

Short communication

An efficient synthesis of *N*-substituted phthalimides using SiO₂-tpy-Nb as heterogeneous and reusable catalystLi Wan^{a,c}, Xiaoning Sun^a, Songjie Shi^a, Jiawei Zhang^a, Xin Li^a, Zhenjiang Li^a, Kai Guo^{a,b,c,*}^a College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, PR China^b State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, Nanjing 210009, PR China^c Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), 30 Puzhu South Road, Nanjing 211816, PR China

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ABSTRACT

A novel and efficient heterogeneous catalyst SiO₂-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.

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1. 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-inflammatories, 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 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 Nb₂O₅ was used as Lewis acid catalyst in various organic reactions [15–17]. Meanwhile, Shimizu and co-workers discovered that Nb₂O₅ 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 Nb₂O₅ catalyst was prepared by calcination from commercial niobic acid Nb₂O₅·nH₂O, which is readily prepared by the hydrolysis of NbCl₅ or Nb(OC₂H₅)₅. High yields of phthalimides from dicarboxylic acid with various amines were obtained, and the catalyst Nb₂O₅ exhibited good recyclability. To further expand the application of metal niobium, water soluble niobium oxalate was chosen as the source of niobium.

* Corresponding author at: State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, Nanjing 210009, PR China.

E-mail address: guok@njtech.edu.cn (K. Guo).

Then we dedicated to investigate an efficient and reusable heterogeneous niobium catalyst, and applied it in continuous flow system to synthesize phthalimides successional.

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.

2. Experimental section

2.1. General procedure for the synthesis of cyclic imides

In a 25 mL sealed tube, the corresponding dicarboxylic acid or anhydride (0.3 mmol), amine (0.3 mmol), catalyst SiO₂-tpy-Nb (10 mol%) were stirred in 1 mL IPA:H₂O = 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 × 3). The combined organic layer was dried over anhydrous Na₂SO₄, 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.

2.2. Recycling of the silica-immobilized catalyst

In a 25 mL sealed tube, *o*-phthalic anhydride (0.3 mmol), *p*-toluidine (0.3 mmol), catalyst SiO₂-tpy-Nb (10 mol%) were stirred in 1 mL IPA:H₂O = 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 × 3), H₂O (30 mL × 2), EtOH (10 mL). Then the catalyst was dried under vacuum at 60 °C for 6 h for next cycle.

2.3. Procedure for the model reaction in continuous flow system

The packed-bed reactor of catalyst SiO₂-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 of the reactor was connected with a back-pressure regulator (8 bar). The reactor was heated in an air bath (110 °C) and flushed with the solvent (IPA:H₂O = 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:H₂O = 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.

3. Results and discussion

The detail of preparation of heterogeneous catalyst SiO₂-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 micrograph (SEM) was recorded to understand morphology of the surface of SiO₂-tpy and SiO₂-tpy-Nb. As can be seen from Fig. 1, the particle size of silica supported tpy-Nb (Fig. 1B) is similar to the silica support tpy (Fig. 1A). It demonstrates that the particles of SiO₂-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 SiO₂-tpy was slick, but roughness on the surface of SiO₂-tpy-Nb was observed which implied the presence of niobium oxalate.

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 SiO₂-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 gave better yields than EtOAc. Similar yields were obtained in CF₃CH₂OH, 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). 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:H₂O = 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:H₂O = 1:2 as the solvent and 10 mol% of catalyst at 110 °C as the optimal conditions for the synthesis of phthalimides. And compared to

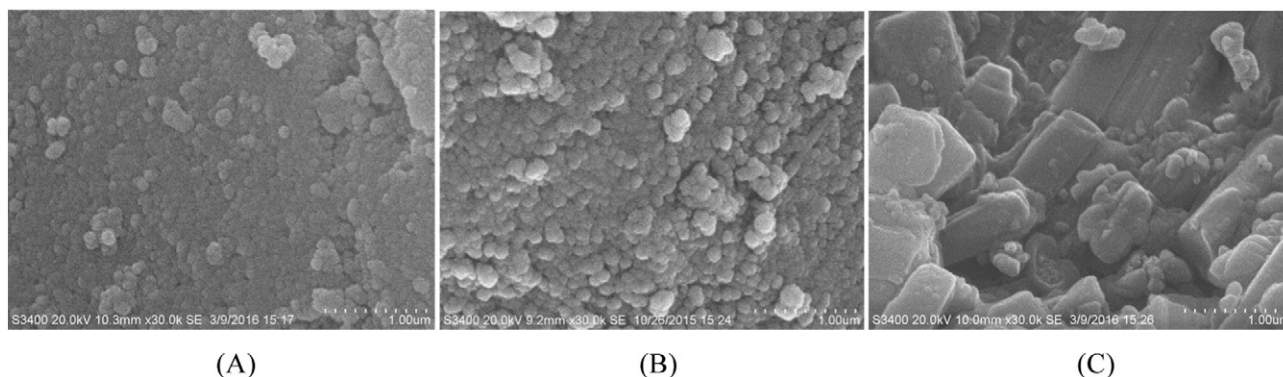


Fig. 1. SEM images of (A) SiO₂-tpy; (B) SiO₂-tpy-Nb; (C) reused SiO₂-tpy-Nb after 8th cycle.

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