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A facile and efficient approach for the synthesis of 3-arylthiazol-2(3*H*)-one

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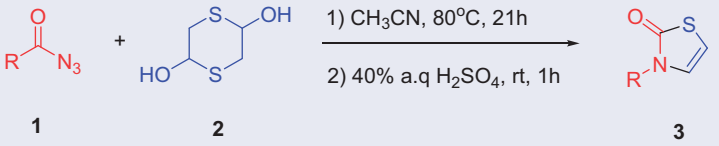
ABSTRACT

A facile and efficient method for synthesis of 3-arylthiazol-2(3*H*)-one through the reaction of acyl azide and 1,4-dithiane-2,5-diol was reported. This reaction proceeded at 80 °C at first and then in acidic condition at room temperature, to afford products in good yields for a wide range of substrates and a possible mechanism has also been proposed.

GRAPHICAL ABSTRACT



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Acyl azide; 3-arylthiazol-2(3*H*)-one; 1,4-dithiane-2,5-diol; facile synthesis; nucleophilic addition

Introduction

The substituted thiazol-2(3*H*)-one fragment is a structural motif in some biologically active compounds (Figure 1). Kenda reported substituted thiazol-2(3*H*)-one derivative **a** as anticonvulsant.[1] Substituted thiazol-2(3*H*)-one derivative **b** could be used as the inhibitor of autotaxin (the autotaxin-lysophosphatidic acid signaling axis has been implicated in inflammation, fibrosis, and tumor progression, rendering autotaxin an attractive drug target).[2] The substituted thiazol-2(3*H*)-one derivative **c** had anti-inflammatory and analgesic activity.[3]

In view of the importance of the thiazol-2(3*H*)-one, a great deal of attention has been given to its organic synthesis, such as K_2CO_3/I_2-mediated transformation from thiazole to thiazol-2(3*H*)-one (Scheme 1-A, equation (1)),[4] the synthesis method using aryl isocyanate and 1,4-dithiane-2,5-diol under microwave condition (Scheme 1-A, equation

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*Yue Zhu and Qilin Wang contributed equally to this work.

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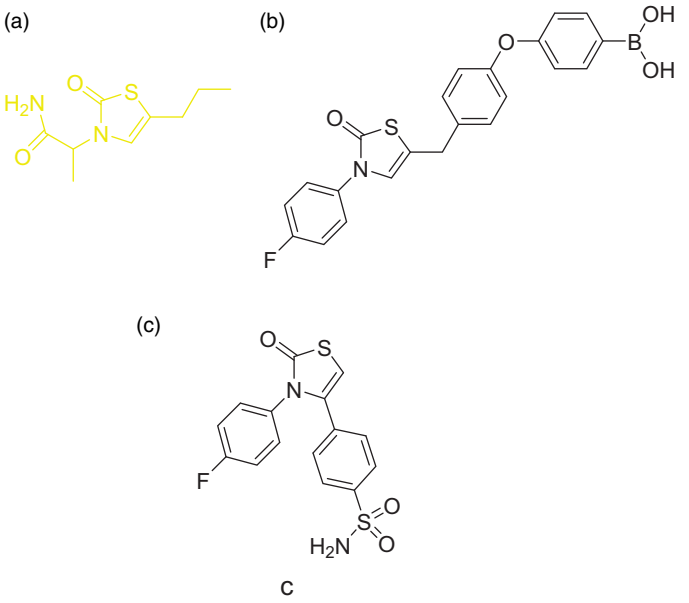
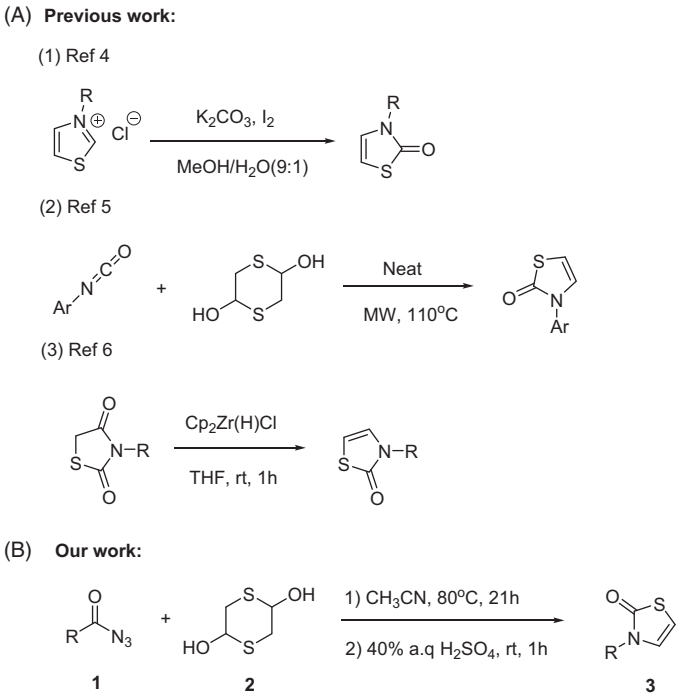
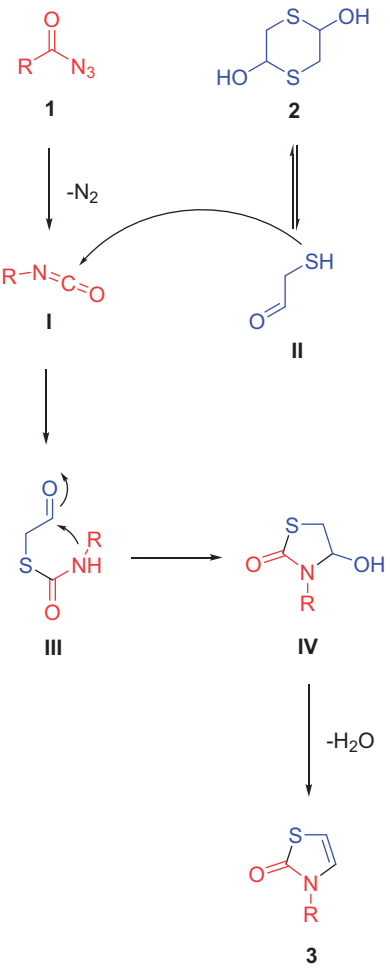


Figure 1. Biologically active compounds contain thiazol-2(3*H*)-one structural motif.



Scheme 1. Synthesis of thiazol-2(3*H*)-one derivatives.



Scheme 2. Proposed mechanism for the synthesis of **3**.

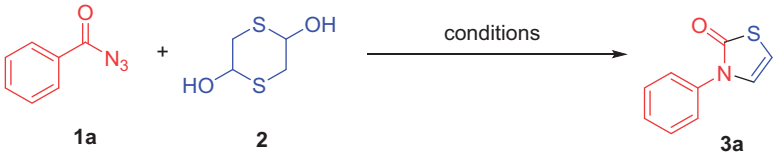
(2)),[5] Schwartz reagent mediated synthesis of thiazol-2(3*H*)-one from thiazolidine-2,4-diones (Scheme 1-A, equation (3)).[6]

Despite these procedures, establishing methods for the construction of thiazol-2(3*H*)-one remains in demand. Herein, we present a facile and efficient protocol for the synthesis of thiazol-2(3*H*)-one with good yields from acyl azide and 1,4-dithiane-2,5-diol (Scheme 1-B). Compared to Scheme 1-A, equation (2), acyl azide is a precursor of isocyanate according to the Curtius rearrangement. Acyl azide can be easily transformed into isocyanate in our reaction avoiding the tough synthesis of isocyanate with toxic starting material phosgene.

Results and discussion

Initially, benzoyl azide **1a** and 1,4-dithiane-2,5-diol **2** were selected as model reactants to optimize the reaction conditions (Table 1). The solvent of the reaction had a

Table 1. Optimization of reaction conditions.[a]



1a 2 3a

Entry	2 (equiv.)	Solvent	T/°C	Conversion[b]/%
1	0.55	Toluene	80	15
2	0.55	Dioxane	80	47
3	0.55	DMF	80	40
4	**0.55**	**MeCN**	**80**	**87(80)[c]**
5	0.55	MeCN	40	0
6	0.55	MeCN	60	70
7	0.55	MeCN	100	82
8	0.525	MeCN	80	81
9	0.75	MeCN	80	87

aReaction conditions: benzoyl azide (0.5 mmol, 1.0 equiv.), 1,4-dithiane-2,5-diol, 2 mL of solvent, disappearance of acyl azide could be monitored by TLC, 21 h, T/°C, then 40% H_2SO_4 (0.125 mmol, 0.25 equiv.) was added, stirred at rt for 1 hour.

bDetermined by LC-MS, based on the disappearance of the starting benzoyl azide. The most efficient entry is highlighted in bold.

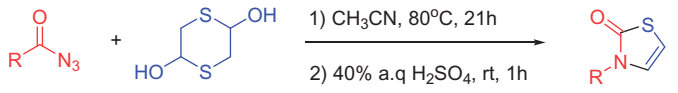
cIsolated yield.

significant impact on the efficiency for the formation of **3a**, and MeCN was found superior to other solvents (Table 1, entries 1–4). Subsequent screening of reaction temperatures showed that 80 °C was the best (Table 1, entries 4–7). Furthermore, optimization of the different stoichiometric amount of 1,4-dithiane-2,5-diol **2** showed that the conversion of **3a** decreased to 81% when the amount of 1,4-dithiane-2,5-diol rose to 0.525 equiv. (Table 1, entry 8). However, there was no improvement after increasing the amount of 1,4-dithiane-2,5-diol to 0.75 equiv. (Table 1, entry 9). On the basis of this initial study, the optimal reactivity was obtained in MeCN at 80 °C when the mole ratio of benzoyl azide and 1,4-dithiane-2,5-diol was 1:0.55 (Table 1, entry 4).

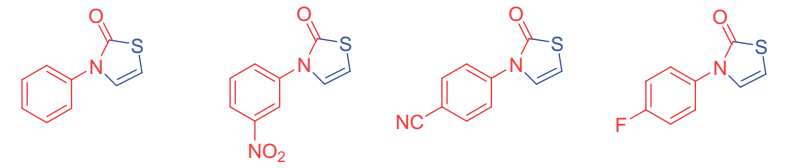
With the optimized reaction conditions in hand, we next investigated the generality and scope of the methodology for the synthesis of 3-arylthiazol-2(3*H*)-one using a set of acyl azides, which were readily prepared according to the literature[7–9] and the results were summarized in Table 2. To our delight, all investigated substrates gave good yields (70 ~ 87%). Aryl acyl azide **1** bearing electron-donating groups afforded the desired products in higher yields than which bearing electron-withdrawing groups (**3g, 3j** compared to **3c, 3d, 3e**; **3h** compared to **3b**). In our tests, the highest yield was obtained when 2-thienyl azide was used as the reagent (**3k**). The structures of 3-arylthiazol-2(3H)-one were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (ESI).

On the basis of the results above, we proposed the following possible mechanism for this reaction, as outlined in Scheme 2. The first step presumably proceeds through the initial formation of mercaptoacetaldehyde **II** from 1,4-dithiane-2,5-diol **2** which undergoes nucleophilic addition to isocyanate **I** generated from acyl azide **1** leading to the formation of intermediate **III.** This intermediate undergoes intramolecular nucleophilic addition to afford product **3** with the elimination of water under acidic condition.

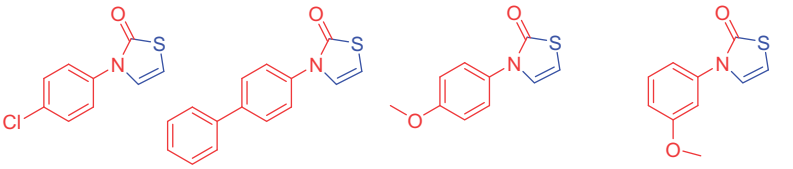
Table 2. Scope of the reaction of acyl azide and 1,4-dithiane-2,5-diol under optimal conditions.[a]



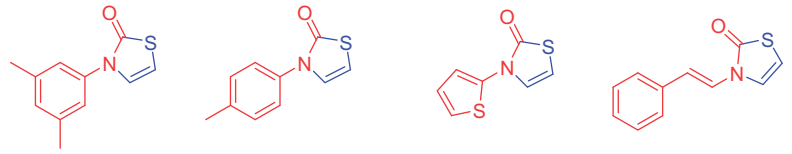
1 2 3



3a 80% | 3b 70% | 3c 70% | 3d 72%



3e 73% | 3f 82% | 3g 85% | 3h 83%



3i 83% | 3j 82% | 3k 87% | 3l 78%

aReaction conditions: acyl azide (0.5 mmol, 1.0 equiv.), 1,4-dithiane-2,5-diol (0.55 equiv.), 2 mL of solvent, disappearance of acyl azide could be monitored by TLC, 21 h, 80 °C, then 40% H_2SO_4 (0.125 mmol, 0.25 equiv.) was added, stirred at rt for 1 hour. Isolated yield.

Conclusion

In summary, we have developed a facile and efficient protocol for the synthesis of 3-arylthiazol-2(3*H*)-one with good yields from acyl azide and 1,4-dithiane-2,5-diol. This reaction has the advantages of available starting materials and simple experimental operation. These features made this reaction as a widely used approach in medicinal chemistry.

Experimental sections

Purifications of reaction products were carried out by chromatography using silica gel (200–300 mesh). Melting points were recorded on a BÜCHI B-540 melting point

apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard ($\delta = 0$) and data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, Q = quartet, m = multiplet), and coupling constant (s) in Hertz. For ^{13}C NMR, TMS ($\delta = 0$) or DMSO ($\delta = 40.45$) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data were obtained using Agilent Technologies 6224 TOF LC/MS. Unless otherwise noted, all reagents were obtained commercially and used without further purification. The starting material acyl azide **1** was prepared according to literature methods.[7–9]

General procedure for the synthesis of 3

A mixture of acyl azide **1** (0.5 mmol), 1,4-dithiane-2,5-diol **2** (0.275 mmol) was stirred in MeCN 2 mL at 80 °C for 21 hours. The disappearance of acyl azide **1** could be monitored by TLC. Then, 40% H_2SO_4 (0.125 mmol, 0.25 equiv.) was added to the solution, stirred at room temperature for 1 hour. After the completeness of the reaction, MeCN was removed under reduced pressure. Water was added to the crude reaction residue. The reaction mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (PET/EA) on silica gel to afford **3a-3l**.

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