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Beckmann Rearrangement : Thiamine hydrochloride as a remarkable catalyst for one-pot synthesis of amides from ketones

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ABSTRACT

Thiamine hydrochloride catalyzed synthesis of amides from ketones including 3-acetyl coumarin *via* Beckmann rearrangement has been reported. The reaction is believed to involve oxime formation, cleavage of C-C bond followed by C-N bond formation in one-pot. Thiamine hydrochloride is stable, cheap, easy to handle and environmentally friendly.

Keywords:
Beckmann rearrangement
thiamine hydrochloride
ketones
amides
acetamidocoumarin

Introduction

Beckmann rearrangement (BKR) is remarkable transformation for the synthesis of amides or lactams from the corresponding ketones. It is often used in the synthesis of natural products and pharmaceuticals.[1] The preparation of amides from ketones occurs in two steps : oxime formation followed by its Beckmann rearrangement. The conventional Beckmann rearrangement of ketoximes makes use of strong Bronsted or Lewis acids such as conc. H_2SO_4, PCl_5 in diethyl ether, HCl in acetic anhydride which results in production of side products, environmental hazards and serious corrosion problems.[2] To overcome these problems, several methods have been reported in the literature for Beckmann rearrangement of ketoximes.[3-9] In view of the importance of direct conversion of ketones to amides, several one-pot methods[10] were developed in the last few decades (**Scheme 1**). However, most of these methods suffered from one or more drawbacks such as expensive reagents, harsh reaction conditions, long reaction time, environmental hazards, tedious work up and separation issues. To overcome these drawbacks, there exists a need to develop one-pot simple, cheap, fast and eco-benign methodologies to carry out this transformation.

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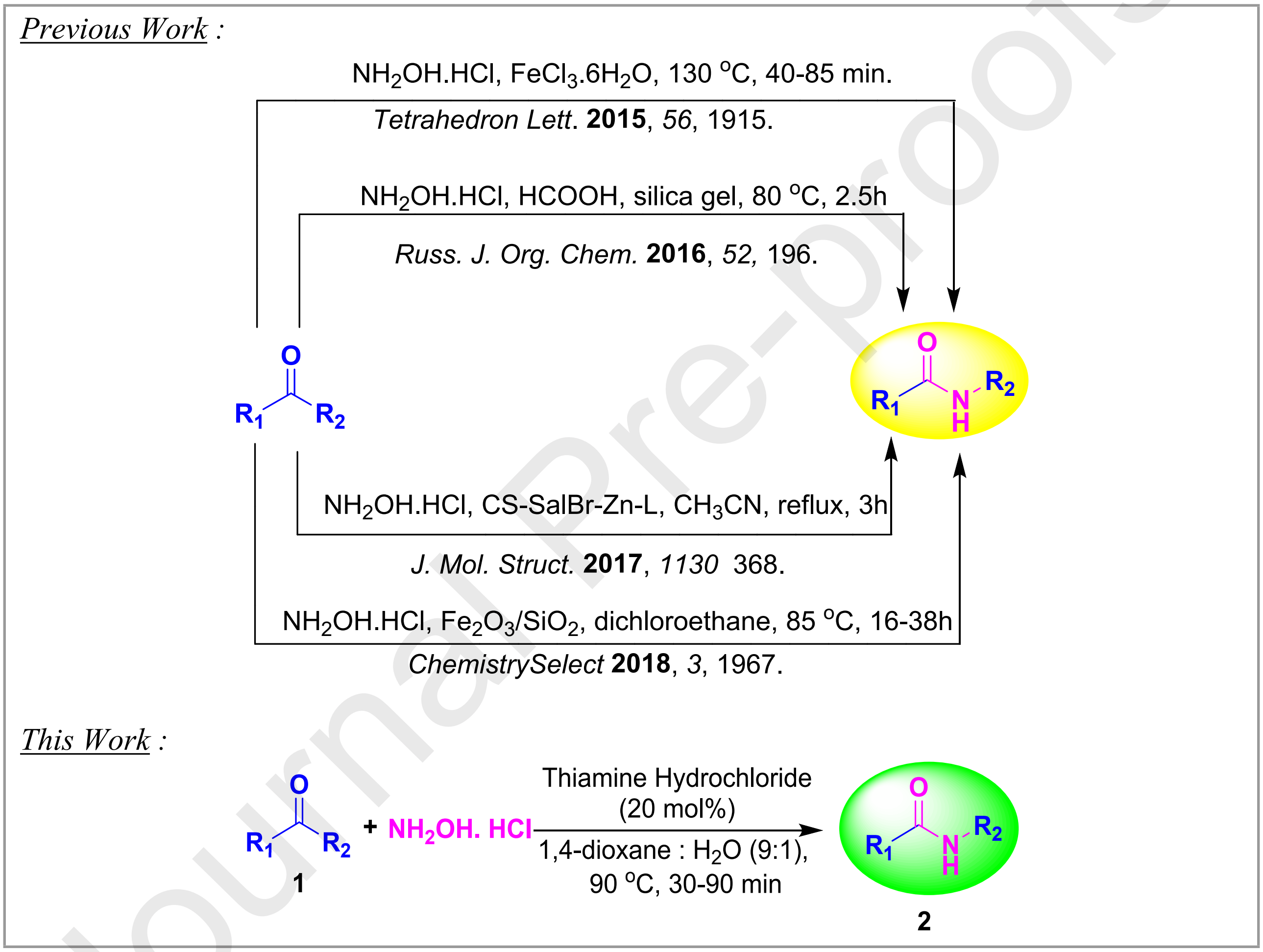
Thiamine hydrochloride also known as Vitamin-B_1 is a colorless organosulfur compound synthesized by bacteria, fungi, and plants. It contains aminopyrimidine and thiazole ring linked by a methylene bridge. Due to its non-toxicity, stability, biodegradability and easy accessibility, several chemists have employed it as a potent catalytic tool for various organic conversions.[11] So, we wished to probe the direct conversion of ketones to amides in presence of catalytic amount of thiamine hydrochloride (**Scheme 1**).



Scheme 1 One-pot synthesis of amides from ketones.

To begin with, a neat mixture of benzophenone oxime (2 mM) and thiamine hydrochloride (30 mol%) was heated at 120 ˚C and conversion to the desired amide was noticed after 30 min (65% yield). However lowering the reaction temperature to room temperature (40˚C) and 90˚C resulted in no product formation or incomplete conversion respectively. Further to explore the possibility of *in situ* formation of oxime followed by its Beckmann rearrangement, a mixture benzophenone (2 mM) **1a**, hydroxylamine hydrochloride (1.2 eq.) and thiamine hydrochloride (30 mol%) was

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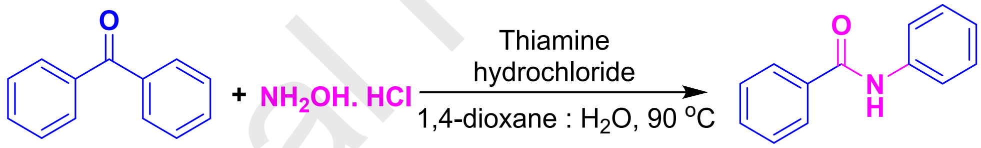
heated at 120 ˚C. To our delight, the formation of desired amide was noticed after 30 min (72% yield). The reaction was also conducted in different solvent systems and the results are summarized in **Table 1**, which reveals that best reaction occurs in dioxane:H_2O (9:1) system (80% yield) (**Table 1,** entry **5**). Thus it was noticed that the addition of about 10% H_2O makes the reaction mixture homogeneous and improves the yield of the product.

Entry	**Solvent systems used**	**Mode of the reaction**	**Yield (in %)**[a]
1.	No solvent (Neat)	120 ˚C	72
2.	1,2-dichloroethane	Reflux	50
3.	1,4-dioxane	Reflux	65
4.	Acetonitrile :H_2O*	Reflux	35
5.	**1,4-dioxane : H_2O***	**90 ˚C**	**80**
6.	Ethanol : H_2O*	Reflux	40

[a] Isolated Yields
* 9:1 mixture

Table 1 Solvent system scan.

Also, during optimization of the reaction conditions, it was observed that 20 mol% of thiamine hydrochloride and 1.5 eq. of hydroxylamine hydrochloride gave the best results (**Table 2**, entry **5**).



1a **2a**

Entry	**Amount of hydroxylamine hydrochloride used (in eq.)**	**Amount of thiamine hydrochloride used (mol %)**	**Time (in min.)**	**Yield (in %)**[a]
1.	1.2	-	60	No reaction
2.	1.5	-	60	No reaction
3.	1.5	10	60	50
4.	1.2	20	60	90
5.	**1.5**	**20**	60	**95**
6.	2	20	60	95
7.	1.5	30	60	90
8.	1.5	50	60	80
9.	1.5	100	60	Inseparable spots on tlc

[a] Isolated Yields

Table 2 Optimization of the amount of hydroxylamine hydrochloride and thiamine hydrochloride.

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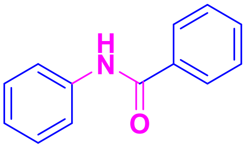
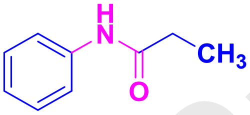
It is pertinent to mention here that Beckmann rearrangement of ketoxime to amide in 90 % yield also occurred with 20 mol% of thiamine hydrochloride in dioxane : H_2O (9:1).

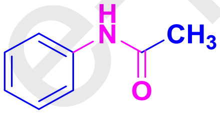
Various ketones having electron donating and electron withdrawing groups were reacted under similar conditions and the results are shown in **Figure 1**. For alkylarylketones only one of the two possible amides were obtained owing to better migratory aptitude of aryl group. 4-nitro-benzophenone yielded 4-nitro-*N*-phenylbenzamide **2l** while 4-methoxy-benzophenone gave inseparable mixture of *N*-(4-methoxyphenyl) benzamide **2m(i)** and 4-methoxy-N-phenylbenzamide **2m(ii)**. In case of **2l** the phenyl group migrated in preference to its 4-nitro counterpart while in **2m** very little preference of 4-methoxyphenyl was observed over the phenyl group. Ketones containing heteroaromatic systems also gave products **2q-2u** in excellent yields. Isatin and ninhydrin also resulted in smooth conversion to the corresponding products **2t** and **2u** respectively.



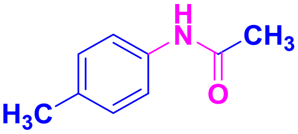
2a
(95%, 60min)



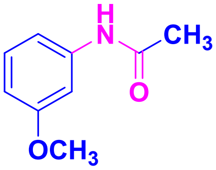
2b
(90%, 30 min)



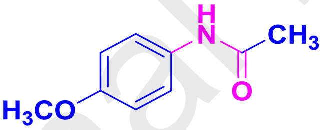
2c
(90%, 30 min)



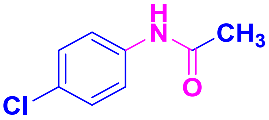
2d
(80%, 40 min)



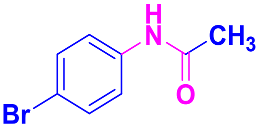
2e
(85%, 40 min)



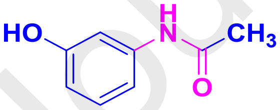
2f
(85%, 70 min)



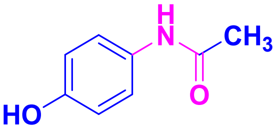
2g
(90%, 30 min)



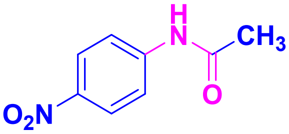
2h
(93%, 30 min)



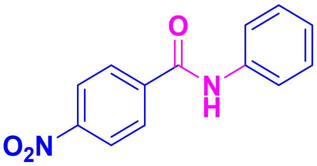
2i
(90%, 30 min)



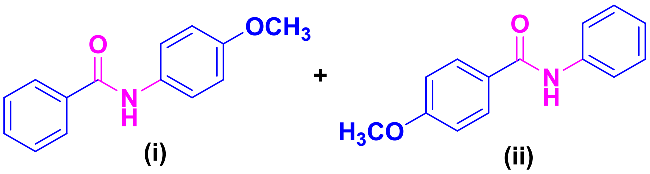
2j
(90%, 30 min)



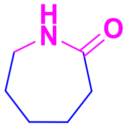
2k
(88%, 30 min)



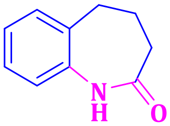
2l
(90%, 30 min)



2m
(90%, 30 min)



2n
(75%, 50 min)



2o
(75%, 50 min)

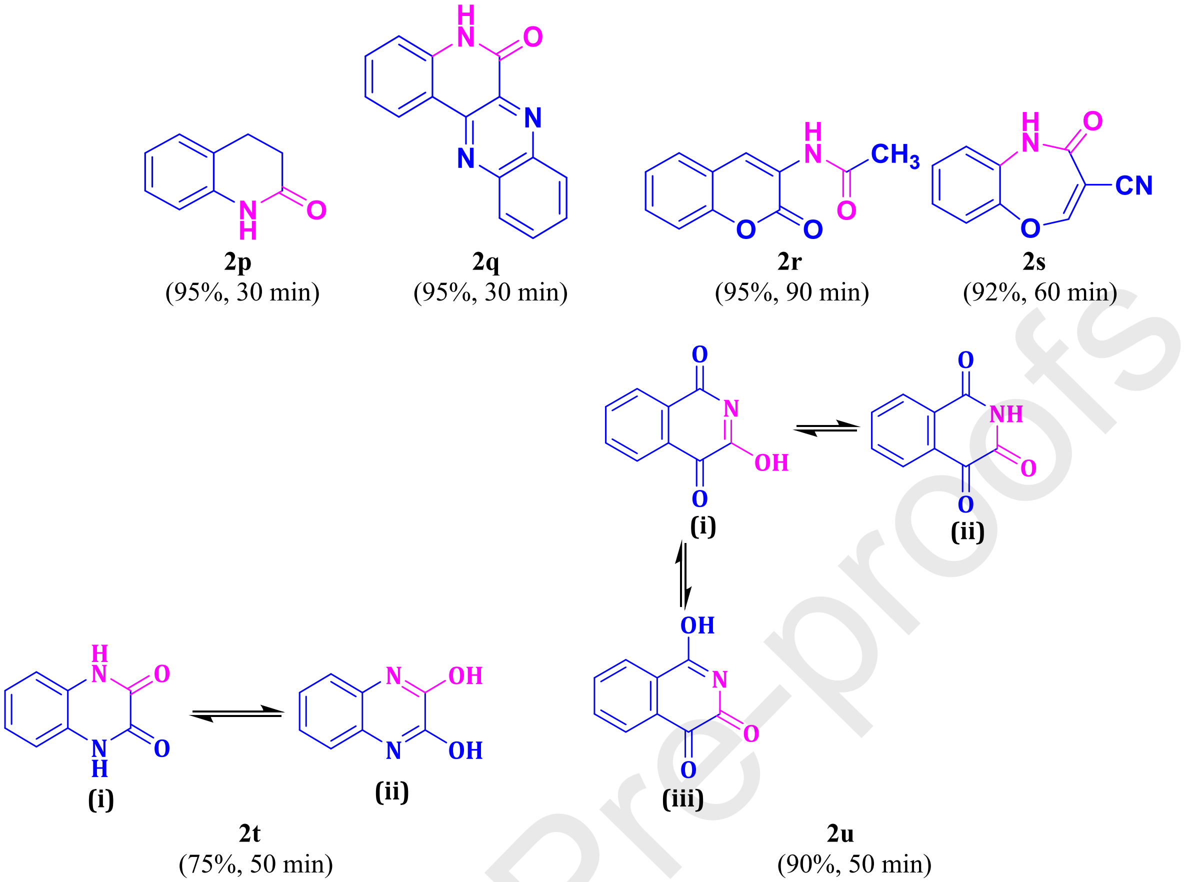


Figure 1 Formation of amides (**2a-2u**) from ketones in presence of Thiamine hydrochloride.

3-acetamidocoumarin **2r** represents a promising class building blocks for designing pharmacologically useful agents for the treatment of various diseases.[12] The present method yields 3-acetamidocoumarin **2r** from 3-acetyl coumarin in excellent yield. The spectral and physical data of **2r** resembles that with the known compound.

Plausible reaction mechanism

Initially thiamine hydrochloride activates the carbonyl carbon of benzophenone **1a** to facilitate the formation of its oxime **A** which undergo thiamine hydrochloride assisted Beckmann rearrangement to give the corresponding amide **2a** (**Scheme 2**).

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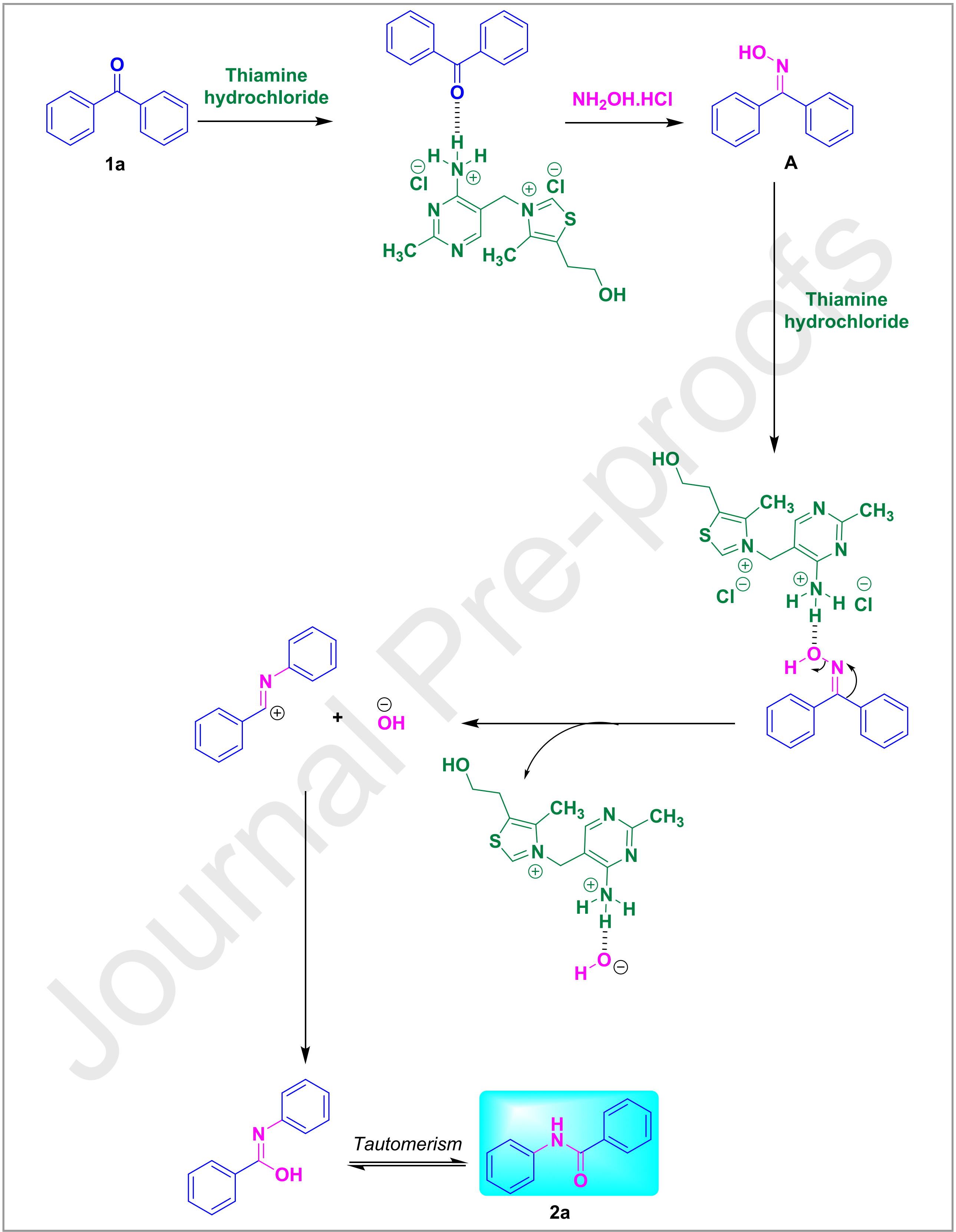

Scheme 2 Plausible reaction mechanism for the synthesis of amides.

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In summary, we have developed thiamine hydrochloride catalyzed direct conversion of ketones to amides in presence of hydroxylamine hydrochloride. This protocol consists of *in situ* formation of ketoxime followed by its conversion to amide in one-pot. In addition to this, precursor for bioactive molecules i.e. 3-acetamidocoumarin can be easily accessed using this protocol.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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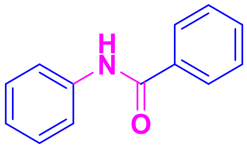

2a
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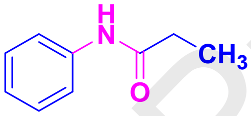

2b
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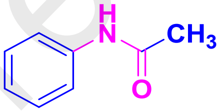
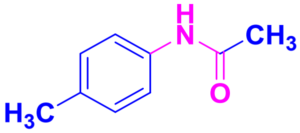
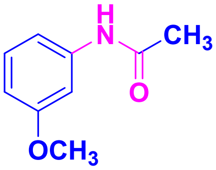


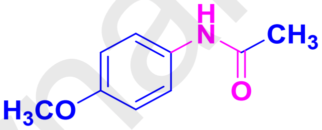
2c
(90%, 30 min)



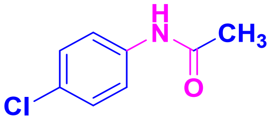
2d
(80%, 40 min)



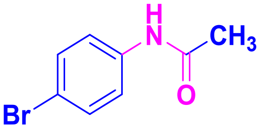
2e
(85%, 40 min)



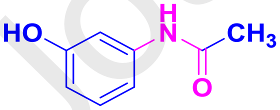
2f
(85%, 70 min)



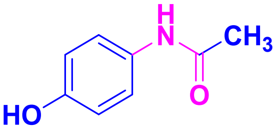
2g
(90%, 30 min)



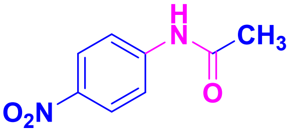
2h
(93%, 30 min)



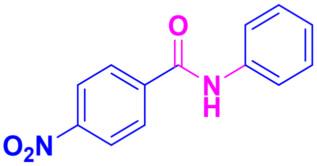
2i
(90%, 30 min)



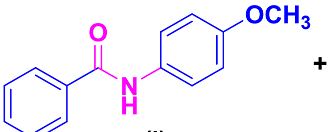
2j
(90%, 30 min)



2k
(88%, 30 min)

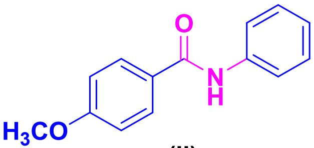


2l
(90%, 30 min)

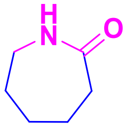


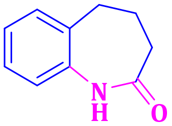
(i)

+



(ii)

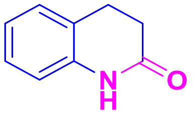




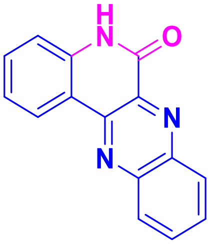
2m
(90%, 30 min)

2n
(75%, 50 min)

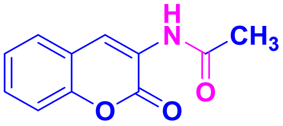
2o
(75%, 50 min)



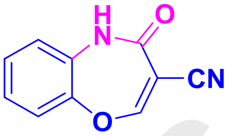
2p
(95%, 30 min)



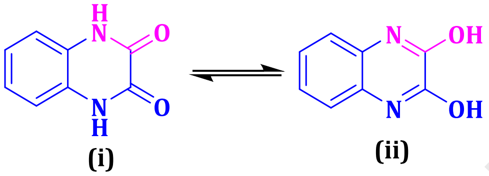
2q
(95%, 30 min)



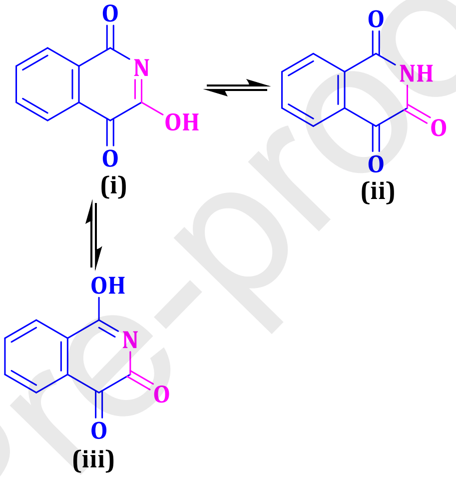
2r
(95%, 90 min)



2 s
(92%, 60 min)



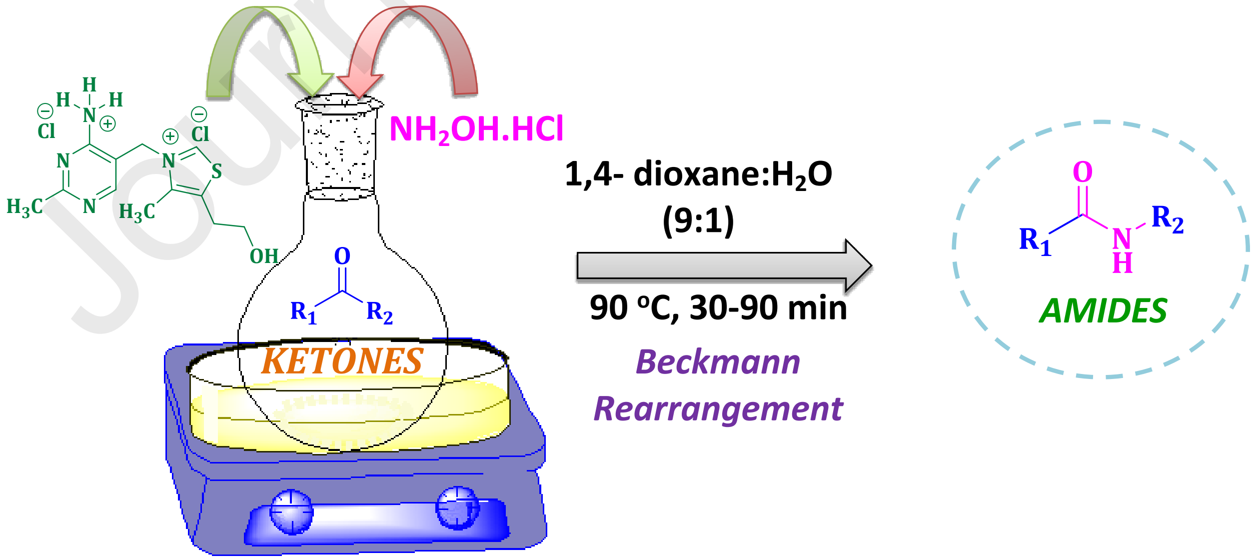
2t
(75%, 50 min)



2u
(90%, 50 min)

Figure 1 Formation of amides (**2a-2u**) from ketones in presence of Thiamine hydrochloride.

GRAPHICAL ABSTRACT



Journal Pre-proofs

Highlights of the Revised Manuscript Ref No. : TETL-D-20-00285

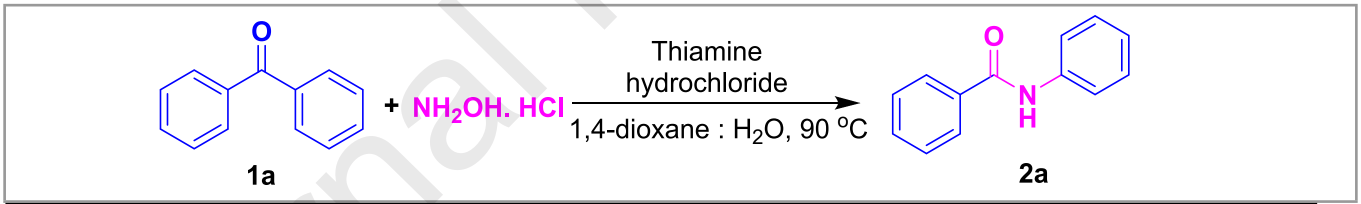
- One-pot conversion of ketones to amides.
- Use of Vitamin-B_1 as environmentally friendly, stable and biodegradable catalyst.
- Easy access to 3-acetamidocoumarin, an important precursor for pharmaceuticals.

Entry	**Solvent systems used**	**Mode of the reaction**	**Yield (in %)**[a]
1.	No solvent (Neat)	120 ˚C	72
2.	1,2-dichloroethane	Reflux	50
3.	1,4-dioxane	Reflux	65
4.	Acetonitrile :H_2O*	Reflux	35
5.	**1,4-dioxane : H_2O***	**90 ˚C**	**80**
6.	Ethanol : H_2O*	Reflux	40

[a] Isolated Yields

* 9:1 mixture

Table 1 Solvent system scan.



Entry	**Amount of hydroxylamine hydrochloride used (in eq.)**	**Amount of thiamine hydrochloride used (mol %)**	**Time (in min.)**	**Yield (in %)**[a]
1.	1.2	-	60	No reaction
2.	1.5	-	60	No reaction
3.	1.5	10	60	50
4.	1.2	20	60	90
5.	**1.5**	**20**	60	**95**
6.	2	20	60	95
7.	1.5	30	60	90
8.	1.5	50	60	80
9.	1.5	100	60	Inseparable spots on tlc

[a] Isolated Yields

Table 2 Optimization of the amount of hydroxylamine hydrochloride and thiamine hydrochloride.

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