Journal of Molecular Catalysis A: Chemical 426 (2017) 542–549

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

The KA^2 coupling reaction under green, solventless, heterogeneous catalysis

Giovanna Bosica*, Roderick Abdilla

Department of Chemistry, University of Malta, Msida MSD 2080, Malta

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form
15 September 2016
Accepted 17 September 2016
Available online 20 September 2016

Keywords:
Solventless
KA^2-coupling
Multi-component
Heterogeneous catalysis
Copper(I) iodide - amberlyst A-21

ABSTRACT

Amberlyst A-21 supported CuI was found to be highly efficient novel heterogeneous catalyst for the three-component reaction between ketones, amines and alkynes, commonly called KA^2-coupling. This inexpensive, easy-to-prepare, simple and recyclable catalyst has been employed in solventless conditions in the KA^2 coupling reaction involving both primary and secondary amines, ketones and various alkynes. The secondary and tertiary propargylamine products were obtained in good to excellent results in moderate reaction times.

1. Introduction

Propargylamines are key intermediates in the synthesis of biologically active compounds such as β-lactams, conformationally restricted peptides and drug molecules [1]. For example both aliphatic *N*-methyl propargylamines and primary propargylamines have been shown to be potent neural rescue agents that can help in the therapy of Parkinson's disease, Alzheimer's and other neurodegenerative diseases [1,2].

Such compounds are usually synthesized by the multi-component A^3-coupling reaction of an aldehyde, an amine and an alkyne to form a tertiary carbon centre. Initially, the latter reaction was catalysed by homogeneous catalysts containing metal ions that could activate the C_{sp}-H of the terminal alkyne. Examples of metal salts which have been used include: silver, gold, mercury, iridium, and copper salts [3–7]. However these reagents are usually moisture sensitive, require the use of an organic solvent and are not easily recoverable. Consequently, heterogeneous catalysts started to be employed such as polystyrene supported silver(I), lanthanum loaded copper(II) oxide, copper(0)-nanoparticles supported on montmorillonite, copper(II) exchanged molecular sieves, copper-aluminium nanocomposites, gold(III)-supported on ceria, nano-zinc sulfide particles among others [8–14].

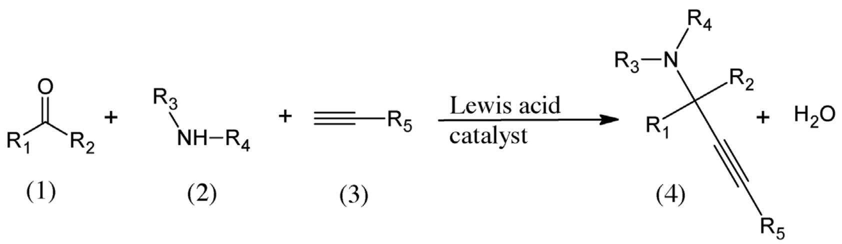
Unlike aldehydes, ketones are much less reactive and have been rarely used in the synthesis of propargylamines which contain a quaternary carbon centre (Scheme 1). Most homogeneous and heterogeneous catalysts employed for the A^3-coupling were not extended to the KA^2 reaction or when utilised gave poor results. For example, the copper(II)-magnetite catalyst gave excellent yields for aldehydes after heating for 3 h at 120 °C, but when ketones were employed poor yields were obtained after 7 days of reaction time [15]. The first major breakthrough in the KA^2 reaction happened when copper(I) iodide was employed in solventless conditions under microwave irradiation to obtain average to good results in short reaction times whilst employing primary amines and cyclohexanone derivatives [16]. When gold(III) bromide was used, it gave moderate to very good results in neat conditions even if only with secondary amines [17]. Copper(II) and copper(I) bromide (in the presence of molecular sieves) were two separate homogeneous catalysts that gave excellent yields [18,19]. Such homogeneous catalysts suffered from one or more of the following disadvantages: expensive, non-recoverable, required solvent and/or involved electromagnetic irradiation.

When heterogeneous catalysts were employed, varying results were obtained. Copper(II) chloride-supported on titania required 24 h and dichloromethane solvent to give average results for two ketones only [20]. However both nano copper(I) oxide/zinc oxide and copper(I)-nano copper-magnetite gave excellent results in short reaction times in solventless conditions [21,22]. Despite this, both catalysts are expensive and preparation is not as simple.

---

* Corresponding author.
E-mail address: giovanna.bosica@um.edu.mt (G. Bosica).

http://dx.doi.org/10.1016/j.molcata.2016.09.028



Scheme 1. Multicomponent coupling of a ketone (1), an amine (2) and an alkyne (3) (KA^2).

Moreover primary amines were not used or gave no products, no linear ketones were employed and only aromatic alkynes were involved.

In a previous study by our research group, copper(I) iodide was successfully loaded onto Amberlyst A-21 for the A^3-coupling (Fig. 1); the catalyst is cheap, easily prepared, reusable and gave excellent results [23]. In continuation of our studies we have now employed this catalyst for the KA^2 reaction involving both primary and secondary amines, aliphatic and aromatic alkynes together with either cyclic or linear ketones in solventless conditions.

2. Experimental

2.1. Materials and methods

All commercially available chemicals were purchased from Aldrich and used without further purification. IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrometer calibrated against a 1602 cm^{-1} polystyrene absorbance spectra. Samples were analysed as a thin film or in a Nujol™ mull between sodium chloride plates. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD® NMR Spectrometer, equipped with an Ascend 500 11.75 T Superconducting Magnet, operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C, and a Multinuclear 5 mm PABBO Probe. Samples were dissolved in deuterated chloroform (with TMS). Mass spectra were performed using a Waters® ACQUITY® TQD system with a tandem quadrupole mass spectrometer after dissolving the sample in methanol. Reactions were monitored using TLC and GC on a Shimadzu GC-2010 *plus* gas chromatograph equipped with a flame ionisation detector and HiCap 5 GC column with dimensions of 0.32 mm (internal diameter) x 30 m (length) x 0.25 mm (film thickness), using nitrogen as carrier gas. The heterogeneity of the catalysis and copper(I) iodide loading on Amberlyst A-21 (A-21) was checked by performing flame atomic absorption spectroscopy (FAAS) using a contrAA® 700 High Resolution Continuum Source Atomic Absorption Spectrometer.

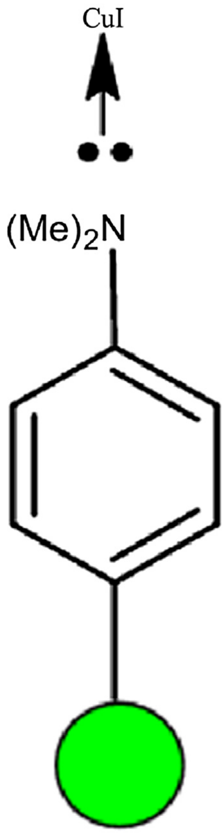


Fig. 1. Structure of copper(I) iodide loaded onto Amberlyst A-21 polymer resin.

2.2. Preparation of Copper(I) iodide on amberlyst A-21 (CuI/A-21)

Copper(I) iodide supported on Amberlyst A-21 was prepared by modifying a previously reported method [24]. A sample of dry Amberlyst A-21 was prepared by placing 10 g of the resin in 50 mL methanol and allowing it to stand for 30 min. After this, the mixture was filtered and washed with 20 mL methanol three times over. This procedure was then repeated in dichloromethane, and the resin was then placed in a vacuum desiccator to dry overnight. A solution of 2.285 g (12 mmol) of copper(I) iodide in 60 mL acetonitrile was then mixed with 4 g of dry Amberlyst A-21 and left stirring overnight at room temperature. Our method therefore used 3 mmol of copper(I) iodide per gram of Amberlyst A-21 instead of 2 mmol per gram. The solvent was subsequently evaporated off and the resulting light green resin was washed with two 15 mL aliquots of acetonitrile, followed by eight 15 mL aliquots of dichloromethane. The resin was dried overnight in a vacuum desiccator and, after confirming a stable weight, the loading of copper per gram of resin (1.64 mmol/g) was calculated by observing the weight increase of the final dried sample of CuI/A-21. This loading was also confirmed by performing an AAS study (see below).

2.3. Procedure for preparation of propargylamines by KA^2 coupling

A nitrogen-flushed 25 mL two-necked flask was loaded with 0.152 g (10 mol% CuI/A-21 with a loading in terms of copper(I) iodide of 1.64 mmol/g) to which the ketone (2.5 mmol), amine (3.0 mmol) and alkyne (3.75 mmol) were added. The mixture was stirred whilst heating in an oil bath at 98 °C in the presence of a nitrogen atmosphere. Upon completion, as judged by TLC which was stained with 2,4-dinitrophenylhydrazine, the reaction was allowed to cool down before the catalyst was filtered and washed with 5 × 2 mL diethyl ether. The crude reaction mixture was concentrated by rotary evaporation before being loaded to a silica-filled chromatographic column. The most common eluent mixtures used were 9:1 or 8:2 *n*-hexane/ethyl acetate. The yields of the purified