Microwave Assisted Mannich Reaction of Terminal Alkynes on Alumina

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Summary. Terminal alkynes, secondary amines, and formaldehyde undergo a Mannich reaction at room temperature in the presence of CuCl on Al\textsubscript{2}O\textsubscript{3} without any organic solvent as reaction medium. The reaction can be promoted by microwave irradiation and is complete within one minute.

Keywords. Alkynes; Alumina; Mannich bases; Microwave irradiation.

Introduction

The Mannich reaction is one of the most important multicomponent reactions in organic chemistry [1]. Mannich bases are of considerable interest and have found applications in chemical and pharmaceutical industry [1g, 2].

A large variety of compounds such as ketones, nitro compounds [1b], amines [3], amides [4], and electron-rich aromatic compounds [1c, 5] can serve as substrates in Mannich reactions. Terminal alkynes also can take part in Mannich reactions to give the corresponding propargylamines which can be further transformed to \(\beta\)-aminoketones [6], aminoalkenes [6b, 7], or aminoalkanes [6b].

Some propargylamines exhibit biological activities. For example, substituted 1-aryl-3-aminopropynes have antiulceration, sedative, hypnotic, antispasmodic, analgesic, and anti-inflammatory effects [8]. Also, a number of 3-phenylpropyn-2-amines (1) have been previously prepared and shown some monoamine oxidase inhibitory, anorexigenic, and blood lipid lowering activity as well as tryptamine-like behavioural effects without any interaction with tryptamine receptors [9].

![Image of molecule 1]

There are several methods for the preparation of propargylamines, e.g. reaction of 1-(\(\alpha\)-aminoalkyl)-benzotriazoles with lithium alkenydes [10] or with sodium

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dialkynyldiethylaluminates [11], reaction of propargyl bromides with secondary amines [12], or reaction of geminal aminoethers with terminal acetylenes [13]. However, the most convenient method for the preparation of 1 is refluxing a solution of a terminal acetylene, a suitable amine, and formaldehyde in a polar solvent, mostly dioxane, in the presence of a catalytic amount of a copper salt (usually CuCl or Cu(OAc)$_2$) [6–8, 14]. Copper salts are frequently used in the reaction, since they have been found to increase the nucleophilicity of the acetylenic substrates towards the Mannich reactants [15]. Recently, Dax et al. have shown that any member of the three components can be immobilized on a resin and subsequently reacted with the other two in the presence of a copper(I) salt to afford the desired Mannich adducts [16].

Here, we report an environmentally benign preparation of propargylamines via a Mannich reaction on Al$_2$O$_3$ without any organic solvent as reaction medium (Scheme 1).

![Scheme 1](image)

**Results and Discussion**

We have previously shown that electron-rich aromatic compounds can be aminoalkylated by a Mannich reaction with appropriate adducts on solid supports assisted by microwave irradiation [5b]. In continuation of our interest in Mannich base synthesis, in peculiar with those assisted by microwave irradiation, we examined the extension of this method to the aminomethylation of terminal alkynes with two different methods.

In method A, a terminal acetylene (2), a secondary amine (3), formaldehyde (used as 37% aqueous solution), CuCl, and neutral alumina were mixed together and stirred at room temperature. The progress of the reaction was monitored with TLC. After 6 h, the products were obtained in good to excellent yields (Table 1). This method can also be applied to bulky secondary amines, such as dibenzylamine and diisopropylamine (Table 1, entries 6 and 7). In the absence of CuCl, the yield of the reaction is negligible.

Method B is basically similar to method A, but the reaction was promoted by microwave irradiation in a domestic microwave oven. The reaction was complete in about one minute. The yields of the products were in the range of 70–94%, i.e. comparable to those obtained from method A (Table 1). The products 4a–i are known compounds; the new products 4j–m were characterized by their NMR spectra and HRMS.

To investigate solid supports other than neutral alumina, we also examined basic and acidic alumina, silica gel, and montmorillonite K-10, but the best results were obtained with neutral alumina.