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A Versatile and Cost-Effective Approach to Automated Laboratory Organic Synthesis

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Abstract:

The application of a commercial laboratory automated synthesis system, the Anachem SK233 Workstation, is described for use in organic synthesis. A novel reactor design feature has been developed to enable the sampling of reactions under ambient to reflux temperatures while maintaining an effective inert atmosphere. Up to 10 reactions can be run simultaneously on the reactor block supplied. Examples are reported of multiple parallel reactions covering a range of chemistries encountered in synthesis encompassing heterogeneous and homogeneous reactions, air-sensitive and aggressive reagents, ambient to full reflux temperature, and full inert atmospheres with concomitant automated HPLC product analysis. The equipment and modifications described are of moderate cost, are robust in use, are of acceptable size for modern chemistry laboratories, and are readily acceptable to practising chemists.

Introduction

In recent years, emerging technologies have led to a reappraisal of working practices within the chemical industry. The pressures of these changes have been felt acutely, particularly within the pharmaceutical sector, where the spiralling costs of modern innovative drug development, together with a desire to shorten the time to market, has led to a number of novel scientific approaches for the discovery of new drug candidates.[1] For example, the impact of massively automated high-throughput screening and combinatorial chemistry approaches has been well documented.[2] While the outcome of these dramatic changes in drug discovery has yet to be fully established, the drive for speeding up the development of many more target structures is very real.[3] Automation of development chemistry[4] could contribute to a potential solution to this anticipated problem.

To successfully automate our work, a system to handle solution-phase chemistry under a variety of reaction conditions, with on-line analytical monitoring, was required. Traditional combinatorial chemistry equipment was predominantly aimed at solid-phase synthesis under a single set of reaction conditions, with no monitoring, and so was unable to meet our needs.

The literature reveals a number of attempts to automate synthetic organic solution-phase chemistry. Despite these ingenious[5−8] and, in many cases, technically inspiring efforts,[9−13] they have not been widely adopted, possibly due to their complexity and limited versatility. Furthermore, by late 1996, very little commercial equipment[14−16] was available that could be used or adapted for our purposes.

While looking for equipment, however, we did come across a possible candidate for evaluation in the Anachem SK233 Workstation.[17] This system consisted of a 10-position reactor block that could be sampled automatically via an *XYZ* robotic arm with subsequent dilution and HPLC analysis. Each reactor tube (ca. 5−25 mL reaction volume) could be stirred magnetically and heated (ambient to 150 °C). A separate reactor block could be used to cover the temperature range from −30 to +70 °C. Control of solvent reflux was accomplished by natural cooling of the exposed half of the reactor tube. An optional water-fed or forced air-fed "reflux" housing over the exposed section of the reactor tubes was also available. It was suggested that an inert atmosphere could be achieved by either capping purged tubes or continuously purging the additional reflux housing. The concept sounded fine, but could we do real chemistry in such equipment? A purchase of one of these units for trial purposes answered many of these questions very quickly.

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(17) The SK233 Workstation was derived from a collaboration between Anachem and Glaxo-Wellcome.

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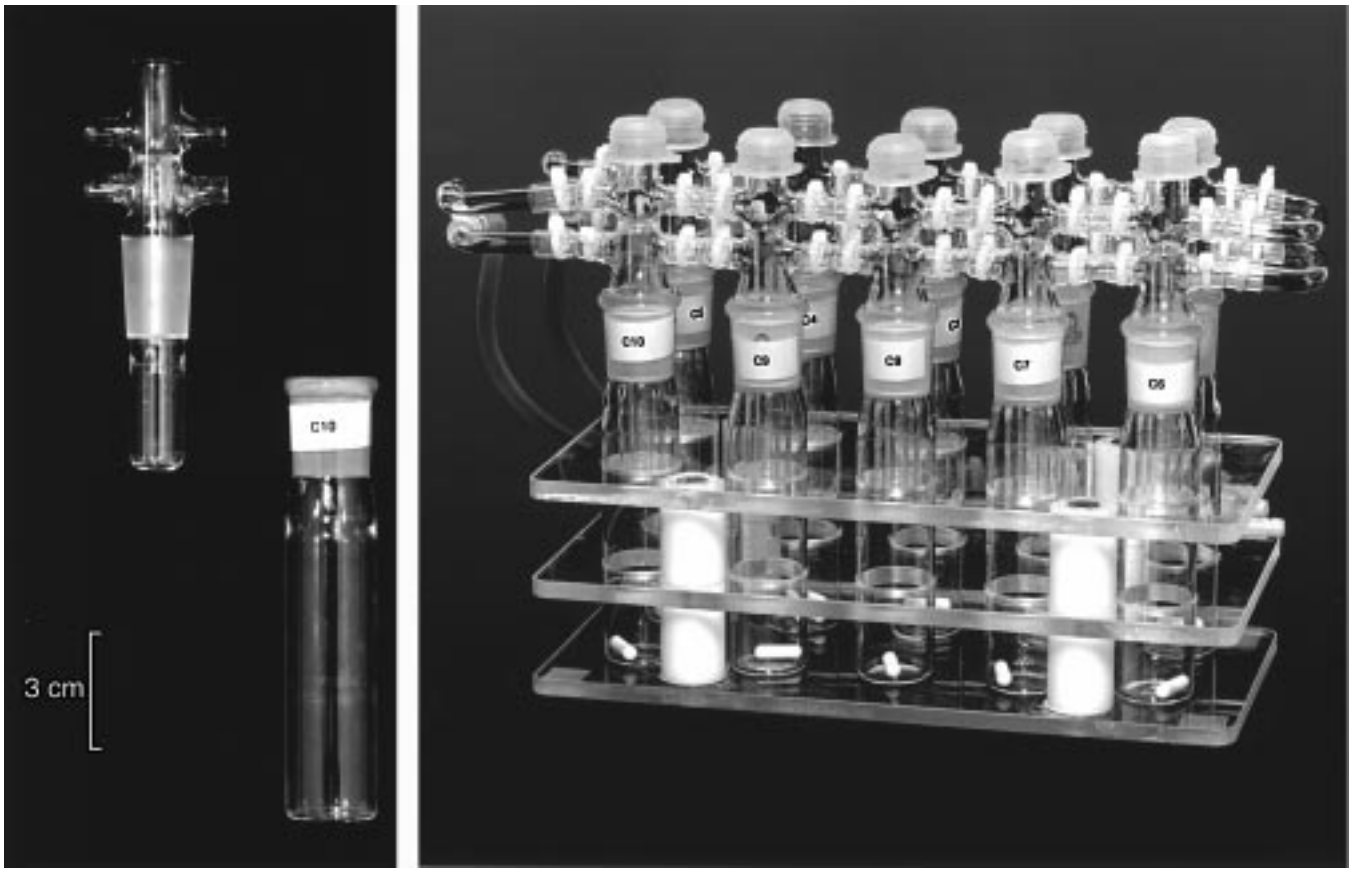


Figure 1. **Tube reactors and coldfinger condensers.**

For the most part, the equipment did as it claimed to do, but for a very restricted range of our chemistry and in a very restricted manner. As well as the usual minor mechanical problems encountered with new and innovative equipment, we identified several key areas that needed to be addressed in order for us to exploit the equipment to our satisfaction.

The most immediate and pressing issue was the need for the equipment to allow us to carry out reactions under inert atmosphere conditions using either subambient cooling or heating under reflux, as the inerting and refluxing capabilities of the system supplied proved to be limited. At the same time, we needed to be able to add reagents to the reactor vessels and take out samples for analysis at any time during the course of the reactions.

After numerous abortive trials, we designed[18] and manufactured what proved to be a very satisfactory solution to this specific problem. The tube reactors supplied were shortened slightly and provided with a female quickfit socket joint. Into this was inserted a coldfinger type condenser with a hollow centre. At the top of the condenser was constructed an inert gas purging arrangement. Above this, the vessel was capped with a septum.[19] Using this condenser/inerting/sampling arrangement (see Figure 1), we were able to fit the SK233 reactor block with the ability to allow us to boil under reflux, under an inert atmosphere, and simultaneously take an analytical sample via an *XYZ* robotic arm using an automated syringe. With a minor modification to the configuration of the condensers, we were able to use subambient cooling or a reaction sequence of both cooling and heating cycles.

The merits of the new condenser became immediately obvious:

(i) The SK233 needed no modification for its use.

(ii) The condensers proved to be easy to fit and remove and were very easy to clean.

(iii) The condensers being of all glass construction, we could easily see what was going on in the reactions.

(iv) The inert atmosphere arrangement proved more than adequate for our purposes.

(v) The operation of the reactor vessels was easy to demonstrate and easy for our chemists to follow.

(vi) The equipment proved to be reliable and robust in operation.

(vii) The new modified reactors could be used for most of our chemical applications, whether with aggressive reagents or with air-/moisture-sensitive compounds and catalysts.

(viii) The condensing capacity of the device (using mains water for cooling) proved outstanding and well up to our requirements (see Table 1).

The individual condenser units were connected together in series for use with the isolated reactor block or in conjunction with the SK233. This multiple condenser arrangement is now known as the REACTarray.[20] This arrangement has proved to be so acceptable to our chemists

(18) Furlong, B. H.; Smith, C. A. (SmithKline Beecham Plc, UK). Patent WO 9908767, 1999.

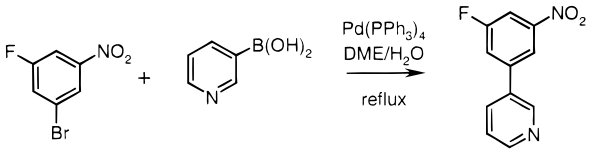
(19) An alternative arrangement is described in ref 13.

(20) The REACTarray is available under licence from Anachem Ltd., 20 Charles St., Luton, Bedfordshire, LU2 0EB, UK.

Table 1. **REACTarray condensing efficiency, demonstrated by solvent weight loss after 2 h at or above reflux temperature**

solvent	block temp, °C	Ar flow, mL min^{-1}	% loss by wt
CH_2Cl_2	45	10	~1.3
MeOH	68	20	~0.8
MeOH	120	20	~3.1
EtOH	120	20	~1.4
2-propanol	120	20	~1.3
toluene	120	20	~0.7

Scheme 1



that it is now used routinely for all chemistries carried out on the reactor block or the SK233.

Results and Discussion

Suzuki Coupling Reaction. To confirm the improved performance of the REACTarray over the reaction tubes supplied, the Suzuki reaction, shown in Scheme 1, was investigated manually on a reactor block. This reaction requires both reflux conditions and a good inert atmosphere.

A fractional factorial experiment was designed (using Design Expert) to look at the effects of concentration, water level, catalyst loading, and boronic acid stoichiometry. Two centrepoints were included in the design to give 10 reactions in all and to ensure that two identical reactions were carried out. The experiment was conducted both in the reaction tubes supplied with the reactor block, fitted with the air-fed "reflux" unit, and in our glassware. The results are shown in Table 2.

It can be seen that when the supplied equipment is used, the results vary widely. In particular, the two centrepoints (entries 6 and 8), which should be identical, give conversions of 51% and 98.5%. In contrast, using our device, the results are spread over a much narrower range, as expected for this reaction, and the centrepoints give results which are in agreement (complete conversion). The results from the REACTarray experiment were analysed using Design Expert to show that, at high concentration (desirable for scale-up), a robust and reliable process can be achieved with a high catalyst loading.

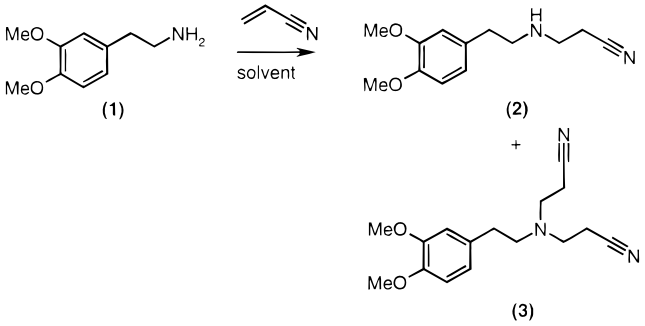
This confirmed the suitability of our device for performing reactions under reflux in an inert atmosphere.

The glassware was then fitted to the SK233, and a wide range of reactions were carried out with automated sampling and on-line HPLC monitoring. This allowed unattended operation of reactions with monitoring over extended time periods, including overnight and over weekends. Reaction scouting, process screening, and process optimisation investigations have all been addressed. Examples below cover homogeneous and heterogeneous reactions, at ambient and elevated temperatures, using air- and moisture-sensitive reagents, under inert atmospheres.

Table 2. **Design and results of fractional factorial Suzuki experiment**

run	factor A, total solvent	factor B, water level	factor C, boronic acid	factor D, catalyst loading	response, % conversion: supplied equipment	response, % conversion: REACT-array
1	1	−1	−1	1	23	91
2	1	−1	1	−1	4	76
3	−1	−1	−1	−1	17.5	84
4	−1	−1	1	1	98	100
5	−1	1	−1	1	98	95
6	0	0	0	0	51	100
7	1	1	−1	−1	18	100
8	0	0	0	0	98.5	100
9	1	1	1	1	99	100
10	−1	1	1	−1	12.5	94

Scheme 2



Solvent Screening of a Michael Addition Reaction. The Michael addition of homoveratrylamine (**1**) to acrylonitrile[21] (Scheme 2) is the first stage in the synthesis of one of our development compounds. It is a straightforward homogeneous reaction, requiring a good inert atmosphere to prevent formation of the CO_2 adduct of the amine, which occurs readily on exposure to air. It can be run neat at ambient temperature; however, complete reaction is slow, taking at least 2 days. An impurity (**3**) due to double addition of acrylonitrile is formed in the reaction at variable levels (up to 3%) and increases with time.

Running the reaction in a solvent was known to result in reduced reaction times. The SK233 was used to screen a range of solvents for the reaction simultaneously in order to select the best one, in terms of reaction time, amount of impurity formed, and suitability for combining with a second synthetic step. Each reaction was set up manually, with automatic sampling, sample preparation, and HPLC analysis of each vessel at preset intervals. This allowed unattended monitoring of the reactions with collection of data outside normal working hours.

Initially, 10 solvents (MeOH, EtOH, IPA, H_2O, DMF, THF, 10% aqueous MeOH, 10% aqueous EtOH, 10% aqueous IPA, and 10% aqueous THF) were screened at ambient temperature, with sampling of each reaction 10 times over a 24-h period (0.5, 2, 3.5, 5, 6.5, 8, 12, 16, 20, and 24

(21) Yamazaki, T. *Yakugaku Zasshi* **1959**, *79*, 1003−1008; *Chem. Abstr.* **1960**, *54*, 5678.

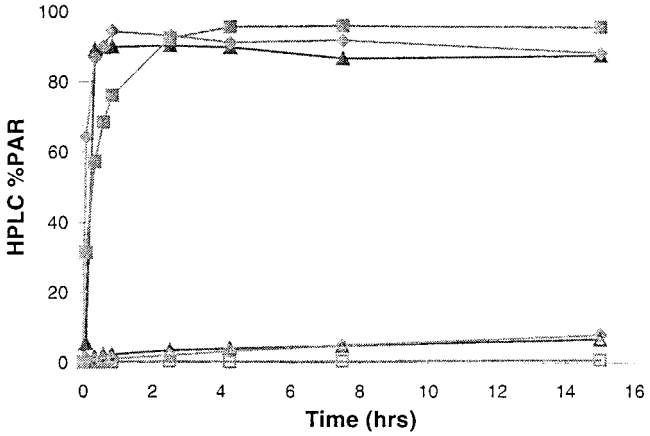


Figure 2. **Michael addition reaction at 60 °C, 1.05 equiv of acrylonitrile. Reaction profiles for product (2) and impurity (3) formation. Products: ▲, water; ■, 2-propanol; ◆, MeOH. Impurities: △, water; □, 2-propanol; ◇, MeOH.**

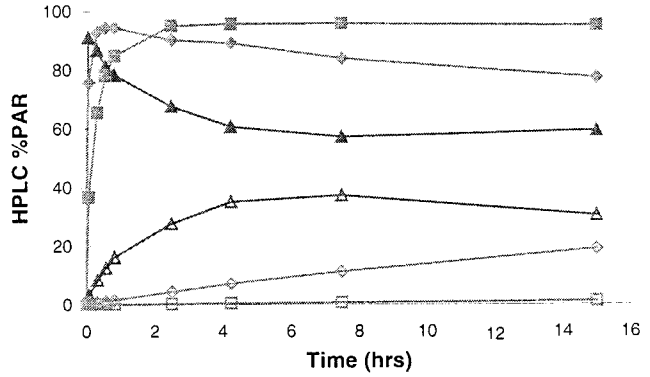


Figure 3. **Michael addition reaction at 60 °C, 1.5 equiv of acrylonitrile. Reaction profiles for product (2) and impurity (3) formation. Products: ▲, water; ■, 2-propanol; ◆, MeOH. Impurities: △, water; □, 2-propanol; ◇, MeOH.**

h). From this experiment, five solvents (MeOH, EtOH, IPA, H_2O, and 10% aqueous THF) were selected for further evaluation. The second set of reactions was run at 60 °C, with stoichiometries of 1.05 and 1.5 equiv of acrylonitrile. As the reactions were expected to be much faster at elevated temperature, sampling was more frequent in the early stages, with each reaction being sampled after 5, 20, 35, and 50 min, and then after 2.5, 4.25, 7.5, and 15 h.

The large amount of data collected in these experiments (180 chromatograms in total) was analysed using Excel, to allow easier interpretation of the results. Reaction profiles for appearance of product (**2**) and impurity (**3**) were generated, and selected examples are shown in Figures 2 and 3. It can be seen that 2-propanol is an excellent solvent for the reaction, with complete conversion achieved within 2.5 h at 60 °C and little formation of impurity (**3**), even in the presence of excess acrylonitrile.

To check reproducibility of the system, the second set of experiments was repeated. In this instance, the SK233 was additionally used to automatically dispense solvents and acrylonitrile. The resulting data and graphs were almost identical to those acquired previously, as illustrated in Figures 3 and 4 and Table 3.

Rapid Screening of Reagents and Solvents. A key step in the preparation of a novel oral carbapenem is the Lewis

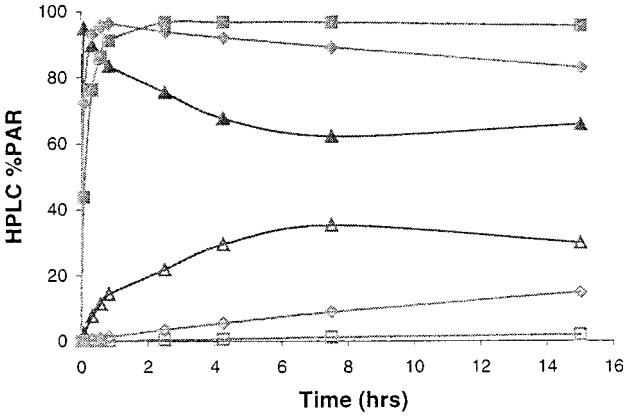
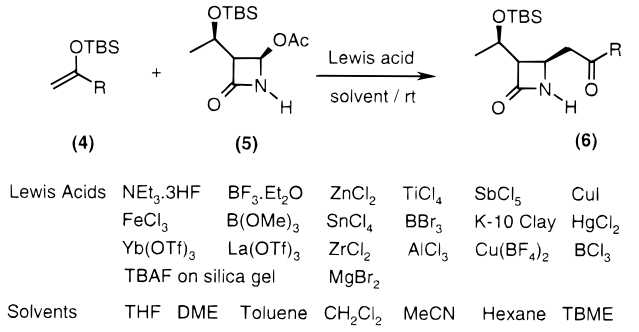


Figure 4. **Michael addition reaction, conditions as for Figure 3, automated addition of solvents and acrylonitrile. Products: ▲, water; ■, 2-propanol; ◆, MeOH. Impurities: △, water; □, 2-propanol; ◇, MeOH.**

Table 3. **Michael addition reaction: comparison of Figure 3 and Figure 4 final time point values, HPLC % PAR**

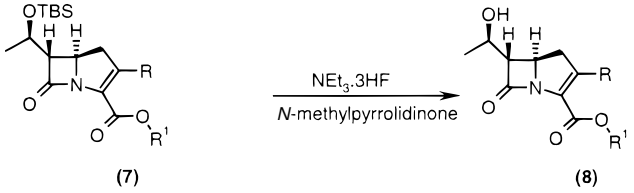
	Figure 3	Figure 4
▲, water product	59	66
■, 2-propanol product	95	96
◆, MeOH product	77	83
△, water impurity	30	30
□, 2-propanol impurity	1	2
◇, MeOH impurity	19	15

Scheme 3



acid-catalyzed addition of silylenol ether (**4**) to acetoxyazetidinone (**5**) (Scheme 3). Initial investigations in traditional glassware indicated that using boron trifluoride etherate in dimethoxyethane gave a reasonable yield (ca. 50%) of desired product ketone (**6**). We wished to investigate the effect of different Lewis acids and solvents on this chemistry to see whether we could obtain an improved yield and a more robust reaction (the product ketone (**6**) is unstable to boron trifluoride etherate under prolonged reaction times). Using the SK233, we were able to screen, in a short period of time, all the combinations of the 20 Lewis acids and 7 solvents (Scheme 3). As expected, boron trifluoride etherate gave good results, although a higher yield was obtained using tetrahydrofuran as the solvent. A number of other effective catalysts were identified, notably, zinc chloride in all solvents (except toluene), magnesium bromide in dichloromethane, and copper(I) iodide in dichloromethane. These results were subsequently verified in traditional glassware.

Scheme 4



Even the notoriously air- and moisture-sensitive reagents such as titanium tetrachloride, boron trichloride, and boron tribromide were handled with ease by the equipment. No white HCl vapour could be seen in the reactors during the reagent addition step, indicating an effective moisture-free environment. The large amount of data generated (some 420 chromatograms in total) was again handled using Excel.

Fluoride Desilylation of a Protected Alcohol. As part of the same carbapenem synthesis, we wished to optimise the fluoride-mediated desilylation of the protected alcohol (**7**) (Scheme 4). Preliminary labwork indicated that a solution yield of 69% could be obtained using 1.1 molar equivalents of fluoride reagent in 10 volumes of *N*-methylpyrrolidinone solvent at 50 °C under nitrogen. However, this reaction was not particularly robust; if it was left too long, the yield of **8** decreased dramatically. Furthermore, increasing the temperature increased the reaction rate but resulted in a lower yield.

We decided to use a design of experiments approach to optimise the reaction. Three factors were considered to be important: temperature, concentration, and stoichiometry of reagent. Using Design Expert software, a three-factor, two-level full factorial design was drawn up, resulting in eight experiments. Four identical centrepoint experiments were included, making 12 reactions in total.

Since temperature was a variable and the reactor block can only be run at one temperature at a time, we performed the 12 experiments in three blocks of four experiments. Each reaction was monitored hourly by HPLC, and solution yields were calculated for each time point by reference to an internal standard, 4-nitroaniline. Design Expert software indicated that a yield of 83% could be expected at 30 °C with 1.25 equiv of fluoride reagent in 4−7 volumes of solvent.

This result was verified by experiment in a traditional round-bottom flask. The optimised conditions have subsequently been used at plant scale with good success.

The 12 experiments were performed in a 3-day period, with HPLC data being transferred to Excel for manipulation. Good reproducibility was seen, with the four centrepoints indicating good sampling by the robot.

Excellent reaction profile data were also obtained. It can be seen from Figure 5 why higher temperatures or prolonged stirring at 50 °C were detrimental to the process. The reaction where all the levels were high (depicted HHH in the figure), i.e., high temperature, high amount of reagent, and high concentration, clearly showed a rapid reaction, reaching a maximum concentration of product after 4 h and then a rapid decomposition of the product. In the experiment where the temperature and amount of reagent were low (HLL), a much slower reaction resulted, but a higher yield was obtained, presumably due to little or no decomposition of the product.

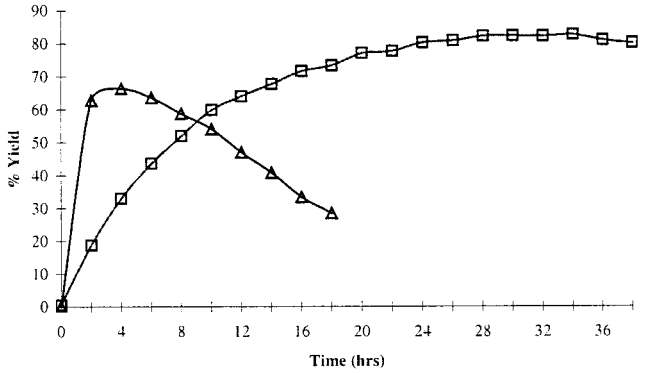
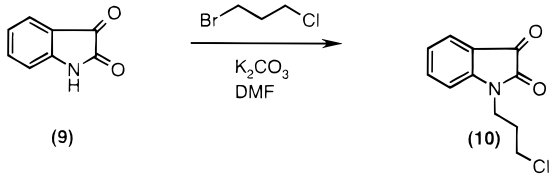
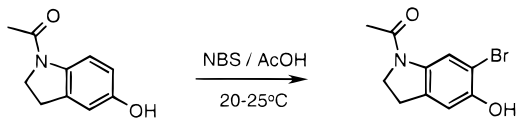


Figure 5. **Desilylation of TBS alcohol (7), reaction profiles for formation of product (8). △, HHH; □, HLL.**

Scheme 5



Scheme 6



Homogeneous Starting Material and Product: Heterogeneous Base. To investigate the viability of handling heterogeneous reaction mixtures with the SK233, the alkylation of isatin (**9**) with 1-bromo-3-chloropropane in DMF with solid potassium carbonate[22] was carried out (Scheme 5). Three identical reactions were set up by dispensing a solution of isatin in DMF to stirred reaction vessels which had been precharged with the base. A visual check showed that efficient mixing was obtained. 1-Bromo-3-chloropropane was added at varying dispense rates, and each reaction was sampled five times over a 10-h period, with duplicate samples being taken at each time point. Analysis of the HPLC results found that reasonable product peak reproducibility was obtained quantitatively (±6%) between duplicate samples and from vessel to vessel. Excellent reproducibility of impurity profile data was observed (main peak area ratio ±0.04%).

Heterogeneous Starting Material and Heterogeneous Product. Following the success of the above example, the ability of the SK233 to handle more difficult heterogeneous reaction mixtures was explored. The chemistry shown in Scheme 6 presented a particular challenge in that the starting material slowly dissolved and the product crystallised out as the reaction proceeded. As a consequence, the reaction was both heterogeneous and viscous, making it difficult to sample. To investigate the effectiveness of the machine to sample efficiently, we performed two sets (0.5 and 1.0 molar equivalents of NBS) of three identical reactions. Each reaction was sampled at three time points (5 min, 45 min,

(22) Radul, O. M.; Zhungietu, G. I.; Rekhter, M. A.; Bukhanyuk, S. M. *Chem. Heterocycl. Compd.* **1983**, *19* (3), 286−288.

and 1.5 h), with duplicate samples taken at the final time point.

HPLC analysis of the samples showed that no meaningful quantitative data could be obtained, because, as expected, the equipment could not accurately aspirate precise amounts of the viscous heterogeneous reaction mixture.[23] However, qualitatively very good reaction profile data were obtained, with good agreement between the replicate reactions and duplicate samples (main peak area ratio ±1%). To verify these results, we dissolved the final reaction mixture in solvent to give an homogeneous mixture. HPLC analysis of this gave a profile comparable to that of the on-line sample. This illustrates clearly that the equipment can be utilised to sample an heterogeneous reaction mixture representatively, though equally clearly there are practical limits to what can be handled.

Conclusion

We have shown that parallel synthesis and automation can play a valuable role in a process chemistry environment. It can assist in increasing throughput and accumulating more high-quality data, while releasing chemists to do other tasks. However, these benefits can only be realised if the equipment can carry out a wide range of chemistry and is acceptable to chemists. By designing our own reactors (by chemists for chemists), we have achieved this.

The SK233 and REACTarray combination has proven to be a versatile tool, capable of performing reactions at reflux, in an inert atmosphere, with aggressive and air-/moisture-sensitive reagents. Reaction monitoring is integral to the system. It is useful for route scouting, process screening, and process optimisation. The system is reliable, reproducible, and convenient to use. Along with these advantages, the equipment described is compact, fitting standard laboratory facilities, and, more importantly, is relatively affordable, being of comparable cost to a modern HPLC system.

Other commercial systems targeted at process development have now become available,[24,25] and others are no doubt "in the pipeline", which may cover some aspects of the equipment described here. We intend to evaluate these alternatives, whilst exploiting the capabilities of the SK233 and REACTarray to the fullest extent.

Experimental Section

The reaction block used was a 10-position RS1000 reactostation from Stem Corp.,[26] capable of heating from ambient temperature to 150 °C with variable-speed magnetic stirring. HPLCs were run on either Gilson or Merck-Hitachi instruments, and the data were collected using Gilson Unipoint software.

Typical Procedure for Suzuki Coupling Reaction. Aryl bromide (250 mg) was charged to the reaction vessels. 1,2-Dimethoxyethane (1.55−7 mL) and water (0.9−2.5 mL), as designated by the experimental design, were added to the vessels, and the reactions were stirred under argon for 5 min. Boronic acid (lithium salt; 1.0−1.3 equiv) was added to the reaction mixture, followed after a further 2 min by tetrakis-(triphenylphosphine)-palladium(0) (0.5−3.0 mol %). The reactions were heated to reflux and stirred under argon at this temperature for 15 h. Each reaction was analysed by HPLC (Zorbax Eclipse XDB-C8 3.5-μm, 4.6- × 75-mm column; 60% MeCN/H_2O; 1.5 mL/min; 265 nm), and the conversion of aryl bromide to the coupled product was calculated.

Typical Procedure for Michael Addition Reaction. Homoveratrylamine (**1**) (1 g) was charged to each reaction vessel, and the vessels were stirred at ambient temperature under argon. Solvent (10 mL) was added to each vessel, and the Stem block was heated to 60 °C. The reactions were then treated with acrylonitrile (1.05 or 1.5 equiv) and were monitored automatically by HPLC over 15 h (Merck RPSelB 4.6- × 125-mm column; 30% MeCN/0.05 M aqueousTFA; 1.5 mL/min; 275 nm).

Typical Procedure for Lewis Acid Screen. A stock solution of the silylenol ether (**4**) (20.9 mmol) and the acetoxy azetidinone (**5**) (17.4 mmol) in 100 mL of the reaction solvent was prepared. An aliquot (7 mL) of this solution was charged by the SK233 to each reaction vessel. An aliquot (1.39 mL) of the selected Lewis acid as a 1.0 M solution in dichloromethane (except for $ZnCl_2$ and $FeCl_3$, which were 1.0 M solutions in diethyl ether) was charged to the specific reaction vessel over 1.4 min. The reactions were stirred at room temperature and automatically sampled (30 μL) at 5 min, 30 min, and 6 h. The samples were diluted with acetonitrile (1.5 mL), mixed, and analysed by LC (Perkin-Elmer C18 HS 3-μm, 3.3-mm × 4.6-cm column; gradient MeCN/water 30:70 to 100:0 over 3 min, 100% MeCN for 1 min, back to 30:70 over 0.03 min, and 30% MeCN for 2 min; 2 mL/min; 246 nm).

Typical Procedure for Desilylation. The solid-protected alcohol **7** (1.0 g) was manually preweighed into each reaction vessel. The appropriate amounts of *N*-methylpyrrolidinone solvent, as designated by the experimental design, containing a precise amount of 4-nitroaniline as internal standard, was dispensed by the SK233, followed by the triethylamine trihydrofluoride complex. The reactions were stirred at the appropriate temperature and sampled hourly (30 μL). The samples were diluted with acetonitrile (1.5 mL), mixed, and analysed by LC (Perkin-Elmer C18 HS 3-μm, 3.3-mm × 4.6-cm column; gradient MeCN/water 30:70 to 100:0 over 3 min, 100% MeCN for 1 min, back to 30:70 over 0.03 min, and 30% MeCN for 2 min; 2 mL/min; 246 nm).

Typical Procedure for Isatin Alkylation. Potassium carbonate (1.2 g) was charged to each reaction vessel, and the stirring was started. A 10% (w/v) solution of isatin (**9**) in DMF was prepared, and 4.9 mL of the solution was dispensed to each reaction. 1-Bromo-3-chloropropane (3.35 mL) was then added at varying dispense rates (2.5−10 mL/min). The reactions were stirred at ambient temperature and monitored overnight by HPLC (Merck RPSelB 4.6- × 125-

(23) These experiments were carried out using the 0.4-mm-i.d. needle supplied. Improved sampling has been demonstrated using a recently fitted 0.8-mm-i.d. needle.
(24) Studt, T. *R&D Mag.* **1997**, *39* (12), 38−42.
(25) Harness, J.; Tedesco, J. *R&D Mag. Suppl.* **1998** (April), 20−25.
(26) Stem Corp., Woodrolfe Road, Tollesbury, CM9 8SJ, UK.

mm column; 35% MeCN/0.05 M NH_4OAc pH 4.5; 1 mL/min; 245 nm).

Typical Procedure for Indoline Bromination. *N*-Acetyl-5-hydroxyindoline (350 mg) was charged to the reaction vessels. Acetic acid (5.8 mL) was dispensed at ambient temperature to the stirred vessels, and then *N*-bromosuccinimide (0.5 or 1 equiv) was added in three portions to each reaction. The reactions were monitored automatically by HPLC over 1.5 h, with repeat samples being taken at the final time point. DMSO was added to the reactions to give complete solution, and a further HPLC analysis was carried out (HPLC conditions: Merck RPSelB 4.6- × 125-mm column; 40% MeCN/0.1% aqueous TFA; 1 mL/min; 256 nm).

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