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An Efficient and Scalable Ritter Reaction for the Synthesis of *tert*-Butyl Amides

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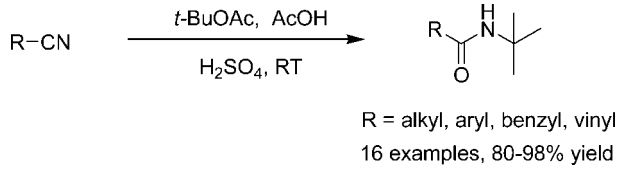
Received November 5, 2008



A scalable procedure for the conversion of nitriles to *N*-*tert*-butyl amides via the Ritter reaction was optimized employing *tert*-butyl acetate and acetic acid. The reaction has a broad scope for aromatic, alkyl, and α,β-unsaturated nitriles.

The Ritter reaction to prepare *N*-*tert*-butyl amides involves the treatment of a nitrile with a *tert*-butyl cation source.[1,2] In general, either isobutylene gas or *tert*-butanol is employed as the *tert*-butyl cation source, which is typically generated in the presence of acid.[3] Although widely used in organic synthesis, the most commonly used reaction conditions have some inherent problems that limit their use on larger scale. For example, isobutylene is a class 4 (highly flammable) gas and there have been reports of exothermic events[1d] when used in this reaction. A cationic polymerization of isobutylene is a likely cause for these exothermic events. On the other hand, the use of *tert*-butanol can be complicated by the melting point (26 °C) leading to a semisolid at room temperature. An attractive alternative is *tert*-butyl acetate due to its ease of handling (bp 97−98 °C), availability as a common solvent, and low cost. However, there are only limited examples of Ritter reactions in which *tert*-butyl acetate is employed to generate the *tert*-butyl cation.[4] This paper describes the optimization and application of an efficient procedure for the Ritter reaction employing *tert*-butyl acetate.

During a recent research program we required a convenient and scalable conversion of an aromatic nitrile to an *N*-*tert*-butyl amide. One previous report employs *tert*-butyl acetate as both the solvent and reagent for this transformation.[4b] The procedure involves dissolving the substrate in *tert*-butyl acetate, adding sulfuric acid at rt, and warming to 42 °C. The author warns of loss of isobutylene gas and recommends the use of a −15 °C condenser. In our hands this transformation provided a clean and fast reaction to furnish our desired amide; however, we observed a rapid and uncontrolled gas evolution. Due to this fast decomposition of the reaction solvent in the presence of a strong acid we deemed this procedure nonscalable.

Focusing on the use of *tert*-butyl acetate as the reagent, we evaluated a wide variety of acids and cosolvents for this reaction.[5] The use of sulfuric acid resulted in full conversion and good assay yields (>80%) in chlorobenzene, isopropyl acetate, and acetic acid. We chose to avoid the use of halogenated solvents; therefore, isopropyl acetate and acetic acid were evaluated further. Slow addition of sulfuric acid (2 equiv) in acetic acid to a mixture of the substrate, *tert*-butyl acetate (7.5 equiv) in acetic acid at 30 °C gave the cleanest reaction profile for our candidate molecule. These conditions were employed in our scale-up facility on multikilo scale to prepare a clinical candidate in high yield.[6] Upon application of these conditions to a simpler aromatic nitrile (4-methoxybenzonitrile) we were able to further lower the reagent stoichiometry (1.8 equiv of sulfuric acid and 2.0 equiv of *tert*-butyl acetate) as well as the temperature (rt) of the reaction.

We believe that the advantage of this reagent combination is the equilibrium that exists between *tert*-butyl acetate and isobutylene in acetic acid.[7] In theory the reaction should be inherently safe, since the generated carbocation either reacts along the desired reaction pathway with the nitrile or is scavenged by acetic acid resulting in the regeneration of *tert*-butyl acetate.[8] Therefore, there exists a controlled and slow release of isobutylene during the reaction (Scheme 1).[9]

We were subsequently able to confirm the superiority of *tert*-butyl acetate in comparison to alternative *tert*-butyl cation precursors when used in acetic acid. Reaction of 4-methoxybenzonitrile was compared by using *tert*-butyl acetate, *tert*-

(1) Early examples of the Ritter reaction: (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048. (b) Benson, F. R.; Ritter, J. J. *J. Am. Chem. Soc.* **1949**, *71*, 4128–4129. (c) Plaut, H.; Ritter, J. J. *J. Am. Chem. Soc.* **1951**, *73*, 4076–4077. (d) Ritter, J. J.; Yonkers, N. Y. U.S. Patent 2,573,673, 1951.

(2) For a review see: Krimen, L. I.; Cota, D. L. *Org. React.* **1969**, *17*, 213–325.

(3) Ritter reactions employing different acids: (a) Sanz, R.; Martinez, A.; Guilarte, V.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Eur. J. Org. Chem.* **2007**, 4642–4645. (b) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 2661–2664. (c) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 8645–8657. (d) Firouzabadi, H.; Iranpoor, N.; Khoshnood, A. *Catal. Commun.* **2008**, *9*, 529–531. (e) Kartashov, V. R.; Malkova, K. V.; Arkhipova, A. V.; Sokolova, T. N. *Russ. J. Org. Chem.* **2006**, *42*, 966–968. (f) Callens, E.; Burton, A. J.; Barrett, A. G. M. *Tetrahedron Lett.* **2006**, *47*, 8699–8701. (g) Garcia Martinez, A.; Martinez Alvarez, R.; Teso Vilar, E.; Garcia Fraile, A.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581–582. (h) Tamaddon, F.; Khoobi, M.; Keshavarz, E. *Tetrahedron Lett.* **2007**, *48*, 3643–3646. (i) Gullickson, G. C.; Lewis, D. E. *Synthesis* **2003**, 681–684.

(4) *tert*-Butyl acetate as *tert*-butyl cation source: (a) Fernholz, H.; Schmidt, H. J. *Angew. Chem., Int. Ed.* **1969**, *8*, 521. (b) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453–1455.

(5) Acids: methanesulfonic acid, sulfamic acid, phosphoric acid, sodium bisulfate, trifluoroacetic acid, ion exchange resins, boron trifluoride−acetic acid complex, sulfuric acid, triflic acid. Solvents: toluene, *N*-methylpyrrolidone, 2-methyltetrahydrofuran, 1,2-dimethoxyethane, cyclopentyl methyl ether, methyl isobutyl ketone, chlorobenzene, isopropyl acetate, acetic acid.

(6) A hazard evaluation of this process, including calorimetry experiments, confirmed its suitability for scale-up. Vent Size Testing revealed that at 80 °C and above, a progressive pressure buildup of isobutylene occurs. This provides a 50 °C safety window between reaction temperature and gas evolution.

(7) Equilibrium between *tert*-butyl acetate and isobutylene in sulfuric acid and acetic acid: Glikmans, G.; Torck, B.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr* **1966**, 1383–1388.

(8) The preparation of *t*-butyl acetate from acetic acid and isobutylene: Johnson, W. S.; McCloskey, A. L.; Dunnigan, D. A. *J. Am. Chem. Soc.* **1950**, *72*, 514–517.

10.1021/jo8024797 CCC: $40.75
Published on Web 02/06/2009

SCHEME 1

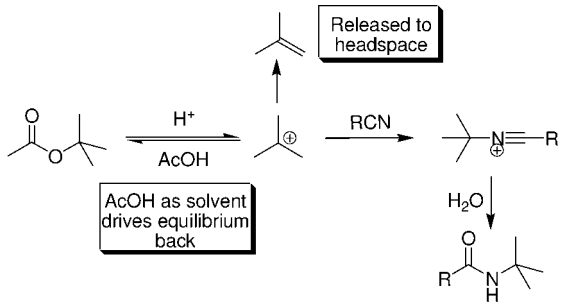
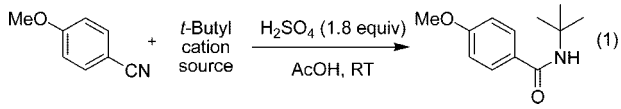


TABLE 1. *tert*-Butyl Cation Source



	tert-butyl cation (2 equiv)	time (h)	conversion HPLC assay (%)
1	*t*-BuOAc	2	98
2	*t*-BuOH	3	92
3	MTBE	19	79

butanol, and MTBE,[10] as shown in Table 1. The fastest and cleanest reaction was observed with *tert*-butyl acetate.

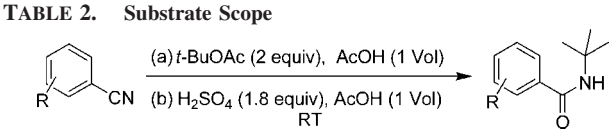
The optimized conditions have a broad substrate scope and provide a practical method for the synthesis of *tert*-butyl amides. The scope was investigated by examining a variety of substrates. In most cases, using the standard conditions, the reaction proceeded smoothly in a few hours. The reactions of aromatic nitriles bearing both electron-donating and electron-withdrawing substituents were efficient and afforded the desired product in excellent isolated yields (80−98%). The conversion of slower reacting substrates can be increased by an additional charge of *tert*-butyl acetate and H_2SO_4. For example, when 4-(2-bromophenoxy)-3-chlorobenzonitrile was employed in the reaction using our optimized procedure (Table 2, entry 6) after 17 h at rt, 90% conversion was achieved. An additional charge of sulfuric acid (0.5 equiv) and *tert*-butyl acetate (0.5 equiv) gave full conversion. To our delight, the reaction conditions are compatible with some acid-sensitive functional groups (Table 2, entries 9−11). In addition, the heterocycle thiophene-2-carbonitrile was efficiently converted to *N*-*tert*-butylthiophene-2-carboxamide (Table 2, entry 14). Also noteworthy is the synthesis of *N*-*tert*-butyl acrylamide from acrylonitrile in 85% yield.

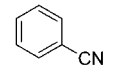
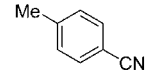
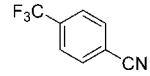
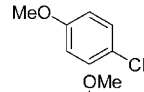
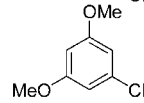
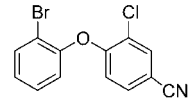
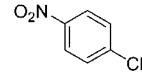
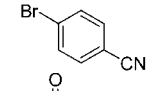
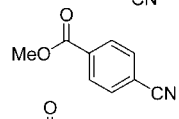
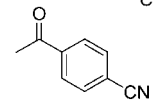
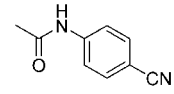
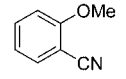
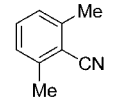
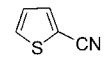
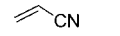
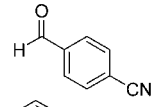
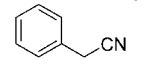
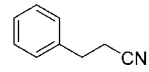
Unfortunately, when 4-aminobenzonitrile was subjected to the reaction conditions, only 20% conversion of the starting material was observed. However, the aniline may be protected as an acetamide and treated under the reaction conditions to provide a high yield of product as shown in Table 2, entry 11. It is worth noting that the BOC protecting group was not compatible with this procedure. In addition, sterically encumbered ortho-substituted derivatives suffered lower conversions and did not achieve full conversion under standard reaction conditions, even when additional acid and *tert*-butyl acetate were

(9) A comparison of the Ritter reaction employing 4-methoxybenzonitrile, *tert*-butyl acetate (5 equiv), and sulfuric acid (1 equiv) in the presence and absence of acetic acid was conducted. *tert*-Butyl acetate levels were monitored by HPLC (212 nm). When no acetic acid was present, 0 equiv of *tert*-butyl acetate was detected after 3 h. When 2 vol of acetic acid was employed as solvent, 0.8 to 1.5 equiv of *tert*-butylacetate was detected after 3 h (depending on the rate of addition of the sulfuric acid).

(10) In addition, MTBE has been used as the *tert*-butyl cation source. Use of MTBE as *tert*-butyl cation: Bonse, G.; Blank, H. U. DE 3002203, 1981.

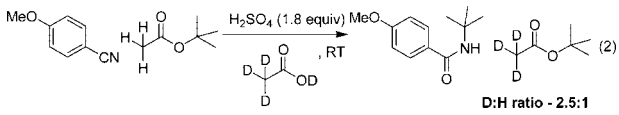
TABLE 2. Substrate Scope



Entry	Substrate	Time	Yield[a]
1		2	90%
2		3	91%
3		2	96%
4		2	92%
5		3	89%
6		20	85%[b]
7		2	82%
8		1	85%[c]
9		2	94%
10		2	82%
11		5	98%
12		17	80%[c,d]
13			no conversion
14		1	93%
15		2	85%
16			multiple products
17		1	94%
18		1	88%

[a] Isolated product. [b] Charged additional sulfuric acid (0.5 equiv) and *tert*-butyl acetate (0.5 equiv) after 17 h. [c] The reaction required 2.5 equiv of *tert*-butyl acetate and 2 equiv of sulfuric acid. [d] Corrected for purity by ^{1}H NMR.

SCHEME 2. Deuterium Incorporation in the *tert*-Butyl Acetate



employed. While 2-methoxybenzonitrile provided amide product in 80%[11] (Table 2, entry 12), the 2,6-dimethyl derivative did not react.

To investigate the equilibrium of acetic acid and *tert*-butyl acetate, a reaction was performed employing d_4-acetic acid as the solvent. Upon completion of the reaction, the residual *tert*-butyl acetate content of the reaction mixture was analyzed by GCMS. Deuterium incorporation in the *tert*-butyl acetate of 2.5:1 (D:H) was observed, confirming the theory that the acetic acid traps the excess *tert*-butyl cation and reduces the loss of the active species (Scheme 2).

In conclusion, a new, safe, scalable, and robust method to perform the Ritter reaction has been developed. We have shown that the use of *tert*-butyl acetate has advantages over alternative *tert*-butyl cation sources. In combination with acetic acid, an internal buffer for isobutylene gas exists, which eliminates the possibility of an uncontrolled gas evolution. The method has broad scope for aromatic, alkyl, and α,β-unsaturated nitriles.

Experimental Section

General Procedure. To a mixture of nitrile (10 mmol, 1 equiv), acetic acid (1 mL/g), and *tert*-butyl acetate (20 mmol, 2 equiv) was added a solution of sulfuric acid (18 mmol, 1.8 equiv) in acetic acid (1 mL/g) over 30 min at rt. The temperature was maintained below 30 °C during the addition. The reaction mixture was aged at rt for 2 h, then assayed by HPLC for completion. Upon complete conversion of the nitrile, the reaction mixture was treated with sodium acetate solution (2 M, aq, 36 mmol). The solid product precipitated from the reaction and was filtered and washed with water (2 × 4 mL/g). The product was dried under high vacuum at 40 °C overnight.

***N*-*tert*-Butyl-4-methoxybenzamide.** To a mixture of 4-methoxybenzonitrile (20.0 g, 150.2 mmol), acetic acid (20.0 mL), and *tert*-butyl acetate (40.5 mL, 300.5 mmol) was added a solution of concentrated sulfuric acid (13.6 mL, 270.4 mmol) in acetic acid (20.0 mL) over 30 min at rt. The temperature was maintained below 30 °C during the addition. The reaction mixture was stirred at rt for 2 h, at which HPLC revealed complete consumption of the starting material. The reaction mixture was quenched with aqueous sodium acetate solution (2 M, 150.0 mL), filtered, and washed with water (2 × 60.0 mL). The product was dried under vacuum at 40 °C to yield a white solid, 28.5 g (92%). No further purification was necessary. Mp 116.60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.80 Hz, 2 H), 6.88 (d, J = 8.80 Hz, 2 H), 5.94 (br s, 1 H), 3.82 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 161.9, 128.5, 128.3, 113.6, 55.4, 51.5, 29.0.

Acknowledgment. The authors wish to thank Burton Lee and Jessica Tan for their help in GCMS analysis. Kevin Turney is acknowledged for HRMS experiments. Joe Tomaskevitch is acknowledged for contributing valuable discussions and experiments regarding the hazard evaluation of this procedure.

Supporting Information Available: Experimental procedures, compound characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8024797

(11) In the case of 2-methoxybenzonitrile the reaction could not be driven to completion by an additional charge of sulfuric acid and *tert*-butyl acetate.