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Amidation of Carboxylic Acids with Amines by Nb₂O₅ as Reusable Lewis Acid Catalyst

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Abstract: Among 28 types of heterogeneous and homogeneous catalysts tested, Nb₂O₅ shows the highest yield for direct amidation of *n*-dodecanoic acid with a less reactive amine (aniline). The catalytic amidation by Nb₂O₅ is applicable to a wide range of carboxylic acids and amines with various functional groups, and the catalyst is reusable. Comparison of the results of the catalytic study and infrared (IR) study of the acetic acid adsorbed on the catalyst suggests that activation of carbonyl group of the carboxylic acid by Lewis acid sites on Nb₂O₅ is responsible for the high activity of Nb₂O₅. Kinetic studies show that Lewis acid sites on Nb₂O₅ is water-tolerant than conventional Lewis acidic oxides (Al₂O₃, TiO₂). In comparison with the state-of-the-art homogeneous Lewis acid catalyst (ZrCl₄) for amidation, Nb₂O₅ undergoes less negative effect of basic additives in the solution, indicating that Nb₂O₅ is a more base-tolerant Lewis acid catalyst than the homogeneous Lewis acid catalyst.

Introduction

Amide bonds constitute the building blocks of pharmaceutically and biologically important compounds.^[1-4] Conventionally, amides are prepared from carboxylic acids and amines via activated carboxylic acid derivatives such as carboxylic acid anhydrides or acyl chlorides or via activation with stoichiometric amount of a condensation agent for activation of carboxylic acid and water removal.^[4] The conventional methods suffer from low atom efficiency and production of byproducts. It is generally accepted that the catalytic synthesis of amides from readily available starting materials is the priority area for the pharmaceutical industry.^[1] As summarized in recent review articles,^[5-9] the direct condensation of carboxylic acids and amines by boron-based^[10-19] or metal-based^[20-26] homogeneous catalysts and oxide-based heterogeneous catalysts,^[27-40] plays a central role in the direct amidation. However, less reactive amines such as

anilines and less reactive carboxylic acids such as α -hydroxycarboxylic acids and benzoic acids are not generally tolerated by previous catalysts. A rare example is a boronic acid catalyst developed by Ishihara,^[13] who have shown that condensation of an equimolar mixture of α -hydroxycarboxylic acids and primary or secondary amines proceeds with a boron-based catalyst under azeotropic reflux conditions in toluene. However, homogeneous catalytic methods have drawbacks of difficulties in catalyst/products separation and catalyst reuse. Moreover, Lewis acidic homogeneous catalysts have potential drawbacks such as suppression of activity by strong coordination of basic functional groups in a substrate (such as heterocyclic groups) and irreversible decomposition of the catalyst by water (as a byproduct). As for heterogeneous catalysts for the direct amidation, previous reports mainly studied N-formylation^[4,32,35] or N-acetylation^[4,39] of amines. Some of the previous heterogeneous system for amidation suffer from drawbacks of limited scope and needs of excess amount of reagent or a special reaction method (microwave heating).^[33,34]

In the course of our continuous studies on the amide bond forming reactions by heterogeneous Lewis acidic catalysts,^[41-43] we have recently reported that Nb₂O₅, prepared by calcination of a commercial niobic acid, acts as base-tolerant Lewis acid catalyst for direct imidation of dicarboxylic acids with amines^[43] and direct amidation of esters with amines.^[42] We report herein that Nb₂O₅ is an effective and reusable catalyst for direct condensation of less reactive carboxylic acids with less reactive amines. Catalytic results show wide applicability of the synthetic method, and IR spectroscopic and kinetic studies show that the high activity of Nb₂O₅ is due to activation of carboxylic acids by Lewis acid sites of Nb₂O₅ with base-tolerant nature.

Experimental

General. Commercially available organic compounds (from Tokyo Chemical Industry or Aldrich) were used without further purification. GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY⁺-1 capillary column (Frontier Laboratories Ltd.) using N₂ and He as the carrier. All reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen. Analytical TLC was performed on a Merck 60 F254 silica gel (0.25 mm thickness). Column chromatography was performed with silica gel 60 (spherical, 63-210 μ m, Kanto Chemical Co. Ltd.). Molecular sieves 4Å (MS4Å) was dehydrated at 100 °C.

Catalyst preparation. Niobic acid (Nb₂O₅·nH₂O, HY-340) was kindly supplied by CBMM. Nb₂O₅ (surface area = 54 m² g⁻¹) was prepared by calcination of niobic acid at 500 °C for 3 h. MgO (JRC-MGO-3), TiO₂ (JRC-TIO-4), CeO₂ (JRC-CEO-3), H⁺-type Y zeolite (HY) with a SiO₂/Al₂O₃ ratio of 4.8 (JRC-Z-HY-4.8), H⁺-type BEA zeolite (HBEA) with a SiO₂/Al₂O₃ ratio

of 25 (JRC-Z-HB25) and H⁺-type MFI zeolite (HMFI) with a SiO₂/Al₂O₃ ratio of 90 (JRC-Z5-90H) were supplied from Catalysis Society of Japan. SiO₂ (Q-10, 300 m² g⁻¹) was supplied from Fuji Silysia Chemical Ltd. ZrO₂·nH₂O was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water by aqueous NH₄OH solution, followed by filtration of precipitate, washing with water three times, and drying at 200 °C. ZrO₂, ZnO, SnO₂, MoO₃, WO₃, Ta₂O₅ and CaO were prepared by calcination (500 °C, 3 h) of the hydrous oxides: ZrO₂·nH₂O, ZnO·nH₂O (Kishida Chemical), H₂SnO₃ (Kojundo Chemical Laboratory Co., Ltd.), H₂MoO₄ (Kanto Chemical), H₂WO₄ (Kanto Chemical), Ca(OH)₂ (Kanto Chemical) and Ta₂O₅·nH₂O (Mitsuwa Chemicals). γ-Al₂O₃ and θ-Al₂O₃ was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) for 3 h at 900 °C and 1000 °C, respectively. Montmorillonite K10 clay and a sulfonic resins (Amberlyst-15® and nafion-SiO₂ composite) were purchased from Aldrich. Fe³⁺-exchanged K-10 (Fe³⁺-mont) was prepared by treating the clay with aqueous solution of FeCl₃·6H₂O for 3 h at room temperature, followed by centrifuging and washing with deionized water four times, and by drying in vacuo at room temperature. The Fe content in Fe³⁺-mont (0.46 wt%) was determined by ICP analysis. Scandium(III) trifluoromethanesulfonate, Sc(OTf)₃, was purchased from Tokyo Chemical Industry. ZrCl₄ was purchased from WAKO. Cs_{2.5}H_{0.5}PW₁₂O₄₀ was prepared by titrating H₃PW₁₂O₄₀ (Nippon Inorganic Color and Chemicals Co.) by aqueous solution of Cs₂CO₃ (0.10 mol dm⁻³) with vigorous stirring, followed by centrifuging and drying at 200 °C.

In situ IR. In situ IR spectra were recorded by a JASCO FT/IR-4200 spectrometer equipped with an MCT detector. For the acetic acid-adsorption IR study, a closed IR cell surrounded by the Dewar vessel was connected to an evacuation system. During the IR measurement, the IR cell was cooled by freezing mixture of ethanol/liquid nitrogen in the Dewar vessel, and the thermocouple near the sample showed -75 ± 5 °C. The sample was pressed into a 40 mg of self-supporting wafer (ϕ = 2 cm) and mounted into the IR cell with CaF₂ windows. Spectra were measured accumulating 15 scans at a resolution of 4 cm⁻¹. After in situ pre-evacuation of the sample at 500 °C for 0.5 h, a reference spectrum of the sample disc was measured at -75 ± 5 °C. Then, the sample was exposed to 2 Pa of acetic acid at -75 ± 5 °C for 120 s, followed by evacuation for 500 s. Then a differential IR spectrum, with respect to the reference spectrum, was recorded at -75 ± 5 °C. The pyridine-adsorption IR study was carried out at 200 °C by a flow-type IR cell connected to a flow reaction system. The IR disc of Nb₂O₅ in the IR cell was first dehydrated under He flow at 500 °C, and then a background spectrum was taken under He flow at 200 °C. Then, H₂O (1.4 mmol/g) was introduced to Nb₂O₅, followed by introduction of pyridine (0.3 mmol/g), purging by He for 600 s, and by IR measurement of adsorbed species at 200 °C.

Catalytic tests. We used as-received solvent without dehydration. The heterogeneous

catalysts, stored under ambient conditions, were used for catalytic reactions without any pretreatment, and thus the catalyst surface was hydrated before the reaction.

Typically, carboxylic acid (1 mmol) and amine (1 mmol) in 2 mL toluene and 50 mg of Nb₂O₅ were added to a reaction vessel (pyrex cylinder) with a reflux condenser and a magnetic starter. The reaction mixture was heated to reflux under N₂ atmosphere and stirred at 400 rpm. For azeotropic removal of water, a funnel containing 0.2 g of MS4Å on a cotton plug was placed in the upper side of the cylinder surmounted by a reflux condenser.

After completion of the reaction, 2-propanol (4 mL) was added to the mixture, and the Nb₂O₅ catalyst was separated by centrifugation. For the catalytic tests in Table 1 and Figures 1, 4, 5, 6 the reaction mixture was analyzed by GC, and yield of the products was determined using *n*-dodecane as an internal standard. For the reactions in Tables 3-5 the product was isolated by column chromatography. Then, the resulting product was identified using GCMS, ¹H-NMR and ¹³C-NMR analyses.

Results and discussion

Catalyst screening. We carried out as a model reaction between equimolar amount of *n*-dodecanoic acid and aniline under azeotropic reflux conditions. Table 1 summarizes the yield of the corresponding amide for various catalysts including metal oxides and standard heterogeneous and homogeneous acid catalysts. Figure 1 shows time-yield profiles for some representative catalysts. It is known that the direct formation of amides from reactive amines and carboxylic acids without catalyst occurs in non-polar solvents under azeotropic reflux conditions.^[21,43,44] For the model reaction in Table 1, we used aniline as one of the least reactive amines in the literature for the thermal amidation reaction.^[21,44] We confirmed that the thermal reaction in the absence of catalyst gave only 1% yield of the amide (entry 1). We screened 17 types of simple metal oxides (entries 2-19) including two of the hydrates (entries 4,11). Among the oxide tested, Nb₂O₅ showed the highest yield (99%) of the amide. In the literature, TiO₂,^[33] ZnO,^[32] Al₂O₃,^[35,36] ZrO₂.nH₂O,^[38] SiO₂,^[27] Fe³⁺-mont,^[39,40] HY^[28] and HBEA^[29] zeolites were reported to be effective for the direct amidation. However, these catalysts showed lower yield than Nb₂O₅. For example, conventional solid Lewis acids^[45,46] such as TiO₂ (entry 5), alumina (entries 8,9) and Fe³⁺-mont (entry 20) gave low to moderate yields (9-66%). Basic oxides (MgO, CaO) were ineffective. In the dehydrative amide condensation reaction, water produced during the reaction can suppress the catalytic activity by strong adsorption on acid sites of catalysts. Thus, water-tolerant acid catalysts may be effective for the reaction. We tested water-tolerant Brønsted acidic heterogeneous catalysts,^[47] such as a high-silica zeolite (HMFI, entry 23), Cs-exchanged heteropoly acid (entry 24) and the acidic resin, Amberlyst-15 (entry 25) and Nafion-SiO₂ (entry 26), and a water-tolerant homogeneous Lewis acid,^[48] such as Sc(OTf)₃

(entry 27). However, these water-tolerant acid catalysts gave lower yield of the amide (2-30%) than Nb₂O₅. Homogenous Brønsted acids such as sulfuric acid (entry 29) and *p*-toluenesulfonic acid (PTSA, entry 30) also gave low yields. A hydrate of Nb₂O₅ called niobic acid (entry 4), which has been studied as water-tolerant Lewis acid catalyst,^[49] gave lower yield (74%) than Nb₂O₅.

Lewis acidity of Nb₂O₅. In our previous IR study of pyridine adsorption on Nb₂O₅, we showed that surface acid sites of dehydrated Nb₂O₅ are mainly Lewis acidic sites (exposed Nb⁵⁺ cations).^[45] Figure 2 shows the IR spectrum of pyridine adsorbed on dehydrated and rehydrated Nb₂O₅. These spectra have basically the same features; the band at 1445 cm⁻¹ due to coordinated pyridine on Lewis acid site (exposed Nb⁵⁺ cations) is dominant rather than the band at 1540 cm⁻¹ due to pyridinium ion due to Brønsted acid sites. The result shows that water does not essentially change the IR spectrum of adsorbed pyridine; Nb₂O₅ is predominantly Lewis acidic even after re-hydration. To investigate the Lewis acid-base interaction between the Nb site and a carbonyl group of a model carboxylic acid, we measured in situ IR spectrum of acetic acid adsorbed on Nb₂O₅. The spectrum (Figure 3) showed a C=O stretching band of the adsorbed acetic acid ($\nu_{\text{C=O}}$) at lower wavenumber (1686 cm⁻¹) than non Lewis acidic oxide, SiO₂ (1703 cm⁻¹) and conventional Lewis acidic oxides: TiO₂ (1695 cm⁻¹) and Al₂O₃ (1697 cm⁻¹). This indicates that the surface of Nb₂O₅ has the most effective Lewis acid sites for activation of the C=O bond of the carboxylic acid.

Base-tolerant catalysis of Nb₂O₅ for amidation. Lewis acidic catalysts for the direct amidation should work even in the presence of water, because the reaction yields water as coproduct. We studied the effect of water removal and water addition on the time-yield profiles for some Lewis acidic metal oxide catalysts (Nb₂O₅, TiO₂ and Al₂O₃) for the model amidation of *n*-dodecanoic acid and aniline (Figure 1). For all the catalysts, the standard azeotropic reflux conditions gave higher activity than the reaction without azeotropic water removal, and the reaction without azeotropic water removal with 3 mmol H₂O in the initial mixture gave the lowest activity. However, the negative impact of the water was lower for Nb₂O₅ than TiO₂ and Al₂O₃. As shown in Figure 4, the initial rate of amide formation with Nb₂O₅ and TiO₂ decreased with increase in the initial concentration of water. This indicates that water inhibits the activity of these catalysts. The slope was lower for Nb₂O₅ than TiO₂, and the reaction orders with respect to water were -0.3 and -1.8 for Nb₂O₅ and TiO₂, respectively. This indicates that water-tolerance of Nb₂O₅ is higher than TiO₂.

ZrCl₄ is a well established Lewis acidic homogenous catalyst for the direct amidation.^[20-22] Generally, the activity of homogeneous Lewis acid can be reduced by water and organic bases. To compare base-tolerance of ZrCl₄ and Nb₂O₅, we measured the yield of the amide in the standard reaction for 30 h with ZrCl₄ or Nb₂O₅ under the azeotropic reflux conditions in the

absence or presence of 0.5 equiv. of basic additives: H₂O, 2,6-dimethylpyridine, pyridine, and triethylamine (Figure 4). Although we used the same molar amount of the catalyst (0.38 mmol), ZrCl₄ was dissolved in the reaction mixture while Nb₂O₅ was insoluble. Clearly, the additive-free condition gave higher yield for both catalysts, but negative effects of the additives were lower for Nb₂O₅ than ZrCl₄. Note that 0.5 mmol of the basic molecules added to the mixture is 172 times larger than the number of surface Lewis acid sites on the Nb₂O₅ catalyst used. This suggests that the active site (Nb⁵⁺ Lewis acid site) interacts preferentially with the reactant (carboxylic acid) in the presence of excess amount of basic molecules. Summarizing the above results, we can conclude that Lewis acid site of Nb₂O₅ has higher tolerance to basic molecules than conventional solid Lewis acids and a typical homogeneous Lewis acid. The water-tolerant character of the Nb⁵⁺ Lewis acid sites of niobium oxide is consistent with the pioneering work by Nakajima et al.^[49]

Performance of Nb₂O₅-catalyzed amidation. As listed in Table 2, the turnover number (TON) with respect to the Lewis acid site of Nb₂O₅ (341) was more than 200 times higher than those of ZrCl₄ (a well established homogenous catalyst for the direct amidation^[20-22]) and Sc(OTf)₃ (a well established “water-tolerant” Lewis acid^[48]). TON of Nb₂O₅ was 5 times larger than that of TiO₂. As discussed in the above section, the higher catalytic efficiency of Nb₂O₅ can be due to the higher water-tolerance and more effective Lewis acid activation of the C=O bond by Nb₂O₅ than TiO₂. It is important to note that the water-tolerance of Nb₂O₅ enabled the amidation without azeotropic water removal; the reaction by Nb₂O₅ under simple reflux condition for 40 h resulted in 96% yield of the amide (Table 1, entry 3).

We studied the reusability of Nb₂O₅. After the standard reaction (Table 1, entry 2), the catalyst was separated from the mixture by centrifugation, followed by washing with acetone, and by drying at 90 °C for 3 h. ICP-AES analysis of the solution confirmed that the content of Nb in the solution was below the detection limit. The recovered catalyst was reused five times without a marked loss of its catalytic activity (Figure 6). For the standard reaction, the reaction was completely terminated by removing the Nb₂O₅ catalyst from the reaction mixture after 4 h (at 19% yield), and further heating of the filtrate for 26 h did not increase the yield. These results indicate that Nb₂O₅ acts as a reusable heterogeneous catalyst.

Then, we explored the generality and scope of the Nb₂O₅-catalyzed direct amidation of carboxyl acids with different amines (Table 3-5). As listed in Table 3, anilines (entries 1-6) with electron-donating and electron-withdrawing functional groups, benzyl amines (entries 7-9) with electron-rich and electron-poor ring, heteroaromatic amine (entry 10), aliphatic primary amines (entries 11-13) with various functional groups (phenyl, -C=C and hydroxyl groups, reacted with equimolar amount of *n*-dodecanoic acid to give the corresponding amide in good to high isolated yields (80-98%). Due to the low nucleophilicity, the least reactive amines, -Br and -Cl

substituted anilines (entries 5,6) and allylamine (entry 12) required higher temperature (reflux in *o*-xylene). A secondary amine, morpholine (entry 14) was also tolerated to give the corresponding tertiary amide in high yield.

Table 4 shows that the method is also effective for the amidation of various carboxylic acids with a less nucleophilic amine, aniline. Linear aliphatic carboxylic acids (entries 1-5) and a less reactive carboxylic acid, benzoic acid (entry 6) were converted to the corresponding amides in good to high isolated yield (81-98%). Amidation of a heteroaromatic carboxylic acid, pyridine-2-carboxylic acid (entry 7), with benzylamine was also succeeded to give 90% yield of the product.

Finally, we tested the amidation of more challenging carboxylic acids (α -hydroxy, β -hydroxy and β -thio carboxylic acids) with various amines under azeotropic reflux in *o*-xylene (Table 5). It should be noted that only one report by Ishihara et al. have succeeded in the direct amidation of α -hydroxy carboxylic acids with amines, but the previous method using MeB(OH)_2 catalyst is not effective for less reactive amines such as aniline.^[13] To our delight, our method was applicable to the synthesis of amides from aniline and α -hydroxycarboxylic acids (entries 1,3) and a β -thiocarboxylic acid (entry 6). The α -hydroxycarboxylic acids include an important biomass-derived chemical, lactic acid (entries 1,2), demonstrating that our method can contribute to production of fine chemicals from biomass feedstock. The method was also effective for the amidation of a β -hydroxycarboxylic acid, salicylic acid (entry 5), with benzylamine and gave the corresponding amide in 95% yield. We tentatively assume that the unprecedentedly efficient catalysis of Nb_2O_5 for the amidation of challenging substrates is caused by the base-tolerant Lewis acid-activation of carboxylic acids, which is evidenced by IR (Figure 2,3) and kinetic studies (Figure 1,4,6).

Conclusion

We have presented a versatile and sustainable method for direct amidation of carboxylic acids with various amines using Nb_2O_5 as a reusable, inexpensive, and commercially available heterogeneous catalyst. This simple and atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as anilines and α -hydroxycarboxylic acids. The Lewis acid site of Nb_2O_5 , as the active site for the amidation, has higher tolerance to the co-present basic molecules (water and tertiary and heteroaromatic amines) than the state-of-the-art homogeneous Lewis acid catalyst for the amidation (ZrCl_4) and conventional Lewis acidic heterogeneous catalysts (Al_2O_3 , TiO_2), which results in higher catalytic activity of Nb_2O_5 than these catalysts.

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Keywords: amidation • carboxylic acids • amines • Lewis acid

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Table 1. Catalyst screening for amidation of *n*-dodecanoic acid with aniline.

Entry	Catalyst	Yield [%] ^[a]
1	no catalyst	1
2	Nb ₂ O ₅	99
3 ^[b]	Nb ₂ O ₅	96
4	Niobic acid	74
5	TiO ₂	51
6	ZnO	21
7	WO ₃	16
8	θ-Al ₂ O ₃	11
9	γ-Al ₂ O ₃	9
10	MoO ₃	9
11	ZrO ₂ · <i>n</i> H ₂ O	9
12	CeO ₂	7
13	ZrO ₂	6
14	Ta ₂ O ₅	6
15	CaO	5
16	SnO ₂	5
17	MgO	1
19	SiO ₂	13
20	Fe ³⁺ -mont	66
21	HY	7
22	HBEA	27
23	HMF1	26
24	CS _{2.5} H _{0.5} PW ₁₂ O ₄₀	7
25	Amberlyst-15	4
26	Nafion-SiO ₂	30
27	Sc(OTf) ₃	2
28	ZrCl ₄	71
29 ^[c]	H ₂ SO ₄	1
30	PTSA	19

^[a] GC yields.^[b] Under reflux conditions without azeotropic water removal for 40 h.^[c] Aqueous solution of 30 wt% H₂SO₄.

Table 2. Summary of IR and kinetic results.

Catalyst	[LA] ^[a] /mmol g ⁻¹	$\nu_{\text{C=O}}$ ^[b] / cm ⁻¹	$n_{\text{H}_2\text{O}}$ ^[c]	TOF ^[d] / h ⁻¹	TON ^[d]
Nb ₂ O ₅	0.058	1686	-0.4	11.4	341
TiO ₂	0.083	1695	-1.8	2.0	61
ZrCl ₄	4.3 ^[e]	-	-	0.006	1.7
Sc(OTf) ₃	2.0 ^[e]	-	-	0.003	0.1

^[a] The number of Lewis acid sites on the surface of oxides Nb₂O₅ and TiO₂ estimated by pyridine adsorption at 200°C, which were reported in ref. 45.

^[b] Position of $\nu_{\text{C=O}}$ IR band of adsorbed acetic acid (Figure 4).

^[c] Reaction order with respect to water (Figure 2).

^[d] Calculated with the number of Lewis acid site and the catalytic results in Table 1.

^[e] Based on molecular weight of the salts.

Table 3. Nb₂O₅-catalyzed amidation of *n*-dodecanoic acid with various amines.

$ \begin{array}{c} \text{O} \\ \parallel \\ n\text{-C}_{11}\text{H}_{23}\text{COOH} + \text{H}_2\text{N-CH}_2\text{-R} \xrightarrow[30\text{ h}]{\substack{50\text{ mg Nb}_2\text{O}_5 \\ 2\text{ mL toluene} \\ \text{azeotropic reflux}}} n\text{-C}_{11}\text{H}_{23}\text{CONH-CH}_2\text{-R} + \text{H}_2\text{O} \\ \text{1 mmol} \qquad \qquad \text{1 mmol} \end{array} $			
Entry	Amine	Product	Yield ^[a] [%]
1			98
2			98
3			97
4			98
5 ^[b]			80
6 ^[b]			97
7			88
8			80
9			94
10			95
11			83
12 ^[b]			98
13			96
14			81

^[a] Isolated yields.^[b] Under *o*-xylene reflux.

Table 4. Nb₂O₅-catalyzed amidation of various carboxylic acids with aniline or benzylamine.

<div><div><div><div><div>$\text{R}-\text{C}(=\text{O})\text{OH}$</div><div>1 mmol</div></div><div>$+$</div><div><div><div>$\text{H}_2\text{N}-\text{C}_6\text{H}_5$</div><div>1 mmol</div></div><div><div><div>50 mg Nb₂O₅</div><div>2 mL toluene</div><div>azeotropic reflux</div><div>30 h</div></div></div><div><div><div>$\text{R}-\text{C}(=\text{O})\text{NH}-\text{C}_6\text{H}_5$</div><div>$+ \text{H}_2\text{O}$</div></div></div></div></div></div></div>			
Entry	Acid	Product	Yield ^[a] [%]
1			80
2			83
3			81
4 ^[b]			98
5			95
6 ^[b]			80
7 ^[b]			90

^[a] Isolated yields.^[b] Under *o*-xylene reflux.

Table 5. Nb₂O₅-catalyzed amidation of α -hydroxy and β -thio carboxylic acids with amines.^[a]

Entry	Acid	Product	Yield [%]
1			69
2			80
3			71
4			65
5			95
6			87

^[a] Carboxylic acid (1 mmol), amine (1 mmol), *o*-xylene (2 mL), azeotropic reflux, 30 h. Yields are based on isolated yields.

Figure 1. Time-yield profiles for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) catalyzed by metal oxides (50 mg) in different conditions: (○) azeotropic reflux; (●) reflux (without azeotropic water removal); (▽) reflux with 3 mmol of H₂O in the initial mixture.

Figure 2. IR spectra of pyridine adsorbed on dehydrated Nb₂O₅ (dashed line) and rehydrated Nb₂O₅ (solid line) at 200 °C.

Figure 3. IR spectra of acetic acid adsorbed on Nb_2O_5 , TiO_2 , $\theta\text{-Al}_2\text{O}_3$ and SiO_2 at $-75\text{ }^\circ\text{C}$.

Figure 4. Initial rate for amidation of *n*-dodecanoic acid with aniline by (○) Nb_2O_5 and (●) TiO_2 as a function of the initial concentration of water ($C_{\text{H}_2\text{O}} = 1.1$ to 3.4 M).

Figure 5. Yield of amide for the reaction of *n*-dodecanoic acid with aniline for 30 h by Nb₂O₅ (50 mg, 0.38 mmol) and ZrCl₄ (50 mg, 0.38 mmol) in the absence and presence of 0.5 mmol of basic additives: water, 2,6-dimethylpyridine, pyridine, triethylamine.

Figure 6. Reusability of Nb₂O₅ (50 mg) for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) in toluene reflux conditions for 30 h.

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and reusable heterogeneous catalyst for direct amidation of carboxylic acids with amines due to base-tolerant Lewis acid catalysis of surface Nb^{5+} sites.

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Shimizu

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Amines by Nb_2O_5 as Reusable Lewis
Acid Catalyst**