Chemical Engineering Journal 270 (2015) 468–475

Contents lists available at ScienceDirect

Chemical Engineering Journal

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

# Continuous metal scavenging and coupling to one-pot copper-catalyzed azide-alkyne cycloaddition click reaction in flow

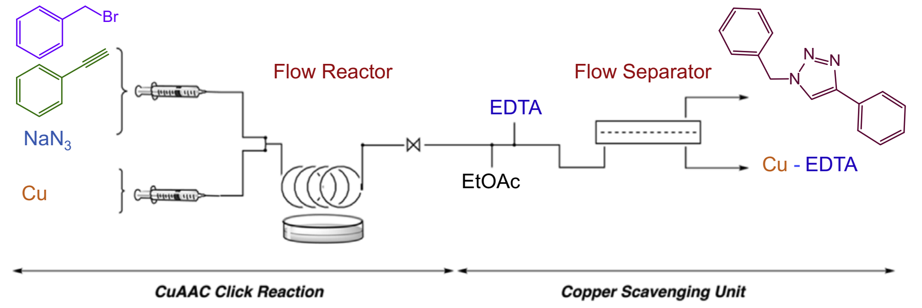
Iris Vural Gürsel, Ferry Aldiansyah, Qi Wang, Timothy Noël *, Volker Hessel *

*Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, Eindhoven 5600 MB, The Netherlands*

## HIGHLIGHTS

- Continuous uninterrupted metal scavenging unit is developed and optimized.
- Effect of several parameters on the scavenging performance is investigated.
- Level of purity required for pharmaceuticals is met in one stage.
- Coupled CuAAC click reaction and copper scavenging is achieved.
- Open door to exploit continuous multi-step synthesis in flow further.

## GRAPHICAL ABSTRACT



## ARTICLE INFO

*Article history:*
Received 6 October 2014
Received in revised form 6 February 2015
Accepted 8 February 2015
Available online 14 February 2015

*Keywords:*
Click chemistry
Metal scavenging
Microextraction
Microreactors
Coupled micro unit operations

## ABSTRACT

Increasing usage of catalytic chemistry calls for efficient removal of metal traces. This paper describes the development and optimization of a scavenger-based extraction in flow to remove metal catalysts. It enables liquid–liquid extraction with slug flow and phase separation with a porous fluoropolymer membrane. The use of this unit for copper scavenging of various copper sources from organic solvent was studied. The effects of scavenger type (EDTA, DTPA, EDDS), concentration and pH were also investigated. Such analysis allowed to achieve extraction performance as high as 99% at pH of the scavenger solution adjusted to 9.4 and molar ratio of scavenger to copper of 10. Process integration is achieved by coupling this unit downstream to a flow reaction using homogeneous metal-based catalysis, i.e. presenting a continuous uninterrupted metal scavenging unit. The copper-catalyzed azide-alkyne cycloaddition click reaction is studied in one-pot eliminating the need to isolate and handle potentially explosive azide. The triazole product is attained in flow with high yield of up to 92% with 30 min residence time. The level of purity requirement for pharmaceuticals is met in one stage of extraction.

## 1. Introduction

Process intensification through micro-process technology allows to reach processing far from state of the art through entirely new and innovative equipment and means of processing in continuous flow mode [1–3]. In the past, it was based mainly on transport intensification that improves mixing and heat exchange [4,5]. More recently, chemical intensification is increasingly explored which uses highly intensified, unusual and typically harsh process conditions to boost micro-processing (high temperature, high pressure, high concentration, safety) [6–11]. The last two mentioned means are an essential part of Green Chemistry. Beyond, as third momentum, process-design intensification heads for simplified and integrated flow process design (Green Engineering) [12]. The latter two intensification fields constitute 'Novel Process Windows', a term coined by Hessel in the past and further developed by our group [1,13–15].

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* Corresponding authors. Tel.: +31 40 2473623 (T. Noël), +31 40 2472973 (V. Hessel).

*E-mail addresses:* t.noel@tue.nl (T. Noël), v.hessel@tue.nl (V. Hessel).

http://dx.doi.org/10.1016/j.cej.2015.02.035
1385-8947/

In the microreactor literature and community it is common to focus largely to one equipment (designed and tested) and its processing. However, with process-design intensification we focus our attention toward the chemical process as a whole, thereby rendering a true holistic picture [16,17]. The majority of microchemical synthesis applications were so far restricted to one or few reaction steps with the separation done offline [18–20]. Microreactors are highly developed at scales up to industrial production [21,22]. However, further development of microseparation units is needed. From about 2011 onwards, there is an increasing number of developed microseparation devices [23]. Still most of these devices have been characterized as stand-alone tools, i.e. without connection to a flow reaction device. The coupling of microseparation units with microreactors is not rare anymore, but still far from being commonly applied. So far, there are only few demonstrations [24–27]. To be able to achieve multi-step synthesis in flow and make the flow process chain complete, further development of microseparators is required.

Since the early investigations in micro process technology, microextraction has received a considerable amount of attention. Microextraction involves mixing and contacting of the organic and aqueous phases and consequently achieving the phase separation. Extraction based on liquid–liquid slug flow in microchannels facilitates convective mass-transfer between the phases [28]. Due to internal circulation flow, high mixing performance is achieved [4]. After extraction the two phases can be easily separated. Effective liquid–liquid separation can be achieved using membranes [29,30]. Separation of the two phases can also be performed with branched hydrophobic and hydrophilic outlets [31,32].

For extraction of copper and a wide range of metals, chelating agent solutions are effective [33]. These scavenging agents extract metal by forming a metal–chelate complex which can further be removed from the solution [34]. It enables high extraction efficiency of the metal and is fast, compatible with many solvents and causes no loss of product. It was used effectively for extraction from spent catalyst [34–36] and also waste waters [37,38]. Most used scavenging agents include ethylene diamine tetraacetic acid, EDTA and diethylene triamine pentaacetic acid, DTPA [39]. Due to their high complexation strength they are effective scavenging agents but are resistant to degradation [36]. Biodegradable [*S*,*S*]-ethylene diamine disuccinic acid ([*S*,*S*]-EDDS) has been proposed as an alternative scavenging agent and it has also been found to have high extraction efficiency [35,36,40].

The copper-catalyzed azide-alkyne cycloadditon (CuAAC) was taken as the reaction of industrial relevance. It is established as one of the most important examples of click chemistry [41–43]. The resulting 1,2,3 triazoles find use in variety of applications from drug discovery and development to material science and chemical biology [41,42,44–47]. Several approaches to perform CuAAC in continuous flow processing have been reported [9,48–50]. This is motivated by improved mass and heat transfer as well as the safety aspects, azide being unstable, and scalability of flow processing opposed to conventional batch procedures. Microwave irradiation was also tested and major reduction in reaction time was observed [48,51,52]. Another advance in this field is generation of the required azides in situ [50–53]. This one-pot methodology eliminates the need to synthesize azide separately in continuous flow [54]. All these examples used heterogeneous catalysis. Although heterogeneous catalysis has advantage of being recyclable, the copper species leach into the solution [48,49]. Scavenger resins in cartridges has been used to remove these copper species from the solution. One example is Quadrapure™ TU that has been successfully used for CuAAC reactions [48,49]. However, the need to periodically replace these cartridges interrupts the continuous process.

A microseparation unit has been developed to achieve continuous uninterrupted extraction of metal catalyst in flow. It involves liquid–liquid extraction based on slug flow with the use of chelating agent and phase separation using porous fluoropolymer membrane. The coupling of CuAAC reaction with continuous copper extraction was achieved in flow in previous studies [9]. However, three stages were required to reduce the copper content of triazole product below the limit for APIs of 15 ppm [55]. Since this is not optimal, more extensive analysis of microseparation unit was needed. This is carried out and presented in this paper. In this study, first the performance of the microseparation unit is benchmarked using EFCE-recommended extraction systems. Also its performance is compared with a similar flow extraction unit described in literature. Then the copper extraction experiments are performed that enable continuous uninterrupted separation of copper species in solution. To achieve the optimum extraction performance, the use of different types of copper catalysts and metal scavengers (EDTA, DTPA and EDDS) are investigated together with variation of metal scavenger concentration and pH. Based on this analysis and optimization of parameters, the copper scavenging unit is coupled to the CuAAC click reaction using homogeneous copper catalyst with the aim to get the triazole product at high yield and purity in one stage of separation.

## 2. Material and methods

### 2.1. General chemicals information

Chemicals were purchased in their highest purity available from Sigma Aldrich. Scavenging solutions from ethylene diamine tetraacetic acid (EDTA) and diethylene triamine pentaacetic acid (DTPA) were prepared by mixing with demineralized water (purified with a Millipore Elix UV-5 machine) and careful addition of ammonium hydroxide ($NH_4OH$) 5 M drop by drop until the solids disappear and the desired pH is achieved. [*S*,*S*]-ethylene diamine disuccinic acid ([*S*,*S*]-EDDS) was purchased as solution (35% water), it is diluted to desired concentration and $NH_4OH$ is added to get the desired pH.

### 2.2. General analytical information

Analysis for performance characterization experiments are done using GC-FID on a Varian 430-GC with a flame ionization detector using a CP-Sil 8 CB column (length 60 m, diameter 0.25 mm, film thickness 0.1 $\mu$m), with helium as the carrier gas. External calibration is performed by making solutions of varying concentrations 0, 2, 4, 6, 8, and 10 wt.% of solute in organic phase. Sample from organic outlet is taken and analyzed for amount of solute.

Analysis for copper scavenging experiment is performed using Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES) from Sysmex SpectroBlue. 1 mL sample of aqueous outlet (containing EDTA–copper complex) is diluted to 100 mL using oven dried volumetric flask, sample is then analyzed using ICP-OES with prior calibration. Calibration is performed by making a calibration curve from 0 to 10 ppm of copper. Calibration samples were prepared using 1000 mg $L^{-1}$ TraceCERT standard solution available from Sigma–Aldrich.

Analysis for one-pot CuAAC click reaction to determine yield of triazole is done using $^1$H NMR. Nuclear magnetic resonance spectra were recorded on a Varian Mercury 400 instrument. All $^1$H NMR are reported in $\delta$ units, parts per million (ppm), and were measured relative to the signal of tetramethylsilane (0 ppm) in deuterated solvent ($CDCl_3$). Prior to NMR analysis, high purity toluene is added as internal standard for quantification of yield. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.