CHAPTER 1

Synthesis of amides using Lewis acid catalyst: Iodine catalyzed Ritter reaction

Part-1

Chemistry of Lewis acids and amides
1.1.1. General overview of Lewis acids

Acid and base reactions are of tremendous importance in organic chemistry, as they are also in inorganic and biochemistry. In 1884, Svante A. Arrhenius defined acids as substances dissociating into protons (H\(^+\)) and the corresponding anions (A\(^-\)) in an aqueous medium.\(^1\) Correspondingly, bases were characterized as substances dissociating into hydroxy-anions (OH\(^-\)) and its respective cations (C\(^+\)). Clearly this concept is restricted to acids and bases like HBr or KOH in water. In 1923 Johannes N. Brønsted and Thomas M. Lowry independently elaborated the extension of the acid-base theory by defining acids as proton-(H\(^+\))-donors and bases as proton-acceptors, no longer restricting the concept to specific substance classes or
solvents.\textsuperscript{2} Following these ideas, a number of reactions could be interpreted accordingly.

Since many reactions do not involve direct proton transfers, the generalization of the acid base definition by Gilbert N. Lewis in 1938, was an important step for the understanding of chemical compounds and their transformations.\textsuperscript{3} A Lewis acid is a compound with electron demand, (i.e.) having an unoccupied orbital which is able to accept an electron pair. On the other hand a Lewis base donates an electron-pair from an occupied orbital. The reaction products of Lewis acids and bases are Lewis adducts, bound through a coordinative (or dative) bond. By joining the two concepts it becomes clear, that a Brønsted acid is a compound consisting of a Lewis base and a proton. This leaves the proton as the smallest of all Lewis acids, bearing free space in its 1s-orbital.

Further refined by Ralph G. Pearson in 1963, Lewis acids and bases are categorized into hard and soft acids and bases (HSAB-concept).\textsuperscript{4} This approach
describes the quality of a bond in a Lewis adduct by consideration of atomic or ionic radii, charge distribution and polarizability.

Accordingly, moieties of small size, high charge density and high polarizing potential are considered “hard”, whereas large radii, low charge densities and low polarizing potential characterize “soft” acids or bases. The association of hard acids with hard bases, and soft acids with soft bases is preferred. This preference is based on the bond character present in these combinations. A bond between a hard acid and a hard base, as in NaCl, has an ionic character, whereas the bond between a soft acid and a soft base results in a combination exhibiting a covalent bond character. With these concepts a manifold of chemical reactions and compounds can be qualitatively described. Especially for the understanding of structure and reactivity of transition metal complexes, the HSAB-concept is of very high value (Scheme 1.1).

\[
\begin{align*}
&\text{LA} + \text{LB} \rightarrow \text{LA} + \text{LB} = \text{LA} + \text{LB} = \text{LA} - \text{LB} \\
&\text{Lewis adduct binding through a coordinative (dative) bond}
\end{align*}
\]

Examples:

\[
\begin{align*}
&\text{H}^+ + \text{OH}^- \rightarrow \text{H}_2\text{O} \\
&\text{F}_3\text{B} + \text{OEt}_2 \rightarrow \text{BF}_3\cdot\text{OEt}_2 \\
&\text{Cl}_4\text{Si} + \text{OC}(\text{CH}_3)_2 \rightarrow \text{Cl}_2\text{SiH}^+\cdot\text{OC}(\text{CH}_3)_2
\end{align*}
\]

Hard acids: \(\text{BF}_3^+, \text{H}^+, \text{Na}^+, \text{K}^+, \text{Fe}^{3+}, \text{Mg}^{2+}\); Hard bases: \(\text{OH}^-, \text{F}^-, \text{Cl}^-, \text{NH}_3, \text{NR}_3\)

Soft acids: \(\text{BH}_3, \text{pd}^{2+}, \text{Au}^+, \text{Cu}^+, \text{SiCl}_4\); Soft bases: \(\text{RSH}, \text{CN}^-, \text{R}_2\text{S}, \text{R}_2\text{P}, \text{CO}\)

LA=Lewis acid, LB=Lewis base
Scheme 1.1: Interaction of Lewis acids and Lewis bases and the HSAB-categorization.

A great potential of Lewis acids is their application in the activation of molecules bearing Lewis basic sites. Thus Lewis acids play a key role for the activation of σ-and π-systems. The formation of σ-complexes is present in the activation of substrates such as carbonyl compounds or imines. Due to the interaction of the lowest unoccupied molecular orbital (LUMO) of the Lewis acid with the highest occupied molecular orbital (HOMO) of the Lewis base, adjacent bonds get polarized and a nucleophilic attack from external or internal nucleophiles is facilitated. This mode of action can be summarized in a commonly accepted catalytic cycle which accounts for this activation mode, “Lewis acid catalysis” (Scheme 1.2).

Scheme 1.2: General reactive principle of Lewis acid catalysis.

Together with Lewis base activation, Brønsted acid activation and Brønsted base activation it represents the pillars of asymmetric catalysis. However, Lewis acid activation is not restricted to σ-electron donors. Some Lewis acids
are very powerful catalysts for the activation of π-electron-systems as well. By these interactions, nucleophilic attacks on allenes, alkenes and alkynes can be efficiently triggered. Usually these catalysts are complexes bearing a “soft” metal center.\textsuperscript{7}

\(\sigma\)-Lewis acids

Some archetypical Lewis acids for \(\sigma\)-donor activations are group 3- and 4-element halides, such as BF\(_3\), AlCl\(_3\), SnCl\(_4\) or SiCl\(_4\). Many other \(\sigma\)-Lewis acids are based on transition metals, such as TiCl\(_4\) and FeCl\(_3\). Based on the periodic table, a vaguely defined borderline between (transition)-metal and (transition)-metal-free Lewis acids can be drawn. As a common example from the main group elements, AlCl\(_3\) finds its application for various purposes.\textsuperscript{8} One important example is the Friedel-Crafts alkylation (see scheme 1.3). This reaction, first reported in 1877 by French chemist Charles Friedel and American chemist James Crafts, is an electrophilic aromatic substitution, occurring through an addition-elimination mechanism.\textsuperscript{9} The role of the Lewis acid is the interaction of its empty orbital with a lone pair of electrons on chlorine. This interaction polarizes the halogen-carbon bond in RCl and results in a higher electrophilicity on carbon. Subsequently a nucleophilic attack by the aromatic ring takes place. Upon rearomatization via elimination of a proton, the product and the catalyst are liberated.
Scheme 1.3: Mechanism of the Friedel-Crafts alkylation of benzene

\[ \text{HCl} + \text{CH}_3 \rightarrow \text{AlCl}_3 \rightarrow \text{R} \]

\[ \text{MeH} \rightarrow \text{Cl-AlCl}_3 \]

\[ \text{R} \rightarrow \text{Cl-Cl} \]

\( \pi \)-Lewis acids

As already mentioned, the activation of multiple carbon-carbon bonds is another domain of Lewis acid catalysis. Here the \( \pi \)-systems of, for example, allenes, alkenes and alkynes are activated. An extremely important reaction using this slightly different mode of action is the Ziegler-Natta polymerization of ethylene or propylene.\(^1\)

Ziegler-Aufbau:

\[ \text{R-} \quad \text{Al} \quad \text{R} \quad \text{+ n+1} \quad \rightarrow \quad \text{R-} \quad \text{Al} \quad \text{R} \quad \rightarrow \quad \text{R-} \quad \text{Al} \quad \text{(R)}_n \]
Scheme 1.4: The Ziegler-Aufbau reaction.

In early studies Ziegler developed the so-called Aufbau-reaction (Aufbau (Ger.) = assembly), the multiple insertion of ethylene into the carbon-aluminium bond of trialkylaluminium compounds (Scheme 1.4).

1.1.2. Application of Lewis acid catalysts in organic synthesis

The use of Lewis acids in organic synthesis, especially in catalysis is one of the most rapidly developing fields in synthetic organic chemistry. In addition, Lewis acid catalysis is one of the key technologies for asymmetric synthesis, and combinatorial chemistry as well as for large-scale production. Lewis-acid (LA)-catalyzed reactions are of great interest because of their unique reactivities and selectivities and mild reaction conditions used. A wide variety of reactions using Lewis acids have been developed, and they have been applied to the synthesis of natural and unnatural compounds. Some of the examples are given below.
Alkylation reactions

Friedel-Crafts alkylations are of great interest due to their importance and common use in synthetic and industrial chemistry. In 1887 Charles Friedel and James Mason Crafts\textsuperscript{11} isolated amylbenzene after the treatment of amyl chloride with AlCl\textsubscript{3} in benzene (Scheme 1.5). This was not only one of the first descriptions of a Lewis acid used in organic synthesis but also the first example of what as later to be called Friedel-Crafts alkylation after its inventors.

\[
\begin{array}{c}
\text{Scheme 1.5: Friedel-Crafts alkylation of amyl chloride with benzene}
\end{array}
\]

Over the intervening years many other Lewis acids including BF\textsubscript{3}, BeCl\textsubscript{2}, TiCl\textsubscript{4}, SbCl\textsubscript{5} and SnCl\textsubscript{4} have been described as catalysts for the FC alkylation.\textsuperscript{12}

Acylation reactions

Friedel–Crafts acylation is the acylation of aromatic rings with an acyl chloride or acid anhydride using FeCl\textsubscript{3} or AlCl\textsubscript{3} as a strong Lewis acid catalyst. Reaction conditions are similar to the Friedel–Crafts alkylation as mentioned above.

\[
\begin{array}{c}
\text{Scheme 1.6: Friedel–Crafts acylation of benzene with acylchloride}
\end{array}
\]

The aldol reactions

The Lewis acid-catalyzed aldol reaction of silyl enol ethers, commonly known as the Mukayama aldol reaction, was first reported in the early seventies.\textsuperscript{13} The titanium-tetrachloride was also used as Lewis acid catalyst for the cross-aldol reactions.\textsuperscript{14} Kobayashi reported\textsuperscript{15} the first Lewis acid catalyzed cross-aldol reaction
in aqueous solution. He examined the effects of lanthanide triflates in the reaction of several silyl enol ethers with benzaldehyde.

![Chemical Reaction]

Scheme 1.7: Lewis acid-catalyzed aldol reaction of silyl enol ether

** Allylation reactions **

The synthesis of homoallylic alcohols via Lewis acid-catalyzed reaction of organo-metallic reagents with a carbonyl compound has been widely studied. The first example of such a Lewis acid-catalyzed allylation reaction in aqueous medium was again reported by Kobayashi. In smooth reaction under the influence of 5 mol% of Sc(OTf)₃, tetra allyltin reacted with several ketones and aldehydes. The much cheaper Yb(OTf)₃ was also used effectively and the Lewis acid could be reused without loss of activity.

![Chemical Reaction]

Scheme 1.8: Lewis acid-catalyzed allylation reaction of benzaldehyde with allylbromide

** Diels-Alder Reaction **

Davies et al. developed aluminum chloride induced reaction between cyclopentadiene and \( \alpha,\beta \)-unsaturated aldehydes resulting in the stereoselective formation of the products of a formal \( [4 + 3] \) cycloaddition. The reaction proceeded by a tandem Diels-Alder reaction/ring expansion. They also reported MeAlCl₂ – catalyzed hetero Diels-Alder reaction.
Scheme 1.9: Lewis acid-catalyzed Diels-Alder reaction of cyclopentadiene and α,β-unsaturated aldehyde

Rearrangement

Lambert et al.\textsuperscript{21} have developed a new Lewis acid-catalyzed [3,3]-Sigmatropic rearrangement and Allenote-Claisen rearrangement between benzyl 2,3-pentadienoate and allyl pyrrolidines using Lewis acid catalyst.

Scheme 1.10: Lewis acid-catalyzed Rearrangement

Yb(OTf)\textsubscript{3}, Sn(OTf)\textsubscript{2}, Cu(OTf)\textsubscript{2}, TiCl\textsubscript{4}, AlCl\textsubscript{3}, FeCl\textsubscript{3}, Zn(OTf)\textsubscript{2} were also used as Lewis acid catalysts for this transformation.

Halogenations

Yamamoto et al.\textsuperscript{22} have reported asymmetric chlorination of ketones using ZrCl\textsubscript{4} as a Lewis acid catalyst.

Scheme 1.11: Lewis acid-catalyzed halogenation
Hintermann, and Tongni, have developed chiral Lewis acid catalyzed asymmetric chlorination and bromination.\textsuperscript{23}

![Chemical structure image](image)

Scheme 1.12: Lewis acid-catalyzed bromination

Oxidation

Michel Vatele et al.\textsuperscript{24} developed the method for the oxidative rearrangement of tertiary allylic alcohols. Most of tertiary allylic alcohols studied were oxidized to their corresponding transposed carbonyl derivatives in excellent to fair yields by reaction with TEMPO in combination with PhIO and Bi(OTf)\textsubscript{3} or copper(II) chloride in the presence of oxygen.

![Chemical structure image](image)

Scheme 1.13: Lewis acid-catalyzed oxidative rearrangement of tertiary allylic alcohol

Reduction

Stephan et al.\textsuperscript{25} have found that the Lewis acid B(C\textsubscript{6}F\textsubscript{5})\textsubscript{3} efficiently catalyzed the direct hydrogenation of imines and the reductive ring-opening of aziridines with H\textsubscript{2} under mild conditions; addition of a bulky phosphine allows the reduction of protected nitriles.

![Chemical structure image](image)

Scheme 1.14: Lewis acid-catalyzed reduction reaction of imines
Addition reaction (Michael addition)

Feringa et al.\textsuperscript{26} observed that the large range of $\beta$-keto esters reacted efficiently with various $\beta$-unsubstituted enones in the presence of a catalytic amount of Yb(OTf)$_3$, to give corresponding product with good yield.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {$\text{R}^1\text{C}=\text{O} + \text{R}\text{O}=\text{O} \xrightarrow{\text{Yb(OTf)$_3$}} \text{R}\text{O}=\text{O}$};
\end{tikzpicture}
\end{center}

Scheme 1.15: Lewis acid-catalyzed Michael addition of $\beta$-keto esters with $\beta$-unsubstituted enones

Mannich-type reaction

For the synthesis of $\beta$-amino ketones the Mannich reaction is one of the most attractive processes. A Lewis acid-catalyzed Mannich reaction can be carried out conveniently in aqueous solution.\textsuperscript{27} An aldehyde, an amine and a vinyl ether reacted in THF/water mixture in the presence of 10 mol\% of Yb(OTf)$_3$, to give $\beta$-amino ketone in 55-100\% yield.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {$\text{R}^1\text{CHO} + \text{R}^2\text{NH}_2 + \text{R}^3\text{O}=\text{O} \xrightarrow{10\text{ mol\%}, \text{Yb(OTf)$_3$, \text{THF/H}_2\text{O}} \text{R}^2\text{NH}=\text{O}$};
\end{tikzpicture}
\end{center}

Scheme 1.16: Lewis acid-catalyzed Mannich-type reaction

1.1.3. General introduction of amides

The amides are a group of organic compounds derived from carboxylic acids and nitrogen compounds, like ammonia and amines providing compounds that contain the $-\text{CONH}_2$, $-\text{CONHR}$, or $-\text{CONR}_2$ groups. They have the ability to bond very strongly to themselves, at other amide sites down the chain, or different chains with amides through hydrogen bonding between the oxygen and the hydrogen from the NH group elsewhere. These are very strong intermolecular bonds.
Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Hermann Fischer discovered the peptide bond (Amide bond) and won the Nobel Prize for Chemistry in 1902 for groundbreaking work on the structure and properties of purines and sugars.

The structure of amides

Amides are made by a chain of carbon atoms with one as a carbonyl bonded to an amine group, which is then bonded to the next carbon to continue the chain.

![Scheme 1.17: Structure of amide](image)

The lone pair of electrons on the nitrogen is delocalized into the carbonyl, thus forming a partial double bond between N and the carbonyl carbon. Consequently the nitrogen in amides is not pyramidal. It is estimated that acetamide is described by resonance structure A for 62% and by B for 28%.

1.1.4. Amide Formation

One or more of the hydrogens of the ammonia are replaced with organic acid groups to produce primary, secondary, or tertiary amide. Primary amides are prepared by reacting ammonia or amines with acid chlorides, anhydrides, or esters. Secondary and tertiary amides are prepared by reacting primary amides or nitriles with organic acids.

Amides are commonly synthesized via reactions of a carboxylic acid with an amine.
Many methods are known for driving the unfavorable equilibrium to the right, because the unification of these two functional groups does not occur spontaneously at ambient temperature, with the necessary elimination of water only taking place at high temperatures (e.g. >200 °C),\(^9\) conditions typically detrimental to the integrity of the substrates. For this reason, it is usually necessary to first activate the carboxylic acid, a process that usually takes place by converting the –OH of the acid into a good leaving group prior to treatment with the amine (Scheme 1.19).

![Scheme 1.19: Principle of the activation process for amide-bond formation.](image)

In order to activate carboxylic acids, one can use so-called coupling reagents, which act as stand-alone reagents to generate compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters.

For the most part, these reactions involve "activating" the carboxylic acid and the best known method, the Schotten-Baumann reaction which involves conversion of the acid to the acid chlorides.

![Scheme 1.20: Schotten-Baumann reaction](image)
Many reviews on coupling reagents have been published.\textsuperscript{30-36} For example DCC,\textsuperscript{37} HOBt,\textsuperscript{38,39} DIC\textsuperscript{40} HOAT,\textsuperscript{41} etc \textsuperscript{42} have been effectively employed for this purpose.

Amide can be synthesized from ketone with hydrogen azide using acid catalyst (Schmidt Reaction).

\[
\begin{align*}
\text{O} & \quad \text{HN}_3 \\
\text{O} & \quad \text{R} \quad \text{R}^1 \\
\text{H}_2\text{SO}_4 & \quad \text{R} \quad \text{NH} \text{R}^1 \\
\end{align*}
\]

Scheme 1.21: Schmidt Reaction

The use of magnesium nitride as a convenient source of ammonia allows a direct transformation of esters to primary amides. Methyl, ethyl, isopropyl, and tert-butyl esters are converted to the corresponding carboxamides in good yields.\textsuperscript{43}

\[
\begin{align*}
\text{O} & \quad \text{Mg}_3\text{N}_2 \\
\text{O} & \quad \text{R} \quad \text{R}^1 \\
\text{MeOH, 80 °C} & \quad \text{R} \quad \text{NH}_2 \\
& \quad \text{R}^1 = \text{alkyl or aryl} \\
& \quad \text{R} = \text{Me, Et, Pr, Bu} \\
\end{align*}
\]

Scheme 1.22: Amide formation from esters

Gunanathan, et al.\textsuperscript{44} have prepared amides from amines and alcohols under mild pressure and neutral, homogeneous conditions using a dearomatized bipyridyl-based PNN Ru(II) pincer complex as a catalyst.

\[
\begin{align*}
\text{H} & \quad \text{H} \quad \text{R} \quad \text{OH} \\
\text{R}^1 & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{Toluene, Reflux, -H}_2 & \quad \text{R} \quad \text{O} \quad \text{N} \quad \text{R}^1 \\
\end{align*}
\]

Scheme 1.23: Synthesis of amides from amine and alcohol
1.1.5. Applications of amides

Uses in organicsynthesis

Recently, Matthias Beller and co-worker reported amine can be prepared from amide using zinc acetate as catalyst.

$$R_1 \text{CONH}_2 + \text{Zn(OAc)}_2 \rightarrow R_1 \text{NH}_2$$

Scheme 1.24: Synthesis of amine from amides

Since Nahm and Weinreb first reported the use of N-methoxy-N-methylamides as carbonyl equivalents, this functional group has rapidly become popular in organic synthesis. The ease of preparation, the limitation of side reactions during nucleophilic addition, and the selective reduction of this moiety to aldehydes has propelled it to the forefront of synthetic utility.

Scheme 1.25: Synthesis of ketone and aldehyde from amides

The main synthetic use of Weinreb amides derives from their reactivity toward nucleophiles. They can be useful for the addition of Grignard or alkyllithium reagents to produce ketones. Other advantages are seen in the selective reduction of the Weinreb amides to the corresponding aldehydes. The chelating ability of the amides provides a stable intermediate that does not form the aldehyde until aqueous workup. This prevents
the over reduction commonly seen with other functionalities. Several reviews and numerous articles on the utility of Weinreb amides have been published.\textsuperscript{46}

Schroeder et al.\textsuperscript{47} synthesized 1,5-disubstituted tetrazoles from amides using diisopropyl azodicarboxylate (DIAD), diphenylphosphoryl azide (DPPA), and diphenyl-2-pyridyl phosphine in THF.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\text{DPPA}};
  \node (B) at (2,0) {\text{DIAD, THF}};
  \node (C) at (0,-1) {\text{NH \begin{align*} O \hspace{1cm} R \end{align*}}};
  \node (D) at (2,-1) {\text{\text{\begin{align*} N^+ \hspace{0.5cm} N^- \end{align*}}}};
  \draw [->] (A) -- (C);
  \draw [->] (B) -- (D);
\end{tikzpicture}
\end{center}

Scheme 1.26: Synthesis of tetrazole from amide

The amides such as dimethylacetamide, dimethylformamide, formamide, N-methylformamide, methylpyrrolidone, 2-pyrrolidone and N-vinylpyrrolidone are often used as very useful common solvents in organic synthesis. Several articles and many reviews are available in literature regarding the use of amides as starting materials or intermediates for the synthesis of several bioactive molecules.

\textbf{Uses in medicinal chemistry}

Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs. For example, Atorvastatin,\textsuperscript{48} the top selling drug worldwide since 2003, blocks the production of cholesterol, contains an amide bond (Fig. 1.1), as do Lisinopril\textsuperscript{49} (inhibitor of angiotensin converting enzyme), Valsartan\textsuperscript{50} (blockade of angiotensin-II receptors),\textsuperscript{51} and Diltiazem (calcium channel blocker used in the treatment of angina and hypertension).\textsuperscript{52}
Acetaminophen or Paracetamol, an amide used as analgesic (pain-killer) and antipyretic (fever reducer). It is commonly used for the relief of headaches, other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. Another amide analgesic Phenacetin was introduced in 1887 by Harmon Northrop Morse. It was one of the first synthetic fever reducers to go on the market. It is also known historically to be one of the first non-opioid analgesics without anti-inflammatory properties. Phenacetin was used in products such as Empirin and APC (aspirin, phenacetin, and caffeine) tablets.
Other commercially used amides include N,N-dimethyl-m-toluamide (DEET) which is used as insect repellent and is intended to be applied to the skin or to clothing, and is primarily used to repel mosquitoes. Lidocaine (Xylocaine) and dibucaine (Nupercaine) were used as common local anesthetic and antiarrhythmic drugs. Lidocaine is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic or as a local anesthetic for minor surgeries.

Uses in industry

Amides are used widely in industry. Amides are found in the plastic and rubber industry, paper industry, water and sewage treatment and colour, in crayons, pencils and inks. Acrylamide and polyacrylamide are the products most widely used in these industries. However, acryl amide is a carcinogen, so can only be used if the chemicals are not intended for consumption. Polyacrylamide is used in its place, mainly therefore, in the treatment of drinking water and sewage, as these are intended for consumption.
Acryl amides are a family ofnylons, including Nomex and Kevlar. Kevlar, a form of polyamide is a very strong material which is about five times as strong as steel, weight for weight. It is used in composites for boat construction, in manufacture of bulletproof vests, and in lightweight mountaineering ropes and skis and racquets.

Nylons are polyamides, first produced on February 28, 1935, by Wallace Carothers at DuPont's research facility at the DuPont Experimental Station. It was used for various purposes. Apart from textiles for clothing and carpets, nylon is also used to make tyre cords.

1.1.6. Lewis acids catalyzed amide formation reactions

Yadav et al.\textsuperscript{53} have used FeCl\textsubscript{3} as Lewis acid catalyst for the synthesis of C-glycosyl amides from isocyanides in good yields with α-selectivity. The use of FeCl\textsubscript{3} makes this method simple, convenient and cost-effective. This is the first report on carbon-Ferrier rearrangement using isonitriles as nucleophiles.

\begin{equation}
\text{HO} \quad \text{RO} \quad \text{OR} \quad \text{R}-\text{NC} \quad \text{FeCl}_3 \quad \text{CH}_2\text{Cl}_2, \text{RT} \quad \text{RO} \quad \text{OR} \quad \text{N}-\text{R} \\
\text{Scheme 1.27: FeCl}_3 \text{ catalyzed amide synthesis}
\end{equation}

Jae Nyoung Kim and co-workers reported InCl\textsubscript{3} has efficiently catalyzed the synthesis of amides from nitriles.\textsuperscript{54} The reaction was carried out in toluene at refluxing temperature with the aid of acetaldoxime as an effective water surrogate to produce amides in high yields.

\begin{equation}
\text{Ph-CN} \quad \text{H}_3\text{C} \quad \text{N} \quad \text{OH} \quad \text{InCl}_3(5 \text{ mol%}) \quad \text{Toluene, reflux} \quad \text{Ph} \quad \text{N} \quad \text{H} \\
\text{Scheme 1.28: InCl}_3 \text{ catalyzed amide synthesis}
\end{equation}
Recently, rare-earth metal triflates have enjoyed extensive applications in a variety of Lewis acid catalyzed organic reactions. Kumar and co-workers developed Yb(OTf)₃-catalyzed amidoalkyl naphthols from aldehyds in ionic liquids.²⁵

![Scheme 1.29: Yb(OTf)₃ catalyzed amide synthesis](image-url)
CHAPTER 1

Synthesis of amides using Lewis acid catalyst: Iodine catalyzed Ritter reaction

Part-2

Iodine-catalyzed synthesis of amides from nitriles via Ritter reaction
1.2.1 Introduction

During the last several decades, Lewis acid catalyzed carbon-nitrogen bond formation has been extensively studied for organic synthesis. Amide formation reaction between nitriles and alcohols or alkenes is one of the most important methods for forming new carbon-nitrogen bond.

1.2.1.1. Ritter reaction

In 1948, J.J. Ritter and P.P. Minieri reported that, treatment of nitriles with alkenes or tertiary alcohols under acidic conditions resulted in the formation of N-tert-alkylamides (scheme 1.30). The formation of N-alkyl carboxamides from aliphatic or aromatic nitriles and carbocations is known as the Ritter reaction. Since its discovery, the Ritter reaction has enjoyed an enormous success and is widely used for the preparation of acyclic amides as well as heterocycles (e.g. lactams, oxazolines, etc.). The general features of this reaction are i) the carbocation can be generated in variety of ways from tertiary, secondary, or benzylic alcohols, alkenes or alkyl halides; ii) the classical reaction conditions involve the dissolution of the nitrile substrate in the mixture of acetic acid and concentrated sulfuric acid followed by the addition of the alcohol or alkene at slightly elevated temperature (50-100 °C); iii) alcohols that are easily ionized (e.g. 2’, and 3’ alcohols, benzylic alcohols) give the best results; iv) besides protic acids, Lewis acids (e.g. SnCl₄, BF₃.OEt₂, AlCl₃, etc.) have been successfully employed in the Ritter reaction to generate the required carbocations; v) the structure of the nitrile compound can be varied widely and most of the substrates containing a cyano group will undergo the reaction, so, for example, besides aliphatic and aromatic nitriles, compounds like cyanogen and cyanamide will also react; and vi) the nitrile substrate may not contain acid sensitive
functional groups that would be destroyed under the strongly acid conditions, but modifications (Ritter-type reactions) that proceed under neutral conditions expanded the scope of the substrates.

![Scheme 1.30: Ritter reaction](image)

The Ritter reaction is most useful in the formation of new carbon-nitrogen bonds, especially in the formation of amides in which the nitrogen has a tertiary alkyl group. Real world applications include Merck’s industrial-scale synthesis of anti-HIV drug Crixivan (indinavir),\textsuperscript{57} the production of the falcipain-2 inhibitor PK 11195; the synthesis of the alkaloid aristotelone;\textsuperscript{58} and synthesis of Amantadine, an antiviral and antiparkinsonian drug.\textsuperscript{59} Other applications of the Ritter reaction include synthesis of dopamine receptor ligands and production of amphetamine from allylbenzene.\textsuperscript{60}

1.2.1.2. Iodine

Iodine was discovered in 1811 by French chemist Bernard Courtois (1777-1838). Iodine is one of the most abundant elements and its toxicity is relatively low. The element occurs primarily in seawater and in solids formed when seawater evaporates. It also exist in nature from many sources such as iodide ions in brines, as an impurity in chile saltpeter and main natural source of iodine is kelp (2000kg seaweed=1kg iodine).

World demand for iodine and organic iodine compounds is as follows: X-ray contrast media (21 %), disinfectants and biocides (20 %), medium of organic reactions (19 %), medicines and pharmaceuticals (16 %), animal feeds (9 %), herbicides (4 %), and photographic (3 %). Chemical functional ability of iodine as disinfectant or biocide
comes from the oxidizing ability of iodine itself, especially for SH groups to disulfides, iodination of aromatic rings in tyrosine and histidine in proteins. Thus, iodine is one of the most simple, less expensive, less toxic oxidants. Today, iodine is an old reagent; however, in view of various functionalizing abilities, it is important as an environmentally benign reagent for organic functional group conversions. The reports on the recent synthetic utility of iodine in organic synthesis are discussed in the literature section.

1.2.2. Review of literature

1.2.2.1. Ritter reactions

To date several methods have been reported in literature for synthesis of amides via Ritter reaction using various catalysts.

Barton et al. (1974)\textsuperscript{61}: N-alkylated amides were prepared from nitrile and alcohols. Chlorodiphenylmethylium hexachloroantimonate was used as catalyst for the activation of primary and secondary alcohols.

$$\begin{align*}
R^1\overset{\text{OH}}{\text{OH}} + \text{RCN} & \xrightarrow{1) \text{Ph}_2\text{CClSbCl}_6} \xrightarrow{2) \text{H}_2\text{O}} R^1\overset{\text{H}}{\text{N}}\overset{\text{O}}{\text{R}} \quad \text{Scheme 1.31}
\end{align*}$$

Martinez et al. (1989)\textsuperscript{62}: They synthesized amide from alcohols and nitriles. Here they have used triflic anhydride for activation of alcohols to obtain good yield.

$$\begin{align*}
\overset{\text{R}^2\overset{\text{R}^3}{\text{OH}}}{\text{OH}} + \text{RCN} & \xrightarrow{1) \text{Tf}_2\text{O}, \text{CH}_2\text{Cl}_2} \xrightarrow{2) \text{NaHCO}_3} \overset{\text{R}^1\overset{\text{H}}{\text{N}}\overset{\text{O}}{\text{R}}}{\text{R}^2\overset{\text{R}^3}{\text{O}}} \quad \text{Scheme 1.32}
\end{align*}$$

Lebedev et al. (2002)\textsuperscript{63}: N-Primary-alkyl amides were obtained by a Ritter-type reaction of nitriles with lower primary alcohols or their esters in the presence of acid.
Reddy et al. (2003): 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.

Jaouen et al. (1981): Benzyl alcohol derivatives reacted with nitriles in the presence of chromium tricarbonyl complexes to give corresponding amides and the complex provided stereochemical controlled product.
Warren et al. (2002): They reported electrophilic activation of Ritter reaction for alkenes with nitriles.

\[
\begin{align*}
R & \text{H} & + & E^+ & \rightarrow & \begin{array}{c}
\text{R} \\
\text{E}
\end{array} & \left[ \begin{array}{c}
\text{R} \\
\text{E}
\end{array} \right] & \text{MeCN} & \rightarrow & \begin{array}{c}
\text{R} \\
\text{Me}
\end{array} & + & \begin{array}{c}
\text{R} \\
\text{Me}
\end{array} & + & \begin{array}{c}
\text{E}
\end{array} & \text{H} & \text{O}
\end{align*}
\]

Scheme 1.36

**Lewisacidcatalyzed Ritterreactions:**

Callens et al. (2006): 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.

\[
\begin{align*}
\text{RCN} & + & \begin{array}{c}
\text{HO} \\
\text{Me} \\
\text{Me}
\end{array} & \rightarrow & \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} & \begin{array}{c}
\text{Me}
\end{array} & \begin{array}{c}
\text{R}
\end{array} & \text{N} & \text{O} & \begin{array}{c}
\text{H}
\end{array} & \begin{array}{c}
\text{R}
\end{array}
\end{align*}
\]

\[\text{1) Bi(Ot)}_3 \quad \text{2) H}_2\text{O}\]

\[R= \text{alkyl, aryl}\]

Scheme 1.37

Reymond and Cossy et al. (2009): A safe and inexpensive synthesis of amides, from benzylic alcohols and nitriles and from t-butyl acetate and nitriles, using a Ritter reaction catalyzed by FeCl\(_3\cdot6\)H\(_2\)O was described.

\[
\begin{align*}
\text{RCN} & \rightarrow & \begin{array}{c}
\text{N} \\
\text{H} \\
\text{t}-\text{Bu}
\end{array} & \begin{array}{c}
\text{R}
\end{array} & \text{FeCl}_3\cdot6\text{H}_2\text{O} & \text{t-BuOAc, H}_2\text{O, 150 }\text{°C}
\end{align*}
\]

\[
\begin{align*}
\text{RCN} & + & \begin{array}{c}
\text{OH} \\
\text{Ar} \\
\text{R}^1
\end{array} & \rightarrow & \begin{array}{c}
\text{Ar} \\
\text{R}^1
\end{array} & \text{NHCOR} & \text{FeCl}_3\cdot6\text{H}_2\text{O} & \text{H}_2\text{O, 150 }\text{°C}
\end{align*}
\]

Scheme 1.38

Varma et al. (2008): They have developed an atom-economic solvent-free synthesis of amides by the Ritter reaction of alcohols and nitriles under microwave
irradiation. This green protocol was catalyzed by solid-supported Nafion®NR50 with improved efficiency and reduced waste production.

![Scheme 1.39](image)

Tamaddon et al. (2007)\textsuperscript{70}: Tertiary alcohols as well as primary and secondary benzylic alcohols react efficiently with nitriles to give the corresponding amides in good to excellent yields in the presence of P\textsubscript{2}O\textsubscript{5}/SiO\textsubscript{2} (60% w/w).

![Scheme 1.40](image)

1.2.2.2. Iodine catalyzed transformations

Iodine has been attracting much attention in synthetic organic chemistry since its discovery in 1811. It is the weakest oxidizer among the halogens and a poor electrophile that often needs the assistance of strong acid. Iodine has several advantages over the vast majority of the other Lewis-acid catalysts, especially the metallic catalysts. Its catalytic potential is intriguingly broad.

Many Iodine-catalyzed transformations have been reported in literature. The reports on the recent synthetic utility of iodine in organic synthesis are discussed below. In the C–C bond formation reactions

A mild, metal-free, and environmentally benign iodine-promoted regioselective C–C and C–N bonds formation of N-protected indole derivatives giving 2,3′-biindoles
and 4-(1H-indol-2-yl)morpholines has been successfully demonstrated. Various bioactive 2, 3′-biindoles and 4-(1H-indol-2-yl) morpholines, bearing electron-rich to moderately electron-poor substituents, can be prepared in moderate to good yields.\textsuperscript{71}

\begin{equation}
\begin{array}{c}
\text{Scheme 1.41: Iodine catalyzed carbon-carbon bond formation}
\end{array}
\end{equation}

Intramolecular cyclization of enamines

The synthesis of 3H-indoles was achieved via the iodine-mediated intramolecular cyclization of enamines. A wide variety of 3H-indole derivatives bearing multifunctional groups were obtained in good to high yields under transition metal-free reaction conditions.\textsuperscript{72}

\begin{equation}
\begin{array}{c}
\text{Scheme 1.42: Iodine catalyzed indole synthesis}
\end{array}
\end{equation}

Treatment of olefins bearing an active methylene group, such as allyl ethyl malonate and α-alkenyl β-ketoesters with iodine in benzene or CH₂Cl₂ results in fused cyclopropane lactone and fused cyclopropane β-ketoester respectively.\textsuperscript{73}

\begin{equation}
\begin{array}{c}
\text{Scheme 1.43: Iodine catalyzed fused cyclopropane lactone synthesis}
\end{array}
\end{equation}
Iodine as acetylation catalyst

While the catalytic activity of iodine in the acetylation of alcohols with acetic anhydride was being studied by Deka and co-workers,74 the following conversion was observed in more than 90% yield in a short reaction time.

$$\text{RCHO} + \text{Ac}_2\text{O} \xrightarrow{\text{I}_2/\text{CHCl}_3} \text{RCH(OAc)}_2$$

\[ R = \text{alkyl, aryl} \]

Scheme 1.44: Iodine catalyzed acetylation

Protection of carboxylic acids as esters using iodine catalyst

Carboxylic acids with a catalytic amount of iodine in methanol provides the corresponding methyl esters smoothly.75 The reaction is not possible with acidic aromatic carboxylic acids and iodine is assumed to oxidize methanol partly during the course of this reaction.

$$\text{RCOOH} \xrightarrow{\text{I}_2 (1.0 \text{ equiv})/\text{MeOH}} \text{R-COOMe}$$

Scheme 1.45: Iodine catalyzed ester synthesis

Iodine in one-pot three-component synthesis

Iodine has been found to be an effective catalyst for one-pot synthesis of homoallyl benzyl ethers under mild reaction conditions.76 Various homoallyl benzyl ethers were synthesized in moderate to high yields by three-component condensation of aldehydes, benzoxystrimethylsilane, and allyltrimethylsilane in presence of iodine (10 mol %) in dichloromethane at 0 °C.

$$\text{R} + \text{H} + \text{SiMe}_3 \xrightarrow{\text{I}_2 (10 \text{ mol %})/\text{DCM, 0 °C}} \text{R}$$

Scheme 1.46: Iodine catalyzed homoallyl benzyl ether synthesis
Iodine catalyzes efficiently the three-component condensation of aldehydes, benzyl carbamate, and allyltrimethylsilane to afford the corresponding protected homoallylic amines in excellent yields.\textsuperscript{77}

\[
\begin{align*}
\text{R} & \text{H} + \text{Cbz}-\text{NH}_2 + \text{SiMe}_3 & \xrightarrow{\text{I}_2 (10\%), \text{CH}_3\text{CN}} & \text{R} + \text{NHCbz} \\
\end{align*}
\]

\textbf{Scheme 1.47: Iodine catalyzed homoallylic amines synthesis}

Iodine-catalyzed oxidation reactions

Aromatic and aliphatic thiols can be smoothly oxidized to the corresponding disulfides by iodine in the presence of pyridine at room temperature as shown in Scheme 1.48.\textsuperscript{78}

\[
\begin{align*}
\text{RSH} & \xrightarrow{\text{I}_2, \text{pyridine}, \text{rt}} & \text{RSSR} \\
\end{align*}
\]

\textbf{Scheme 1.48: Iodine catalyzed oxidation}

Yadav et al.\textsuperscript{79} demonstrated the aromatization of 4-substituted Hantzsch 1,4-dihydropyridines to the corresponding pyridines in high yields by iodine in methanol.

\[
\begin{align*}
\text{ErO}_2\text{C} & \text{Me} & \xrightarrow{\text{I}_2 (1.0 \text{ equiv})} & \text{MeO} \\
\text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} \\
\end{align*}
\]

\textbf{Scheme 1.49: Iodine catalyzed aromatization}

Jun Ji and co-workers reported,\textsuperscript{80} the electrophilic substitution reactions of indoles with various aromatic aldehydes using a catalytic amount of I\textsubscript{2} under solvent-free conditions. The corresponding bis(indolyl)methanes were obtained in excellent yields.
Scheme 1.50: Iodine catalyzed bis(indolyl)methane synthesis

Panneer Selvam et al. have described a convenient and efficient one-pot synthesis of substituted amidophenols using iodine as catalyst at room temperature under neat condition. \(^{81}\)

Scheme 1.51: Iodine catalyzed amidophenol synthesis

Iodine was established as a good mediator and reagent in organic synthesis. \(^{82}\) For a long time iodine has been recognized as a good catalyst and reagent in carbohydrate chemistry also. \(^{83}\) Recently Marjan Jereb et al. \(^{84}\) reported many transformations of molecules containing oxygen functional groups using iodine as catalyst.

1.2.3. Present work

In recent years there has been considerable interest in the one-pot reaction using Lewis acid as catalyst due to their diversity, efficiency and rapid access to complex and highly functionalized organic molecules. Pioneering work by several research groups in this area has already established the versatility and uniqueness of one-pot synthetic protocols as a powerful methodology for the synthesis of diverse structural scaffolds required in the search of novel therapeutic molecules. In the past decade there have been tremendous developments in the iodine catalyzed one-pot reactions and great efforts have been paid to find and develop newer methodologies.
Several iodine catalyzed transformations have been reported in literature using alcohols such as benzyl, allyl, and propargyl alcohols as starting materials that reacted with various nucleophiles in the presence of 2-20 mol % of I₂ to form the corresponding products. The property of iodine to catalyze the elimination of water from hydroxy compounds has been known for almost a century while primary and secondary benzylic alcohols furnished ethers at elevated temperatures under solvent free reaction conditions. Benzylic and aliphatic alcohols were converted into nitriles in the presence of a twofold excess of iodine in aqueous NH₄OAc and many such transformations were reported but there is no report found in literature for the synthesis of amides from alcohols and nitriles using iodine as catalyst. Therefore, we have planned to study the iodine catalyzed Ritter reaction for the synthesis of amides. In this work, we have developed a simple and practical method for the synthesis of amides and N-tert-butyl amides starting from nitriles and alcohols (Scheme 1.52).

\[
\begin{align*}
\text{CH}_2\text{COR} + \text{R}^1\text{CN} & \xrightarrow{\text{I}_2 (20 \text{ mol} \%)} \xrightarrow{\text{H}_2\text{O} (2 \text{ equiv}), 110 ^\circ\text{C}} \text{CH}_2\text{CONR}^1 \\
\text{CH}_2\text{C} \equiv \text{CHCN} + \text{R}^1\text{CN} & \xrightarrow{\text{I}_2 (20 \text{ mol} \%)} \xrightarrow{\text{H}_2\text{O} (2 \text{ equiv}), 110 ^\circ\text{C}} \text{CH}_2\text{CONR}^1
\end{align*}
\]

\[R = R^1 = \text{alkyl, aryl}\]

Scheme 1.52: Iodine catalyzed Ritter reaction

1.2.4. Results and discussion

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.

After several trials, iodine with two equivalents 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 concentration of the catalyst using toluene as 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 using sealed tubes. The reaction worked in a much better way at 110 °C in a sealed tube (Table 1.1).

Table 1.1 Iodine - catalyzed Ritter reaction of I with MeCN in different solvents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent$^a$</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)$^b$</th>
<th>Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeNO$_2$</td>
<td>100</td>
<td>8</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>MeNO$_2$</td>
<td>50</td>
<td>8</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>110</td>
<td>4</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Xylene</td>
<td>150</td>
<td>4</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>80</td>
<td>6</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Alcohol I (1 mmol), nitrile (1.1 mmol), solvent (10 volume), sealed tube
$^b$ Conversion of I monitored by LC-MS
$^c$ Isolated yield
The conditions described in the entry 3 of Table 1.1 were found to be suitable for the synthesis of various other amides in good yields, and the results are summarized in Tables 1.2 and 1.3.

The generality and scope of this protocol was evaluated for both aromatic and aliphatic alcohols, and a variety of nitriles. 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, 19). When secondary benzyl 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, resulted in a very low conversion (10%).

Table 1.2 Ritter reaction of various alcohols and nitriles catalyzed by iodine

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alcohol</th>
<th>Nitrile</th>
<th>Amide</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Alcohol" /></td>
<td><img src="image2" alt="Nitrile" /></td>
<td><img src="image3" alt="Amide" /></td>
<td>4.0</td>
<td>85&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Alcohol" /></td>
<td><img src="image5" alt="Nitrile" /></td>
<td><img src="image6" alt="Amide" /></td>
<td>4.0</td>
<td>84&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Alcohol" /></td>
<td><img src="image8" alt="Nitrile" /></td>
<td><img src="image9" alt="Amide" /></td>
<td>4.0</td>
<td>60&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Alcohol" /></td>
<td><img src="image11" alt="Nitrile" /></td>
<td><img src="image12" alt="Amide" /></td>
<td>5.0</td>
<td>62&lt;sup&gt;86&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 20 mol% I<sub>2</sub>, 110 °C, H<sub>2</sub>O (2 equiv).

<sup>b</sup> Reaction time in hours.

<sup>c</sup> Isolated yield.
<table>
<thead>
<tr>
<th>5</th>
<th><img src="image1" alt="Molecule 5" /></th>
<th><img src="image2" alt="Molecule 6" /></th>
<th>5.0</th>
<th>64&lt;sup&gt;87&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image3" alt="Molecule 7" /></td>
<td><img src="image4" alt="Molecule 8" /></td>
<td>4.0</td>
<td>75&lt;sup&gt;88,89&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td><img src="image5" alt="Molecule 9" /></td>
<td><img src="image6" alt="Molecule 10" /></td>
<td>3.0</td>
<td>91&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td><img src="image7" alt="Molecule 11" /></td>
<td><img src="image8" alt="Molecule 12" /></td>
<td>6.0</td>
<td>44&lt;sup&gt;90&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Molecule 13" /></td>
<td><img src="image10" alt="Molecule 14" /></td>
<td>4.0</td>
<td>66&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td><img src="image11" alt="Molecule 15" /></td>
<td><img src="image12" alt="Molecule 16" /></td>
<td>4.0</td>
<td>88&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td><img src="image13" alt="Molecule 17" /></td>
<td><img src="image14" alt="Molecule 18" /></td>
<td>6.0</td>
<td>82&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td><img src="image15" alt="Molecule 19" /></td>
<td><img src="image16" alt="Molecule 20" /></td>
<td>5.0</td>
<td>80&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td><img src="image17" alt="Molecule 21" /></td>
<td><img src="image18" alt="Molecule 22" /></td>
<td>6.0</td>
<td>85&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td><img src="image19" alt="Molecule 23" /></td>
<td><img src="image20" alt="Molecule 24" /></td>
<td>5.0</td>
<td>60&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td><img src="image21" alt="Molecule 25" /></td>
<td><img src="image22" alt="Molecule 26" /></td>
<td>6.0</td>
<td>70&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
1.2.5. Plausible mechanism

In the mechanism proposed, we invoke the formation of ether as suggested in the Ritter reaction of alcohols catalyzed by FeCl₃. 6H₂O. 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 1.53).
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 1.54. It is presumed that iodine catalyzes the reaction as a mild Lewis acid. 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.

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 acetate has been used as the carbocationic source. In an earlier report, synthesis of tert-butyl amides has been achieved using H$_2$SO$_4$ and acetic acid at room temperature$^{54}$ 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 was carried out at high temperature (110 °C), our method avoids the use of corrosive H₂SO₄ and uses only catalytic amount of iodine. 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.⁶¹

![Scheme 1.55](image)

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 1.3.

Table 1.3 Ritter reaction of various nitriles with tert-butyl acetate catalyzed by iodine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Amide</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>6.0</td>
<td>65⁶⁴</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>6.0</td>
<td>44⁹⁶</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>5.0</td>
<td>87†</td>
</tr>
</tbody>
</table>

40
1.2.6. Conclusion

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.
1.2.7. Experimental section

General experimental procedure for the synthesis of amides: A mixture of alcohol (1 mmol), nitrile (1.1 mmol), iodine (20 mol%) and water (2 equiv) were placed in a sealed tube and heated to 110 °C for the appropriate time as mentioned in Table 1.2. After completion of the reaction (reaction monitored by TLC), saturated sodium thiosulfate in water was added and extracted with EtOAc. The organic layer was separated and washed with water, brine and dried over sodium sulfate, concentrated to furnish the desired amides. When ever necessary, the obtained amides were purified by crystallization using petroleum ether/ethyl acetate (8:2).

General experimental procedure for the 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 to 110 °C for the appropriate time as mentioned in Table 1.3. After completion of the reaction (reaction monitored by TLC), saturated sodium thiosulfate in water was added and extracted with EtOAc, the organic layer was separated and washed with water, brine and dried over sodium sulfate and concentrated. The obtained tert-butyl amides were purified by flash chromatography.

1.2.8. Characterization of the products

Melting points, IR, LC-MS and $^1$H, $^{13}$C NMR, data of some unknown compounds are given below. All other known compounds data were cross checked with reported data in literature.

4-Isopropyl-N-(1-phenylethyl)benzamide (3): Off-white solid. Isolated yield: 60%, mp 129-130 °C. IR (neat): 3335, 1632 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 8.73 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H) 7.3-87.41 (m, 2H), 7.30–7.34 (m,
4H), 7.20-7.24 (m, 1H), 5.18 (m, 1H), 2.96 (m, 1H), 1.48 (d, J=7.2 3H), 1.23 (d, J = 6.8 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$): δ 165.93, 152.18, 145.51, 132.70, 128.66, 127.98, 126.99, 126.55, 126.50, 48.81, 33.83, 24.14, 22.75. MS: m/z Calcd for C$_{18}$H$_{21}$NO: 267.16; Found: 268.2 (M$^+$). Anal. Calcd for C$_{18}$H$_{21}$NO: C, 80.86; H, 7.92; N, 5.24; O, 5.98%. Found: C, 80.80; H, 7.99, N, 5.22%.

2-(4-Bromophenyl)-N-(1-phenylethyl)acetamide (7): Isolated yield: 91%, mp 111-112 °C. IR (neat): 3285, 1644 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 8.56 (d, J = 7.6 Hz, 1H), 7.49 (m, 1H), 7.29–7.33 (m, 4H), 7.20-7.20 (m, 3H), 4.92 (m, 1H), 3.44 (s, 2H), 1.36 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$): δ 169.17, 145.02, 136.37, 131.71, 131.48, 128.71, 127.09, 126.38, 119.98, 48.43, 42.01, 22.97. MS: m/z Calcd for C$_{14}$H$_{16}$BrNO: 318.22; Found: 320 (M+2). Anal. Calcd for C$_{14}$H$_{16}$BrNO: C, 60.39; H, 5.07; Br, 25.11; N, 4.40; O, 5.03%. Found: C, 60.37; H, 5.09; N, 4.25%.

N-(1-(2-Bromophenyl)ethyl)benzamide (9): White solid. Isolated yield: 66%, mp: 168-169 °C. IR (neat): 3296, 1630 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 8.98 (d, J = 7.2 Hz, 1H), 7.89–7.91 (m, 2H), 7.53-7.60 (m, 3H), 7.47–7.50 (t, 2H), 7.36–7.39 (t, 1H), 7.16–7.20 (m, 1H), 5.4 (m, 1H) 1.45 (d, J = 7.2 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$): δ 166.11, 144.60, 134.78, 132.94, 131.74 129.10, 128.70, 128.53, 127.90, 127.46, 122.48, 49.06, 21.53. MS: m/z Calcd for C$_{15}$H$_{14}$BrNO: 304.18; Found: 330 (M+2).Anal. Calcd for C$_{15}$H$_{14}$BrNO: C, 59.23; H, 4.64; N, 4.60; O, 5.26%. Found: C, 59.20; H, 4.67; N, 4.55%.

N-(1-(2-Bromophenyl)ethyl)-4-isopropylbenzamide (10): White solid.Isolated yield: 88%, mp: 183-184 °C. IR (neat): 3337, 1632 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 8.98 (d, J = 7.6 Hz, 1H), 7.852 (d, J = 8.0 Hz 2H), 7.52-7.59 (m, 2H), 7.33–7.38 (m, 3H), 7.15–7.19 (m, 1H), 5.36-5.40 (m, 1H), 2.5–2.51 (m, 1H) 1.44 (d, J =

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6.8 Hz 3H), 1.23 (d, J = 6.8 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$): δ 166.04, 152.33, 144.71, 132.91, 132.47, 129.03, 128.47, 128.05, 127.46, 126.57, 122.50, 49.02, 33.85, 24.14, 21.54. MS: m/z Calcd for C$_{18}$H$_{20}$BrNO: 345.07; Found: 346 (M$^+\)$. Anal. Calcd for C$_{15}$H$_{14}$BrNO: C, 62.44; H, 5.82; Br, 23.08; N, 4.05; O, 4.62%. Found: C, 62.40; H, 5.84; Br, 23.10; N, 4.0%.

N-(1-(2-Bromophenyl)ethyl)-2-phenylacetamide (11): White solid. Isolated yield: 82%, mp: 158–159 °C. IR (neat): 3236, 1638 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 8.74 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz 1H), 7.14–7.41 (m, 8H), 5.09-5.16 (m, 1H), 3.4 (s, 2H), 1.32 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$): δ 169.67, 144.28, 136.75, 132.95,129.44, 129.08, 128.60, 128.42, 127.24, 126.76, 122.45, 48.43, 42.65, 21.75. MS: m/z Calcd for C$_{18}$H$_{14}$BrNO: 318.21; Found: 320 (M+2). Anal. Calcd for C$_{15}$H$_{14}$BrNO: C, 60.39; H, 5.07; Br, 25.11; N, 4.40; O, 5.06%. Found: C, 60.28; H, 5.12; N, 4.2%.

N-Benzhydryl-4-isopropylbenzamide (15): White solid. Isolated yield: 70%, mp: 166–168 °C. IR (neat): 3333, 2959, 1493 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 9.21 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.33–7.39 (m, 10H), 7.25–7.30 (m, 2H), 6.4 (d, J = 8.8 Hz, 1H), 2.96 (m, 1H), 1.23 (d, J = 6.8 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$): δ 166.35, 152.38, 142.89, 132.52, 128.52, 128.28, 127.41, 126.56, 56.75, 33.86, 24.13. MS: m/z Calcd for C$_{23}$H$_{23}$NO: 329.4; Found: 330 (M$^+$). Anal. Calcd for C$_{23}$H$_{23}$NO: C, 83.85; H, 7.04; N, 4.25; O, 4.86%. Found: C, 83.98; H, 7.09; N, 4.21%.

N-Benzhydryl-2-(3-fluorophenyl) acetamide (19): White solid. Isolated yield: 76%, mp: 147–148 °C. IR (neat): 3293, 1650 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ (ppm) 9.07 (d, J = 8.8 Hz, 1H), 7.34-7.37 (m, 5H), 7.24–7.32 (m, 6H), 7.04–7.13 (m, 3H),
6.12 (d, J = 8.4 Hz, 1H), 3.60 (s, 2H), $^{13}$C NMR (DMSO-d$_6$): $\delta$ 169.32, 163.69, 161.28, 142.86, 139.64, 139.57, 130.4, 128.83, 127.81, 127.43, 125.63, 116.3, 113.7, 113.49, 56.56, 42.17. MS: m/z Calcd for C$_{23}$H$_{23}$NO: 319.37; Found: 320.2 (M$^+$).

Anal. Calcd for C$_{23}$H$_{23}$NO: C, 78.98; H, 5.68; F, 5.95; N, 4.39; O, 5.01%. Found: C, 78.76; H, 5.73; N, 4.21%.

N-tert-butyl-4-isopropylbenzamide (23): White solid. Isolated yield: 87 %, mp: 148-149 °C. IR (neat): 3333, 1633 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): $\delta$ (ppm) 7.70–7.72 (m, 2H), 7.6 (s, 1H), 7.30-7.28 (m, 1H), 2.90-2.96 (m, 1H), 1.37 (s, 9H), 1.22 (d, J = 8.0 6H). $^{13}$C NMR (DMSO-d$_6$): $\delta$ 166.76, 151.67, 134.10, 127.90, 126.32, 51.10, 33.78, 29.08. 24.17. MS: m/z Calcd for C$_{14}$H$_{21}$NO: 219.32; Found: 220.2 (M$^+$).

Anal. Calcd for C$_{14}$H$_{21}$NO: C, 76.67; H, 9.65; N, 6.39; O, 7.29%. Found: C, 76.12; H, 9.83; N, 6.2%.

N-tert-butyl-2-methyl-5-nitrobenzamide (24): White solid. Isolated yield: 81%, mp: 100–102 °C. IR (neat): 3386, 1650 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): $\delta$ (ppm) 8.15-8.18 (m, 2H), 8.02 (s, 1H), 7.54 (d, J = 8.4 1H), 2.43 (s, 3H), 1.38 (s, 9H). $^{13}$C NMR (DMSO-d$_6$): $\delta$ 167.15, 145.63, 143.81, 139.78, 132.07, 123.81, 122.04, 51.47, 28.86, 19.70. MS: m/z Calcd for C$_{12}$H$_{16}$N$_2$O$_2$: 236.27; Found: 237.0 (M$^+$). Anal. Calcd for C$_{12}$H$_{16}$N$_2$O$_2$: C, 61.00; H, 6.83; N, 11.86; O, 20.32%. Found: C, 61.12; H, 7.55; N, 11.74%.

N-tert-butyl-4-methoxy-2-nitro-benzamide (25): White solid. Isolated yield: 86%, mp: 101–102 °C. IR (neat): 3232, 1626 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): $\delta$ (ppm) 8.13 (s, 1H), 7.47–7.52 (m, 2H), 7.27–7.30 (m, 1H), 3.87 (s, 3H), 1.34 (s, 9H). $^{13}$C NMR (DMSO-d$_6$): $\delta$ 165.31, 160.24, 148.63, 130.85, 126.47, 119.02, 109.36, 56.59, 51.31, 28.71. MS: m/z Calcd for C$_{12}$H$_{16}$N$_2$O$_4$: 252.26; Found: 253.2 (M$^+$). Anal. Calcd for C$_{12}$H$_{16}$N$_2$O$_4$: C, 57.13; H, 6.39; N, 11.10; O, 25.37%. Found: C, 57.05; H, 6.45; N, 11.13%.
N-tert-butyl-2-(3-fluorophenyl)acetamide (29): White solid. Isolated yield: 86%, mp: 105–106 °C. IR (neat): 3280, 1644 cm⁻¹. \(^1\)H NMR (DMSO-d₆): δ (ppm) 7.73 (s, 1H), 7.30–7.36 (m, 1H), 7.02–7.08 (m, 3H), 3.38 (s, 2H), 1.25 (s, 9H). \(^{13}\)C NMR (DMSO-d₆): δ 169.48, 163.68, 161.26, 140.21, 130.38, 125.47, 116.15, 113.48, 50.55, 43.02, 28.90. MS: m/z Calcd for C\(_{12}\)H\(_{16}\)FNO: 209.26; Found: 210.2 (M⁺).

Anal. Calcd for C\(_{12}\)H\(_{16}\)FNO: C, 68.88; H, 7.71; F, 9.08; N, 6.69; O, 7.65%. Found: C, 68.92; H, 7.67; N, 6.65%.
1.2.8.1. Spectra

$^1$H NMR (400 MHz, DMSO-d$_6$) of Compound 3

$^{13}$C NMR (100 MHz, DMSO-d$_6$) of Compound 3
$^1$H NMR (400 MHz, DMSO-d$^6$) of compound 7

$^{13}$C NMR (100 MHz, DMSO-d$^6$) of compound 7
$^1$H NMR (400 MHz, DMSO-d$_6$) of compound 9

$^{13}$C NMR (100 MHz, DMSO-d$_6$) of compound 9
$^1$H NMR (400 MHz, DMSO-d$_6$) of compound 10

$^{13}$C NMR (100 MHz, DMSO-d$_6$) of compound 10
**1H NMR 400 MHz, DMSO-d₆** of compound 15

**13C NMR (100 MHz, DMSO-d₆)** of compound 15
$^1$H NMR (400 MHz, DMSO-d$_6$) of compound 19

$^{13}$C NMR (100 MHz, DMSO-d$_6$) of compound 19
$^1$H NMR (400 MHz, DMSO-d$_6$) of compound 23

$^{13}$C NMR 100 MHz, DMSO-d$_6$) of compound 23
$^1$H NMR (400 MHz, DMSO-$d_6$) of compound 24

$^{13}$C NMR (100 MHz, DMSO-$d_6$) of compound 24
$^1$H NMR (400 MHz, DMSO-d$_6$) of compound 25

$^{13}$C NMR (100 MHz, DMSO-d$_6$) of compound 25
$^1$H NMR (400 MHz, DMSO-d$_6$) of compound 29

$^{13}$C NMR (100 MHz, DMSO-d$_6$) of compound 29
1.3. References


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