Tetrahedron Letters 52 (2011) 5943–5946

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalytic synthesis of amides from nitriles via the Ritter reaction

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ARTICLE INFO

Article history:
Received 13 June 2011
Revised 25 July 2011
Accepted 22 August 2011
Available online 7 September 2011

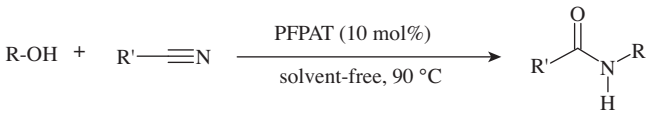
Keywords:
Pentafluorophenyl ammonium triflate
Organocatalyst
Alcohols
Nitrile

ABSTRACT

A simple, inexpensive, environmentally friendly, and efficient route for the synthesis of a wide variety of amides in high yields via the Ritter reaction of alcohols with nitriles has been demonstrated. Pentafluorophenyl ammonium triflate (PFPAT) is used as an organocatalyst and is air-stable, cost-effective, easy to handle, and easily removed from the reaction mixtures.

The *N*-*tert*-butyl amide group is found in many natural and synthetic biologically active materials, and its derivatives are applied in various pharmaceutical and biochemical fields.[1,2] The simple and straightforward procedure reported by Ritter in 1948 involves condensation of alcohols, suitably substituted alkenes, or tertiary halides, with nitriles in the presence of a stoichiometric amount of a strong acid, typically H_2SO_4, and often together with a highly ionizing solvent, such as AcOH, forming amides upon hydrolysis.[3,4] The main disadvantage of the classical Ritter procedure is the use of an excess amount of corrosive sulfuric acid, which has limited its applicability to compounds containing functional groups stable to acid. The classical Ritter reaction requires several modifications to overcome its limitations. Some of the modified methods are as follows: Nafion-H as a solid catalyst,[5,6] Nafion-H along with microwave irradiation,[7] formic acid under reflux,[8] $HBF_4{\cdot}Et_2O$,[9] 2,4-dinitrobenzenesulfonic acid,[10] $HClO_4$-functionalized silica-coated nanoparticles,[11] liquid HF,[12] TMS–CN/H_2SO_4 as a reagent for the synthesis of formamides,[13] *t*-BuOAc instead of *t*-BuOH as a carbocation precursor,[14] Tf_2O/ROH as an in situ source of ROTf,[15] metal complexes,[16] $Bi(OTf)_3$ and other metallic triflates,[17] I_2,[18] ionic liquids,[19] and a nitrosonium salt to effect the Ritter reaction of halides with nitriles.[20] However, these methods suffer from the disadvantages, such as high cost, poor availability or toxicity of the reagents, and extended reaction times. Additionally the main drawback of almost all the existing methods is that the catalysts decompose during the aqueous work-up and their recovery is often impossible. Reymond and co-workers[21] found that $FeCl_3$ catalyzed the Ritter reaction of nitriles with benzylic alcohols as well as the Ritter reaction of nitriles with *t*-BuOAc producing, respectively, benzylic amides and *t*-butyl-protected primary amides. However, realizing the fact that metal-free organocatalysis has drawn considerable interest from chemists, and that metal-free homogeneous catalysis is advantageous for designing suitable drugs devoid of any metal content, it would be desirable to develop this reaction using metal-free Lewis acid catalysts.[22] Organocatalysts have gained importance due to the economic and environmental considerations.[23] These catalysts are generally less expensive, highly reactive, eco-friendly, easy to handle, reduce reaction times, impart greater selectivity, and can be applied under less demanding reaction conditions, such as rigorously anhydrous or anaerobic conditions. Pentafluorophenylammonium triflate (PFPAT)[24] has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity, stability to air, and water tolerance. In this regard and in connection with our previous work,[25] herein, we report the Ritter reaction of various nitriles with alcohols **1**–**5** and *tert*-butyl acetate using PFPAT as an efficient organocatalyst (Scheme 1).

Initially, in order to investigate the catalytic activity of PFPAT in the Ritter reaction, we examined its efficiency in a model reaction between benzonitrile (2.0 equiv) and *tert*-butanol (2.2 equiv) under neat conditions at 90 °C to give the corresponding N-substituted amide in 90% yield (Table 1, entry 3). After some efforts, a



Scheme 1.

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0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.08.121

Table 1
Ritter reaction of various alcohol and nitriles catalyzed by PFPAT

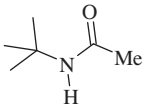
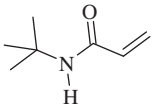
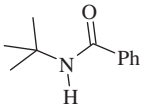
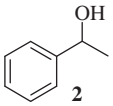
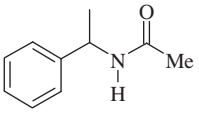
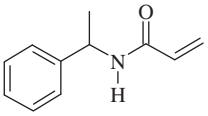
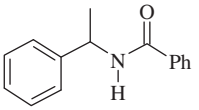
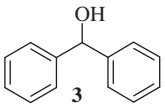
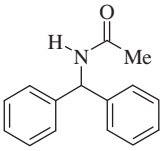
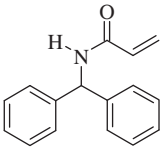
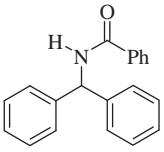
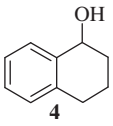
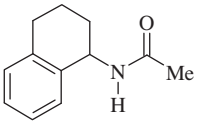
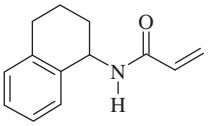
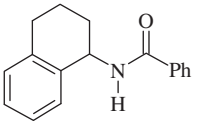
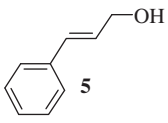
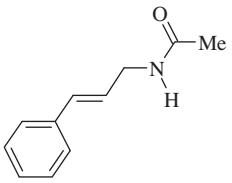
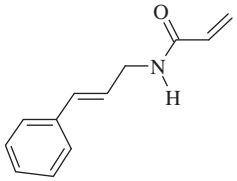
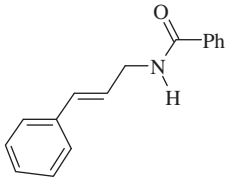
Entry	Alcohol	Nitrile	Amide	Time (h)	Yield (%) Ref
1	 **1**	MeCN		2	90[11]
2	1			2	92[11]
3	1	PhCN		3	90[19]
4	 **2**	MeCN		2	95[18]
5	2			2	95[11]
6	2	PhCN		3	92[18]
7	 **3**	MeCN		1	95[18]
8	3			1	95[11]
9	3	PhCN		1	92[18]
10	 **4**	MeCN		2	95[11]
11	4			2	95[11]
12	4	PhCN		2.5	92[11]
13	 **5**	MeCN		3	90[11]

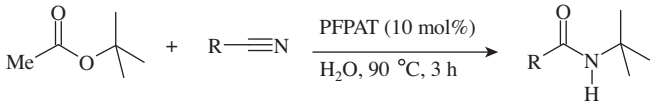
Table 1 (*continued*)

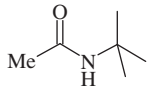
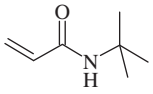
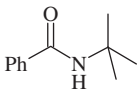
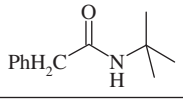
Entry	Alcohol	Nitrile	Amide	Time (h)	Yield (%) Ref
14	5			3	95[11]
15	5	PhCN		3	90[11]

catalytic amount of PFPAT (10 mol %) was found to be superior for this functional transformation. We decided to generalize this new protocol by subjecting it to various substituted alcohols and nitriles, and a series of N-substituted amides were prepared in high yields. The reaction was general and various benzylic amides were obtained using different nitriles and benzylic alcohols. The reaction of alcohol **1** with MeCN led to the expected amide in 90% isolated yield (Table 1, entry 1). Acrylonitrile appeared to be a suitable nitrile which reacted with **1** to give the corresponding amide in 92% yield (Table 1, entry 2). Benzhydrol **3** also reacted quickly with MeCN, acrylonitrile, and PhCN to produce the corresponding amides in 95%, 95%, and 92% isolated yields, respectively (Table 1, entries 7–9). This method could be extended to allylic alcohol, cinammyl alcohol, and a benzyl alcohol. The results of the present study are summarized in Table 1.

To further expand the scope of this process, we next examined the reactions between benzonitrile and *tert*-butyl acetate. As expected, these substrates underwent smooth, one-pot conversion to give the corresponding N-substituted amide in an excellent yield (Scheme 2, entry 3).

Subsequently, the Ritter reaction of *tert*-butyl acetate was extended to various aromatic and aliphatic nitriles and a range of *tert*-butyl amides was isolated in good to excellent yields under these conditions (Scheme 2, entries 1–4). Although the amount of catalyst had been optimized to 10 mol %, a lesser amount (5 mol %) also worked but led to longer reaction times. In addition, the PFPAT catalyst was easily separated from the reaction mixture after work-up; washing with NaOH aqueous solution removed CF_3SO_3H, followed by distillation under reduced pressure ($C_6F_5NH_2$: bp 153 °C at 760 mmHg).



Entry	Nitrile	Product	Yield % ref
1	Me-CN		90[11]
2			92[11]
3	Ph-CN		90[18]
4	Ph-CH_2CN		90[18]

Scheme 2. Preparation of *N-tert*-butyl amides using PFPAT.

In conclusion, we have developed a simple chemoselective methodology for a modified Ritter reaction using PFPAT as an organocatalyst. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following advantages: (i) PFPAT is easy to prepare from commercially available pentafluoroaniline and triflic acid, (ii) short reaction times, (iii) ease of product isolation/purification, (iv) no side reactions, (v) low costs and simplicity in process and handling, and (vi) metal-free synthesis avoiding toxic reagents and solvents.

Experimental

General experimental procedure for the synthesis of amides

Alcohol (2 mmol) and nitrile (2.2 mmol) were mixed with PFPAT (10 mol %) under neat conditions at 90 °C, until complete disappearance of the starting alcohol (as monitored by TLC). After cooling to room temperature, the organic phase was washed with aqueous 1 M NaOH solution (1 ml). The separated organic phase was evaporated under reduced pressure to give a crude residue, which was purified by distillation or by column chromatography (hexane–EtOAc).

General experimental procedure for the synthesis of tert-butyl amides

tert-butyl acetate (2 mmol), nitrile (2.2 mmol), and H_2O (2 mmol) were mixed with PFPAT (10 mol %) and heated to 90 °C, until complete disappearance of the starting nitriles (as monitored by TLC). After cooling to room temperature, the organic phase was washed with aqueous 1 M NaOH solution (1 ml). The separated organic phase was evaporated under reduced pressure to give a crude residue, which was purified by distillation or by column chromatography (hexane–EtOAc). The products were characterized by comparison of their physical and spectral data with those of authentic samples. Spectroscopic data for selected examples:

(Table 1, entry 3): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.03 Hz, 2H), 7.43–7.52 (m, 3H), 5.98 (br s, 1H, NH), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 136.3, 131.5, 128.9, 127.2, 52.1, 29.3.

(Table 1, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.72 (m, 2H), 7.30–7.50 (m, 8H), 6.44 (br s, 1H, NH), 5.30 (t, J = 6.8 Hz, 1H), 1.62 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 143.5, 135.2, 131.9, 129.1, 128.8, 127.9, 127.3, 126.7, 49.6, 22.1.

(Table 1, entry 9): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.87 (m, 2H), 7.52–7.57 (m, 1H), 7.46–7.50 (m, 2H), 7.38–7.42 (m, 4H), 7.30–7.38 (m, 6H), 6.80 (br s, 1H), 6.50 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 141.9, 134.6, 132.1, 129.1, 129.8, 128.3, 127.9, 127.5, 57.8.

Acknowledgment

This research was supported by the Islamic Azad University, Ayatollah Amoli Branch.

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