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SHORT COMMUNICATION

An efficient synthesis of *N-tert*-butyl amides by the reaction of *tert*-butyl benzoate with nitriles catalyzed by $Zn(ClO_4)_2{\cdot}6H_2O$

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Abstract
An efficient, mild and inexpensive synthesis of *N-tert*-butyl amides from the reaction of nitriles (aryl, benzyl and *sec*-alkyl nitriles) with *tert*-butyl benzoate catalyzed by the employment of 2 mol% $Zn(ClO_4)_2{\cdot}6H_2O$ at 50 °C under the solvent-free conditions is described. The reaction with aryl nitriles was carried out well and afforded the *N-tert*-butyl amides in 87–97% yields after 1 h. The benzyl and *sec*-alkyl nitriles also proceeded well and produced the *N-tert*-butyl amides in 83–91% yields after 5 h.

Keywords Ritter reaction · *Tert-butyl* benzoate · $Zn(ClO_4)_2{\cdot}6H_2O$ · Amides · Solvent-free

Introduction

The *N-tert*-butyl amide compounds have wide application in organic synthesis (Clayden et al. 2007) and drug synthesis (Mao et al. 2017). Especially, a lot of drug molecules containing *N-tert*-butyl amide functionality have been explored to cure various diseases. For example, Finasteride (Ahmed and Al-Abd 2018) and Epristeride (Baine et al. 1994) have been developed for the treatment of benign prostatic hyperplasia. On the other hand, Indinavir (Rossen et al. 1995), nelfinavir (Sanchez et al. 2018) and Saquinavir (Ghosh et al. 1997) have been used as a component to treat HIV, whereas, CPI-1189 (Hensley et al. 2000) is a candidate for neuro-protective therapy in humans with HIV-associated CNS disease.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11696-018-0586-4) contains supplementary material, which is available to authorized users.

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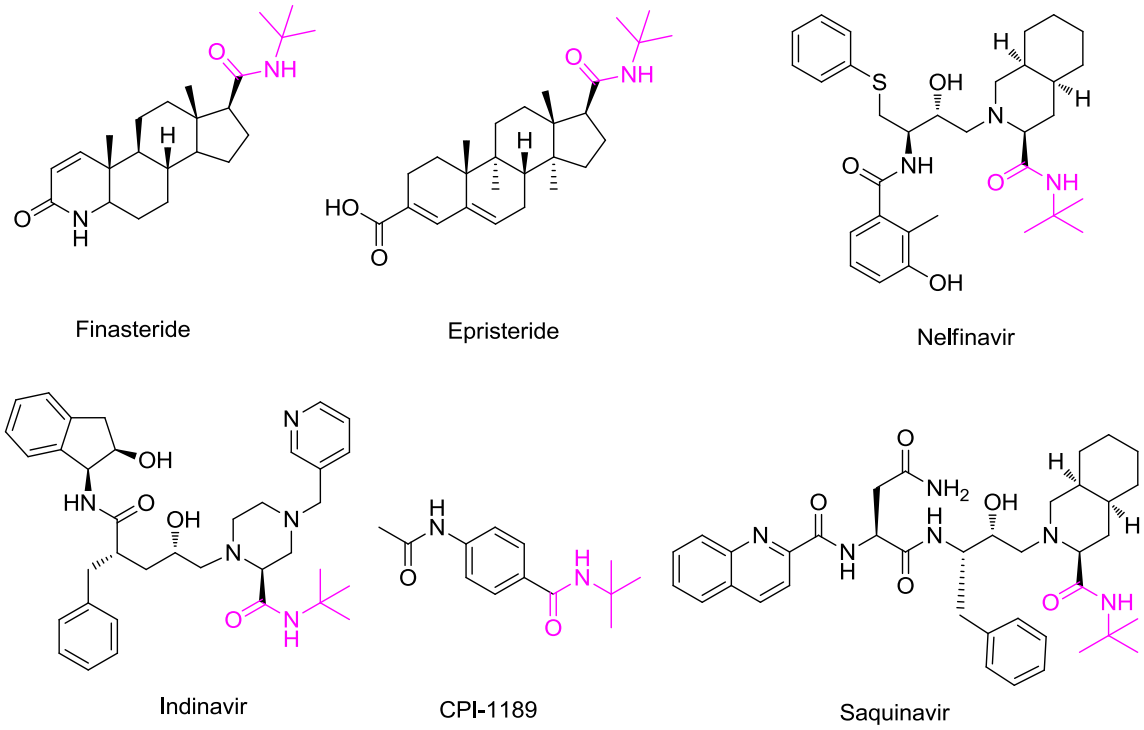
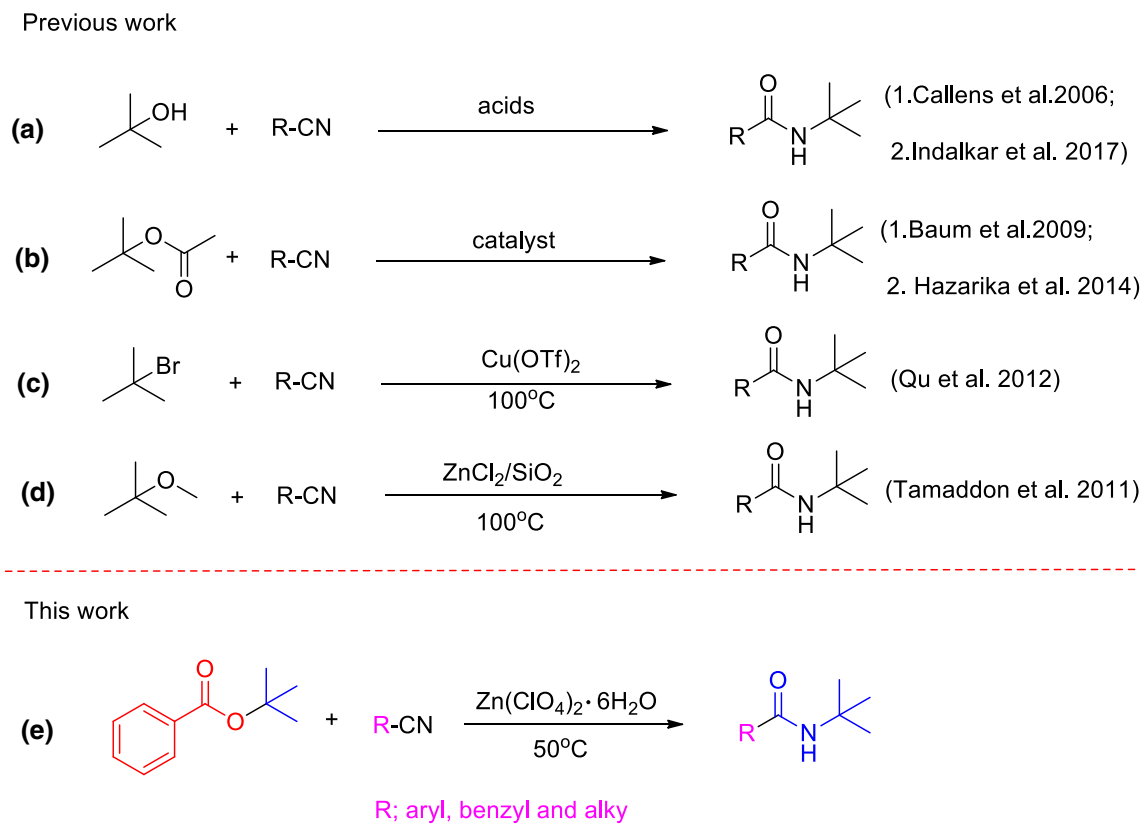




Scheme 1 Synthesis of *N-tert*-butyl amides by Ritter reaction

Usually, the *N-tert*-butyl amide compounds were synthesized by acylation of amines (Valeur and Bradley 2009). On the other hand, various alternative methodologies like Staudinger reaction (Gololobov and Kasukhin 1992), the Schmidt reaction (Lang and Murphy 2006), the oxidative amidation of aldehydes and alcohols (Chang et al. 2010; Krabbe et al. 2016), aminocarbonylation reaction (Wannberg and Larhed 2003), amidation of aryl halides (Jiang et al. 2011), and oxidation of imines (Larsen et al. 1991) were also used to form amides. Although effective, the strategies often used highly hazardous reagents following a stoichiometric amount of and difficultly separated byproducts. In recent years, direct amides from nitriles via Ritter reaction have gained much attention for its atomic economy (Jiang et al. 2014). In general, *tert*-butanol was employed to react with nitriles to form *N-tert*-butyl amides in the presence of acids (Callens et al. 2006; Indalkar et al. 2017). Furthermore, some alternatives including *tert*-butyl acetate (Baum et al. 2009; Hazarika and Baishya 2014), *tert*-butyl bromide (Qu et al. 2012) and methyl *tert*-butyl ether (Tamaddon and Tavakoli 2011) also have been developed for this transformation. Despite convenient, some drawbacks like using solvents and acids, high reaction temperature, long reaction time and high catalyst loading led to restrict its application on large scale. For example, Milne et al. (Baum et al. 2009) used *tert*-butyl acetate in acetic acid along with an excess amount of corrosive H_2SO_4 to synthesize *N-tert*-butyl amides. Hazarika et al. (2014) reported one-pot sequential Schmidt and Ritter reactions with *tert*-butyl acetate for the synthesis of *N-tert*-butyl amides in acetic acid. Tamaddon's group (Tamaddon and Tavakoli 2011) transformed methyl *tert*-butyl ether to *N-tert*-butyl amides in the presence of $ZnCl_2/SiO_2$ as a recyclable heterogeneous catalyst at 100 °C under solvent-free condition. Moreover, Qu et al. (2012) adopted *tert*-butyl bromide to produce *N-tert*-butyl amides at 100 °C. Hence, the need for the development of a novel, mild, effective, Lewis-catalyzed synthetic method for the synthesis of *N-tert*-butyl amides is in demand.

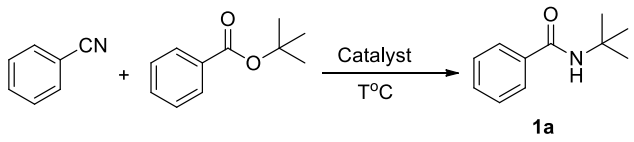
In this paper, we wish to report a new and efficient procedure for the transformation of nitriles with *tert*-butyl benzoate by the use of $Zn(ClO_4)_2{\cdot}6H_2O$ as a catalyst under solvent-free conditions (Scheme 1, path (e)). And our research expands the scope of the substrates and *tert*-butyl benzoate is first used in Ritter reaction to form *N-tert*-butyl amides.

Experimental

Materials and instruments

All reagents were purchased from commercial sources and used without further purification. Melting points were determined on a RY-1 hot stage microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 MHz instrument in $CDCl_3$; chemical shifts (δ) were given in part per million (ppm) relative to TMS as an internal standard. All reactions were monitored by TLC on silica gel GF-254 glass plates (E.Merck) and viewed under UV light at 254 nm. The HRMS spectra were obtained on a Thermo Finnigan spectrometer, model MAT 95XP.

Table 1 Optimization of reaction conditions[a]



1a

Entry	Catalyst (mol%)	T °C	Time (h)	Yield (%)[b]
1	$ZnCl_2$ (5)	60	12	41
2	$Zn(OTf)_2$ (5)	60	6	84
3	$Zn(OAc)_2{\cdot}2H_2O$ (5)	60	12	36
4	ZnO (5)	60	12	NR
5	$ZnBr_2$ (5)	60	12	44
6	$Zn(ClO_4)_2{\cdot}6\mathbf{H_2O}$ (5)	60	1	88
7	$Zn(AcAc)_2$ (5)	60	12	NR
8	$ZnSO_4{\cdot}H_2O$ (5)	60	12	NR
9	$Zn(ClO_4)_2{\cdot}6H_2O$ (1)	60	1	54
10	$Zn(ClO_4)_2{\cdot}6H_2O$ (2)	60	1	86
11	$Zn(ClO_4)_2{\cdot}6H_2O$ (10)	60	1	89
12	$Zn(ClO_4)_2{\cdot}6H_2O$ (2)	RT	1	Trace
13	$Zn(ClO_4)_2{\cdot}6H_2O$ (2)	40	1	69
14	$Zn(ClO_4)_2{\cdot}6\mathbf{H_2}$ **(2)**	50	1	94
15	$Zn(ClO_4)_2{\cdot}6H_2O$ (2)	80	1	93

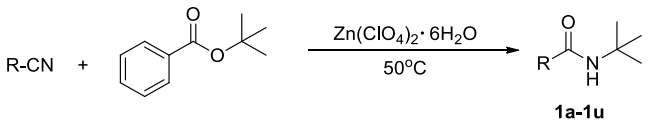
[a]*Tert*-butyl benzoate (5.5 mmol) and benzonitrile (5 mmol) were used

[b]Isolated yields

Typical experimental procedure for the reaction of nitriles and tert-butyl benzoate

A mixture of nitrile (5 mmol), *tert*-butyl benzoate (5.5 mmol) and $Zn(ClO_4)_2{\cdot}6H_2O$ (2 mol%) was placed in a round bottom flask. Then, the reaction mixture was heated at 50 °C for the given time. After completion of the reaction monitored by thin layer chromatography (TLC), the reaction mixture was quenched with 5-ml water. Then the reaction system was added 10 ml aqueous NaOH solution (1 mol/L) and continued to be stirred 5 min and extracted with ethyl acetate (3 × 10 ml). The organic layers were collected, combined, washed with water (3 × 10 ml), dried over anhydrous Na_2SO_4, and concentrated under vacuum.

Table 2 Reaction of nitriles and *tert*-butyl benzoate[a]



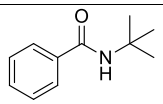
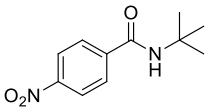
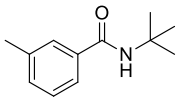
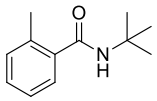
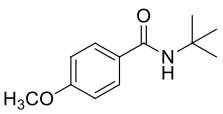
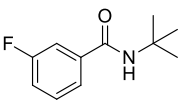
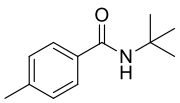
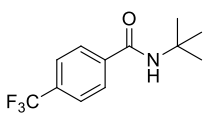
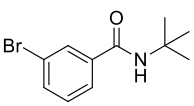
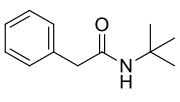
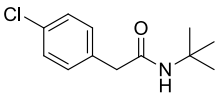
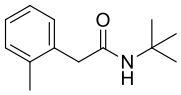
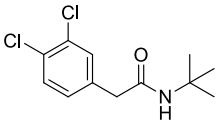
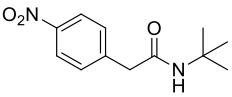
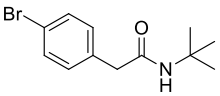
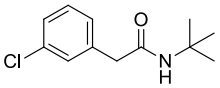
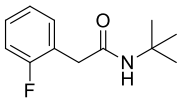
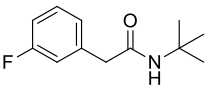
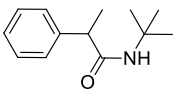
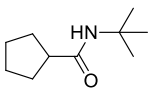
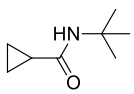
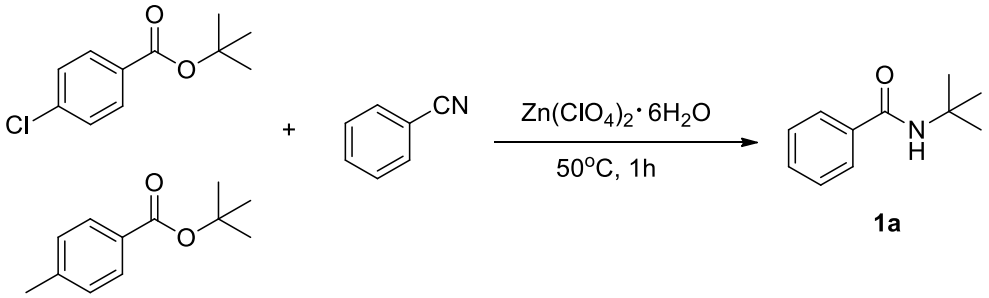
Entry	R	Time(h)	Product	Yield(%)[b]
1	C_6H_5	1	 **1a**	94
2	4-$NO_2C_6H_4$	1	 **1b**	87
3	3-$CH_3C_6H_4$	1	 **1c**	95
4	2-$CH_3C_6H_4$	1	 **1d**	93
5	4-$CH_3OC_6H_4$	1	 **1e**	90
6	3-FC_6H_4	1	 **1f**	95
7	4-$CH_3C_6H_4$	1	 **1g**	92
8	4-$F_3CC_6H_4$	1	 **1h**	97
9	3-BrC_6H_4	1	 **1i**	94
10	$C_6H_5CH_2$	5	 **1j**	89

Table 2 (continued)

Entry	R	Time(h)	Product	Yield(%)[b]
11	4-$ClC_6H_4CH_2$	5	 **1k**	85
12	2-$CH_3C_6H_4CH_2$	5	 **1l**	90
13	3,4-$Cl_2C_6H_4CH_2$	5	 **1m**	84
14	4-$NO_2C_6H_4CH_2$	5	 **1n**	87
15	4-$BrC_6H_4CH_2$	5	 **1o**	89
16	3-$ClC_6H_4CH_2$	5	 **1p**	91
17	2-$FC_6H_4CH_2$	5	 **1q**	83
18	3-$FC_6H_4CH_2$	5	 **1r**	87
19	$C_6H_5CHCH_3$	5	 **1s**	86
20	Cyclopentyl	5	 **1t**	89
21	Cyclopropyl	5	 **1u**	90

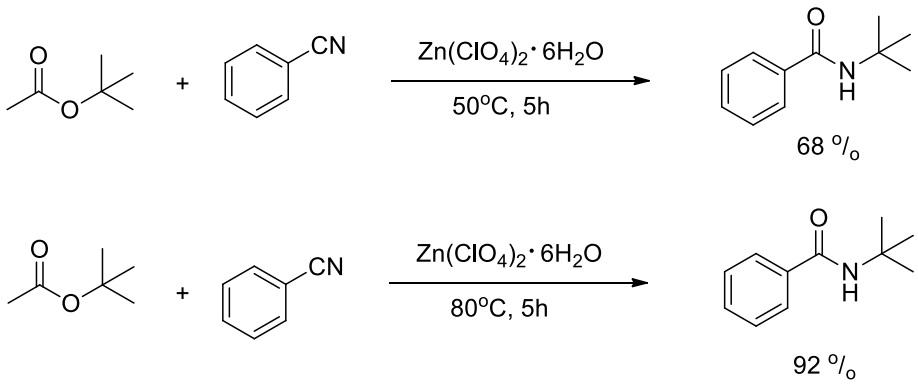
[a] *Tert*-butyl benzoate (5.5mmol), nitriles (5mmol) and Zn(ClO4)2·6H2O (2 mol%) were used

[b] Isolated yields

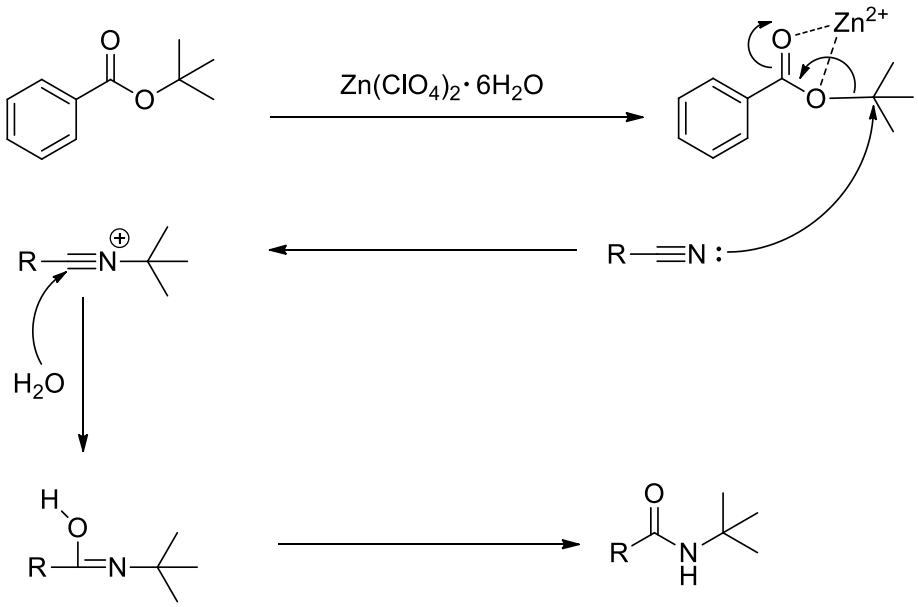


Scheme 2 *Tert*-butyl 4-methylbenzoate and *tert*-butyl 4-chlorobenzoate reacted with benzonitrile

Scheme 3 The reaction of *tert*-butyl acetate with benzonitrile



Scheme 4 Proposed mechanism for $Zn(ClO_4)_2{\cdot}6H_2O$-catalyzed Ritter reaction



The pure product was obtained by directly passing through a silica gel (200–300 mesh) column using petroleum ether/ethyl acetate and identified by ^{1}H NMR and ^{13}C NMR.

Characterization of new compound

N-(tert-butyl)-2-(3, 4-dichlorophenyl) acetamide (1 m) White powder. M.p. 148–150 °C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.41–7.35(m, 2H), 7.12–7.10(m, 1H), 5.31(s, 1H), 3.40(s, 2H), 1.32(s, 9H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 168.89, 135.56, 132.66, 131.24, 131.16, 130.63, 128.60,

51.61, 43.53, 28.71. HRMS calcd. for $C_{12}H_{15}C_{l2}NO[M+H]^+$ requires 259.0531, found 259.0533.

N-(tert-butyl)-2-(3-chlorophenyl) acetamide(1p) White powder. M.p. 127–129 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.29–7.14(m, 4H), 5.28(s, 1H), 3.43(s, 2H), 1.31(s, 9H). ^{13}CNMR (100 MHz, $CDCl_3$) δ: 169.36, 137.38, 134.55, 130.04, 129.37, 127.39, 127.31, 51.48, 44.26, 28.70. HRMS calcd. for $C_{12}H_{16}ClNO[M+H]^+$ requires 225.0920, found 225.0922.

N-(tert-butyl)-2-(2-fluorophenyl) acetamide(1q) White powder. M.p. 102–103 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.31–7.23(m, 2H), 7.11–7.04(m, 2H), 5.40(s, 1H), 3.48(s, 2H), 1.30(s, 9H). ^{13}CNMR (100 MHz, $CDCl_3$) δ: 169.08, 162.13(q, J_{C-F} = 244 Hz), 131.59(q, J_{C-F} = 4 Hz), 129.05(q, J_{C-F} = 9 Hz), 124.48(q, J_{C-F} = 4 Hz), 122.78(q, J_{C-F} = 16 Hz), 115.57(q, J_{C-F} = 22 Hz), 51.34, 37.93, 28.66. HRMS calcd. for $C_{12}H_{16}FNO[M+H]^+$ requires 209.1216, found 209.1217.

Results and discussion

To explore the procedure, benzonitrile was employed as a model compound for the reaction with *tert*-butyl benzoate to screen the reaction conditions (Table 1). The results are summarized in Table 1. At the beginning, 5 mol% of $ZnCl_2$ was first used in this transformation at 60 °C; fortunately, the corresponding *N*-(*tert*-butyl)benzamide(**1a**) was obtained with moderate yield in 41% after 12 h (Table 1, entry 1). Then, a range of Zn catalysts like $Zn(OTf)_2$, $Zn(OAc)_2{\cdot}2H_2O$, ZnO, $ZnBr_2$, $Zn(ClO_4)_2{\cdot}6H_2O$, $Zn(AcAc)_2$ and $ZnSO_4$ were checked again for this reaction, in which $Zn(ClO_4)_2{\cdot}6H_2O$ showed the best catalytic effect and afforded an excellent yield of the desired product *N*-(*tert*-butyl)benzamide(**1a**) (Table 1, entry 6). However, the catalysts like $Zn(OTf)_2$, $Zn(OAc)_2{\cdot}2H_2O$, and $ZnBr_2$ produced the *N*-(*tert*-butyl) benzamide(**1a**) in moderate–good yields (Table 1, entries 2, 3 and 5). Whereas, ZnO, $Zn(AcAc)_2$ and $ZnSO_4$ did not work in this transformation (Table 1, entries 4, 7 and 8). The further optimization revealed that the yield was critically affected by the amount of catalyst employed. The yield decreased to 54% by employment of 1 mol% catalyst. By switching the amount of $Zn(ClO_4)_2{\cdot}6H_2O$ to 2 mol% and 10 mol%, the *N*-(*tert*-butyl)benzamide(**1a**) was obtained with 86% and 89% yield, respectively (Table 1, entries 10, 11). Although yields by employment of 5 mol% (88%) and 10 mol% (89%) catalyst were slightly increasing, 2 mol% catalyst was thought to be enough for this reaction. When the reaction was carried out at room temperature, only trace amount of *N*-(*tert*-butyl)benzamide(**1a**) was detected by TLC after 1 h. By raising the temperature to 40 °C, the reaction afforded a good yield of the product (**1a**) with 69% after 1 h (Table 1, entry 13). Moreover, it was worth noting that while operating at 50 °C, the yield of *N*-(*tert*-butyl) benzamide(**1a**) was improved dramatically to 94% (Table 1, entry 14). When the reaction was conducted at 80 °C, a 93% yield of *N*-(*tert*-butyl)benzamide(**1a**) was obtained (Table 1, entry 15). Therefore, 50 °C was sufficient for this transformation.

The generality of this $Zn(ClO_4)_2{\cdot}6H_2O$-mediated effective synthesis of *N-tert*-butyl amides with *tert*-butyl benzoate and nitriles was subsequently investigated. The substrate scope for the nitriles is summarized in Table 2. The reaction was compatible with a variety of substituents on the nitrile substrates including aryl nitriles and benzyl nitriles and afforded the corresponding *N-tert*-butyl amides in good–excellent yields (Table 2, **1a–1s**). Moreover, the substituents on the *para*, *meta* and *ortho* site of the aryl nitriles and benzyl nitriles could not influence the reaction and furnish the products with high yields. It was observed that the reaction of *tert*-butyl benzoate with 3-methylbenzonitrile, 4-methylbenzonitrile, 4-methylbenzonitrile afforded the *N*-(*tert*-butyl)-3-methylbenzamide(**1c**), *N*-(*tert*-butyl)-2-methylbenzamide(**1d**), and *N*-(*tert*-butyl)-4-methylbenzamide(**1g**) in 95%, 93% and 92% yields, respectively. What is more, the reaction of benzyl nitriles prolonged the reaction time to 5 h for obtaining the best yield. On the other hand, *sec*-alkyl nitriles also could be carried out well and afforded the *N-tert*-butyl amides in excellent yields (Table 2, entries 20, 21).

This method was also suitable to other liquid *tert*-butyl benzoate. For example, *tert*-butyl 4-methylbenzoate and *tert*-butyl 4-chlorobenzoate were used to react with benzonitrile and afforded the corresponding *N*-(*tert*-butyl) benzamide(**1a**) in 92% and 94% yields, respectively (Scheme 2). It was noted that there were no remarkable electronic effects on this reaction.

Furthermore, the catalyst $Zn(ClO_4)_2{\cdot}6H_2O$ was also used to check the reaction of *tert*-butyl acetate with benzonitrile. It was found that a moderate yield of *N*-(*tert*-butyl) benzamide(**1a**) was obtained at 50 °C after 5 h. Then raising the reaction temperature to 80 °C, an excellent yield of *N*-(*tert*-butyl)benzamide(**1a**) could also be obtained after 5 h (Scheme 3).

The mechanism for this sequential reaction can be explained by the already established mechanisms of the Ritter reaction (Tamaddon and Tavakoli 2011), involved in this novel method (Scheme 4).

Conclusions

In summary, we devised an effective and mild protocol for the synthesis of *N-tert*-butyl amides from nitriles with *tert*-butyl benzoate using $Zn(ClO_4)_2{\cdot}6H_2O$ as a catalyst under solvent-free condition. The present work involves several practical advantages like the employment of mild reaction

conditions, short reaction time, under solvent-free condition, and an easy workup procedure.

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