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One-Pot Sequential Schmidt and Ritter Reactions for the Synthesis of *N*-*tert*-Butyl Amides

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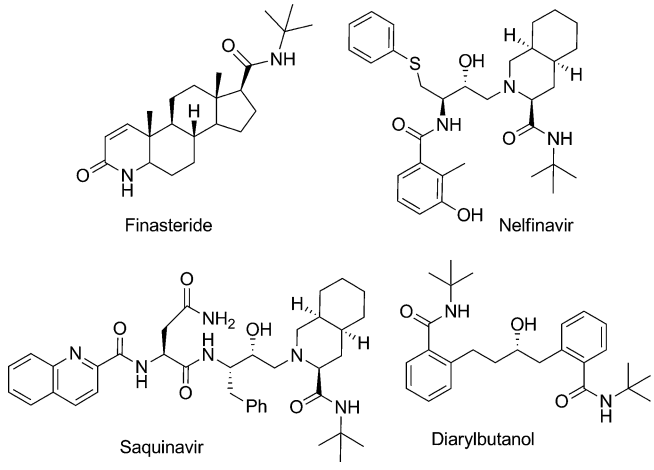
Keywords: Amides / Aldehydes / Schmidt reaction / Ritter reaction

The first example of the direct conversion of benzaldehydes into their corresponding *N*-*tert*-butyl amides through a Schmidt reaction/Ritter reaction sequence is described. A reagent mixture consisting of NaN_3 and $HBF_4{\cdot}OEt_2$ in acetic acid efficiently reacts with aromatic and conjugated (α,β-unsaturated) aldehydes to produce nitrile derivatives, which in situ undergo a Ritter reaction with *tert*-butyl acetate to afford the corresponding *N*-*tert*-butyl amides in almost quantitative yields. The method needs no column chromatography purification. The wide substrate scope as well as the ready availability of the reagent system also make this protocol convenient.

Introduction

The *N*-*tert*-Butyl amide moiety is an important functionality that is present in a variety of drug molecules such as finasteride and nelfinavir.[1,2] Finasteride is known for the treatment of benign prostatic hyperplasia (BPH), whereas nelfinavir works as a protease inhibitor for the treatment of human immunodeficiency virus (HIV). Similarly, saquinavir, the first HIV protease inhibitor, is currently undergoing clinical evaluation and contains the *N*-*tert*-butyl amide moiety.[3] Moreover, Agouron Pharmaceuticals has recently synthesized some diarylbutanols[4,5] that also bear the *N*-*tert*-butyl amide moiety. These molecules are known to exhibit potent anti-HIV protease activities as well.

The well-known Schmidt reaction[6] has been used for the direct conversion of ketones and acids into their corresponding amide[7] and amine[8] analogues. However, the successful execution of the Schmidt reaction of aldehydes is limited because of the formation of other products such as formanilides along with nitriles.[9] Recently, Prabhu and coworkers established an efficient chemoselective Schmidt reaction for the synthesis of nitriles from aldehydes by using sodium azide and an excess amount of triflic acid at room temperature.[10] It has also been established that nitrile groups undergo the Ritter reaction with *tert*-butyl carbocation species to produce the corresponding *N*-*tert*-butyl amides.[11] Generally, researchers have used either methylpropene gas or *t*BuOH[12g,12h] as the source of the *tert*-butyl cation in the presence of an acid promoter[12] for this purpose. Moreover, only a few reports are available in which



tert-butyl acetate is used as the source of the *tert*-butyl carbocation for the synthesis of *N*-*tert*-butyl amides through the Ritter reaction.[13] Recently, Milne's research group developed a scalable method for the synthesis of *N*-*tert*-butyl amides directly from nitriles by employing *tert*-butyl acetate in acetic acid along with an excess amount of corrosive H_2SO_4.[14] Hence, the need for the development of a novel synthetic method for the synthesis of *N*-*tert*-butyl amides is in demand. Usually, *N*-*tert*-butyl amides are prepared directly from aldehydes through an oxidative amidation process in the presence of a *tert*-butylamine salt by using an oxidizing agent and a base.[15] However, the yields of the *N*-*tert*-butyl amide derivatives are not satisfactory, and yields of only 40–50% have been obtained in most of these methods. Nowadays, one-pot multicomponent reactions are becoming synthetically and environmentally more attractive than traditional reactions for carrying out multistep processes in a single operation because of the reduction in the reaction time and also the minimization of costs and undesired wastes.[16] In our efforts toward the de-

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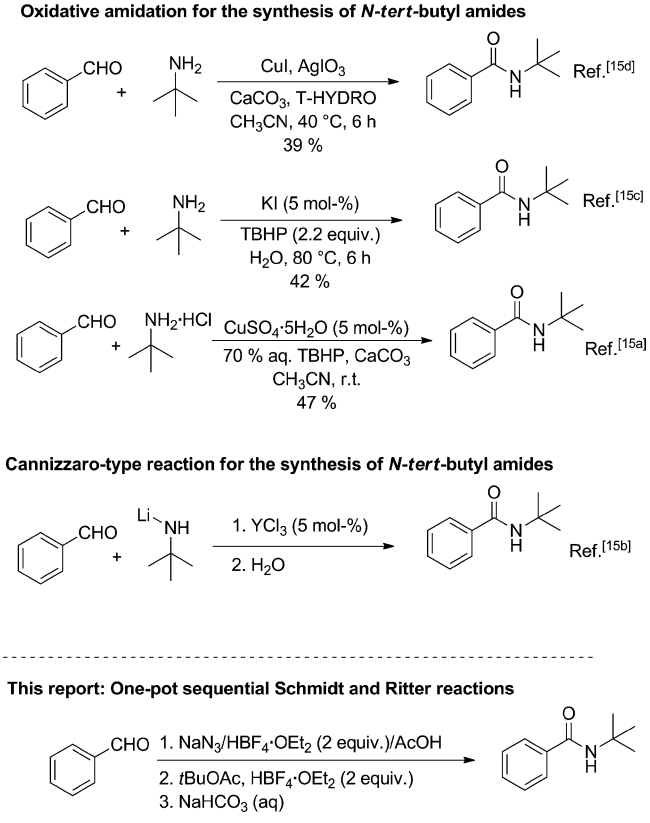
velopment of one-pot synthetic approaches,[17] we present herein a one-pot novel synthetic method for the conversion of aryl and conjugated (α,β-unsaturated) aldehydes into their corresponding *N*-*tert*-butyl amides by using NaN_3/HBF_4·OEt_2/*t*BuOAc in acetic acid through sequential Schmidt and Ritter reactions. To the best of our knowledge, this is the first example of sequential Schmidt/Ritter reactions in one pot for the synthesis of *N*-*tert*-butylbenzamides directly from aryl aldehydes (Scheme 1).

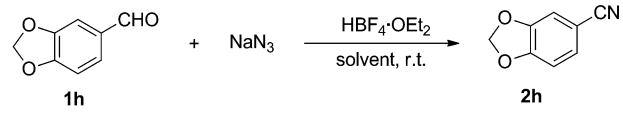


Scheme 1. Synthesis of *N*-*tert*-butylbenzamide directly from benzaldehyde. T-HYDRO = 69–70% TBHP in water. TBHP = *tert*-butyl hydroperoxide.

Results and Discussion

Initially, we attempted the Schmidt reaction of piperonal (**1h**; 1.0 mmol) with NaN_3 (1.5 mmol) by using HBF_4·OEt_2 (1 equiv.) in acetonitrile (Table 1, Entry 1). As expected, piperonitrile (**2h**) was formed in 65% yield. To enhance the yield of **2h** we used an excess amount of HBF_4·OEt_2. Upon using 2 equiv. of HBF_4·OEt_2, product **2h** was obtained in 95% yield (Table 1, Entry 3). Then, we decided to convert **2h** directly into *N*-*tert*-butyl amide derivative **3h** in one pot through sequential Schmidt and Ritter reactions. Given that acetonitrile was used as the solvent in the above Schmidt reaction, we changed the medium of the reaction, as both product and medium contained the nitrile group. Thus, the reaction was performed in solvents other than acetonitrile to avoid the competitive formation of two *N*-*tert*-butyl amide derivatives. Upon performing the Schmidt reaction of **1h** in solvents such as THF, CH_2Cl_2, DMF, and toluene, the reaction did not yield **2h** (Table 1, Entries 4–7). Similarly, the reaction in $CHCl_3$ and EtOAc did not proceed to completion and gave a low yield of **2h** (Table 1, Entries 8 and 9).

Table 1. Optimization studies for the synthesis of piperonitrile (**2h**) from piperonal (**1h**).[a]



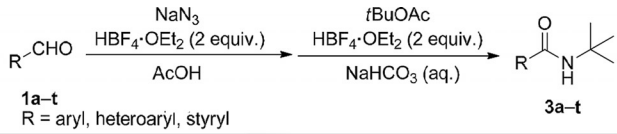
Entry	HBF_4·OEt_2 [equiv.]	Solvent	Time [h]	Yield [%][b,c]
1	1.0	CH_3CN	1	65
2	1.5	CH_3CN	1	77
3	2.0	CH_3CN	1	95
4	2.0	THF	3	n.r.
5	2.0	CH_2Cl_2	4	n.r.
6	2.0	DMF	4	n.r.
7	2.0	toluene	4	n.r.
8	2.0	$CHCl_3$	4	46
9	2.0	EtOAc	3	53
10	2.0	AcOH	1	95

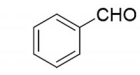
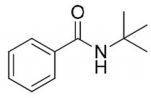
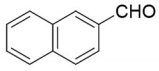
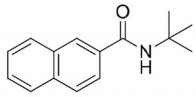
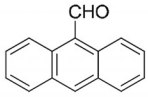
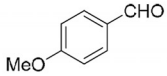
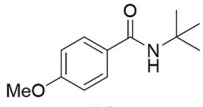
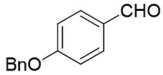
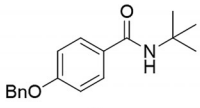
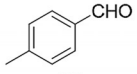
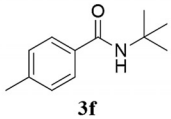
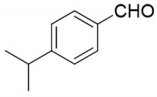
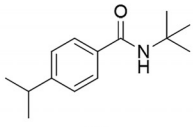
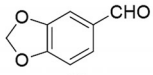
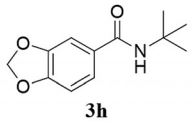
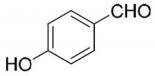
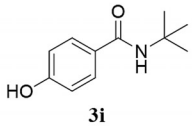
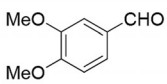
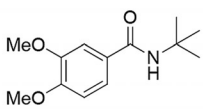
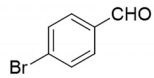
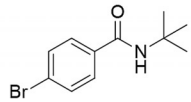
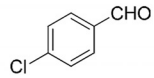
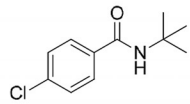
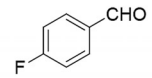
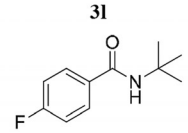
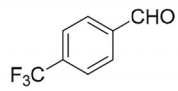
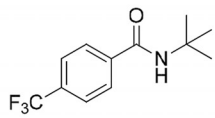
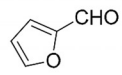
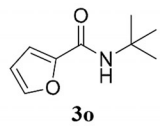
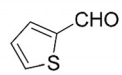
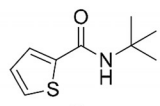
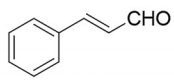
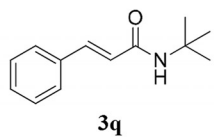
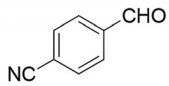
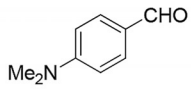
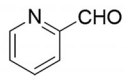
[a] Reaction conditions: Reaction performed with **1h** (1.0 mmol), NaN_3 (1.5 mmol), and HBF_4·OEt_2 (2.0 mmol) in solvent (2 mL). [b] The yield of product **2h** was obtained by ^1H NMR spectroscopy. [c] n.r. = no reaction.

Thus, we performed the Schmidt reaction in acetic acid to give **2h** in 95% yield (Table 1, Entry 10). Repeating the same reaction in acetic acid followed by the Ritter reaction with *tert*-butyl acetate (2.0 mmol) by adding further 2 equiv. of HBF_4·OEt_2 in one pot afforded *N*-*tert*-butyl amide derivative **3h** in almost quantitative yield (Table 2, Entry 8). Thus, the optimal reaction conditions involve the use of **1h** (1 mmol), NaN_3 (1.5 mmol), HBF_4·OEt_2 (4.0 mmol), and *t*BuOAc (2.0 mmol) at room temperature (Scheme 2).

To generate a clear picture of the scopes and limitations of this novel protocol, we tried to explore the protocol with various aromatic and conjugated aldehydes (Table 2, Entries 1–20). Unsubstituted aryl aldehydes such as benzaldehyde (**1a**) and 2-naphthaldehyde (**1b**) smoothly underwent the sequential Schmidt and Ritter reactions to give their corresponding *N*-*tert*-butyl amide derivatives **3a** and **3b** in 91 and 93% yield, respectively (Table 2, Entries 1 and 2). In contrast to the above unsubstituted aryl aldehydes, the Schmidt and Ritter sequence of reactions of sterically hindered 9-anthracenecarbaldehyde (**1c**) was not successful; an unidentified mixture of compounds was obtained instead of the corresponding *N*-*tert*-butyl amide **3c** (Table 2, Entry 3). It was already confirmed from the optimized reaction conditions with **1h** that this protocol was very much effective with aryl aldehydes bearing electron-donating substituents. Actually, *p*-anisaldehyde (**1d**), *p*-(benzyloxy)benzaldehyde (**1e**), *p*-tolualdehyde (**1f**), *p*-isopropylbenzaldehyde (**1g**), and 3,4-dimethoxybenzaldehyde (**1j**) also underwent the reaction to give **3d**, **3e**, **3f**, **3g**, and **3j** in almost quantitative

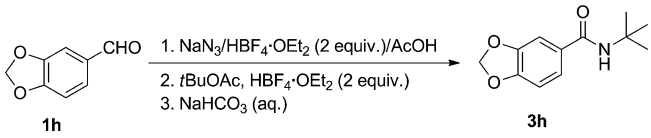
Table 2. Scope of the sequential Schmidt and Ritter reactions in one pot.



Entry	Substrate	Product	Time [h]	Yield [%][a]
1	 **1a**	 **3a**	4.0	91
2	 **1b**	 **3b**	3.0	93
3	 **1c**	mixture of products	6.0	–
4	 **1d**	 **3d**	3.0	95
5	 **1e**	 **3e**	3.0	92
6	 **1f**	 **3f**	3.0	93
7	 **1g**	 **3g**	3.0	92
8	 **1h**	 **3h**	2.5	94
9	 **1i**	 **3i**	3.0	85
10	 **1j**	 **3j**	3.0	89
11	 **1k**	 **3k**	4.0	84
12	 **1l**	 **3l**	4.0	83
13	 **1m**	 **3m**	4.0	80
14	 **1n**	 **3n**	5.0	79
15	 **1o**	 **3o**	4.0	78
16	 **1p**	 **3p**	4.0	80
17	 **1q**	 **3q**	4.5	89
18	 **1r**	mixture of products	5.0	–
19	 **1s**	mixture of products	5.0	–
20	 **1t**	n.r.	12.0	–

[a] Yield of isolated product. [b] n.r. = no reaction.

yields (Table 2, Entries 4–7 and 10). Similarly, an aryl aldehyde with a free hydroxy substituent [*p*-hydroxybenzaldehyde (**1i**)] also afforded its respective *N*-*tert*-butyl amide derivative **3i** in very good yield (Table 2, Entry 9). Aryl aldehydes with electron-withdrawing substituents also underwent the Schmidt and Ritter reactions, but their *N*-*tert*-butyl amide derivatives were obtained in slightly lower yields relative to those offered by substrates with electron-



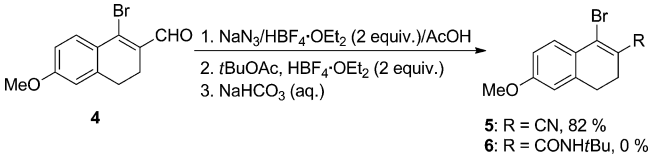
Scheme 2. One-pot sequential Schmidt and Ritter reactions of piperonal.

donating substituents (Table 2, Entries 11–14; used 3 equiv. of $HBF_4{\cdot}OEt_2$ in each step of the sequence).

Interestingly, the reaction of heteroaromatic aldehydes, that is, 2-furfuraldehye (**1o**) and 2-thiophenecarbaldehyde (**1p**) also afforded their corresponding *N*-*tert*-butyl amide derivatives **3o** and **3p**, respectively, in very good yields (Table 2, Entries 15 and 16). This methodology was equally effective with conjugated (α,β-unsaturated) aldehydes and worked well with (*E*)-cinnamaldehyde (**1q**) to afford *N*-*tert*-butyl amide derivative **3q** in excellent yield (Table 2, entry 17).

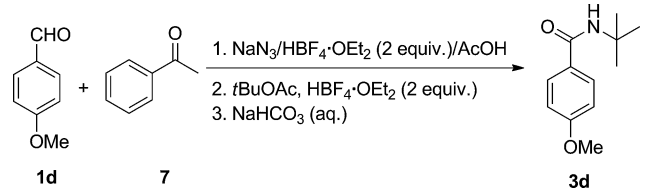
Reactions with *p*-cyanobenzaldehyde (**1r**) and 4-(dimethylamino)benzaldehyde (**1s**) did not yield the desired *N*-*tert*-butylbenzamides **3r** and **3s**; instead, we obtained an unidentified mixture of products in each case (Table 2, Entries 18 and 19). Similarly, pyridine-2-carbaldehyde (**1t**) did not undergo the reaction to afford **3t** after a reaction time of 12 h (Table 2, Entry 20).

Furthermore, we also performed the reaction with β-bromo-α,β-unsaturated aldehyde **4** to give **6**, but the reaction produced the corresponding β-bromo-α,β-unsaturated nitrile **5** as the Schmidt product in 82% yield (Scheme 3).



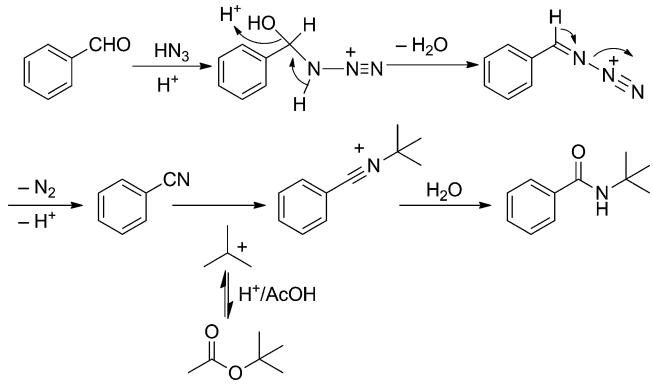
Scheme 3. Sequential Schmidt and Ritter reactions with β-bromo-α,β-unsaturated aldehyde **4**.

Finally, we also explored the tolerance of other functional groups such as ketones under the reaction conditions. Thus, treatment of an equimolar mixture of *p*-anisaldehyde (**1d**) and acetophenone (**7**) with $NaN_3/HBF_4{\cdot}OEt_2/t$BuOAc in acetic acid delivered *N*-*tert*-butyl amide **3d** as the sole product. Acetophenone (**7**) remained intact in the reaction and was recovered in almost quantitative yield (Scheme 4).



Scheme 4. Chemoselective synthesis of *N*-*tert*-butyl amide.

The mechanism for this sequential reaction can be explained by the already established mechanisms of each step, that is, the Schmidt[10] and Ritter[14] reactions, involved in this novel method (Scheme 5).



Scheme 5. Proposed mechanism for the sequential Schmidt and Ritter reactions.[10,14]

Conclusions

A novel one-pot sequence involving Schmidt and Ritter reactions was developed for the first time for the synthesis of *N*-*tert*-butyl amide derivatives in very good to excellent yields directly from aldehydes by using $NaN_3/HBF_4{\cdot}OEt_2/t$BuOAc in acetic acid at ambient temperature. Different unsubstituted and substituted aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents underwent the sequence. This methodology was also found to be equally effective with conjugated (α,β-unsaturated) aldehydes. The main advantage of this methodology is that it does not require column chromatography for purification of the products. This novel protocol for sequential Schmidt and Ritter reactions is a new entry in the area of synthetic organic chemistry for the synthesis of *N*-*tert*-butyl amide derivatives directly from aldehydes in a one-pot operation.

Experimental Section

General Methods: Melting points were measured with a Büchi B-540 melting point apparatus. IR spectra were recorded with a Shimadzu FTIR-8400 spectrometer. NMR spectra were recorded with Bruker DPX 300 MHz and AV500 Avance-III 500 MHz FT-NMR spectrometers by using tetramethylsilane as an internal standard. All commercially available regents were used without further purification. All experiments were monitored by thin-layer chromatography by using aluminum precoated silica gel TLC plates (Merck). After elution, the plates were visualized under UV illumination at 254 nm for UV-active materials. Further visualization was achieved by staining with anisaldehyde charring solution.

General Experimental Procedure for the Schmidt–Ritter Reaction: $HBF_4{\cdot}OEt_2$ (2 mmol, 2 equiv.) was added to a solution of aryl aldehyde (1 mmol, 1 equiv.) and NaN_3 (1.5 mmol, 1.5 equiv.) in acetic acid (2 mL), and the mixture was stirred for 1 h. *tert*-Butyl acetate (2.0 mmol, 2.0 equiv.) was added, followed by $HBF_4{\cdot}OEt_2$ (2 mmol, 2 equiv.). The mixture was stirred for further 2–4 h. Upon completion of the reaction (TLC), a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The solid product that precipitated from the mixture was filtered and washed thoroughly with distilled water (50 mL). The solid was dried under vacuum to give the pure product. Further purification was not necessary in most cases. Compounds **3g**, **3k**, **3m**, and **3n** were additionally purified by

recrystallization from hexane. Compounds **3a**, **3d**, **3f**, **3k**, **3n**, **3p**, and **3q** are known in the literature;[14,15] their structures were confirmed by comparison of their analytical data with the reported data. Full characteristic data of all new compounds are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Spectral data and copies of the ^{1}H NMR and ^{13}C NMR spectra for all final products.

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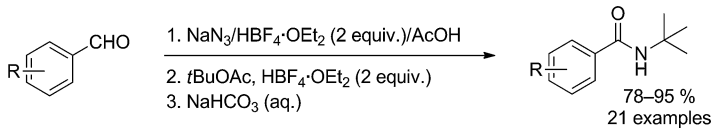

A mixture of $NaN_3/HBF_4{\cdot}OEt_2$ in AcOH reacts efficiently with aromatic and conjugated (α,β-unsaturated) aldehydes to produce nitrile derivatives, which in situ undergo a Ritter reaction with *tert*-butyl acetate to afford the corresponding *N*-*tert*-butyl amides. The method needs no column chromatography purification, has a wide substrate scope, and uses readily available reagents.

Sequential Reactions

N. Hazarika, G. Baishya* 1–6

One-Pot Sequential Schmidt and Ritter Reactions for the Synthesis of *N*-*tert*-Butyl Amides

Keywords: Amides / Aldehydes / Schmidt reaction / Ritter reaction

