# Iodine-catalyzed one-pot synthesis of amides from nitriles via Ritter reaction

Palani Theerthagiri [a,b], Appaswami Lalitha [a,*], Pirama Nayagam Arunachalam [b]

[a] Department of Chemistry, Periyar University, Salem 636 011, India
[b] Syngene International Ltd, Biocon Park, #2 and 3, Bommasandra, Jigani Link Road, Bangalore 560 099, Karnataka, India

## ARTICLE INFO

## ABSTRACT

Ritter reactions of alcohols and *tert*-butyl acetate with various nitriles were performed using iodine as a mild and effective catalyst under heating conditions to afford the corresponding amides in good to excellent yields.

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Modification of already existing synthetic methodologies has received greater attention in recent years from both industrial and academic research communities. The construction of carbon–nitrogen bond is one of the most important fundamental processes in organic and bioorganic chemistry as peptides and proteins are formed by amide bonds. The *N-tert*-butyl amides are pharmaceutically important compounds in pharmaceutical industries[1,2] and serve as precursors to the corresponding amines. Therefore there is a great deal of interest in the synthesis of amides. Earlier, amides were prepared by the condensation of carboxylic acids with amines using various coupling agents.[3] Ritter reported efficient protocol for the synthesis of amides by the reaction of nitriles with substituted alkenes or alcohols using concentrated sulfuric acid. However, as an alternative to sulfuric acid, now other acid catalysts,[4–7] Bronsted acids,[8] Nafion,[9] Fe-montmorllonite K-10[10] are employed in the Ritter reaction. Ritter reaction using *tert*-butyl acetate instead of alcohol was also reported to be catalyzed by sulfuric acid,[11] or Bi(OTf)$_3$.[6] Ritter reaction involving benzylic alcohols or *tert*-butyl acetate with various nitriles has been reported using FeCl$_3$·6H$_2$O,[12] as a catalyst. Ritter-type amidation of alkyl boron derivatives with nitriles has been described.[13] However, most of these methods have several disadvantages such as (i) usage of corrosive acid catalysts, (ii) usage of toxic and moisture sensitive catalysts, and (iii) usage of more expensive metal triflates. Moreover the recently reported FeCl$_3$·6H$_2$O catalyzed Ritter reaction protocol was not successful to produce *N-tert*-butyl amides from *tert*-butanol. To circumvent the disadvantages, we wish to introduce molecular iodine as a mild and efficient catalyst for this transformation. Currently iodine has received considerable attention as a mild catalyst because of its non-toxic nature coupled with cheap and ready availability making iodine as a promising catalyst for Ritter reaction under mild and neutral conditions. In addition to this, no stringent dry condition is necessary in this reaction.

Recent studies indicate that iodine can be effectively used as a catalyst for acetylation,[14] protections and deprotections, oxidations, three-component synthesis of protected homoallylic amines,[15] direct oxidative conversion of alkyl halides into nitriles, synthesis of bis(indolyl) methanes,[16] alkylation of active methylene compounds,[17] synthesis of amidophenol,[18] etc., surprisingly, to the best of our knowledge there are no previous examples of iodine being used as a catalyst for the Ritter reaction.

The activation of alcohols to generate the carbocation is thought to be difficult due to the poor leaving ability of the –OH group in the absence of any catalyst. In the present study, alcohols **I–IV** and the *tert*-butyl acetate were used with a variety of aromatic/aliphatic nitriles for the synthesis of the corresponding amides.

Reaction of 1-phenylethanol (**I**) with acetonitrile was taken as a model reaction to optimize the reaction conditions (Scheme 1).
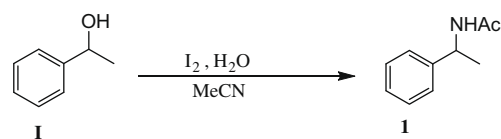


**Scheme 1.**

\* Corresponding author. Tel.: +91 427 2345271; fax: +91 427 2345124.
*E-mail address:* lalitha2531@yahoo.co.in (A. Lalitha).

**Table 1**
Iodine-catalyzed Ritter reaction of **I** with MeCN in different solvents

| Entry | Solvent[a] | Temp (°C) | Time (h) | Conversion[b] (%) | Yield[c] (%) |
|-------|-----------|-----------|----------|-------------------|--------------|
| 1 | MeNO$_2$ | 100 | 8 | 50 | — |
| 2 | MeNO$_2$ | 50 | 8 | 10 | — |
| 3 | Toluene | 110 | 4 | 100 | 85 |
| 4 | Xylene | 150 | 4 | 100 | 80 |
| 5 | THF | 80 | 6 | 30 | — |

[a] Alcohol **I** (1 mmol), nitrile (1.1 mmol), solvent (10 volume), sealed tube.
[b] Conversion of **I** monitored by LC–MS.
[c] Isolated yield.

After several trials, iodine with 2 equiv of water was found to be the best to provide the desired amide in good yield. To optimize other reaction conditions, the reaction was performed using different solvents and toluene was found to be superior to others. The reaction was also monitored to find out the influence of different concentrations of the catalyst using toluene as a solvent and 20 mol % of iodine was found to be the optimum. To find out the optimum temperature, the reaction was carried out at different temperatures and even at reflux conditions the conversion was found to be only 50% and this prompted us to study the reaction

**Table 2**
Ritter reaction of various alcohols and nitriles catalyzed by iodine
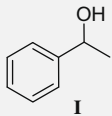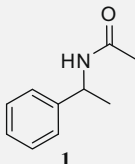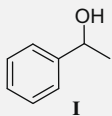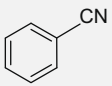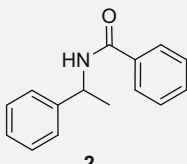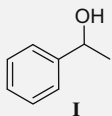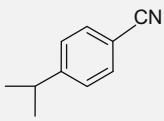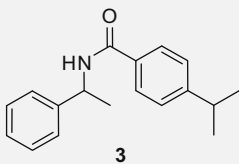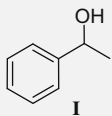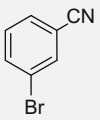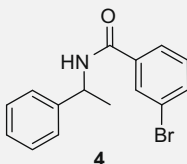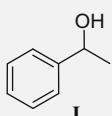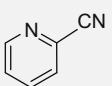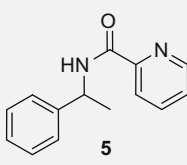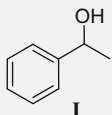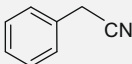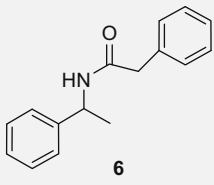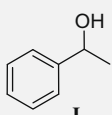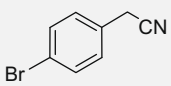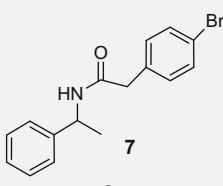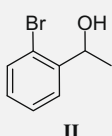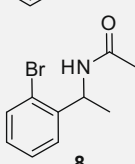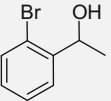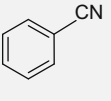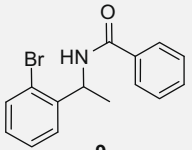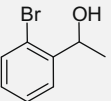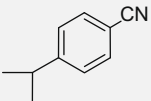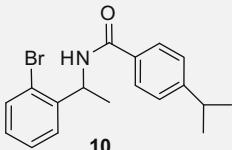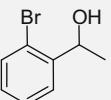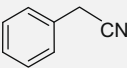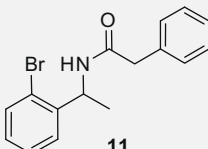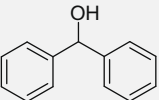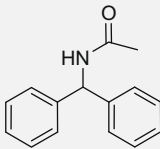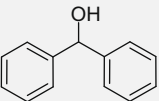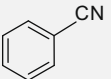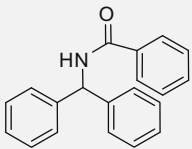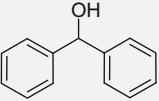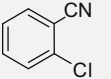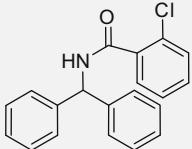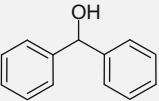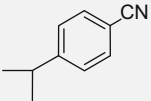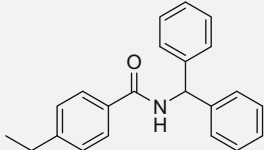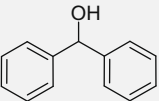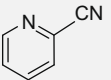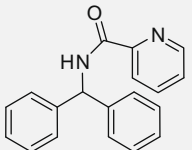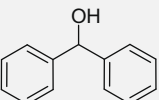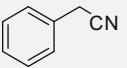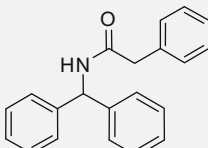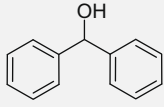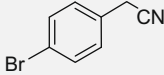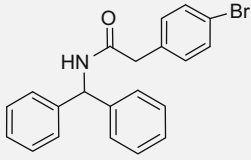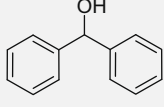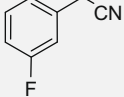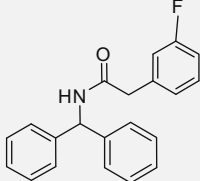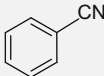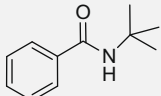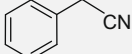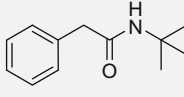
| Entry[a] | Alcohol | Nitrile | Amide | Time[b] (h) | Yield[c] (%) |
|----------|---------|---------|-------|-------------|--------------|
| 1 | I | MeCN | 1 | 4.0 | 85[12] |
| 2 | I | | 2 | 4.0 | 84[12] |
| 3 | I | | 3 | 4.0 | 60[d] |
| 4 | I | | 4 | 5.0 | 62[19] |
| 5 | I | | 5 | 5.0 | 64[20] |
| 6 | I | | 6 | 4.0 | 75[21,22] |
| 7 | I | | 7 | 3.0 | 91[d] |
| 8 | II | MeCN | 8 | 6.0 | 44[23] |

**Table 2** (*continued*)

| Entry[a] | Alcohol | Nitrile | Amide | Time[b] (h) | Yield[c] (%) |
|---|---|---|---|---|---|
| 9 | II | | 9 | 4.0 | 66[d] |
| 10 | II | | 10 | 4.0 | 88[d] |
| 11 | II | | 11 | 6.0 | 82[d] |
| 12 | III | MeCN | 12 | 5.0 | 80[12] |
| 13 | III | | 13 | 6.0 | 85[12] |
| 14 | III | | 14 | 5.0 | 60[24] |
| 15 | III | | 15 | 6.0 | 70[d] |
| 16 | III | | 16 | 6.0 | 66[24,25] |
| 17 | III | | 17 | 5.0 | 95[26] |

(*continued on next page*)

**Table 2** (*continued*)

| Entry[a] | Alcohol | Nitrile | Amide | Time[b] (h) | Yield[c] (%) |
|---|---|---|---|---|---|
| 18 | III | | 18 | 6.0 | 40[24] |
| 19 | III | | 19 | 7.0 | 76[d] |
| 20 | IV | | 20 | 8.0 | 60[11] |
| 21 | IV | | 21 | 8.0 | 63[11] |

[a] Alcohol (1 mmol), nitrile (1.1 mmol), solvent (10 volume), 110 °C, sealed tube.
[b] Reactions were monitored by LC–MS.
[c] Isolated yield.
[d] Novel compounds.
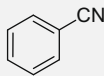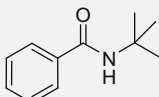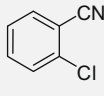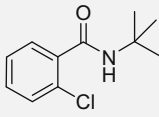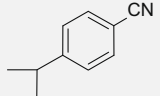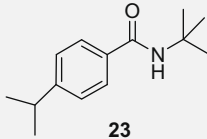
using sealed tubes. The reaction worked in a much better way at 110 °C in a sealed tube (Table 1).

The conditions described in the entry 3 of Table 1 were found to be suitable for the synthesis of various other amides in good yields, and the results are summarized in Tables 2 and 3.

The generality and scope of this protocol were evaluated for both aromatic and aliphatic alcohols, and a variety of nitriles.[30] In all these cases, the Ritter reaction proceeded and yielded the desired amides in good to excellent yields including some novel amides (entries 3, 7, 9, 10, 11, 15, and 19). When secondary benzyl

**Table 3**
Ritter reaction of various nitriles with *tert*-butyl acetate catalyzed by iodine

$$Ar\text{-}CN \xrightarrow[\substack{t\text{-BuOAc (2 equiv), H}_2\text{O (2 equiv)} \\ \text{Toluene, 110 °C}}]{I_2\ (20\ \text{mol \%})} Ar\text{-}\underset{\underset{H}{}}{\overset{O}{C}}\text{-N}\text{-}t\text{-Bu}$$

| Entry[a] | Nitrile | Amide | Time[b] (h) | Yield[c] (%) |
|---|---|---|---|---|
| 1 | | 20 | 6.0 | 65[11] |
| 2 | | 22 | 6.0 | 44[29] |
| 3 | | 23 | 5.0 | 87[d] |

**Table 3** (continued)

| Entry[a] | Nitrile | Amide | Time[b] (h) | Yield[c] (%) |
|---|---|---|---|---|
| 4 | O₂N—⟨CN⟩—CH₃ (O₂N, CN, methyl substituted benzene) | **24** (N-tert-butyl amide with O₂N and methyl) | 7.0 | 81[d] |
| 5 | MeO—⟨CN⟩—NO₂ | **25** | 6.0 | 86[d] |
| 6 | pyridine-2-CN | **26** | 6.0 | 72[27] |
| 7 | F₃C—⟨CN⟩ | **27** (CF₃) | 6.0 | 86[11] |
| 8 | MeO—⟨CN⟩ | **28** | 4.0 | 83[11] |
| 9 | F-substituted benzyl CN | **29** | 6.0 | 80[d] |
| 10 | Br—⟨CH₂CN⟩ | **30** | 5.0 | 82[28] |

[a] Nitrile (1.1 mmol), *tert*-butyl acetate (2 mmol), solvent (10 volume), 110 °C.
[b] Reactions were monitored by LC–MS.
[c] Isolated yield after column chromatography.
[d] Novel compounds.

or *tert*-butyl alcohols are used as substrates, amides are produced in good yields. On the other hand primary benzyl alcohol on treatment with phenyl cyanide under the same conditions, disappointingly, results in a very low conversion (10%).

In the mechanism proposed, we invoke the formation of ether as suggested in the Ritter reaction of alcohols catalyzed by FeCl₃·6H₂O.[12] The ether leads to the formation of carbocation which attacks the nitrile to give the amide. When the reaction was carried out in the absence of water, it has been observed that ether **B** was the major product and no amide was formed. While ether formation was observed at low temperatures (60 °C), at higher temperatures (110 °C) amide was found to be the only product (Scheme 2). In one of the experiments, ether **B** was isolated and confirmed by NMR. The plausible mechanism for the iodine-catalyzed Ritter reaction is given in Scheme 3. It is presumed that iodine catalyzes the reaction as a mild Lewis acid.[18] The molecular iodine is believed to activate the alcoholic OH to give intermediate A, which on combination with another alcohol molecule yields the ether **B**. In the presence of iodine, **B** may afford **C** which may then be converted to the carbocation **D**. The attack of the carbocation on the nitrile followed by water addition may provide the amide.
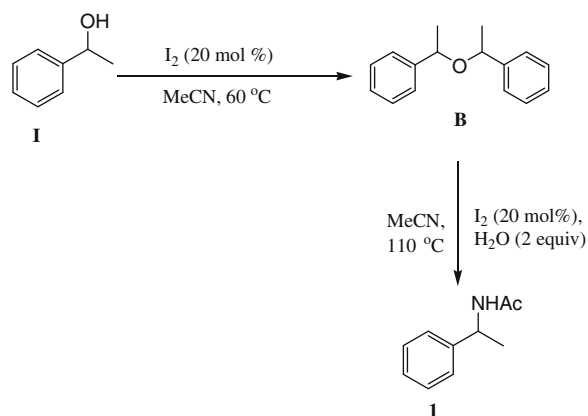


**Scheme 2.**

Next, we turned our attention to the synthesis of *N-tert*-butyl amides from *tert*-butyl acetate and nitriles under the reflux conditions. As the yields with the *tert*-butyl alcohol are less, *tert*-butyl
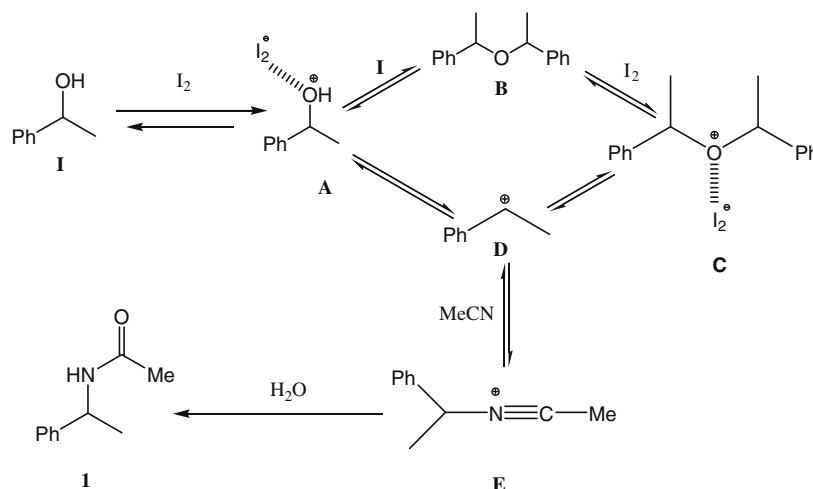
**Scheme 3.**
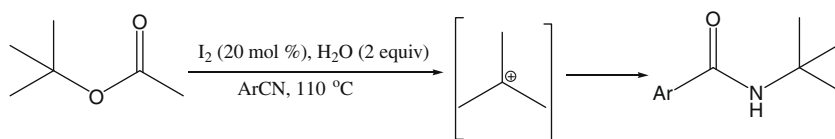


**Scheme 4.**

acetate has been used as the carbocationic source. In an earlier Letter, synthesis of tert-butyl amides has been achieved using $H_2SO_4$ and acetic acid at room temperature[11] where they describe the convenient synthesis of only the tert-butyl amides but the present protocol can be effectively used for the synthesis of both benzyl and tert-butyl amides. Though the reaction is carried out at high temperature (110 °C), our method avoids the use of corrosive $H_2SO_4$ and uses only catalytic amount of iodine (Scheme 4). Therefore this is an eco-friendly reaction. This reaction is useful to prepare bulky amides, which may be useful in the preparation of the hindered amines by hydrolysis.[6]

The scope of this reaction was investigated by examining a variety of nitriles and in most of the cases, using the same conditions, the reaction proceeded smoothly in a few hours with good yields and the results are summarized in Table 3.[31]

The formation of amides in good yields as seen from Table 3, is sufficient to show that tert-butyl acetate served as a better source of tert-butylcarbocation. The reaction of PhCN with t-BuOAc in toluene at 110 °C in the presence of molecular iodine (20 mol %) produced the amide (**20**) in 65% isolated yield. The yields of most of the other amides are more than 80%, whereas only 45% amide **22** was obtained using around 30 mol % of iodine and 3 equiv of tert-butyl acetate.

In conclusion we have developed a simple, convenient, and efficient protocol for the synthesis of amides and N-tert-butyl amides from alcohols, tert-butyl acetate and nitriles by Ritter reaction using catalytic amount of iodine in a sealed tube. This catalytic reaction is an inexpensive and eco-friendly process.

## Acknowledgment

## Supplementary data

## References and notes

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30. *General experimental procedure for synthesis of amides:* A mixture of alcohol (1 mmol), nitrile (1.1 mmol), iodine (20 mol %), and water (2 equiv) was placed in a sealed tube and heated to 110 °C for the appropriate time as mentioned in Table 2. After completion of the reaction (monitored by TLC), saturated sodium thiosulfate in water was added and extracted with ethyl acetate. The organic layer was separated and washed with water and brine and dried over sodium sulfate, concentrated to furnish the desired amides. When necessary, the obtained amides were purified by crystallization using petroleum ether/ethyl acetate (8:2).
31. *General experimental procedure for synthesis of tert-butyl amides:* A mixture of *tert*-butyl acetate (2 equiv), nitrile (1 mmol), iodine (20 mol %), and water (2 equiv) were placed in a RB flask and heated to110 °C for the appropriate time as mentioned in Table 3. After completion of the reaction (monitored by TLC), saturated sodium thiosulfate in water was added and extracted with ethyl acetate, the organic layer was separated and washed with water and brine and dried over sodium sulfate and concentrated. The obtained *tert*-butyl amides were purified by flash chromatography.