

Boron trifluoride etherate; highly efficient catalyst for synthesis of *tert*-butylamides via modified Ritter reaction in solvent free condition

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Highly efficient method for the preparation of *N-tert*-butyl amides by reaction of nitriles with *tert*-butylacetate is described using boron trifluoride etherate in solvent free condition. Selective amidation of benzonitrile in the presence of acetonitrile was also achieved.

Keywords: Modified Ritter reaction; Boron trifluoride etherate; Nitriles; *tert*-Butylacetate, *N-tert*-Butyl amides

1. INTRODUCTION

The elimination of volatile organic solvents in organic chemistry is a most important goal in green chemistry. Solvent-free organic reactions make syntheses simpler, save energy, and prevent solvent wastes, hazards, and toxicity. These would be especially important during industrial production [1]. The Ritter reaction makes possible the conversion of a group, capable of giving a relatively stable carbonium ion, to a substituted amide by reaction with a nitrile in the presence of a strong acid [2]. The classical Ritter reaction is the reaction of alkenes, tertiary or benzylic alcohols with nitriles in concentrated sulfuric acid. Several modifications have been attempted to improve classical Ritter reaction conditions. However, as an alternative to sulfuric acid, other acid catalysts such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [3], Fe^{3+} -Montmorillonite [4], $\text{Bi}(\text{OTf})_3$ [5], $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/\text{AcCl}$ [6], $\text{P}_2\text{O}_5/\text{SiO}_2$ [7], Nafion [8] and $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ [9] are employed in the classical Ritter reaction.

Ritter reaction using *tert*-butylacetate instead of alcohol was also reported to be catalyzed by sulfuric acid [10, 11] $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ [12], $\text{ZnCl}_2/\text{SiO}_2$ [13], I_2 [14] and Amberlyst-15 [15]. Lewis acids are another class of acid catalyst. In general, they are milder than Bronsted acids and more importantly, template effects are to be expected as they are sterically bulkier than a proton. As such, the utilization of Lewis acids is rapidly increasing. Lewis acid catalyzed reactions continue to attract increasing attention in to the modern organic synthesis scenario [16].

In connection with our research to develop application of Ritter reaction for synthesis of polyamides [17], and polyether amides [18]. Here, we have investigated the potential of most commonly available Lewis acids, boron trifluoride etherate for the synthesis of *N-tert*-butyl amides from *tert*-butylacetate with nitriles via modified Ritter reaction in solvent free condition

2. EXPERIMENTAL

All chemicals were purchased from Merck chemical company. Melting points were recorded on an electro thermal melting point apparatus. The NMR spectra were recorded in CDCl₃ with TMS as an internal standard on a Bruker advance DRX 400 MHz spectrometer. IR spectra were determined on a SP-1100, P-UV-Com instrument. Purity determination of the products was accomplished by TLC on silica gel poly gram SIL G/UV 254 plates. Products were separated by simple filtration, and identified by comparison IR, and ¹H NMR spectra, with those reported for authentic samples.

2.1. Ritter Reaction of tert-butyl acetate (general procedure)

A solution of nitrile (3 mmol) in *tert*-butyl acetate (3 mmol) was prepared. Then BF₃.Et₂O (1 mmol) was added to the solution and the reaction mixture was stirred for 2-5 h at 70 °C. The progress of the reaction was monitored by TLC using (ethylacetate/n-hexane 1:4). After the completion of the reaction, the reaction mixture was quenched with saturated NaHCO₃ solution. Then, the solid residue was filtered and recrystallized from water to afford pure crystals of the proper amides in 74-96% yields.

2.2. Spectral data for selected compounds

2.2.1. N-tert-butyl-3-methylbenzamide (Table 1, entry 4)

Yield 96%; m.p.: 96-97 °C. IR (KBr): 3382, 2962, 1643, 1529, 1447, 748 cm⁻¹. ¹H NMR (400 MHz CDCl₃) δ = 1.49 (s, 9H), 2.4 (s, 3H), 5.95 (br s, 1H), 7.28-7.56 (m, 4H) ppm.

2.2.2. N,N'-di-tert-butylisophthalamide (Table 1, entry 7)

Yield 87%; m.p.: 204-207 °C. IR (KBr): 3272, 3068, 2969, 1639, 1548, 1307, 680 cm⁻¹. ¹H NMR (400 MHz CDCl₃) δ = 1.49 (s, 18H), 6 (br s, 2H), 7.28-8.11 (m, 4H) ppm.

2.2.3. N-tert-butylchloromethylacetamide (Table 1, entry 9)

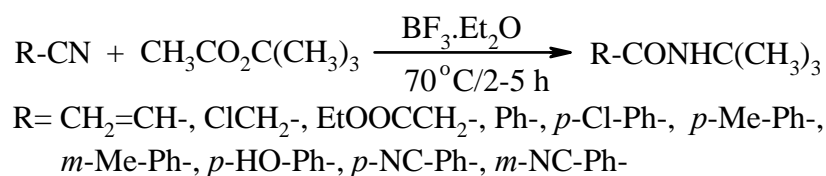
Yield 93%; m.p.: 79-81 °C. IR (KBr): 3311, 2977, 1683, 1554, 1222, 673 cm⁻¹. ¹H NMR (400 MHz CDCl₃) δ = 1.40 (s, 9H), 3-96 (s, 2H), 6.38 (br s, 1H) ppm.

2.2.4. Ethyl 3-(tert-butylamino)3-oxopropanoate (entry 10)

Yield 94%; m.p.: 90-93 °C; IR (KBr): 2991, 2979, 1720, 1629, 1498, 1043, 736 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.45 (s, 9H), 1.47 (t, 3H), 2.43(s, 2H), 4.54 (q, J=6.8, 2 H) 11.25 (br, s, 1H) ppm.

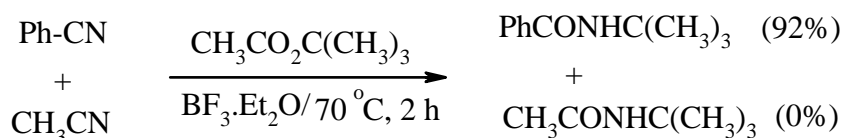
3. RESULTS AND DISCUSSION

A variety of *N-tert*-butylamides were prepared from *tert*-butylacetate and the corresponding aromatic and aliphatic nitriles in the presence of BF₃.Et₂O in good yields in solvent free condition (Scheme 1).



Scheme 1

It is worth mentioning that the corresponding amide in each case was isolated by simple crystallization from water in good yields (Table 1, entries 1-10). The reaction of benzonitrile derivatives with *t*-BuOAc produced corresponding *N*-*tert*-butylamide in 74-96% isolated yield (Table 1, entries 1-7). Also, acrylonitrile, chloroacetonitrile and cyanoethyl acetate give good to excellent isolated yield with *t*-BuOAc in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Table 1, entries 8-10). Additionally, competitive $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyzed Ritter reaction of *tert*-butylacetate with equimolar amounts of benzonitrile and acetonitrile leads to the selective formation of *N*-*tert*-butylbenzamide in good yield, whereas acetonitrile remained unchanged (**Scheme 2**).



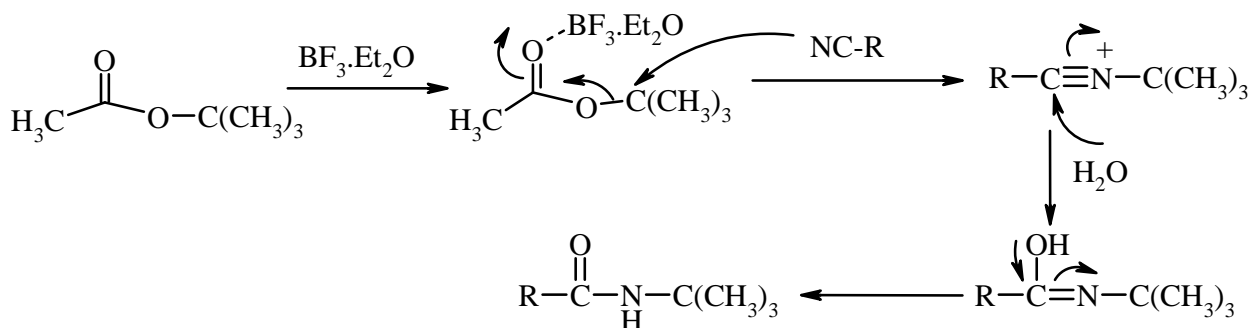
Scheme 2

Table 1. Amidation of *tert*-butylacetate with nitriles by $\text{BF}_3 \cdot \text{Et}_2\text{O}$.

Entry	Nitriles	Product ^a	Time/h	Yield (%) ^b	Ref.
1			2	92	12
2			2	94	13
3			2	95	13
4			2	96	15
5			4	74	15
6	<i>m</i> -NC-C ₆ H ₄ -CN	<i>m</i> - ^t BuNHOC-C ₆ H ₄ -CONH ^t Bu	5	87 ^c	15
7	<i>p</i> -NC-C ₆ H ₄ -CN	<i>p</i> - ^t BuNHOC-C ₆ H ₄ -CONH ^t Bu	5	92 ^c	15
8			3	78	13
9	ClCH_2CN	$\text{ClCH}_2\text{CONH}^t\text{Bu}$	3	93	15
10	$\text{NCCH}_2\text{COOEt}$	^t BuNHCOCH ₂ COOEt	3	94	15

^aAll entries were carried on nitrile (3 mmol), *t*-BuOAc (3 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1 mmol) at 70 °C. ^b All yields refer to isolated products. ^c Nitrile (1.5 mmol) is used.

It is reasonable to assume that the present reaction is initiated that by Lewis acidity and oxophilicity of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ which promote the modified Ritter reaction via coordination to oxygen atoms of ester and facilitation of C-O cleavage by attacking of nitrile group (**Scheme 3**).



Scheme 3

4- CONCLUSION

We have developed a simple, convenient and practical method for modified Ritter reaction using boron trifluoride etherate, which is easy to available and represent effective catalytic activity for the amidation of *tert*-butyl acetate with nitriles in solvent free condition.

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