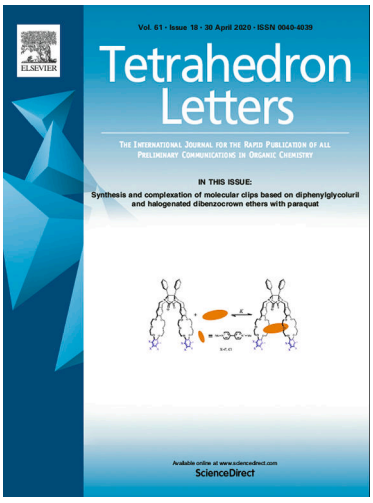
Journal Pre-proofs



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A $KHSO_4$ Promoted Tandem Synthesis of 1,3,4-thiadiazoles from Thiohydrazides and DMF Derivatives

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Abstract An efficient, simple and environmentally benign method for the construction of 1,3,4-thiadiazole skeletons via the tandem coupling and cyclization of thiohydrazides with DMF derivatives in the presence of $KHSO_4$ has been reported. This method reveals good reactivity and functional group tolerance, and a broad series of 1,3,4-thiadiazoles were obtained in moderate to good yields.

Keywords 1,3,4-thiadiazoles; $KHSO_4$; Synthesis

Introduction

1,3,4-thiadiazoles represent a prevalent and important class of compounds which exhibit diverse pharmacological activities such as antibacterial, anticancer, antitubercular and anti-inflammatory.[1,2] For example, acetazolamide,[3] which contains the 1,3,4-thiadiazole structure motif has been approved as the diuretic, whereas cefazedone has shown a broad spectrum of antibacterial activity against various pathogens.[4] In addition, another 1,3,4-thiadiazole derivative BAS0338872 has also been reported as a potent Src/Abl tyrosine kinase inhibitor for the potential treatment of chronic myeloid leukemia (Figure 1).[5] It is worth noting that these important biological effects are mainly attributed to the thiadiazole key skeleton,[6] thus much effort has been devoted to finding out facile and efficient methods for the synthesis of 1,3,4-thiadiazoles.

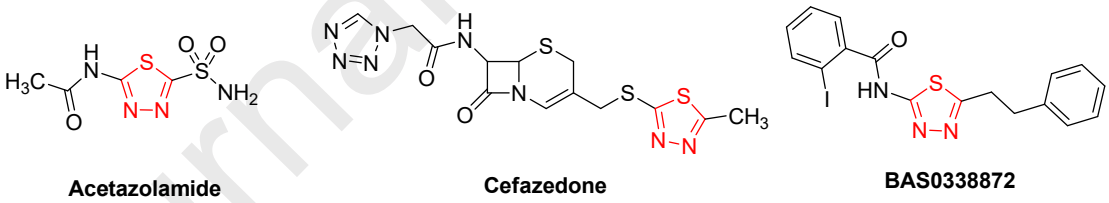
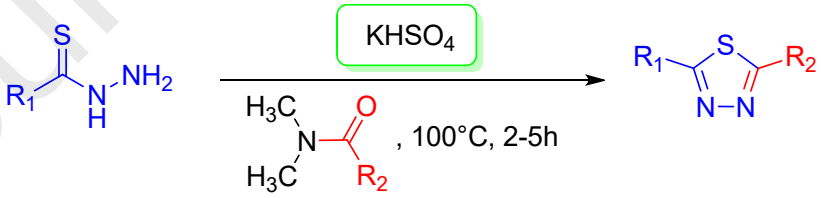


Figure.1 Some bioactive compounds contain 1,3,4-thiadiazole motif.

As of now, several approaches have been developed to synthesize 1,3,4-thiadiazoles, generally involve the dehydration of thioacylhydrazides or oxidative cyclization of thiohydrazones.[7] Thioacylhydrazides prepared from thiohydrazides with carboxylic acids, aryl chlorides, amides or nitriles are used as crucial intermediates to obtain thiadiazoles with several dehydrated reagents including p-TsCl/TEA,[8] $POCl_3$,[9] H_2SO_4,[10] EDCI,[7] PPA[11] and so on. Alternatively, in situ cyclization of thiohydrazones in the presence of some oxidants such as PhI/H_2O_2,[12] Br_2,[13] $FeCl_3$[14] or Eosin Y/O_2[15] have also been proposed as a common method to afford 1,3,4-thiadiazoles. Besides the traditional

synthesis, some elegant methods have been reported in recent years. Zhu[16] and co-workers reported a novel protocol to produce 1,3,4-thiadiazole from the hydrazides and aryl halide via isocyanide insertion. In addition, Taha[17] presented another method by treating isothiocyanate with hydrazides to form 1,3,4-thiadiazoles under basic condition. However, these existing methodologies are more or less inconvenient due to the addition of hazardous, corrosive or unavailable regents, and the requirement of a transition metal or strong acidic catalyst also makes them unattractive. Hence, the development of a convenient, economical and environmentally benign synthesis procedure to this scaffold is still valuable.

Recently, transamidation of amides with amines has been recognized as a convenient and straightforward strategy for amide bond formation.[18,19] Various promotors such as concentrated HCl,[20] Fe(III),[21] $B(OCH_2CF_3)$,[22] [Ni(quin)2][23] and L-Proline[24] have been applied for catalyzing the reaction. Despite significant progress, it is still demanded to deveople novel, green and cost-effective catalysts due to the drawbacks of these promoting agents. To our delight, we fortunately found that a mild and inexpensive catalyst $KHSO_4$ can carry out the N-formylation and N-acylation of amines with high yield and good selectively. More importantly, we also observed that $KHSO_4$ can catalyze the intramolecular cyclization of thioacylhydrazides as a dehydrating agent under non-stringent conditions. Therefore, in a continuation of our ongoing research,[25] herein, we would like to describe an eco-friendly, facile and inexpensive method to prepare 1,3,4-thiadiazoles from thiohydrazides and N, N-Dimethylformamide (DMF) derivativities utilizing $KHSO_4$ both as transamidation and dehydrating agent for the first time. (**Scheme 1**).



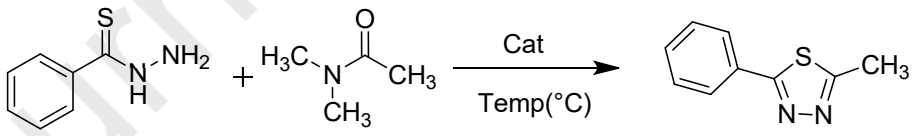
Scheme 1. Synthetic procedure for 1,3,4-thiadiazoles

Results and discussion

Based on our previous work,[25] The initial investigation of the reaction was focused on the screening of catalysts by using a model reaction of benzothiohydrazide with N, N-dimethylacetamide (DMA). As shown in table 1, the screening study revealed that the catalyst played an essential role in this reaction.

No desired product **3a** was observed when the model reaction was carried out without any other additives (Table 1, entry 1), whereas acids such as HAc and TsOH could catalyze this reaction (Table 1, entries 2-3). Notably, when an acidic salt $KHSO_4$ (3 equiv.) was employed, the reaction could also afford the target product **3a** in moderate isolated yield (Table 1, entry 4). This encouraging finding intrigued us to investigate other inorganic salts including $CaCl_2$, $Cu(OAc)_2$, $FeCl_3$, NaH_2PO_4 and NH_4Cl. Interestingly, $CaCl_2$ and $Cu(OAc)_2$ failed to promote this reaction, while $FeCl_3$, as well as NaH_2PO_4 and NH_4Cl provided the desired product in inferior yield (Table 1, entries 5–9), thus $KHSO_4$ was found to be a suitable catalyst for this reaction. Then, the effect of different amounts of $KHSO_4$ on the reaction outcome was examined. To our delight, an incremental increase in the yield was observed by increasing the loading of $KHSO_4$ and 5.0 equiv. of $KHSO_4$ was sufficient for the complete conversion of **1a** and obtained the desired product **3a** in 86% yield (Table 1, entries 10–11). Next, the performance of the reaction under different temperature was also evaluated. Increasing the temperature did not provide any further positive influence on the yield of **3a**, conversely, impurities such as 2,5-diphenyl-1,3,4-thiadiazole derived from the self-condensation of **1a** were generated in higher temperature leading to a lower yield (Table 1, entry 12). Similarly, decreasing the temperature from 100 °C to 80 °C prolonged the reaction time and resulted in the decrease of the yield too (Table 1, entry 13), so the optimal temperature was 100 °C. Finally, the ultimately reaction parameters were selected as 5 equiv. of $KHSO_4$ in DMA at 100 °C.

Table 1. Optimization of the reaction conditions[a]



1a **3a**

Entry	Catalyst (equiv.)	Temp (°C)	Time (h)	Yield (%)[b]
1	-	100	5	NR[c]
2	HAc (3.0)	100	5	50
3	TsOH (3.0)	100	5	65
4	$KHSO_4$ (3.0)	100	5	67
5	$CaCl_2$ (3.0)	100	5	trace
6	$FeCl_3$ (3.0)	100	5	45
7	$Cu(OAc)_2$ (3.0)	100	5	trace

8	NaH_2PO_4 (5.0)	100	5	30
9	NH_4Cl (5.0)	100	5	42
10	$KHSO_4$ (4.0)	100	5	75
11	$KHSO_4$ (5.0)	100	5	86
12	$KHSO_4$ (5.0)	130	5	74
13	$KHSO_4$ (5.0)	80	8	60

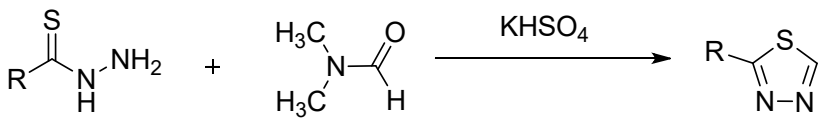
[a] Reaction conditions: benzothiohydrazide (0.1 g, 0.6 mmol, 1.0 equiv.) and DMA (1 mL).

[b] Isolated yield.

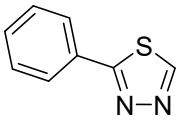
[c] No reaction

Under the optimized reaction conditions, the substrate scope and versatility of the reaction was subsequently explored, and the results are summarized in table 2. To our delight, the protocol was compatible with benzothiohydrazides containing a range of functional groups, little influence of electronic properties was observed on their reactivity. For example, benzohydrazides with electron-donating groups on the para-position of benzene ring, such as OCH_3 and CH_3, yielded the corresponding products in 77% and 80% yield, respectively (Table 2, entries **2b**, **2c**). On the other hand, benzohydrazides bearing electron-withdrawing groups such as F, Cl, also gave the desired product with a yield ranging from 82% - 85% (Table 2, entries **2d**, **2e**). Additionally, the position effect of the substituents on the reaction outcome was not obvious, 3-methyl benzothiohydrazide underwent the reaction smoothly and provided the corresponding product in 78% yield (Table 2, **2f**). Likewise, dimethyl substituted benzothiohydrazide **1g** was found to be reactive too and transformed into the target compound **2g** in lower yield (72%) under the standard reaction conditions. It is important to note that the steric hindered substrate naphthalene-2-carbothiohydrazide **1h** was also well-tolerated and furnished the reaction with 70% yield (Table 2, **2h**). Grippingly, heterocyclic thiohydrazide derivatives such as thiophene-2-carbothiohydrazide and furan-2-carbothiohydrazide were suitable for the reaction and resulted in the corresponding products **2i** and **2j** in good yields.

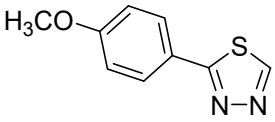
Table 2. Substrate scope with respect to substituted benzothiohydrazides [a]



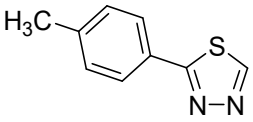
1 **2**



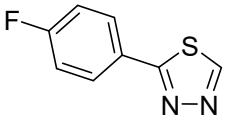
2a, 84%



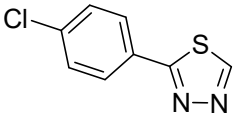
2b, 77%



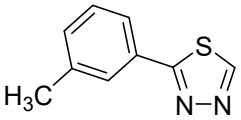
2c, 80%



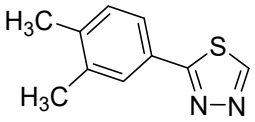
2d, 85%



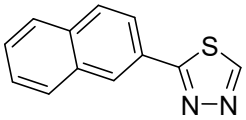
2e, 82%



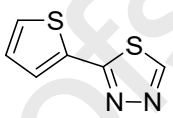
2f, 78%



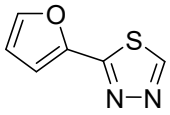
2g, 72%



2h, 70%



2i, 82%

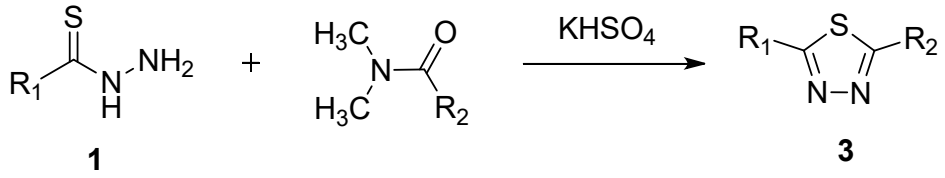


2j, 83%

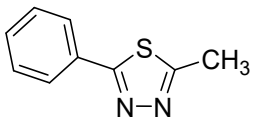
[a] Reagents and conditions: benzothiohydrazides (1.2 mmol), $KHSO_4$ (5.0 equiv.) and DMF (2 mL), 100 °C for 2 h, air, isolated yield.

Inspired by the success synthesis of 2-substitued 1,3,4-thiadiazole derivatives, we then turned our attention to synthesize 2,5-disubstitued 1,3,4-thiadiazoles. DMA, N, N-Dimethylpropionamide (DMPA), N, N-dimethylbenzamide (DMBA) and N, N-dimethyl-2-phenylacetamide instead of DMF were applied to this protocol under the optimized condition (table 3). Similarly, treatment of **1a-j** with DMA produced the corresponding products in moderate to good yields (70 - 86%) (Table 3, **3a-j**). Likewise, when DMF was replaced by DMPA, the reaction also took place efficiently and provided the desired product **3k** with a yield of 75%. However, in the case of DMBA, additional reaction time (12 h) was required and the desired product was obtained in inferior yield (69%) probably owing to the steric hinderance (Table 3, **3l-m**). Deserved to be noted, for the N, N-dimethyl-2-phenylacetamide and N,N-dimethyl-2-phenylpropanamide substrates, they can also participate in the same reaction, but higher temperature (130 °C) was required to accomplish the reaction compared with other derivatives (Table 3, **3n-q**).

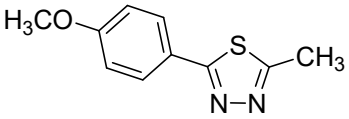
Table 3. Substrate scope with respect to DMF derivatives[a]



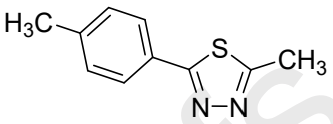
1 **3**



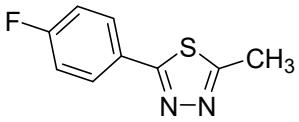
3a, 86%



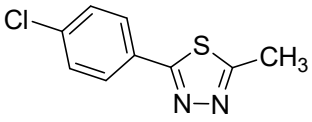
3b, 77%



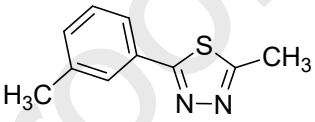
3c, 80%



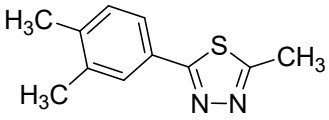
3d, 81%



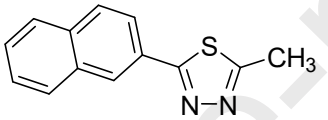
3e, 83%



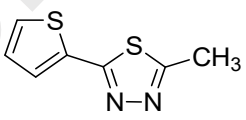
3f, 74%



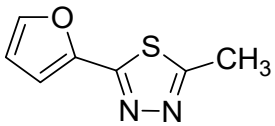
3g, 77%



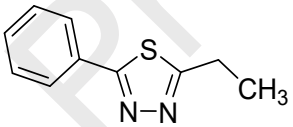
3h, 70%



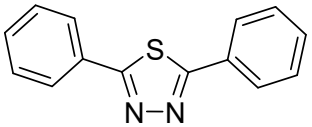
3i, 76%



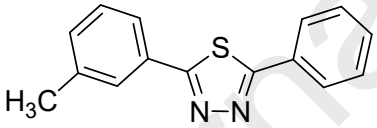
3j, 78%



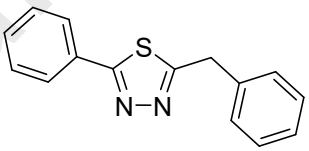
3k, 75%



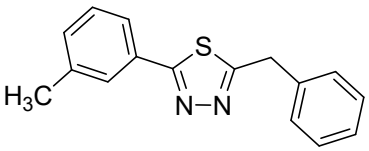
3l[b], 69%



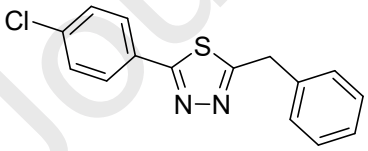
3m[b], 60%



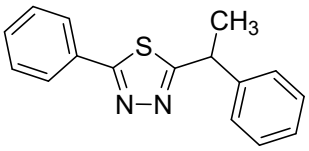
3n[c], 63%



3o[c], 55%



3p[c], 58%



3q[d], 42%

[a] Reaction conditions: thiohydrazide (1.2 mmol), $KHSO_4$ (5.0 equiv.) and DMA (2 mL), 100 °C, 5 h, air, isolated yield.

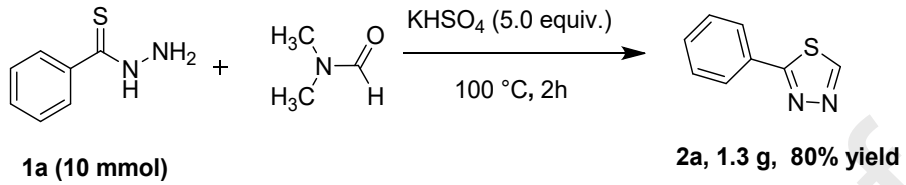
[b] Reaction conditions: benzothiohydrazide (1.0 mmol), $KHSO_4$ (5.0 equiv.) and DMBA (5.0 mmol), 100 °C, 12 h, air, isolated yield.

[c] 130 °C, 3 h

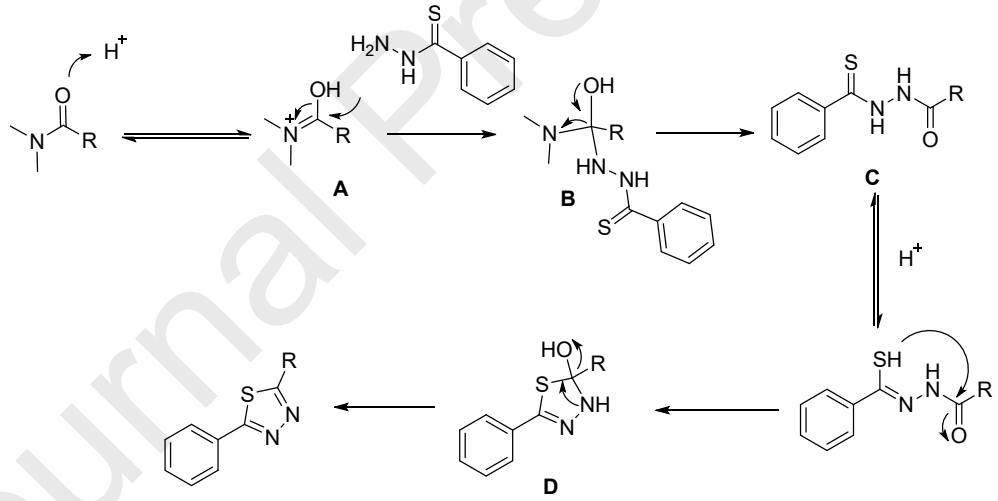
[d] 130 °C, 6 h

Furthermore, in order to investigate the efficiency of this process, the method was extended for a gram-scale synthesis (Scheme 2). Fortunately, the desired product **2a** was isolated by column chromatograph in 80% yield.

Scheme 2. Gram Scale synthesis experiment



Based on the literature[20,26] and our previous work, we have proposed a plausible mechanism depicted in scheme 3. Firstly, amide was activated by H^+ afforded by $KHSO_4$ to produce cationic intermediate **A**, which was attacked by benzothiohydrazides results in the formation of a tetrahedral intermediate **B**. Breakdown of intermediate **B** lead to the intermediate **C**. Then, cyclization via nucleophilic attack of thiol group on the carbonyl group afforded intermediate **D** and a subsequent dehydration of intermediate **D** finally provided the 1,3,4-thiadiazoles.



Scheme 3. A plausible mechanism for the synthesis of 2,5-disubstituted 1,3,4-thiadiazoles

Conclusion

To sum up, an efficient, simple and economical synthetic protocol for the preparation of 1,3,4-thiadiazoles via the direct coupling and dehydration of thiohydrazides and DMF derivatives has been developed. This process employing $KHSO_4$ as the only promoter would provide a better synthetic option for the synthesis of 1,3,4-thiadiazoles.

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Highlights

- Facile synthesis of 1,3,4-thiadiazoles from thiohydrazides with DMF derivatives.
- $KHSO_4$ promoted the reaction both as coupling and dehydrating agent.
- Operationally simple catalysis and Solvent-free conditions.

Graphical abstract