



One-pot synthesis of *N-tert*-butyl amides from alcohols, ethers and esters using $\text{ZnCl}_2/\text{SiO}_2$ as a recyclable heterogeneous catalyst

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ABSTRACT

$\text{ZnCl}_2/\text{SiO}_2$ has been found to be an efficient and reusable catalyst for conversion of alcohols, ethers and esters to corresponding amides via the Ritter reaction in high yield. It was found that benzonitrile reacted with *tert*-butyl acetate faster than the other sources of *tert*-butyl carbocation.

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1. Introduction

Heterogeneous supported catalysts have been gained much attention in recent years, as they possess a number of advantages [1–3]. Immobilization of catalysts on solid support improves the available active site, stability, hygroscopic properties, handling and reusability of catalysts [4] which all factors are important in industry. Therefore, use of supported and recoverable catalysts in organic transformations has economical and environmental benefits. Due to the stability and high surface area, silica has been widely used as support [5–7]. Among silica impregnated catalysts, silica supported zinc chloride ($\text{ZnCl}_2/\text{SiO}_2$, silzic) has been prepared and characterized by Upadhyaya and Samant [8]. In spite of ZnCl_2 , silzic is highly water tolerant, non-corrosive and stable solid catalyst with elevated Lewis acid property. Silzic has been used as a recoverable Lewis acid catalyst in the Pinacol–Pinacolone rearrangement [8], Biginelli reaction [9], protection of heteroatoms [10] and Mannich reaction [11].

The classical Ritter reaction is the reaction of tertiary or benzylic alcohols with nitriles in concentrated sulfuric acid [12]. Recently, various modified versions of this reaction have been reported for amidation of nitriles by relatively stable *in situ*-generated carbocations from alcohols, ethers, silyl ethers, alkylborons, esters, alkenes and carbonium salts [13–21] by using heterogeneous and homoge-

neous acidic catalysts. These methods often led to the development of more eco-friendly protocols. We have also developed a useful heterogeneous alternative for the Ritter reaction using heterogeneous catalyst $\text{P}_2\text{O}_5/\text{SiO}_2$ [5]. Meanwhile, some of these methods are limited by use of excess harmful organic reagents or mineral acids, low yield of products and long reaction times. Thus, development of modified efficient and reliable Ritter reaction remains as a field of researches. In continuation of our interest in the use of supported catalysts [5], herein we report the Ritter reaction of various nitriles with *tert*-butyl alcohol, esters and ethers using silzic as an efficient heterogeneous catalyst (Scheme 1).

2. Experimental

2.1. Preparation of catalyst

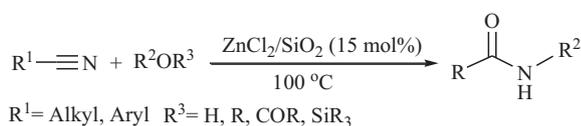
Supported ZnCl_2 on silicagel was prepared according to the previous procedure [8]. Thus, 10% (w/w) $\text{ZnCl}_2/\text{silica}$ gel (silzic 10%) was easily prepared by co-grinding of anhydrous zinc chloride (1 g) with dry silica gel (9 g) in an agate mortar at room temperature for 20–25 min. Careful mixing is required to attain uniform dispersion of ZnCl_2 over silica surface. This results in formation of homogenized, white free flowing powder which was further activated in vacuum at 80 °C for 2 h [8].

2.2. General experimental procedure for the Ritter reaction

To a stirred mixture of the *tert*-butyl acetate (10 mmol) and nitrile (5 mmol) was added 0.15 mol% of supported ZnCl_2 on SiO_2

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Scheme 1. The Ritter reaction in the presence of silicic catalyst.

(10%, w/w) in a round bottom flask equipped with condenser at 100 °C for the given times (Table 2). For microwave-assisted reactions the above premixed mixture irradiated at 500 w in a domestic MW oven. Progress of the reaction was followed by TLC. After completion of the reaction, the resulting mixture was extracted with EtOAc (5 × 10 ml). Then the organic layer was washed with 10% NaHCO₃ and water, dried over Na₂SO₄ and concentrated to give the products.

2.3. Reusability of catalyst

The recovered catalyst was regenerated by washing with EtOAc and drying under microwave irradiation. Using the recycled catalyst for two consecutive times in the Ritter reaction of benzonitrile and *tert*-butyl acetate furnished the product with no significant decreasing of reaction yield.

2.4. Selected spectral data

2.4.1. *N*-*tert*-Butyl-3-nitrobenzamide (Table 2, Entry 3)

White needles (EtOH:H₂O), 90% yield, mp = 128–130 °C. FT-IR: ν_{max} (neat) 3359, 1644, 1520, 1348 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ : 1.56 (s, 9H, (CH₃)₃), 6.06 (br s, 1H, NH), 7.77 (t, 1H, J = 8 Hz), 8.15 (d, 1H, J = 8 Hz), 8.36 (d, 1H, J = 8 Hz), 8.55 (s, 1H, ph) ppm. ¹³C NMR (125 MHz, CDCl₃) δ : 29.2, 52.7, 121.93, 126.11, 130.18, 131.07, 133.51, 138, 164.82 ppm.

2.4.2. *N*-*tert*-Butyl-4-(trifluoromethyl)-benzamide (Table 2, Entry 6)

White needles (EtOH:H₂O), 86% yield, mp = 135 °C. FT-IR: ν_{max} (neat) 3266, 1641 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆) δ : 7.79 (d, 2H, J = 10 Hz), 7.97 (d, 2H, J = 10 Hz), 8.03 (br s, 1H, NH) ppm.

2.4.3. *N*-*tert*-Butyl-2-(4-chlorophenyl)-acetamide (Table 2, Entry 13)

White needles (EtOH:H₂O), 85% yield, mp = 122–126 °C. FT-IR: ν_{max} (neat) 3302, 1636 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ : 1.32 (s, 9H, (CH₃)₃), 3.45 (s, 2H, CH₂), 5.29 (br s, 1H, NH), 7.21 (d, 2H, J = 8.35 Hz), 7.34 (d, 2H, J = 8.35 Hz) ppm. ¹³C NMR (125 MHz, CDCl₃) δ : 29.1, 44.4, 51.8, 129.4, 131, 133.4, 134.3, 170.1 ppm.

2.4.4. *N*-*tert*-Butyl-4-methylbenzamide (Table 2, Entry 11)

White needles (EtOH:H₂O), 92% yield, mp = 116 °C. FT-IR: ν_{max} (neat) 3352, 1634 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆) δ : 1.36 (s, 9H, (CH₃)₃), 2.38 (s, 3H, CH₃), 7.22 (d, 2H, J = 10 Hz), 7.69 (d, 2H, J = 10 Hz), 7.66 (br s, 1H, NH) ppm.

2.4.5. *N*-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)benzamide (Compound 2)

¹H NMR (500 MHz, DMSO-*d*₆) δ : 2.25 (3H, s); 7.00 (2H, d, J = 8.0 Hz), 7.20–7.50 (m, 11H), 7.60–7.90 (2H, m), 8.14 (d, 1H, J = 8.0 Hz), 8.86 (d, 1H, J = 8.0 Hz), 9.88 (br s, 1H, NH).

3. Results and discussion

In our preliminary experiments and in order to optimize the reaction conditions, a model reaction between benzonitrile and *tert*-butyl acetate was carried out in the presence of various

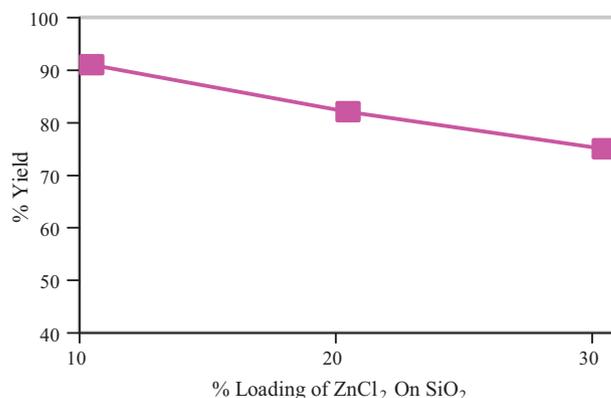


Fig. 1. Effect of catalyst loading on the yield of *N*-*tert*-butylbenzamide.

amounts of unsupported ZnCl₂ at 100 °C under solvent-free conditions. Despite of the progress of reactions (TLC monitoring) a sticky reaction mixture was obtained in all cases, while reaction yielded a mixture of *N*-*tert*-butyl benzamide and benzamide in 60% yield using 10 ml% of unsupported ZnCl₂ after 5 h. Increasing the amounts of catalyst and reaction time not only did not raise the reaction yield but also resulted in the hydration of benzonitrile and formation of benzamide as competitive product. These results prompted us to focus our attention on the Ritter reaction using heterogeneous ZnCl₂. However, we studied the catalytic effect of 10 ml% of ZnCl₂ dispersed on 0.1 g of silicagel, alumina and Celite for the similar reaction. We found that dispersed ZnCl₂ on silicagel gave the better results in terms of reaction time and yield. Then, 10% and 30% (w/w) ZnCl₂/silicagel was carefully prepared according to the previous reported procedure by co-grinding of anhydrous zinc chloride with dry silicagel [9].

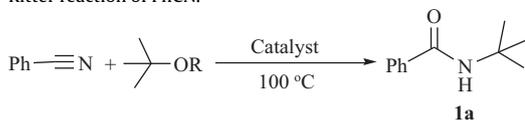
As % yield and selectivity of the obtained products depends on the loading of catalyst, we studied the effect of % loading ZnCl₂ onto SiO₂ on % yield for the Ritter reaction of benzonitrile with *tert*-butyl acetate as model substrates at 100 °C (Fig. 1). Monitoring of the reactions showed that use of 30% (w/w) ZnCl₂/silicagel contributed to the lower yield of *N*-*tert*-butylbenzamide, due to the formation of undesired benzamide product via competitive hydration of benzonitrile.

Owing to the best yield of *N*-*tert*-butylbenzamide (1a), the Ritter reaction of benzonitrile with various sources of *tert*-butyl cation include *tert*-butyl methyl ether, *tert*-butyltrimethyl silyl ether, *tert*-BuOH and *tert*-butyl acetate was investigated in the presence of 10% (w/w) of supported ZnCl₂ on SiO₂ in comparison to unsupported ZnCl₂ at various conditions (Table 1).

The illustrated results in Table 1 obviously reveals that 15 mol% of supported ZnCl₂ on SiO₂ (10%, w/w) is an advanced alternative. The optimized conditions for reactions were the molar ratio of 2:1:0.15 for *tert*-butyl cation generator, benzonitrile and silicic at 100 °C and solvent-free conditions. Although silicic provides a heterogeneous media for the amidation of nitriles with various sources of *tert*-butyl cation, the reaction of *tert*-butyl acetate was superior.

Subsequently, the Ritter reaction of *tert*-butyl acetate and cyclohexyl acetate was extended to the various aromatic and aliphatic nitriles and a range of *tert*-butyl and cyclohexyl amides were isolated in good to excellent yields under these conditions (Table 2). Acrylonitrile converted to acrylamide and amidation of malononitrile with *tert*-butyl acetate produced the desired monoamide (Table 2, entries 15 and 16). No Ritter reaction took place with cyano pyridines as well as simple primary alcohols under these conditions, even after long reaction times.

Furthermore, microwave assisted silicic catalyzed Ritter reactions of propionitrile and benzonitrile with *tert*-butyl acetate were

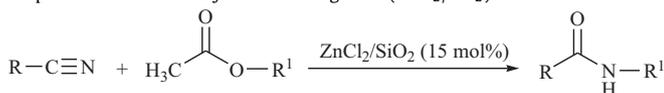
Table 1
Ritter reaction of PhCN.

Entry	R	Catalyst (mol%)	Time/yield ^a (h)/(%)
1	H	ZnCl ₂ /SiO ₂ (15)	4/85
2	CH ₃	ZnCl ₂ /SiO ₂ (15)	4/82
3	<i>t</i> -Bu	ZnCl ₂ /SiO ₂ (15)	3.5/87
4	<i>t</i> -Bu	ZnCl ₂ /SiO ₂ (10)	3.5/80
5	COCH ₃	ZnCl ₂ /SiO ₂ (20)	3/88
6	COCH ₃	ZnCl ₂ /SiO ₂ (15)	2/91
7	COCH ₃	SiO ₂ (15)	12/40
8	COCH ₃	ZnCl ₂ (15)	4/78 ^b
9	COCH ₃	ZnCl ₂ /HOAc (15)	4/81
10	SiMe ₃	ZnCl ₂ /SiO ₂ (15)	4/86
11	H	ZnCl ₂ /HOAc (15)	6/82 ^b
12	H	ZnCl ₂ (15)	4/74 ^b

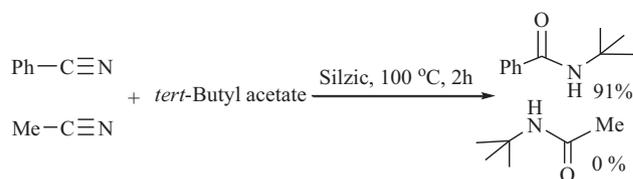
^a Isolated yield.^b As a mixture with benzamide.

attempted at different powers ranging from 500 to 950 w. In the most appropriate power 500 w, microwave irradiation of reaction mixtures produced the corresponding amides in 90 and 93% yields at short times (~120 s). The speeding up of the reaction under microwave irradiation possibly will be streamlined on the basis of the huge polarity of the reaction mixture.

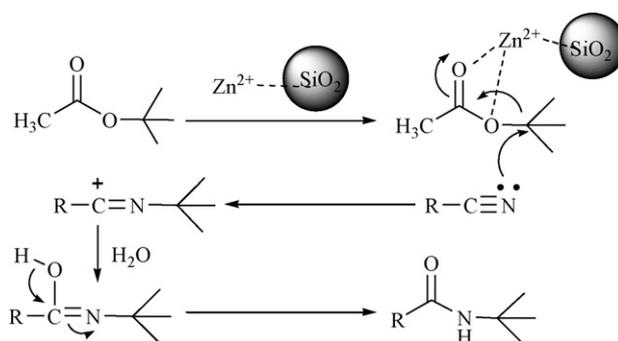
The chemoselectivity of the silzic-catalyzed Ritter reaction was examined by parallel reactions of *tert*-BuOH, *tert*-BuOCOCH₃ and *tert*-BuOCH₃ with benzonitrile for 2 h. It was found that benzonitrile reacted with *tert*-butyl acetate much faster than the other sources of *tert*-butyl carbocation. Greatly facilitated heterolytic cleavage of C–O bond of *tert*-butyl acetate by silzic is rationalized by the leaving group superiority of acetate than OH or OR groups. In addition, competitive silzic-catalyzed Ritter reaction of *tert*-butyl

Table 2
Preparation of *N*-*tert*-butyl amides using silzic (ZnCl₂/SiO₂).

Entry	R	R ¹	Time (h)	Yield ^a (%)
1	C ₆ H ₅	<i>tert</i> -Butyl	2	89
2	C ₆ H ₅	Cyclohexyl	3.5	78 ^b
3	3-NO ₂ -C ₆ H ₄	<i>tert</i> -Butyl	11	90
4	4-NO ₂ -C ₆ H ₄	<i>tert</i> -Butyl	10	87
5	4-NO ₂ -C ₆ H ₄	Cyclohexyl	10	75 ^b
6	4-CF ₃ -C ₆ H ₄	<i>tert</i> -Butyl	8	85 ^b
7	4-Cl-C ₆ H ₅	<i>tert</i> -Butyl	5	90
8	3-Cl-C ₆ H ₅	<i>tert</i> -Butyl	6	90
9	3-Cl-C ₆ H ₅	Cyclohexyl	8	76 ^b
10	4-MeO-C ₆ H ₄	<i>tert</i> -Butyl	6	92
11	4-Me-C ₆ H ₄	<i>tert</i> -Butyl	5	92
12	Terephthalonitrile	<i>tert</i> -Butyl	5.5	88
13	CH ₃	<i>tert</i> -Butyl	5	85
14	CH ₃	Cyclohexyl	6	78 ^b
15	4-Cl-C ₆ H ₄ CH ₂	<i>tert</i> -Butyl	6	85
16	2-Cl-C ₆ H ₄ CH ₂	<i>tert</i> -Butyl	8	85
17		<i>tert</i> -Butyl	4	90
18		<i>tert</i> -Butyl	5	91
19		<i>tert</i> -Butyl	4.5	86

^a Isolated yield.^b 30% (w/w) ZnCl₂/silicagel was used and product was purified by recrystallization.**Scheme 2.** The chemoselectivity of the silzic-catalyzed Ritter reaction.**Table 3**
Recyclability of the ZnCl₂/silicagel in the Ritter reaction of benzonitrile and *tert*-butyl acetate.

Run no.	Time (h)	Yield (%)
1	2	90
2	2	89
3	3	88
4	5.5	83

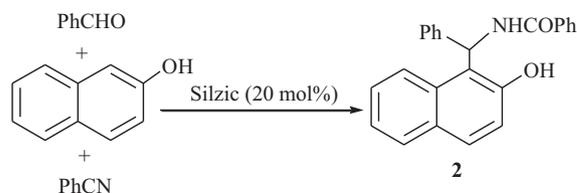
**Scheme 3.** Proposed mechanism for silzic-catalyzed Ritter reaction.

acetate (1 mmol) with a mixture of benzonitrile and acetonitrile under optimized conditions led to the selective formation of *N*-*tert*-butylbenzamide in high yield. However, no chemoselectivity was observed for cyclohexanol versus dicyclohexyl ether (**Scheme 2**).

Reusability of catalyst is an important factor for its upgrade use. The recovered silzic from the Ritter reaction of benzonitrile and *tert*-butyl acetate was reused successfully two times and it was found that more than this, elongation of the reaction time up to 2 h was observed due to the significant loss of activity of catalyst (**Table 3**).

From mechanistic point of view, the catalytic efficiency of supported Zn²⁺ in this reaction maybe attributed to its Lewis acidity and oxophilicity which both promote the Ritter reaction via coordination to oxygen atoms of ester and facilitation of C–O cleavage by attack of nitrile group. Thus, according to the electronic effects, we proposed the following mechanism (**Scheme 3**).

Finally, Ritter type reaction of PhCN, β -naphthol and benzaldehyde in the presence of ZnCl₂/SiO₂ (20 mol%) produced the corresponding amidoalkyl naphthol in 70% isolated yield which structurally confirmed by its ¹H NMR spectra (**Scheme 4**).

**Scheme 4.** Ritter-type three-component condensation.

4. Conclusion

In conclusion, we have developed a simple chemoselective methodology for modified Ritter reaction using silzic as a reusable catalyst. The products were obtained in high yields and could be used in the synthesis of biologically active compounds.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2011.01.013.

References

- [1] G. Sartori, R. Maggi, *Chem. Rev.* 113 (2010) PR1–PR54.
- [2] A.K. Chakraborti, R. Gulhane, *J. Chem. Soc. Chem. Commun.* (2003) 1896–1897.
- [3] G. Neri, G. Rizzo, C. Crisafulli, L. Deluca, A. Donato, M.G. Musolino, R. Pietropaolo, *Appl. Catal. A: Gen.* 295 (2005) 116–125.
- [4] J.H. Clark, *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH, Weinheim, 1994, p. 126.
- [5] F. Tamaddon, M. Khoobi, E. Keshavarz, *Tetrahedron Lett.* 48 (2007) 3643–3646.
- [6] L. Mamani, A. Heydari, M. Sheykhan, *Appl. Catal. A: Gen.* 384 (2010) 122–127.
- [7] J.S. Yadav, B.V. Subba Reddy, T. Pandurangam, Y. Jayasudan Reddy, M.K. Gupta, *Catal. Commun.* 9 (2008) 1297–1301.
- [8] D.J. Upadhyaya, S.D. Samant, *Appl. Catal. A: Gen.* 340 (2008) 42–51.
- [9] R. Gupta, M. Gupta, S. Paul, R. Gupta, *Can. J. Chem.* 85 (2007) 197–201.
- [10] H.R. Shaterian, F. Khorami, R. Doostmohammadi, A. Amirzadeh, M. Ghashang, *Phosph. Sulfur Silicon* 184 (2009) 2227–2237.
- [11] A.A. Jafari, F. Moradgholi, *Acta Chim. Slov.* 56 (2009) 744–748.
- [12] J.Y. Ritter, P.P. Minier, *J. Am. Chem. Soc.* 70 (1948) 4045–4048.
- [13] P. Theerthagiri, A. Lalitha, P.N. Arunachalam, *Tetrahedron Lett.* 51 (2010) 2813–2819.
- [14] B.V. Subba Reddy, N. Sivasankar Reddy, Ch. Madan, J.S. Yadav, *Tetrahedron Lett.* 51 (2010) 4827–4829.
- [15] T. Abe, H. Takeda, Y. Miwa, K. Yamada, R. Yanada, M. Ishikura, *Helv. Chim. Acta* 93 (2010) 233–241.
- [16] C. Cazorla, E. Metay, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.* 50 (2009) 6855–6857.
- [17] B. Anxionnate, A. Guerinot, S. Reymond, J. Cossy, *Tetrahedron Lett.* 50 (2009) 3470–3473.
- [18] J.C. Baum, J.E. Miline, J.A. Murry, O.R. Thiel, *J. Org. Chem.* 74 (2009) 2207–2209.
- [19] M. Dos Santos, B. Crousse, D. Bonnet Delpon, *Tetrahedron Lett.* 50 (2009) 857–859.
- [20] M. Barbero, S. Bazzi, S. Cadamuro, S. Dughera, *Eur. J. Org. Chem.* 3 (2009) 430–436.
- [21] V. Polshettiwar, R.S. Varma, *Tetrahedron Lett.* 49 (2008) 2661–2664.