ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c4cc01054j

Received 10th February 2014,
Accepted 18th March 2014

DOI: 10.1039/c4cc01054j

www.rsc.org/chemcomm

# A novel oxidative procedure for the synthesis of benzamides from styrenes and amines under metal-free conditions†

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**An interesting procedure for the oxidative synthesis of amides from styrenes and amines has been developed. Various primary amides were formed in moderate yields (25–81%). Secondary amides can be produced in moderate yields as well (41–68%). Notably, no transition metal catalyst was needed for this transformation. This is the first example of oxidative transformation of styrenes to benzamides.**

Amides are an important class of building blocks in modern organic synthesis, with broad applications in advanced materials and pharmaceuticals, *etc.* Traditionally, amides were produced by the reaction of carboxylic acid derivatives with the corresponding amine analogues.[1] In recent years, several other procedures have been developed as well, such as transition metal-catalyzed aminocarbonylation of organohalides,[2] oxidative amidation of aldehydes and alcohols,[3] oxidation of amines,[4] rearrangement reactions and so on.[5]

As our society develops, 'sustainable development' has been accepted as common knowledge by our community. In respect of the synthetic methodology development, procedures not requiring hazardous or expensive reagents are more desired. Hence, methods under transition metal catalyst-free conditions are more matched with the requests of 'green chemistry'. For example, the group of Lei reported metal-free alkoxycarbonylation,[6] C–H activation,[7] and oxidation of alcohols.[8] Our group developed several metal-free methodologies as well.[9] Here, we wish to report our new discovery on metal-free oxidative transformation of styrenes to the corresponding benzamides by using TBHP as the oxidant.

In 1 mL of ammonia (25 w% in $H_2O$), using TBHP (10.8 equiv., 70% in $H_2O$; 1.5 mL) as the oxidant at 105 °C, 62% of benzamide was isolated after 16 hours with total conversion of styrenes. At lower temperature, or decreased loading of TBHP, the yield of benzamide dropped because of the reduced conversion and selectivity. Benzoic acid and non-identifiable by-products were detected in the reactions.

As shown in Table 1, various functional groups are tolerable under the identical conditions and gave the desired benzamides in moderate to good yields. *para-*, *ortho-*, and *meta-*Methyl-substituted styrenes were transformed into the corresponding benzamides in 25–56% isolated yields (Table 1, entries 2–6). 48–60% of ether-substituted benzamides were produced from their parent styrenes (Table 1, entries 8 and 9). 2-Vinylnaphthalene can be applied as the substrate as well (Table 1, entry 10). Chloro- and bromo-decorated benzamides were isolated in 45–63% yields (Table 1, entries 11–15). 68–72% of trifluoromethyl- and nitro-substituted benzamides were isolated under the same conditions (Table 1, entries 16 and 17). Interestingly, 51% of 4-aminobenzamide was isolated from the corresponding 4-aminostyrene without further optimization as well (Table 1, entry 18). Notably, 2-vinylpyridine and 4-vinylpyridine as examples of heterocyclic alkenes were successfully oxidized and gave the desired amides in 78–81% isolated yields as well (Table 1, entries 19 and 20). It is worth mentioning that aliphatic alkenes such as 3-phenylpropene and 1-hexene failed in the reaction with ammonia under our conditions.

In order to see the generality of this methodology, we carried out the testing of styrene with various amines in addition to ammonia (Table 2). 41–68% of *N*-alkyl-substituted benzamides were isolated by the reaction of styrene with different amines. Aniline as the substrate was tested as well, but no desired product was formed (Table 2, entry 6). Additionally, 4-methoxyaniline and benzyl amines were tested as they are more nucleophilic then aniline, but no amides were isolated.

In order to understand the reaction pathway, several control experiments were performed (Scheme 1). To our surprise, 56% of benzamide was isolated by using alpha-methylstyrene as the substrate, while no reaction was observed when using

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc01054j

Table 1 Synthesis of primary amides from styrenes[a]

| Entry | Substrate | Product | Yield[b] |
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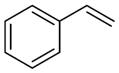
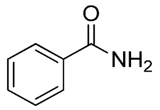
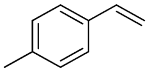
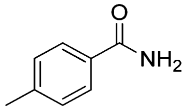
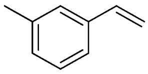
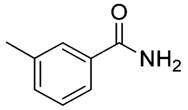
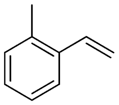
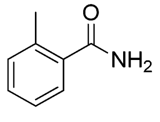
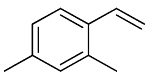
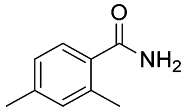
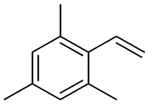
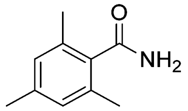
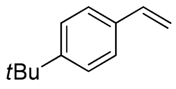
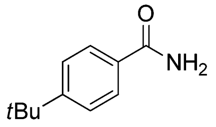
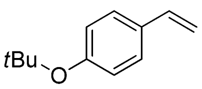
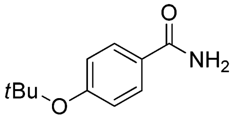
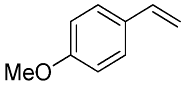
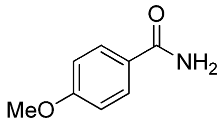
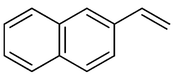
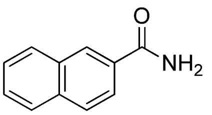
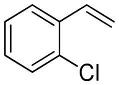
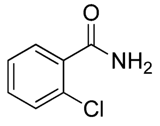
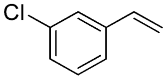
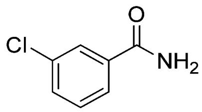
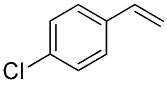
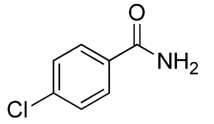
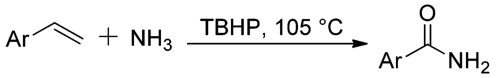
| 1 |  |  | 62 |
| 2 |  |  | 56 |
| 3 |  |  | 52 |
| 4 |  |  | 50 |
| 5 |  |  | 35 |
| 6 |  |  | 25 |
| 7 |  |  | 62 |
| 8 |  |  | 60 |
| 9 |  |  | 48 |
| 10 |  |  | 52 |
| 11 |  |  | 53 |
| 12 |  |  | 50 |
| 13 |  |  | 56 |

Table 1 (*continued*)



| Entry | Substrate | Product | Yield[b] |
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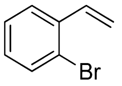
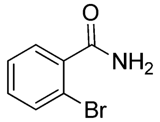
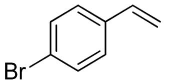
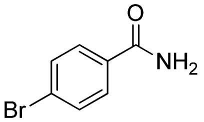
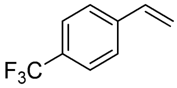
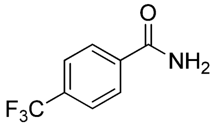
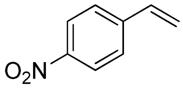
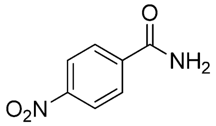
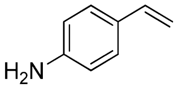
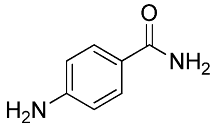
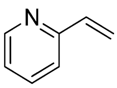
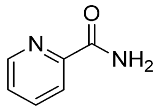
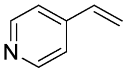
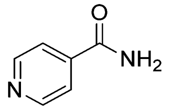
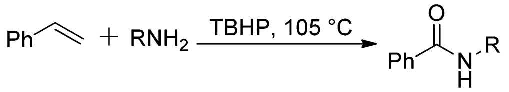
| 14 |  |  | 45 |
| 15 |  |  | 63 |
| 16 |  |  | 68 |
| 17 |  |  | 72 |
| 18 |  |  | 51 |
| 19 |  |  | 78 |
| 20 |  |  | 81 |

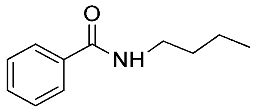
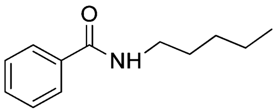
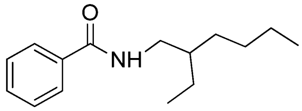
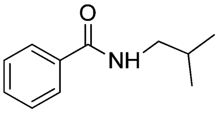
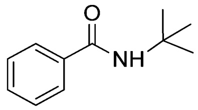
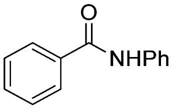
[a] Styrenes (1 mmol), $NH_3$ (13 equiv., 25% in $H_2O$; 1 mL), TBHP (10.8 equiv., 70% in $H_2O$; 1.5 mL), 105 °C, 16 h. [b] Isolated yields.

beta-methylstyrene as the starting material under identical conditions. In the absence of ammonia, 60% of benzaldehyde was produced and the oxidative amidation of benzaldehyde with ammonia to give benzamide in the presence of TBHP is already known.[9b] Under the same reaction conditions, no benzamide could be formed by using benzoic acid instead of styrenes which implies that benzoic acid cannot be the intermediate. TEMPO as a radical scavenger was added to our model system and the reaction was totally inhibited. We thought that an epoxide might be the intermediate for oxidative transformation of styrenes to benzaldehydes under our conditions, but no benzaldehyde could be detected starting from 2-phenyloxirane. More detailed mechanistic studies and further synthetic applications of this transformation are in progress in our lab.

Based on these experiments, we believe that benzaldehydes should be the reaction intermediates from styrenes. Then the formed aldehydes react with amines and give the corresponding amides in the presence of an oxidant (Scheme 2).

Table 2 Synthesis of secondary amides from styrene and amines[a]



| Entry | Product | Yield[b] |
|---|---|---|
| 1 |  | 48 |
| 2 |  | 55 |
| 3 |  | 41 |
| 4 |  | 52 |
| 5 |  | 68 |
| 6 |  | 0 |

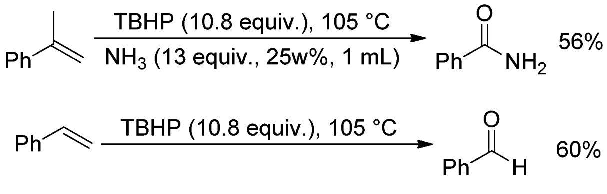
[a] Styrene (1 mmol), amines (1 mmol), TBHP (10.8 equiv., 70% in $H_2O$; 1.5 mL), 105 °C, 16 h. [b] Isolated yields.

In conclusion, a novel methodology for amide preparation has been developed. Readily available styrenes and amines were applied as substrates. In the presence of TBHP, various benzamides were formed in moderate to good yields (25–81%). Notably, no transition metal catalyst was needed for this novel transformation. This is the first example of oxidative transformation of styrenes to benzamides.

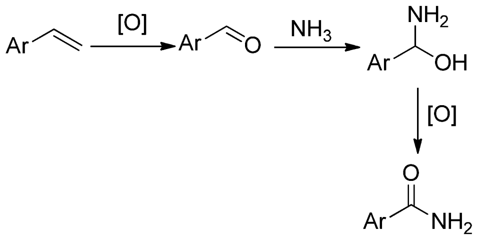
**Experimental.** *General comments*. All reactions were carried out under air. Reactions were monitored by TLC analysis (pre-coated silica gel plates with fluorescent indicator UV254, 0.2 mm) and visualized under 254 nm UV light or iodine. Chemicals were purchased from Aldrich, Alfa Aesar and unless otherwise noted were used without further purification. All compounds were characterized by $^{1}H$ NMR and $^{13}C$ NMR spectroscopies. $^{1}H$ spectra were recorded on Bruker AV 300 and AV 400 spectrometers. $^{13}C$ NMR spectra were recorded at 282 MHz. GC was performed on an Agilent 6890 chromatograph using a 30 m HP5 column. All yields reported refer to isolated yields.

*A general procedure for the oxidative synthesis of primary amides*. Ammonia (25% in water; 1 mL) and styrenes (1 mmol) were added to pressure tube equipped with a stirring bar. Then, TBHP (70% in $H_2O$; 1.5 mL) was added and the final solution was kept at 105 °C for 16 h. The mixture was cooled to room temperature and the solvent was removed under vacuum. The pure product was isolated by using column chromatography.

*A general procedure for the synthesis of secondary amides*. Amines (1 mmol), and styrenes (1 mmol) were added to pressure tube equipped with a stirring bar. Then, TBHP (70% in $H_2O$; 1.5 mL) was added and the final solution was kept at 105 °C for 16 h. The mixture was cooled to room temperature and the solvent was removed under vacuum. The pure product was isolated by using column chromatography.



Scheme 1 Control experiments.



Scheme 2 Proposed reaction pathway.

## Notes and references

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