CHAPTER-1

Introduction

1.1 Introduction

Amides or more precisely “carboxamides” are the derivatives of carboxylic acids [1]. The hydroxyl group of a carboxylic acid is replaced by the amino group (-NH_2, -NHR’ or -NR’R”) in amides.

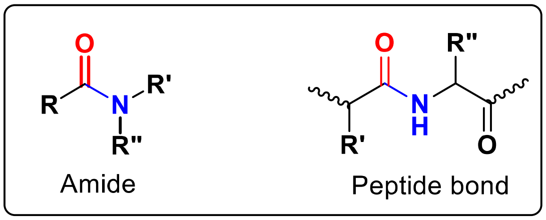


Figure 1.1 Amide bond

Amide molecule comprises a central carbon atom possessing a double bond to oxygen and a single bond to nitrogen[R-(C=O)-N] in their classical representation. The presence of this (O=C)-NH bond in proteins is referred to as a peptide bond [2]. However, the lone pair on the nitrogen atom is delocalized over the carbonyl group, thus leading to a partial double bond between nitrogen and carbon. According to Linus Pauling (1931), there is almost 40% of the double bond character in the C-N bond of the amide which is perhaps responsible for the unique planarity of amides.

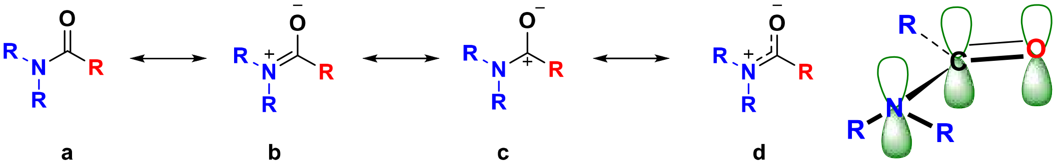


Figure 1.2 Resonance in amide bond

Consequently, all three bonds of the nitrogen in amides are not fully pyramidal like amines but planar [3]. The whole feature corresponding to this planer and partially double-bonded amide bond is referred to as amidic resonance. This amidic resonance imparts an increased stabilization to the amide bond and makes it one of the most robust species in organic chemistry [4-5].

The amidic resonance reduces the electrophilicity of carbonyl carbon of amide to a significant magnitude. It is evident from textbooks that, in comparison to acyl halides, acyl anhydrides, and carboxylic acid esters, amides do not undergo nucleophilic addition reactions readily, as a consequence, amides are significantly less useful as acyl donors than their ester and acid chloride analogues. Additionally, primary and secondary amides are benign towards the addition of strong nucleophiles such as Grignard reagents or similar while they deprotonate at nitrogen and the conclusion is that the rupture of the amide N-C bond requires high activation energy [6-7].

1.2 Structure of Amides

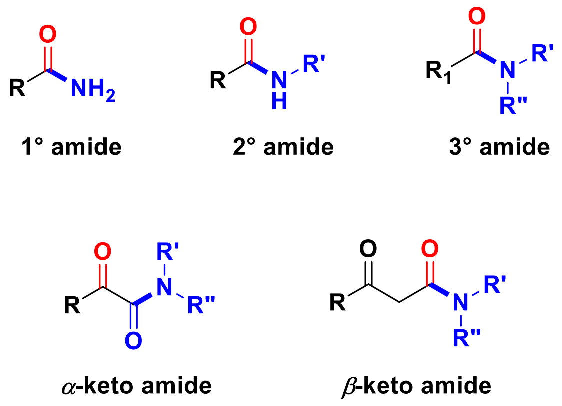


Figure 1.3 General structures of amides

Mainly, amides have generic structures such as $RCONH_2$, where the NH_2 group is free and are called a primary amide. When one hydrogen of NH_2 is replaced by an alkyl or aryl group such as RCONHR', it is known as a secondary amide, and tertiary amides are

RCONR'R”, where both the hydrogens of amine are substituted. Some additional amide classes depend on the carboxylic acid-derived parts such as imides, α-keto amide and β-keto amide. Cyclic amides are called lactams [1-2].

1.3 Amides in nature, medicine and daily life

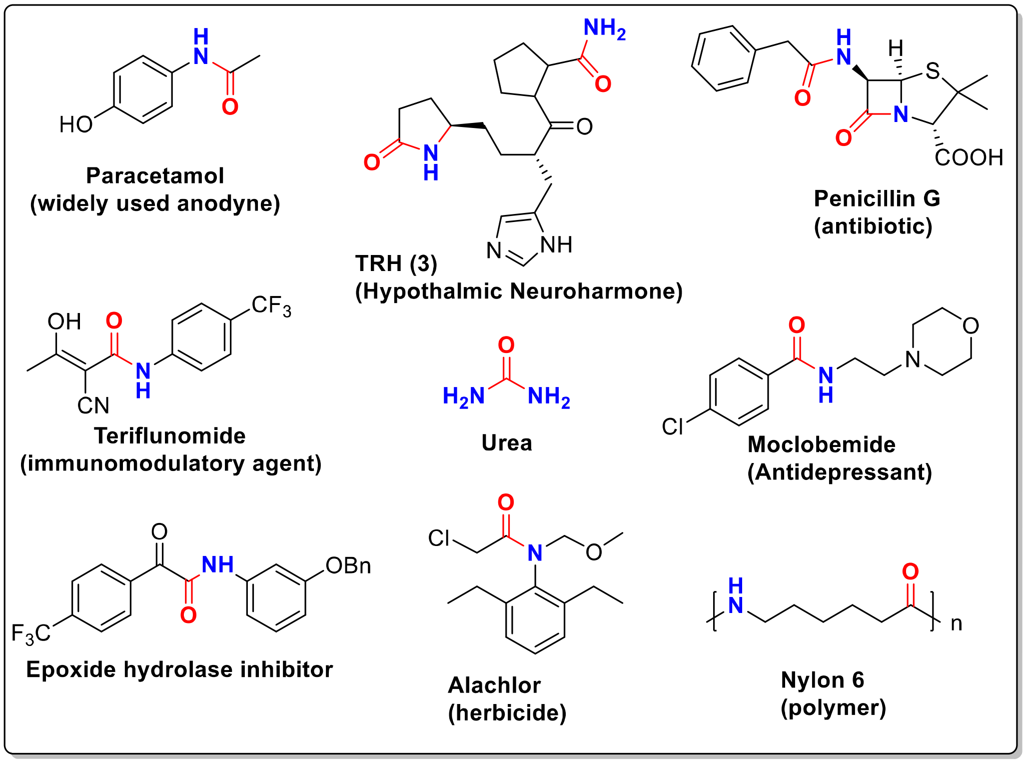
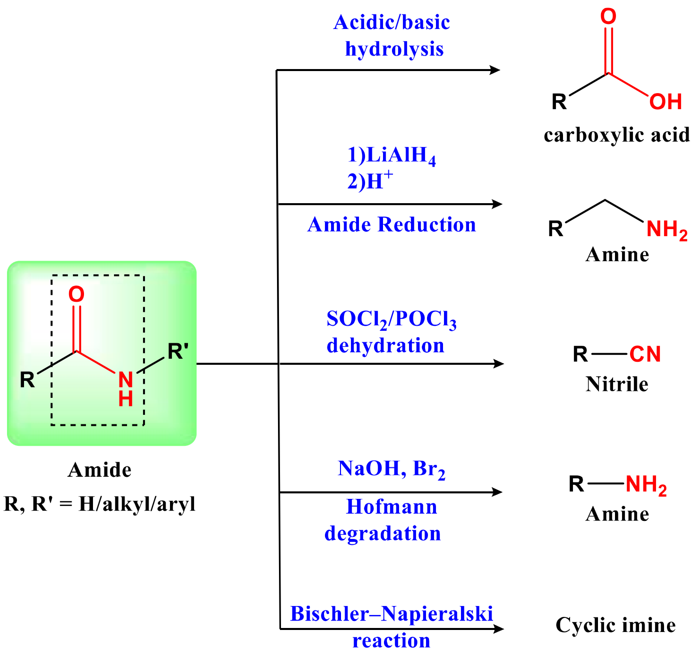


Figure 1.4 Examples of some important amides.

Amides are one of the most fundamental functional groups omnipresent in chemistry, biology, and materials science [3, 8, 9]. Their widespread presence in nature (e. g. in proteins, peptides, alkaloids, hormones and innumerous natural products) makes them essential structures to be explored. They are proven to be potential drugs such as paracetamol (analgesic), penicillin G (antibiotic), teriflunomide (immunomodulatory agent), moclobemide (antidepressant), isoniazid (antituberculous agent), and various other classes of pharmaceuticals like frovatriptan, niraparib, lenvatinib, and labetalol. In drug discovery, amidation reactions are performed reactions by medicinal chemists because 25% of existing drugs and 33% of new drug candidates contain amide framework in their structures [10, 11]. Moreover, fertilizers like urea, herbicides such as alachlor and nylon which is an important polymer, are amides. Amides are widely used in the synthesis of materials of daily use like engineering plastics, lubricants, fertilizers, detergents, natural products, proteins, peptides, and pharmaceuticals core structural units [2-5].

1.4 Synthetic Importance of Amides

Due to their increased stability imparted by resonance, amides are relatively stable. Amides do not undergo a nucleophilic attack readily, also amides are weaker bases which altogether makes them less reactive towards function group interconversion reactions. The remarkable stability of amides makes some of the selective organic reactions involving amide bond cleavage extremely difficult. Traditionally, from the textbook knowledge, it is clear that amides are being used as precursors for some distinct reactions and we can convert them into different functional groups under specific reaction conditions [12]. Though simply heating with water does not work in the case of amides but amides hydrolyse in acidic or basic mediums to provide corresponding carboxylic acids via the nucleophilic addition of water [13]. Amides can also be converted to amines in the presence of lithium aluminium hydride. The nucleophilic hydride attacks the electrophilic polar carbonyl group of the amide creating the tetrahedral intermediate, a metal alkoxide complex, which disintegrates into the product amine [12].



Scheme 1.1 Amides as precursors of different molecules.

Primary amides can be converted to primary amines by an alternative route also which is Hoffman Bromo-amide degradation. In the presence of NaOH and Br_2 primary amide rearranges itself to primary amine through nitrene intermediate [14]. Dehydration of amides is an efficient and fundamental method for the synthesis of nitriles. In the presence of strong dehydrating agents such as $POCl_3$, P_2O_5 or $SOCl_2$ [12], primary amides provide nitriles by the almost same mechanism. Additionally, amides can yield cyclic imines by Bischler-Napieralsky reaction [15]. Amides are employed in the transformation leading to polyamides which give rise to some excellent and stable polymers such as Kevlar and nylon 66 [16].

1.5 Reactivity of Amides

As discussed earlier, amidic resonance is an interesting and most prominent feature of the amide bond due to the delocalization of nonbonding electron pairs of nitrogen over the π* system of the carbonyl group. In planer amides, the resonance energy associated with the stabilization is around 15–20 kcal/mol, which has contributed tremendously to sustaining living systems by controlling the reactivity of proteins and peptides [2]. Destruction of amidic resonance can separate the two functional groups amino and ketone which in turn shall behave significantly different in terms of stability and reactivity of classic amide bonds. Amides are nucleophilic at the oxygen atom which imparts rotation encircling the N–C(O) bond and destroys nN→π*C=O delocalization of electron pairs [17, 18, 19]. This induces structural and electronic changes in the amide bond, resulting in increased charge at the nitrogen atom and loss of the planarity of the bond. In other words, twisting around amide bonds uncovers a new aspect of amide reactivity and the process has been termed ground sate destabilization [20-24]. It is a powerful tool to transform classically inert amides into easily modifiable functional groups. The amide bond twisting mechanism is already present in biochemical processes such as protein N-glycosylation, peptide hydrolysis, and *cis-trans* isomerization of proteins [25].

1.6 Activated or Twisted Amides

Twisted amides can be traced back to the bridged lactams [26-31] where the amide bond is placed in such a rigid bridged ring system with locked conformations. In this case, no amidic resonance is possible. In 1998 and 2006 Kirby [26] and Stoltz [27] group respectively, reported full characterization of some classic twisted amide examples which showed a significant reduction in amidic resonance and were highly reactive amino-ketones in nature.

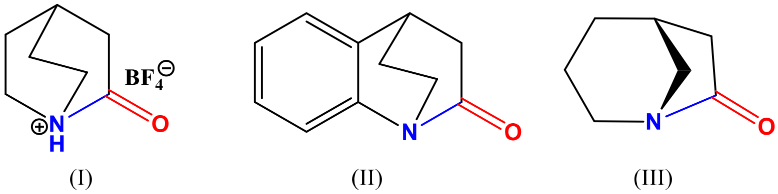
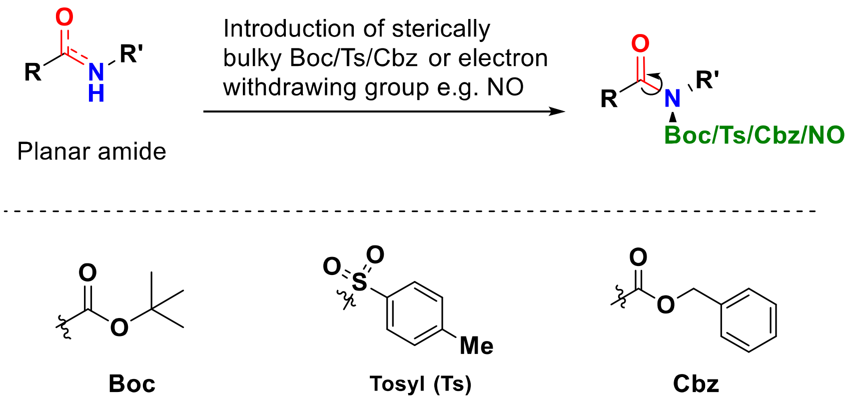


Figure 1.5 Structures of bridged lactams regarded as classical twisted amides.

The magnitude of distortion can be decided by Winkler–Dunitz distortion parameters [30] χN (piramidalisation at nitrogen atom), τ (twist angle) and χC (C-pyramidalization), including the additive Winkler–Dunitz parameter (τ + χN). τ is 0° for planar amide bonds and 90° for fully perpendicular bonds; χN and χC are 0° for planar bonds and 60° for fully pyramidalized amide bonds. However, acyclic amides are synthetically are of great use and activation of acyclic amides has gathered significant attention from synthetic chemists. In order to activate amides, ground state stabilization can be achieved in two ways, where the first being electronic activation. The second method we can consider geometric modification of the amide bond by twisting and pyramidalization. For achieving electronic activation, an electron-withdrawing group is introduced on the nitrogen atom of an amide bond. These groups pull back the electron from the amide bond and thus revert back the electron flow towards the $n_N \rightarrow \pi^*_{C=O}$. Consequently, amides show a weaker N−C(O) conjugation with more electrophilic carbonyl carbon. Similarly, twisting of amide bonds can be performed by attaching sterically bulky substituents at the nitrogen atom of the amide bond to achieve selective activation of the amides.



Scheme 1.2 Methods for activation of amides.

1.7 Categories of Activated Amides

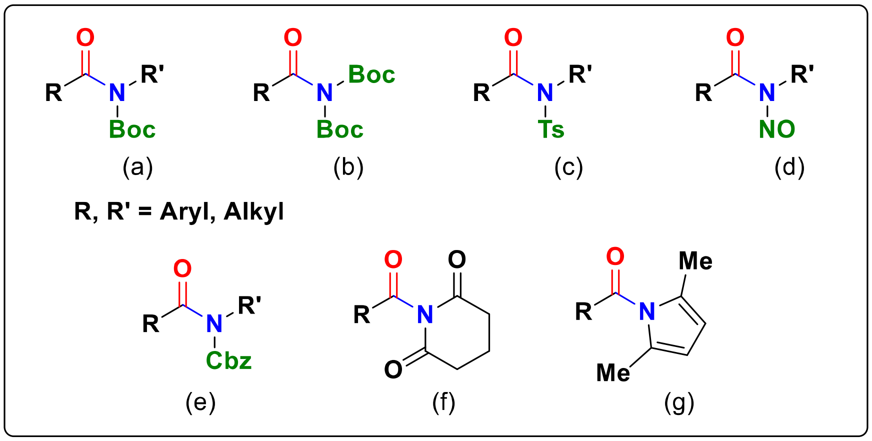
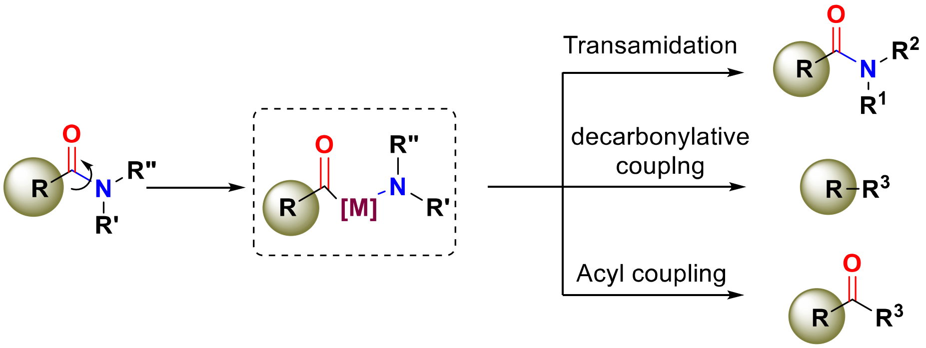


Figure 1.6 Some important categories of activated amides.

The general categories of amides that undergo N−C bond activation through ground state destabilization can be given as cyclic imides, *N*-acyl-sulfonamides, *N*-mono-Boc amides, *N*,*N*-Boc$_2$-amides, *N*-Cbz-amides, *N*-nitroso-amides, *N*-heterocyclic amides. All these cases show significant distortion around amidic planarity and reduction in nN→π^*C=O conjugation by a combination of twist and electronic activation. *N*-nitroso-amides and *N*-heterocyclic amides can be activated electronically [31-34].

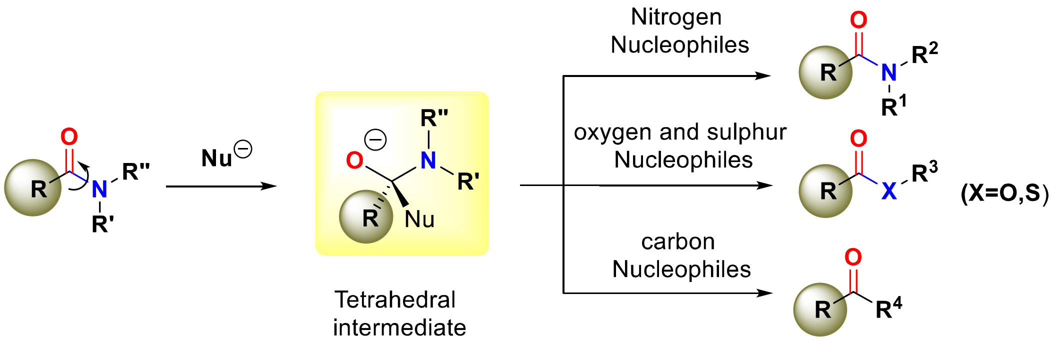
1.8 Strategies for amide activation

Amide activation strategies have been demonstrated in two broad categories, (i) Direct transition-metal catalyzed amide activation through metal insertion [21, 35, 36] and (ii) Transition metal-free amide activation via nucleophilic addition [21, 37]. Direct transition-metal catalyzed amide activation includes a class of transformations like acyl coupling, decarbonylative coupling, transamidation reaction and radical coupling. All of them involve metals inserted between weak distorted C-N bonds of amide leading to the cross-coupled product.



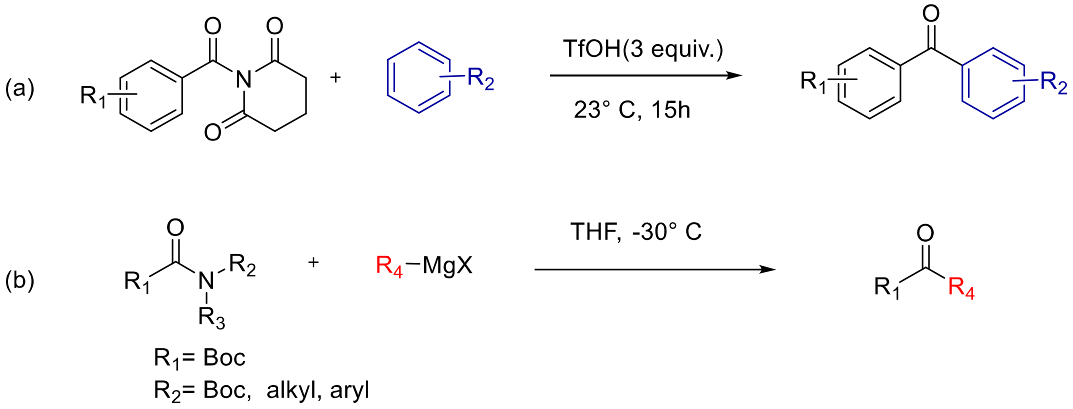
Scheme 1.3 Transition metal-catalyzed amide activation.

For this thesis work, we focused on the second approach, i.e. transition metal-free amide activation. Initially, primary or secondary amides are subjected to site-selective *N*-activation, followed by nucleophilic addition leading to tetrahedral intermediate, which collapses to give the desired product. These transition metal free diversification of activated amides include transamidation reactions to obtain new amides [38], esterification reactions of activated amides employing alcohols and phenols as nucleophiles to obtain esters [40] and metal free Friedel-Crafts acylation of twisted amides [39].

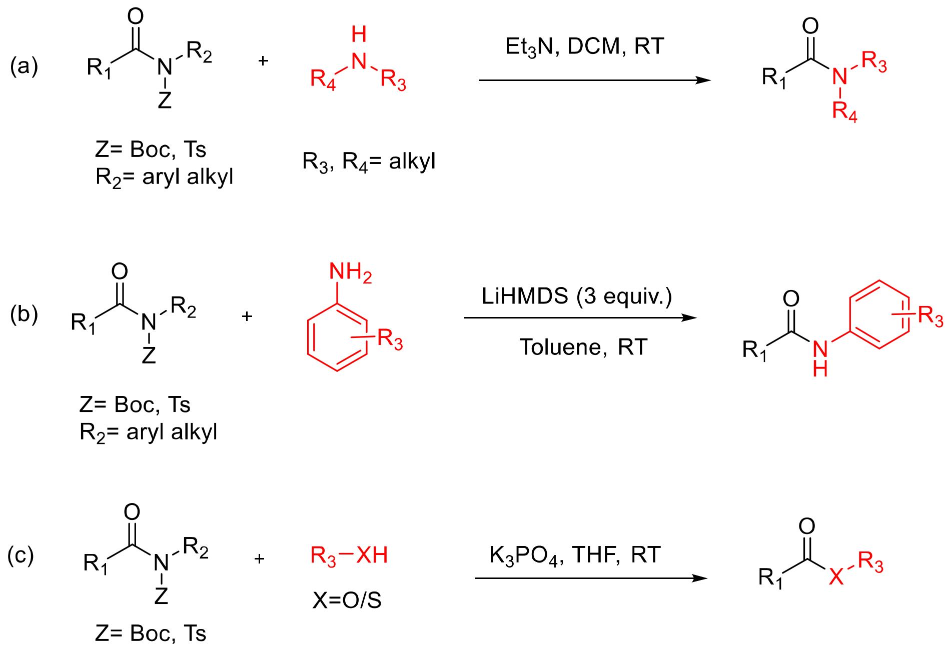


Scheme 1.4 Transition metal free amide activation.

Moreover, carbon nucleophiles such as Grignard reagent [41] and enolizable carbonyl compounds [42] also react in the similar way to yield corresponding ketones or other carbonyl compounds respectively.



Scheme 1.5 Formation of C-C bond via transition metal-free amide activation. (a) Friedel-Crafts acylation of twisted Amides, (b) Synthesis of aryl ketones from activated amides.



Scheme 1.6 Formation of C-N bond via transition metal-free amide activation. (a) Friedel-Crafts acylation of twisted amides, (b) Synthesis of aryl ketones from activated amides.

1.9 Conclusion

Undoubtfully amides are very important precursors in chemistry and biology. They are very stable and can be stored for a longer period and handled easily. The diversification of amides by N-C bond cleavage is becoming a prominent tool in synthetic organic chemistry due to the prevalence of the amide bond in nature. However, the direct use of amides in functional group transformations needs harsh reaction conditions. It is mainly due to the planarity of the amides. Introducing a bulky group on the nitrogen of the primary and secondary amides destroys the planarity of amides through which functional group transformations were achieved. In fact, among the different ways of activations, this approach allows easy functional group transformations in amides.

1.10 Objectives of the thesis work

The objective of this thesis was to further explore *N*-activated amides as precursors for different organic transformations. Based on the literature reports and our group work, the objective of the thesis has been framed as follows,

1. Diversification of *α*–ketoamides via transamidation reactions with alkyl and benzyl amines at room temperature.
2. Synthesis of *N*-Aryl *α*–Ketoamides, *α*–Ketoesters, *α*–Ketothioesters and their applications in quinoxalinone preparation.
3. Synthesis of acyl hydrazides from amides and hydrazine hydrate under metal-free conditions at room temperature.
4. Synthesis of 1,3-dicarbonyl compounds using *N*-Cbz amides as an acyl source under transition metal-free conditions at room temperature.

1.11 References

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