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 PII:
 S1566-7367(16)30319-3

 DOI:
 doi:10.1016/j.catcom.2016.09.005

 Reference:
 CATCOM 4774

To appear in: Catalysis Communications

Received date:7 July 2016Revised date:19 August 2016Accepted date:6 September 2016



Please cite this article as: Li Wan, Xiaoning Sun, Songjie Shi, Jiawei Zhang, Xin Li, Zhenjiang Li, Kai Guo, An efficient synthesis of *N*-substituted phthalimides using  $SiO_2$ -tpy-Nb as heterogeneous and reusable catalyst, *Catalysis Communications* (2016), doi:10.1016/j.catcom.2016.09.005

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### An efficient synthesis of N-substituted phthalimides using

### SiO<sub>2</sub>-tpy-Nb as heterogeneous and reusable catalyst

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#### **ABSTRACT:**

A novel and efficient heterogeneous catalyst  $SiO_2$ -tpy-Nb was developed, and its application in the preparation of *N*-substituted phthalimides from *o*-phthalic acids or anhydrides with amines provides the desired products in good to excellent yields. The catalyst was stable and recoverable for eight consecutive cycles without a significant loss in its activity. Furthermore, the catalyst is applicable in continuous flow which indicates its potential utilization in industrialization.

Keywords: phthalimide, niobium, terpyridine, heterogeneous, continuous flow

### INTRODUCTION

The cyclic imides especially phthalimide and its derivatives are a core motif of numerous natural products and designed pharmaceutical molecules due to their broad range of applications as anti-inflammtories, anticonvulsants, analgesics, immunomodulatory, herbicidal and insecticidal agents [1-4]. Moreover, phthalimide analogues have found extensive utilization as dyes, polymers, and in different branches of material sciences [5,6]. Owing to the increasing biological and industrial importance of cyclic imides especially phthalimide and its derivatives, the synthetic

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methodology of these molecules has emerged as a topic of interest for synthetic chemists. The most commonly used strategy for the synthesis of phthalimides involves condensation of phthalic acids or anhydrides and primary amines in refluxing organic solvents [7]. Those high boiling point solvents such as acetic acid, DMF, and dioxane are mostly used in the preparation of phthalimides [8]. Synthesis in solvent-free conditions also could be achieved by refluxing a mixture of phthalic anhydride with the amine [9] or by utilizing DABCO as catalyst at room temperature [10]. In addition, microwave irradiation as a heating method was also investigated in the presence or absence of organic solvents [11]. Generally, high yields of phthalimides were given within just a few minutes. Besides, ionic liquids attract considerable interest in the context of green synthesis because of their wide acceptability as alternative green reaction media. However, most of the traditional methods are not entirely satisfactory due to lengthy reaction times, the use of toxic solvents and auxiliary reagents. And the ionic liquids still suffer from the relatively expensive cost for practical utilization.

Recently, many novel synthetic routes from nitriles, halides, alkyne, cyclic amines, isocyanates, and phthalimide using transition-metal catalysis or excess amounts of I(III) oxidant have been reported [12-14], but most of them are homogeneous catalytic methods which bring the concern of difficulties in catalyst/products separation, reusability of expensive catalysts and heavy metal contamination in pharmaceutical applications. In regard to the development of efficient, economical and greener protocol with additional advantage of catalyst recyclability, heterogeneous catalyst is emerging as an alternative over previous homogeneous protocols. Very recently, water-tolerant Nb<sub>2</sub>O<sub>5</sub> was used as Lewis acid catalyst in various organic reactions [15-17]. Meanwhile, Shimizu and co-workers discovered that  $Nb_2O_5$  exhibited base-tolerant catalytic activity for the direct cyclic imide synthesis from dicarboxylic acids with amines and ammonia under mild conditions [18,19]. Generally, the Nb<sub>2</sub>O<sub>5</sub> catalyst was prepared by calcination from commercial niobic acid Nb<sub>2</sub>O<sub>5</sub> $nH_2O$ , which is readily prepared by the hydrolysis of NbCl<sub>5</sub> or Nb( $OC_2H_5$ )<sub>5</sub>. High yields of phthalimides from dicarboxylic acid with various amines were obtained, and the catalyst  $Nb_2O_5$  exhibited good recyclability. To further expand the application of metal niobium, water soluble niobium oxalate was chosen as the source of niobium. Then we dedicated to investigate an efficient and reusable heterogeneous niobium catalyst, and applied it in continuous flow system to synthesis phthalimides successional.

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In the past few decades, silica gel is widespread used as support in the field of heterogeneous catalyst. Because it is very cheap and easily functionalization to anchor the desired ligands to the surface [20]. Lately, polypyridyl transition-metal complexes have received much attention in the field of ion sensors [21,22]. And a great number of polypyridyl complexes have been used as optical sensors for various anions and metal cations by taking advantage of their distinguished photophysical properties [23,24]. Simultaneously, the terpyridines as tridentate ligands have gained increasing interest because of their efficient and stable chelating ability to transition metals [25]. Terpyridine nickel and palladium complexes have been used to catalyze classical cross-coupling reactions, and satisfactory results were obtained [26-28]. Herein, we wish to describe an novel alternative method using silica gel supported the complex of terpyridine (tpy) with niobium oxalate as catalyst to produce phthalimide derivatives from *o*-phthalic acids or anhydrides and amines as the reagents.

#### **EXPERIMENTAL SECTION**

General procedure for the synthesis of cyclic imides. In a 25 mL sealed tube, the corresponding dicarboxylic acid or anhydrate (0.3 mmol), amine (0.3 mmol), catalyst SiO<sub>2</sub>-tpy-Nb (10 mol%) were stirred in 1 mL IPA:H<sub>2</sub>O = 1:2 at 110 °C for 14 h. After the reaction completed, the mixture was cooled to room temperature and extracted with ethyl acetate (20 mL  $\times$  3). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using EtOAc/*n*-hexene as eluent to afford the products.

**Recycling of the silica-immobilized catalyst.** In a 25 mL sealed tube, *o*-phthalic anhydride (0.3 mmol), *p*-toluidine (0.3 mmol), catalyst SiO<sub>2</sub>-tpy-Nb (10 mol%) were stirred in 1 mL IPA:H<sub>2</sub>O = 1:2 at 110 °C for 14 h. After the reaction completed, the mixture was diluted with ethyl acetate (20 mL). The catalyst was filtered and washed with EtOAc (30 mL  $\times$  3), H<sub>2</sub>O (30 mL  $\times$  2), EtOH (10 mL). Then the catalyst was dried under vacuum at 60 °C for 6 h for next cycle.

**Procedure for the model reaction in continuous flow system.** The packed-bed reactor of catatlyst SiO<sub>2</sub>-tpy-Nb was assembled according to the procedures in previous literatures [29,30]. 1.5 g catalyst was packed in a PFA tube (OD 11.25 mm, ID 7.25 mm), then the tube was put into an air bath. The inlet of the reactor was connected to a HPLC pump via PFA tubing and the outlet

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of the reactor was connected with a back-pressure regulator (8 bar). The reactor was heated in an air bath (110  $^{\circ}$ C) and flushed with the solvent (IPA:H<sub>2</sub>O=1:2). A flask fitted with rubber cap was charged with *o*-phthalic anhydride (6.0 mmol), *p*-toluidine (6.0 mmol) and 60 mL IPA:H<sub>2</sub>O = 1:2. The flow rate of starting materials was set to be 20.0 µL/min, the residence time was 30 min. After reaching steady state (15-20 min as monitored by GC analysis), the resulting mixture was collected into test tubes. The crude reaction mixture was diluted with EtOAc, and then filtered through celite before GC analysis.

### **RESULTS AND DISCUSSION**

The detail of preparation of heterogeneous catalyst SiO<sub>2</sub>-tpy-Nb was illustrated in the supporting information [31]. The loading of terpyridine was determined to be 1.01 mmol/g by means of the nitrogen content calculated by elemental analysis. The content of niobium was 0.89 mmol/g based on the analysis of ICP result. Scanning electron micrography (SEM) was recorded to understand morphology of the surface of SiO<sub>2</sub>-tpy and SiO<sub>2</sub>-tpy-Nb. As can be seen from Figure 1, the particle size of silica supported tpy-Nb (Figure 1B) is similar to the silica support tpy (Figure 1A). It demonstrates that the particles of SiO<sub>2</sub>-tpy has a good mechanical stability during the immobilization step. Meanwhile, the surface morphology of these two samples are different evidently. It shows that the surface of SiO<sub>2</sub>-tpy was slick, but roughness on the surface of SiO<sub>2</sub>-tpy-Nb was observed which implied the presence of niobium oxalate.



Figure 1. SEM images of (A) SiO<sub>2</sub>-tpy; (B) SiO<sub>2</sub>-tpy-Nb; (C) reused SiO<sub>2</sub>-tpy-Nb after 8th cycle

In order to evaluate the activity of silica supported tpy-Nb in the synthesis of phthalimide, o-phthalic acid and p-toluidine were chosen as model substrates. In the preliminary experiments, the reaction was carried out in various solvents with the catalyst SiO<sub>2</sub>-tpy-Nb (10 mol% of niobium content) at 100 °C for 14 h. As is shown in Table 1, the polar solvents of various alcohols

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gave better yields than EtOAc. Similar yields were obtained in CF<sub>3</sub>CH<sub>2</sub>OH, isopropanol, *n*-butyl alcohol and 2-methyl-2-butanol (Table 1, entries 3 to 7). To develop an economic and environmentally friendly reaction system, we employed water as the solvent in the reaction. Slightly increase in the yield was observed in the model reaction (Table 1, entry 10). Therefore, we utilized the organic/aqueous co-solvent to investigate the optimal reaction conditions. The combination of three alcohols with water were screened in different volume ratio (Table 1, entries 11 to 19). The highest yield was obtained in the co-solvent of IPA:H<sub>2</sub>O=1:2 (Table 1, entry 17). The yield decreased to 72% when the ratio of water increased to 1:4 (Table 1, entry 20). Next, we test the influence of reaction temperature at 90 °C, 110 °C, 120 °C respectively. Excellent yield was obtained when the reaction was performed at 110 °C (Table 1, entry 22). Thus, we selected IPA:H<sub>2</sub>O=1:2 as the solvent and 10 mol% of catalyst at 110 °C cas the optimal conditions for the synthesis of phthalimides. And compared to niobium oxalate, 79% conversion of starting material was given under the optimal conditions (Table 1, entry 24). It indicated the catalyst SiO<sub>2</sub>-tpy-Nb was more efficient in this reaction.

Table 1 Optimization of reaction conditions<sup>a</sup>

	ĊĽ	Сон + H <sub>2</sub> N Са	at. 10 mol% solvent temp.	$\downarrow - $
	ll O 1a	2a		Ö 3a
	Entry	Solvent	Temp. (°C)	Conversion(%) <sup>b</sup>
C	1	EtOAc	100	11
	2	CH <sub>3</sub> OH	100	19
7	3	EtOH	100	32
	4	CF <sub>3</sub> CH <sub>2</sub> OH	100	38
	5	isopropanol (IPA)	100	36
	6	<i>n</i> -butyl alcohol	100	37
		(NBA)		
	7	2-methyl-2-butanol	100	39
		(TAA)		
	8	tert-butanol (TBA)	100	13
	9	isobutanol (IBA)	100	34
	10	$H_2O$	100	53
	11	NBA:H <sub>2</sub> O=1:2	100	52
	12	NBA:H <sub>2</sub> O=1:1	100	41
	13	NBA:H <sub>2</sub> O=2:1	100	36
	14	TAA:H <sub>2</sub> O=1:2	100	52
	15	TAA:H <sub>2</sub> O=1:1	100	61

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16	TAA:H <sub>2</sub> O=2:1	100	46
17	IPA:H <sub>2</sub> O=1:2	100	83
18	IPA:H <sub>2</sub> O=1:1	100	75
19	IPA:H <sub>2</sub> O=2:1	100	65
20	IPA:H <sub>2</sub> O=1:4	100	72
21	IPA:H <sub>2</sub> O=1:2	90	78
22	IPA:H <sub>2</sub> O=1:2	110	95 (90) <sup>c</sup>
23	IPA:H <sub>2</sub> O=1:2	120	89
$24^d$	IPA:H <sub>2</sub> O=1:2	110	79
$25^{e}$	IPA:H <sub>2</sub> O=1:2	110	75

<sup>*a*</sup> Reaction conditions: *o*-phthalic acid (0.3 mmol), *p*-toluidine (0.3 mmol), SiO<sub>2</sub>-tpy-Nb (10 mol%), solvent (1.0 mL), 14 h. <sup>*b*</sup> Determined by the analysis of GC results. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> The catalyst was niobium oxalate. <sup>*e*</sup> The catalyst was Niobic acid (Nb<sub>2</sub>O<sub>5</sub>·nH<sub>2</sub>O).

To survey the generality of the catalytic protocol, a variety of substituted *o*-phthalic acids and amines were tested under the optimized conditions. Good to excellent yields were obtained from *o*-phthalic acid with different groups substituted anilines (Table 2, **3a-3d**). Although the substituent 2,6-diisopropyl is bulky, the desired product was still given in 84% yield (Table 2, **3b**). This result implies the steric effect is negligible in our catalytic system. Only moderate yields were obtained when chlorine substituted at 4 and 5 position of *o*-phthalic acid (Table 2, **3e** and **3f**), except for the reaction with 4-fluoroaniline (Table 2, **3g**). Nevertheless, electron-donating group substituted *o*-phthalic acid produced the corresponding products in satisfied yields with anilines substituted by methyl and chlorine (Table 2, **3h** and **3i**). Meanwhile, electron-rich and electron-poor benzylamines exhibited highly reactivity with *o*-phthalic acid to obtain the desired phthalimides in good yields (Table 2, **3j-3l**).

Table 2 Substrate scope of various *o*-phthalic acids with amines<sup>*a,b*</sup>



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<sup>*a*</sup> Reaction conditions: substituted *o*-phthalic acid (0.3 mmol), amine (0.3 mmol), SiO<sub>2</sub>-tpy-Nb (10 mol%), IPA:H<sub>2</sub>O=1:2 (1.0 mL), 14 h. <sup>*b*</sup> Isolated yields are given in parentheses.

Next, commercial available or easily prepared *o*-phthalic anhydrides were explored with a broad range of amine under the optimal conditions. As a result, both electron-rich as well as electron-poor anilines and benzylamines gave good to excellent yields of the corresponding phthalimides (Table 3, **5a-5k**). Halogen substituents (Table 3, **5b**, **5f**, **5i**, **5k**) were well tolerated by the catalytic system, which should prove useful for further functionalizations by cross-coupling chemistry. Gratifyingly, high yields were obtained from 2-furanmethanamine with *o*-phthalic anhydrides (Table 3, **51-5m**). In addition, low activity amines, such as cyclohexylamine, cyclopentylamine and propylamine, were reacted with 4-methylphthalic anhydride to afford the desired products in moderate yields. Notably, good yield was obtained from 3-aminopropynethe, the corresponding product which has significant utilization in the synthesis of potential anticancer agents [32], hybrid crown macrocycles [33] and novel polymeric materials [34].

Table 3 Substrate scope of various *o*-phthalic anhydrides with amines<sup>*a,b*</sup>



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<sup>*a*</sup> Reaction conditions: substituted *o*-phthalic anhydride (0.3 mmol), amine (0.3 mmol),  $SiO_2$ -tpy-Nb (10 mol%), IPA:H<sub>2</sub>O=1:2 (1.0 mL), 14 h. <sup>*b*</sup> Isolated yields are given in parentheses.

For a heterogeneous catalyst, it is important to examine its ease of separation and good reusability. The recyclability of the prepared catalyst  $SiO_2$ -tpy-Nb was investigated in the reaction of *o*-phthalic anhydride with *p*-toluidine under the optimal conditions. After carrying out the reaction, the mixture was diluted with ethyl acetate and filtered. The catalyst was separated by simple filtration and washed with ethyl acetate several times. Then the catalyst was dried under vacuum, and can be reused directly without further purification. The recovered catalyst was used in the next run, and almost consistent activity was observed for next eight consecutive cycles (Figure 2). In addition, a SEM observation of the recovered catalyst after eighth cycles was made, and there was obvious change in the morphology and the size in comparison to the fresh catalyst (Figure 1C). And the content of niobium in the reaction mixture was < 2 ppm determined by ICP analysis. These results revealed that the decrease in catalytic activity of  $SiO_2$ -tpy-Nb in subsequent runs. Encouraged by the excellent durability of catalyst, we applied it in the continuous flow

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system to investigate the scalability of this method. The catalyst  $SiO_2$ -tpy-Nb packed-bed was assembled which would provide efficient mixing and enhanced mass and heat transfer to improve the reaction efficiency. The model reaction was employed in the packed-bed reactor, and 82% yield was obtained for a 30 min residence time (see Supporting Information for details).



Figure 2 Recycling experiment

A hot filtration test was conducted to figure out whether the catalytic process involved in the homogeneous fashion. When the model reaction mixture was stirred at 110 °C for 6 h (yield 59%), the catalyst was then removed by filtration at the reaction temperature. The filtrate was reacted for an additional 12 h. The reaction continued, although the conversion did not reach the level obtained in the normal manner, which means that at least a part of catalytic activity of the catalyst was assigned to a homogeneous way. And this can be explained by a "release and recapture" mechanism as described in previous literature [35].

### CONCLUSIONS

In conclusion, we have developed a novel and efficient heterogeneous terpyridine niobium catalyst for the preparation of various *N*-substituted phthalimides from *o*-phthalic acids or anhydrides with amines. And this method provides a convenient access to 5-methyl-2-(prop-2-yn-1-yl)isoindoline-1,3-dione in high yield, which has potential anticancer bioactivities and important application in novel polymeric materials. Meanwhile, the catalyst exhibits highly stability and recyclability for eight cycles without a significant loss of its catalytic activity, which make this procedure more environmentally acceptable. In addition, the application of the catalyst SiO<sub>2</sub>-tpy-Nb in continuous flow system demonstrates its potential in industrialization.

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### ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (21502090 and 21522604), Natural Science Foundation of Jiangsu Province (BK20150942 and BK20150031) and the National Key Basic Research Program of China (2012CB725204). We also thank the financial support from Top-notch Academic Programs Project of Jiangsu Higher Education Institutions (TAPP).

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# An efficient synthesis of *N*-substituted phthalimides using SiO<sub>2</sub>-tpy-Nb as heterogeneous and reusable catalyst

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Graphical abstract

A novel and efficient heterogeneous catalyst  $SiO_2$ -tpy-Nb was developed to prepare *N*-substituted phthalimides from *o*-phthalic acids or anhydrides with amines in good to excellent yields.

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### Highlights

1. A novel heterogeneous catalyst  $SiO_2$ -tpy-Nb was developed to prepare N-substituted phthalimides.

2. The catalyst was stable and recoverable for eight cycles without significant loss in its activity.

3. The catalyst is applicable in continuous flow which indicates its utilization in industry.

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