Automated reaction optimisation of the enantioselective α-arylation of aldehydes via SOMO catalysis

Jay C. Conrad, Jongrock Kong, Brian N. Laforteza, and David W. C. MacMillan* Merck Centre for Catalysis at Princeton University, Princeton, New Jersey, 08544
Jake Grace. Chemspeed Technologies, Northampton, UK

Introduction

Recent work in the MacMillan group has demonstrated a new mode of organocatalytic activation (SOMO catalysis). The proposed mechanism involves the participation of a 3π-radical cation species in a variety of unprecedented asymmetric bond forming reactions. [1] These studies have included the first examples of stereoselective α-allylic alkylation, [1b] α-enolation [1c] and α-vinylation [1d] of aldehydes. Based on these results it was hypothesised that the α-arylation of aldehydes might be plausible via SOMO catalysis (Fig. 1). This was, indeed, found to be the case. [2] Herein we describe the automated optimisation of the reaction conditions for this novel transformation.

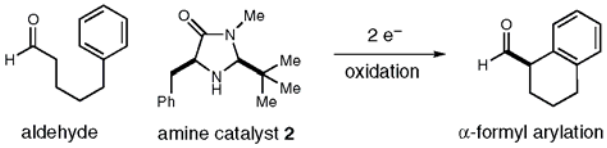


Figure 1. Enantioselective α-arylation of aldehydes via SOMO catalysis.

Experimental

Reactions to optimise the number of equivalents of pivalic acid and water and find the ideal concentration of the reaction were carried out in 2 mL reactors at 0.05 mmol (aldehyde) scale, according to the following protocol:
1. $[Fe(phen)_3]\cdot(PF_6)_3$ was delivered by the overhead gravimetric solid dispensing unit (SDU).
2. $NaHCO_3$ was delivered by the SDU.
3. The atmosphere within the accelerator hood was purged out with N_2 for 1 h.
4. The reactors were evacuated (5 mbar) and filled with N_2 five times.
5. The reactors were cooled to –20 °C and kept under a N_2 atmosphere.
6. Degassed CH_3CN was dispensed by the 4-needlehead (4NH).
7. Stock solutions of catalyst, water, additive and substrate were added with the 4NH.
8. The reactors were degassed again by evacuating (5 mbar) and filling with N_2 five times.
9. Under a N_2 atmosphere, the reactors were vortexed at 800 rpm for 24 h.
10. Internal standard (methyl benzoate) was added as a stock solution to the reactions (by the 4NH).
11. To precipitate out the solids 1.5 mL of ether was added, and the reactions warmed to room temperature
12. To avoid any precipitate, the 4-needlehead was then used to sample 100 µL of the reaction mixture from 1 cm above bottom of the reactor into a 96-well plate. The sample was then diluted with 1 mL of toluene and analysed by GC-FID. The yield was referenced to the response of the internal standard.

Results

The number of equivalents of pivalic acid was varied between 0 and 1, the results are summarised in Fig. 2. 0.3 eq was found to be the optimum amount. Next the relationship between concentration and number of equivalents of water was investigated. The results of this screen are shown in Fig. 3. The starting point of 1 eq H_2O at 0.1 M, gave 70 % yield and 97 % ee; after optimisation, a yield of 80 % with 98 % ee was achieved using 0.5 eq H_2O at 0.2 M.

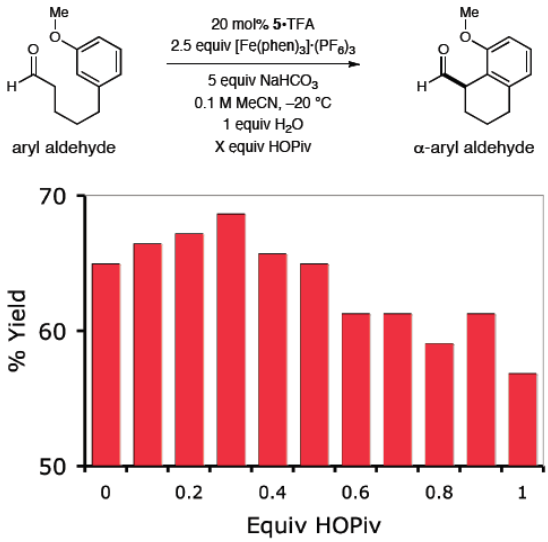


Figure 2. Optimisation of the equivalents of pivalic acid.

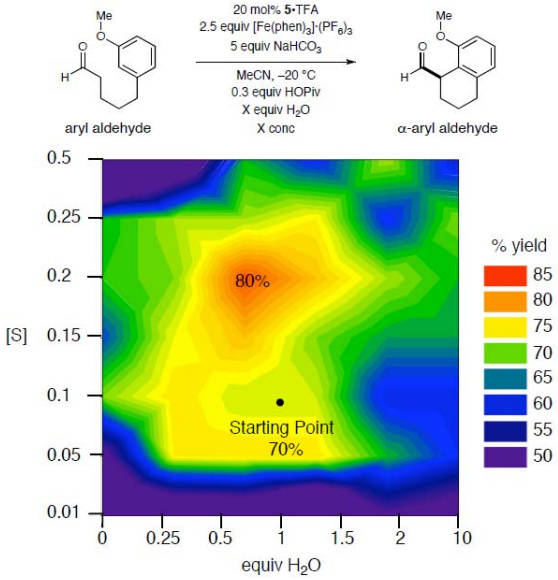


Figure 3. Optimisation of the reaction concentration; and equivalents of H_2O.

Summary

The fast and efficient optimisation of reaction conditions on the Chemspeed Synthesizer Cattest, has boosted the development of a new, important asymmetric bond forming reaction.

References

1. (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D.W. C. *Science* **2007**, *316*, 582. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (c) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (d) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494.

2. Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 7 Deer Park Drive, Suite L • Monmouth Junction • NJ 08852 • U.S.A. • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Understanding the Pathogenesis of Diabetis II:
Automated Preparation of Potential GLUT 5 Carrier Inhibitors

J. Girniene, A. Tatibouët, P. Rollin, ICOA, UMR 6005, Université d'Orléans, Orléans, France
Christelle Lorin, Chemspeed Technologies, Augst, Switzerland

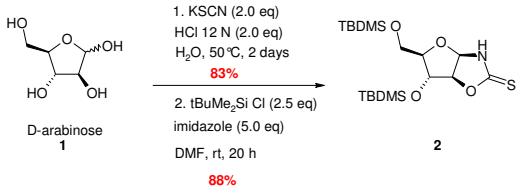
Pharmaceuticals & Agrochemicals

General

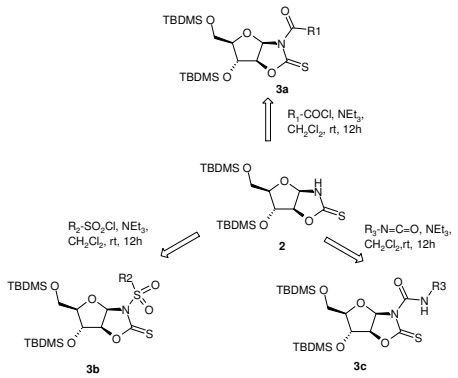
- D-fructose consumption in mammals is effected via a special carrier, GLUT 5. With regard to the importance of the sugars assimilation process in cells (here studies related to the pathogenesis mechanisms of diabetes II), the understanding of both the structure and the function of GLUT 5 is crucial.
- Different furano-type sugars have been shown to act as specific inhibitors of GLUT 5.[1, 2, 3] D-arabinose-derived oxazolidinethiones (OZT) displaying a rigid conformation are therefore interesting intermediates to be evaluated.

Reaction Sketch

- Synthesis of the precursor



- Preparation of the 1,3-oxazolidinethiones library



Objectives

- Automate a three-step procedure in solution phase including work-up (liquid/liquid extractions, evaporations) and on-line HPLC analysis.
- Perform challenging evaporations of high boiling solvents like water and DMF at 50°C.
- Rapidly screen suitable reagents for the N-functionalisation step.

Experimental set-up

- The first two steps were executed in an array of 100 mL reactors. The work-up involved the evaporation of 50 mL of water and 60 mL of DMF at 50°C and liquid/liquid extractions.

After filtration through a pad of silica gel, precursor **2** was tested in reactions with different acyl chlorides, sulfonyl chlorides and isocyanates on a small scale in the 2 mL array of reactors for evaluation of the reactivity.

•Successful N-functionalisation reactions were repeated in arrays of 13 mL reactors including a complete work-up.

•On-line HPLC and TLC analysis were performed.

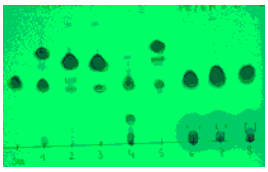
Picture 1: Reactions performed on a 1 mL scale in an array of 2 mL reactors

Picture 2: Automated liquid / liquid extraction carried out in the 13 mL reactors arrays

Results from HPLC analysis

R1	Yield (area %)
4-chlorobenzoyl	68.5
2-chlorobenzoyl	sm
furoyl	sm
cyclopropanecarbonyl	decomposed
benzoyl	82.5
acetyl	91.2
chloroacetyl	decomposed
cyclohexylcarbonyl	80

Table1: synthesis of **3a**



Picture 3: automated TLC-synthesis of **3a**

R2	Yield (area %)
dansyl	sm
propyl	sm
quinoline	57.4
2-naphtyl	68.6
trichloromethane	sm
tosyl	43
mesyl	48.3
2-thiophene	sm
phenylmethane	40.2
benzene	sm

Table 2: synthesis of **3b**
sm: starting material

R3	Yield (area %)
pentyl	10
cyclohexyl	98.4
1-naphtyl	33.4
chloroacetyl	sm
allyl	94.4
phenyl	22.4
3-chlorophenyl	sm
benzyl	87.4
isopopyl	sm
butyl	sm

Table 3: synthesis of **3c**

Summary

•Potential GLUT 5 inhibitors have been prepared using a three-step procedure and combining different scales of reaction.

•Compound **2** was shown to have only a low reactivity towards acylation, sulfonylation and reactions with isocyanates. Long reaction time with uncertain outcome make this example an ideal application for automation.

•Further experiments involving more reactive sugars substrates are currently under investigation.

[1-] Tatibouët A. ; Yang J. ; Morin C. ; Holman G. D., *Bioorg. Med. Chem.* **2000**, 8, 1825-1833
[2-] Gueyrard D., Grumel V., Leoni O., Palmieri S., Rollin P. *Heterocycles* **2000**, 52, 827-843.
[3-] Girniene J., Gueyrard D., Tatibouët A., Sackus A., Rollin P.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Parallel Synthesis of an Aminothiazole Library Including Fully Automated Workup

H.-P. Buchstaller, Merck KGaA Darmstadt, Germany
Ulrich Hackler, Josef Schröer, Chemspeed Technologies, Rheinstrasse 32, CH-4302 Augst, Switzerland

Pharmaceuticals & Agrochemicals

Objective

- Synthesis of an aminothiazole library in a fully automated fashion (Fig. 1).
- Several hundred compounds in quantities of about 40 mg were prepared.
- Aminothiazoles should be synthesized as a free base.
- Work-up of the crude reaction mixture was integrated into the program.

Reaction sketch

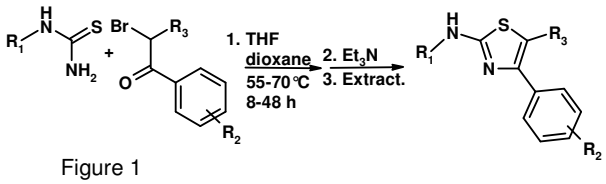
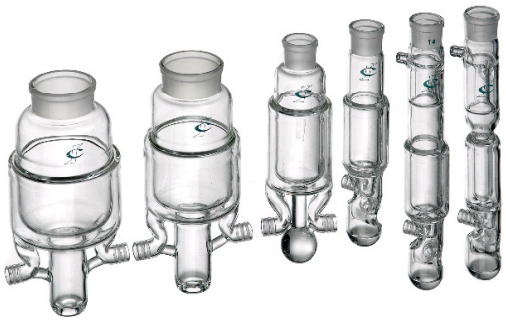


Figure 1

Experimental Set-Up

- Experiments were programmed and performed at Merck KGaA Darmstadt on their Chemspeed synthesizer equipped with 48 reactors (13 mL each).
- A 1:1 mixture of substituted thioureas and bromo-ketones was incubated at 55-70°C in THF or dioxane for 8-48h.
- Release of products was achieved by adding 400 µL triethylamine in chloroform, and extraction of the organic phase with 1.0 mL water at 50°C. The solvent was removed in vacuo, yielding 30-50 mg of free thiazole in purities greater than 90% in most of the cases (according to analytical HPLC). No further purification was required. Work-up of the crude reaction mixture was integrated into the program.



Picture of the different glass reactor sizes for Chemspeed automated synthesis platforms

Analytics

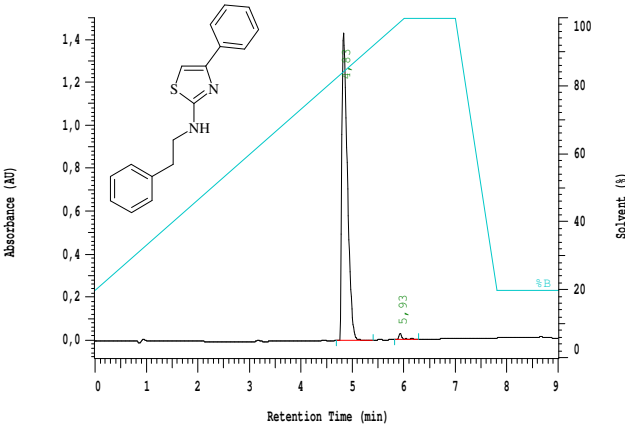


Figure 2: HPLC-chromatogram of a representative example

Results

- A library of 440 aminothiazoles, each one in form of its free base, has been synthesized. thioureas and bromo-ketones was incubated at 55-70°C in THF or dioxane for 8-48h.
- Due to the low solubility and occasionally great differences in reactivity of some of the building blocks, fine tuning of the reaction conditions was sometimes necessary.
- In the latter case changing the solvent from THF to dioxane, and incubating at an elevated temperature (70°C), gave similar results in a shorter period of time (i.e.: THF, 55°C, 48h incubation vs dioxane, 70°C, 8h incubation). As a representative example the HPLC-chromatogram of one of the aminothiazoles is given above (Fig. 2).

Summary

- Based on a modified procedure described by Bailey [1] a library of 440 aminothiazoles, each one in form of its free base, has been synthesized on Chemspeed's synthesizer.

[1] Bailey et al., *Bioorg. Med. Chem. Lett.*, 1409-1414, *12*, **(1996)**

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

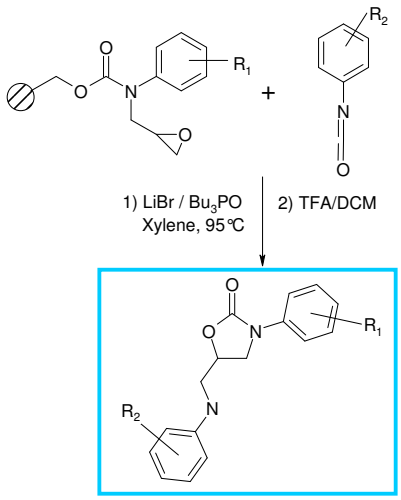
First Example of a Fully Integrated SPOS Workflow:
Synthesis of 80 Oxazolidinones Including Automated Resin Dispensing and On-line Cleavage with the Accelerator SLT 100

Michel Calderini, Stefan Bender, Hans-Peter Buchstaller, Merck, Darmstadt, Germany
Jérôme Giovannoni, Josef Schröer, Chemspeed Technologies, Augst, Switzerland

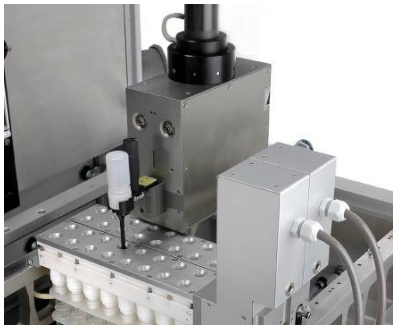
Pharmaceuticals & Agrochemicals

General
Oxazolidinones are a new antimicrobial class with a unique mechanism of action, active against resistant Gram-positive bacteria. We describe the synthesis of 80 oxazolidinones[1] by the combination of 5 solid-supported epoxides and 16 isocyanates in a fully integrated approach.

Reaction Sketch



Protocol
- 80 µmol of the 5 resins were automatically transferred to the reactors by the **Solid Dispensing Unit** with high precision and accuracy (see picture 1).
- Resins were washed 5 times with Xylene.
- An excess of the 16 isocyanates was added to the reactors by the **4-needles** liquid handling head.
- The catalyst was transferred to the reactors under stirring and reaction mixture was heated to 95°C.
- The reaction mixture was refluxed for 4 hours.
- After cooling down to room temperature, the resins were washed with Xylene, DMF, DMF/DCM and DCM.
- The final products were cleaved with TFA/DCM and collected in 8ml vials after automated SPE filtration.



Picture 1 : automated resin dispensing in a reactor

Results
All samples were analyzed by LC/MS. The expected compounds were detected by MS in all the samples.

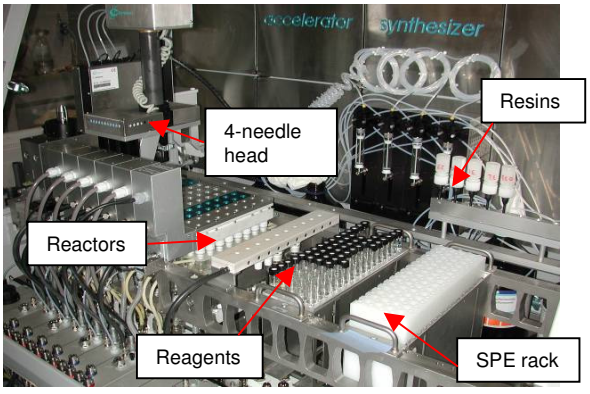
Isocyanate	Resin 1	Resin 2	Resin 3	Resin 4	Resin 5
1	90	95	86	60	88
2	88	79	92	89	84
3	73	89	Mixt.	82	Mixt.
4	89	Mixt.	68	56	63
5	55	87	85	Mixt.	85
6	92	70	94	92	Mixt.
7	93	92	85	78	87
8	78	69	88	91	79
9	93	96	89	73	95
10	92	Mixt.	80	91	73
11	80	90	65	Mixt.	89
12	83	82	85	59	70
13	88	78	62	80	66
14	88	84	84	60	85
15	76	60	92	Mixt.	67
16	Mixt.	Mixt.	Mixt.	91	Mixt.

Table 1 : HPLC purity at 220 nm

- The average purity of compounds is approximately 70%
- 70% of the samples have a purity above 70%

Conclusion
This example impressively demonstrates the unique features of the **Accelerator SLT100**. In a fully unattended run, we could achieve on the same instrument, the dispensing of the resins into the reaction vessels, the transfer of the liquid reagents (catalyst and isocyanates), the completion of the reaction and the cleavage and collection of the final products. The entire procedure was accomplished in less than 24 hours.

The experimental set-up is shown in picture 2



Picture 2 : Experimental set-up of the SLT100

[1] Solid Phase Synthesis of Oxazolidinones by Cycloaddition of Resin-Bound Epoxides with Isocyanates; Buchstaller H.-P.; J. Comb. Chem.; 2003; 5(6); 789-793.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Utilising high throughput technologies for determination of the reaction mechanism of the L-proline catalysed aldol reaction – solubility and miscibility screening

K. Novakovic, M. J. Willis, A. R. Wright. School of Chemical Engineering & Advanced Materials, University of Newcastle, UK
J. Grace. Chemspeed Technologies, Northampton, UK

Pharmaceuticals & Agrochemicals

Introduction

Robotic workstations are used mainly to support parallel chemistry or screening for new compounds and catalysts.[1] But their potential to provide useful information regarding commercial, chemical engineering, safety, and environmental aspects of process development is not yet fully explored. For instance, it is known that downscaling can alter the relative significance of physical phenomena, in particular dispensing, the accurate control of transport processes, mixing, solid and fluid dynamics; all of which may impact on the rate and reproducibility of reactions at larger scale.[2] If high throughput technologies (HTT) are to be successfully extended to process development, experimental results must be meaningful and reproducible throughout scale up. Here we describe the use of a Chemspeed SLT106 to determine the optimum conditions (choice of solvent(s), concentrations of reactants and catalyst) prior to scale up for kinetic analysis and reaction modelling. Stage 1 comprised the initial screening of potential solvents through the assessment of the solubility and miscibility characteristics of the reactants and catalyst. In Stage 2 (described in the another application note) the concentrations of reactants and catalyst that are appropriate for carrying out the reaction at larger scale were determined. In Stages 3 and 4 (not described here)[3] experiments were performed to generate suitable data for detailed mechanistic modelling, a reaction network was proposed and kinetic rate constants estimated. The reaction used as the case study was the L-proline catalysed aldol reaction between *p*-nitrobenzaldehyde and acetone (Figure 1).[4]

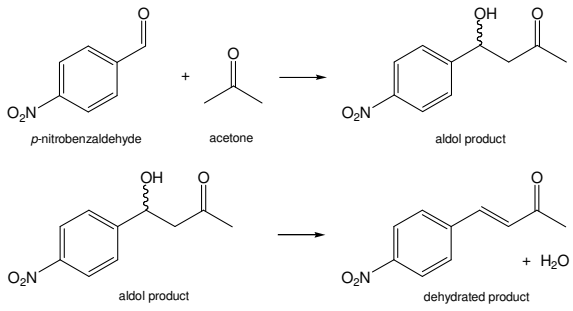


Figure 1. The L-proline catalysed aldol reaction.

Experimental

In stage 1 the maximum concentrations to maintain a homogeneous system for *p*-nitrobenzaldehyde and L-proline in a range of solvents were determined. 10 mL of solvent was added to a reaction array on the synthesiser and held at 20°C, then solid was added to the solvent, by Chemspeed's Overhead Gravimetric Solid Dispensing Unit (SDU) (Figure 2), with agitation. Small portions were added to the reactors until precipitation occurred, at which point solid dispensing was stopped and samples taken for GC-MS analysis to check for side reactions. The point at which precipitation occurred was monitored visually; however, one can conceive the use of a turbidity probe to further automate this process. The miscibility of the solvents was assessed by adding 5 mL of each solvent to a reactor, agitating for a few minutes and making a visual check.

Results

The results of stage one are shown in Table 1 and identified DMSO (1.695 moldm^{-3}) as the best solvent for *p*-nitrobenzaldehyde, followed by acetone (0.234 moldm^{-3}) and acetonitrile (0.131 moldm^{-3}).

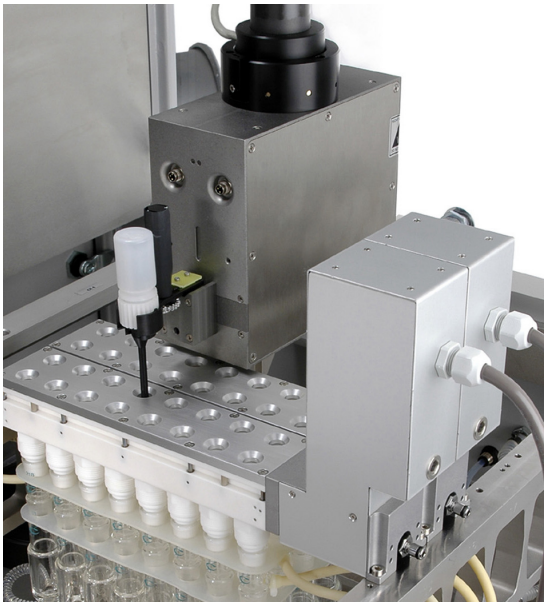


Figure 2. Chemspeed's overhead gravimetric solid dispensing unit (SDU) delivering the solid *p*-nitrobenzaldehyde and L-proline for the solubility screen.

For L-proline water was the best solvent (5.576 moldm^{-3}), but is unsuitable as it negates the enantioselectivity of the reaction, methanol (1.0197 moldm^{-3}) and acetone (0.0104 moldm^{-3}) are the next best candidates. Analysis showed no side reactions, and all solvents were shown to be mutually miscible.

	Reactant / solubility (mol dm^{-3})	
Solvent	*p*-nitrobenzaldehyde	L-proline
DMSO	1.695	-
Acetonitrile	0.131	-
Acetone	0.234	0.0104
Water	-	5.576
Methanol	-	1.0197

Table 1. The maximum concentrations for each reactant in the solvents tested.

Summary

Chemspeed's synthesiser is a valuable tool for early process research; e.g: solubility and miscibility screening. The high throughput approach facilitating a significant reduction in necessary time and effort versus a manual approach.

References

1. Hagemeyer A, Strasser P, Volpe AF (2004) High-throughput screening in heterogeneous catalysis. Wiley-VCH, New York

2. Hoyle W (ed) (1999) Pilot plants and scale-up of chemical processes II, vol 236. Royal Society of Chemistry, Cambridge, UK

3. Novakovic K, Willis MJ, Wright AR (2008) Utilising high throughput technologies for the determination of the reaction network of the L-proline catalysed aldol reaction Clean Techn Environ Policy 10:155–163

4. Manuel M, Marques B (2005) Asymmetric cross-aldol reactions of aldehydes: a formidable synthetic challenge. In: Organic chemistry highlights. Available at: http://www.organic-chemistry.org/Highlights/2005/25June.shtm

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Utilising high throughput technologies for the determination of the reaction mechanism of the L-proline catalysed aldol reaction – optimising reaction conditions

K. Novakovic, M. J. Willis, A. R. Wright. School of Chemical Engineering & Advanced Materials, University of Newcastle, UK
J. Grace. Chemspeed Technologies, Northampton, UK

Pharmaceuticals & Agrochemicals

Introduction

In another application note in this series we discussed the use of high throughput techniques to determine the maximum possible concentrations for maintaining a homogeneous system of *p*-nitrobenzaldehyde and L-proline in a range of potential solvents for the L-proline catalysed aldol reaction (Figure 1). Here we extend the application of Chemspeed's synthesiser to optimising the concentrations of each reactant in the system prior to scale up and kinetic modelling.

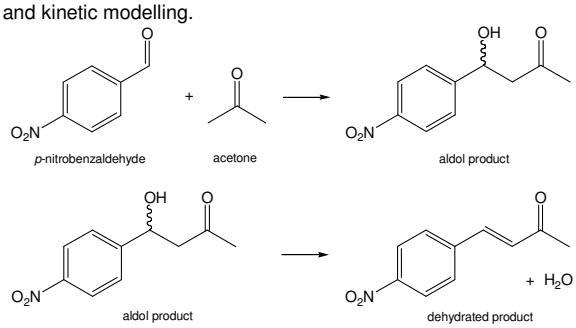


Figure 1. The L-proline catalysed aldol reaction.

Experimental

In stage 2, the optimum conditions for scale up were determined. Based on the results from stage 1 DMSO was found to be the optimal solvent for *p*-nitrobenzaldehyde and methanol the one for L-proline. In the first iteration of stage 2, the concentrations of *p*-nitrobenzaldehyde, acetone and L-proline were screened at high and low concentration with 6 samples being taken from each reaction over 24 hours. A second iteration was also performed using acetone as the solvent for both *p*-nitrobenzaldehyde and L-proline. Three concentrations for *p*-nitrobenzaldehyde and 5 for L-proline were screened, giving a total of 15 experiments (Table 1). Again 6 samples were removed for analysis over a 24 hour period.

Results

It was found that the higher the concentration of L-proline the greater the conversion of *p*-nitrobenzaldehyde, but also that the conversion of *p*-nitrobenzaldehyde was greater than the combined amounts of aldol and dehydrated product, suggesting that at least one side reaction was present. The aldol product was found to be racemic, prompting the second iteration of experiments.

Reactor	*p*-nitrobenzaldehyde (mol/dm^3)	L-proline (mol%)	L-proline (mol/dm^3)	L-proline soluble
1	0.2	0	0	–
2	0.2	4	0.008	Yes
3	0.2	8	0.016	No
4	0.2	40	0.08	No
5	0.2	80	0.16	No
6	0.1	0	0	–
7	0.1	4	0.004	Yes
8	0.1	8	0.008	Yes
9	0.1	40	0.04	No
10	0.1	80	0.08	No
11	0.01	0	0	–
12	0.01	4	0.0004	Yes
13	0.01	8	0.0008	Yes
14	0.01	40	0.004	Yes
15	0.01	80	0.008	Yes

Table 1. The concentrations used in the second iteration.

The results from the second iteration are summarised in Figure 2 as plots of the conversion of *p*-nitrobenzaldehyde and formation of aldol and dehydrated product vs the mol % of L-proline at starting concentrations of *p*-nitrobenzaldehyde of 0.01 moldm^{-3}, 0.1 moldm^{-3} and 0.2 moldm^{-3}. With no L-proline added to the system the conversion of *p*-nitrobenzaldehyde was found to be low, but approximately equal to formation of aldol and dehydrated product. In reactions with L-proline present an increase in the concentration of L-proline resulted in an increase in the conversions of *p*-nitrobenzaldehyde, aldol and dehydrated product. The results obtained from the homogeneous systems (initial concentration of *p*-nitrobenzaldehyde 0.01 moldm^{-3}) indicated that increasing the amount of L-proline above 40 mol% (relative to *p*-nitrobenzaldehyde) does not significantly increase the amount of aldol and dehydrated product formed. All the reactors containing L-proline suffered from a mass imbalance between the amount of *p*-nitrobenzaldehyde consumed and the amount of aldol and dehydrated product made, indicating the presence of at least one side reaction. Therefore although the reactants and catalyst were used with no additional solvents a side reaction occurred. The e.e. of aldol produced was measured to be in the region of 73% after 24 h.

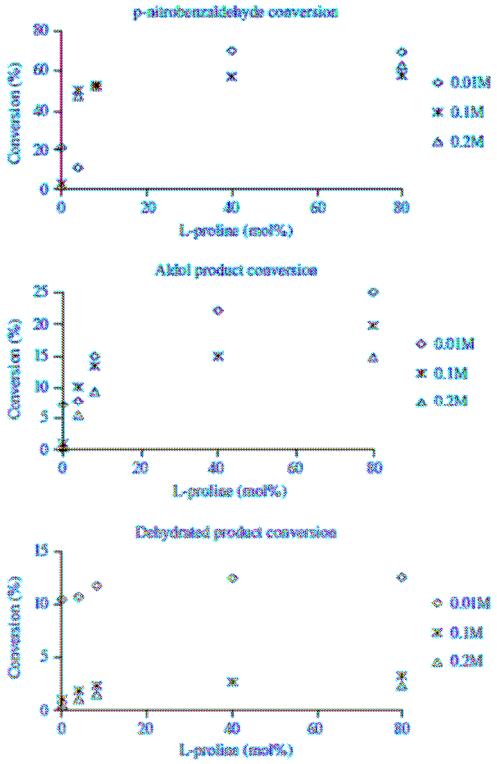


Figure 2. Conversion plots for iteration 2.

Summary

Using Chemspeed's synthesiser we have demonstrated how reaction parameters can quickly (1-2 iterations) and easily be optimised prior to scale up for detailed mechanistic modelling study.[1] Typically reducing the necessary experimental time from several weeks to a matter of days.

References

1. Novakovic K, Willis MJ, Wright AR (2008) Utilising high throughput technologies for the determination of the reaction network of the L-proline catalysed aldol reaction Clean Techn Environ Policy 10:155–16

Amide Coupling Reactions on the Chemspeed Synthesizer

Jake Grace. Chemspeed Technologies, Northampton, UK

Pharmaceuticals & Agrochemicals

Introduction

Amide couplings are a workhorse reaction in organic synthesis, [1] acid chlorides react rapidly with amines, and yields are usually excellent. Consequently the reaction (Figure 1) is routinely used in the preparation of chemical libraries. Herein we describe the use of Chemspeed's SLTII synthesis platform (Figure 4), to demonstrate the completely automated synthesis and work-up of a series of amides for the preparation of a typical library. All reagents (both solids and liquids) were dispensed using either the robotic system's 4-needlehead liquid handler (4NH) or overhead gravimetric solid dispending unit (SDU). Reactions took place in Chemspeed's reactor arrays (Figure 3), which provide precise temperature control and efficient vortex mixing. When the reactions were complete, they were automatically worked-up, the solvent was evaporated in the glass arrays, the crude product was extracted, washed with water, the aqueous layer was extracted again, the combined organics were evaporated and finally extracted into DMF for analysis and prep HPLC.

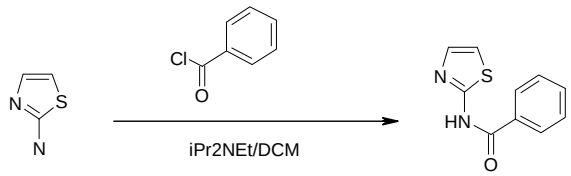


Figure 1. An example of an amide coupling reaction.

Figure 4. Chemspeed's SLTII synthesis platform.

Workflow

The solid thiazole derivative was dispensed into a Chemspeed reactor block containing an array of 13 mL double jacket reactors (Figure 3), using the overhead, gravimetric solid dispensing unit (SDU). It was suspended in CH_2Cl_2, which was dispensed with the 4-needlehead liquid handler (4NH). Vortex agitation (800 rpm) was started, followed by dispenses of the acid chlorides (2.0 eq) and Hunig's base (2.0 eq), again using the 4NH. The mixture was stirred at room temperature overnight, then the reaction mixture was evaporated, the crude product was extracted into EtOAc, washed with H_2O, the organic layer was removed, the aqueous layer extracted with

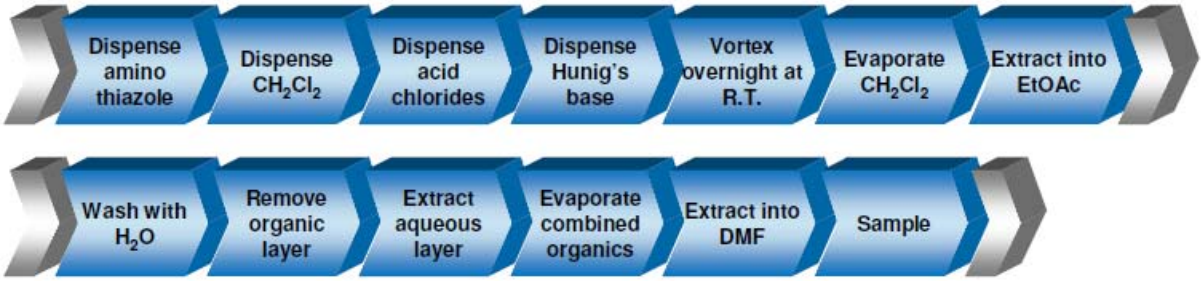


Figure 2. A typical amide coupling reaction workflow on the SLTII.

Figure 3. An array of 16 x 13 mL double jacketed glass reactors for use on the Chemspeed synthesiser.

EtOAc and the combined organic layers were evaporated, extracted into DMF, filtered, and sampled. The workflow is represented schematically in Figure 2.

Summary

Chemspeed's SLTII synthesis workstation with up to 192 double-jacket reactors has been shown to be capable of fully automating the reaction preparation, synthesis and work-up of large amide libraries at the discovery stage in the pharmaceutical and agrochemical industries.

References

1. *Chem. Soc. Rev.*, 2009, **38**, 606 - 631

Note: this work was carried out for a customer in order to evaluate the capability of the system. Therefore, no analytical data are available.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201
(2011)

Stereoselective Complexation of Small Peptides and Amino Acid Carboxylates in Aqueous Solution:

Automated, Parallel Synthesis of a Guanidinio-Carbonyl Pyrrole Receptor Library

Martin Heil, Carsten Schmuck*, Institute for Organic Chemistry, University of Würzburg, Germany
Michael Dechantsreiter, Ulrich Hackler, Chemspeed Technologies, Augst, Switzerland

Pharmaceuticals & Agrochemicals

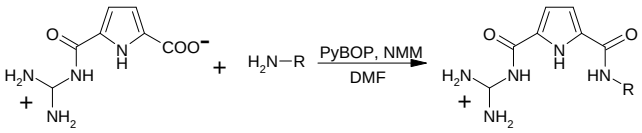
Introduction

- Integration of a complex reaction and workup sequence (incubation, filtration, evaporation of DMF and precipitation of the product).
- A new type of receptor for the sequence selective recognition of amino acids and small peptides under aqueous conditions is introduced.
- An already optimized reaction procedure was implemented on the ASW2000 without changes in the reaction protocol.

Objective

- Fast and efficient synthesis of a receptor library for further studies (NMR-titration experiments), as part of a joint research project between Chemspeed and the University of Würzburg, Germany.
- A deeper understanding of supramolecular struc-tures (protein-substrate recognition) in aqueous media.

Experimental Set-up



Picture 1

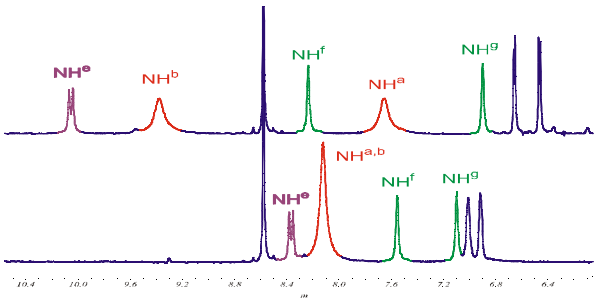
- Amine and acid incubated 16h at r.t. in the presence of PyBOP (Picture 1).
- Filtration over Celite (removal of insoluble starting material).
- Parallel evaporation of DMF under reduced pressure
- Precipitation of the products as pikrates in methanol

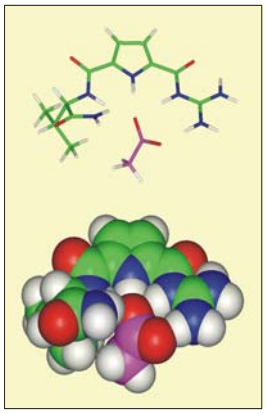
Picture 2

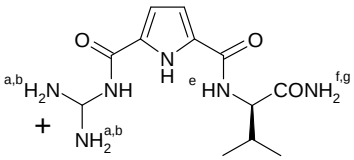
- The experiment was carried out on a Chemspeed synthesizer (Picture 2) equipped with 13mL filtration kits, utilizing disposable filters.

Results

- 96 new receptors have been synthesized in a single overnight run.
- The complex reaction protocol could be im-plemented without modifications.
- NMR-studies of the receptors in DMSO-D_6 with 40% water show that 1:1-complexes with acetate, amino acids and small peptides are forming spontaneously.
- Only those hydrogen atoms, that should be involved in complexation of the substrate, according to the model predictions, show downfield shifts, i.e. participate in the complexation event (Picture 3).







Picture 3: ^{1}H-NMR spectra and calculated structure. With R = Val and acetate as substrate (Macro Model 6.5 Amber force field)

Summary

- A library of 96 new receptors has been synthesized.
- The receptor can bind amino acids and oligo peptides in aqueous media.
- Further studies with this promising new approach are under way.

[1] Schmuck, C.; Heil, M.: "Peptide binding by one-armed recep-tors in water: screening of a combinatorial library for binding of Val-Val-Ile-Ala." *ChemBioChem.* **2003**, *4*, 1232-1238.

[2] Schmuck, C., Geiger, L.: "Carboxylate Binding by Guanidinio-carbonyl Pyrroles: From Self-Assembly to Peptide Receptors", *Curr. Org. Chem.* **2003**, *7*, 1485-1502.

Chemspeed Technologies • **www.chemspeed.com**
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Automated Click Chemistry – Synthesis of a Triazole Library

Dagmar Kail, PharmBioTec GmbH, Saarbrücken, Germany
Rui Fraga, Chemspeed Technologies AG, Augst, Switzerland

Pharmaceuticals & Agrochemicals

Introduction

PharmBioTec's department of Drug Discovery focuses on the synthesis of small, drug-like molecules for a broad range of therapeutic targets. Usually a large number of compounds is needed to identify active species, or to improve the activity/pharmacokinetic profile of an initial hit. Instead of employing time and labor-intensive bench work, PharmBioTec has chosen another path, that of automation. Towards this end PharmBioTec has acquired the most flexible platform for organic synthesis on the market: Chemspeed's ISYNTH. This modular robotic platform enables library synthesis and work-up in easy to use disposable reactors. It is suited for low and high temperatures, for handling liquids / solids and working under inert or reactive gas pressure atmosphere.

Objectives

- Synthesize a library of 32 triazoles in a fully automated protocol, including work-up and sampling, starting from commercially available boronic acids and alkynes
- Compare yields obtained in the manual and automated procedures

Experimental Set-up

ISYNTH, a software-driven robotic platform containing:

- Solid Dispensing Unit
- 4-Channel Liquid Handling Unit
- 20 mL Disposable Glass Reactors
- Phase-separation cartridges for automated work-up

Workflow

Results

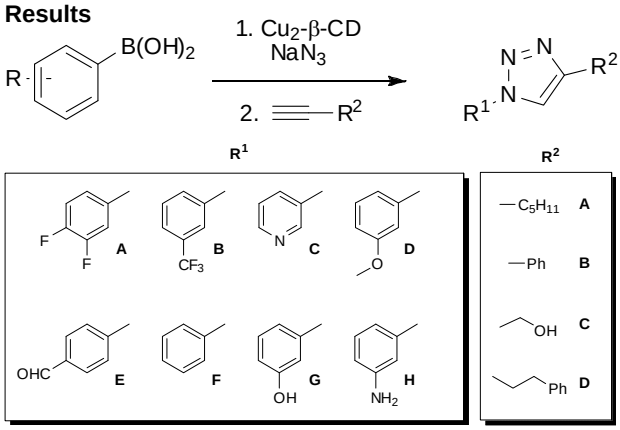
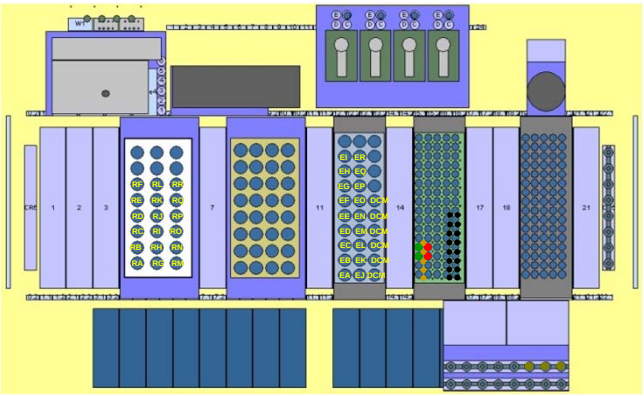


Figure 1 – Overview of prepared compounds

All reaction steps, including work-up, were performed in the ISYNTH platform.



A: RA-RR (Reaction-Zone)
B: EA-ER (Extraction-Zone)
C: DCM
Cu-CD-Complex, Sodium Azide, Alkynes, HPLC-Samples, $MgSO_4$

Figure 2 – Schematic layout of the experiment, showing storage positions of raw materials and reaction wells.

Crude products were purified by preparative HPLC if their purity was below 95%. The average yields obtained were above 30% and comparable to manual procedure [1].

Conclusions

A library of 32 triazoles was synthesized on the ISYNTH platform, with an average purity of 96% (after HPLC). Generation of such libraries is achieved in the same time as it takes for a single compound manually.

Reference

[1] Kaboudin, B.; Abedi, Y.; Yokomatsu, T. *Org. Biomol. Chem.* **2012**, *10*, 4543–4548

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Department of Chemistry, University of York • Heslington, York, YO10 5DD • U.K. • Phone +44 1904 409 579

Parallel synthesis in the undergraduate teaching labroratory

Claire McDonnell, Marie Keating, Melissa Crilly, Sheila Flynn, Cornelia Haas, Robert Hanlon & Miriam Kennedy. School of Chemical and Pharmaceutical Sciences, Dublin Institute of Technology, Kevin Street, Dublin 8, Ireland
Jake Grace. **Chemspeed Technologies**, Northampton, UK

Pharmaceuticals & Agrochemicals

General

Parallel synthesis and combinatorial chemistry are important and powerful tools widely utilised in research and development throughout the chemical and pharmaceutical industries. Whilst many science graduates will have an appreciation of these techniques, gained from their undergraduate lectures, very few have any hands-on experience as the sort of equipment necessary for such experiments is usually only available in industrial or academic R & D labs. In order to bridge this knowledge gap Dublin Institute of Technology (DIT) now provide their final year undergraduates with invaluable know-how by giving them access to a Chemspeed parallel synthesis station as part of their practical course. The intention is to improve the interface between research and learning at DIT.

Experimental

An experiment was designed to give students an insight into the potential benefits of parallel synthesis. The experiment involved the synthesis of 8 esters with characteristic fragrances. [1] All reactions were carried out in a Chemspeed's 16 x 13 mL array of double jacketed glass reactors, fitted with an array of reflux condensers with filtration capability (Figure 1).

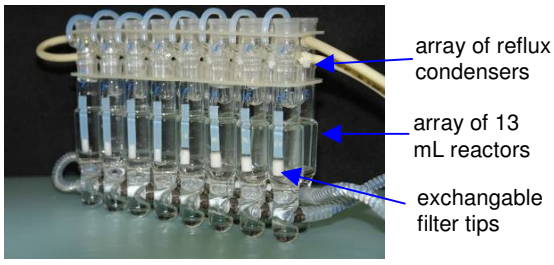


Figure 1: A 16 x 13 mL glass reactor array with reflux and filtration capabiity.

The target esters and their characteristic smells are shown (Figure 2). The workflow developed is as follows:

1. Addition of reagents
2. Heat to 65 °C under reflux and vortex, 800 rpm, 40 mins
3. Cool to 15 °C and vortex for a further 15 mins
4. Addition of EtOAc and Na_2CO_3 (aq), vortex, 1250 rpm, 5 mins; leave the layers to separate (5 mins) and remove the aqueous layer
5. Wash with a further portion of Na_2CO_3 (aq), conditions as above
6. Add $MgSO_4$ and vortex, 500 rpm, 5 mins
7. Filter from the left to the right-hand side of the reactor block
8. Add a second portion of EtOAc to the left-hand side of the reactor block and filter left to right
9. Evaporation of EtOAc by placing the reactors under vacuum, heat to 60 °C and vortex, 1000 rpm

Each ester has a characteristic smell and after the synthesis the students performed a "fragrance test" on the products as well as analysing them by GC-MS and ^1H NMR spectroscopy.

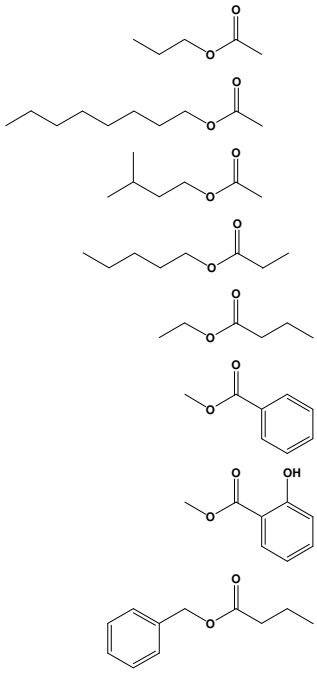


Figure 2: The esters synthesised in parallel.

Results

When asked to evaluate the parallel synthesis experiments they had performed, students reported:
1. That they welcomed the opportunity to use a piece of equipment that is usually reserved for research labs.
2. That they felt the experience will be of benefit when applying for jobs.
3. That performing parallel synthesis reactions reinforced their understanding of medicinal chemistry lectures.

Following the success of the course, the parallel synthesis of hydrazones [2] will be piloted in advanced practical sessions this academic year. Experiments using click chemistry [3] for the production of triazole analogues; and solid phase peptide synthesis are currently in development for roll out in coming years.

Conclusion

Apart from being vital components in the armoury of R & D labs in today's competitive environment; Chemspeed's automated synthesis platforms can, in combination with a well devised and delivered undergraduate practical course, be an invaluable learning tool for the scientists of tomorrow.

References

[1] D. Birney & S. Starnes, *J. Chem. Ed.* 1999, 1560-1561.
[2] S. Wolkenberg, & A. Su, *J. Chem. Ed.* 2001, 78, 748-785.
[3] F.Pagliai, T. Pirali, E. Del Grosso, R. Di Brisco, G. C. Tron, G. Sorba, A. A. Genazzani, *J. Med. Chem.* 2006, *49*, 467-470.

High-Throughput Compound Library Synthesis For Protein-Protein Interaction Studies

F. Mahuteau-Betzer, M. Barthe, J. Florent, D. Grierson, **Institut Curie-CNRS**, Orsa
T. Geldbach, A. Abou-Hamdan **Chemspeed Technologies**, Augst, CH

Pharmaceuticals & Agrochemicals

Introduction

Flat fused polyheterocycles can mimic the activity of the natural regulator p21waf1/CIP1, inhibiting the interaction of PCNA with the p66 sub-unit of DNA polymerase δ (see Figure 1).

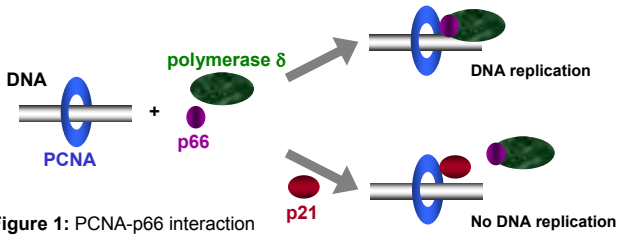


Figure 1: PCNA-p66 interaction

As certain active compounds exhibit cyctotoxic properties *in vivo* it is of interest to find alternatives on the molecular level which would be devoid of cyctotoxicity, possess more drug-like properties (ADME), and be more readily accessible to synthesis. Such alternative scaffolds may include diarylamino ethers, benzanilides and stilbenes.

The HTS of our library has been realized on a protein microchip. A fragment of the p66 protein was fixed onto a plastic chip. To each spot was subsequently added a solution of fluorescent labelled PCNA + a molecule from the Curie/CNRS compound library. The protein microchip is incubated, washed and scanned. The absence of fluorescence indicates that our small molecule inhibits the PCNA-p66 interaction.

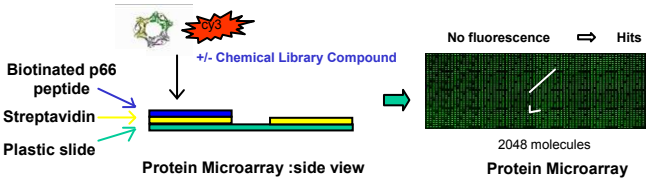
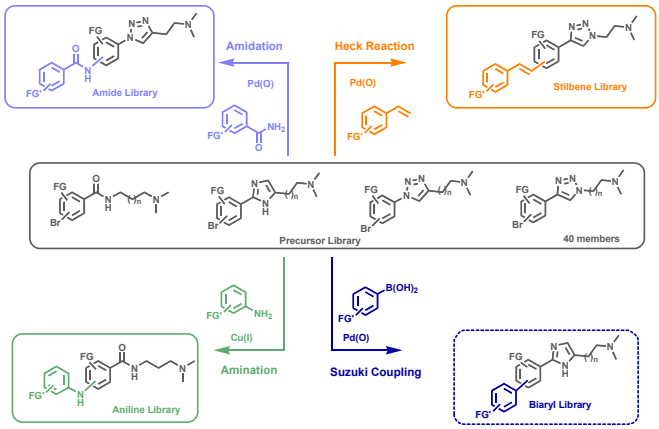


Figure 2: Schematic representation of the screening procedure

Experimental Set-up

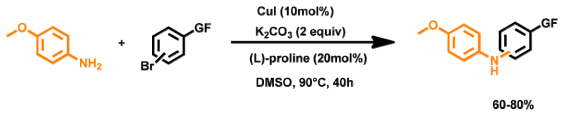
The different routes to the chosen scaffolds for potential inhibition of the p66/PCNA interaction are outlined in Scheme 1.



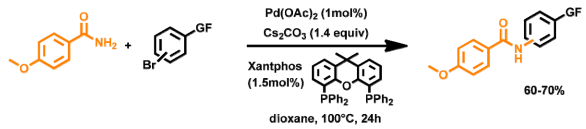
Scheme 1: Routes to potential p66/PCNA inhibitors

For an high-throughput approach, it is important that the synthesis is short, flexible and efficient, yielding the target molecule in good purity and this is achieved following the synthetic pathways shown in Scheme 2.

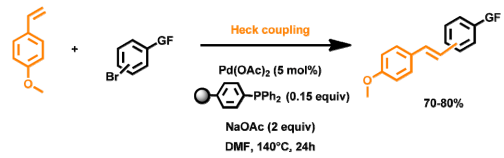
Aniline Library prepared via Copper catalysis



Benzanilide Library prepared via Palladium catalysis



Stilbene Library prepared via Heck reaction



Scheme 2: Reaction conditions and pathways for automated synthesis

Results and Conclusions

By using a Chemspeed synthesizer (Figure 3 and 4), fast and efficient syntheses of the library were achieved. In the case of the stilbene library, polymer-supported phosphines were employed to facilitate purification of the final product. As the last step the crude product was passed through a filtration cartridge loaded with a supported thiol to absorb the palladium catalyst. Products were usually synthesised on a 0.5 – 1 mmol scale with an average purity of > 95%.

Figure 3: Automated synthesis workstation (left)

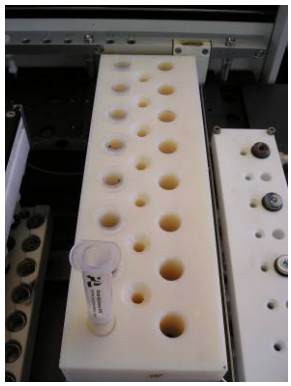


Figure 4: SPE-rack for automated extraction/ filtration (below)

Use of a robotic system for automated synthesis can markedly accelerate and facilitate the synthesis of large molecule libraries. The Chemspeed synthe-sizer allows for a fully automated workflow, from the reaction preparation to the purification and optionally on line analysis.

* ***All scientific results are courtesy of Institut Curie-CNRS***

Chemspeed Technologies • **www.chemspeed.com**
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Development of a 1st Generation MKP-1 Probe

Peter Wipf and Leah Fow. Department of Chemistry, University of Pittsburgh, Pittsburgh, USA
Jake Grace. Chemspeed Technologies, Northampton, UK

University of Pittsburgh
Pittsburgh Molecular Libraries Screening Center

CHEMSPEED TECHNOLOGIES

Pharmaceuticals & Agrochemicals

Introduction

Mitogen-activated protein kinase phosphatase (MKP-1) is a member of the tyrosine phosphatase superfamily that dephosphorylates and inactivates mitogen-activated protein kinase (MAPK) substrates, such as p38, JNK and Erk. MAPK-phosphatase inhibitors could be useful probes for cellular signal transduction, immuneresponse, oncogenesis and apoptosis research. However, to date, no potent and selective MKP-1 inhibitors are known.

The cyclopenta[c]quinoline carboxylic acid scaffold (Figure 1) was found to be a promising general motif for phosphatase inhibition. It is small, compact and, importantly, readily amenable to diversification. Modification is possible at the 5-membered ring (red), aromatic 6-membered ring (blue) or at R^3 (green) (Figure 1).

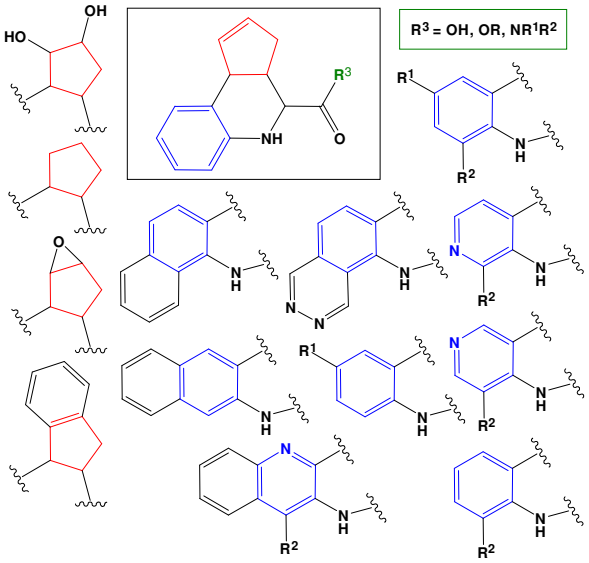


Figure 1. The cyclopenta[c]quinoline carboxylic acid scaffold.

Experimental

All reactions were carried out in 13 mL double jacketed reactors (Figure 2) on a Chemspeed automated synthesis robot, enabling automated reagent additions, heating / cooling, agitation, sampling, work-up and analysis to be carried out completely unattended.

Figure 2. An unattended array of 16 x 13 mL glass reactors used in Chemspeed's ASW2000

Results

The scope of the Hetero-Diels-Alder reaction was utilised in the preparation of the initial diversity set (Figure 3). Then selective backbone and side chain functionalities were added (Figure 4).

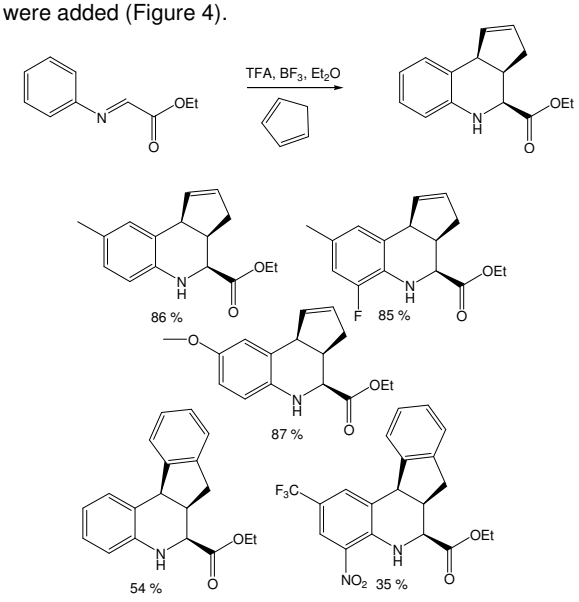


Figure 3. The Hetero-Diels-Alder Reaction.

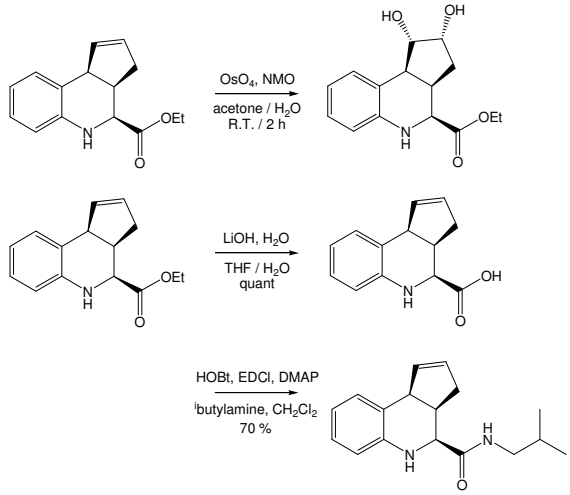


Figure 4. Backbone and side-chain modifications.

Conclusions

Chemspeed's automated synthesis platforms are powerful tools in achieving the goals of developing innovative new methodologies in diversity-orientated organic synthesis and providing access to libraries of diverse chemical structures at the University of Pittsburgh.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Suzuki Reactions on the Chemspeed Swave

Jake Grace. Chemspeed Technologies, Northampton, UK

Pharmaceuticals & Agrochemicals

Introduction

The Suzuki reaction has become a mainstay transformation in the organic chemist's toolkit, enabling efficient carbon-carbon bond formation (Figure 1). [1] A fact that was highlighted by the award, to its inventor, of a share of the 2010 Nobel Prize in chemistry. Running these reactions under microwave irradiation has been shown to vastly accelerate them. Reactions that take many hours under thermal conditions are completed in just minutes when run in microwave reactors. [2] Microwave systems are now available with automated transfer of capped vials to the microwave cavity and back, but don't provide complete automation of the entire workflow. In such cases reaction preparation of up to several hundred vials is carried out either manually or on automated liquid handlers. But with many of these reaction mixtures sitting for many hours before reaching the microwave, decomposition and side reactions can cause potentially good transformations to appear ineffective. These difficulties can be avoided by completely automating the workflow using sequential reaction preparation, microwave reaction and work-up. Here we describe such a process on Chemspeed's SLT2 synthesis platform (Figure 4).

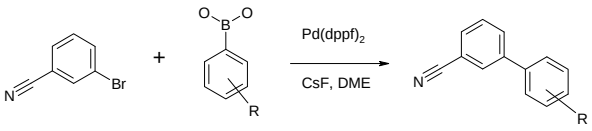


Figure 1. A typical Suzuki reaction.

Figure 4. Chemspeed's Swave platform with microwave.

Workflow

A typical workflow will start with sample or reaction preparation, which will involve dispensing solids (aryl bromide, boronic acid, CsF, and catalyst / ligand); liquids (solvent and any liquid reagents); and capping and crimping the vial (Figure 3). The prepped vial will then be transferred to the microwave, and microwave heating will begin. At this point the preparation of a second reaction vial can begin. Once the first reaction is complete, the tube will be removed from the microwave cavity and placed back in a rack, the second tube can be transferred to the microwave to begin its reaction, then work-up of tube one can begin – this will typically involve filtration, liquid-liquid extraction, concentration to dryness, and finally extraction into a suitable solvent – followed by the preparation of tube 3… The workflow is schematically represented in Figure 2.

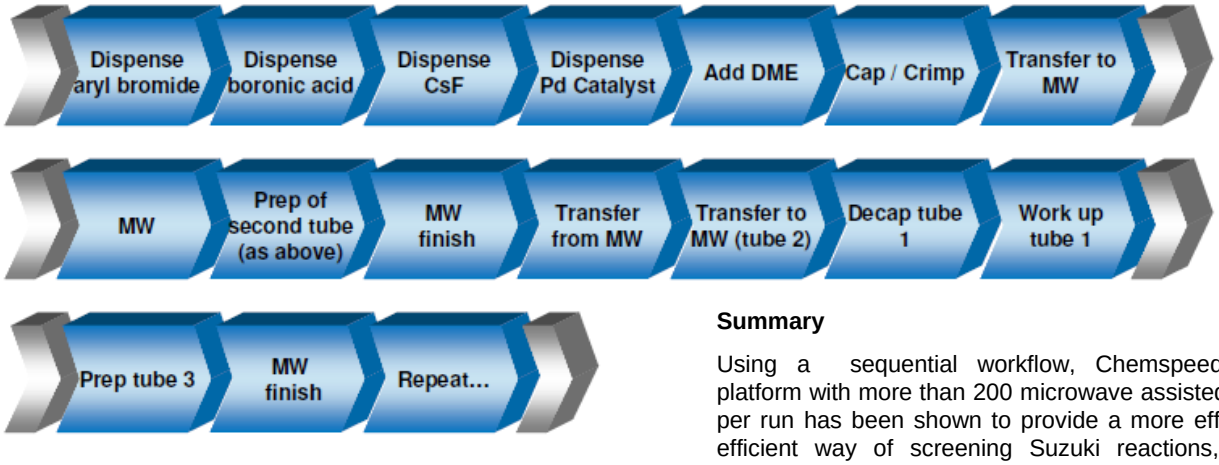


Figure 2. A typical Suzuki reaction workflow on the Swave.

Figure 3. A selection of microwave vials.

Summary

Using a sequential workflow, Chemspeed's Swave platform with more than 200 microwave assisted reactions per run has been shown to provide a more effective and efficient way of screening Suzuki reactions, than the traditional approach of batch reaction preparation followed by sequential microwave reaction. It also affords the benefit of automated work-up, and provides a convenient analytical sample at the output.

References

1. Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, 95, 2457-2483

2. Microwave-Assisted Organic Synthesis; Lidstrom, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2004.

Note: this work was carried out for a customer in order to evaluate the capability of the system. Therefore, no analytical data are available.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201
(2011)

Utilising the substance handling capability of Chemspeed's Swing platform for library synthesis

Marcus Koppitz. Bayer Schering Pharma AG, Berlin Germany
Jake Grace. Chemspeed Technologies, Northampton, UK

Bayer HealthCare
Bayer Schering Pharma

CHEMSPEED TECHNOLOGIES

Pharmaceuticals & Agrochemicals

Introduction

Whilst efficiency is extremely important when conducting any form of parallel synthesis, library synthesis in support of medicinal chemistry programs can add considerable challenges due to the wide scope of the chemistry utilised. Any automated system will need to be very flexible to be able to support this. Chemspeed's Swing platform meets the flexibility and efficiency needs of such automated medicinal chemistry library synthesis departments by combining efficient liquid handling with a hugh range of potential formats (including custom developments) for housing reagents and conducting reactions. Herein we describe the synthesis of libraries from 96 to 720 compounds using a range of chemical transformations (Figure 1).

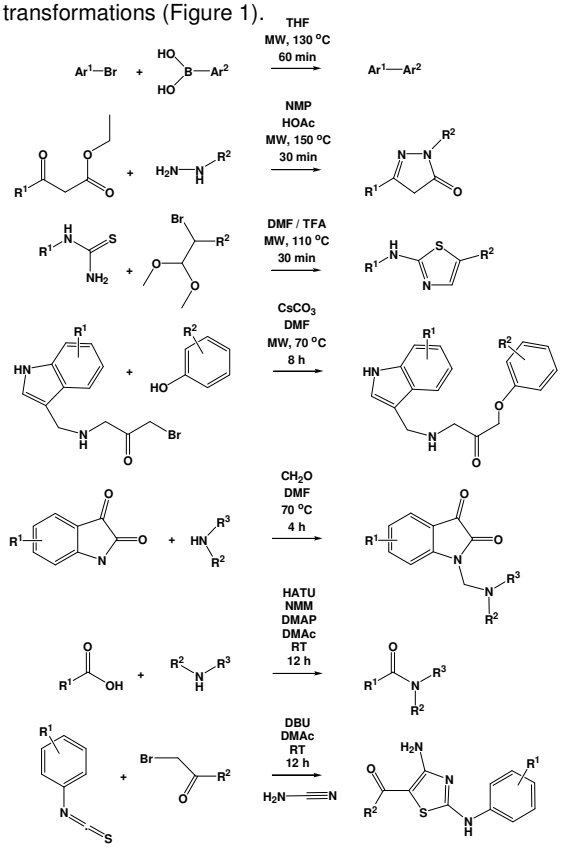


Figure 1. The diversity of typical chemical transformations routinely carried out on the Swing platform.

Experimental

Reactions are carried out on a 0.1 and 0.3 mmol scale, all reagents are handled as solutions and dispensed with Chemspeed's 4-needlehead (Figure 2). The tray of the Swing is layed out (Figure 2) with reagent storage in 360 x 8 mL vials for building blocks, 30 x 60 mL vials for scaffolds and 6 x 1000 mL for larger volume reagents. Reaction vessels are either standard 48 well MTP, or custom racks containing 48 x 6 mL vials (again with a MTP footprint) for microwave synthesis. Reactions are carried out off-line on dedicated heater / shakers or in microwave reactors allowing greater throughput. Once the system has done its pipetting into 2 MTPs they can be removed and undergo reaction whilst other blocks are being prepared.

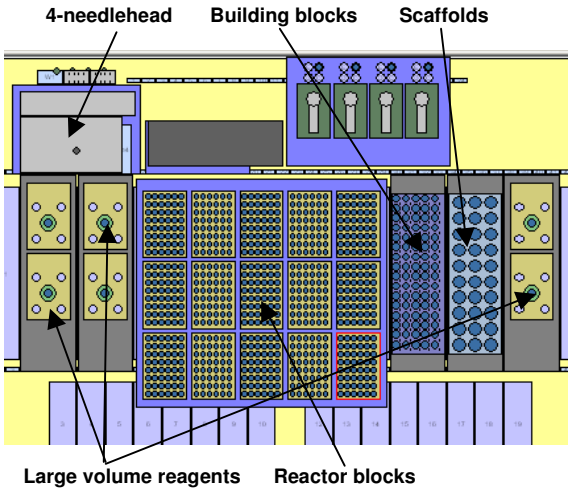


Figure 2. The set up of the Swing tray for reaction preparation.

After the reactions are complete as little preparatory work as possible is done before HPLC analysis (Figure 3). If reactions are conducted in HPLC compatible solvents and contain no solid material, the plates can be loaded directly onto HPLC autosamplers. Whilst incompatible solvents are evaporated and the residue redissolved in up to 5 mL of DMSO. Samples containing solids are filtered using 48-well filter plates.

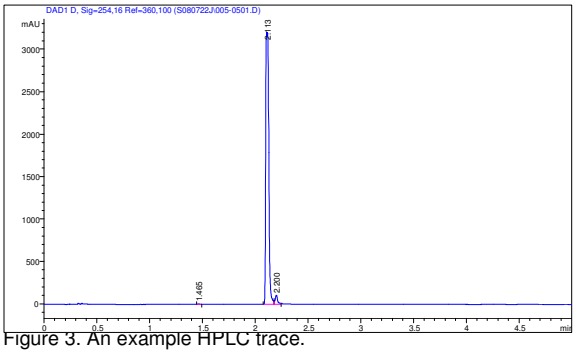


Figure 3. An example HPLC trace.

Conclusions

The efficient production of compound libraries only becomes possible when all the bottlenecks in the process are ironed out. Chemspeed's Swing platform is an excellent solution for releiving such bottlenecks in reaction preparation. And combined with a large reagent repository, microwave synthesis capability, high throughput work up and analysis, and appropriate data management software, can contribute to output of around 3500 compounds per person per year. [1]

References

1. M. Koppitz., *J. Comb. Chem.*, **2008**, 10, 573-579

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Optimising Reaction Conditions for the Asymmetric Transfer Hydrogenation of C=O Bonds on the ASW-2000

Helen A. McManus, Sarah M, Barry, Patrick J. Guiry. Department of Chemistry, UCD, Dublin, Ireland
Pher G. Andersson. Department of Organic Chemistry, Uppsala University, Uppsala, Sweden
Jake Grace. **Chemspeed Technologies**, Northampton, UK

Pharmaceuticals & Agrochemicals

General

The asymmetric reduction of carbonyl groups to form enantiopure secondary alcohols is a key process in synthetic organic chemistry. [1] In recent years catalytic asymmetric transfer hydrogenation [2] has established itself as the method of choice for these syntheses. It is operationally simple and the hydrogen sources generally employed (IPA, HCO_2H) are non-hazardous, easily available and cheap. Although many catalysts have excellent substrate scope, a single system is yet to be found that is applicable to the huge range of transformations of interest, and screening is a necessary tool to find optimum conditions for the substrate in question. Herein we describe work done to optimise the catalyst system employed for the enantioselective reduction of acetophenone, using pyrrolidine-oxazoline derived ligands (Figure 1) and several metal precatalysts. [3]

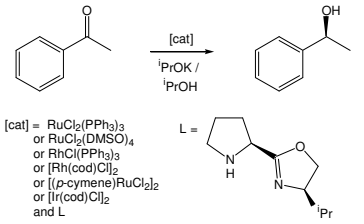


Figure 1: The asymmetric transfer hydrogenation of acetophenone with pyrrolidine-oxazoline ligands.

Experimental Set-Up

All reactions were carried out under an atmosphere of dry nitrogen on a Chemspeed automated synthesizer, equipped with 2 reactor blocks supporting 16 x 13 mL arrays of glass reactors (Figure 2). The metal precursors (5.0 µmol) were placed in one reactor block and to these were added ligand (as a solution in IPA) and dry IPA (total volume ~ 3 mL). The resulting mixtures were heated at reflux for 30 mins and after cooling to 25 °C, this catalyst solution (2.5 µmol) was added to the second reaction block, to which acetophenone (0.5 mmol) and dry IPA (3.4 mL) had previously been added. ^{i}PrOK (12.5 µmol) was added to initiate the reactions. Samples were taken while vortexing at 1 hr and 10 hrs and analysed by chiral GC for conversion and ee. The reaction time was 10 hrs.

Figure 2: Array of Chemspeed 16 x 13 mL glass reactors used in the study.

Results

Six metal complexes of ruthenium, rhodium and iridium were screened with L (Figure 1) to find the optimal metal precursor for the system. The results are collected in Table 1: $RuCl_2(PPh_3)_3$, $RuCl_2(DMSO)_4$, $RhCl(PPh_3)_3$ and $[Rh(cod)Cl]_2$ were all found to be inactive. $[(p\text{-cymene})RuCl_2]_2$ gave poor conversion (2 %) and moderate ee (62 %), entry 1. $[Ir(cod)Cl]_2$ gave more promising results, 79 % conversion and 43 % ee after 10 hrs, entry 2, and the reaction conditions were optimised using this metal-ligand combination. Conditions were varied by changing temperature, catalyst loading and metal to ligand ratio. Changing the metal to ligand ratio had very little influence on conversion or ee, entries 2-5. An attempt to increase the ee by lowering the temperature and increasing catalyst loading, entry 6, was unsuccessful. Halving the amount of base initiator had a small positive effect on the ee, but degraded the conversion, entries 7 & 8. Increasing the catalyst loading from 1 – 2 mol % gave increased yield, but had no effect on ee, entries 7 & 9.

	Metal	M / L	Con (%)	ee (%)
1	$[(p\text{-cymene})RuCl]_2$	2	2	62
2	$[IrCl(cod)]_2$	1.2	79	43
3	$[IrCl(cod)]_2$	2	80	43
4	$[IrCl(cod)]_2$	3	78	42
5	$[IrCl(cod)]_2$	4	84	42
6[a]	$[IrCl(cod)]_2$	2	65	41
7	$[IrCl(cod)]_2$	2	63	42
8[b]	$[IrCl(cod)]_2$	2	19	49
9[c]	$[IrCl(cod)]_2$	2	88	41

[a]Acetophenone:base:metal = 20:5:1; temp = 0 °C; [b]Acetophenone:base:metal = 200:2.5:1; [c]Acetophenone:base:metal = 100:5:1

Table 1: Results of the optimisation of conditions for the catalytic transfer hydrogenation of acetophenone.

Summary & Conclusion

Chemspeed's automated synthesizer is the ideal tool for fast and reliable optimisation of reaction conditions in the catalytic asymmetric transfer hydrogenation of acetophenone. A variety of metal precursors have been screened with a new set of ligands and the reaction conditions have been optimised. In this study $[Ir(cod)Cl]_2$ was the most active precursor, whilst $[(p\text{-cymene})RuCl_2]_2$ gave the highest ee.

References

[1] Ohkuma, T., Kitamura, M., Noyori, R. *Catalytic asymmetric synthesis*; 2nd ed. Wiley: New York, 2000; pp 34 – 83.
[2] Noyori, R., Hashiguchi. S., *Acc. Chem. Res.*, 1997, 97 – 102.
[3] McManus, H. A., Barry,S. M., Andersson, P.G., Guiry, P. J., *Tetrahedron*, 2004, 3405 – 3416.

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201

Automated, Microwave Assisted Alkene Synthesis via Wittig Reaction: Unattended Library Synthesis on Chemspeed SWAVE Synthesizer

Julien Gros, **Chemspeed Technologies**, Augst, Switzerland

Pharmaceuticals & Agrochemicals

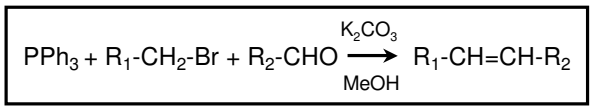
General

The Wittig reaction is an efficient method for alkene synthesis, which can be completed up to ten times faster via microwave irradiation compared to conventional heating.

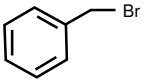
Objective

- Fully unattended, automated synthesis via Wittig reaction in 24 vials on the SWAVE.
- Compare the reactivity of different alkyl halides and aldehydes.
- Assess the existence of a "cooling while heating (cwh) effect".

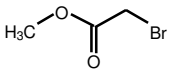
Reaction sketch



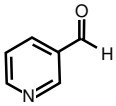
Alkyl halide 1



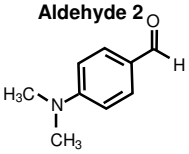
Alkyl halide 2



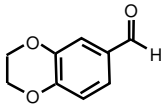
Aldehyde 1



Aldehyde 2



Aldehyde 3

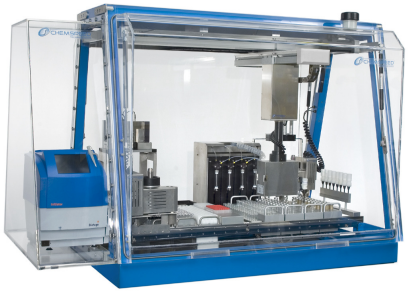


Experimental Set-Up

- 3 aldehydes x 2 alkyl halides → 6 compounds
- Cooling while heating on / off → 12 samples
- Each sample duplicated → 24 samples
- Automated sequential workflow:
  - Precise* dispensing of solid and liquid reagents
  - Cap, crimp, transport vial to microwave
  - Heat for 5 min at 150°C with magnetic stirring
  - Prepare next reaction mixture while heating
  - Transport vial back from microwave to rack and transport next vial to microwave
  - Decap all vials at the end of the application

*Examples:

	Target amount	Actual dosing range
Aldehyde 2	89.5 mg	89.7 - 91.0 mg
PPh_3	393.4 mg	393.1 - 394.6 mg

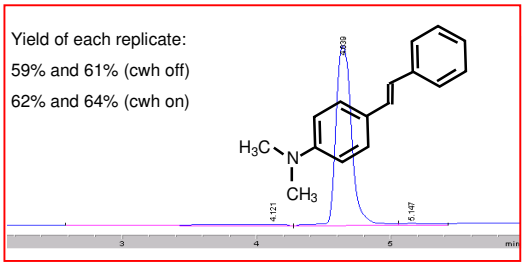


Chemspeed SWAVE synthesizer

Results

- All samples were analysed by LC/MS and yields determined by the internal standard method.
- The average yield (%) of every two replicates is reported in the following table.

	Alk. hal. 1 cwh off	Alk. hal. 2 cwh off	Alk. hal. 1 cwh on	Alk. hal. 2 cwh on
Aldehyde 1	63	86	61	84
Aldehyde 2	60	72	63	68
Aldehyde 3	51	63	57	61



- Bromoacetate (alk. hal. 2) is more active than benzyl bromide (alk. hal. 1): the nucleophilic substitution of Br^- by PPh_3 is indeed facilitated by the α-carbonyl group.
- Lower yields are obtained with Aldehyde 3 compared to the other aldehydes, which can be explained by - I and - M effects.
- Cooling while heating doesn't have any significant effect.

Conclusion

Microwave assisted synthesis of 24 samples via Wittig reaction was successfully automated and performed in 4 hours using only 1/16th of the vial capacity of the SWAVE.

Results are in accordance with literature and theory [1].

References

[1] www.biotagepathfinder.com - Wittig Olefin Synthesis

Chemspeed Technologies • www.chemspeed.com
Headquarters • Rheinstrasse 32 • 4302 Augst • Switzerland • Phone +41 61 816 95 00 • Fax +41 61 816 95 09
U.S. Office • 113 North Center Drive • North Brunswick • NJ 08902 • U.S.A . • Phone +1 732 329 1225 • Fax +1 732 329 1226
U.K. Office • Caxton House, Northampton Science Park • Kings Park Road • Northampton, NN3 6LG • U.K. • Phone +44 1604 654 200 • Fax +44 1604 654 201