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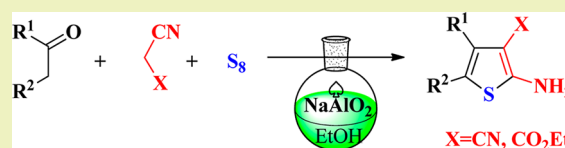
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Facile Synthesis of 2-Aminothiophenes Using  $\text{NaAlO}_2$  as an Eco-Effective and Recyclable CatalystRongxian Bai,<sup>†</sup> Ping Liu,<sup>†</sup> Jian Yang,<sup>†</sup> Changhui Liu,<sup>†</sup> and Yanlong Gu<sup>\*,†,‡</sup><sup>†</sup>Key Laboratory for Large-Format Battery, Materials and System, Ministry of Education, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Road, Hongshan District, Wuhan 430074, China<sup>‡</sup>State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou 730000, China

## Supporting Information

**ABSTRACT:** Substituted 2-aminothiophenes were synthesized through Gewald reaction by using an easily available solid base catalyst, sodium aluminate. Cost-effectiveness, mild and environmentally benign conditions, and excellent catalytic performance are the features of this system. Furthermore, the  $\text{NaAlO}_2$  catalyst can be swimmingly recovered and reused in this reaction.

**KEYWORDS:**  $\text{NaAlO}_2$ , Gewald reaction, 2-Aminothiophenes, Multicomponent reaction



## INTRODUCTION

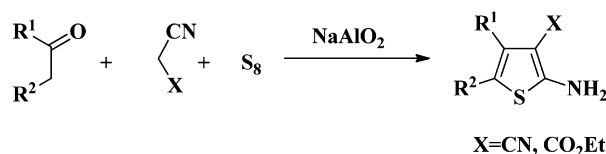
The development of straightforward methods for the synthesis of valuable complex molecules is a central task of current organic chemists.<sup>1–3</sup> In this context, development of multicomponent reactions is of prime importance.<sup>4–8</sup> Substituted 2-aminothiophenes are significant intermediates in organic synthesis, which have been usually employed as building blocks to synthesize agrochemicals, dyes, natural products, and conductivity-based sensors.<sup>9–12</sup> Moreover, the thiophene ring is also found in many natural and synthetic biologically active compounds.<sup>13,14</sup> Therefore, 2-aminothiophenes synthesis has recently attracted considerable attention.<sup>9,15–20</sup> Many protocols have been reported for 2-aminothiophenes preparation.<sup>9,13,15–21</sup> Among all the reported methods, Gewald reaction has gained significant attention, which is a three-component assembly of an active nitrile, a ketone, and elemental S (Scheme 1).<sup>15–20</sup> Many organic bases, such as

(THF),<sup>11,12</sup> which has a detrimental effect on the environment. Therefore, great efforts have been paid to developing an efficient and environmental-friendly heterogeneous catalyst system to synthesize the title compounds.<sup>18–20</sup> However, in many cases, the use of volatile organic solvent is still mandatory, which defeats to some extent the purpose of developing an eco-efficient system with a solid catalyst. Therefore, a need exists to develop a heterogeneous catalyst that is able to allow us to perform the reaction under a green solvent or solvent-free condition.

Although the use of solid catalysts in organic reaction allowed us to take advantage of their characteristics, such as environmental compatibility, reusability, operational simplicity, nontoxicity, noncorrosiveness, the preparation of heterogeneous catalysts is frequently associated with a tedious procedure, which includes generally consecutive steps of precipitation, aging, drying, and calcination. This defeated thoroughly the purpose of employing a solid catalyst. In addition, the catalytic activity of a man-made solid catalyst is often affected by many factors, such as precursor and conditions of preparation and pretreatment. This often results in a difficulty of reproducing the catalytic properties. It is conceivable that all these drawbacks can be avoided if the heterogeneous catalyst is a commercially available chemical. To this end, we have initiated a research program concerning the use of bulky and easily available chemicals as solid catalysts for organic reactions.<sup>8</sup>

$\text{NaAlO}_2$  is a significant commercial inorganic chemical owing to its applicable versatility. Sodium aluminate is widely used in water treatment, dishwasher detergents, paint pigments, paper making, concrete, and so forth.<sup>22–25</sup> However, sodium aluminate has been seldom applied as a catalyst of synthetic

Scheme 1. Synthesis of 2-Aminothiophenes



diethylamine, morpoline, imidazole, triethylamine, pyridine, and 1,1,3,3-tetramethylguanidine lactate, were proved to be viable catalysts for this reaction.<sup>12,15–17</sup> However, the established reaction systems based on the uses of these homogeneous bases as catalysts are often plagued by many intrinsic problems including corrosion of the reactor, difficulty of recycling catalyst, and the generation of waste. Furthermore, these systems are often associated with the use of hazardous polar solvents, such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), 1,4-dioxane, and tetrahydrofuran

Received: December 1, 2014

Revised: April 28, 2015

Published: May 11, 2015



Table 1. Synthesis of 2-Aminothiophenes Catalyzed by  $\text{NaAlO}_2^a$ 


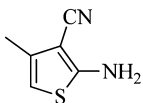

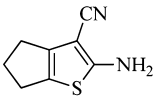

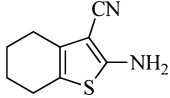

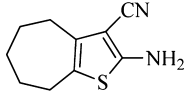

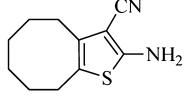
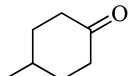
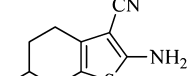

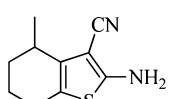

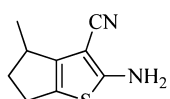
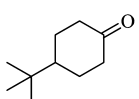
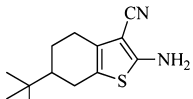
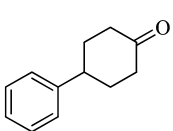
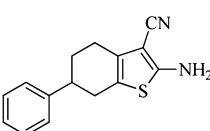
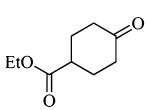
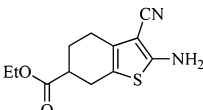
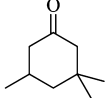
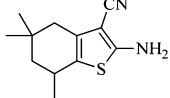
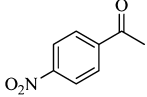
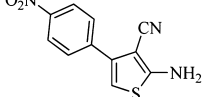
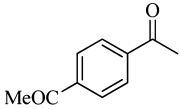
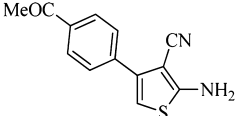
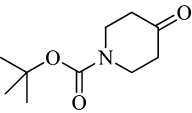
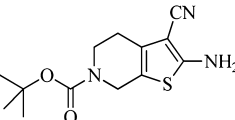
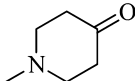
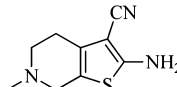
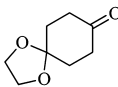
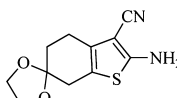
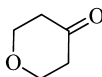
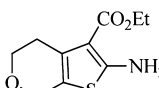

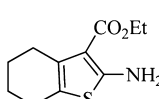

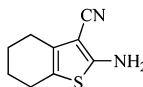
Entry	Ketone	Product	Time (h)	Yield (%) <sup>b</sup>
1			10	38
2			10	62
3			10	91
4			10	94
5			10	69
6			10	91
7			10	60
8			10	43
9			10	87
10			10	91
11			10	38
12			10	30
13			10	30

Table 1. continued

Entry	Ketone	Product	Time (h)	Yield (%) <sup>b</sup>
14			10	26
15			10	92
16			10	90
17			10	91
18			16	97 <sup>c</sup>
19			16	73 <sup>c</sup>
20			6	94 <sup>d</sup>

<sup>a</sup>Reaction conditions: malononitrile, 0.50 mmol; malanonitrile:ketone:elemental S = 1:1:1.1; 60 °C, anhydrous ethanol, 1.0 mL. <sup>b</sup>Isolated yields.

<sup>c</sup>Malononitrile substituted by ethyl 2-cyanoacetate. <sup>d</sup>Malononitrile, 10.0 mmol; malanonitrile:ketone:elemental S = 1:1:1.1; 60 °C; the product was obtained by silica gel column chromatography.

reaction. The great potential of sodium aluminate as a catalyst has been identified by us and others quite recently.<sup>23–25</sup> However, until now, it has been used only in transesterification reaction. In view of its mild basicity, eco-friendliness, low cost, and good availability, more application examples of NaAlO<sub>2</sub> as a base catalyst are expected in the future.

In continuation of our research to explore eco-efficient transformations under environmentally benign conditions,<sup>26–30</sup> in this study, we investigated, for the first time, NaAlO<sub>2</sub> as a solid catalyst to produce the title thiophene derivatives through Gewald reaction. The established system is not only efficient for the synthesis of target compounds but also endowed by many salient features of sodium aluminate, such as cost-effective and recyclable catalyst, environmental benign solvent system, and easy isolation of product.

## EXPERIMENTAL SECTION

**Typical Procedure for Catalytic Reaction.** The Gewald reaction was implemented in a 20 mL V-type tube that was armed with a triangle magnetic stirring bar. In a typical reaction, elemental S (0.55 mmol), ketone (0.5 mmol), and malononitrile (0.5 mmol) were mixed. Then, sodium aluminate (0.025 mmol) and anhydrous ethanol (1.0 mL) were added. The mixture was then heated to 60 °C under stirring. After reaction, the solid catalyst was separated by a simple decantation after centrifugation, and then washed with anhydrous

ethanol (4 × 1.0 mL) and dried at 110 °C for 6 h. Thereafter, it was reused for the next run. The organic liquids were combined together. The volatile components were then removed under vacuum. The desired product was obtained by preparative thin-layer chromatography.

**Procedure for Catalyst Recycling.** A new charge of reactants was added in a V-type flask that contained the recovered dry catalyst, and then the mixture was submitted to the next run. The operational procedure for all reused experiments was the same as the above-mentioned typical procedure.

**Product Analysis.** The characterization and analysis method of products are described elsewhere.<sup>26–30</sup>

## RESULTS AND DISCUSSION

**Synthesis of Different 2-Aminothiophenes Catalyzed by Sodium Aluminate.** Initially, malononitrile was selected as a model substrate to react with elemental S and a variety of ketones. The reaction was performed in anhydrous ethanol at 60 °C using sodium aluminate as a catalyst, and the results are listed in Table 1. As you can see, all the ketones successfully produced the expected thiophene derivatives in moderate to good yields. Acetone gave the low yield due perhaps to its instability, which cannot be avoided even under the protection of an inert atmosphere (entry 1).<sup>15</sup> Cycloheptanone and cyclohexanone gave higher yield than that of cyclopentanone

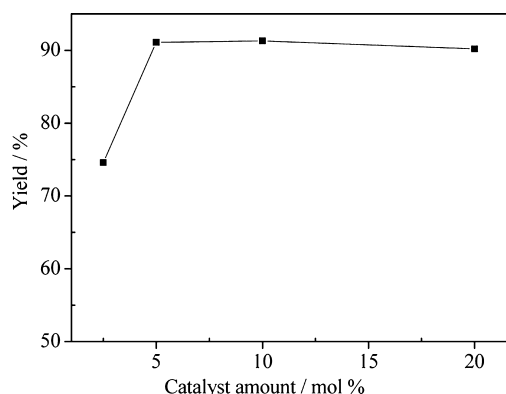
under the identical conditions (entries 2–4). Remarkably, when the former two were used, the yields of the desired 2-aminothiophenes reached over 90%. It demonstrated that the efficiency of the Gewald three-component reaction was significantly affected by the structure of ketone component, and the increase of the carbon number of the ring for cyclic ketones improved the yield. Yayebee et al. have investigated Gewald synthesis of 2-aminothiophenes by using aldehydes as substrates. And they also found that the yield of 2-aminothiophene increased with the carbon-number increase of aldehydes.<sup>18,19</sup> However, this tendency was not always viable. In the case of the cyclooctanone, the yield dropped drastically (entry 5). It may be ascribed to a superposition of several factors. The pivotal one should result from nonbonded repulsive interaction between the CH<sub>2</sub> protons in the ring of cyclooctanone.<sup>31</sup>

Having these results in hand, some other cyclopentanone and cyclohexanone derivatives were then examined in a sodium aluminate catalyst system. 4-Methylcyclohexanone participated readily in the Gewald reaction, and the yield reached 91% (entry 6). However, the reaction with its congener, 2-methylcyclopentanone, performed sluggishly, and only 60% of yield was obtained (entry 7). A similar trend was also seen in the reaction of cyclopentanones. The reactivity of 2-methylcyclopentanone was lower than that of cyclopentanone (entry 8). These results indicated that the existence of an *ortho*-substituent group in five- and six-membered cyclic ketones has a detrimental effect on the Gewald reaction. It can be attributed to the stereo hindrance effect. Some other *para*-substituted cyclohexanone derivatives, such as 4-phenylcyclohexanone and 4-(*tert*-butyl) cyclohexanone, were also employed in the Gewald reaction by using sodium aluminate as a catalyst, and the expected products were obtained in generally satisfactory yield (entries 9 and 10). However, when ethyl 4-oxocyclohexanecarboxylate was used, the yield was rather poor, and reached only 38% (entry 11). Because of the fact that some other inseparable products were detected, we deduced that the low yield might result from a competitive intervention of the ester group toward the interaction of the ketone carbonyl and basic catalyst,<sup>4,10,11</sup> which decreased the reaction selectivity. A *meta*-substituted cyclohexanone, 3,3,5-trimethylcyclohexanone, was also tested. However, the yield amounted only to 30% (entry 12). Moreover, some acetophenone derivatives were also investigated by using sodium aluminate as catalyst. Due to the poor activity, the yield obtained was lower than 30% (entries 13 and 14). N-containing heterocyclic cyclohexanone and O-containing heterocyclic cyclohexanone were also examined in the desired Gewald reaction, and the corresponding 2-aminothiophenes were obtained in ≥90% yields (entries 15–17). Furthermore, when the malononitrile component was replaced by the ethyl 2-cyanoacetate, good yield was also achieved (entries 18 and 19). Especially, in the case of dihydro-2H-pyran-4(3H)-one, the yield of the corresponding 2-aminothiophene reached 97%.

It is significant to note that the use of sodium aluminate as a catalyst for Gewald reaction provided an additional advantage in terms of the aspect of greenness. In many reported systems, polar solvents, such as DMF, alcohols, THF, DMSO, and 1,4-dioxane, are often adopted.<sup>11,12,14</sup> The present Gewald reaction was carried out in ethanol, which is regarded as an environmentally safe solvent for organic synthesis. Furthermore, the reaction could be scaled up with also good efficiency. For instance, the reaction of cyclohexanone (10.0 mmol) with

malononitrile (10.0 mmol) and elemental S (11.0 mmol) gave the corresponding 2-aminothiophene in 94% yield (1.68 g) (entry 20). This result is comparable to that of homogeneous catalyst L-proline,<sup>32</sup> which, however, cannot be recycled.

**Influence of Amount of NaAlO<sub>2</sub> on the Synthesis of 2-Aminothiophenes.** The reaction of cyclohexanone, malononitrile, and elemental S was chosen as a model reaction to study the influence of amount of NaAlO<sub>2</sub> on the synthesis of 2-aminothiophene, and the results are shown in Figure 1. In the

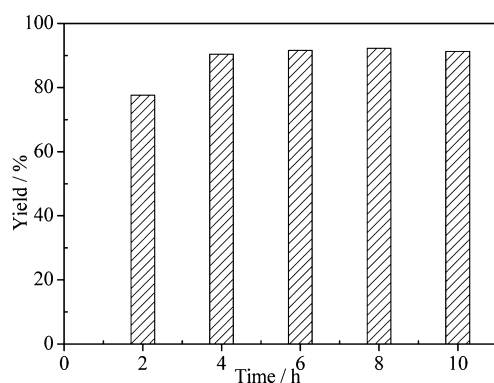


**Figure 1.** Influence of amount of NaAlO<sub>2</sub> on 2-aminothiophenes synthesis (cyclohexanone, 0.50 mmol; malononitrile, 0.50 mmol; elemental S, 0.55 mmol, anhydrous ethanol, 1.0 mL; 60 °C, 6.0 h).

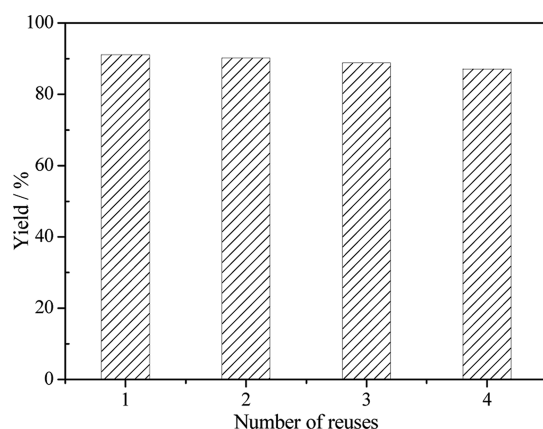
absence of NaAlO<sub>2</sub>, only a trace amount of desired product was obtained after 6 h of reaction. The yield of 2-aminothiophenes was significantly improved by putting catalytic amount of NaAlO<sub>2</sub> into the substrates. The systematic investigation about the catalyst amount on the synthesis revealed that the reaction yield evidently depended on the dosage of the sodium aluminate. Increasing the NaAlO<sub>2</sub> amount improves the yield of the desired product on account of the increased numbers of active sites and also of the enriched contact opportunity between sodium aluminate and the reactant. The yield of the product arrived at 91% when 5 mol % of NaAlO<sub>2</sub> was used. The use of 10 mol % of catalyst did not give further improvement in the yield. Therefore, we selected 5 mol % of catalyst for the next experiments. It is worth noting that Gewald synthesis performed with such amount of catalyst should be practically useful considering the low cost of the catalyst and its possibility of recycling.

**Influence of Reaction Time on 2-Aminothiophenes Synthesis.** Figure 2 displays the effects of reaction time on the reaction between cyclohexanone, malononitrile, and elemental S. In the first 6 h, the reaction yield increased quickly with the increase of the reaction time. Thereafter, the yield increase is not significant. The maximum yield of the desired Gewald 2-aminothiophenes was obtained with 6 h of reaction.

**Recycling of NaAlO<sub>2</sub> Catalyst.** A key factor to consider for the potential practical application of a solid catalyst is its amenability to recycling. For this purpose, reusability of NaAlO<sub>2</sub> was examined and the results are presented in Figure 3. It was found that the NaAlO<sub>2</sub> could be reused four times without notable descent of its activity. The sodium content in organic phase obtained from the third run of the reaction is 10.2 ppm (measured by AAS). The result indicated that a slight leaching of ionic species occurred during the reaction, which can be linked to the slight decrease of the catalytic activity. Furthermore, an unavoidable physical loss of NaAlO<sub>2</sub> during its



**Figure 2.** Influence of reaction time on 2-aminothiophenes synthesis (cyclohexanone, 0.50 mmol; malononitrile, 0.50 mmol; elemental S, 0.55 mmol; sodium aluminate, 5 mol %, anhydrous ethanol, 1.0 mL 60 °C).



**Figure 3.** Recycling of NaAlO<sub>2</sub> catalyst (cyclohexanone, 0.50 mmol; malononitrile, 0.50 mmol; elemental S, 0.55 mmol; anhydrous ethanol, 1.0 mL; sodium aluminate, 5 mol %, 60 °C, 6.0 h).

recycling is also responsible for the observed decrease of the catalytic activity.

#### Activity Comparison of NaAlO<sub>2</sub> with Other Catalysts.

The reaction yield of cyclohexanone, malononitrile, and elemental S was compared with that reported in the literature, and the results are displayed in Table 2. With the exception of ZnO (commercial product), all the solid bases are able to produce the desired product in reasonable yields under mild

**Table 2.** Activity Comparison of NaAlO<sub>2</sub> with Other Catalysts

catalyst	time (h)	temp. (°C)	solvent	yield (%)	ref
NaAlO <sub>2</sub>	6	60		94	
nano-ZnO	10	100		85	18
commercial ZnO	10	100		70	19
MgO–La <sub>2</sub> O <sub>3</sub>	1	78	ethanol	90	20
L-proline	10	60	DMF	97	32
Et <sub>3</sub> N <sub>3</sub> /H <sub>2</sub> O	7	r.t.		89	33
[bmlm]OH	2	60		88	34
CaO	1	78	ethanol	90	35
MgO–Al <sub>2</sub> O <sub>3</sub>	8	60	ethanol	91	36
KF/Al <sub>2</sub> O <sub>3</sub>	3.5	78	ethanol	91	37
Cs <sub>2</sub> CO <sub>3</sub>	3	70	ethanol	91	38
KG-60-piperazine	4	80	ethanol	42	39

conditions. The catalytic ability of NaAlO<sub>2</sub> is much better than that of Et<sub>3</sub>N<sup>33</sup> and ionic liquid [bmlm] OH catalyst<sup>34</sup> and comparable to a homogeneous catalyst, L-proline, which, however, has to be used in combination with DMF solvent. From the comparison with all the other heterogeneous catalyst,<sup>18–20,35–39</sup> it is easy to identify that sodium aluminate is indeed an advantageous solid catalyst for Gewald reaction. Salient features of this system are mild and environmentally benign conditions, excellent catalytic performance, and low cost of the catalyst.

## CONCLUSION

In summary, sodium aluminate was proved to be a cost-effective and recyclable catalyst for the synthesis of 2-aminothiophene derivatives via Gewald reaction from ketones, malononitrile, and elemental sulfur. The readily commercial availability, ease of use, and high activity of sodium aluminate make it a highly accessible catalyst for the synthesis of 2-aminothiophenes. Sodium aluminate may be applicable in many other organic transformations, and we are actively working on this line.

## ASSOCIATED CONTENT

### Supporting Information

Material and apparatus, characterization (NMR, IR, AAS), spectra data and spectra of compounds, and product analysis. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/sc500763q.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (21173089 and 21373093) and the Fundamental Research Funds for the Central Universities of China (2014ZZGH019). The authors thank for Analytical and Testing Center of HUST, Chutian Scholar Program of the Hubei Provincial Government and the Cooperative Innovation Center of Hubei Province.

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