Sutherland Research Group
Chemical Engineering & Applied Chemistry
Aston University
Aston Triangle
Birmingham B4 7ET
Telephone: +44 (0) 121 3593611
Fax: +44 (0) 121 3594094
E-mail: a.j.sutherland@aston.ac.uk
www.ceac.aston.ac.uk/andy_sutherland/ajsweb.htm

1st November 2002

Evaluation of Carousel 6 Place Reaction Station*

The performance of the Carousel 6 Place Reaction Station has been evaluated under normal laboratory conditions. The Carousel has also been used in our research activities and examples from this are given. The study included:

1. Evaluation of reflux performance
2. Heating performance (rate of heating)
3. Stirring bars evaluation
4. Comments on glassware
5. Other comments
6. Examples of synthesis using the Carousel 6 Place Reaction Station

1. Evaluation of reflux performance

The performance of the reflux head was evaluated to investigate the rate of loss of solvents.

Three situations were investigated:

(1) Using the normal laboratory water supply (~20^{o}C) to cool the reflux head.
(2) As for (1) but with the Suba Seals removed.
(3) As for (1) but with cooling from a recirculating chiller unit set at 0ºC.

In each case the solvent under investigation (150ml) was placed in each of 6 standard 250ml flasks (RR99050) with an elliptical rare earth stirring bar (RR99064) under slight nitrogen pressure and brought to reflux. Solvent loss was monitored over a 24 hour period taking an average value from the 6 flasks. The results are presented in **Table 1**.

Overall the system performed extremely well with very little solvent loss even using the normal laboratory water supply and with the Suba Seals removed. Solvent loss is not surprisingly less for higher boiling solvents and with the Suba Seals in place. Using a recirculating chiller with the coolant temperature at 0^{o}C reduced solvent losses further (see **Table 1**).

---

* Testing procedures were undertaken by S Cummins, M M^{c}Cairn and S Ryley who also compiled this report.

Table 1

Solvent	Suba Seals Fitted?	Base Temperature (°C)	Coolant Temperature (°C)	% Solvent Loss after hrs shown 3hrs	6hrs	9hrs	24hrs
Diethyl Ether	Yes	40	20	0	0	X	2.6
Diethyl Ether	No	40	20	2.6	2.6	X	8
Diethyl Ether	No	40	0	X	X	X	4.6
Dichloromethane	Yes	40	20	0	0	0	0
Dichloromethane	No	40	20	0	0.6	X	3.3
Dichloromethane	No	40	0	X	X	X	1.3
Dichloromethane	No	46	20	0	0	X	5.3
Dichloromethane	No	46	0	X	X	X	1.3
Acetone	Yes	66	20	0.6	1.3	1.3	2.6
Acetone	Yes	66	0	X	X	X	1.3
THF	Yes	70	20	0	0	0	0
Ethanol	Yes	87	20	0	1.3	1.3	3.3
Toluene	Yes	120	20	0	0	0	0

X – no reading taken

2. Heating performance (rate of heating)

The Carousel 6 Place Reaction Station reached its maximum recommended base temperature of 180°C in 30 minutes from ambient with 6 flasks each containing 150ml of ethylene glycol.

3. Stirring Bar Evaluation

Two stirring bars were evaluated:
RR99064 elliptical rare earth 25mm (as currently supplied with Carousel)
001.2638.RE elliptical rare earth 38mm

The stirring bars performance was evaluated in acetone (150ml) to which increasing amounts of potassium carbonate (K_2CO_3) were added. Stirring was assessed after each addition of potassium carbonate with the stirrer setting noted at the point just before coupling was lost and the maximum vortex recorded. The results are shown in **Table 2**.

Table 2

Stirring Bar	Weight of K_2CO_3 added (g)	Setting where Coupling Lost	Maximum Vortex (mm)
RR99064	0	10	Full depth
001.2638.RE	0	9	Full depth
RR99064	2	10	Full depth
001.2638.RE	2	7.5	Full depth
RR99064	4	10	Full depth
001.2638.RE	4	7	~5
RR99064	6	10	Full depth
001.2638.RE	6	7	~2
RR99064	8	10	Full depth
001.2638.RE	8	6	No vortex
RR99064	10	10	Full depth
001.2638.RE	10	6	No vortex
RR99064	12	10	Full depth
001.2638.RE	12	No stirring	0
RR99064	14	10	Near full depth
001.2638.RE	14	No stirring	0

Stirring Bar	Weight of K_2CO_3 added (g)	Setting where Coupling Lost	Maximum Vortex (mm)
RR99064	16	10	~15
001.2638.RE	16	No stirring	0
RR99064	18	10	~10
001.2638.RE	18	No stirring	0
RR99064	20	10	~5
001.2638.RE	20	No stirring	0
RR99064	22	0	0
001.2638.RE	22	No stirring	0

N.B. Full depth indicates a vortex from liquid surface to the stirring bar.

The RR99064 elliptical rare earth stirring bar performed well, still stirring when 20g of potassium carbonate had been added. In contrast the much larger and heavier bar 001.2638RE produced a poor vortex (~2mm) when only 6g of potassium carbonate had been added and had stopped stirring completely with 12g added. This was disappointing as it was hoped that the larger bar would have given improved results with solid suspensions.

4. Comments on Glassware

The Carousel 6 Place glassware is quick and easy to assemble and the use of Rodaviss fittings also ensures easy disassembly and freedom from sticking joints.

A comprehensive range of glassware is available including:

250ml round bottomed reaction flasks with removable reflux tubes (RR99040)

These can be transferred directly to a standard rotary evaporator, using the adaptors supplied. Solvent evaporation and ease of use was comparable to standard 250ml round bottomed flasks.

250ml long neck round bottomed reaction flasks (RR99050)

One-piece flask and reflux tube. Just slip into the Carousel 6 Place Reaction Station, screw on the cap and the reflux system is ready to go.

250ml two neck round bottomed reaction flasks (RR99047) with dropping funnels (RR99048) and solid addition funnels (RR99049).

Dispensing liquid and viscous liquid reagents into the two neck flasks is straightforward to accomplish as the Suba Seals of the dropping funnels are easily penetrated and re-seal well.

All glassware was easily interchangeable and the use of Rodaviss fittings as standard gave a high degree of security and an absence of seized joints.

The system proved itself under vacuum. For example polyethylene glycol (PEG) was heated to 115 ºC under high vacuum and a good vacuum was maintained.

For further details of chemistry performed see Section 6.

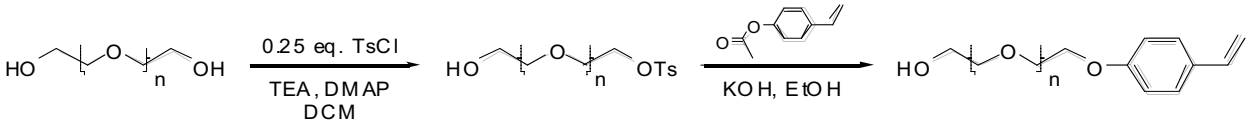
5. Other Comments

This is a well-designed and sturdy piece of laboratory equipment. The small footprint is ideal for operation in fume cupboards, areas where space is at an absolute premium. The Carousel 6 Place Reaction Station occupies a fraction of the amount of space in the fume cupboard that 6 conventional systems (mantles, oil baths etc.) would.

6. Examples of Synthesis Building Block / Intermediate Synthesis etc

Synthesis of α–styryl-poly(oxyethylene glycol)$_{300}$[i]

The following experimental protocol demonstrates some aspects of working with 250ml two-necked round bottomed flasks on the Carousel 6 Place Reaction Station.



Step 1. Synthesis of poly(oxyethylene glycol)$_{300}$ mono-p-toluene sulfonate

Reactions were performed using two-neck round-bottomed flasks (RR99047) with dropping funnels, septa ports, reflux tubes and PTFE valve caps. The Carousel was connected to a manifold supplying nitrogen or vacuum. Poly(oxyethlene glycol) was dried initially *in situ* in the Carousel flask by evacuating at 120ºC for 40 minutes. A solution of tosyl chloride (11.71g, 0.06 moles, 1 equiv.) in CH_2Cl_2 (30ml) was added dropwise over 30 minutes to a solution of poly(oxyethylene glycol)$_{300}$ (72.3g, 4 equiv.), triethylamine (33.9ml, 4 equiv.) and 4-(dimethylamino)pyridine (0.371g, 0.05 equiv.) in CH_2Cl_2 (130ml). (CH_2Cl_2 distilled from calcium hydride). The resultant mixture was left to stir overnight at room temperature. The reaction mixture was then washed with distilled water (2 x 100ml), saturated sodium bicarbonate solution (2 x 100ml) and saturated citric acid solution (2 x 100ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give poly(oxyethylene glycol)$_{300}$ mono-*p*-toluene sulfonate as a pale yellow liquid (21.022g, 77%). This material was reacted on without further purification.

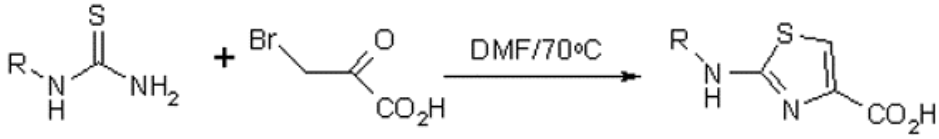
Step2. Synthesis of α–styryl-poly(oxyethylene glycol)$_{300}$

Potassium hydroxide (1.66g, 0.026 moles, 1 equiv.) was weighed into a two-neck flask (RR99047). A magnetic stirring bar was added, a condenser tube fitted and the assembly placed in the Carousel station. The top of the condenser was connected to the N_2 line and then the screw fastening between flask and condenser tightened. The flask was then evacuated and filled with N_2 three times. EtOH (50ml) was injected through the septum and the mixture stirred until all the KOH dissolved. 4-Acetoxystyrene (4.25ml, 0.026 moles, 1 equiv.) was injected through the septum and the mixture was stirred at room temperature for 1 hour. A further solution of potassium hydroxide (1.66g, 0.026 moles, 1 equiv.) in EtOH (40ml) was then injected through the septum and the flask brought to reflux (Fuzzy logic thermometer set to 100ºC) for 1 hour. A solution of poly(oxyethylene glycol)$_{300}$ mono-*p*-toluene sulfonate (from step 1.) in EtOH (30ml) was injected through the septum into the reaction mixture and the mixture was left to reflux overnight. The reaction mixture was then transferred to a single neck flask (RR99041) with Buchi attachment and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (5% v/v EtOH in CH_2Cl_2) furnished α–styryl-poly(oxyethylene glycol)$_{300}$ as a yellow oil (6.811g, 54%).

Synthesis of 2-amino-4-carboxythiazole building blocks

The following reaction was undertaken as a real world example of the simultaneous synthesis of six pharmaceutically relevant building blocks. The procedure tested many of the operating procedures of the Carousel 6 Place as described above.

The protocol for this reaction was based on a robust and well-designed synthetic route of library compounds developed by Watson *et al* [ii] at GlaxoSmithKline, Stevenage, UK. The general reaction scheme is given below and the individual reaction details are summarised in Table 3.



Reactions were performed using the two-neck round bottomed flasks with dropping funnels, septa ports, reflux tubes and PTFE caps - all dried and maintained under a slight positive nitrogen pressure using standard laboratory procedures. Each of the 6 thiourea solids (5 mmoles, 1 equiv.) was transferred, *via* solid addition funnel, to the pre-assembled round bottomed flasks in the Carousel and the dropping funnel fitted. Dry DMF (50ml) was then transferred to each flask via the dropping funnel septa. A solution of bromopyruvic acid (0.84g in 5ml dry DMF, 5 mmoles, 1 equiv.) was transferred to each dropping funnel and the solutions added drop-wise to the round bottomed flasks over a 10 minute period with stirring at room temperature. The Carousel temperature was then increased to 70ºC for 5 hours. The reaction mixtures were then allowed to cool and each reaction was quenched by the drop-wise addition of diethylamine (0.025ml in 2.5ml EtOH) over a 10 minute period. Each Carousel round bottomed flask was then removed and placed onto a rotary evaporator using the adaptor supplied. The reaction solvent was then removed on the rotary evaporator. Analysis of each compound was performed at this stage. ^{1}H and ^{13}C NMR spectra and APCI mass spectra were obtained on a Brüker AC300 and a Finnigan LCQ ion-trap mass spectrometer respectively.

The analytical data for these compounds confirmed that, in each case, the reaction had proceeded extremely well to give giving 6 high purity products. MS showed only product related peaks and ^{1}H and ^{13}C NMR only very small traces of extraneous material. NMR also indicated the presence of traces of DMF and diethylamine hydrobromide, however the purity of each of the 6 products was greater than 95% (excluding DMF and diethylamine hydrobromide).

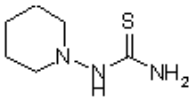
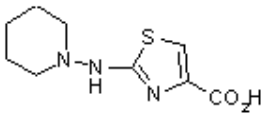
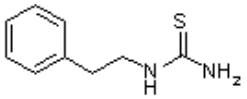
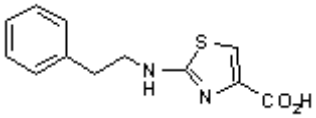
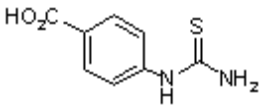
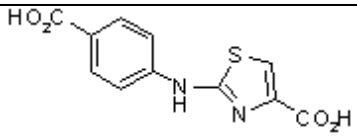
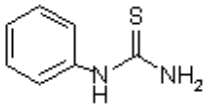
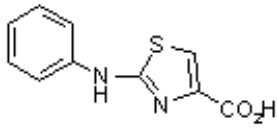
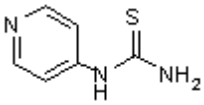
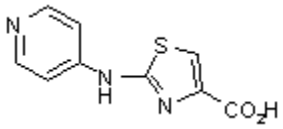
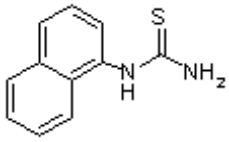
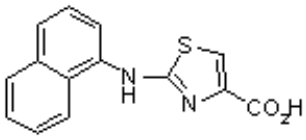
reaction variation	thiourea	Mass 5 mmoles thiourea / g	thiazole
1		0.72	
2		0.90	
3		0.98	
4		0.76	
5		0.77	
6		1.01	

Table 3. 2-Aminothiazole reaction variations

[i] M. C. M^{c}Cairn, S. R. Tonge and A. J. Sutherland, *J. Org. Chem.* **2002**, 67, 4847-4855.
[ii] N. Bailey, A. W. Dean, D. B. Judd, D. Middlemiss, R. Storer, and S. P. Watson, *Bioorg. & Med. Chem. Lett.*, **1996**, 6, 12 1409-1414.