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# Synthesis of amides using the Ritter reaction with bismuth triflate catalysis

Emmanuel Callens,[a] Andrew J. Burton[b] and Anthony G. M. Barrett[a,*]

[a]*Department of Chemistry, Imperial College London, Exhibition Road, London SW7 2AZ, United Kingdom*
[b]*Chemical Development, GlaxoSmithKline, Medicines Research Centre, Stevenage SG1 2NY, United Kingdom*

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**Abstract**—*N-tert*-Alkyl and aryl amides were obtained by a Ritter reaction of various nitriles with *tertiary* alcohols in the presence of a catalytic amount of bismuth triflate.

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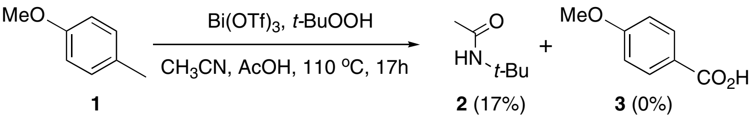
The synthesis of an amide from the reaction of a nitrile with a substituted alkene or alcohol using a stochiometric amount of sulfuric acid, the Ritter reaction, is an important transformation in organic synthesis.[1] The reaction is especially useful for the preparation of bulky amides, which may be hydrolyzed to yield hindered amines. As an alternative to sulfuric acid, the Ritter reaction may be catalyzed by metal complexes (Cr, Sb)[2–4] trifluoromethanesulfonic anhydride[5] or boron trifluoride etherate.[6] Nevertheless, the main disadvantages of these procedures are the use of toxic catalysts or an excess amount of corrosive acids. Recently, a method for the conversion of aromatic nitriles to the corresponding *N-tert*-butylamides with *tert*-butyl acetate catalyzed by sulfuric acid has been reported.[7]

During the course of our work on bismuth catalyzed benzylic oxidation reactions,[8] we examined the reaction of 4-methylanisole **1** with *tert*-butyl hydroperoxide in the presence of bismuth triflate and acetonitrile. This reaction gave *N-tert*-butylacetamide **2** (17%) instead of the expected 4-methoxybenzoic acid **3** (Scheme 1).

Since there are no previous examples of the use of metal triflates as catalysts in the Ritter reaction with the exception of trimethylsilyl triflate,[9] we sought to extend our preliminary observations to a range of nitriles and tertiary alcohols.

After screening various reaction conditions, we found that the Ritter reaction could be carried out using a tertiary alcohol and an excess of a nitrile with 5–20 mol % of a metal triflate in the presence of water. Presumably under these reaction conditions, catalysis is effected by triflic acid.[10] We subsequently investigated various metal triflates using benzonitrile and *tert*-butanol as the substrates. Table 1 summarizes the results obtained for the Ritter reaction.

The control Ritter reaction using trifluoromethanesulfonic acid (20 mol %) gave *tert*-butylbenzamide (93%). Ytterbium triflate (20 mol %) (entry 2) was ineffective. Scandium triflate (entry 3) and hafnium triflate (entry 4) gave the desired amide (57% and 67%, respectively). Catalysis by bismuth triflate[10b] (20 mol %) (entry 5) pro-



**Scheme 1.**

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[*] Corresponding author. Tel.: +44 20 75945767; fax: +44 20 75945805; e-mail addresses: agmb@imperial.ac.uk.c; agmb@ic.ac.uk

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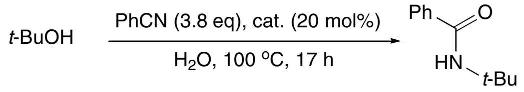
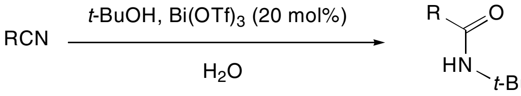
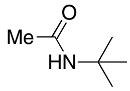
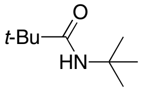
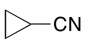
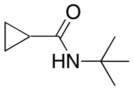
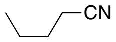
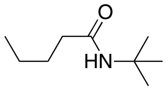
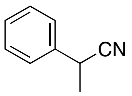
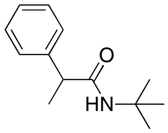
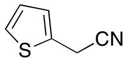
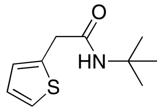
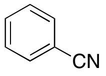
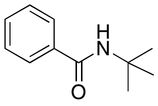
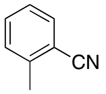
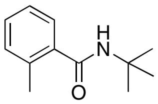
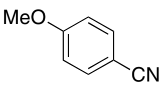
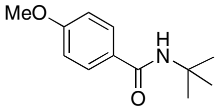
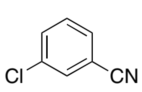
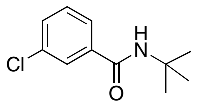
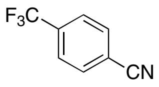
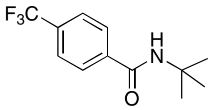
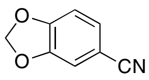
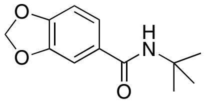
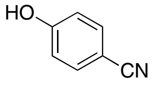
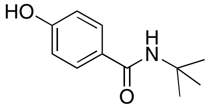
**Table 1.** Ritter reaction of *tert*-butanol with benzonitrile: study of various metal triflate catalysis



| Entry | Catalyst (mol %) | Yields of *tert*-butylbenzamide (%) |
|---|---|---|
| 1 | TfOH (20) | 93 |
| 2 | $Yb(OTf)_3$ (20) | No reaction |
| 3 | $Sc(OTf)_3$ (20) | 56 |
| 4 | $Hf(OTf)_4$ (20) | 67 |
| **5** | **$Bi(OTf)_3$ (20)** | **87** |
| 6 | $Bi(OTf)_3$ (10) | 77 |
| 7 | $Bi(OTf)_3$ (5) | 68 |

**Table 2.** Ritter reaction of aliphatic and aromatic nitriles with *tert*-butanol



| Entry | Substrate (R–CN) | *N*-*tert*-butyl-amide | Isolated yields (%) |
|---|---|---|---|
| 1 | Me–CN |  | 85 |
| 2 | *tert*-Bu–CN |  | 87 |
| 3 |  |  | 95 |
| 4 |  |  | 95 |
| 5 |  |  | 80 |
| 6 |  |  | 96 |
| 7 |  |  | 85 |
| 8 |  |  | 75 |
| 9 |  |  | 86[a] |
| 10 |  |  | 77[a] |
| 11 |  |  | 95[a] |
| 12 |  |  | 50[a] |
| 13 |  |  | 84[a] |

[a] The reaction (see typical procedure) was conducted with $PhNO_2$ (0.3 mL).

ceeded in comparable yields to triflic acid. Decreasing the amount of bismuth triflate resulted in a decrease in the yield of the product (entries 6 and 7). It is clear from Table 1 that bismuth triflate outperforms other metal triflates.

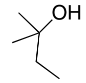
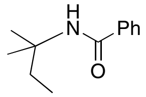
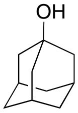
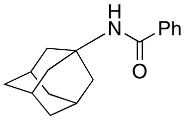
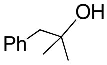
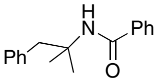
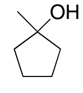
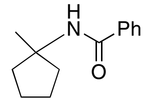
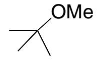
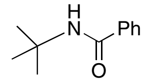
The bismuth triflate catalyzed Ritter reaction was applied to a range of nitrile derivatives with *tert*-butanol, as the tertiary alcohol (Table 2).

Under these conditions, the aliphatic nitriles acetonitrile (entry 1), the bulky pivalonitrile (entry 2) and cyclopropyl cyanide (entry 3) were converted to the corresponding amides in good yields (85–95%). Valeronitrile (entry 4), in spite of its lipophilic linear chain, afforded the corresponding amide in 95% yield. Both α-methylbenzyl cyanide (entry 5) and 2-thiophenacetonitrile (entry 6) gave the corresponding amides in good yields as well (80, 96%). Good yields were also observed with benzonitrile (entry 7) and 2-methylbenzonitrile (entry 8). These are less nucleophilic substrates than aliphatic nitriles. Because all the nitriles reported in entries 1–8 are liquids, we investigated the possibility of applying this procedure to solid nitriles by adding a suitable co-solvent. Most solvents were ineffective, however, nitrobenzene proved to be applicable. When 4-methoxybenzonitrile (entry 9) was allowed to react in the presence of nitrobenzene, it gave the desired amide in 86% yield. The use of nitrobenzene as an additive was successfully extended to aryl amides with both electron withdrawing and electron donating substituents (entries 10–13) also produced with modest to excellent conversions (50–95%).

After applying the bismuth-catalyzed Ritter reaction for the synthesis of *N*-*tert*-butyl amides, we examined variation of the tertiary alcohol using benzonitrile as the substrate. The results are summarized in Table 3.

Ritter reaction of benzonitrile with 2-methyl-butan-2-ol (entry 1), adamantanol (entry 2), 2-methyl-1-phenylpropan-2-ol (entry 3) or 1-methyl-cyclopentanol (entry 4) gave the corresponding amides in 92%, 91%, 85% and 82% yields, respectively, without any competing rearrangement reactions. Interestingly, *tert*-butyl methyl ether (entry 5) yielded the amide 92% resulting from the cleavage of the ether (92% yield). Indeed, the use of bismuth triflate to mediate the cleavage of *tert*-butyl

**Table 3.** Ritter reaction of tertiary alcohols with benzonitrile

| Entry | Substrate | Alkylbenzamide | Isolated yields (%) |
|---|---|---|---|
| 1 |  |  | 92 |
| 2 |  |  | 91 |
| 3 |  |  | 85 |
| 4 |  |  | 82 |
| 5 |  |  | 92 |

ethers has precedent.[11] This result suggests that the bismuth-catalyzed Ritter reaction should be applicable to other *tert*-butyl ethers.

### Typical procedure: synthesis of *tert*-butylbenzamide

*tert*-Butanol (77.4 µL, 0.8 mmol) was added with stirring to a solution of bismuth triflate (105 mg, 0.16 mmol) and benzonitrile (0.4 mL, 3.89 mmol) in water (0.2 mL). After 17 h at 100 °C, the mixture was cooled and poured into aqueous KOH solution (20% w:v; 5 mL) to neutralize the acid and precipitate the catalyst. The product was extracted with dichloromethane (2 × 5 mL) and the organic phase was filtered, rotary evaporated and chromatographed (cyclohexane:EtOAc 9:1 to 1:1) to afford *tert*-BuNHCOC$_6$H$_5$ (131 mg, 92% yield) as a white solid: mp 123–125 °C (CH$_2$Cl$_2$) (lit.[12] mp 123–124 °C) IR (thin film) 3438, 1663, 1580, 1514, 1365 cm$^{-1}$ $^1$H NMR $\delta_H$ (CDCl$_3$, 400 MHz) $\delta_H$ 1.45 (9H, s), 6.08 (1H, br s), 7.33–7.44 (3H, m), 7.70 (2H, m) $^{13}$C NMR $\delta_C$ (CDCl$_3$, 100 MHz) 29.3, 52.0, 127.1, 128.8, 131.4, 136.3, 167.3 MS (CI+) *m/z* 178 (M+H)$^+$; 195 (M+NH$_4$)$^+$, 355 (2M+1)$^+$ HRMS Calcd for C$_{11}$H$_{16}$NO (M+H)$^+$ 178.1232, found: (M+H)$^+$, 178.1225.

In summary, a general procedure for the conversion of nitriles into amides using a catalytic amount of bismuth triflate instead of corrosive acids has been developed.

## Acknowledgements

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