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Ammonium Nitrate: A Biodegradable and Efficient Catalyst for the Direct Amidation of Esters under Solvent-free Conditions

Perla Ramesh and Nitin W. Fadnavis*

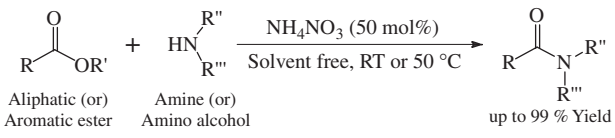
Natural Products Chemistry Division, Indian Institute of Chemical Technology, Uppal Road, Hyderabad-500 007, India

(E-mail: fadnavis@iict.res.in)

A simple, metal-free, and environment-friendly procedure is developed for the direct conversion of esters to amides using ammonium nitrate as a catalyst under solvent-free conditions. Aryls, heteroaryls, and aliphatic esters are easily converted to the corresponding amides in excellent isolated yields (85–99%). An enantiopure ester and amine were both shown to react without racemization. The methodology has been successfully applied to preparation of procainamide.

The preparation of an amide bond is one of the fundamental transformations in medicinal chemistry laboratories and organic synthesis.[1] Generally, starting from esters, a three-step sequence of hydrolysis, activation, and treatment with an amine is performed. The direct synthesis of amides from carboxylic acid esters can be carried out using metal complexes such as $Sb(OEt)_3$,[2] $Zr(O\textit{t}\text{-}Bu)_4$–HOAt,[3] $AlMe_3$,[4] NaOMe,[5] KO*t*-Bu,[6] DABAL-Me_3,[7] and MgX_2.[8] Other catalysts like InI_3,[9] zinc dust,[10] *N*-heterocyclic carbine,[11] DBU,[12] triazabicyclo[4.4.0]dec-5-ene,[13] and 1,2,4-triazole-DBU[14] have also been reported. Very recently, the organo-base-catalyzed amidation of esters with amino alcohols has been reported.[15] However, most of these systems involve organic solvents and metal catalysts. Herein, we report a simple, metal-free, and environment-friendly conversion of esters to amides in the presence of ammonium nitrate under the solvent-free condition. Aryls, heteroaryls, and aliphatic esters are converted to the corresponding amides with amines as well as with amino alcohols in good to excellent isolated yields (Scheme 1).

The amides of cyclic amines like piperidine, pyrrolidine, and morpholine exhibit a wide range of biological activities. For example, piperidine amide derivatives act as enzyme inhibitors,[16] larvicidal agents,[17] hepatoprotective agents,[18] TRP agonists,[19] etc. Pyrrolidine amide derivatives also have a wide range of biological activities such as antibacterial activity[20] and cytotoxic activity towards the human cervical carcinoma cell line HeLa.[21] The preparation of such amide derivatives by the reaction between the amine and the ester can, in principle, be carried out by a simple heating of the mixture together. However, this reaction is slow and is accompanied by impurity formation when the amine is exposed to high temperature for extended periods. It is interesting to use a biodegradable and nontoxic catalyst for the reaction.



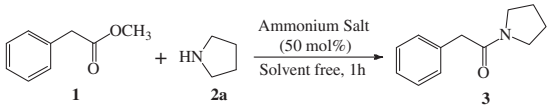
Scheme 1. Direct conversion of ester to amide using ammonium nitrate as catalyst under solvent-free condition.

Ammonium salts have been employed as catalysts for the aldol condensation,[22] synthesis of imidazo[1,2-α]pyridines,[23] Claisen–Schmidt reaction,[24] synthesis of 2,4,5-trisubstituted imidazoles,[25] synthesis of fused 4*H*-chromene derivatives,[26] amidation of phenol derivatives,[27] etc., and we envisaged that these could be used for the amidation reaction as well. Initially, a model reaction of methyl phenylacetate (**1**) (1 equiv) and pyrrolidine (**2a**) (3 equiv) to form 2-phenyl-1-(pyrrolidin-1-yl)ethanone (**3**) was chosen to identify an appropriate ammonium salt (50 mol % of ester) as a catalyst. A range of ammonium salts were screened for the reaction under solvent-free conditions at room temperature for 1 h and most of them provided moderate to good yields of the amide (Table 1), with ammonium nitrate as the best catalyst. In the absence of catalyst, amide formation did occur, but in low yields (5–7%). A control reaction with ammonium nitrate without amine also showed that ammonium nitrate by itself did not give any amide product under the experimental conditions. Similarly, amidation reaction using phenylacetic acid instead of the ester derivative also failed to produce any amide product.

To optimize the reaction, further experiments were carried out at different ester to amine mole ratios and by varying the concentration of ammonium nitrate. The reactions were carried out at room temperature for 1 h, and the yields were determined by HPLC analysis. We observed that the product yield (based on ester) increases with amine concentration as expected for a bimolecular reaction. The yield increases further on addition of ammonium nitrate up to a certain level and then decreases with increased ammonium nitrate concentration. At a high concentration of ammonium nitrate, the reaction stops completely (curve A, Figure 1).

These observations can be explained as follows. The ammonium salt provides the proton to protonate the carbonyl

Table 1. Effect of different ammonium salts on amide formation[a]



Entry	Ammonium salt	Yield/%[b]
1	NH_4Cl	62
2	NH_4NO_3	82
3	NH_4SCN	75
4	$HCOONH_4$	73
5	NH_4OAc	69
6	$(NH_4)_2CO_3$	56
7	No catalyst	5

[a]Reaction conditions: **1** (1.0 mmol), **2a** (3.0 mmol), and ammonium salt (50 mol %) at room temperature under solvent-free condition for 1 h. [b]Product yield based on HPLC analysis.

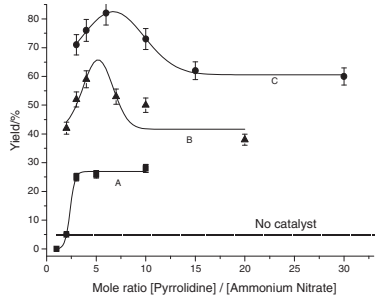
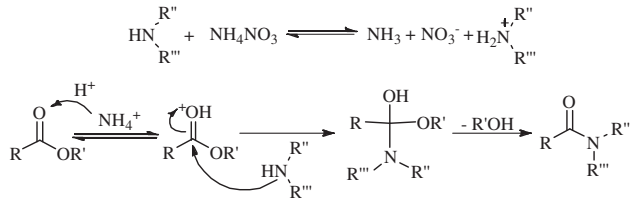


Figure 1. Effect of mole ratios on the yield of product at room temperature. Reaction period was 1 h. Mole ratio of amine to ester = 1 (curve A); 2 (curve B); 3 (curve C).



Scheme 2. Proposed mechanism for the synthesis of amide from ester using ammonium salt as catalyst.

group. Attack by the amine gives a tetrahedral intermediate, which then converts to amide with the liberation of alcohol. At the same time, an equilibrium exists between the protonated forms of ammonia and the amine (Scheme 2).

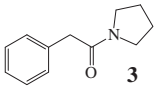
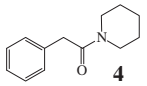
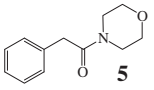
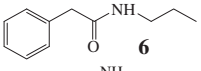
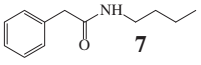
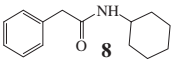
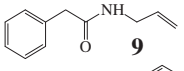
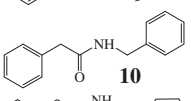
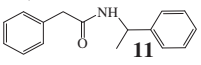
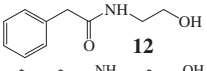
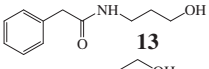
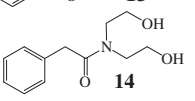
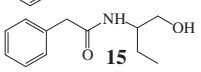
At a given amine concentration, the addition of ammonium nitrate on one hand, facilitates the protonation of the ester carbonyl and the subsequent attack of nucleophilic amine. On the other hand, proton transfer from the ammonium ion to the amine causes a decrease in the effective concentration of the nucleophile, and a consequent decrease in yield. At optimum conditions, the two processes are complementary and lead to high yields. Based on the results in Figure 1 and further optimization, a reaction period of 12 h and mole ratios of ester, amine, and ammonium nitrate of 1:3:0.5 respectively were determined to be optimal.

Tables 2 and 3 show the scope of our reaction, wherein the amidation of various esters with amines that include cyclic, acyclic, primary, and secondary amines and amino alcohols are described.

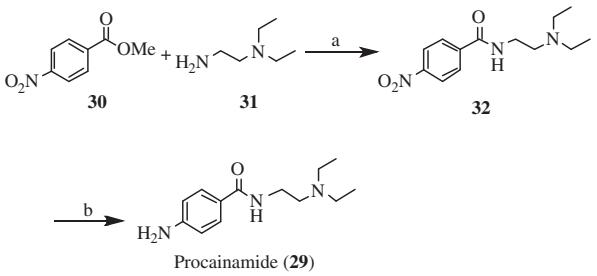
Our methodology was applied to the preparation of procainamide (**29**), an antiarrhythmic drug,[28] also used to treat Wolff–Parkinson–White syndrome[29] (Scheme 3).

In conclusion, amides can be directly synthesized from esters by reaction either with amines or with amino alcohols under solvent-free conditions using readily available, cheap, and biodegradable ammonium nitrate as a catalyst. Although ammonium nitrate is perceived as an explosive, under normal handling conditions, ammonium nitrate is not harmful. Most of the reactions described here have been conducted at room temperature to 50 °C. It is also possible to substitute ammonium nitrate with ammonium thiocyanate or ammonium formate, although with slightly lesser yield. The protocol is simple, metal-free, and environmentally benign. The methodology has been successfully applied to preparation of procainamide.

Table 2. Amidation of methyl phenylacetate with various amines and amino alcohols[a]

Entry	Amine	Product	Yield/%[b]
1	 **2a**	 **3**	99
2	 **2b**	 **4**	99
3	 **2c**	 **5**	94[b]
4	 **2d**	 **6**	99
5	 **2e**	 **7**	99
6	 **2f**	 **8**	97
7	 **2g**	 **9**	99
8	 **2h**	 **10**	96[b]
9	 **2i**	 **11**	89[b]
10	 **2j**	 **12**	99
11	 **2k**	 **13**	99
12	 **2l**	 **14**	99
13	 **2m**	 **15**	96

[a]Reaction conditions: 10 mmol of ester, 30 mmol of amine, and 5 mmol ammonium salt at room temperature for 12 h. [b]Reaction carried out at 50 °C for 24 h. [c]Isolated yields.



Scheme 3. Synthesis of procainamide. Reagents and conditions: a) NH_4NO_3 (50 mol %), rt, 12 h, 98% yield; b) Pd–C, $HCOONH_4$, MeOH, rt, 2 h, 95% yield.

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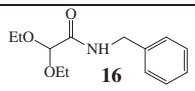
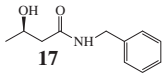
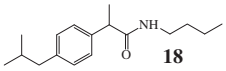
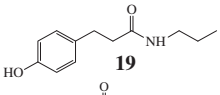
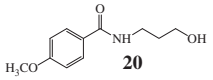
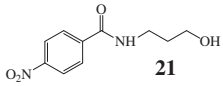
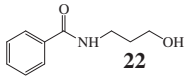
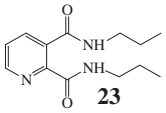
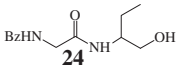
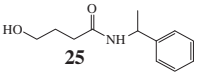
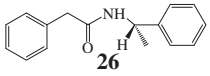
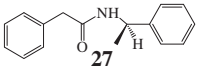
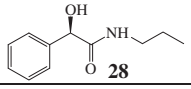
Supporting Information is available electronically on J-STAGE.

Table 3. Amidation of various methyl esters with various amines under solvent-free condition[a]

Entry	Amine	Product	Yield/%[b]
1	**2h**	 **16**	97
2	**2h**	 **17**	99
3	**2e**	 **18**	86
4	**2d**	 **19**	96
5	**2k**	 **20**	94[c]
6	**2k**	 **21**	98
7	**2k**	 **22**	95
8	**2d**	 **23**	96[d]
9	**2m**	 **24**	94
10	**2i**	 **25**	97
11	(*S*)-**2i** (97% ee)	 **26**	90[c] (97% ee)
12	(*R*)-**2i** (97% ee)	 **27**	89[c] (97% ee)
13	**2d**	 **28**	97 (>99% ee)

[a]Reaction conditions: 10 mmol of ester, 30 mmol of amine, and 50 mol % ammonium nitrate at room temperature for 12 h. [b]Isolated yields of products. [c]Reaction carried out at room temperature for 24 h. [d]Reaction conditions: 10 mmol of ester, 60 mmol of amine and 100 mol % ammonium nitrate at room temperature for 12 h.

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