# Yttria-Zirconia Based Lewis Acid: An Efficient and Chemoselective Catalyst for Acylation Reactions

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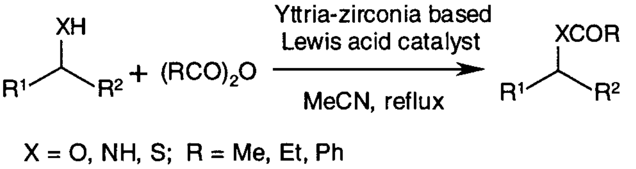
**Abstract:** Yttria-zirconia based strong Lewis acid efficiently catalyzes acylation of alcohols, amines and thiols under environmentally safe, heterogeneous reaction conditions with high selectivity and in excellent yields.

**Key words:** yttria-zirconia based Lewis acid, heterogeneous catalysis, acylation reaction, chemoselectivity

The acylation of alcohols, amines, and thiols by acyl chloride or acid anhydride under basic conditions is a well established reaction in organic synthesis.[1] The most commonly employed basic catalysts for this purpose are 4-(dimethylamino)pyridine and 4-pyrrolidinopyridine (PPY).[2] The Lewis acid catalyzed acylation of alcohols and amines with acid anhydride is a mild, strategic alternative to basic and nucleophilic catalysts. Some procedures have been developed wherein Lewis acid catalysts such as $Cu(OTf)_2$,[3] $TaCl_5$,[4] TMSOTf,[5] $Sc(OTf)_3$,[6] $In(OTf)_3$,[7] $CoCl_2$,[8] $Bu_3P$[9] have been used for acyl transfer reactions in alcohols. More recently, the use of montmorillonite K-10 and KSF[10] as heterogeneous catalysts has been reported to effect acylation reactions. As part of a research program aimed at developing a new solid catalyst and its subsequent application for various organic transformations, the yttria-zirconia based Lewis acid was found to be an extremely efficient catalyst for the Diels-Alder reaction[11] and transesterification of β-keto esters.[12] This prompted us to use this catalyst for acylation reactions, and here we report that an yttria-zirconia based Lewis acid serves as an excellent catalyst for the acylation of alcohols, thiols and amines (Scheme).



**Scheme**

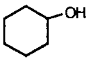
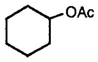
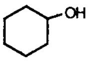
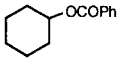
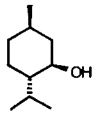
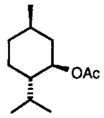
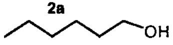
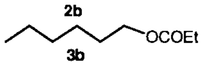
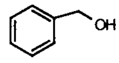
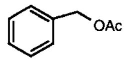
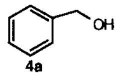
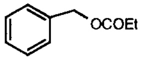
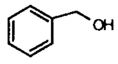
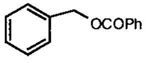
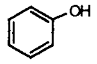
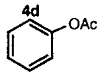
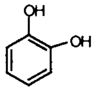
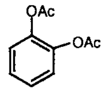
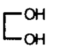
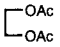
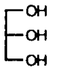
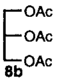
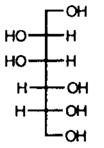
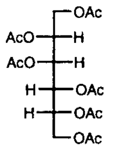
Thus, when a variety of alcohols were treated with acid anhydrides in the presence of a catalytic amount of the new yttria-zirconia based catalyst, the corresponding acetates were obtained in excellent yields. In a typical experimental procedure, acid anhydride (11 mmol; 1.1 equiv. per OH, $NH_2$ or SH) was added dropwise to a solution of alcohol, amine, or thiol (10 mmol) in dry acetonitrile (5ml) containing catalyst (20% by weight), and the mixture was refluxed for the indicated length of time (Table 1–3). The reaction was monitored by TLC. After completion of reaction, the catalyst was filtered and the filtrate was concentrated, diluted with water (15 ml) and extracted with $CH_2Cl_2$ (2 × 20 ml). The organic layer was separated, washed with 10% aq. $NaHCO_3$, brine, water and dried over $Na_2SO_4$. The solvent was removed and the crude product was chromatographed on a silica gel column to afford the pure product. After the reaction, the catalyst is recovered with retention of its catalytic activity. It can be further reactivated for reuse by heating it at 500 °C in the presence of air. The substrates examined in our studies and the results obtained are summarized in Table 1–3.

Thus, the present procedure for acylation is quite general as a wide range of structurally varied alcohols such as open chain, cyclic and aromatic ones underwent acylation with acid anhydrides. However, the reaction of alcohols with benzoic anhydride is found to be sluggish and hence a little longer time is required to complete the reaction affording relatively low yield of the products (Table 1, entries 2,7). The efficacy of the yttria-zirconia based catalyst can be clearly visualized in the acetylation of polyhydroxy compounds under similar conditions. For example, both aliphatic and aromatic polyols were acetylated in very high yield (Table 1, entries 9–12). Another noteworthy feature of this methodology is that polyol such as D-mannitol underwent exhaustive acetylation smoothly demonstrating the practical utility of this method (Table 1, entry 12).

In order to explore the generality and scope of the yttria-zirconia based Lewis acid catalyzed reaction, the procedure has been extended to a variety of other substrates such as amines and thiols. Thus, the aromatic and aliphatic amines were successfully acylated in the presence of a yttria-zirconia based Lewis acid catalyst (Table 2).

Another notable feature of the reaction is that even a hindered amine was acylated in very high yield (Table 2, entry 2). In a similar manner acylation of thiols was also achieved by this procedure in excellent yields (Table 2, entries 6-8). Encouraged by this finding, it was felt worthwhile to study the reactivity pattern of different kinds of amino alcohols, mercapto alcohols and diols for acylation reaction over yttria-zirconia Lewis acid catalyst. The results of this study are presented in Table 3.

**Table 1** The yttria – zirconia based Lewis acid[11] catalyzed acylation of alcohols and polyols

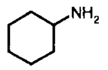
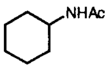
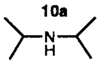
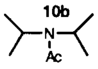
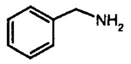
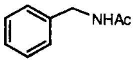
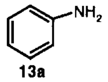
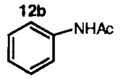
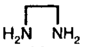
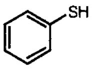
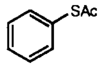
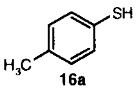
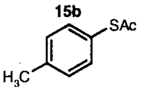
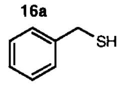
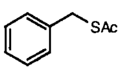
| Entry | Alcohol | Anhydride | Reaction Time (h) | Product[a] | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  **1a** | $Ac_2O$ | 4 |  **1b** | 99 |
| 2 |  **1a** | $(PhCO)_2O$ | 10 |  **1c** | 68 |
| 3 |  **2a** | $Ac_2O$ | 6 |  **2b** | 96 |
| 4 |  **3a** | $(EtCO)_2O$ | 3.5 |  **3b** | 88 |
| 5 |  **4a** | $Ac_2O$ | 6 |  **4b** | 94 |
| 6 |  **4a** | $(EtCO)_2O$ | 4 |  **4c** | 87 |
| 7 |  **4a** | $(PhCO)_2O$ | 15 |  **4d** | 71 |
| 8 |  **5a** | $Ac_2O$ | 12 |  **5b** | 97[c] |
| 9 |  **6a** | $Ac_2O$ | 5 |  **6b** | 98 |
| 10 |  **7a** | $Ac_2O$ | 6 |  **7b** | 96 |
| 11 |  **8a** | $Ac_2O$ | 8 |  **8b** | 99 |
| 12 |  **9a** | $Ac_2O$ | 10 |  **9b** | 94 |

[a]Products were characterized by spectroscopic data and also by comparison with the authentic sample.[13] [b]Yields refer to isolated pure products. [c]1.5 eq. of acetic anhydride with respect to the substrate was used for the completion of reaction.

Thus, it was observed that the reaction is chemoselective for the amino alcohols as the amine, being more nucleophilic than the alcohol, was acylated faster giving the corresponding *N*-acetate product in excellent yield (Table 3, entry 1). Similarly the hydroxyl group of 2-mercapto ethanol reacted preferentially over the thiol affording the corresponding acetate in very high yield (Table 3, entry 2). In the case of 1,2-diol, we observed preference in the acylation for primary alcohol over secondary; however a mixture of mono and di-acylated products was obtained (Table 3, entry 3). The chemoselectivity in acylation reactions with respect to different functional groups is in accordance with those observed by us in the trans-esterification reaction.[12]

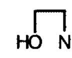
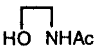
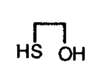
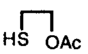
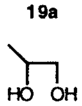
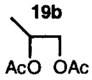
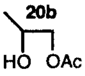
In conclusion, we have shown that an yttria-zirconia based Lewis acid serves as an efficient and chemoselective catalyst for acylation of alcohols, amines and thiols. The notable feature of this methodology is that even hindered substrates can be acylated in high yields under mild conditions. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of workup and recyclability of the catalyst are noteworthy.

**Table 2** The yttria – zirconia based Lewis acid catalyzed acetylation of amines and thiols

| Entry | Substrate | Reaction Time (h) | Product[a] | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **10a** | 2.5 |  **10b** | 97 |
| 2 |  **11a** | 3.5 |  **11b** | 91 |
| 3 |  **12a** | 2 |  **12b** | 95 |
| 4 |  **13a** | 2.5 |  **13b** | 99 |
| 5 |  **14a** | 2.5 |  **14b** | 99 |
| 6 |  **15a** | 10 |  **15b** | 97 |
| 7 |  **16a** | 6 |  **16b** | 94 |
| 8 |  **17a** | 6 |  **17b** | 97 |

[a]Products were characterized by spectroscopic data and also by comparison with the authentic sample.[13] [b]Yields refer to isolated pure products.

**Table 3** Chemoselective acetylation of amino alcohol, mercapto alcohol and diol catalyzed by yttria – zirconia based Lewis acid catalyst

| Entry | Substrate | Reaction Time (h) | Product[a] | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **18a** | 4[c] |  **18b** | 98 |
| 2 |  **19a** | 12[d] |  **19b** | 84 |
| 3 |  **20a** | 10[d] |  **20b**<br> **20c** | 10<br>76 |

[a]Products were characterized by spectroscopic data and also by comparison with the authentic sample.[13] [b]Yields refer to isolated pure products. [c]Reaction was performed at room temperature. [d]Reaction was carried out at 40 °C.

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(11) **Procedure for the preparation of the catalyst**: The catalyst was prepared by treating a mixture of aqueous solutions of yttrium nitrate and zirconyl nitrate (molar ratio 16:84) with aqueous ammonia (28%) under vigorous stirring until a pH value of 8.5 was achieved and a precipitate was formed. This

precipitate was washed with deionized water, dried at 110°C, treated with 2N sulfuric acid, dried again at 120°C for 24 h. The subsequent programmed calcination at 500°C for 3 h at a heating rate of 2°C min$^{-1}$ resulted in a highly acidic material. The chemical composition of the final catalyst (determined by XRF technique) was found to be 82.6 mol% Zr, 15.6 mol% Y and 1.8 mol% S. The physicochemical characterization of the catalyst was carried out by X-ray powder diffraction, FTIR, potentiometric titrations, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and $N_2$ adsorption techniques. For details, see: Keshavraja, A.; Hegde, V. R.; Pandey, B.; Ramaswamy, A. V.; Kumar, P.; Ravindranathan, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2143; U. S. Patent. **1999**, 5932752.

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(13) Selected spectroscopic data: **1c:** Colorless liquid: IR $\nu_{max}$ / cm$^{-1}$ (Neat): 2980, 1740, 1464, 1215; $^1$H NMR; 1.25-2.1 (m, 10H), 5.03 (m, 1H), 7.47 (m, 3H), 8.03 (m, 2H). **3b:** Colorless liquid: IR $\nu_{max}$ /cm$^{-1}$ (Neat): 3020, 2980, 1727, 1500, 1215; $^1$H NMR; 0.87 (t, *J* = 6.3, 3H), 1.15 (t, *J* = 6.3, 3H), 1.17-1.7 (m, 8H), 2.4 (q, *J* = 6.3, 2H), 4.1 (t, *J* = 6.3, 2H). **4b:** Colorless liquid: IR $\nu_{max}$ /cm$^{-1}$ (Neat): 2936, 1727, 1357, 1240; $^1$H NMR; 2.1 (s, 3H), 5.11 (s, 2H), 7.36 (s, 5H). **9b:** Colorless liquid: IR $\nu_{max}$ /cm$^{-1}$ (Neat): 3065, 1759, 1363, 1200; $^1$H NMR: 2.08 (s, 6H). 2.085 (s, 6H). 2.09 (s, 6H), 4.14 (m, 4H), 5.07 (m, 2H), 5.44 (m, 2H). **10b:** Colorless liquid: IR $\nu_{max}$/cm$^{-1}$ (Neat): 3277, 2913, 1630, 1545, 1437, 1241; $^1$H NMR: 1-1.95 (m, 10H), 2.05 (s, 3H), 3.75 (m, 1H), 3.95 (s, 1H). **15b:** Colorless liquid: IR $\nu_{max}$ /cm$^{-1}$ (Neat): 3060, 2923, 1720; $^1$H NMR: 2.4 (s, 3H), 7.4 (s, 5H). **18b:** Colorless liquid: IR $\nu_{max}$ /cm$^{-1}$ (Neat): 3303, 3097, 2935, 1655, 1558, 1431, 1066; $^1$H NMR: 1.93-2.03 (d, 3H), 3.35 (m, 2H), 3.7 (m, 2H), 5.18 (bs, 1H), 6.67 (s, 1H). **19b:** Colorless liquid: IR $\nu_{max}$ /cm$^{-1}$ (Neat): 3441, 2926, 1729, 1403; $^1$H NMR: 1.7 (s, 1H), 2.06 (s, 3H), 2.9 (t, *J* = 4.8 Hz, 2H), 4.3 (t, *J* = 4.8 Hz, 2H).

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