Ceria–Vanadia/Silica-Catalyzed Cascade for C–C and C–O Bond Activation: Green One-Pot Synthesis of 2-Amino-3-cyano-4H-pyrans

Surya Narayana Maddila, Suresh Maddila, Werner E. van Zyl, and Sreekantha B. Jonnalagadda[a]

We designed a ceria–vanadia/silica (Ce–V/SiO$_2$) heterogeneous catalyst and used it for the green and efficient synthesis of 2-amino-3-cyano-4H-pyran derivatives. The green reaction was a multicomponent one-pot condensation of 5,5-dimethylcyclohexane-1,3-dione, aromatic aldehyde, and malononitrile in an eco-compatible solvent (ethanol). The catalyst was synthesized and fully characterized by powder X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), and Brunauer–Emmett–Teller (BET) surface area analysis. The reported procedure offers a number of advantages including decreased reaction times, mild conditions, high yields, operational simplicity, and environmentally benign and simple work-up procedures. Furthermore, the catalyst is economical, fully recyclable, and reusable for over five runs while preserving its high activity. The synthesized 2-amino-3-cyano-4H-pyran products can later be used for pharmaceutical purposes.

Multicomponent reactions (MCRs) are exciting new synthetic protocols geared toward heterocyclic scaffolds as building blocks of biological and medicinal importance.\textsuperscript{[1,2]} MCRs have many advantages over conventional linear-type syntheses by virtue of their convergence, productivity, facile execution, and high yields.\textsuperscript{[3]} Moreover, MCRs conform to green principles, such as one-pot conversions and atom efficiency, in addition to other conditions optimal for the synthesis of heterocyclic compounds.\textsuperscript{[4–6]} These single-step processes have distinctive suppleness in generating molecular diversity combined with minimization of time, cost efficiency, and moderate reaction conditions.

In the recent past, heterogeneous mixed metal oxide catalysts started to receive greater attention. Such systems are successfully utilized in the augmentation of heterocyclic synthesis and green reaction protocols.\textsuperscript{[7]} Heterogeneous catalytic processes based on metal oxide catalysts are simpler, highly efficient, and eco-friendly with greater selectivity.\textsuperscript{[8]} Heterogeneous catalysts possess added advantages such as thermal stability, shape selectivity, acidic or basic nature, nontoxic crystalline solids, and easy handling.\textsuperscript{[9]} Easy salvage and reusability are additional benefits. Hence, considering current legislation and industry needs, the use of heterogeneous catalysts is a notable option for one-pot synthesis involving multicomponent reactions.

Silica (SiO$_2$) is an efficient and cheap support material, which can readily promote the activity of the supported metal catalysts. SiO$_2$ has good acid–base properties, a nontoxic nature, and high chemical thermal stability.\textsuperscript{[10]} It has high surface area and carries a vast concentration of active sites. SiO$_2$ by itself, or in combination with metals (composites), has been used in organic synthesis.\textsuperscript{[10]} This acid–base bifunctional catalyst has emerged as an attractive option as support material for the activation and stabilization of ceria and vanadia. The crystalline structure of SiO$_2$ has been reported as a key factor in explaining the structure–activity relationships of mixed oxides of cerium (Ce) and vanadium (V) catalysts as the Ce–V/SiO$_2$ solid material possesses both Brønsted and Lewis acid centers.\textsuperscript{[11]}

Due to variety of therapeutic, pharmacological, biological, and agricultural applications for heterocycles in the fields of organic, pharmaceutical, medicinal, and combinatorial chemistry, heterocyclic compounds have gained importance as catalysts.\textsuperscript{[12–13]} The pyrans and benzopyrans received significant attention in heterocyclic synthesis,\textsuperscript{[14]} as they possess an oxygen heteroatom and exhibit diverse biological properties such as antibacterial and antifungal,\textsuperscript{[15]} anticancer,\textsuperscript{[16]} anti-inflammatory,\textsuperscript{[17]} antitumour,\textsuperscript{[18]} anti-HIV,\textsuperscript{[19]} and anti-Alzheimer activities\textsuperscript{[20]} and is also used for treatment of disorders in the central nervous system.\textsuperscript{[21]} Applications of pyran-containing compounds as ligands in coordination chemistry, herbicidal, and insecticidal in pesticide chemistry are also well documented.\textsuperscript{[22]} A large number of molecules bearing the pyran moiety display a wide-ranging spectrum of pharmacological activities in conditions such as asthma, hypertension, urinary diseases, and ischaemia, and currently, many are in use in the treatment of variety of diseases.\textsuperscript{[22–26]} Thus, the synthesis of substituted pyran derivatives has been the topic of many research investigations, and several approaches have been pursued using various catalysts, including hexamethylenetetramine-bromine (HMTAB),\textsuperscript{[27]} \(\text{H}_2\text{P}_2\text{W}_9\text{O}_{24}\cdot\text{H}_2\text{O}\),\textsuperscript{[28]} rare-earth perfluoroacetonate (RE(PFO)$_2$),\textsuperscript{[29]} phenylboronic acid,\textsuperscript{[30]} silica-gel-supported polyphosphoric acid (PPA-SiO$_2$),\textsuperscript{[31]} per-6-amino-β-cyclodextrin,\textsuperscript{[32]} L-proline,\textsuperscript{[33]} 4-dimethylaminopyridine (DMAP),\textsuperscript{[34]} 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF$_4$])\textsuperscript{[35]} MNP@P[imEt][Br],\textsuperscript{[36]} tetra-n-
butylammonium fluoride (TBAF)\(^{[37]}\) amongst others. However, many of these procedures have one or more drawbacks such as moderate yields, requirement of expensive reagents, toxic organic solvents, stoichiometric catalysts, extreme reaction conditions, lengthy procedures, or long reaction times. Moreover, in many cases, the catalysts used are not recyclable. Therefore, the development of an effective and facile procedure with high generality for the synthesis of 4H-pyran derivatives was timely and of considerable interest.

In continuing our research in developing new methodologies for the synthesis of heterocycles\(^{[14,39]}\) and synthesis of biologically active heterocyclic molecules\(^{[40–45]}\), we here communicate an efficient method for the synthesis of 2-amino-3-cyano-4H-pyran derivatives (4a–I) in high yields in the presence of a heterogeneous and reusable Ce–V/SiO\(_2\) catalyst under green conditions.

To establish the optimum reaction conditions, to maximize the yield, and decrease reaction times, the reaction was investigated under varied conditions of catalysts and solvents. The initial experiment was conducted with 5,5-dimethylcyclohexane-1,3-dione 1 (1 mmol), benzaldehyde 2a (1 mmol), and malononitrile 3 (1.2 mmol) in aqueous media, without any catalyst at RT, and no reaction was observed. Even after 24 h under reflux conditions, the reaction showed no product (Table 1, entries 1 and 2). The same reaction was repeated with ethanol as solvent, but no product was obtained even after 12 h (Table 1, entry 3). Interestingly, a trace amount of the predicted product was observed, when MgO, Mn/Al\(_2\)O\(_3\), or V/Al\(_2\)O\(_3\) were used as catalysts in the ethanol media (Table 1, entry 4–6), but no reaction was apparent in presence of strongly basic catalysts, such as piperidine or K\(_2\)CO\(_3\) and ethanol as solvent (Table 1, entries 7&8). The acidic catalysts PTSA, SiO\(_2\), and ZnCl\(_2\) were attempted, but found to be less effective as reactions gave only 21–34% yield of the expected product (Table 1, entries 9–11). The scope of reaction in the presence of the l-proline and also ionic liquids such as (Bmim)BF\(_4\) and (Bmim)OH was also explored, but yields were low (Table 1, entries 12–14). With CeO\(_2\)/ SiO\(_2\) and V\(_2\)O\(_5\)/SiO\(_2\) as a catalyst in ethanol, yields of 55% and 58% were obtained, respectively (Table 1, entries 15, 16). This could be due to the high surface area of V\(_2\)O\(_5\) on silica which increases the availability of vanadium active sites for the reaction. Furthermore, we examined HClO\(_4\)/SiO\(_2\) catalyst to afford less yield 45%. Then, we investigated the range of Ce–V/SiO\(_2\), which is a bifunctional acid–base catalyst, with ethanol as solvent. The reaction was repeated under similar conditions using Ce–V/SiO\(_2\) which gave an excellent yield of 95% in 1 h once optimum dopant percentage had been established.

The impact of cerium or vanadia loading on silica in tuning its catalytic efficiency was further investigated. To find the ideal loading of Ce–V on SiO\(_2\) on catalyst activity, reactions with 1%, 2%, and 4% Ce–V-doped SiO\(_2\) were carried out under otherwise comparable conditions. The percentage of Ce–V loading was found to have an influence on the reaction yield as well as reaction time (Table 1, entries 18–20). Using 1% Ce–V/SiO\(_2\) catalyst yielded 79% product in 2.5 h under ethanol solvent conditions (Table 1, entry 18). A 2% Ce–V loading was found optimal with 95% yield in 1 h (Table 1, entry 19). A further increase of metal loading (4%) led to a slightly decreased yield (89%) (Table 1, entry 20). We were pleasantly surprised to discover the MCR was successful in only 1 h at RT. The expected substituted pyrans (4a) were produced selectively and in good yield (95%) (Table 1, entry 19). Although it took about 1 h for the reaction to complete, the Ce–V/SiO\(_2\) catalyzed reaction was found to start almost immediately. Reaction products were identified and confirmed by spectral and other analytical data. Excellent selectivity and yield could be achieved due to the nature of the chosen catalyst with high surface area, which presumably enhanced the accessibility of the substrate to the anchored acidic and basic groups.

The surface properties of the SiO\(_2\) can be modified by loading cations of various properties. An optimal distribution of the acidic and basic sites due to loading of Ce–V on SiO\(_2\) possibly contributed to its enhanced catalytic efficiency, which is evident from the high yield, selectivity, and speed of the reaction achieved in the title reaction. In the proposed MCR, we speculate that the Ce–V/SiO\(_2\) catalyst displays greater efficiency compared with the other catalysts investigated due to a synergetic effect between ceria and vanadia. Taking advantage of the proven performance of 2% Ce–V/SiO\(_2\) as catalyst for the MCR, we then focused on further improving the reaction efficiency. We screened for changes in the variation of Ce–V catalyst loading on silica support. The results are summarized (Table 2, entries 1–3) and indicate that an increase in loading of Ce–V on SiO\(_2\) from 10 mg to 30 mg, resulted in an increased yield from 71% to 95%. A further in-

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**Table 1. Optimization conditions for the synthesis of 2-amino-3-cyano-4H-pyran derivatives by Ce–V/SiO\(_2\) catalyst.**

| Entry | Catalyst | Solvent | Condition | Time [h] | Yield [%] |
|-------|----------|---------|-----------|----------|-----------|
| 1     | No catalyst | H\(_2\)O | RT        | 24       | –         |
| 2     | No catalyst | EtOH    | Re flux   | 24       | –         |
| 3     | No catalyst | EtOH    | Re flux   | 12       | –         |
| 4     | MgO (50 mg) | EtOH    | Re flux   | 10       | Trace     |
| 5     | Mn/Al\(_2\)O\(_3\) (50 mg) | EtOH    | Re flux   | 12       | Trace     |
| 6     | V/Al\(_2\)O\(_3\) (50 mg) | EtOH    | Re flux   | 12       | Trace     |
| 7     | Piperidine | EtOH    | Re flux   | 12       | –         |
| 8     | K\(_2\)CO\(_3\) | EtOH    | Re flux   | 7        | 21        |
| 9     | PTSA      | EtOH    | Re flux   | 8        | 27        |
| 10    | SiO\(_2\) | EtOH    | Re flux   | 5        | 34        |
| 11    | ZnCl\(_2\) | EtOH    | Re flux   | 4.5      | 38        |
| 12    | l-proline | EtOH:H\(_2\)O | Re flux | 4.5      | 38        |
| 13    | (Bmim)BF\(_4\) | EtOH:H\(_2\)O | Re flux | 4        | 32        |
| 14    | (Bmim)OH | EtOH:H\(_2\)O | Re flux | 4        | 29        |
| 15    | CeO\(_2\)/SiO\(_2\) | EtOH    | Re flux   | 2        | 55        |
| 16    | V\(_2\)O\(_5\)/SiO\(_2\) | EtOH    | Re flux   | 2        | 58        |
| 17    | HCIO\(_4\)/SiO\(_2\) | EtOH    | Re flux   | 2.5      | 45        |
| 18    | 1% Ce–V/SiO\(_2\) (30 mg) | EtOH    | RT        | 2.5      | 79        |
| 19    | 2% Ce–V/SiO\(_2\) (30 mg) | EtOH    | RT        | 1        | 95        |
| 20    | 4% Ce–V/SiO\(_2\) (30 mg) | EtOH    | RT        | 1        | 89        |
| 21    | 2% Ce–V/SiO\(_2\) (30 mg) | MeOH    | RT        | 2        | 89        |
| 22    | 2% Ce–V/SiO\(_2\) (30 mg) | CH\(_3\)COCH\(_3\) | RT | 2.5      | 78        |
| 23    | 2% Ce–V/SiO\(_2\) (30 mg) | DMF     | RT        | 2.5      | 86        |
| 24    | 2% Ce–V/SiO\(_2\) (30 mg) | THF     | RT        | 3        | 69        |
| 25    | 2% Ce–V/SiO\(_2\) (30 mg) | Toluene | RT        | 4        | 65        |

[a] All products were characterized by IR, \(^1^H\) NMR, \(^13^C\) NMR, \(^19^F\) NMR, and high-resolution mass spectrometry (HRMS) spectral analysis. [b] Isolated yields. [–] No reaction.
crease in loading of catalyst had only a marginal effect on product yield (Table 2, entries 4&5).

Secondly, because solvents play an important role in design of MCRs, we also studied the influence of solvent in the title reaction. The efficiencies of various solvents including methanol, acetonitrile, dimethylformamide (DMF), tetrahydrofuran (THF), and toluene were compared under otherwise identical reaction conditions. We found that the reaction proceeded smoothly in protic solvents. Among all the screened solvents, EtOH was found to be the superior solvent for this multicomponent reaction. It is noteworthy to mention that from the results of optimization (Table 1, entries 21–25), the reaction temperature and polarity of the solvent appear to be important for this multicomponent reaction to achieve clean products in good to excellent yields. Polar protic solvents enhance the rate of reaction, whereas for the nonpolar solvents, the rate of the reaction was sluggish.

The wider scope of this MCR was further explored with other reagents. Choosing the optimized conditions for the synthesis of 4a, that is, 30 mg of Ce–V/SiO₂ at RT and ethanol as solvent (Scheme 1), we investigated the reactions with varied structurally different aldehydes (2a–l) for the MCR. To our delight, most of the reactions afforded the desired 2-amino-3-cyano-4H-pyran derivatives with excellent selectivity (4a–l) and yields (87–95%), and with no by-products. The results are summarized in Table 3. Interestingly, the MCRs with substrates bearing both electron-donating and electron-withdrawing groups on the aromatic ring performed well and gave corresponding target molecules in excellent yields. Structures of all the products (4a–l) were established and confirmed on the basis of their spectral data: ¹H NMR, ¹³C NMR, ¹⁵N NMR (gradient heteronuclear single quantum coherence, GHSQC), and Fourier-transform infrared (FTIR) spectroscopy and high-resolution mass spectrometry (HRMS).

Figure 1 shows the X-ray diffraction (XRD) patterns of the Ce–V/SiO₂ powder catalyst calcined at 450 °C. The CeO₂ diffraction peaks at 2θ = 29.6°, 31.7°, 36.5°, 49.1°, and 67.2° compare well with the standard database file (JCPDS34-0394). The mixed oxide shows the Ce–VO₂ phase in accord with the standard database file (JCPDS12-757, with sharp diffraction peaks at 2θ = 22.2°, 26.2°, 32.2°, 42°, 56.6°, and 71.8°. As can be seen from the figure, the vanadium oxide sample showed sharp diffraction peaks at 2θ = 17.3°, 29.1°, 38.1°, and 49° (JCPDS41-1426). There are no other peaks, except V₂O₅, CeO₂, and CeVO₄ in XRD patterns for the Ce–V/SiO₂ sample, implying bulk purity.

The scanning electron microscopy (SEM) micrograph (Figure 2a) displays agglomeration of metal oxide particles which is caused by the calcination of the Ce–V/SiO₂ catalyst, and these aggregates are in the size range from 0.81–2.00 μm. Energy-dispersive X-ray spectroscopy (EDS) semi-quantitative analysis of this catalyst showed that Ce and V are homogeneously distributed in the catalyst (Figure 2b), and the metal ratio (Ce:V) is also in agreement with the inductively coupled plasma (ICP) elemental analysis. The catalyst morphologies as indicated by the SEM image clearly point out the homogeneity in shapes for the sample and high crystallinity. Inductively coupled plasma optical emission spectrometry (ICP-OES) analysis showed that the cerium to vanadium metal ratio is equal. The transmission electron microscopy (TEM) micrograph (Figure 3) showed that the calcined catalyst has a cubic-like structure, which is characteristic of typical vanadate. These cubic planar structures are in the size of 21±3 nm. The selected area diffractions showed that catalyst is polycrystalline in nature, which is further supported by the XRD diffractogram.

The nitrogen adsorption–desorption isotherms for the Ce/V-silica supported catalyst are shown in Figure 4. All the prepared catalysts have a similar pattern in adsorption–desorption
isotherms and display the characteristic hysteresis loop of a type-IV isotherm (IUPAC) lying in the p/p₀ range of 0.7–0.85, demonstrating mesoporous character and indicates a small pore size and good homogeneity of the catalyst. A quite narrow and monomodal pore size distribution was obtained for the Ce–V doped on silica. This further indicated that the average pore size has increased with increasing the loading amount of silica. For the 2 wt% Ce–V loaded catalyst, the parameters are specific surface area (17.1 m²g⁻¹), pore size (0.0139 cm³g⁻¹), and total pore volume (74 Å³). The low surface area of the prepared catalysts compared with the bare silica support was probably due to the good dispersion of Ce–V on the surface of silica.

The reusability of any heterogeneous catalyst is one of the most important parameters for potential commercial applications. The reusability of the catalyst was assessed in the synthesis of 2-amino-3-cyano-4H-pyran derivatives (Figure 5). Gratifyingly, the heterogeneous Ce–V/SiO₂ could be recovered effectively from the reaction mixture by simple filtration and by washing the catalyst twice with acetone and drying at 70–80 °C under reduced pressure for 2 h to make it ready for a later run. There was no loss of Ce–V loading on silica observed which was confirmed by ICP-OES analysis. The catalyst was tested for six runs. It was observed that recovered catalyst can be recycled in subsequent runs with minimal loss of its activity only after five runs, which might be due to the agglomeration of Ce–V.

Figure 2. a) SEM image of Ce–V/SiO₂ catalyst (white scale bar = 10 μm); b) SEM-EDX image of Ce–V/SiO₂ catalyst.

Figure 3. TEM spectra of Ce–V/SiO₂ catalyst (white scale bar = 100 nm).

Figure 4. N₂ adsorption and desorption spectra and pore size distribution of Ce–V/SiO₂ catalyst.

Figure 5. Recyclability of Ce–V/SiO₂ catalyst.
In conclusion, we report an environmentally benign and an efficient one-pot multicomponent green synthesis of 2-amino-3-cyano-4H-pyrano derivatives using Ce–V/SiO\(_2\) as catalyst in green solvent and with good atom efficiency. This simple and recyclable heterogeneous catalyst, Ce–V/SiO\(_2\), shows high catalytic activity for multicomponent reactions. The current method has several advantages such as short reaction times, excellent yields, high purity of products, cost-effectiveness, use of small amounts of inexpensive catalyst, and use of an environmentally benign green solvent.

**Experimental Section**

Ce–V-loaded silica mixed oxide (Ce–V) with a Ce:V molar ratio of 1:1 was synthesized by the wet impregnation method.\(^{[46–48]}\) Ce(NO\(_3\))\(_2\)·6H\(_2\)O (62 mg for 1%, 124 mg for 2% and 250 mg for 4% Aldrich-99%), and VOSO\(_4\)·xH\(_2\)O (63 mg for 1%, 126 mg for 2% and 252 mg for 4%; Aldrich-97%) were dissolved in distilled water (50 mL), and this was followed by the addition of SiO\(_2\) (2.0 g, Aldrich). The reaction mixture was continuously stirred for 4 h at RT, and the mixture was further dried in an oven at 110°C overnight, and then calcined in air flow at 500°C for 4 h to obtain the various 1, 2, and 4 wt% of mixed oxides of Ce–V-loaded silica catalysts.

**General procedure for the synthesis of 2-amino-3-cyano-4H-pyrano derivatives**

A mixture of 5,5-dimethylcyclohexane-1,3-dione 1 (1 mmol), aromatic aldehyde 2 (1 mmol), and malononitrile 3 (1.1 mmol) were dissolved in EtOH (10 mL) at RT. The reaction mixture was stirred for 4 h at RT, and the mixture was further dried in an oven at 110°C overnight, and then calcined in air flow at 500°C for 4 h to obtain the various 1, 2, and 4 wt% of mixed oxides of Ce–V-loaded silica catalysts.

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