity, ranging from −2 to +6.[11] In addition, our lab has reported a metal-free approach to benzothiazoles from benzyl chlorides and 2-mercaptan anilines using elemental sulfur as traceless oxidizing angent (Scheme 1c). Furthermore, benzyl chloride derivatives are a family of inexpensive organic intermediates and served as new and potential acyl sources.[12,13]

Herein, we report an elemental sulfur mediated redox condesation from benzyl chlorides and *o*-chloronitrobenzenes for the synthesis of 2-substituted benzothiazoles under metal-free

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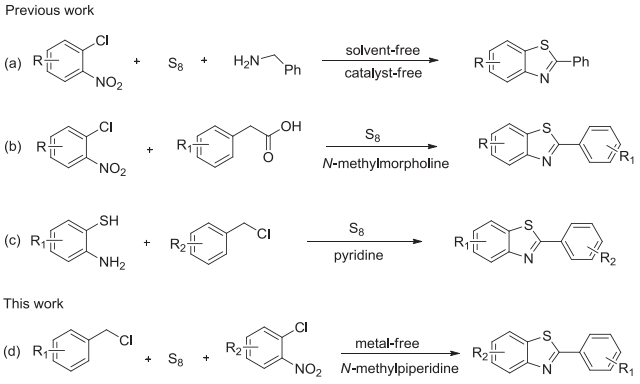
http://dx.doi.org/10.1016/j.tet.2017.07.013
0040-4020/



Scheme 1. Access to 2-Substituted Benzothiazoles.

conditions (Scheme 1d).

2. Results and discussion

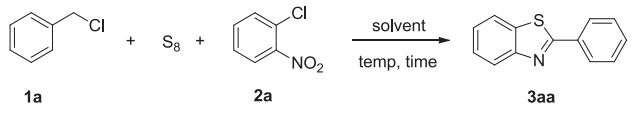
As an exploratory study, benzyl chloride (**1a**) and *o*-chloronitrobenzene (**2a**) were chosen as test substrates in the presence of elemental sulfur (Table 1). As we expected, when the reaction was carried out in *N*-methylpiperidine at 120 °C for 24 h under nitrogen atmosphere, the desired product **3aa** was obtained in 60% yield (entry 1). The amount of elemental sulfur was an important factor for the yield of the product. And the use of 1.5 equiv elemental sulfur led to a higher yield of **3aa** (entries 2–3). To determine the effect of temperature on this approach, these reactions were checked (entries 4–6), and the reaction yield increased to 80% when the temperature was decreased to 110 °C (entry 5). We then investigated the impact of solvent on reaction yield (entries 7–8), and it proved that *N*-methylpiperidine was superior to others. Furthermore, reducing the reaction time to 18 h or prolonging to 36 h resulted in lower yields (entries 9–10). Thus, the optimized conditions were confirmed: 2.0 equiv of benzyl chloride **1a**, 1.0 equiv of *o*-chloronitrobenzene **2a** and 1.5 equvi of element sulfur in *N*-methylpiperidine (1.5 mL) at 110 °C for 24 h under a nitrogen atmosphere (entry 4).

Now the optimal reaction conditions had been identified, the scope of the multicomponent one-pot reaction was investigated (Table 2). We first focused on the influence of various benzyl chlorides on the reaction. The reaction with benzyl chlorides bearing electron-donating groups could be smoothly transformed into the desired products (**3ab-3ah**). Furthermore, benzyl chlorides possessing 3, 4-dimethoxy or *p-tert*-butyl also provided the corresponding products in good yields (**3ag-3ah**). Additionally, this transformation also showed satisfactory tolerance of halogen groups (**3ai-3an**), which provide useful handles for further transformations through traditional cross-coupling reactions. It is noteworthy that simple methyl or bromine group at the *para*- and *meta*-positions (**3ab, 3ac** and **3ak**) underwent the redox process to afford the expected products in good yields, whereas giving slightly inferior yields when the substituents at *ortho*-position (**3ad, 3al**), probably as a result of steric hindrance. However, we found that the electron-deficient substituents did obviously affect the efficiency on the reaction **(3ao-3ar**). The stronger were the substituents, the lower were the yields. When benzyl chloride linked with nitro group on the benzene ring, no product was obtained (**3ar**). Besides, α-naphthyl and biphenyl group substrates were also compatible to give **3as-3at** in 65% and 47% yields, respectively. Notably, heteroaromatic methyl chlorides also worked well under standard conditions and offered **3au-3ax** in moderate to good yields. On the other hand, we also evaluated readily available substituted *o*-chloronitrobenzenes tolerance in the present reaction conditions subsequently. Much to our satisfaction, the presence of the electron-donating groups such as methyl and methoxyl group promoted the yields of the reaction (**3ba-3da**). Besides, the *o*-chloronitrobenzenes bearing halo-substituted groups were all well-tolerated under the standard reaction conditions and transformed smoothly into expected products in 73%, 72%, 69% and 73% yields, respectively (**3ea-3ha**).

To gain insights into the reaction mechanism, control experiments were performed under standard conditions as highlighted in Scheme 3. First, each couple of starting materials was heated together at 110 °C for 24 h in *N*-methyilpiperidine (Scheme 2, eqs. 1–3): Treatment of benzyl choride **1a** with *N*-methylpiperidine was transformed into 1-benzyl-1-methylpiperidine chloride; In contrast, reaction of sulfur with **2a** did not work and all starting materials were recovered unchanged. Notably, when 1 equiv or 2 equiv radical trapping reagent TEMPO was added to the reaction mixture, the expected product **3aa** was obtained in 53% and 30% yields, respectively, which was lower than that under standard conditions. Thus it indicated that a radical pathway might be involved (Scheme 2, eq. 4).

On the basis of these above experiments and previous literature,[9,10,12,13] a plausible mechanism is proposed in Scheme 3. At first, benzyl chloride **1a** undergoes *N*-methylpiperidine to produce 1-benzyl-methylpiperidinium chloride **A**. After that, in the presence of elemental sulfur, **A** is oxidized to form polysulfide **B** and the radical intermediate **C** is generated by the sulfur extrusion, which reacts with the nitro group of **2a** to yield **D** subsequently. Then by the means of sulfuration of the methylene, the intermediate **D** can be converted into **E**, which eventually undergoes a cascade reaction of cyclization and reduction to afford the desired product **3aa**.

Table 1
Optimization of the reaction Conditions[a].



1a 2a 3aa

entry	solvent	S (equiv)	temp (°C)	yield[b] (%)
1	*N*-methylpiperidine	1	120	60
2	*N*-methylpiperidine	1.5	120	75
3	*N*-methylpiperidine	2	120	70
4	***N*-methylpiperidine**	**1.5**	**110**	**80**
5	*N*-methylpiperidine	1.5	100	78
6	*N*-methylpiperidine	1.5	90	40
7	pyridine	1.5	110	20
8	Triethylamine	1.5	110	60
9[c]	*N*-methylpiperidine	1.5	110	71
10[d]	*N*-methylpiperidine	1.5	110	72

[a] Reaction conditions: benzyl chloride (1 mmol), *o*-chloronitrobenzene (0.5 mmol) in solvent (1.5 mL) under a nitrogen atmosphere for 24 h at the specified reaction temperature.
[b] Isolated yield.
[c] 18 h.
[d] 36 h.

3. Conclusion

In summary, we have developed a novel and facile approach that elemental sulfur mediated direct construction of 2-substituted benzothiazoles from readily available *o*-chloronitrobenzenes and benzyl chlorides in the absence of transition metal. This approach afforded 2-substituted benzothiazoles in satisfactory yields with good substrate tolerance. The reaction makes the process attractive and practical, which is free from the use of metal or external