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Facile access to 3,5-symmetrically disubstituted 1,2,4-thiadiazoles through phosphovanadomolybdic acid catalyzed aerobic oxidative dimerization of primary thioamides†

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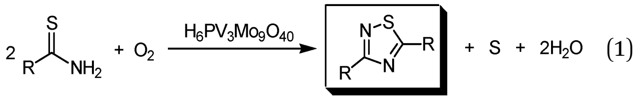
In the presence of Keggin-type phosphovanadomolybdic acids, *e.g.*, $H_6PV_3Mo_9O_{40}$, oxidative dimerization of various kinds of primary thioamides including aromatic, heterocyclic, and aliphatic ones efficiently proceeded to give the corresponding 3,5-disubstituted 1,2,4-thiadiazoles in excellent yields.

1,2,4-Thiadiazoles are some of the most important heterocycles and have recently found their important utilization as pharmacophores.[1] The commercial antibiotic cefozopran (SCE-2787) contains the 1,2,4-thiadiazole scaffold,[2] and a number of 1,2,4-thiadiazole derivatives with unique biological activities, *e.g.*, acetylcholinesterase inhibitors, angiotensin II receptor antagonists, and G-protein coupled receptors, have been synthesized to date.[3] In addition to their use as pharmacophores, thiadiazoles are potentially useful as pesticides and corrosion inhibitors.[1,4]

3,5-Unsymmetrically disubstituted 1,2,4-thiadiazoles have generally been synthesized by intramolecular oxidative cyclization of amidinothioureas and 1,3-dipolar cycloaddition of nitrile sulfides to nitriles.[1,5] Oxidative dimerization of primary thioamides is the most frequently utilized reaction for synthesis of 3,5-symmetrically disubstituted ones.[6–14] Despite numerous efforts towards the development of oxidative dimerization of primary thioamides, challenges still remain because almost all the previously reported oxidative dimerization systems employ metal and organic-based stoichiometric oxidants such as selenoxides,[6] telluroxides,[6,7] hypervalent iodines,[8] pentylpyridinium tribromide,[9] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[10] *N*-bromosuccinimide,[11] dimethyl sulfoxide,[12] and *tert*-butylhydroperoxide[13] (Table S1, ESI†). In addition, some of these systems require large amounts of additives (Table S1, ESI†). The choice of the oxidant determines the practicability and efficiency of systems, and molecular oxygen is regarded as the greenest oxidant. With regard to the use of molecular oxygen for oxidative dimerization of primary thioamides, to date there has been only one report concerning the photocatalytic system using eosin Y (Table S1, ESI†),[14] to the best of our knowledge.

Here, we found that Keggin-type phosphovanadomolybdic acids can act as efficient homogeneous catalysts for oxidative dimerization of primary thioamides using molecular oxygen as the sole oxidant without any additives and photoirradiation. In the presence of $H_6PV_3Mo_9O_{40}$, various kinds of structurally diverse primary thioamides including aromatic, heterocyclic, and aliphatic ones could be converted into the corresponding 3,5-symmetrically disubstituted 1,2,4-thiadiazoles in excellent yields under mild reaction conditions (30 °C, 1 atm O_2) [eqn (1)].‡ Although phosphovanadomolybdic acids have been reported to be catalytically active for various oxidation reactions,[15] their use for oxidative dimerization of primary thioamides has never been reported so far.



(1)

Firstly, the oxidative dimerization of thiobenzamide (**1a**) to 3,5-diphenyl-1,2,4-thiadiazole (**2a**) was carried out using $H_6PV_3Mo_9O_{40}$ (5 mol%) at 30 °C under 1 atm of molecular oxygen in various solvents. The reaction hardly proceeded in the absence of $H_6PV_3Mo_9O_{40}$ in any solvents. The choice of the solvents was very crucial, as shown in Table 1. Water and chloroform were poor solvents (Table 1, entries 1 and 4) because **1a** and $H_6PV_3Mo_9O_{40}$ were almost insoluble in water and chloroform, respectively. Except for water and chloroform, the catalytic performance of $H_6PV_3Mo_9O_{40}$ was much dependent on the acceptor numbers of solvents used.[16] The yields of **2a** increased with an increase in the acceptor numbers, and methanol (41.3) and ethanol (37.1) with higher acceptor numbers were the most suitable solvents, affording **2a** in almost quantitative yields within 0.5 h (Table 1, entries 2 and 3). Acetonitrile (18.9) and acetone (12.5) also gave high yields of **2a** (Table 1, entries 5 and 6). It is known that the reduction potentials (oxidation abilities) of heteropolyanions

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† Electronic supplementary information (ESI) available: Experimental details, data of **2a–2h**, Table S1, Fig. S1–S3, and Scheme S1. See DOI: 10.1039/c4cc02313g

Table 1 Oxidative dimerization of thiobenzamide (**1a**) to 3,5-diphenyl-1,2,4-thiadiazole (**2a**) in various solvents[a]

Entry	Solvent	Acceptor number[b]	Time (h)	Yield of **2a** (%)
1	Water	54.8	2	14
2	**Methanol**	**41.3**	**0.5**	**96**
3	**Ethanol**	**37.1**	**0.5**	**>99**
4	Chloroform	23.1	2	7
5	Acetonitrile	18.9	2	86
6	Acetone	12.5	2	75
7	1,4-Dioxane	10.8	2	19

[a] Reaction conditions: **1a** (0.5 mmol), $H_6PV_3Mo_9O_{40}$ (5 mol%), solvent (4 mL), O_2 (1 atm), 30 °C. Yields were determined by HPLC using naphthalene as an internal standard. In all cases, **2a** was selectively produced without formation of benzonitrile and benzamide. [b] The values of acceptor numbers of solvents were cited from ref. 16.

shift to more positive potentials with an increase in the acceptor numbers of solvents.[17] This shows that reduced heteropolyanions are more stabilized by solvents with higher acceptor numbers.[17] From the above results, we hereafter mainly use ethanol as the solvent (not methanol, for safety reasons).

Next, the catalytic activities of various kinds of heteropoly acids (5 mol%) were examined for the oxidative dimerization of **1a** to **2a** in ethanol. As summarized in Table 2, the desired product **2a** was significantly obtained only when the reaction was performed using phosphovanadomolybdic acids, and the catalytic activities increased with an increase in vanadium contents ($H_4P\mathbf{V}Mo_{11}O_{40} < H_5P\mathbf{V_2}Mo_{10}O_{40} < H_6P\mathbf{V_3}Mo_9O_{40}$) (Table 2, entries 2–4). In these cases, **2a** was selectively produced without formation of benzonitrile and benzamide. Air could be used for the oxidative dimerization while the reaction rate was smaller than that in O_2 (Table 2, entry 5). Under an Ar atmosphere, just the stoichiometric amount of **2a** with respect to vanadium species employed (15 mol%) was produced (Table 2, entry 6), indicating that molecular oxygen can act as the terminal oxidant for the present oxidative dimerization.

Table 2 Oxidative dimerization of thiobenzamide (**1a**) to 3,5-diphenyl-1,2,4-thiadiazole (**2a**) using various catalysts[a]

Entry	Catalyst	Atmosphere	Yield of **2a** (%)
1	$H_3PMo_{12}O_{40}$	O_2	3
2	$H_4PVMo_{11}O_{40}$	O_2	24
3	$H_5PV_2Mo_{10}O_{40}$	O_2	63
4	$\mathbf{H_6PV_3Mo_9O_{40}}$	$\mathbf{O_2}$	**85**
5	$H_6PV_3Mo_9O_{40}$	Air	35
6	$H_6PV_3Mo_9O_{40}$	Ar	15
7	$H_4SiMo_{12}O_{40}$	O_2	4
8	$H_5SiVMo_{11}O_{40}$	O_2	7
9	$H_3PW_{12}O_{40}$	O_2	2
10	$H_4PVW_{11}O_{40}$	O_2	3
11	$H_5PV_2W_{10}O_{40}$	O_2	5
12	$H_6PV_3W_9O_{40}$	O_2	8
13	$H_4SiW_{12}O_{40}$	O_2	2
14	$H_5SiVW_{11}O_{40}$	O_2	3
15[b]	V_2O_5	O_2	2
16[b]	$NaVO_3$	O_2	2
17[b]	$VO(acac)_2$	O_2	2
18[c]	$V_2O_5 + H_3PMo_{12}O_{40}$	O_2	2
19[c]	$NaVO_3 + H_3PMo_{12}O_{40}$	O_2	2
20[c]	$VO(acac)_2 + H_3PMo_{12}O_{40}$	O_2	2

[a] Reaction conditions: **1a** (0.5 mmol), heteropoly acid (5 mol%), ethanol (4 mL), O_2 or Ar (1 atm), 30 °C, 10 min. Yields were determined by HPLC using naphthalene as an internal standard. In all cases, **2a** was selectively produced without formation of benzonitrile and benzamide. [b] Vanadium (15 mol%). [c] Vanadium (15 mol%) + $H_3PMo_{12}O_{40}$ (5 mol%).

In the presence of vanadium-free heteropoly acids such as $H_3PMo_{12}O_{40}$, $H_4SiMo_{12}O_{40}$, $H_3PW_{12}O_{40}$, and $H_4SiW_{12}O_{40}$, the oxidative dimerization hardly proceeded (Table 2, entries 1, 7, 9, and 13). Although these results suggest that vanadium is an indispensable component for the present oxidative dimerization, simple vanadium compounds such as V_2O_5, $NaVO_3$, and $VO(acac)_2$ (acac = acetylacetonato) hardly catalyzed the oxidative dimerization (Table 2, entries 15–17). In addition, the oxidative dimerization hardly proceeded in the presence of simple mixtures of $V_2O_5 + H_3PMo_{12}O_{40}$, $NaVO_3 + H_3PMo_{12}O_{40}$, and $VO(acac)_2 + H_3PMo_{12}O_{40}$ (Table 2, entries 18–20). Therefore, the substitution of vanadium into heteropoly acid frameworks is important to obtain the high catalytic performance.[18,19]

The effects of heteroatoms as well as polyatoms were also very significant. The phosphorous-centered $H_4\mathbf{P}VMo_{11}O_{40}$ gave **2a** in a moderate yield, while the oxidative dimerization hardly proceeded in the presence of the silicon-centered $H_5\mathbf{Si}VMo_{11}O_{40}$ (Table 2, entry 2 *vs.* entry 8). With regard to polyatoms, molybdenum ($H_4PV\mathbf{Mo}_{11}O_{40}$) was better than tungsten ($H_4PV\mathbf{W}_{11}O_{40}$) (Table 2, entry 2 *vs.* entry 10). It is well known that the reduction potentials of phosphometalates are generally higher than those of silicometalates and that molybdates are much easily reduced in comparison with tungstates.[20]

Under the optimized reaction conditions, we examined the substrate scope for the present oxidative dimerization using 5 mol% $H_6PV_3Mo_9O_{40}$. Various kinds of primary thioamides including aromatic, heterocyclic, and aliphatic ones could be converted into the corresponding 3,5-disubstituted 1,2,4-thiadiazoles in high yields (Fig. 1). Products could readily be isolated by simple extraction using *n*-hexane.‡ The oxidative dimerization of thiobenzamide derivatives, which contain electron-donating as well as electron-withdrawing substituents on the phenyl rings, efficiently proceeded to afford the corresponding 3,5-diarylsubstituted 1,2,4-thiadiazoles in high yields without formation of nitriles and primary amides (Fig. 1, entries 1–5). The 10 mmol-scale reaction of **1a** was also effective and gave a quantitative yield (HPLC) of **2a** for 0.5 h. The amounts of $H_6PV_3Mo_9O_{40}$ could be much reduced; even when using 0.4 mol% $H_6PV_3Mo_9O_{40}$, **2a** was obtained in 93% yield for 5 h, which corresponds to the turnover of 233 based on $H_6PV_3Mo_9O_{40}$ (Fig. 1, entry 2). In the case of 4-chlorothiobenzamide, no dechlorination proceeded (Fig. 1, entry 4). Heterocyclic thioamides such as furan-2-carbothioamide and thiophen-2-carbothioamide gave the corresponding 3,5-disubstituted 1,2,4-thiadiazoles in high yields (Fig. 1, entries 6 and 7). Notably, less reactive aliphatic thioamides such as thioacetamide and thiopropionamide could also be converted into the corresponding 3,5-dialkylsubstituted 1,2,4-thiadiazoles (Fig. 1, entries 8 and 9), while nitriles were formed as byproducts to some extent (10–18%) in these cases.

The color of the reaction solution changed to dark green or dark blue immediately at the beginning of the reaction (Fig. S1, ESI†),§

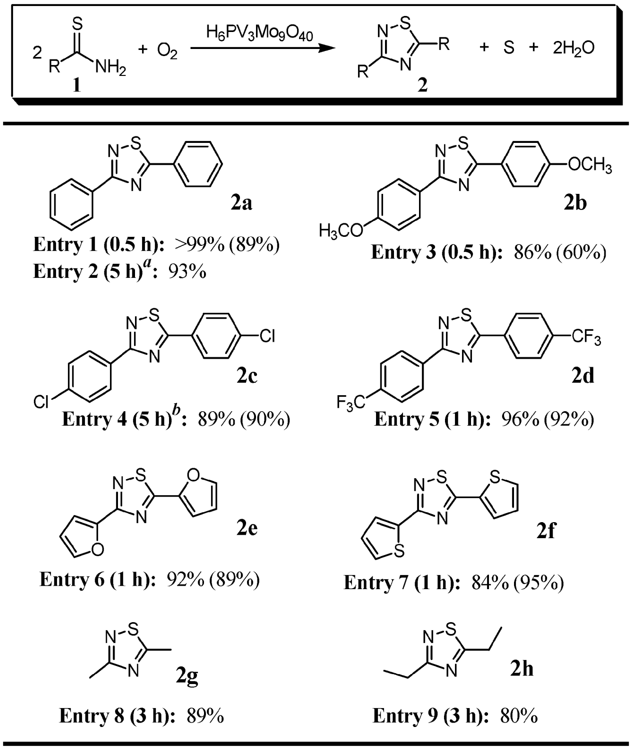

Fig. 1 Scope of the $H_6PV_3Mo_9O_{40}$-catalyzed oxidative dimerization of primary thioamides. Reaction conditions: **1** (0.5 mmol), $H_6PV_3Mo_9O_{40}$ (5 mol%), ethanol (4 mL), O_2 (1 atm), 30 °C. Yields were determined by HPLC or GC using naphthalene as an internal standard (see the ESI†). In the oxidative dimerization of aliphatic thioamides, nitriles were formed as byproducts to some extent (10% for entry 8 and 18% for entry 9). Values in the parentheses are the isolated yields after complete conversion of **1** (see the ESI for the detailed conditions†). [a] $H_6PV_3Mo_9O_{40}$ (0.4 mol%). [b] Acetonitrile (4 mL).

suggesting that heteropoly acids are reduced by primary thioamides (**1**) during the oxidative dimerization. The color gradually changed to orange-yellow with the formation of elemental sulfur according to the consumption of **1** (Fig. S1, ESI†). The $H_6PV_3Mo_9O_{40}$-catalyzed oxidative dimerization of **1a** was strongly suppressed by the presence of a radical scavenger of 2,2,6,6-tetramethylpiperidine 1-oxyl (Fig. S2, ESI†), indicating that radical intermediates are involved in the present oxidative dimerization. It has been reported that phosphovanadomolybdic acids, *e.g.*, $H_5PV_2Mo_{10}O_{40}$, can generate cation radical species from sulfides through single-electron oxidation and that the vanadium sites play important roles in the single-electron oxidation.[19] Similarly, in the present case, cation radical species are possibly generated by single-electron oxidation of primary thioamides (step 1 in Scheme S1, ESI†).[14] Then, the dimerization of the sulfur radical species likely proceeds (step 3 in Scheme S1, ESI†), followed by dehydrosulfurization to afford the corresponding 3,5-disubstituted 1,2,4-thiadiazoles (step 4 in Scheme S1, ESI†) with the formation of elemental sulfur. The overall reaction is expressed as eqn (1), and the possible reaction mechanism is shown in Scheme S1 (ESI†).

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Notes and references

‡ Procedure for oxidative dimerization: **1** (0.5 mmol), $H_6PV_3Mo_9O_{40}$ (5 mol%), naphthalene (0.1 mmol, internal standard), and ethanol (4 mL) were placed in a Pyrex-glass tube reactor with a magnetic stir bar, and the reaction was carried out at 30 °C in 1 atm of O_2. During the reaction, the conversion of **1** and the yield of **2** (based on **1**) were periodically monitored by HPLC or GC analysis (Fig. S3, ESI†). As for product isolation, naphthalene was not used. After complete conversion of **1**, *n*-hexane (25 mL) and water (25 mL) were added to the reaction mixture, followed by extraction with *n*-hexane (25 mL × 3) to afford **2**.

§ The color of the ethanol solution of $H_6PV_3Mo_9O_{40}$ without **1** was orange-yellow.

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