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PII:	S0040-4039(15)01022-9		
DOI:	http://dx.doi.org/10.1016/j.tetlet.2015.06.029		
Reference:	TETL 46421		
To appear in:	Tetrahedron Letters		
Received Date:	20 April 2015		
Revised Date:	4 June 2015		
Accepted Date:	11 June 2015		



Please cite this article as: Jung, B., Park, K., Song, K.H., Lee, S., Continuous flow reactions in water for the synthesis of propargylamines via a metal-free decarboxylative coupling reaction, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.06.029

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Tetrahedron Letters

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#### Continuous flow reactions in water for the synthesis of propargylamines via a metalfree decarboxylative coupling reaction

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#### ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: Flow reaction Decarboxylative coupling Propargylamine Metal-free Propiolic acid A range of propargylamines was synthesized via the metal-free decarboxylative coupling of alkynyl carboxylic acids with amines and paraformaldehyde in water, using a continuous flow reaction system. Aryl- and alkyl-substituted propiolic acids were found to react with secondary amines in the presence of paraformaldehyde, at 140 °C in water to give the desired propargylamines in good yield.

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In recent years, the development of environmentally benign methodologies has received considerable attention in the fine chemical industry, with novel green processes being developed and published in increasing numbers.<sup>4</sup> Important examples of green reaction systems for synthetic chemistry include recyclable catalysts<sup>2</sup> and the use of ionic liquids<sup>3</sup> as solvents. In addition, the development of water-based reaction systems is of particular importance in relation to green chemistry as the majority of waste arises from organic solvents.<sup>4</sup> However, although water is an abundant and cheap solvent, it is problematic for use in reactions requiring temperatures greater than 100 °C. Special equipment for high-pressure use is therefore required for such reactions.

The continuous flow reactor is an economical and efficient process system that can often be used to replace lower efficiency batch reactors. Continuous flow reactors have preferentially been used in organic synthesis, as a number of flow reactors can be placed in parallel to afford the desired product on a large scale without the requirement for large-scale reactors.<sup>5</sup> In addition, this system has a high surface area-to-volume ratio, thus providing efficient heat and mass transfer.<sup>6</sup> Moreover, the flow reaction system displays good resistance to high solvent vapor pressures, and can therefore be employed in reactions requiring temperatures greater than the boiling point of the solvent.

The propargylamine moiety is an important bioactive compound,<sup>7</sup> and has been used as a building block for the

preparation of versatile heterocyclic derivatives, such as pyrroles,<sup>8</sup> pyrrolidines,<sup>9</sup> pyrrolophanes,<sup>10</sup> aminoindolizines,<sup>11</sup> and oxazolidinones.<sup>12</sup> A number of preparation methods have been reported for propargylamines,<sup>13</sup> including the transition metal-catalyzed A<sup>3</sup>-coupling reaction.<sup>14</sup> This reaction is a three-component reaction between an alkyne, an amine, and an aldehyde, employing catalysts based on gold,<sup>15</sup> iridium,<sup>16</sup> zinc,<sup>17</sup> mercury,<sup>18</sup> nickel,<sup>19</sup> iron,<sup>20</sup> indium,<sup>21</sup> and copper.<sup>22</sup>

With relation to our ongoing studies for the decarboxylative coupling reaction of alkynyl carboxylic acids,<sup>23</sup> we developed a copper-catalyzed three component reaction between aldehydes, amines, and alkynyl carboxylic acids for the preparation of propargylamines.<sup>23s</sup> It was found that this three-component reaction could be carried out in the absence of transition metal catalysts when paraformaldehyde was employed as the aldehyde source.<sup>23n</sup> In addition, the metal-free A<sup>3</sup>-coupling reaction between phenylpropiolic acid, morpholine, and paraformaldehyde in water at 100 °C gave the desired propargyl amine in 97% yield.

We therefore chose to expand this green process, by attempting to carry out the  $A^3$ -coupling reaction with a variety of amines. Disappointingly, low yields of the desired coupled products were obtained in the majority of cases. We therefore chose to employ the continuous flow reaction system to address the yield issues, as this system allowed the use of

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Scheme 1. Synthesis of propargylamines via an A<sup>3</sup> coupling reaction.

 Table 1. Optimized conditions for the solubility of the three reagents in water<sup>a</sup>

Entry	Phenylpropiolic acid	Morpholine	Paraformaldehyde	Solubility
1	+	-	-	Low <sup>b</sup>
2	_	+	_	High <sup>c</sup>
3	-	-	+	High <sup>c</sup>
4	+		+	Low <sup>b</sup>
5	+	+	_	High <sup>c</sup>

<sup>a</sup>All reagents were dissolved in water (26.0 mL). Phenylpropiolic acid (1.930 g), morpholine (1.150 g), and paraformaldehyde (0.396 g) were used in the solubility tests. Key: + = reagent present; - reagent absent.

<sup>b</sup>Low: Undissolved or precipitated solids were present,

<sup>c</sup>High: No undissolved or precipitated solids were observed

reaction temperatures in excess of the boiling point of the reaction solvent. The high pressure feed in a flow reaction system could prevent a solvent from vaporization at higher temperature. Therefore, we herein report a metal-free synthesis of propargyl amines in water using a continuous flow reactor system.

In order to carry out the metal-free decarboxylative coupling reaction using a flow system with water as solvent, we first studied the solubility of all reagents. Phenylpropiolic acid was found to be insoluble in water, even at temperatures up to 100 °C. However, when phenylpropiolic acid and morpholine were mixed together in water, the solubility of both reagents increased, and a clear solution was observed. In contrast, paraformaldehyde was found to be soluble in water.

Based on the solubility results, two reservoirs were prepared for carrying out the reaction. The first reservoir contained an aqueous solution of phenylpropiolic acid and morpholine, while the second reservoir contained an aqueous solution of paraformaldehyde. Each reservoir was connected to the flow channel and their flow rate was controlled by means of a syringe pump. The two flow channels were connected to a tee-union mixer and a mixture of the two solutions was allowed to flow through a piece of tubing placed in an oil bath. In order to address issues relating to high pressure within the tubing, a backpressure regulator was attached to the end of the tubing channel. The reaction mixtures were allowed to flow at a rate that ensured a 1 h residence time at 100 °C, giving the desired product in 6% yield (entry 1). In order to improve the yield, the temperature of the system was increased (entries 2-4). This was

found to result in a significant increase in yield of the desired product. In addition, when the residence time was doubled, yields of 89% at 120 °C and 96% at 140 °C were obtained (entries 5 and 6), with the conditions of entry 6 being chosen as the optimal conditions for the reaction. However, when the reaction was conducted in the pressure vessel at 140 °C for 2 h, the reaction yield was 76% (entry 7).

 Table 2. Optimized reaction conditions for the continuous flow reactor<sup>a</sup>



Entry	Temp. (°C)	Residence Time (h) <sup>b</sup>	Pressure (bar)	Yield (%)
1	100	1	1.2	6
2	120	1	2.0	73
3	140	1	4.0	91
4	150	1	5.0	92
5	120	2	2.0	89
6	140	2	4.0	96
7°	140	2	3.6 <sup>d</sup>	76

<sup>a</sup>Reservoir **A**: Phenylpropiolic acid (13.2 mmol) and morpholine (13.2 mmol) were dissolved in water to a final volume of 26 mL. Reservoir **B**: Paraformaldehyde (13.2 mmol) was dissolved in water to a final volume of 26 mL. The reagent solutions in the two reservoirs were allowed to flow through the reaction tube. Flow rate = 0.0837 mL/min = 0.0419 mmol/min = 2.5 mmol/h.

<sup>b</sup>Residence time: 1 h = 1/16 inch tube, 10 m; 2 h = 1/16 inch tube, 20 m.

<sup>c</sup>Reaction was conducted in the pressure vessel at 140  $^{\circ}$ C.

<sup>d</sup>Vapor pressure of reaction mixture in the vessel.

Following successful optimization of the reaction conditions, we then chose to extend the substrate scope of the reaction. A range of amines was tested, and the results can be seen in Table  $3.^{24}$  Cyclic amines pyrrolidine (2b), piperidine (2c), and azepane (**2d**) were reacted with phenylpropiolic acid and paraformaldehyde in the flow reactor to give the corresponding propargylamines in 89%, 96%, and 88% yield, respectively (entries 1-3). A<sup>3</sup>-coupling reactions using acyclic amines diallylamine (2e), and N- methylbenzylamine (2f) also gave the desired propargylamines in good yield (entries 4 and 5). In addition, it was found that the substrate scope could be further expanded to vary the alkyl-substituted propiolic acids used in the

reaction. Reactions of morpholine (2a) with 2-butynoic acid (1b), 2-pentanoic acid (1c) and 2-octynoic acid (1d) gave the desired propargylamines in good yield (entries 6 - 8). When 2-octynoic acid (1d) was allowed to react with pyrrolidine (2b) and paraformaldehyde, the desired propargylamine 3db was formed in 88% yield. (entry 9). In addition, the reaction with piperidine (2c) also showed good yield (entry 10). We found that all results showed better yield than those of the batch reactions.<sup>23n</sup> In contrast, all primary amines including cyclohexylamine (2g) and aniline (2h) studied gave unsatisfactory results compared to secondary amines (entries 11 and 12). This is comparable to the results obtained for the reaction under batch conditions.<sup>23n</sup>

#### Table 3. Synthesis of propargylamine in water using the continuous flow process<sup>a</sup>



<sup>a</sup>Reservoir A: Substituted propiolic acid 1 (13.2 mmol) and amine 2 (13.2 mmol) were dissolved in water to a final volume of 26 mL. Reservoir B: Paraformaldehyde (13.2 mmol) was dissolved in water to a final volume of 26 mL. The reagent solutions in the two reservoirs were allowed to flow through the reaction tube in an oven at 140 °C for 2 h. Flow rate = 0.0837 mL/min.

<sup>b</sup>All compounds were characterized by comparison of their 1H and 13C NMR spectra with authentic samples and/or literature data.

<sup>c</sup>The yield was isolated after 3 h.

<sup>d</sup>The yield from the batch reaction.

6786.

In order to confirm the metal-free condition in the flow reaction system, the reaction solution was subjected to ICP-MS. Based on this data, the metal concentrations were not exceed hundreds of ppb.

In conclusion, we have developed an environmentally friendly and economical continuous flow reaction system for the preparation of propargylamines *via* a metal-free decarboxylative coupling. The reaction was carried out in water in the absence metal catalysts or other additives. The desired propargylamine products were formed in good yield with stoichiometric quantities of the reagents, unlike in the batch reaction where an excess was required. Further studies on detailed mechanism are underway in our laboratory.<sup>25</sup> In addition, the only waste products derived from the A<sup>3</sup>-coupling reaction reported herein were CO<sub>2</sub> and H<sub>2</sub>O. Finally, this continuous flow system has enhanced heat and mass transfer characteristics and was suitable for use at elevated temperatures beyond those of the solvent boiling point.

#### Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2012R1A1A2044286) and the National Research Foundation of Korea Grant funded by the Korean Government (MEST) (2012, University-Institute cooperation program). Spectral data were obtained from the Korea Basic Science Institute, Gwangju Branch.

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  - 24. *Typical experimental procedure*. Aryl or alkyl substituted propiolic acid (13.2 mmol) and amine were dissolved in water (26.0 mL) and stirred at room temperature for 1 h. The resulting mixture was transferred to reservoir **A**, which was connected to the reaction tube. Paraformaldehyde

(13.2 mmol) was then dissolved in water (26.0 mL) and stirred at 90 °C for 1 h and cooled to room temperature. This solution was transferred to reservoir **B**, which was also connected to the reaction tube. The solutions of reagents in the two reservoirs were allowed to flow through the reaction tube in an oven at 140 °C for 2 h. The flow rates for the two solutions were set 0.0837 mL/min, and the rates were controlled by means of a syringe pump. The resulting crude reaction mixture was collected, and extracted with diethyl ether. The organic phase was then washed according to an acid and base workup process, and dried over anhydrous MgSO4. The desired product was then obtained by evaporation of the organic solvent. 3aa was obtained with 96% yield. 3aa: 1H NMR (300 MHz, CDCl3) & 7.46 - 7.42 (m, 2H), 7.36 - 7.13 (m, 3H), 3.87 - 3.65 (m, 4H), 3.50 (s, 2H), 2.78 - 2.44 (m, 4H); 13C NMR (75 MHz, CDCl3) & 131.4, 128.0, 127.9, 122.7, 85.3, 83.8, 66.6, 52.1, 47.83.

25. It is not clear which step is a rate-determining step in the metal free decarboxylative coupling reaction. We failed to detect any intermediate in this reaction pathway.

#### **Graphical Abstract**

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