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# $SO_4^{2-}/Ce_xZr_{1-x}O_2$-catalyzed Synthesis of *N-tert*-Butylamides from Various Nitriles under Solvent-free Conditions

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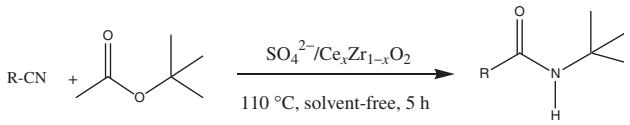
The synthesis of *N-tert*-butylamides using $SO_4^{2-}/Ce_xZr_{1-x}O_2$ catalysts under solvent-free conditions is reported. The methodology has several advantages such as reusability of the catalyst, solvent-free conditions, easy workup, and comparable yield of *N-tert*-butylamides. A variety of aliphatic, aromatic, and acid-sensitive substrates give high to moderate yields of the corresponding *N-tert*-butylamides. Surface acidities of the catalysts were correlated with the results obtained. To the best of our knowledge, this is the first report of a modified Ritter reaction on $SO_4^{2-}/Ce_xZr_{1-x}O_2$ using *tert*-butyl acetate as carbocationic source.

*N-tert*-Butylamides are important synthetic intermediates in the pharmaceutical industry.[1] They prevent 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-induced reduction of dopamine levels which is the main cause for Parkinson's disease.[2] They are also utilized in the synthesis of benzamides.[3] Synthesis of *N-tert*-butylamides can be achieved by either Ritter reaction or anodic oxidation of di-*tert*-butyl disulfides.[4] As the synthesis based on anodic oxidation gives the undesirable side product, viz., di-*tert*-butyl tetrasulfides, Ritter reaction is the more favored route. Ritter reaction involves the synthesis of amides from olefins or alcohols with nitriles. In the modified form of the Ritter reaction, *tert*-butyl alcohol,[5] *tert*-butyl methyl ether, and *tert*-butyl acetate are used as a source of carbocations. *tert*-Butyl acetate is readily handled and available, and is better for the synthesis of *N-tert*-butylamides.

Homogenous catalysts such as bismuth triflate,[6] sulfuric acid,[7] $FeCl_3$,[8] and iodine[9] are reported for the synthesis of *N-tert*-butylamides via modified Ritter reaction. However, with the current environmental concerns, replacement of "non-green" reagents by "green" solid acid catalysts has industrial significance. The reported methodologies have some disadvantages such as requirement of acetic acid for slow release of isobutylene gas and specially designed reaction vessels. Hence there is a need for the development of a suitable catalytic protocol which can overcome these drawbacks.

Sulfated zirconia is a well-explored solid acid catalyst[10] whose catalytic activity has been found to be influenced by the incorporation of transition-metal oxides.[11] In the present study, Ce(IV)-incorporated sulfated zirconia catalysts were tested for the modified Ritter reaction. In this catalyst system, the Brønsted acid sites arise from the weakening of O–H bond by inductive effect (−I) of neighboring sulfate groups and the Lewis acidity of the electron-deficient $Zr^{+4}$ is enhanced by the electron-withdrawing nature of the sulfate groups. The incorporation of Ce(IV) forms a thermally stable solid solution with zirconia with high surface area and acidity.[14]

In continuation of our efforts for the development of efficient catalytic protocol for various organic transformation,[12] we herein report the synthesis of *N-tert*-butylamides using various nitriles and *tert*-butyl acetate with $SO_4^{2-}/Ce_xZr_{1-x}O_2$ as a reusable catalyst under solvent-free conditions (Scheme 1).




**Scheme 1.** $SO_4^{2-}/Ce_xZr_{1-x}O_2$-catalyzed amidation of *tert*-butyl acetate.

**Table 1.** Effect of different catalysts on the amidation of *tert*-butyl acetate with benzonitrile[a]

| Entry | Catalyst | $E_i$ /mV[b] | Acidity /mmol $g^{-1}$ [c] | Yield /%[d] |
|---|---|---|---|---|
| 1[e] | None | — | — | NR[h] |
| 2[e] | $CeO_2$ | 27 | 0.3 | NR |
| 3 | $ZrO_2$ | 55 | 0.8 | 17 |
| 4 | $SO_4^{2-}/CeO_2$ | 154 | 1.22 | 19 |
| 5 | $SO_4^{2-}/ZrO_2$ | 168 | 2.07 | 27 |
| 6[f] | $SO_4^{2-}/CeO_2 + SO_4^{2-}/ZrO_2$ | — | — | 39 |
| 7[g] | $SO_4^{2-}/Ce_{0.02}Zr_{0.98}O_2$ | 440 | 3.17 | 49 |
| 8[g] | $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ | 560 | 4.23 | 78 |
| 9[g] | $SO_4^{2-}/Ce_{0.10}Zr_{0.90}O_2$ | 450 | 3.52 | 64 |
| 10[g] | $SO_4^{2-}/Ce_{0.15}Zr_{0.85}O_2$ | 460 | 3.50 | 58 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl acetate (2 mmol), catalyst (20 wt %) of benzonitrile, solvent free, 5 h, 110 °C. [b]$E_i$: Inital electrode potential (mV). [c]Surface acidity values determined by *n*-butylamine potentiometric titration method. [d]Isolated yield. [e]10 h. [f]10 wt % each of catalyst with respect to benzonitrile. [g]$SO_4^{2-}/Ce_xZr_{1-x}O_2$ ($x = 0.01$–$0.015$ mol % of Ce added in the catalyst determined by EDAX method. [h]NR: no reaction.

The $SO_4^{2-}/Ce_xZr_{1-x}O_2$ ($x = 0.02$–$0.15$ mol %) catalysts were prepared by precipitation followed by impregnation. An acidic solution of cerium sulfate ($Ce(SO_4)_2 \cdot 4H_2O$ was added to the previously prepared $Zr(OH)_4$. This was followed by drying at 110 °C for 24 h and calcining at 650 °C for 2 h.[13]

In order to find out the best catalytic system suited for the synthesis of *N-tert*-butylamides, the reactions were carried out under solvent-free conditions using various metal oxides, surface-modified metal oxides, and mixed metal oxides (Table 1). It should be pointed out that when the reaction of benzonitrile with *tert*-butyl acetate at 110 °C was carried out without catalyst, no product was observed even after prolonged reaction time (Table 1, Entry 1). Also no product was observed with $CeO_2$ alone, whereas $ZrO_2$ gave 17% yield of the product amide (Table 1, Entries 2 and 3).

**Table 2.** Effect of solvents on the amidation of *tert*-butyl acetate with benzonitrile[a]

| Entry | Solvent | Yield/%[b] |
|---|---|---|
| 1 | Solvent free | 78 |
| 2 | Water | 34 |
| 3 | Toluene | 22 |
| 4 | Xylene | 25 |
| 5 | Dioxane | 55 |
| 6 | THF | 49 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl acetate (2 mmol), solvent: 5 mL, 5 h, 110 °C, $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst (20 wt %) of benzonitrile. [b]Isolated yield.

The reaction in the presence of sulfated $CeO_2$ and $ZrO_2$ enhanced the yield of the product (Table 1, Entries 4 and 5). Sulfated ceria and sulfated zirconia (10 wt % each) gives yield up to 39% of the amide (Table 1, Entry 6). The results reveal that $SO_4^{2-}/Ce_xZr_{1-x}O_2$ catalysts (Table 1, Entries 7–10) show better performance over the other metal and composite oxides. The effect of the Ce content on the amidation reaction was also studied (Table 1, Entries 7–10). $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst shows better performance with 78% yield over other compositions of $SO_4^{2-}/Ce_xZr_{1-x}O_2$. Hence $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst was selected for further studies. The higher activity of $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst could be attributed to the higher amount of (4.23 mmol $g^{-1}$) acidic sites. Also the initial electrode potential (560 mV) indicates the presence of very strong acid sites (Table 1, Entry 7).

Our goal was to avoid the use of organic solvents for the synthesis of *N*-*tert*-butylamides so as to make the protocol environmentally benign. When the reaction was performed under solvent-free conditions, 78% yield was obtained (Table 2, Entry 1). We also investigated the effect of solvents on the reaction. The reaction was carried out in different solvents such as water, toluene, xylene, dioxane, and THF (Table 2, Entries 2–6). In various solvents the transformation of nitrile to amide, was sluggish. On the contrary, under solvent-free conditions, maximum yield was obtained.

The reactions were carried out at different temperatures (30 to 130 °C, Table 3, Entries 1–5). It was observed that beyond 110 °C there was no effect of temperature on the yield of the product. The influence of catalyst loading was also tested (Table 4, Entries 1–6). The yield increased when catalyst loading was increased from 5 to 25 wt % (Table 4, Entries 1–5). It was observed that further increase of catalyst loading did not show any considerable increase in the yield (Table 4, Entry 6). Hence 20 wt % of catalyst amount was found to be optimum for further studies (Table 4, Entry 4).

The effect of different *tert*-butyl carbocationic sources such as *tert*-butyl methyl ether, *tert*-butyl alcohol, and *tert*-butyl acetate (Table 5, Entries 1–3) was studied. *tert*-Butyl acetate gave best results with $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst under the given experimental conditions (Table 5, Entry 1).

In order to investigate the generality of the above protocol, the reaction was carried out using a variety of structurally diverse nitriles with *tert*-butyl acetate as carbocation source to the corresponding amide using $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ under solvent-free conditions. The differences in the yield of the corresponding amide products were found to be influenced by the nitrile substituents. The reaction of benzonitrile with *tert*-butyl acetate gave 78% yield of the desired product within 5 h (Table 6, Entry 1). Aromatic nitriles with electron-withdrawing and electron-donating functional groups such as –OH and –Cl gave excellent yields of the desired product (Table 6, Entries 2–4). We also observed that the position of the substituent on the aromatic ring did not have much influence on the yield. The protocol was also tested for the reaction of aliphatic nitriles under the optimized reaction conditions.

In case of malononitrile at 110 °C, 65% yield of the desired amide was obtained (Table 6, Entry 5). Aliphatic nitriles with electron-withdrawing and electron-donating groups such as benzyl, methyl, *n*-butyl, and acetate gave moderate to high yields (Table 6, Entries 6–10). Unsaturated nitriles such as acrylonitrile also underwent smooth conversion without affecting the ethylenic bond and afforded 84% yield of the amide (Table 6, Entry 11). Thus aromatic, aliphatic as well as acid-sensitive nitriles were found to be viable for this transformation.

We also investigated the reusability of the catalyst. After separation by filtration, the catalyst was washed several times with acetone and heated at 120 °C for 2 h before the next catalytic cycle. The catalyst is reusable up to five consecutive cycles without any remarkable loss of activity (Table 7, Entries 1–5).

The possible reaction mechanism of the modified Ritter reaction with $SO_4^{2-}/Ce_xZr_{1-x}O_2$ catalysts involves the cleavage

**Table 3.** Effect of temperature on the amidation of *tert*-butyl acetate with benzonitrile[a]

| | Entry | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Temp/°C | 30 | 60 | 80 | 110 | 130 |
| Yield/%[b] | NR[c] | 31 | 51 | 78 | 78 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl acetate (2 mmol), solvent free, 5 h, catalyst (20 wt %) of benzonitrile. [b]Isolated yield. [c]NR: no reaction.

**Table 4.** Effect of catalyst loading on the amidation of *tert*-butyl acetate with benzonitrile[a]

| | Entry | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Catalyst/wt % | 5 | 10 | 15 | 20 | 25 | 30 |
| Yield/%[b] | 17 | 35 | 50 | 78 | 79 | 79 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl acetate (2 mmol), solvent free, 5 h, 110 °C, catalyst (wt %) of benzonitrile. [b]Isolated yield.

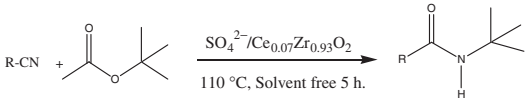
**Table 5.** Effect of different tertiary butyl cation sources on the amidation of *tert*-butyl acetate with benzonitrile[a]

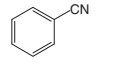
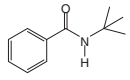
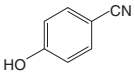
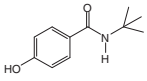
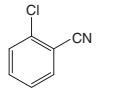
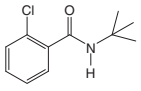
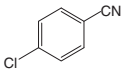
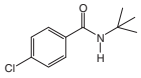
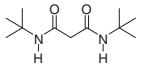
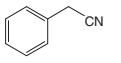
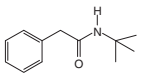
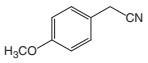
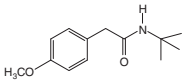
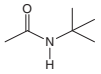
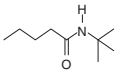
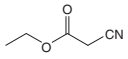
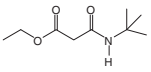
| Entry | *tert*-Butyl cation source | Yield/%[b] |
|---|---|---|
| 1 | *tert*-Butyl acetate | 78 |
| 2 | *tert*-Butyl alcohol | 23 |
| 3 | *tert*-Butyl methyl ether | 34 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl cation source (2 mmol), solvent free, 5 h, 110 °C, $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst (20 wt %) of benzonitrile. [b]Isolated yield.

**Table 6.** Amidation of *tert*-butyl acetate with various nitriles over $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst[a]




| Entry | Nitrile | Amide | Yield/%[b] |
|---|---|---|---|
| 1 |  |  | 78 |
| 2[c] |  |  | 84 |
| 3[c] |  |  | 87 |
| 4[c] |  |  | 89 |
| 5 |  |  | 65 |
| 6 |  |  | 93 |
| 7 |  |  | 86 |
| 8 | $CH_3CN$ |  | 80 |
| 9 |  |  | 74 |
| 10 |  |  | 79 |
| 11 |  |  | 84 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl acetate (2 mmol), $SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$ catalyst (20 wt %) of benzonitrile, solvent free, 5 h, 110 °C. [b]Isolated yield. [c]Solid nitriles 3 equivalents of *tert*-butyl acetate used. All compounds are reported in the literature.[14]

**Table 7.** Catalyst reusability[a]

| Run | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Yield/%[b] | 78 | 78 | 75 | 72 | 71 |

[a]Reaction conditions: benzonitrile (1 mmol), *tert*-butyl acetate (2 mmol), solvent free, 5 h, 110 °C, catalyst (20 wt %) of benzonitrile. [b]Isolated yield.

of the alkyl–oxygen bond of the *tert*-butyl acetate. The coordination of the acyloxy oxygen atom to the acid sites of the catalyst leads to the formation of a carbocation. Then, the nitrile attacks the cationic center followed by the addition of water during the aqueous workup to give the desired products. The cleavage at the alkyl–oxygen bond of the *tert*-butyl acetate is due to the stability of *tert*-butyl carbocation by the (+I) inductive effect of the three methyl groups.

In conclusion, this paper describes a convenient route for the synthesis of *N*-*tert*-butylamides using $SO_4^{2-}/Ce_xZr_{1-x}O_2$ as solid acid catalysts. To the best of our knowledge, this is the first report of a modified Ritter reaction on $SO_4^{2-}/Ce_xZr_{1-x}O_2$ using *tert*-butyl acetate as carbocation source. Also this methodology is applicable to various electron-rich, electron-deficient, and acid-sensitive nitriles. The catalyst are reusable up to five consecutive cycles without much loss of catalytic activity.

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