



CeO₂-catalyzed one-pot selective synthesis of N-alkyl amides from nitriles, amines and water

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ABSTRACT

Among 13 kinds of metal oxides, ceria (CeO₂) shows the highest catalytic activity for one-pot selective synthesis of the secondary amide from 2-cyanopyridine and *n*-octylamine as a test reaction. CeO₂ acts as a reusable heterogeneous catalyst, and it is effective for the secondary amide formation from various nitriles and amines in high yields (73% to >99%). Pharmacologically important products such as heteroaromatic N-alkyl amides and morpholine amide are effectively synthesized, indicating that CeO₂ can be a practically useful catalyst. A proposed mechanism includes (1) hydration of nitrile to the primary amide and (2) transamidation of the primary amide with amine as the rate-limiting step. This reaction mechanism provides a reason why the present catalytic system gives high selectivity.

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1. Introduction

The construction of amide bonds is one of the most important fundamental processes in organic and bioorganic chemistry as peptides and proteins include amide bonds. Synthesis of N-alkyl amides (secondary and tertiary amides) has been of great interest, because they are synthetic intermediates of numerous natural products, polymers, pesticides and pharmaceuticals [1]. Despite their importance, the majority of amide bond syntheses involve the use of stoichiometric amounts of coupling reagents, which makes them expensive and wasteful procedures [2]. Recently, direct amidation of carboxylic acids with amines by boric acids [3–7] or transamidation of amide with amine by Al(III), Sc(III), group 4 metal complexes (Ti, Zr, Hf) [8–12] were reported as effective catalytic systems for the amide bond syntheses. In the view of green chemistry, heterogeneous catalyst should be used for the amide bond syntheses. However, only a few heterogeneous catalysts have been reported to be effective for direct amidation of carboxylic acids with amines [13–17]. As an alternative method, catalytic one-pot amidation from nitriles and amines, first developed by Murahashi et al. [18], is a potentially useful method for green and economical synthesis of N-alkyl amides [18–22]. Various catalytic methods using homogeneous metal catalysts have been reported [18–20,23,24], though they have disadvantages including difficulty in catalyst/product

separation, use of organic solvent, high price, and low activity for hydration of heteroaromatic nitriles due to their strong coordination to the metal centers. Use of recyclable heterogeneous catalyst is ideal from environmental and practical viewpoints. However, to the best of our knowledge, there is only one report on heterogeneous catalysts (ZrO₂ and Nb₂O₅) for the amidation from nitriles and amines [21], which suffers from high reaction temperature (180–230 °C) and low yield. Although heteroaromatic amides are pharmacologically important [25], there is no report of one-pot synthesis of them from heteroaromatic nitriles by heterogeneous catalysts.

CeO₂ has acid–base and redox properties and has been used as an effective catalyst for various organic reactions [26–28] such as dehydration of alcohols [29–35], alkylation of aromatic compounds [36–38], dimerization of alcohols [39–43], aldehydes, esters [43] and carboxylic acids [44,45] to ketones, cyclization of diols [46], reduction of benzoic acid [47]. Most of CeO₂-catalyzed reactions were carried out at high temperature (typically 200–500 °C). In view of the organic synthesis and the green chemistry, it is important to study CeO₂-catalyzed organic reactions below 200 °C. As for CeO₂-catalyzed reactions at low temperature (<200 °C), Tomishige et al. recently reported the carbonate synthesis from CO₂ and alcohols at 150 °C [48–51]. In this system, nitriles as dehydration reagents are converted to amide and small amount of esters. Our research group found that CeO₂ acted as a highly active catalyst for substrate-specific hydration of nitriles at low temperature (30–100 °C) [52]. Kinetic studies showed a mechanism involving nucleophilic attack of OH^{δ−} species to nitriles as a key step. Based on these findings, we hypothesized that reaction

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