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Graphical Abstract

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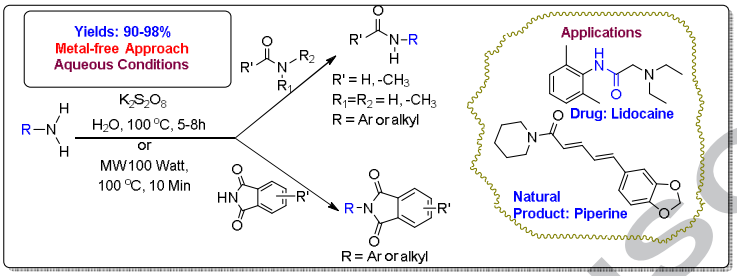

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A metal-free approach for transamidation of amides with amines in aqueous media

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ABSTRACT

An efficient, environmentally benign and a mild protocol for transamidation of amides with variety of amines in presence of $K_2S_2O_8$ using stoichiometric quantity in aqueous conditions has been established. This method works under conventional thermal conditions and in microwave irradiation as well. A series of amides have been prepared using this reaction and this is a greener protocol for transamidation, which offers diverse kind of substrate scope with exclusive product formation (yields 90-98%).

Introduction

Amides are very prevalent in nature, since all peptides and proteins are polymers of the natural α-amino acids.[1] Amide bonds are considered to be very important from medicinal and industrial chemistry point of view and are useful in serving as versatile building blocks in preparation of bioactive products such as peptides, peptidomimetics, proteins, drugs or drug intermediates and also useful in polymer chemistry, agrochemicals, etc.[2] These bonds are ubiquitously present in many of the natural products and pharmaceutical products.[3]

Presently, there have been many recent developments in this field, as researchers are focused on developing novel, atom-economical and environmentally benign methods for amidation. There are number of amide bond bearing molecules that are commonly used in the reactions in medicinal chemistry and these bonds are inherent part of many natural products. Some of the representative and important natural products like piperine, capsaicin, *N*-acetyl-anthranilic acid, taxol, penicillin-G, etc. posses amide bond and drugs such as lidocaine, carbocaine, articaine, amoxicillin, valsartan, acetazolamide, protirelin, atorvastatin, captopril, enalapril and many others also have amide bonds (Fig. 1). The cyclic amides or especially *β*-lactums are considered as versatile building blocks for synthesis of several bioactive molecules.[4]

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Numerous methods have been reported for the preparation of carboxamides in the literature using conventional methods by coupling of carboxylic acid derivatives or acyl halides, anhydrides, aldehydes and alcohols with amines.[5,6] In a report by Galat and Elion shows, aliphatic or aromatic amines were conveniently acylated using hydroxylammonium hydrochloride salts.[7] Apart from this there are many methods available for amide bond formation including the name reactions such as Schmidt, Ugi, Passerini, Chapman, Bodroux reaction, etc.[8]

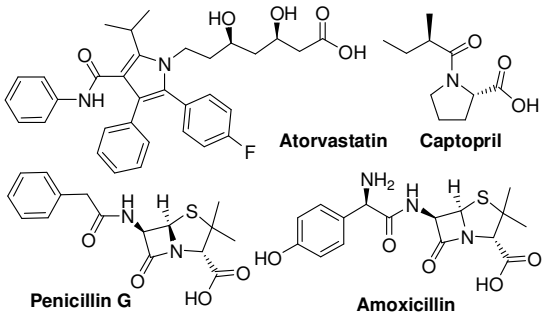
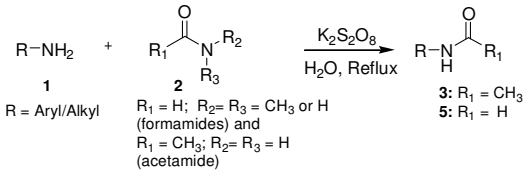


Figure 1. Structures of some important natural products or drug molecules bearing amide bonds

Transamidation of amides with amines could be an alternative and attractive tool for obtaining amide bond bearing substrates. Recently, Stahl *et al.*[9] and Myers *et al.*[10] reported preparation of secondary and tertiary amides. Several metal complexes have also been used for transamidation by different groups including

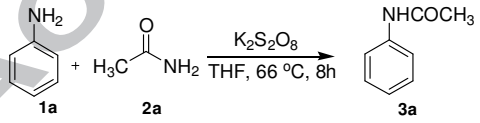
Fe(III), zirconocene dichloride, scandium triflate, $AlCl_3$, $Ti(NMe_2)_4$, lanthanides, polymer-bound $HfCl_4$ and many more.[9,11] Because of high stability of amide groups they are rarely used as acylating agents, they are relatively inert in comparison with other acyl donors and therefore uncatalyzed transamidation reactions require forced reaction conditions. The reactions under metal-free conditions are attractive for their advantages of being environmentally friendly and inexpensive nature. There are few reports available for metal-free transamidation of amides with amines like using boric acid, hydroxylamine hydrochloride, or selenium dioxide-mediated amidation. etc.[2a,12] Metal-free reactions are gaining importance because of problems related to heavy metal health hazards and have been the focus of recent research interest. There is a need to develop more metal-free methods for transamidation. As a part of our continued interests in the development of metal-free reactions,[13] we now report a metal-free strategy for the transamidation of amides with amines using $K_2S_2O_8$ to give amides. As shown in scheme 1, respective transamidated products viz. acetamides 3 or formamides 5, are obtained from arylamines.



Scheme 1. General scheme for transamidation of amides with amines using $K_2S_2O_8$ in aqueous media

Results and discussion

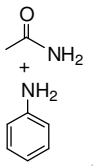
Our studies started with the reaction of aniline 1a and acetamide 2a, using $K_2S_2O_8$ under metal-free condition, in this reaction acetanilide 3a was formed in optimal yields (~70 %), when the reaction was carried out at reflux using tetrahydrofuran as solvent as shown in scheme 2. We initiated optimization of reaction by screening of different solvents that could affect or improve the yields. The reaction in water has given the excellent results (Table 1), maximum (95%) yield was obtained. Comparatively low yields were obtained with other solvents like toluene, DCM, MeOH, ACN, and also in water:ACN (1:1) mixture. However, it is pertinent to mention that in case of DMF as a solvent, transamidated *N*-formyl product was obtained. There was no product formation observed when DMSO was used as solvent. Even though, the reaction has given product in many solvents, we opted to work with water for conducting future reactions because of its unique nature or properties and several other advantages over organic solvents.



Scheme 2. Transamidation of acetamide with aniline for formation of acetanilide **3a**

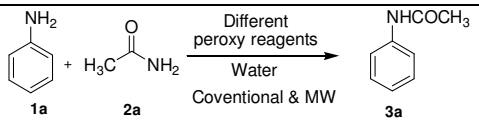
In continuation with the optimization studies, the nature of peroxy bond linkage present in the $K_2S_2O_8$ was also explored by screening different peroxy group bearing reagents viz. H_2O_2, *m*-CPBA, TBHP and oxone (Table 2) to find its role. In this screening $K_2S_2O_8$ was found to be the best for this transamidation reaction. But this reaction requires the use of stoichiometric quantity of the $K_2S_2O_8$ for its completion. The lower equivalents (<1 eq.) of $K_2S_2O_8$ affected the yields and an excess equivalent does not show any effect. However, as a background control reaction, without $K_2S_2O_8$, the reaction does not move forward. After optimizing these conditions using conventional heating protocol, we moved our focus on optimizing the reaction under microwave irradiation conditions. In this direction different conditions were tried for finding the best conversion of substrates (Table 2).

Table 1. Screening of solvents for optimization of transamidation reaction of acetamide with aniline

Entry	Reactants	Product	Solvent	Temp °C	Yields[a] (%)
1		**3a**	Water	80	85
2			Water	100	95
3			ACN	82	73
4			Toluene	111	82
5			THF	66	70
6			DCM	40	65
7			DMSO	189	No Reaction

[a]The yields are after column chromatography

Table 2. Screening of peroxy reagents and optimization of microwave conditions for transamidation reaction of acetamide with aniline



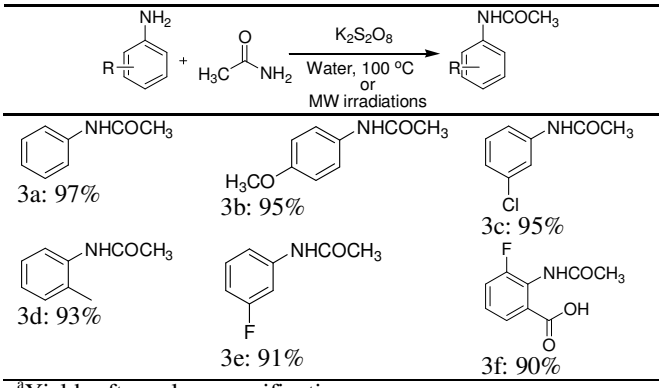
	Optimization using conventional heating in water at 100 °C			Optimization of microwave conditions using $K_2S_2O_8$ and water as solvent			
	Reagent	Time (h)	Yield (%) 3a	MW Power (Watts)	Temp. °C	Time (Min)	Yield (%) 3a
1	H_2O_2	8	15	100	50	5	7
					80	5	30
2	*m*-CPBA	8	15		100	7	75
3	TBHP	8	25		100	10	>95
4	Oxone	8	10	150	50	5	35
5	$K_2S_2O_8$	8	95		80	5	65
					100	7	>95
					100	10	>95

[a]The yields are after column chromatography

In the optimization study under microwave conditions, $K_2S_2O_8$ was used for optimizing the reaction. However, best results were obtained, when the reaction was conducted using 100Watt microwave power at 100 °C temperature for 10 minutes, more than 95% yield of acetanilide 3a was reported. Even, the reaction works well under solvent-free microwave irradiation conditions also, with little lower yields. All future reactions were performed using optimized condition under microwave irradiation.

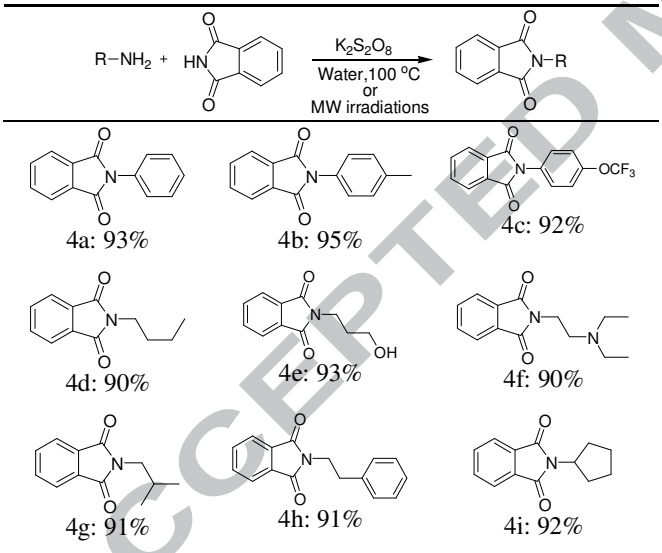
Having established a viable transamidation protocol under relatively mild conditions using both strategies i.e. by conventional thermal strategy and in microwave irradiation conditions, we turned our attention to explore the scope of present reaction for finding generality of reaction. In this direction different kind of substrates were chosen and could be converted to respective amides by using this transamidation (Table 3-5).

Table 3. Examples of transamidated products by reaction of acetamide with various arylamines[a]



[a]Yields after column purification

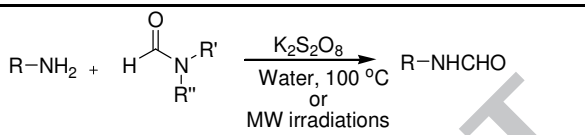
Table 4. Examples of transamidated products by reaction of pthalimides with various aliphatic/aromatic amines[a]

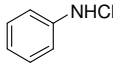
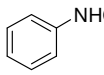
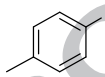
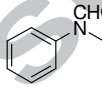
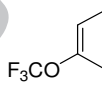
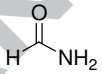
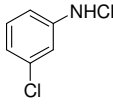
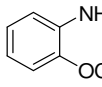
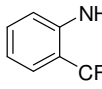
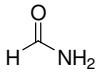
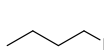
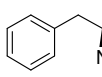
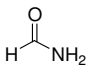
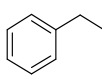
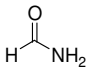
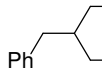


[a]Yields after column purification

We subsequently carried out reactions under optimized conditions for different amides, where acetamide and formamide or dimethylformamide could be successfully converted to respective transamidated products when treated with different amines like aryl or alkyl amine substrates. All kind of substitutions were found to be acceptable and accommodated on arylamines in this reaction. The reaction with aliphatic and aromatic amines works extremely well as can be seen in different examples shown in Table 3-5. Amazingly, the reaction with benzamides could not undergo this transformation after repetitive experiments under optimized conditions. Also, the heteroarylamines like 2-pyridylamine, 5-aminoindole, 3-aminopyridine have not given the desired product.

Table 5. Transamidation or N-formylation of alkyl/arylamines with formamide / *N,N′*-dimethylformamide[a]

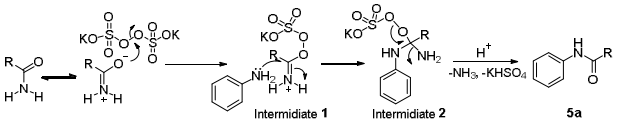


Entry	Amide	Product	Yield
1			5a: 98%
2			5b: 95%
3			5c: 97%
4			5d: 97%
5			5e: 98%
6			5f: 95%
7			5g: 96%
8			5h: 94%
9			5i: 96%
10			5j: 95%
11			5k: 97%
12			5l: 95%

[a]Yields after column purification

A further interesting application of this protocol was the conversion of phthalimide into *N*-substituted derivatives. phthalimide was used for transamidation reaction with various anilines and different aliphatic amines could be converted in to corresponding transamidated products easily under optimized conditions (Table 4). The peroxy reagent could play a role in launching and offering *N*-protection of different amines and this method can be used as a protection strategy for different applications in synthetic organic chemistry. The present strategy could be an economical route to obtain phthalimide-protected derivatives and its extension for protection of aminoacid derivatives could also be a useful protocol. This reaction works well with branched amines, nitrogen and free hydroxyl group bearing amine substrates also.

Here, it is important to note that as mentioned earlier while optimization of the reaction conditions, when *N,N'*-Dimethylformamide was used as a solvent, corresponding *N*-formylated product was obtained in excellent yield (Table 5). The examples for transamidation of formamide or *N,N'*-dimethylformamide with various arylamines and alkyl amines are presented in Table 5. Different kinds of amines were used for *N*-formylation reaction; all were found to give excellent yields. Typically, an amino acid *i.e.* L-phenylalanine methylester hydrochloride was subjected for transamidation using present protocol (Table 5, entry 10), the transamidated *N*-formyl product was formed and there was no change in configuration and optical purity, thus this method can be useful in asymmetric synthesis also. Similarly, many other amino acids can also be tranamidated using this method. In case of secondary amines, 4-benzylpiperidine was subjected for this reaction; the transamidated product with excellent yield was obtained (Table 5, entry 12) and also diphenylamine has given the desired product (Table 5, entry 4) in excellent yields. Some examples of aryl amines or aliphatic amines are shown in Table 5.



Scheme 3. Plausible mechanism for the formation transamidated product from amide with aniline

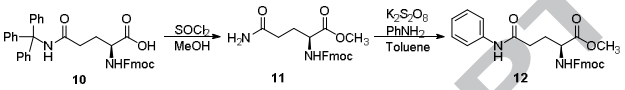
From the mechanistic point of view, the time monitored experiment was conducted. In this study, various intermediates were observed along with the product formation in good amount at the time of 30 min in conventional heating reaction. At very first instance, there is a cleavage of peroxy bond of $K_2S_2O_8$ by mixing an amide with this reagent and forms adduct i.e. intermediate 1, as shown in scheme 3. By addition of aniline on intermediate 1, it gets converted to intermediate 2. This finally releases the ammonia and gives $KHSO_4$ and further forms the required transamidated product 5a.

Entry	Amide/Starting material	Drug molecule or Natural Product	Yield (%)
1	NH_2COCH_3	Phenacetin	**6**: 94%
2	NH_2COCH_3	Paracetamol	**7**: 96%
3		Lidocaine	**8**: 95%
4		Piperine	**9**: 83%

Figure 2. Application of present reaction for synthesis of various drugs and natural products

To further expand the scope of present reaction, application study for the synthesis of various drugs and natural products was carried out. In this direction, different drugs such as phenacetin[5,14a] paracetamol[6,14a] and lidocaine[7,14b] were synthesized. However, natural product like piperine[8,14c] was also synthesized using present approach, as shown in fig. 2. Several other drugs/drug intermediates or natural products can also be synthesized using present method.

In view of the applications in peptide synthesis, a reaction with protected glutamine *i.e.* methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-glutaminate 11 was conducted, which was prepared from its *N*-trityl protected form 10, this compound 11 could be transamidated with aniline to give 12 as shown in scheme 4. The reaction of this protected glutamine 11 was tried with glycine methyl ester, amazingly, which could not undergo this transformation. Further studies are planned to explore the details about this reactions.



Scheme 4. Transamidation reaction of protected glutamine with aniline

In conclusion, we have demonstrated $K_2S_2O_8$ mediated transamidation protocol of amides with amines using greener and mild approach in aqueous media by following conventional heating and microwave irradiation strategy. As illustrated by variety of the examples, present reaction is applicable for transamidation of acetamide, formamide and phthalimide substrates with various alkyl or arylamines. The scope of present reaction is shown by application in the synthesis of representative examples of drugs or natural products. The present method can find applications in various fields of organic synthesis, medicinal chemistry or drug discovery.

Acknowledgments

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