

## SOPHAS – An Innovative Solution to Automation of Organic Synthesis

a report by

**Zinsser Analytic GmbH**

SOPHAS® (solution and solid phase synthesiser) represents a new generation of automatic synthesisers for solid and solution phase synthesis. It can be used for synthesis development, as well as a high-throughput synthesiser, to synthesise up to 864 compounds in a single run. The unique filtration technique and liquid-handling features and its open architecture allow the use of any chemistry or synthesis strategies with maximum flexibility.

### The Idea Behind SOPHAS

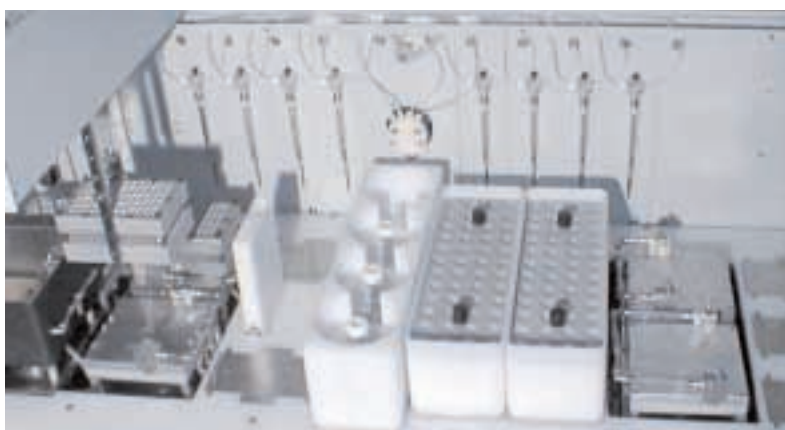
SOPHAS started as a development project when only a few synthesisers for organic synthesis were available. They were mostly peptide synthesisers with modified reactors, featuring heating and cooling and mechanical agitation. Most of them were following the original idea of the simultaneous multiple peptide synthesiser (SMPS) 350, which was introduced in 1989 by Zinsser Analytic. They all had limitations in, for example:

- throughput (12 to 96 reactors);
- chemistry (only one or two system liquids, limited number of reagents);
- speed (slow liquid deliveries, slow in reaching reaction temperatures);
- capacity (only one reactor block);
- versatility (fixed, unchangeable layout of the workbench); and
- flexibility (inflexible peptide chemistry-orientated software).

The chemists were looking for suitable tools to cope with the increasing demand of new compounds to be synthesised. They were demanding, for example:

- a choice of various reactor types with inert conditions, variety of volumes, reflux possibilities;
- higher throughput (256, 384 and more synthesis per run);

**Figure 1: SOPHAS® Workbench with Robotic Arm Transporting a 96-well Reactor Block to a Vortex-heating Station**



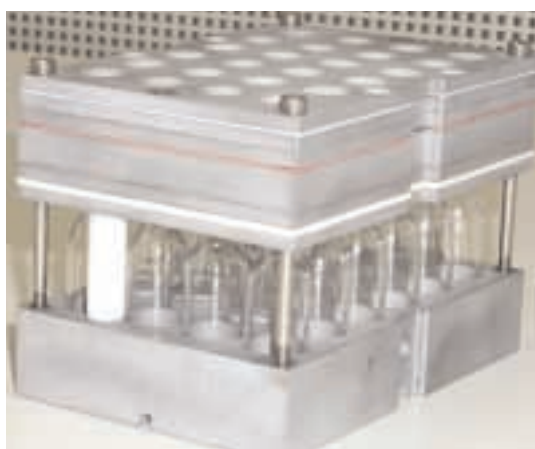
- flexibility of the layout of the workbench (monomer positions, reagents);
- more space on the workbench for additional steps such as cleavage, solid phase extraction;
- comfort in handling (software and hardware);
- flexibility in chemistry (inert conditions, liquid synthesis, scavenger addition); and
- reliability of hardware and software.

Inspired by discussions with many chemists in combinatorial chemistry and with Zinsser Analytic's experience in software and hardware development of liquid-handling systems, the engineering project of SOPHAS was originated with a new hardware concept.

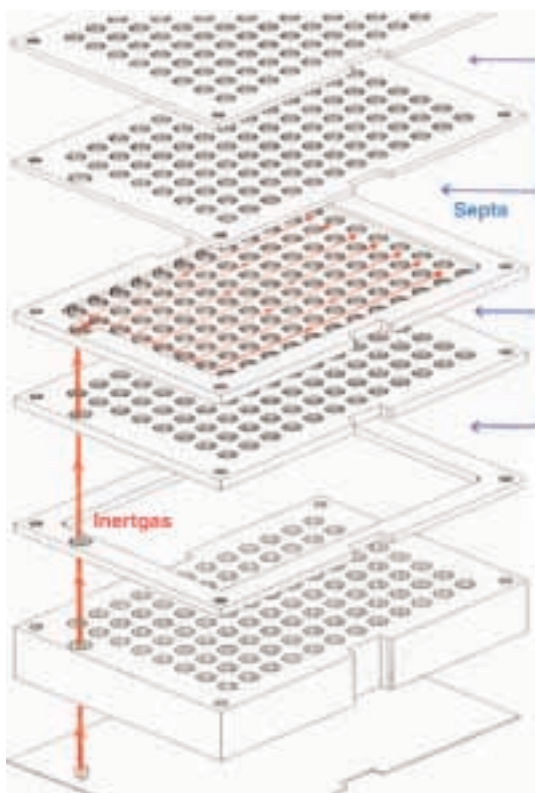
SOPHAS is based on an X,Y,Z liquid-handling robot offering two workbench sizes – 120cm and 200cm long – with an integrated robotic arm and four independent unique three-channel pipetting probes with variable spacing. A six-way valve organises the delivery of solvents and gases (four system solvents of any choice, two gases such as nitrogen and argon). A unique three-channel probe was engineered that can supply three media (reagents, vacuum, gases) simultaneously, while the centre channel is designed for inverted filtration. In all work positions of the racks



**Figure 2: Desyre® Reflux Reactor Block with 24 Reactors (7ml)**



**Figure 3: Schematic of the Desyre® 'Sandwich' Construction**



and reactor blocks, inert gas (argon or nitrogen) is supplied automatically. For reliable mixing, high speed, low noise vortexers with heating or cooling are integrated in the workbench. Controlled by scheduling software, the robotic arm moves the reactor blocks to the various workstations (parking, cooling, heating, washing, reagent addition, cleavage, etc.).

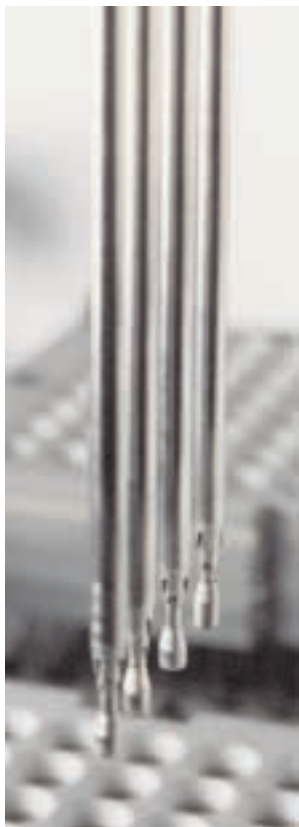
The integrated robotic arm with a payload of more than 1,500g is stronger than most common laboratory robots. It can execute pick and place functions all over the workbench, pick up additional tools (sensors, etc.) and carry the reactor blocks to the various synthesis modules on the workbench (vortexers with heating and cooling, park and cleavage positions).

Special sandwich or layered reaction blocks with the footprint of standard 96-well plates have been designed for eight, 24, 48 or 96 glass or polytetrafluoroethylene (PTFE) (Teflon) reactors (1–40ml). For sealing pierceable septa of modified silicones, polyurethane, PTFE and fluorinated ethylene propylene (FEP) derivatives are provided with specific resistance to the solvents and reagents involved in synthesis. The carrier and sealing plates are made from special aluminium for fast heat transfer. The sealing plates and septa can be combined to the special requirements of the synthesis.

Besides the seals, the reaction block can have a gas chamber in between two layers of seals to block off moisture and oxygen. A 24-well reactor block has been introduced recently with special glass reactors and a cooling chamber that is flooded automatically with cold air or nitrogen during the heating and vortexing cycle of the reaction to allow efficient refluxing. On a standard SOPHAS system, nine reactor blocks can be processed simultaneously. When using reactor blocks with 96 reactors each, 864 syntheses can be run in parallel. Each block can have its own chemistry. Reaction time, temperature gradients and washing cycles are defined individually for each block in the software.

The inverted filtration allows the transportation of the reaction blocks with the robotic arm. The triaxial probes have a filtration and delivery channel in the centre, surrounded by two additional coaxial channels. The centre channel filters through a 20 $\mu$  stainless steel mesh, which avoids the possibility of clogging and cross-contamination by resin, as the beads only have minimum contact with a small area of the wires of the filter mesh. The probes can deliver and aspirate reagents, solvents and gases alternatively and simultaneously. This allows mixing with nitrogen during the addition of reagents or addition and mixing of two reagents/solvents at the same time, for example. The probes, also supported by software calculations, provide automatic adjustment of the inert gas blanket inside the reactor. With the triaxial probes, a new, highly efficient washing procedure has been introduced into solid phase synthesis.

The newly developed vortexers with a specially chosen amplitude and high speed (up to 1,800rpm) achieve reliable and thorough mixing for solutions (and generate separations) and solid phase reactions, without crushing the resin. The vortexer functions – speed, temperature, fixation of the reactor block, positioning for liquid handling and control of inert gas and nitrogen for cooling – are controlled individually by internal microprocessors that communicate to the central controller and software of SOPHAS. The standard configuration of SOPHAS has five hotplate vortexers (ambient to 150°C) and one refrigerated vortexer (-40°C or -80°C).

**Figure 4: Sophas Triaxial Probes**

The system performs cleavage automatically at the end of the synthesis and distributes the samples in deep well plates. Purification by automatic solid phase extraction can be included as an option.

Modern WindowsNT software with simple drag and drop techniques lets the user design their synthesis on the screen easily, copy and modify stored syntheses and even modify a synthesis in progress without stopping the run. A synthesis run is composed by combining methods, reagents and functions using the Windows drag and drop functions. Files can be imported from external databases (Excel®, Oracle®, etc.), from molecular design software or as American standard code for information interchange (ASCII) files. A simulation run checks the feasibility and correct data input and calculates the time, total demand of solvents and reagents and the waste volume of the synthesis run.

The software enables the user to optimise all hardware parameters. To judge the running synthesis, the screen shows the workbench with all the modules in place. Colour changes visualise the actual steps of a synthesis. All synthesis steps are protocolled. In the case of a breakdown (power failure) during the run, the system can be restarted automatically or manually at the last completed step.

#### Experience with SOPHAS

Users of SOPHAS are experiencing good synthesis results. Various chemistries have been processed

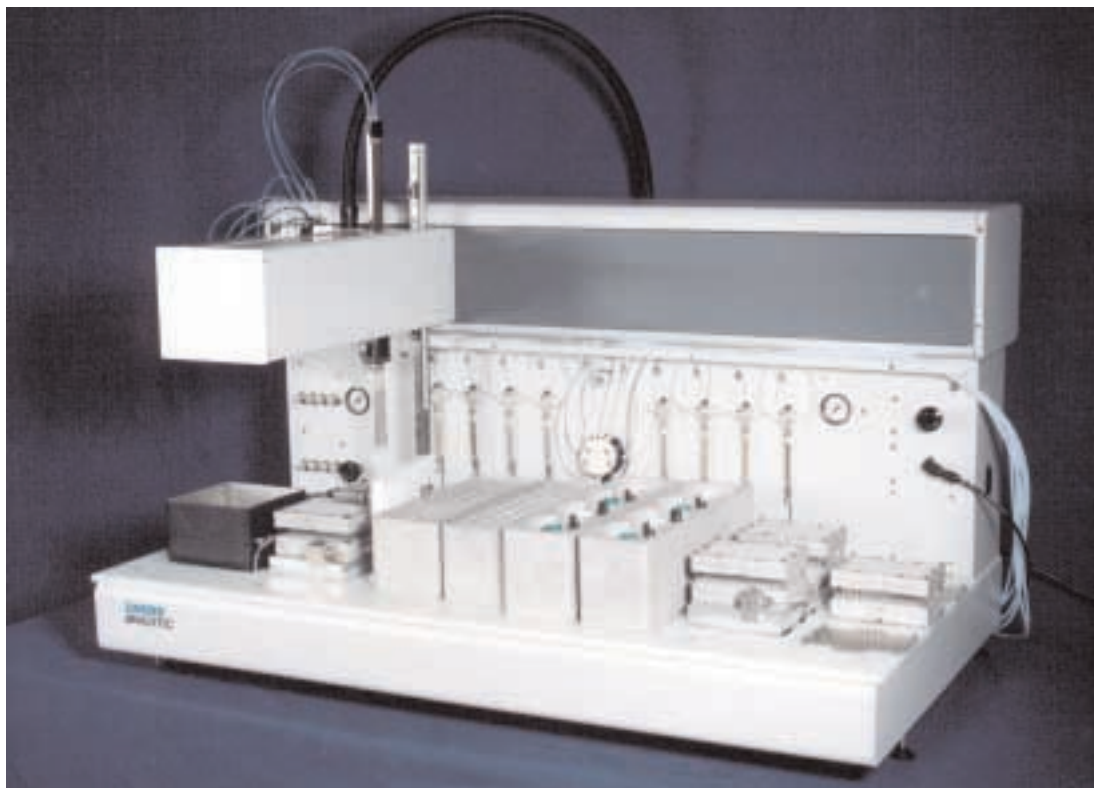
**Figure 5: Pick-up Powder Tool for Distribution of Synthesis Resin and Scavenger Resin**

successfully on SOPHAS, such as

- amide, sulphonamide, urea formations;
- reductive animation;
- palladium coupling (Heck, Suzuki);
- mitsunobu;
- Michael addition;
- n-alkylation;
- n-alkylation of amide potassium bis(trimethylsilyl) (KHMDS); and
- deprotection (9-Fluorenylmethoxycarbonyl (Fmoc), tert-butyloxycarbonyl (Boc), b-(trimethylsilyl)-ethoxycarbonyl (TEOC)).

The synthesis results all showed remarkable high purity of the final product. The high quality of the synthesis product can be seen as a result of the precise liquid handling, fine control of the reaction temperatures, reliable mixing and unique washing procedures allowed by the SOPHAS hardware and software. Instead of just adding a solvent and after a short soak time aspirating the solvent under vacuum through a frit on the bottom of the reactor, SOPHAS aspirates the washing solvent through the centre channel of its probe and simultaneously adds washing solvent from the second channel and nitrogen through the third channel. During this process, the resin is 'tumbled' around, as in a washing machine. There is no sedimentation of resin; it is always freely floating in the washing solvent. At the end of each washing step, resin that might stick to the mesh of the filter is blown off by nitrogen and

Figure 6: SOPHAS Standard System with 120cm-long Workbench



washed off from the side of the probe by a small flush of solvent before the probe moves out of the reactor.

The washing technique of SOPHAS is:

- thorough;
- inert (always under gas);
- fast (four reactors at a time);
- efficient (no resin loss);
- reliable (no cross-contamination); and
- safe (the resin always stays wet).

### Options

SOPHAS is designed as an 'open workbench', allowing the user to implement additional tools. It is possible to pick up with the robotic arm and there are sensors to monitor the temperature and pH value in each reactor and save them in a database. Also, the arm can pick up a powder pipette to fill the reactors with resin or add scavenger resins during the synthesis. Pick-up tools are also available for monitoring the synthesis run, i.e. collecting samples from the reactors into chromatography vials or plates for high-performance liquid chromatography (HPLC) analysis or spotting them directly on thin-layer chromatography (TLC) plates. A new pick-up tool is becoming available for the detection of phase separation in solutions.

On the platform, temperature-controlled positions can be provided for reagents and barcode identification of the monomers can be installed.

### Conclusion

With SOPHAS, a new generation of synthesisers has been created that simultaneously produces a large number of compounds in a single run in semi-micro scale under inert atmosphere.

As the reaction blocks can be moved on the platform to the various synthesis modules, all components of the hardware are used more economically than on current systems. This has increased the throughput dramatically, compared with other systems (864 versus 24, 48 or 96). The possibility of applying different types of synthesis parameters to different reaction blocks in a single synthesis run makes it an extremely flexible synthesis tool.

In a single run, different chemistries and strategies can be tested for a certain synthesis target by using varying parameters, volume gradients, different reaction times, temperatures, washing procedures and coupling strategies. The unique filtration and washing procedures allow new and more efficient procedures for the washing steps of the synthesis to achieve a better end-product.

The open design makes SOPHAS ideal for solid phase synthesis as well as for solution phase synthesis and, because of its capability in handling dry powders, synthesising catalysts. In combination with the pick-up tools for sampling for HPLC analysis or direct TLC spotting, SOPHAS is becoming a valuable tool for synthesis and process development. ■