



Multicomponent Synthesis of *N*-Substituted β -Amino Carbonyl Scaffolds Using Nickel Sulphate as Catalyst

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Abstract: We report an efficient, mild and rapid approach for the synthesis of β -amino carbonyl scaffolds via three component coupling of aromatic aldehydes, enolizable ketones and nitriles in presence of acetyl chloride by using nickel sulphate as a new and highly effective catalyst under solvent free conditions. Our continuing interest in developing this methodology as a novel route to access highly functionalized structural scaffolds in a cost-effective, environmentally friendly and more importantly, a process requires less operational skill and conditions.

Introduction

The traditional chemical industry was a hazardous and polluting one. It generated stoichiometric amounts of waste, causing much pollution of both air and water. Today, the escalating costs of petrochemicals and increasing energy and raw material consumption forcing a change. As a consequence, the industry demands from chemists the development of new reaction methodologies to obtain novel compounds in a fast, clean and efficient way (Rothenberg, 2008; Zhu, 2005). In this scenario, multicomponent reactions (MCRs) offer an alternative to the traditional synthesis mainly because it is based on available starting materials, operationally simple, easily automatable, resource effective, atom economical and ecologically benign. Mannich-Type products, specifically β -amino carbonyl compounds are useful chiral building blocks for the synthesis of β -amino acids, β -lactams, β -amino alcohols, and so forth (Kobayashi and Ishitani, 1999; Cordova, 2004). These class of compounds are generally

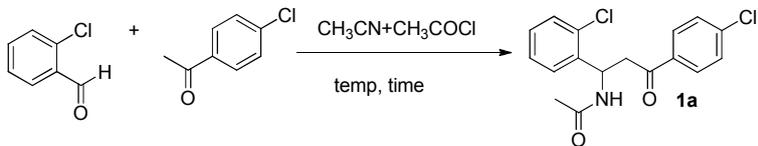
synthesized by chiral Lewis acids assisted catalytic asymmetric reactions of imines derived from aldehydes and amines with enolate compounds.

Several efficient Lewis acids have been reported over the years (Kobayashi *et al.*, 2010; Ishitani *et al.*, 2000; Josephsohn *et al.*, 2004) and a recent attraction in this field is the development of the concept of bifunctional catalysis, wherein both partners of a bimolecular reaction are simultaneously activated, is very powerful for developing efficient asymmetric catalysts (Shibasaki *et al.*, 2007, 2008, 2009; Kanai *et al.*, 2005; Matsunaga *et al.*, 2008). Even though these chiral Lewis acids have proven to be efficient for many reactions, a major drawback is that most Lewis acids are unstable in presence of water and some of them are even moisture sensitive and also based on multi-step programme demands high synthetic skill. As an efficient alternative to the synthesis of Mannich-Type products, we and other groups have developed a one pot multicomponent protocol based on the

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Table 1. Optimization of reaction conditions



Entry	Loading(mol%)	T/°C	Time	Yield(%)
1	5	rt	4h	76
2	10	rt	4h	78
3	15	rt	4h	79
4	20	rt	4h	83
5	5	60	4h	76
6	10	65	4h	70
7	20	70	4h	80

coupling between an aldehyde, an enolizable ketone, and a nitrile molecule in the presence of an acid chloride and an acid catalyst (Rao *et al.*, 2003; Bahulayan *et al.*, 2012; Maghsoodlou *et al.*, 2007; Khodaei *et al.*, 2005). Several efficient catalysts have been reported by various research groups which includes SnCl₄/SiO₂ (Mirjalili *et al.*, 2009), Cu(OTf) (Pandey *et al.*, 2005), Sc(OTf)₃ (Heravi *et al.*, 2010) Mn(bpdo)₂Cl₂/MCM-41 (Khan *et al.*, 2006) etc. Until recently, the scope of this three component process was limited to the synthesis of β-acetamido carbonyl compounds. Recent developments in this area, particularly from our laboratory (Bahulayan *et al.*, 2003, 2012; Shinu *et al.*, 2009, 2011), revealed that this process is highly useful for the one step synthesis of highly functionalized organic intermediates.

Our continuing interest in developing this methodology as a novel route to access highly functionalized structural scaffolds in a cost-effective, environmentally friendly and more importantly, a process requires less operational skill and conditions; we considered the possibility of performing this

reaction in very mild conditions for the incorporation of a large variety of substrates. For this, we decided to follow this reaction in the presence of nickel sulfate.

Results and discussion

We have initiated our studies with the synthesis of the β-amido carbonyl compound using nickel sulphate and optimization of the reaction conditions. In the first round of optimizations, the reaction between 2-chlorobenzaldehyde and 4-chloroacetophenone was selected as the model reaction for the screening purpose. Optimizations were carried out in terms of the amount of catalyst, reaction time and temperature while keeping acetonitrile as solvent in all the cases. Taking into account of our previous experiences with Mont. K10 (Bahulayan *et al.*, 2003) and Selectfluor™ (Shinu *et al.*, 2009), we decided to carry out the screening experiments at room temperature and at the boiling point of acetonitrile. We found that a room temperature reaction with 20 mol% of the catalyst gives the maximum yield- 83% (Table 1, entry 4).

After the optimization reactions, the substrate scope studies were carried out with

catalyst. Sequential addition of aldehyde,

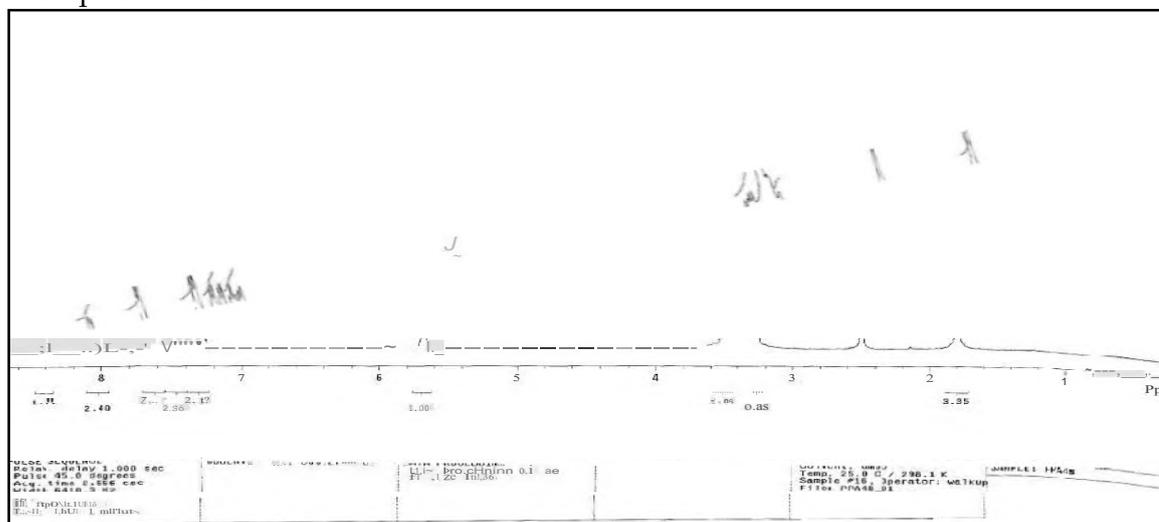


Fig. 1. ¹H NMR spectrum of compound 1a

ketone and acetyl chloride in the presence of nickel sulphate in acetonitrile resulted in the rapid formation of the product. With a very low amount of the catalyst (20 mol %), the reaction reached completion in 4 hours as indicated by TLC. Here the nitrile source acted as both reagent and solvent. FT-IR spectroscopy is very useful for following the reaction. In the FT-IR spectrum, the disappearance of the aldehyde peak followed by the appearance of amide peak at 1650 cm⁻¹ is a clear indication about the commencement of the reaction. The structure of the product was confirmed via ¹H NMR, FT-IR and mass spectral studies. All the reactions yielded clean products that can be directly used for analysis. The reaction conditions were mild and avoided the use of environmentally hazardous chemicals.

In the ¹H NMR spectrum, (Figure 1) a doublet obtained at $\delta = 8.39-8.37$ is due to the NH proton of the acetamido group. A multiplet obtained between 7.60-7.28 is attributed to the presence of aromatic protons of the two benzene rings. The methylene protons are in different chemical environments due to the presence of the adjacent chiral carbon. In the ¹H NMR spectrum, these two proton signals are observed between $\delta 3.49-3.44$ and between $\delta 3.31-3.25$ respectively. Both these signals

observed as doublet of doublets with approximately equal coupling constants (20 and 24 Hz) and the splitting of signals is occurred due to the spin-spin couplings of the protons of the same carbon and of the adjacent chiral carbon. The CH proton is observed as a singlet at $\delta 5.68$. Finally, the methyl protons are observed as a singlet at $\delta 1.74$.

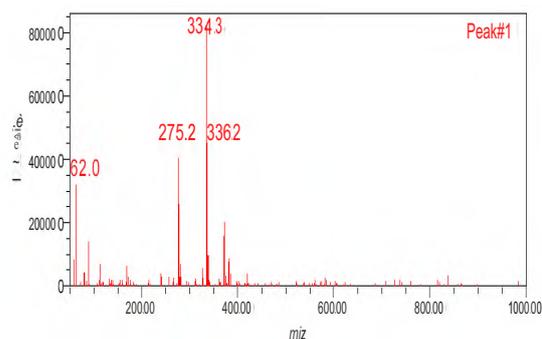
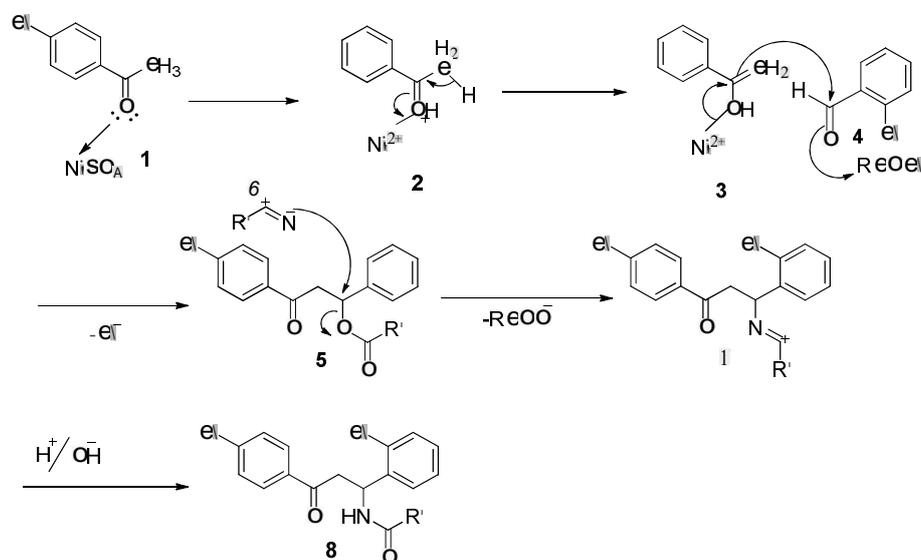


Fig. 2. Mass spectrum of compound 1a

The suggested mechanism of the reaction is shown in Scheme 1. The reaction is initiated by the co-ordination of the carbonyl oxygen of the ketone moiety with the metal atom of the catalyst. Nickel sulphate acts as a Lewis acid and thus activates the enol 3 formation. The addition of aldehyde moiety 4 followed by acid chloride to this complex resulted in the carbon-carbon bond formation to



Scheme 1. Proposed mechanism for the formation of β -amido carbonyl scaffolds using nickel sulphate as catalyst.

produce a β -acyloxy ketone derivative **5**. The acyloxy group in **5** is then displaced by the more nucleophilic nitrogen of the nitrile to produce a stable cation intermediate **7**. Addition of water leads to the formation of the β -amino ketone derivative **8**.

Conclusion

In summary, we have reported the efficiency of nickel sulphate catalysts for the synthesis of β -amino carbonyl compounds (Mannich type products) via four-component coupling reaction. The study reveals that the catalyst is more efficient in catalyzing the reaction. The method offers several advantages such as high yields, short reaction times, mild reaction conditions, simple experimental procedures, cost effectiveness and tolerance to a wide variety of reactants. The catalysts used are environmentally friendly, inexpensive and highly efficient. Using the peptide type scaffolds thus produced, many macrocyclic compounds of pharmaceutical importance can be developed using suitable MCRs coupled with other organic name reactions. Since many nickel salts are commercially available, the study can be extended to explore their possibility also.

That is, in addition to the alternate Mannich type reaction reported here, the work can be extended to many other name reactions.

Experimental

Materials

Chemical reagents were purchased from the Merck Chemical Company in high purity. All the materials were of commercial grade reagent.

Typical Experimental Procedure for One Pot Three Component Coupling Reactions of Aldehydes with α -Substituted Ketones and Acetonitrile with Nickel sulphate as Catalyst.

A 100 mL RB flask was charged with a solution of the aryl aldehyde (1.25 mmol), aryl ketone (1.25 mmol), acetyl chloride (3 mL) and acetonitrile (5 mL) in the presence of nickel sulphate (0.1g). The resulting mixture was then set to stir continuously for 4 hours at room temperature. After the completion of the reaction as indicated by TLC, the reaction mixture was diluted with distilled water and stirred well. The precipitate obtained was collected by filtration, washed with distilled water (3 x 20 mL) and dried under vacuum.



The dried solid was then washed with diethyl ether (3 x 15 mL) and air-dried to yield the pure β -amino acid derivative. The product was identified by comparing its NMR and IR values.

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