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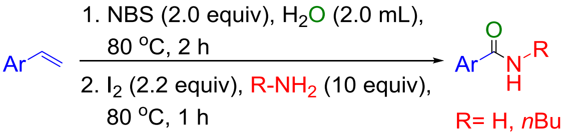

☑ Metal-free protocol

☑ Inexpensive reagents

☑ Water as an oxygen source and a solvent

☑ Good yields of the products

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Tandem Synthesis of Aromatic Amides from Styrenes in Water

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ABSTRACT

An expedient one-pot synthesis of aromatic amides has been reported from styrenes in the presence of *N*-bromosuccinimide and iodine by using aqueous ammonia in water. The reaction proceeds through the formation of α-bromoketone as an intermediate in the presence of NBS and water. α-Bromoketone on reaction with iodine forms bromodiiodoketone which on nucleophilic substitution with aqueous ammonia gives aromatic amide. Substituted aromatic amides were obtained in good yields with wide functional group compatibility.

Introduction

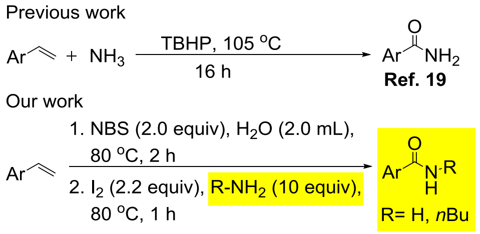
Amides fall under a category of well-known and widely utilized molecules since they exist as integral structural units of a variety of natural products.[1-3] Moreover, amides have been extensively employed in the manufacturing of pharmaceutical compounds due to their wide range of biological activities e.g. antifungal, antiprotozoal, anti-inflammatory, etc.[4] Various amide derivatives such as primary amides, aromatic and heteroaromatic amides have been used as precursors for the synthesis of numerous biomolecules, agrochemicals, plastics, detergents, lubricants, and are crucial parts of many established drugs.[4,5]

Particularly, primary amides are important intermediates in organic synthesis as a result of their facile conversion into nitriles, primary amines and heterocycles.[6] In this context, several methods have been developed by researchers to synthesize amides. Classical synthesis of primary amides involves the reaction of various starting materials such as acyl halides, esters, aldehydes, and mixed anhydrides with ammonia or its equivalent.[7]

Other approaches used for the synthesis of primary amides involve reduction of acyl azides and acyl hydrazides,[8] as well as hydration of nitriles in presence of acids, bases and transition metal catalysts.[9] Aldoximes undergo rearrangement in presence of transition metal catalysts to produce amides.[10] In addition, metalloporphyrins-catalyzed oxidation of terminal alkynes,[11] ruthenium-catalyzed dehydrogenative coupling of primary alcohols with amines,[12] direct oxidation of benzyl amines/ benzyl alcohols,[13,14] aerobic oxidative amidation of methylarenes,[15] palladium-catalyzed aminocarbonylation of aryl halides,[16] are some other methods used for the preparation of amides.

Considering the necessity to develop a ecofriendly method in order to reduce impact on environment, many researchers have reported several environment-friendly protocols, which include i] I_2 mediated direct transformation of acetophenones, carbinols to benzamides by using aq. ammonia in water,[17] ii] combination of I_2 with NaN_3 in presence of a base to form benzamides from acetophenones,[18] iii] conversion of styrenes to benzamides in the presence of TBHP and aq. ammonia or amines at 105 °C for 16 h,[19] iv] use of Cu_2O as a catalyst and TBHP as an oxidant to obtain benzamides from aldehydes and ammonium chloride,[20] v] Cu_2O catalyzed reaction of phenylacetic acids and α-hydroxyphenyl acetic acids with aq. ammonia in water to obtain benzamides.[21] Recently, benzamides have also been prepared from ethylarenes.[22]

Although scientists have developed these methods with aims to improve yields of amides and reduce environmental hazards, majority of these synthetic protocols suffer from drawbacks such as use of transition metal catalyst, hazardous as well as expensive reactants/ reagents, organic solvents, longer reaction times, higher reaction temperatures and low yield of products. Hence, development of economically viable and environmentally benign protocol is ever demanding and never ending process. In view of our continuing interest in development of C-H functionalization inspired protocols for the synthesis of key building blocks,[23] herein we report the synthesis of aromatic amides from styrenes in presence of NBS and iodine by using aq. ammonia in water as a solvent (Scheme 1).



Scheme 1. Tandem synthesis of aromatic amides from styrenes.

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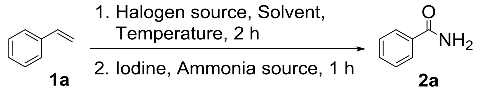
Initially, the reaction of styrene (**1a**) with 2.0 equiv *N*-chlorosuccinimide (NCS) as a halogen source as well as an oxidant in H_2O was carried out at 80 °C for 2 h. Iodine (2.2 equiv) and 30% aq. ammonia solution (10 equiv) were added and heating was continued for 1 h to afford benzamide (**2a**) in 65% yield (Table 1, entry 1). The same reaction in the presence of *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) produced benzamide **2a** in 80% and 68% yields, respectively (Table 1, entries 2 and 3). To improve the yield of reaction, we next studied the effect of temperature. The reaction at 70 °C and 90 °C offered benzamide **2a** in 70% and 75% yields, respectively (Table 1, entries 4 and 5). Further, different solvents namely DMSO, DMF and MeOH were screened for this reaction instead of H_2O. But, the reactions in these solvents could form benzamide **2a** only in trace amounts (Table 1, entries 6-8). This clearly highlighted the key role of H_2O as an oxygen source as well as a solvent in this reaction. We also used different ammonia sources such as $(NH_4)_2CO_3$, $(NH_4)_2SO_4$, NH_4Cl and $HCOONH_4$ for this reaction instead of aq. ammonia to check the possibility of enhancement in the yield (Table 1, entries 9-12). However, all of these reactions were failed to produce benzamide **2a**. Thus, use of 2.0 equiv NBS and 2.2 equiv I_2 at 80 °C with a combined time of 3 h in water as a solvent was found to be the best reaction condition for the conversion of styrene **1a** to benzamide **2a** resulting in 80% yield of the product.

Table 1 Optimization of reaction conditions.[a]

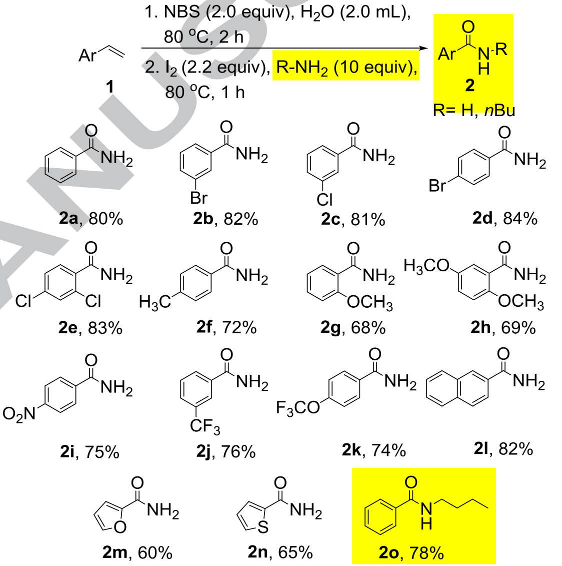


Entry	Halogen source	Ammonia source	Solvent	Yield (%)[b]
1	NCS	$NH_3.H_2O$	H_2O	65
2	**NBS**	**$NH_3.H_2O$**	**H_2O**	**80**
3	NIS	$NH_3.H_2O$	H_2O	68
4[c]	NBS	$NH_3.H_2O$	H_2O	70
5[d]	NBS	$NH_3.H_2O$	H_2O	75
6[e]	NBS	$NH_3.H_2O$	DMSO	trace
7[e]	NBS	$NH_3.H_2O$	DMF	trace
8[e]	NBS	$NH_3.H_2O$	MeOH	trace
9[f]	NBS	$(NH_4)_2CO_3$	H_2O	ND
10[f]	NBS	$(NH_4)_2SO_4$	H_2O	ND
11[f]	NBS	NH_4Cl	H_2O	ND
12[f]	NBS	$HCOONH_4$	H_2O	ND

[a] Reaction conditions: styrene **1a** (1.0 mmol), halogen source (2.0 mmol) and solvent (2.0 mL) were heated at 80 °C for 2 h, then iodine (2.2 mmol), ammonia source (10 mmol) were added and heating continued at 80 °C for 1 h.
[b] Isolated yields.
[c] Reaction performed at 70 °C.
[d] Reaction performed at 90 °C.
[e] Reaction performed with different solvents.
[f] Reaction performed with different ammonia sources. ND= Not Detected.

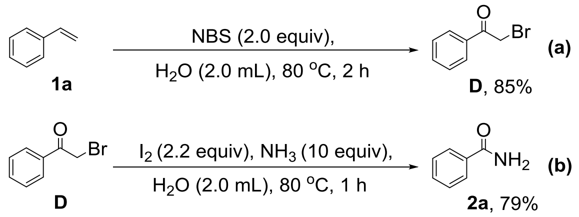
With optimized reaction conditions in hand, we investigated the scope and limitations of this one-pot reaction by using different substituted styrenes. Various functional groups were found to be compatible under the optimized reaction conditions forming the desired products **2a-2o** (Table 2) in good yields. Styrene **1a** furnished benzamide **2a** in 80% yield under the optimized reaction conditions. Styrenes bearing halogen substituents such as 3-Br, 3-Cl, 4-Br and 2,4-Cl_2 offered corresponding benzamides **2b-2e** in yields ranging from 81-84%. Styrenes with electron-donating substituents such as 4-Me, 2-OMe and 2,5-di-OMe afforded respective benzamides **2f-2h** in 68-72% yields. Styrenes bearing electron-withdrawing substituents such as 4-NO_2, 3-CF_3 and 4-OCF_3 produced corresponding benzamides **2i-2k** in good yields (74-76%). Similarly, 2-vinylnaphthalene formed corresponding product **2l** in 82% yield. Heteroarylethylenes such as 2-vinylfuran and 2-vinylthiophene formed respective products **2m** and **2n** in 60% and 65% yields, respectively. The scope of this reaction was extended by replacing aq. ammonia with *n*-butylamine. The reaction offered corresponding amide **2o** in 78% yield. We also attempted one reaction with *trans*-β-methylstyrene as the starting substrate. We observed the formation of 2-amino-1-phenylpropan-1-one and 2-amino-2-bromo-1-phenylpropan-1-one under the optimized reaction conditions confirmed by GC-MS. However, we did not observe the formation of benzamide as no haloform reaction took place due to presence of terminal methyl group.

Table 2 Tandem metal-free synthesis of aromatic amides from styrenes.[a,b]



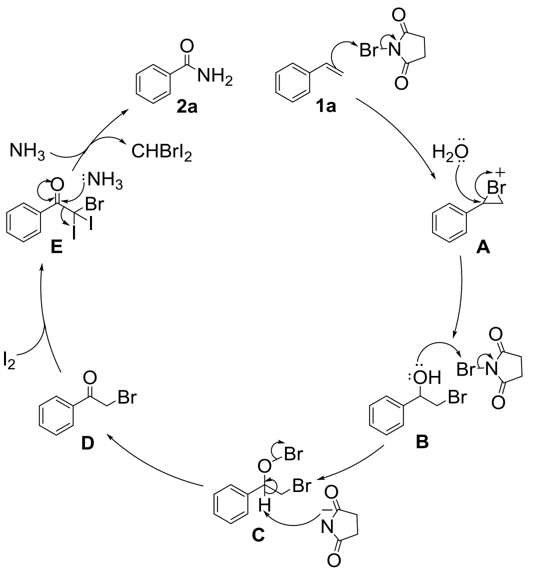
[a] Reaction conditions: substituted styrene **1** (1.0 mmol), NBS (2.0 mmol) and water (2.0 mL) were heated at 80 °C for 2 h, then iodine (2.2 mmol), 30% aq. ammonia or *n*-butylamine (10 mmol) were added and heating continued at 80 °C for 1 h.
[b] Isolated yields.

To gain insights into the reaction mechanism, few control experiments were performed (Scheme 2). When styrene (**1a**) was reacted with NBS in water at 80 °C for 2 h, formation of α-bromoacetophenone (**D**) was observed (Scheme 2, a). This indicated that the reaction involves formation of α-bromoacetophenone (**D**) as an intermediate. α-Bromoacetophenone (**D**) on reaction with iodine and aq. ammonia in water produced benzamide **2a** in good yields (Scheme 2, b).



Scheme 2. Control experiments.

On the basis of control experiments, a plausible mechanism for this transformation is depicted in Scheme 3. Initially, styrene (**1a**) in the presence of NBS forms cyclic bromonium ion **A** which undergoes a ring opening through nucleophilic attack of H_2O to give bromohydrin **B** as an intermediate. Bromohydrin **B** in the presence of NBS undergoes oxidation to form α-bromoacetophenone (**D**).[24] Intermediate **D** on subsequent iodination with iodine forms bromodiiodoketone **E** which on haloform reaction with aq. ammonia offers benzamide (**2a**).



Scheme 3. Proposed reaction mechanism.

In conclusion, we have developed an efficient and practical one-pot synthesis of substituted benzamides from easily available styrenes in the presence of *N*-bromosuccinimide and iodine by using aq. ammonia in water. Use of inexpensive reagents, water as an oxygen source as well as a solvent, metal-free conditions, broad substrate scope, good yields of benzamides are notable features of this protocol. We strongly believe that this protocol will be widely used for the synthesis of benzamides.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/.

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29. General experimental procedure for the synthesis of aromatic amides: A sealed tube equipped with a magnetic stirring bar was charged with styrene **1** (1.0 mmol), NBS (2.0 mmol) and water (2.0 mL) at room temperature. The resulting mixture was heated to 80 ^{o}C for 2 h. After disappearance of the reactant (monitored by TLC), reaction mixture was cooled to room temperature. To this reaction mixture molecular iodine (2.2 mmol) and 30% aq. ammonia solution or *n*-butylamine (10 mmol) were added and it was heated to 80 ^{o}C for 1 h. After completion of the reaction (monitored by TLC), saturated $Na_2S_2O_3$ solution (10 mL) was added to the reaction mixture, and it was extracted with ethylacetate (2×10 mL). The organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by column chromatography on 60–120 mesh silica gel using ethylacetate: *n*-hexane (1:2) as the eluent to obtain the corresponding benzamide **2**.

Highlights of the work

- A metal-free tandem protocol
- An efficient access to aromatic amides from readily available styrenes
- Use of inexpensive reagents such as *N*-bromosuccinimide (NBS) and iodine with easy operational procedure
- Use of water as an oxygen source as well as a solvent
- Wide functional group compatibility and good yields of the products