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An open-source approach to automation in organic synthesis: The flow chemical formation of benzamides using an inline liquid-liquid extraction system and a homemade 3-axis autosampling/product-collection device

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ABSTRACT

Several open-source hardware and software technologies (RAMPS, Python, PySerial, OpenCV) were used to control an automated flow chemical synthesis system. The system was used to effect the synthesis of a series of benzamides. An inexpensive Raspberry Pi single board computer provided an electronic interface between the control computer and the RAMPS motor driver boards.

1. Introduction

Automation, particularly since the industrial revolution, has had a profound impact on the technological and economic evolution of human society. There are now very few areas of human activity which have not seen the introduction of significant automation in one form or another.[1] It is, therefore, somewhat surprising that chemical synthesis (at least in the majority of academic research laboratories) is still performed using largely the same apparatus and labour intensive techniques developed when the discipline was still young. Whilst a number of very well engineered and robust automated chemical synthesis platforms are available commercially, and have obtained growing popularity in industrial research laboratories, their relatively high price often puts them beyond the reach of many academic research groups.

In a growing context of chemist-led technological innovation,[2] we have been interested in using open-source hardware and software technologies to develop alternative low-cost automation platforms for chemical synthesis.

In the last two decades or so, a number of significant developments have taken place which have made enabling technologies much more accessible to 'non experts'. In terms of coding, the advent of high-level scripting languages, like Python,[3] have made it easier to write highly functional programs without the need to understand underlying low-level processes. A major attraction of Python is the availability of a vast array of libraries that provide specific functionality across a diverse range of application areas. These often act as wrappers around code written in computationally more efficient languages such as C/C++ or Fortran. In terms of electronic hardware, the growing availability of easy to program microcontrollers (such as Arduino,[4] PICAXE[5] and PyBoard/MicroPython[6]) as well as General-Purpose-Input-Output (GPIO) enabled single-board computers (such as the Raspberry Pi[7] and BeagleBoard[8]) has enabled the ready interfacing of control systems with electronic machinery and components.[9] In addition to the technologies themselves, the community-driven models of open

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innovation and applications that have evolved alongside them have also played a major role in their success and popularity.[10]

In our previous work,[11] we carried out a series of acid catalysed silyl group deprotections using a homemade 3-axis autosampler and a series of motor actuated valves to select and load starting materials into a holding loop and to control the liquid flow through the system. In that case, whilst the selection of the starting materials was automated, the collection of reaction products into separate containers was not and switching between the collection vessels had to be performed manually.

In this manuscript we describe an improved automation system which selects and loads starting materials and also collects products into separate collection flasks.

Shown in Fig. 1 (top) is a simplified schematic representation of our previous system. Starting materials were taken from the autosampler and loaded into the holding loop by means of Syringe Pump 1 (the holding loop was not completely filled, thereby avoiding contamination of Syringe Pump 1). The common reagent was loaded into Syringe Pump 2 and, after switching of valves, the Piston Pump and Syringe Pump 2 would push the two solutions through the reaction/purification zone and product flow streams would emerge at the outlet to be collected in suitable vessels. As the autosampler was not also being used to collect products, the necessary flushing of the residual starting material (in the line between the autosampler and 3-Way Valve 2) into a waste channel could be left until after the reaction had completed (by moving Syringe Pump 1 back to its original starting position).

For our updated autosampling/product-collection system, the flushing of the line to the autosampler could not be left until after the reaction had completed as the residual starting material would then end up in the product collection vessel. In order to incorporate this step in a way which minimised the amount of additional hardware required, we added an extra 3-Way Valve and a secondary Holding Loop (Fig. 1, bottom). This would allow Syringe Pump 1 to load the required starting material into Holding Loop 1 and then, after switching of 3-Way Valves 2 and 4 and moving of the autosampler needle to the waste position, to flush out the residual starting material (between the autosampler and 3-Way Valve 4) by moving back to its original position. After moving the autosampler needle to the correct collection vessel, the Piston Pump could then be used to push the starting material flow stream through the reaction system. The volume of Holding Loop 2 was chosen to be slightly higher than that of Holding Loop 1 in order to prevent unwanted premature mixing of the starting material with the common reagent stream (from Syringe Pump 2).

In order to demonstrate the operation of the system, we sought to carry out the flow chemical[12] formation of a series of benzamides, **4**, using benzoyl chloride, **1**, as the common limiting reagent and a series of primary amines, **2**, as the liquid-liquid extractable[13] starting materials used in excess (Scheme 1). In order to facilitate rapid reaction in the flow system at room temperature, we also planned to use 2 equivalents of 4-dimethylaminopyridine (DMAP, **3**) as the liquid-liquid extractable stoichiometric base due to its ability to also act as a nucleophilic catalyst.[14] One of the key limitations of flow chemistry is that it is generally incompatible with reactions that form precipitates. As the most likely precipitate from the reactions in our solvent of choice (dichloromethane) would be the HCl salt of DMAP, we carried out preliminary solubility studies of this material (which was made by the addition of aqueous HCl to DMAP in THF solution).

Unsurprisingly, the material was insoluble in neat dichloromethane at realistic concentrations. Acetonitrile was attempted as a cosolvent but this did not provide significant additional solubility. Methanol did prove to be a useful cosolvent and a 3:1 mixture of dichloromethane: methanol was found capable of dissolving DMAP-HCl at a concentration of at least 0.17 M. When reactions between dichloromethane solutions of benzoyl chloride (**1**) and methanolic solutions of excess benzylamine (**2a**) and DMAP (**3**) were attempted, although the reactions proceeded rapidly at room temperature, in the absence of precipitation and with all of the excess DMAP and amine being efficiently removed by extraction with aqueous HCl, the amide product **4a** was accompanied by small

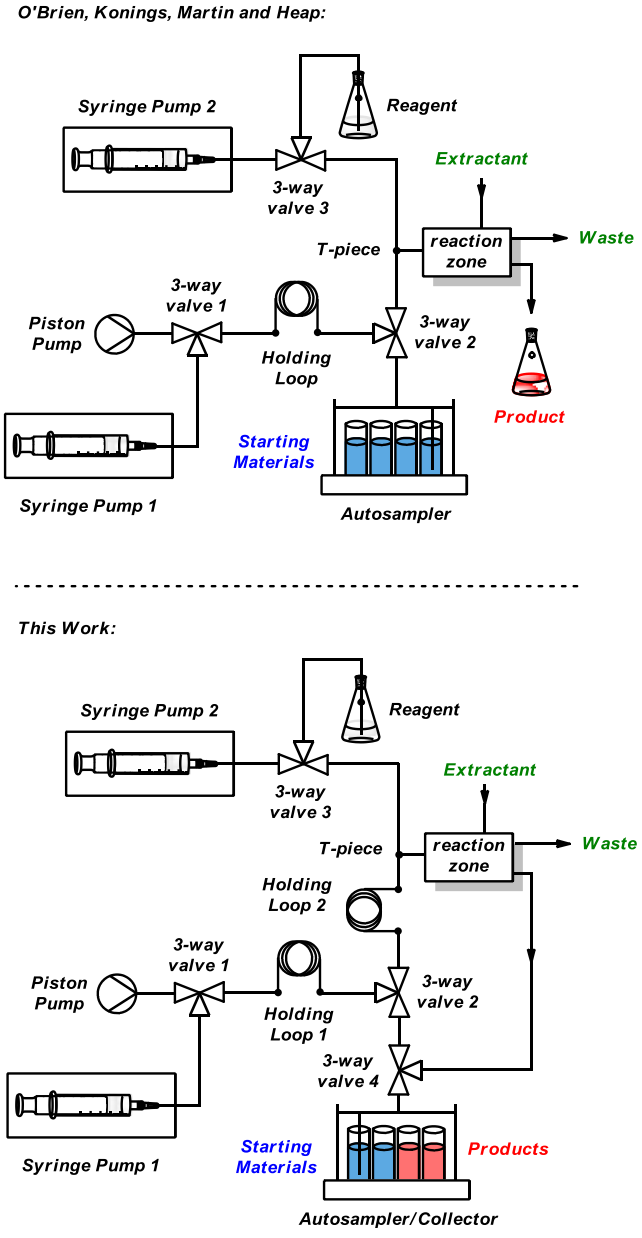
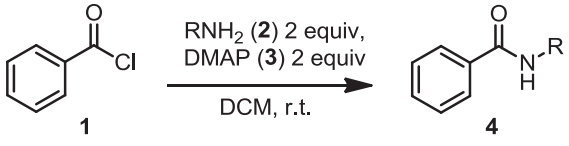


Fig. 1. Simplified schematic of our previous (top) and current (bottom) reaction systems.



Scheme 1.