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The Lab of the Future

The importance of remote monitoring and control

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ABSTRACT: Chemical laboratories and the equipment within them have changed very little over the last two centuries. However, the introduction of enabling technologies and their impact on current working practices is starting to redefine the laboratory environment. In this article the application of remote control software applied to real applications of flow-based synthesis are demonstrated and the related improvements in efficiency and safety discussed.
The use of webcams to remotely monitor synthetic procedures is described along with the associated enhancements that can be achieved.
We envisage that the integration of these techniques with portable devices such as mobile telephones will form part of the lab of the future.

INTRODUCTION

The demands and expectations of modern organic synthesis to deliver new innovative products to the community are immense. Whilst the knowledge and methods used by synthetic chemists have advanced at a phenomenal pace the general laboratory architectures and tools of the trade have, by comparison, changed very little. For example, much of the glassware, flasks, condensers and separating funnels that are in common usage today would have been found in laboratories going back over two centuries. Likewise, laboratories are still constructed on the same basic design comprising of work benches, associated areas for equipment and fume cupboards to vent obnoxious materials. Nevertheless, the safety, working conditions and analytical capabilities invested in modern laboratories has improved vastly over their early counterparts.
Advances in automation and other synthesis enabling technologies are already significantly impacting on the way we conduct science (1). As a result the working regimes and work flows that are being determined by these new practices necessitate fundamental changes to the physical infrastructure and resource allocation needed to perform good synthesis. Consequently the laboratory of the future is likely to be a very different environment both in design and utility. In order to justify the high initial cost associated with these new requirements a 24 hour, 7 days a week working regime will need to be established that also more closely follows the principals of a green agenda. To initiate the process of change, especially for conducting multi-step synthesis sequences, we have advocated the use of immobilised reagents and scavengers to better manipulate precious intermediates and purify products (2). These techniques facilitate recycling and can dramatically reduce downstream processing methods associated with the many unit operations needed to work-up typical solution phase batch mode reactions. Moreover, by linking these methods to continuous or plug-flow chemistries using microreactors and similar devices, even greater opportunities arise. Such methods allow more precise control of mass/heat transfer, access to a wider selection of temperature and pressure conditions and improved containment of hazardous/reactive intermediates or obnoxious materials (3, 4).
A beneficial and logical advance in the use of these methods would be to extend the operating time of these reactors in a safe and monitored fashion thereby leading to more complex and challenging multi-step sequences directly affording drug substances or even natural products (5, 6). However, these new concepts will demand a corresponding change in working practice such that new levels of remote monitoring and control will be necessary.
Here, we report some of our initial developments directed at addressing these requirements employing modern technology such as webcams and mobile telephones to port information and facilitate remote access to laptop computers and flow chemistry equipment.

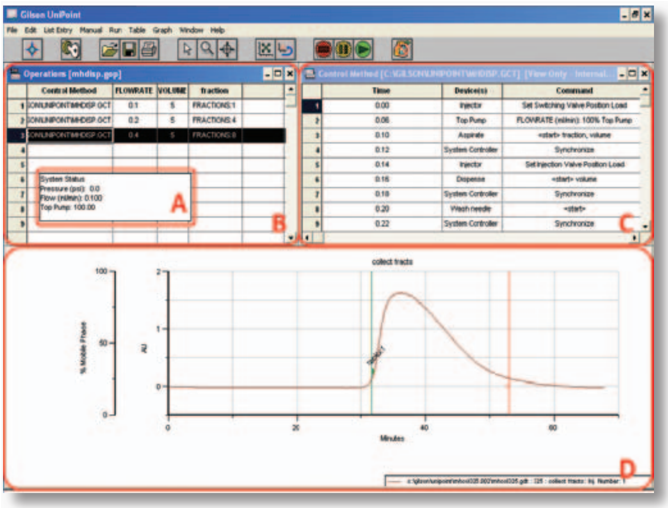


Figure 1. Gilson Unipoint. A: Pressure and flow rate information. B: List of reactions to be run. C: Sequential list of system commands. D: Live UV trace showing fraction collector status and product fractions collected.

REMOTE CONTROL AND DATA INTERROGATION REQUESTS

Flow chemistry is an ideal candidate for remote control; the machinery used to carry out the synthetic operations has a variety of different sensors measuring, for example, temperature and pressure. Reaction critical failures in the system such as the occurrence of a leak or generation of a blockage can therefore be readily detected by the pressure sensors as abnormally low or high pressures. The resulting signal can then be used to instigate a predefined safety shutdown protocol allowing the reaction to be halted and system to be placed into a safe dormant state until an operator has the time to evaluate the fault and rectify the issue.

Almost all commercially manufactured flow reactors nowadays have an interface allowing external communication and control of the device. This can be as straightforward as a contact switch to allow simple on/off control of a pump or switching of a valve or *via* a USB or RS232 serial port to a computer to allow more complex commands to be relayed. The associated software used to communicate with the device can be as simple as a terminal program where text commands can be sent to devices to, for example, set a flow rate, rotate a valve to a specified position or induce heating of a component to a specified temperature. More bespoke and dedicated software available for commercial flow systems permit more specific measurements to be recorded and data to be plotted as real-time graphs. Furthermore, whole sequences of commands can be assembled, compiled and sent to the units to fulfil structured routines made of many individual tasks giving complete control over every aspect of the reactor's configuration and working capabilities. For example, a process can be initiated or terminated, the flow rate modified and the reactor temperature changed. A series of these commands can be programmed in advance allowing a synthetic procedure to be operated and completed automatically. Since the computer operating the flow device can be attached to the internet, remote desktop software easily allows these operations to be completed by the user from anywhere in the world. The readouts from the various sensors on the machine are displayed in essentially real-time on the computer screen allowing the user to fully monitor the reaction, again from any remote location.

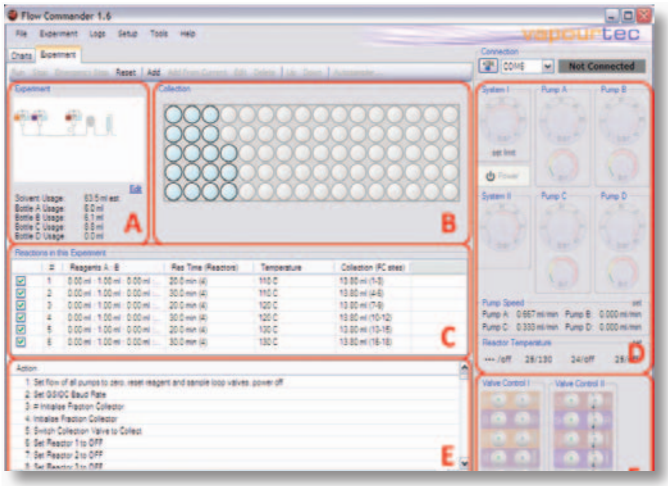


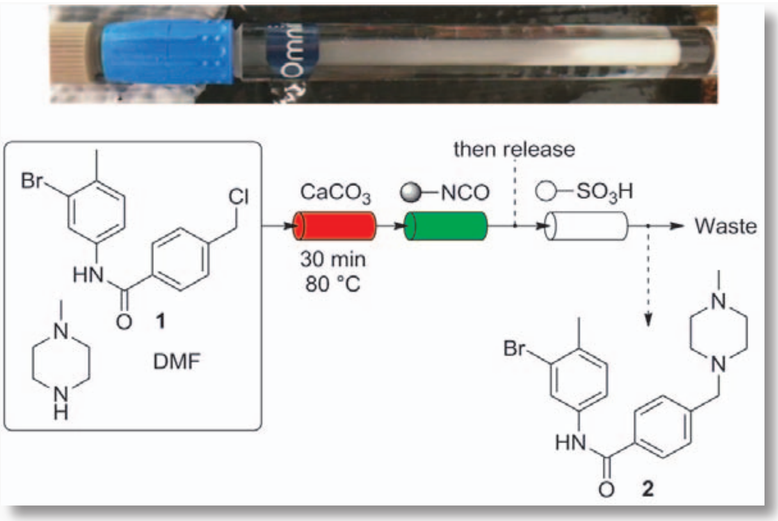
Figure 2. Vapourtec Flow Commander front display. A: Graphical depiction of reactor. B: Overview of collected fractions. C: Reaction runs. D: Detailed pressure, temperature, pump speed and air content display. E: Detailed command list.

Figure 3. Webcam mounted in vented cabinet and live images captured during use.

For example, our group has been developing a flow-based synthesis of 5-amino-4-cyano-1,2,3-triazoles *via in-situ* generation of aryl azides from anilines and reaction with malonitrile (7). In these transformations a flow-reactor was set up with multiple starting materials loaded into vials in an autosampler that were processed sequentially to produce the various library products. A fraction collector triggered by the UV absorption of the product was used to collect the different materials as they were produced. The system was controlled by Gilson Unipoint software (8) running a program to automate the synthesis hence allowing a series of analogues to be produced automatically and continuously over two days. A remote desktop application was used to remotely view the status of the reaction throughout the extended working period to ensure correct functioning of the equipment. Similarly, the Vapourtec Flow Commander software (6) allows the control of a Vapourtec R2/R4 flow chemistry system (9) and contains an interface designed to mimic the front display panel of the instrument. In addition further information such as individual pump pressures and power consumption are also available that are not accessible on the standalone unit itself. Use of this software *via* a remote desktop connection allows control from any site capable of delivering an internet connection and thereby providing the operator with detailed knowledge usually only available to the privileged user working in the laboratory. Reaction planning and system preparation can be performed externally from the workplace and therefore saving wet chemistry laboratory time. In addition, the software displays the amount of air present in the reactor pumps allowing the user to make an informed decision to attend to or abort the reaction under study.

VISUALISATION *VIA* WEBCAMS

Visual observation of experiments in real time is a crucial component of any synthesis procedure. Whether these are simply to record colour or temperature changes, or involve checking for precipitation or equipment failure, they all contribute to the development of suitable operating protocols. Therefore in order to allow "eyes-on" remote monitoring of equipment and reactions, we have mounted a number of cameras on our flow equipment contained in fume hoods in our laboratory.



Scheme 1. Flow synthesis of an imatinib intermediate with image showing 2 sequestered on silica-supported sulfonic acid.

The positioning of the cameras is such that they constantly film the events happening without impeding the work of the chemist. In addition, the elevated position of the cameras meant their operation was unaffected by any chemical contamination and the degree of solvent attack minimised. The removable mounting of the cameras also allows for repositioning of the camera if alternative views are required. The cameras are connected to a low voltage power source and to a local area network. A standard computer in the laboratory write-up area facilitates both viewing and recording of the video streams from all the cameras. In addition, the video streams can be made available to the departmental network thus allowing access from any internet connection anywhere in the world *via* a virtual private network (VPN) connection.

This type of visual monitoring has been particularly useful in our group's flow based synthesis of imatinib, the active ingredient in Gleevec, a treatment for chronic myeloid leukaemia developed by Novartis (10). In one particular step of this synthesis, as shown in Scheme 1, a solution of benzyl chloride **1** and *N*-methylpiperazine in DMF were reacted upon elution through a column of $CaCO_3$ maintained at 80°C. The output of this column was then directed into a column containing a polymer-supported isocyanate to scavenge any unreacted *N*-methylpiperazine then into a column of silica-supported sulfonic acid to sequester the product allowing any unreacted **1** to flow to waste.

The product (**2**) was subsequently released in a purified form by treatment with a solution of a base, which also acted as a solvent switch, directly into the next reaction step.

However, passage of the reacting solution through two columns of immobilised reagent caused significant dispersion of the product resulting in long and unpredictable reaction times. Fortunately, as the product was sequestered onto the silica-supported sulfonic acid, its appearance changed from partially translucent to opaque giving a good visual illustration of the extent to which the product had been trapped and hence the progress of the flow stream (Scheme 1).

A webcam was therefore set up to monitor the silica column enabling the reaction to be initiated at the end of the day and left to run overnight. During the evening, the webcam live stream could be viewed on a remote computer to determine the progress of the reaction. If the opacity had reached the end of the column or did not appear to be moving following successive views the reactor was stopped by issuing a simple power off command to the heater and pump. The success of these commands was checked by sending a further command to return the state of the devices. This process allowed lab chemistry to be performed when the lab would otherwise be inaccessible (outside classical working hours and circumventing lone worker restrictions) whilst reducing solvent wastage through constant overnight pumping. In repeated runs it would be possible to create a grey scale rastered image of the process thereby allowing simple statistical control software to assess the extent of such visual changes permitting the integration of additional automation into the process. Such techniques would be very valuable for control of processes by using optical density or colour change measurements to trigger subsequent events such as the addition of further reagents or initiation of a quenching protocol.

ACCESS TO CHEMISTRY FROM MOBILE TELEPHONES AND HAND-HELD DEVICES

The advent of portable devices with touch sensitive, high resolution displays and connectivity allowing access to the internet from any location with a cellular data signal has given rise to many possibilities for controlling laboratory automation and gathering information on the progress of reactions. Video streams from webcams positioned in our laboratory are already accessible from linked mobile phones with a video application installed. In addition to this, a remote desktop application allows control of the lab computer and hence our ability to control the flow device *via* a mobile phone.

Collaboration to perform reactor set-up, solve problems and discuss results is therefore possible regardless of the time and location of co-workers thus improving our productivity and output.

Using these tools, users can quickly ensure the safe operation of processes from any location, and intervene if necessary without a direct computer connection.

THE FUTURE

We believe the lab of the future must respond to the opportunities that will be provided by a combination of internet, webcams, mobile telephone technology and remote monitoring and control devices.

Innovative deployment of these systems leads to enhanced safety and improved data acquisition particularly as they relate to the developing area of multi-step chemistry using flow reactors. The additional enhancements that accrue from using these methods also provides opportunities for safe 24/7 working regimes while integrating with lifestyle patterns that benefit from remote monitoring techniques.

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