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Continuous flow reactions in water for the synthesis of propargylamines via a metal-free decarboxylative coupling reaction

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ABSTRACT

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.

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.[1] Important examples of green reaction systems for synthetic chemistry include recyclable catalysts[2] and the use of ionic liquids[3] 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.[4] 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.[5] In addition, this system has a high surface area-to-volume ratio, thus providing efficient heat and mass transfer.[6] 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,[7] and has been used as a building block for the preparation of versatile heterocyclic derivatives, such as pyrroles,[8] pyrrolidines,[9] pyrrolophanes,[10] aminoindolizines,[11] and oxazolidinones.[12] A number of preparation methods have been reported for propargylamines,[13] including the transition metal-catalyzed A^3-coupling reaction.[14] This reaction is a three-component reaction between an alkyne, an amine, and an aldehyde, employing catalysts based on gold,[15] iridium,[16] zinc,[17] mercury,[18] nickel,[19] iron,[20] indium,[21] and copper.[22]

With relation to our ongoing studies for the decarboxylative coupling reaction of alkynyl carboxylic acids,[23] we developed a copper-catalyzed three component reaction between aldehydes, amines, and alkynyl carboxylic acids for the preparation of propargylamines.[23s] 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.[23n] In addition, the metal-free A^3-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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