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An efficient method for the conversion of aromatic and aliphatic nitriles to the corresponding *N*-*tert*-butyl amides: a modified Ritter reaction

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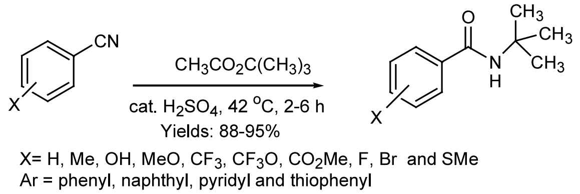
Abstract—Aromatic and aliphatic nitriles react with *tert*-butyl acetate in the presence of a catalytic amount of sulfuric acid to give the corresponding *N*-*tert*-butyl amides in excellent yields. © 2003 Published by Elsevier Science Ltd.

The conversion of a nitrile to the corresponding *N*-*tert* butyl amide is a very useful transformation in organic synthesis; the product *N*-*tert*-butyl amides are pharmaceutically important[1] and also serve as precursors to the corresponding amines.

The amidation of alcohols with nitriles in the presence of concentrated sulfuric acid is known as the Ritter reaction.[2] This method works well only in the case of tertiary alcohols under strongly acidic conditions, thus limiting its applicability to compounds containing functional groups stable to acid. Some alternative methodologies available are the use of chromium tricarbonyl complexes of benzylic alcohols with nitriles in sulfuric acid,[3] reaction of chlorophenylmethylium hexachloroantimonate with alcohols in nitrile solvents,[4] reaction of alcohols with nitriles in the presence of transition metal compounds,[5] reaction of triflouromethanesulfonic anhydride with alcohols in the presence of nitriles,[6] and reaction of benzyl alcohols with nitriles in the presence of boron trifluoride therate.[7] Recently, amidation of primary and secondary benzylic alcohols with different nitriles has been reported using Fe^{+3}-Montmorillonite K10.[8] Many of these methods suffer from at least one of the following issues: limited availability of reagent, hygroscopicity, low yield, tedious product isolation, longer reaction time and competing side reactions. To our knowledge there is no method reported in the literature for the synthesis of *N*-*tert*-butyl amides from nitriles using esters. Our approach was to generate the *tert*-butyl cation from a non-alcoholic source.[9] To this end, *tert*-butyl acetate in the presence of a catalytic amount of concentrated sulfuric acid as the proton source[10] was found to be the best source of *tert*-butyl cation. A wide range of aromatic nitriles containing both electron donating and withdrawing substituents on the aromatic ring as well as aliphatic nitriles were converted to their corresponding amides using these new reaction conditions (Table 1).



This method is efficient and practical, giving the *tert*-butyl amides in high yields (88–95%).

It was found that the rate of conversion of the nitriles to the corresponding amides is highly dependent on a number of factors: source of the *tert*-butyl cation, solvent, acid, and acid–solvent combination. For the initial study, excess di-*tert*-butyl dicarbonate[$(Boc)_2O$] and TFA (5.0 equiv.) were used as the *tert*-butyl cation source. Under these conditions, 4-methoxybenzonitrile (**1a**) produced the corresponding amide **1b** in 80% yield after reaction at room temperature for 5 days. After screening various reaction conditions to increase the rate of reaction, it was found that *tert*-butyl acetate and

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Keywords: modified Ritter reaction; nitriles; *tert*-butyl acetate; *N*-*tert*-butyl amides.

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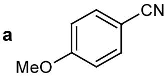
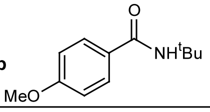
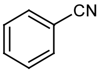
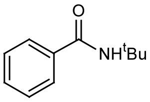
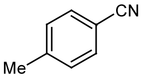
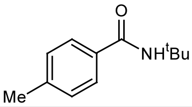
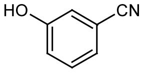
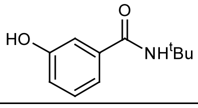
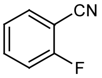
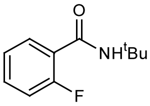
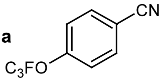
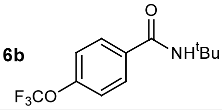
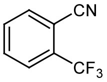
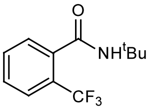
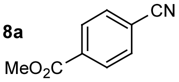
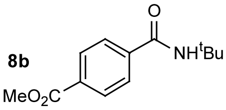
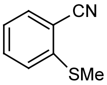
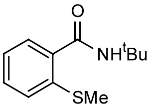
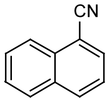
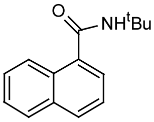
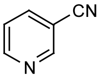
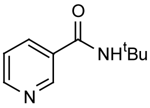
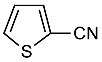
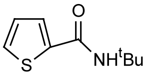
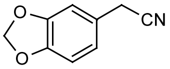
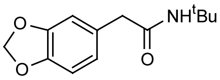
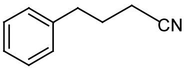
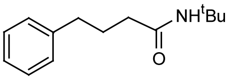
Table 1.

Table

Entry	Substrate[a]	Product	Time (h)	Yield (%)[b]
1	**1a** 	**1b** 	2	95
2	**2a** 	**2b** 	2.5	91
3	**3a** 	**3b** 	2	93
4	**4a** 	**4b** 	1.5	93
5	**5a** 	**5b** 	2.5	90
6	**6a** 	**6b** 	2	95
7	**7a** 	**7b** 	5	88
8	**8a** 	**8b** 	3	92
9	**9a** 	**9b** 	6	90
10	**10a** 	**10b** 	4	86
11	**11a** 	**11b** 	5	95**
12	**12a** 	**12b** 	1	92
13	**13a** 	**13b** 	2	94
14	**14a** 	**14b** 	2	93

[a] All entries were carried on 10 mmol scale using H_2SO_4 (0.5mL, 1.8 mmols) and *tert*-butyl acetate (7.5mL) at ~42 °C;

[b] All the products **1b** to **14b** were crystallized from the reaction mixture by the addition of water.

** 0.7 mL H_2SO_4 is used.

sulfuric acid were very efficient for this transformation. 4-Methoxybenzonitrile (**1a**, entry 1; 10 mmol), was treated with 0.25 mL (4.7 mmol) of sulfuric acid in (7.5 mL) *tert*-butyl acetate at 42°C for 2 h to obtain the corresponding amide **1b** in 95% yield. However the conversion of benzonitrile (**2a**, entry 2) under similar reaction conditions took more than 12 h to complete. The reaction rate was decreased significantly when a catalytic amount of water was added. Alternatively, increasing the sulfuric acid concentration (from 0.25 to 0.5 mL) increased the reaction rate considerably and the reaction was completed in <3 h. Using these optimized reaction conditions, *p*-tolylnitrile (**3a**, entry 3), 3-hydroxybenzonitrile (**4a**, entry 4), and 2-(methylthio)benzonitrile (**9a**, entry 9) were converted to their corresponding amides in high yield. Electron deficient substrates like 2-fluorobenzonitrile (**5a**, entry 5), 4-(trifluoromethoxy)benzonitrile (**6a**, entry 6), 2-(trifluoromethyl)benzonitrile (**7a**, entry 7), and 4-carbomethoxybenzonitrile (**8a**, entry 8) underwent smooth conversion to afford the amides in excellent yields. Other examples, such as the bicyclic 1-cyanonapthalene (**10a**, entry 10) and the heteroaromatic 3-cyanopyridine (**11a**, entry 11) and 2-cyanothiophene (**12a**, entry 12) also underwent smooth conversion. The method also worked effectively for a benzylic nitrile (entry 13) and an aliphatic nitrile (entry 14).

A mechanistic study of this transformation is under investigation and will be reported in due course.

In conclusion, a simple, efficient and practical method for the conversion of aromatic and aliphatic nitriles to the corresponding *N*-*tert*-butyl amides has been developed.

General procedure for the conversion of nitriles to *N*-*tert*-butyl amides

To a stirred solution of 4-methoxy benzonitrile (13.3 g, 100 mmol) in *tert*-butyl acetate (75.0 mL) in a 250 mL three-necked round bottom flask equipped with condenser,[11] temperature probe and an additional funnel was added conc. sulfuric acid (5.0 mL) slowly at room temperature in about 5 min. The resulting solution was stirred at ~42°C for ~2.0 h to complete the reaction. The reaction mixture was poured into cold aqueous 20% $KHCO_3$ solution (250 mL) to neutralize the acid and precipitate the product. The product was filtered,[12] washed with cold water and dried under vacuum to give the amide **1b** (19.5 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69(d, $J=8.8$ Hz, 2H, aromatic), 6.90 (d, $J=8.8$ Hz, 2H, aromatic), 3.84 (s, 3H, OMe), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 161.9, 128.5, 128.2, 113.6, 55.4, 51.5, 28.9; IR (KBr) 3400–3300(br), 1630 cm^{-1}; HR MS calcd for $C_{12}H_{17}NO_2$: 207.1259. Found: 207.1258.[13]

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9. Reaction of ethers with nitriles see; Eugene E. M. US Patent Serial No. 72, 773.
10. Work is in progress to demonstrate the conversion of carboxylic acids to the *tert*-butyl esters using *tert*-butyl acetate as a *tert*-butyl source.
11. It is recommended to use a condenser with −15°C coolant (ethylene glycol and water mixture circulated through RC 6CS Lauda, Brinkmann) to prevent the loss of isobutylene.
12. All the products **1b** to **14b** were crystallized from the reaction mixture by the addition of water.
13. (a) Rubottom, G. M.; Pichardo, J. L. *Synth. Commun.* **1973**, *3*, 18; (b) Rubottom, G. M. *J. Chem. Edu.* **1974**, *51*, 616; (c) Tsai, S. C.; Rubottom, G. M. *Org. Mass Spectrometry* **1974**, *9*, 601.