# Microwave-assisted preparation of amides using a stable and reusable mesoporous carbonaceous solid acid

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An efficient and green microwave assisted protocol to prepare amides from amines *via N*-acylation using acidic polysaccharide derived mesoporous materials provides quantitative yields of amides in short reaction times.

### Introduction

Amide bond formations are one of the most important transformations carried out in pharmaceutical synthesis,<sup>1</sup> accounting for 65% of all preliminary screening reactions in industrial medicinal chemistry laboratories as recently reported.<sup>2</sup> Amides also represent a very important family of intermediates widely employed in the preparation of fine chemicals, cosmetics and food additives.<sup>1-3</sup> However, the majority of the current employed protocols to form amides involve the use of stoichiometric activated toxic and corrosive reagents (*e.g.* acid anhydrides and/or acyl chlorides) with poor atom economy that generate considerable waste.<sup>4,5</sup> Furthermore, an excess of these reagents is normally needed to achieve optimum amide yields and the reaction is water-sensitive with the efficient removal of water being a critical factor in the systems.<sup>5,6</sup>

The development of cleaner syntheses are key to reducing the environmental impact of amide formations.<sup>2</sup> In this regard, the direct reaction of amines with carboxylic acids remains the most attractive approach.<sup>26,7</sup> These types of reactions are arguably best carried out without catalysis where possible, however, reaction conditions remain harsh in order to accomplish direct amide formation.<sup>8</sup>

A range of greener catalytic methodologies have been reported for the preparation of amides. These include the *N*-acylation of amines with organic acids<sup>7,9</sup> (Scheme 1), the use of solid supported reagents (*e.g.* polymer-bound acylating agents),<sup>10</sup> arylboronic or boronic acid derivatives,<sup>6,11</sup> and the use of microwave irradiation.<sup>5,10,12,13</sup> Many different catalysts have been reported for the acylation of amines including transition metal salts,<sup>14</sup> immobilised ionic liquids on mesoporous materials,<sup>7c</sup> and solid acid catalysts.<sup>7</sup>



Scheme 1 Catalysed N-acylation of amines using organic acids.

We have previously reported the preparation of acidic polysaccharide-derived mesoporous materials (Starbon<sup>®</sup> acids) and their activity in a range of acid catalysed reactions including esterifications,<sup>15-17</sup> etherifications,<sup>16</sup> alkylations,<sup>15</sup> and acylations<sup>15</sup> under microwave irradiation.

Inspired by the reported results of Narender *et al.*<sup>7a</sup> and Choudary *et al.*<sup>7b</sup> that employed solid acids in the acylation of amines under conventional heating, we aimed to bring together the advantages of using a highly active and reusable water tolerant solid acid (Starbon<sup>®</sup> acid) as well as a microwave assisted protocol that is believed to enhance the rates of reactions as well as improving yields and potentially influencing selectivities in organic synthesis.<sup>18,19</sup> Herein, we report the efficient and atom economic preparation of amides *via N*-acylation of primary and secondary amines under microwave irradiation using a Starbon<sup>®</sup> acid as the acylation reagent.

## Experimental

Starbons<sup>®</sup> acids were synthesized as recently reported in the literature.<sup>15-17</sup> The material carbonised at 400 °C (herein after referred to as Starbon<sup>®</sup>-400) was chosen for its ideal hydrophilicity/hydrophobicity ratio and subsequently functionalised by suspending in H<sub>2</sub>SO<sub>4</sub> (10 mL acid/g material) and heated for 4 h at 80 °C. After sulfonation, the solid acid was washed with distilled water until the washings were neutral, conditioned in boiling toluene (150 °C, 4 h) and water (100 °C, 3 h) and finally oven dried overnight (100 °C) before being tested in the catalytic reaction. Sulfonated materials are denoted as Starbon<sup>®</sup>-400-SO<sub>3</sub>H.

A typical *N*-acylation was carried out by reacting 2 mmol of the amine with 2 mmol acetic acid and 0.1 g catalyst in a tube using microwave radiation at 300 W (120–130 °C maximum temperature reached) for 1–10 minutes. A general procedure to isolate the formed amides was performed as follows: the residue was then redissolved in DCM (5 mL), washed with brine (5 mL), diluted HCl (5 mL), brine (5 mL), diluted NaOH (5 mL), brine (5 mL), dried over MgSO4, and the solvent evaporated under vacuum to yield the corresponding amide. Starbon<sup>®</sup> acids were filtered off from the mixture after reaction completion, washed with methanol and acetone and dried at 100 °C prior to their reuse in the reaction.

Microwave experiments were carried out in a CEM-DISCOVER model with PC control and monitored by sampling aliquots of reaction mixture that were subsequently analysed by GC/GC-MS using an Agilent 6890 N GC model equipped, with

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a 7683B series autosampler, fitted with a DB-5 capillary column and an FID detector. Experiments were conducted in a closed vessel (pressure controlled) under continuous stirring.

#### **Results and discussion**

The use of acetic acid in the *N*-acylation reaction instead of the corrosive acetyl chloride and the lachrymator acetic anhydride provides many advantages from both economical and environmental standpoints, and water is the only byproduct. The *N*-acylation of aniline (primary amine) was chosen as reaction test to compare the activity of a range of solid acid catalysts including acidic clays, zeolites and Al-MCM-1 materials. The results are shown in Fig. 1. Initially, a 1:1 ratio amine:acetic acid, 0.1 g catalyst, maximum microwave power output (300 W) and 15 min irradiation were selected as reaction conditions, in a similar way to previously reported results.<sup>15</sup>



**Fig. 1** Conversion and selectivity to amide (Sel Amide) of various solid acids in the *N*-acylation of aniline with acetic acid [*Reaction conditions*: 2 mmol aniline, 2 mmol AcOH, 0.1 g cat., microwave, 300 W (maximum power), 130 °C (maximum temperature reached), 15 min].

Blank runs in the absence of catalyst provided almost no conversion of starting material after microwaving for 15 min (Table 1, Blank).

Quantitative conversion of the starting material was found in less than 15 min reaction under microwave irradiation using Starbon<sup>®</sup>-400-SO<sub>3</sub>H. Comparatively, the reaction rates using other solid acids were found to be between 5 to 10 times slower than that of the Starbon® acid. With Starbon® acid being the optimum catalyst for the reaction, the next step was to optimise the reaction parameters. As expected, a decrease in the microwave power and/or catalyst loading had a detrimental effect on the amide yield. Interestingly, the selectivity to amide was not significantly altered by changing these parameters and in general all solid acids were extremely selective to amide formation. The time of microwave irradiation and the catalyst loading were probably the most important parameters in the reaction. For most of the solid acids (excluding Starbon®), reasonable conversions (>50%) were only achieved at significantly longer times of irradiation (45 min and over) and/or doubling the quantities of catalyst (from 0.1 to 0.2 g).

In an attempt to broaden the scope of the methodology, a range of amines were employed as starting materials in the acylation reaction. The results are summarised in Table 1. 
 Table 1
 N-Acylation of a range of amines with acetic acid using

 Starbon®-400-SO<sub>3</sub>H as catalyst and acetic acid as acylating agent under microwave irradiation<sup>a</sup>

| Entry  | Amine                            | Product                              | Time/<br>min | Conversion <sup>e</sup><br>(mol%) | S <sub>amide</sub><br>(mol%) |
|--------|----------------------------------|--------------------------------------|--------------|-----------------------------------|------------------------------|
| Blank⁵ | NH <sub>2</sub>                  | NHCOCH <sub>3</sub>                  | 15           | <10                               | >98                          |
| 1      |                                  | NHCOCH <sub>3</sub>                  | 10           | 90 (87)                           | >99                          |
| 2      | O <sub>2</sub> N NH <sub>2</sub> | O <sub>2</sub> N NHCOCH <sub>3</sub> | 2            | >99 (92)                          | >98                          |
| 3      | CI NH2                           | CI NHCOCH <sub>3</sub>               | 2            | >99 (95)                          | >99                          |
| 4      | HO NH2                           | HO NHCOCH3                           | 3            | >95 (89)                          | >99                          |
| 5      | MeO NH2                          | MeO NHCOCH <sub>3</sub>              | 3            | 89 (83)                           | >99                          |
| 6      | NH <sub>2</sub>                  | NHCOCH3                              | 5            | 87 (79)                           | >99                          |
| 7      | NH <sub>2</sub>                  | NHCOCH3                              | 0.6          | >99 (94)                          | >98                          |
| 8      | N-H                              | NCOCH <sub>3</sub>                   | 3            | >99 (94)                          | >99                          |
| 9      | NH <sub>2</sub>                  | NHCOCH <sub>3</sub>                  | 1            | >99 (92)                          | >99                          |
| 10     | MH <sub>2</sub>                  | NHCOCH3                              | 15           | 77                                | >99                          |
| 11     |                                  | NCOCH <sub>3</sub>                   | 15           | 68                                | >99                          |
| 12     | NH <sub>2</sub>                  | NHCOCH <sub>3</sub>                  | 15           | 82                                | >95                          |

<sup>*a*</sup> 2 mmol amine, 2 mmol AcOH, 0.1 g Starbon-400-SO<sub>3</sub>H, microwave, 300 W (maximum power output), 130 °C (maximum temperature reached). <sup>*b*</sup> Blank reaction in the absence of catalyst. <sup>*c*</sup> Isolated yields, where appropiate, are given in brackets.

A wide variety of primary and secondary aromatic, aliphatic and cyclic hindered and unhindered amines were effectively and selectively converted into their corresponding amides under mild conditions and with short times of reaction (0.5 to 15 min). Of note was also the remarkable tolerance of the reaction to susbtituents (from electron withdrawing to electron donating groups) and functionalities in the amines. The water-tolerant partially hydrophilic Starbon® acid is believed to push the equilibrium forward to the formation of amides without the need to remove the water generated in the acylation (which normally reverses the equilibrium and destroys the amide). This property may be due to the Starbons unusual starchlike structure which is still present at low temperatures of carbonisation (<400 °C);<sup>20</sup> this is consistent with our previous observation of Starbon® catalytic activity in water.<sup>21</sup> In order to demonstrate the true scope of the proposed methodology,

| Table 2  | N-Acylation                            | of    | benzylamine   | with  | а  | range    | of   | acids           | using |
|----------|--|-------|---------------|-------|----|----------|------|-----------------|-------|
| Starbon® | <sup>®</sup> -400-SO <sub>3</sub> H as | s cat | alyst under m | icrow | av | e irradi | atic | on <sup>a</sup> |       |

| Entry  | Acid              | Time/min | Conversion <sup>b</sup><br>(mol%) | S <sub>amide</sub><br>(mol%) |
|--------|-------------------|----------|-----------------------------------|------------------------------|
| 1<br>2 | Н₃С–СООН<br>∕СООН | 0.6<br>5 | >99 (94)<br>94 (89)               | >98<br>>99                   |
| 3      | СООН              | 5        | 90 (86)                           | >98                          |
| 4      | ноос              | 15       | >99                               | 75 <sup>c</sup>              |
| 5      | Соон              | 10       | >99 (92)                          | >99                          |
| 6      | СООН              | 10       | 88 (84)                           | >99                          |

<sup>*a*</sup> 2 mmol benzylamine, 2 mmol acid, 0.1 g Starbon-400-SO<sub>3</sub>H, microwave, 300 W (maximum power output), 130 °C (maximum temperature reached). <sup>*b*</sup> Isolated yields, where appropriate, are given in brackets. <sup>*c*</sup> Selectivity to diamide.

a range of carboxylic acids were employed as reagents in the *N*-acylation of benzylamine (Amine Entry 7, Table 1). Results included in Table 2 proved the applicability of the protocol, as the Starbon<sup>®</sup> acid afforded quantitative yields of amides in less than 15 min of microwave irradiation. Of note were results obtained using succinic acid (1,4, butanedioic acid) in the reaction (Table 2, entry 4). Quantitative yield of diamide could be obtained in less than 30 min reaction under microwave irradiation.

The highly active sulfonated starbon was easily recovered from the reaction mixture whereupon the reaction rates returned to the background values. The recovered Starbon could be added to fresh substrate solutions giving almost identical activity and selectivity to the amides after 3 reuses to that observed in the first run (*e.g.* 3rd Starbon<sup>®</sup> acid reuse, aniline + acetic acid, 87% conversion, 99% selectivity to the amide compared to the 90% conversion, 99% selectivity obtained for fresh Starbon<sup>®</sup> acid). The catalyst is very stable under the reaction conditions, in good agreement with previously reported results that already proved the outstanding properties of this acidic polysaccharide-derived mesoporous material.<sup>15–17,20,21</sup>

#### Conclusions

In conclusion, our efficient, atom economic and environmentally friendly protocol allowed the preparation of a wide range of intermediates for pharmaceuticals (*e.g.* acetanilide and *N*-acetyl*p*-aminophenol) and fine chemicals. A variety of amides were successfully prepared from a range of amines and acids used as reagents in a 1:1 ratio, in a protocol that was demonstrated to be independent of the substrate combination and, most importantly, of the efficient removal of water that has been reported to be critical in order to achieve high amide yields.<sup>22</sup> The Starbon<sup>®</sup> acid is a renewable and environmentally compatible catalyst that can easily be obtained from biomass, and has proven to be highly active, selective and reusable in the *N*-acylation of amines with acetic acid under microwave irradiation. Our

solid acid exhibited remarkably improved activities compared to commercially available alternatives.

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