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Low Temperature Chemistry: Keep Your Cool

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Low temperature chemistry

Keep your cool

Experts in very low temperature chemistry discuss the myriad benefits of this challenging technology with Dr Cynthia Challener

In fine chemical synthesis, controlling reactivity in order to maximise selectivity for the desired product is paramount for the development of costeffective processes. The method of control varies according to the chemistry involved but careful selection of raw materials, catalysts and solvents and the use of certain pressures and temperatures often play important roles.

The use of temperatures down to -80ºC or even -100ºC can be very beneficial for certain processes.In reactions where different isomers are readily produced at room temperature, very low temperatures can often allow selective formation.

In other cases, highly reactive intermediates will decompose at room temperature but will be stable enough at cold temperatures to enable the reaction to occur in good yields. Processes that involve gases can also be much more manageable when carried out at temperatures below the boiling point of such substances.

“We see low temperature technology as one of many enabling technologies with potential applications across all market sectors,” observes Tony Jones, head of marketing and sales in Saltigo’s pharma business. “As our customers move towards more sophisticated molecules with more challenging synthesis requirements, there is growing interest in low temperature technology.”

Dr Adriano Indolese, head of process development for RohnerChem agrees that low temperatures make it possible to achieve the level of selectivity necessary for the production of the increasingly complex molecules required by the pharmaceuticals, agrochemicals and other fine and speciality chemical sectors.

For Archimica, cryogenic chemistry is a very important core technology that makes it possible to produce a wide range of speciality building blocks and intermediates. Dr Andreas Meudt, managing director of global R&D and new business development, says that the technology’s real value lies in combination with expertise in organometallics and selective reductions. Such chemistries allow the economic synthesis of a broad variety of products, like boronic acids, aldehydes, styrenes, halogenated products and many others.

Ash Stevens developed capability in low temperature chemistry in order to meet the specific needs of its customers. “This technology has become one important part of a general toolbox of technologies for the pharma industry,” says president and CEO Dr Stephen Munk.

Simply having cryogenic assets is not enough, however. Established expertise in this area and a broad portfolio of other technologies are required to deliver high quality products and services. Unlike the aforementioned large manufacturers, SynQuest Labs has developed expertise in the use of low temperature distillation processes.

“We specialise in the small-scale manufacture and purification of gaseous fluorinated molecules and have found that low temperature distillation is an extremely effective method for the quantities we work with," explains company president Rick Du Boisson. "Reactions with these reactive gaseous compounds may also require the use of cryogenic temperatures."

Low temperature processes are not suitable for all manufacturers of fine and speciality chemicals, however. The large-scale purification of the gases produced at lab- and pilot plant-scale by SynQuest, for example, would not be economically feasible using cryogenic methods. Instead, high pressure systems are employed.

Scaling up more traditional processes can pose challenges as well. For instance, vessels intended for low temperature operation require special attention. Areas where jackets, flanges or valves will be subjected to the low temperature conditions are of particular concern, according to Todd Aplin, R&D manager of Albemarle's fine chemistry services business. "Failure to properly match each material's expansion coefficients could result in leaks or other related problems," he says.

For those companies using liquid nitrogen to provide cooling, a choice must be made between applying it directly to the jacket and using liquid nitrogen to cool a heat transfer fluid.

"The cooling method will be dictated by the plant layout and the logistics of transferring the liquid nitrogen," says Aplin. In addition, the vent for the nitrogen gas must be located in a remote area with access limited to prevent worker exposure to oxygen-deficient atmospheres.

Most companies seem to prefer to use liquid nitrogen to cool a heat transfer fluid but some do cool directly. Saltigo, **Ash Stevens**, SynQuest and RohnerChem elected to use a secondary coolant to achieve low reactor temperatures. Materials of construction include hastelloy, stainless steel and labscale glassware.

Archimica, on the other hand, uses a specially designed cooling system which has liquid nitrogen flowing though metal tubes and does not require a secondary cooling system. The reaction mixture does not have any direct contact with the liquid nitrogen, but cooling is very efficient and fast, according to Meudt, and allows even lower temperatures than in secondary cooling systems.

Issues with increased solvent viscosities must also be considered, Aplin adds. Operating at low temperature conditions can result in surprisingly high solvent viscosities. This can and does have a negative impact on internal heat transfer coefficients. Figure 1 shows internal heat transfer coefficients for three typical solvents in a large reactor. A similar mass transfer coefficient effect also operates.

"Careful consideration of the geometry used for the addition of reactants and how the reaction mixture will be mixed are needed to help ensure that the large-scale operation will give results similar to the development work it was based upon," stresses Aplin. He adds that pre-cooling reactants to the desired operating temperature is helpful in preventing local 'hot spots' that can lead to problems with by-product formation and yield.

For example, halogen-metal (HM) exchange reactions, such as lithium-halogen exchange using *n*-butyl lithium (BuLi) and an aryl bromide, are commonly conducted at low temperatures for many reasons. BuLi can be sufficiently active that it reacts with solvent or other species instead of the desired starting material resulting in unwanted by-product formation. Once formed, the desired aryl lithium can be sufficiently unstable that its decomposition dominates the reaction.

"Unfortunately, using low temperature conditions does not guarantee the desired results," Aplin notes. "Low temperatures will typically prevent side reactions of the BuLi, but the aryl lithium intermediate can still have a limited stability". Aryl lithiums containing nitrogen can be especially unstable, so a continuous operation is preferred over batch in such cases.

He continues: “When scaling up HM reactions, one must develop a thorough understanding of the stability of the aryl lithium intermediate at a range of temperatures and times. Not only does this data provide acceptable operating ranges at full scale, it will also aid in troubleshooting any issues that may arise.” Aplin adds that the products from HM reactions can be very sensitive to the work-up conditions as well. At scale, it may be preferable to quench the reaction while at low temperature to avoid by-product formation. Meudt, however, disagrees to some extent.

“In more than 100 cryogenic reactions which Archimica has scaled up over the past ten years, the stability of the organolithium intermediate has never been an issue, even if the substrate contains other functional groups with nitrogen, oxygen or halide,” he says. “One key is the selection of a suitable solvent that can completely suppress side reactions like rearrangements to isomeric products under cryogenic conditions.”

In addition to these engineering challenges, there is also a strong perception in the industry that cryogenic technologies are too expensive compared to the benefits they provide. Again, Meudt argues otherwise.

“In our experience, the cooling costs are far outweighed by higher yields and additional product purity. By combining cryogenic chemistry with other technologies like hydrogenations, enzymatic chemistry and cross-couplings, a broad variety of APIs and intermediates can be accessed by short and highyielding syntheses,” he says.

Archimica’s investments in cryogenic equipment reflect this positive view. It has more than 60 m3 of -100ºC reactor volume, including eight full-scale reactor trains (8,000 litre cryogenic reactors in both hastelloy and stainless steel), plus pilot (500-3,000 litres) and kilo-lab (50 litres) equipment. With its cooling technology, temperatures of -80°C can be achieved in very short time periods while very small (±2°C) temperature ranges can be kept for very long periods of time, according to Meudt.

Whilst Archimica has broad capabilities in cryogenic chemistry including lithiations *ortho* to halogens, lithiations with BuLi, other alkyl lithiums or LDA and reductions with LAH, NaBH4, Selectride and other modified reagents, its unique technology for lithiations using lithium granules rather than BuLi is of particular interest.

The company developed a special system which includes a special metal tube incorporating an internal valve to provide an inert atmosphere, for introducing the granules and other reagents without exposure to air. “Developing this was crucial to the success of this method, as any exposure of the granules to air results in decreased yields,” Meudt remarks.

With the special delivery system, yields for lithiations using the lithium granules are often 10-20% higher than those done with BuLi. The alkyl lithium is produced *in situ* and is present in only minute concentrations at any given time. As a result, it reacts almost immediately, leading to higher yields and selectivities (Figure 2).

Another benefit is the ability to create an almost endless array of possible lithiating reagents. Commercially available alkyl lithiums are limited. With this approach, however, Archimica can, for example, produce cyclohexyl lithium or hundreds of different reagents, then choose the one that provide the highest selectivity and yield for a given reaction.

This means increased yields and cost savings. In addition, the cost of the lithium granules or the alkyl halide used to form the *in situ* lithiating reagent is lower than that of the pre-formed alkyl lithium reagents, so further savings can be achieved. The technology does not work for every single lithiation reaction but Meudt believes that there could be significant cost savings where it replaces BuLi. In Archimica's experience, the probability of success for this technology is approximately 80%.

Like lithiation reactions, Friedel-Crafts acylation chemistry has been widely used for the synthesis of speciality chemicals. Aplin says that this has not been done at low temperature but Albemarle has developed such a process that allows access to superior products with less effort than more conventional conditions. One example is the acylation of an aromatic ether (anisole or diphenyl ether) with an acid chloride (acetyl chloride or propionyl chloride) using aluminum chloride in DCM.

"It is common to observe the formation of difficult to remove tarry by-products in carrying out this reaction at 25°C. Conducting the reaction at -40°C and carefully quenching with water while still at a low temperature results in the elimination of tar formation and gives a higher desired *para* regioselectivity in the isolated product," Aplin says. Even at low temperature, the acylation of an activated aromatic using aluminum chloride and acid chloride goes to completion in about one hour.

In the last two years, Albemarle has added 3,750 litres of non-GMP capacity to complement its existing cryogenic pilot facility in Tyrone, Pennsylvania. The company also added over 10,000 litres of cryogenic cGMP capacity to its multi-product API and intermediates facility in Orangeburg, South Carolina. Reactions are typically run at internal temperatures of -70°C to -80°C in these new reactors (*pictured*).

Saltigo has also invested in low temperature chemistry in response to demands from the market for a suitable range of technologies for scale-up and commercialisation. "Our experience in low temperature chemistry makes it possible to predict scale-up characteristics accurately, maximising process yields, improving productivity and attaining an exceptionally high degree of selectivity with associated high product quality," Jones claims.

The company's low temperature equipment, ranging from 100 to 12,000 litres, has been designed to be integrated into both its dedicated product units and its multipurpose facilities. Internal reactor temperatures down to -100°C can be reached.

"We can increase our cooling capacity to match the thermodynamics of each reaction by employing electrically-driven cryogenic compressor units," says Jones. As well as giving excellent low temperature control, these units are designed to operate efficiently and thus minimise energy costs. Saltigo carries out a very broad range low temperature reactions,
for example reductions with complex hydrides, every form of organometallic, Grignard and catalytic reactions and reactions with different Lewis acids.

RohnerChem's capability in low temperature chemistry relates to its core expertise in the synthesis of speciality aromatic building blocks for APIs and other applications, according to Indolese.

"Cryogenic technology makes it possible for us to synthesise aromatic building blocks not easily accessible via traditional chemistry. We consider it to be an extension of our core business offering," he says. The company also has expertise in the production and use of organometallic catalysts and Grignard reagents.

Grignard reactions, lithiations, Suzuki couplings, carboxylations and reactions with acyl chlorides are key examples of the low temperature chemistry that Rohner carries out in its 60, 400 and 2,500 litre hastelloy reactors and at laboratory scale (Figure 3). Most reactions are done at low temperature in order to achieve higher levels of selectivity, which result in improved yields and purities.

Ash Stevens offers a broad range of technologies and considers low temperature chemistry to be an important tool that enables the company to produce APIs in the most efficient and cost effective manner possible. “Our cryogenic capabilities are integrated with our other offerings, which magnifies the benefits they provide,” states Munk.

One specific example is the use of the Matteson homologation reaction to prepare a chiral boronic ester, a reaction that involves formation of a C-C bond with very high asymmetric selectivity. This chemistry proceeds at low temperature and **Ash Stevens** uses it in the synthesis of the API bortezomib, which is found in the drug Velcade.

Cryogenic temperatures are necessary to provide the desired level of enantioselectivity, Munk adds. “For us, the real power of low temperature chemistry is the ability to induce a chiral centre with very high selectivity. There is only a very small difference in energies between enantiofaces when inducing a chiral centre; carrying out reactions at such a low temperature makes it possible to differentiate between these energy states and follow one path selectively.”

The company also carries out other organometallic chemistry at low temperature, such as lithiations with BuLi and reactions with LDA. Whilst the equipment it uses was not custom-built for **Ash Stevens**, Munk stresses that suppliers were extensively evaluated and the reactors and cooling equipment was chosen very carefully.

“I recommend that anyone looking to add cryogenic capabilities to their offerings spend time finding the right equipment vendor that best fits with his or her operations. You absolutely need a supplier you can trust and rely on,” he says.

Having access to reliable equipment is certainly a necessity when handling highly reactive substances such as elemental fluorine and other fluorinated compounds, which is the speciality of SynQuest. The company has developed many fluorinated compounds that have helped in the search for replacements for CFC and HCFC refrigerants, solvents for electronic applications, building blocks for synthesis of pharmaceuticals and fine chemicals and analytical reference standards, all of which are produced on a small scale.

Larger quantities of products requiring low temperature chemistry can be manufactured at the former Girindus site at Künesbeck in Germany, where SynQuest’s parent company, Central Glass of Japan, has a GMP facility. At that site, 100, 500 and 1,200 litre stainless steel reactors can be taken down to -80ºC.

At its own facility, SynQuest operates glass reactors of up to 100 litres. Typical low temperature chemistry here includes ammoniations with liquid ammonia and lithiations with butyl lithium. For processes using elemental fluorine, which is extremely reactive, temperature control is critical for both selectivity and safety.

“Even at -78ºC, it is sometimes difficult to achieve the preferred level of selectivity,” says Adam Alty, the company vice president.

In addition, a key raw material of the company - hexafluoropropene - exists as a gas, and low temperature reaction conditions are necessary for processes using this compound. SynQuest converts hexafluoropropene into several different building blocks used by the pharmaceuticals industry and other fine chemical-consuming sectors (Figure 4).

Many other substances manufactured at SynQuest are also gases and they require special distillation methods. The company has developed expertise in low temperature gas distillation for these products. The desired compound is separated from impurities by passing it through a condenser filled with dry ice in a liquid, often acetone. The purified product is collected in cylinders that are cooled with liquid nitrogen or dry ice to a temperature below the boiling point of the gas.

“This low temperature distillation method is a rather specialised technology and any employees operating the equipment must have special training,” Du Boisson comments. He adds that most people in the plant have well over ten years of experience in low temperature distillation processes.

Whether purifying or reacting a gaseous compound, synthesising a single enantiomer of a complex chiral molecule or controlling the selectivity of a process involving a highly reactive raw material, low temperature capabilities make it possible to achieve high yields of the desired product, often more cost-effectively than traditional methods.

“Although low temperature chemistry poses unique challenges to the process chemist and engineer, through careful study and planning, cryogenic operations can provide high value chemical products that may be difficult to access by other means,” Aplin comments.

And most of these manufacturers expect the demand for such capabilities to increase. “We clearly expect further growth in the use of cryogenic technologies but we also expect that the number of serious players in this field will come down to a few, in line with the ongoing focus of Big Pharma on few selected suppliers,” Meudt states.

“Further, we do not expect that biocatalytic or other new technologies, including microreactor technology, will be a serious threat to low temperature chemistry over the next decade. As we have the assets already and the cooling costs are only very small per kilo of product, the only real reason for microreactors should be higher yields and we have not observed this for all reactions tested so far.”