Ritter Reaction in Subcritical Water: An Efficient and Green Method for Amides Synthesis

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Received June 06, 2011: Revised September 02, 2011: Accepted September 16, 2011

Abstract: Ritter reaction was carried out efficiently in subcritical water with catalytic amount of trifluoromethanesulfonic acid. The amides were formed in good to excellent yields from secondary alcohols and *tert*-butanol with various nitriles.

Keywords: Alcohol, amide, nitrile, ritter reaction, subcritical water, trifluoromethanesulfonic acid.

INTRODUCTION

The synthesis of amide through the reaction of nitrile with alcohol or alkene in the presence of stochiometric amount of sulfuric acid (H_2SO_4) is the typical Ritter reaction [1]. Since the original report in 1948, it has gained much attention due to its atomic economy and application in biologically molecules synthesis [2]. However, the large amount of toxic and corrosive acids is the major drawback which results in environmental pollution and applicability limitation. Thus, a number of methods have been explored to decrease the amount of the acids in recent years. Catalytic Ritter reaction has been realized by cobalt(II) chloride [3], Fe^{3+}-montmodlonite [4], 2,4-dinitrobenzenesulfonic acid (DNBSA) [5], boron trifluoride [6], perfluorinated sulfonic acid resin (Nafion-H) [7], silica sulfuric acid [8], o-Benzenedisulfonimid [9], ferric trichloride [10], Iodine [11] and so on [12]. These catalytic protocols are efficient and cost-saving. But the longer reaction time, the limited substrate spectrum, the using of one of the substrates (nitriles or alcohols) or other toxic organic solvent as the reaction medium are the common disadvantages. So it is still desirable to develop more effective, economical and green Ritter reaction.

Nowadays, great attention has been drawn to the use of water as solvent for organic synthesis [13]. Compared with other organic solvents, water has many incomparable advantages such as inexpensive, environmentally compatible, nontoxic, widely available and so on. To the best of our knowledge, there is only one report about water as the solvent in the Ritter reaction. Firouzabadi *et al.* reported the dodecatungstopsphoric acid ($H_3PW_{12}O_{40}$) catalyzed amidation reaction of alcohols and protected alcohols in water [14]. Although good to excellent yields were obtained, the reaction time was long and the variety of alcohols was limited. So the development of more effective, economical and green Ritter reaction is still desirable.

As is known to all, subcritical water ($150 < T < 370$ ˚C, $0.4 < p < 22$ MPa) possesses some special chemical and physical properties. It has been used as a solvent in many organic reactions and brought surprising and unforeseen results [15]. In this paper, we wish to report a catalytic, efficient and green Ritter reaction in subcritical water. This is the first time that the subcritical water was used as a solvent to get amides from alcohols.

RESULTS AND DISCUSSION

The reaction of 1-phenylethanol (**1a**) with acetonitrile was taken as a model reaction to develop the optimum reaction conditions. Firstly, we carried out the reaction in the absence of any additional catalysts in water at 160℃ for 5h. But only trace product was obtained. We reasoned that the acidity of water was not enough for promoting the Ritter reaction which usually requires strong acid. So we added catalytic amount of several strong acids to increase the acidity of the reaction system. To our surprise, 36-55% yields were obtained when 10 mol% H_2SO_4, 4-methylbenzenesulfonicacid, methanesulfonic acid and trifluoromethanesulfonic acid (TfOH) were added (Table **1**, entries 2-5). Among these acids, the TfOH was the best catalyst. To improve the yield, we increased the temperature to 200℃. Higher yield was obtained (Table **1**, entry 6). However, prolonging the reaction time to 10 hours, the yield of amide was no obvious change (Table **1**, entry 7). So we futher increased the catalyst loading of TfOH to 20 mol% and the yield of **2a** was raised to 76% (Table **1**, entry 8). Considering the solubility of starting materials in water, we added 0.1 equiv sodium dodecyl sulfate (SDS) in the reaction system. As expected, the yield was increased to 82% (Table **1**, entry 9). To compare with the Firouzabadi`s catalyst, we carried out a control catalytic Ritter reaction (Table **1**, entry 10). The results showed that the catalytic efficiency of dodecatungstophosphoric acid was lower than TfOH at the same reaction condition. We also took the reaction at reflux condition with the dodecatungstophosphoric acid and TfOH as the catalyst (Table **1**, entries 11 and 12). But only trace product was obtained in both reactions.

With the optimal conditions in hand, the generality of this protocol was explored. A series of secondary alcohols (**1a-i**) and various nitriles were used in the reaction. As shown in Table **2**, the reaction of 1-(naphthalen-2-yl)ethanol

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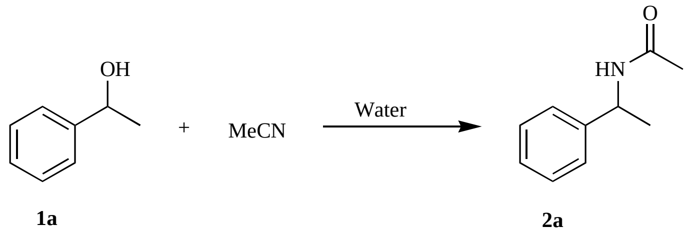
1875-6255/12 $58.00+.00

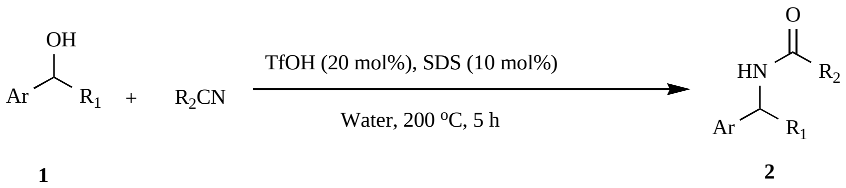


Scheme 1.

Table 1. Ritter Reaction of 1a and MeCN in Water with Different Catalysts

Entry	Catalyst	Temp (℃)	T (h)	Yield (%) [e]
1	-	160	5	Trace
2	H_2SO_4	160	5	45
3	4-methylbenzenesulfonicacid	160	5	36
4	Methanesulfonic acid	160	5	42
5	TfOH	160	5	55
6	TfOH	200	5	62
7	TfOH	200	10	64
8 [b]	TfOH	200	5	76
9 [c]	TfOH, SDS	200	5	82
10 [d]	$H_3PW_{12}O_{40}$, SDS	200	5	55
11 [d]	$H_3PW_{12}O_{40}$, SDS	100	5	trace
12 [c]	TfOH, SDS	100	5	trace

[a] Alcohol (0.2 mmol), nitrile (0.8 mmol), water (0.2 mL), catalyst (10 mol%).
[b] 20 mol% TfOH.
[c] 20 mol% TfOH, 10 mol% SDS.
[d] 20 mol% $H_3PW_{12}O_{40}$, 10 mol% SDS.
[e] Isolated yield based on the alcohol.



Scheme 2.

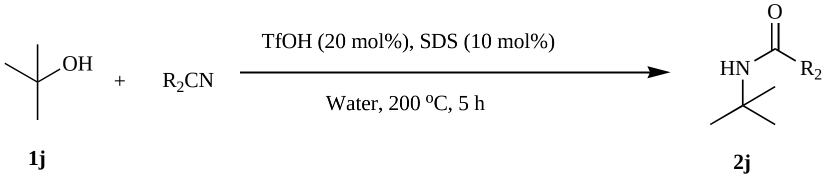
Table 2. Ritter Reaction of Secondary Alcohols and Nitriles in Subcritical Water with TfOH[a]

Entry	Alcohol	Ar	R_1	R_2	Amide[b]	Yield (%) [c]
1	**1a**	Ph	Me	Me	**2a$_1$**	82
2	**1b**	2-naphthyl	Me	Me	**2b$_1$**	86
3	**1c**	2-ClC_6H_4	Me	Me	**2c$_1$**	70
4	**1d**	3-ClC_6H_4	Me	Me	**2d$_1$**	73
5	**1e**	4-ClC_6H_4	Me	Me	**2e$_1$**	75
6	**1f**	4-BrC_6H_4	Me	Me	**2f$_1$**	72
7	**1g**	4-$MeOC_6H_4$	Me	Me	**2g$_1$**	-
8	**1h**	Ph	Et	Me	**2h$_1$**	65
9	**1i**	Ph	Ph	Me	**2i$_1$**	81

(Table 2). Contd…..

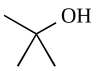
Entry	Alcohol	Ar	R_1	R_2	Amide^b	Yield (%) ^{c}
10	**1a**	Ph	Me	C_6H_5	**2a**$_2$	76
11	**1b**	2-naphthyl	Me	C_6H_5	**2b**$_2$	80
12	**1c**	2-ClC_6H_4	Me	C_6H_5	**2c**$_2$	67
13	**1d**	3-ClC_6H_4	Me	C_6H_5	**2d**$_2$	71
14	**1e**	4-ClC_6H_4	Me	C_6H_5	**2e**$_2$	74
15	**1f**	4-BrC_6H_4	Me	C_6H_5	**2f**$_2$	70
16	**1g**	4-$MeOC_6H_4$	Me	C_6H_5	**2g**$_2$	-
17	**1h**	Ph	Et	C_6H_5	**2h**$_2$	62
18	**1i**	Ph	Ph	C_6H_5	**2i**$_2$	78
19	**1a**	Ph	Me	$C_6H_5CH_2$	**2a**$_3$	71
20	**1b**	2-naphthyl	Me	$C_6H_5CH_2$	**2b**$_3$	81
21	**1c**	2-ClC_6H_4	Me	$C_6H_5CH_2$	**2c**$_3$	68
22	**1d**	3-ClC_6H_4	Me	$C_6H_5CH_2$	**2d**$_3$	72
23	**1e**	4-ClC_6H_4	Me	$C_6H_5CH_2$	**2e**$_3$	74
24	**1f**	4-BrC_6H_4	Me	$C_6H_5CH_2$	**2f**$_3$	79
25	**1g**	4-$MeOC_6H_4$	Me	$C_6H_5CH_2$	**2g**$_3$	trace
26	**1h**	Ph	Et	$C_6H_5CH_2$	**2h**$_3$	67
27	**1i**	Ph	Ph	$C_6H_5CH_2$	**2i**$_3$	88
28	**1a**	Ph	Me	CH_2=CH	**2a**$_4$	-

[a] Alcohol (0.2 mmol), nitrile (0.8 mmol), water (0.2 mL), catalyst (20 mol%), SDS (10 mol%).
[b] Amides (entry 1-20, 23, 25, 27) are known and compared with authentic samples [refs. 5, 11, 12(e), 17].
[c] Isolated yield based on the alcohol.



Scheme 3.

Table 3. Ritter Reaction of Tertiary Butanol and Nitriles in Subcritical Water with TfOH^a

Entry	Alcohol	R_2	amides^b	Yield (%) ^{c}
1		Me	**2j**$_1$	71
2		C_6H_5	**2j**$_2$	81
3		$C_6H_5CH_2$	**2j**$_3$	74
4		CH_2=CH	**2j**$_4$	-

[a] Alcohol (0.2 mmol), nitrile (0.8 mmol), water (0.2 mL), catalyst (20 mol%), SDS (10 mol%).
[b] Amides (entry 1-3) are known [11, 12(f)].
[c] Isolated yield based on the alcohol.

1b and acetonitrile gave the desired amides with good yield (86 %, Table **2**, entry 2). The electron-deficient benzylic alcohols **1c**-**f** also reacted well with acetonitrile and 70%, 73%, 75%, 72% yields were obtained respectively (Table **2**, entries 3-6). However, it should be noted that the electron-rich benzylic alcohol **1g** gave no product of amide (Table **2**, entry 7) [16]. The reason for this is unclear. Bulky alcohols such as 1-phenylpropan-1-ol and diphenylmethanol were also appropriate substrates for this protocol. Bigger steric hindrance in 1-phenylpropan-1-ol give lower yield of **2h**$_1$ (65%, Table **2**, entry 8). The existence of two phenyl groups made the intermediate carbenium ions more stable which lead to higher yield of **2i**$_1$ (81%, Table **2**, entry 9). Different nitriles such as benzonitrile and 2-phenylacetonitrile were also proved to be efficient in the reaction. The desired products were obtained with moderate to good yields. (Table

2, entries 10-15, 17-18, 19-24, 26-27). The acrylonitrile however was an unsuitable substrate for this protocol and the white polymer product was found (Table **2**, entry 28).

In respect that the products *N*-tert-butyl amides are important amine precursors in pharmaceuticals, we carried out the reactions between tertbutyl alcohol **1j** and nitriles. The results are summarized in Table **3**. Except for the acrylonitrile, the other three nitriles were worked smoothly. The desired *N*-tertbutyl-amides were obtained in 71%, 81% and 74% respectively.

Mechanistically, we think that the mechanism of this protocol follows the traditional way. The alcohol firstly generates the carbenium ion or ether (which can be translated to the carbenium ion) under the effect of acid. Then the carbenium ion reacts with the nitrile to produce a nitrilium ion. The latter is trapped by water resulting in amides. Why only trace products were obtained at reflux condition? We thought that the subcritical water plays an important role. Firstly, the subcritical water's dielectric constant is much lower than the ambient water which causes the solubility of organics to increase. Secondly, the subcritical water has a higher dissociation constant than the ambient water which makes it easy to ionize and increase the acidity of the reaction system greatly. These two reasons make the differences.

CONCLUSION

In summary, we have described a practical and efficient Ritter reaction in subcritical water. Electro-withdrawing aromatic secondary alcohols, bulky secondary alcohols and tert-butanol can be converted to the corresponding amides in high yield. The absence of organic solvent and the use of water make this procedure non-toxic, inexpensive, and eco-friendly. We believe that this simple, green catalytic protocol provides an alternative way to prepare amides.

EXPERIMENTAL

All starting materials were of the commercially available (analytical grade) and used without further purification. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354-92. Melting poits were measured with SGW X-4 melting point apparatus. ^{1}H NMR (300 or 600 MHz) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm (**δ**) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, **δ** 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). ESIMS spectra were recorded on BioTOF Q.

General Procedure for the Synthesis of amides: A mixture of alcohol (1 mmol), nitrile (4 mmol), SDS (0.1 mmol), trifluoroacetic acid (0.2mmol) and water (2 mL) was added to a sealed tube and heated to 200℃. Then the temperature was maintained for five hours. After the reaction mixtures were cooled to room temperature, the crude solution was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvents under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane/EtOAc = 4/1) to give the pure products.

ACKNOWLEDGEMENTS

We are grateful for the financial supports from the National Natural Science Foundation of China (21102115), the youth founds of Sichuan Province (2010JQ0048), Sichuan Education Department project (09ZA110) and the Key Laboratory of Natural Medicine and biotechnology, Xihua University (XZD0821-09-1).

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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