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Greener solvents for solid-phase organic synthesis

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Abstract: Solid-phase organic synthesis is an essential method for the rapid synthesis of complex biological structures and libraries of small organic molecules. However, it is often associated with the use of large quantities of problematic solvents for the removal of excess reagents and reaction by-products. Given that solvent will often be the biggest contributor to waste generated in the average pharmaceutical/fine-chemical process, its exchange for a more desirable alternative often presents the biggest gains in terms of reducing environmental impact. This review aims to explore recent approaches to performing solid-phase organic synthesis, and associated solid-phase peptide synthesis, in neoteric solvents and reaction media that present greener alternatives.

Keywords: green chemistry; greener solvents; ICGC-6; solid-phase synthesis; SPOS; SPPS.

Introduction

The concept of solid-phase organic synthesis (SPOS), where a chemical transformation is performed upon an insoluble solid-support, was first reported by the Nobel Laureate Bruce Merrifield more than half a century ago [1]. Since this seminal report, SPOS has found widespread application in many aspects of modern organic synthesis, proving to be a particularly invaluable tool in the rapid construction of complex biological molecules and diverse libraries of small organic compounds. As SPOS typically offers many advantages over conventional solution-phase synthesis; such as the ease of product isolation *via* filtration, the ability to use substantial excesses of reagents, to drive reactions to completion, and the ease of handling, which has allowed many aspects of SPOS to be automated [2].

SPOS does however, present a major issue in the fact that the resin must be washed between procedures to remove excess reagents and by-products, generating large quantities of contaminated organic solvent waste. Some commonly used solvents for this include the reprotoxic polar aprotic solvents, dimethylformamide (DMF), dimethylacetamide (DMA) and *N*-methyl pyrrolidone (NMP). These are all classified amongst the Substances of Very High Concern (SVHC) under Registration, Evaluation, Authorisation and restriction of CHemicals (REACH), meaning they are likely to see restrictions in their use in the near future [3, 4]. Other extensively used solvents for SPOS include dichloromethane and diethyl ether, which are widely regarded as highly problematic solvents and are a high priority for replacement in the context of green chemistry [5].

Additionally, within the pharmaceutical and fine chemical industry solvent use has been found to typically account for much of the waste generated by a typical batch chemical operation. Constable et al. [6] have previously reported that 80–90 % of the waste mass generated by typical batch chemical operations will

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often come from the solvent. More recently, estimates from the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS-GCIPR) have shown 56 % of the mass needed to produce 1 kg of an active pharmaceutical ingredient (API) will come from solvent [7]. Accordingly, the overall toxicity profile of a given process is often defined by the solvent, meaning exchange of a solvent for one with more desirable health, safety or environmental characteristics will often provide the biggest gains in terms of reducing the environmental impact.

This however, is not so simple in SPOS as the use of an insoluble solid-support places additional considerations on the solvent, when compared to traditional solution-phase chemistry. Most notably adequate solvation of the solid-support, more commonly known as swelling, which is often considered as the most important prerequisite for SPOS [8]. Inadequate swelling will result in poor active site accessibility and diminished reaction rates, due to poor mass transfer between the bulk solution-phase and the solid-support [9].

For the above reasons, there has been a significant amount of interest in recent years on more sustainable approaches to SPOS, particularly in the field of solid-phase peptide synthesis (SPPS), the most common application of SPOS [10]. Herein, this review aims to explore recent approaches to greener SPOS/SPPS, which focus on the use of alternative reaction media, such as water, greener organic solvents and compressed carbon dioxide, highlighting interesting approaches that have utilised a combination of green principles along the way. Sustainable approaches to peptide synthesis using solution-phase methods [11] as well as solventless means, such as ball milling [12, 13], have been omitted as this is beyond the scope of this review.

Water

The use of water as a reaction solvent in synthetic chemistry has received considerable attention in recent years [14]. Due to it being cheap, safe and environmentally benign, it is a highly desirable alternative to conventional organic solvents. As such, much of the early work on the development of greener SPOS has focused on its use, however, there are various challenges that need to be overcome for this to be achieved, particularly for SPPS. In SPPS the peptide is typically assembled from the *C*- to the *N*-terminus through an iterative method, by coupling suitably *N*-protected amino acids followed by their deprotection. Many protecting groups exist for this process, with the most commonly used examples being the *t*-butyloxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) groups, for solution- and solid-phase peptide synthesis respectively, both of which have very limited solubility in water. Additionally, adequate solvation of the solid-support by water is a very important consideration. For the above reasons the use of water in SPPS remained an unexplored challenge for many years.

Hydrophilic protecting groups

One of the earliest approaches to this has been the use of water soluble *N*-protecting groups and coupling agents. Various examples have been described within the literature for solution-phase peptide chemistry, but it was not until the work of Kawasaki and co-workers in 2001 that the entire process of SPPS in water was realised [15, 16]. This was in part only possible with the development of polyethylene glycol (PEG)-based resins, which being amphiphilic in nature are more easily swollen by a wider variety of solvents [17]. The 2-(phenyl(methyl)sulfonio)ethoxycarbonyl (Pms) group **1** was developed as a water soluble *N*-protecting group that can be easily removed by treating with a 5 % sodium bicarbonate solution (Fig. 1). The endogenous opioid peptide Leu-enkephalinamide (H-Tyr-Gly-Gly-Phe-Leu-NH_2) was prepared in a 61 % yield, using the water soluble 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride (WSCD) and *N*-hydroxy-5-norbornene-2,3-dicarboximide (HONB) coupling reagents on a PEG-grafted Rink amide resin. Notably, the addition of a non-ionic surfactant (0.2 % Triton X) was necessary for the coupling and washing procedures

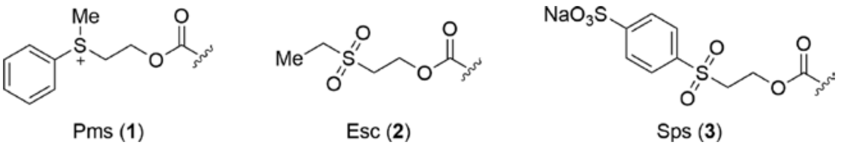

Fig. 1: Water soluble protecting groups reported by Kawasaki and co-workers.

to suitably enhance the swelling of the resin in water. Additionally, the method for preparing the Pms-amino acids was not applicable for Met or Cys, however, this was addressed in a subsequent communication [18].

The Pms protecting group was unfortunately found to be rather unstable, due to the onium salt present. For this reason, Kawasaki and co-workers later went on to develop additional protecting groups for SPPS in water (Fig. 1). The 2-ethanesulfonylethoxycarbonyl (Esc) **2** group was found to be moderately base labile and moderately polar, giving it good solubility in aqueous and organic solutions, producing the test peptide Leu-enkephalinamide in a 71 % isolated yield [19]. However, the lack of aromatic functionality, excluding the aromatic amino acids, made it undesirable at the time as they are not detectable by optical absorbance spectroscopy, making them unsuitable for automated SPPS. This resulted in the development of the 2-(4-sulfophenylsulfonyl)ethoxycarbonyl (Sps) **3** group which was found to have high base lability and high water solubility, and was used to produce the Leu-enkephalinamide peptide in 61 % yield [20]. Whilst these represented highly promising results for SPPS in water, none of the conditions outlined produced Leu-enkephalinamide in an isolated yield greater than methods utilising Fmoc-protected amino acids in organic solvents.

Fmoc- and Boc-protected nanoparticles

The additional steps associated with the synthesis of hydrophilic protecting groups are not favourable in the context of green chemistry due to the desire to prevent waste, reduce energy consumption and minimise derivatisation in synthetic procedures. For these reasons Hojo and co-workers sought an alternative approach for SPPS in water using Fmoc- and Boc-protecting groups, which are widely used in peptide synthesis and are commercially available, but as previously mentioned are sparingly soluble in water. Hojo and co-workers therefore prepared aqueous dispersions of Fmoc-protected amino acids, using zirconium oxide beads and PEG in a ball mill, generating nanoparticles between 250 and 500 nm in diameter, with the hope that the increased surface area of the nanoparticles would improve their homogeneous mixing with the SPPS resin in water [16, 21].

The prepared water-dispersible nanoparticles were then utilised in the synthesis of Leu-enkephalinamide, producing the target pentapeptide in 67 % yield. Importantly, control reactions using unprocessed Fmoc-amino acids and unprocessed Fmoc-amino acids in the presence of PEG failed to produce the target peptide in significant quantities. Additionally, the use of a non-ionic surfactant (0.5 % Trition-X) for the preparation of the nanoparticles and deprotection steps produced Leu-enkephalinamide in a much improved 79 % yield. It must also be mentioned that Hojo and co-workers demonstrated that the dispersed nanoparticles can be easily removed from the aqueous waste stream, through filtration or ultracentrifugation. Subsequent publications by Hojo and co-workers have also gone on to demonstrate the application of similar water-dispersible Boc-nanoparticles, as well as the use of efficient microwave heating to reduce coupling times from 1 h to 3 min [22, 23].

Enzymatic synthesis

The use of enzymes, specifically proteases, for the construction of peptides on solid-supports was first reported by Flitsch and co-workers [24]. The use of these enzymes presents a significant challenge as the equilibrium between amide bond formation or hydrolysis, for proteases in water, lies largely towards hydrol-

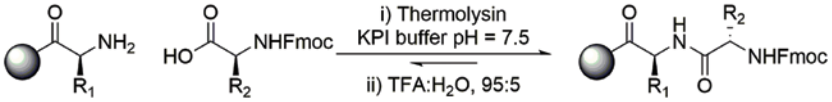

Fig. 2: Thermolysin catalysed peptide synthesis upon a solid support.

ysis. Traditionally, this was overcome using organic co-solvents or using highly concentrated solutions. However, by having the amino component affixed to a solid-support, in this case PEGA, a copolymer of PEG and polyacrylamide (PA), Flitsch and co-workers found the equilibrium can be forced to favour amide bond formation (Fig. 2) [24]. Additionally, the use of enzymes was shown to be highly enantioselective, with only the L,L-diastereomer observed when a racemic acyl donor was used.

Initially, this was just restricted to the synthesis of simple dipeptides, with good yields only obtained using hydrophobic amino acids. However, suitable protection of the polar or charged side chains with a hydrophobic protecting group allowed a much wider range of amino acids to be tolerated [25]. The limitation in this methodology occurs when the construction of larger peptides is attempted. Using an iterative process, in a similar manner to conventional SPPS, required the use of chemical deprotections of the Fmoc-protected amino acid, using piperidine in DMF (20 % *v*/*v*). Additionally, in the preparation of polyleucine peptides, beyond tetraleucine, hydrolysis of the peptide started to compete with the synthesis, resulting in a mixture of products.

Microwave assisted synthesis

Attempts to use commercially available Boc- or Fmoc-protected amino acids in aqueous reactions have typically required the development of complex synthetic methods. Galanis et al. [26] have recently described a rather simple method for the coupling of Boc-protected amino acids to PEG-based resins in water using water soluble coupling reagents and microwave irradiation. The use of Boc-protecting groups is important as they are easily removed under acidic conditions, with Galanis et al. using 1N $HCl_{(aq)}$ for the deprotection steps. This represents the first example of SPPS that utilises water for both coupling and deprotection steps, with only a small quantity of methanol being used for washing the resin. The developed methodology was then applied to the synthesis of Leu-enkephalin (H-Tyr-Gly-Gly-Phe-Leu-OH), in a rather disappointing 67 % crude purity. However, addition of a surfactant (0.5 % Trition-X100) for both coupling and deprotection steps, which is known to enhance the swelling properties of PEG-based resins in water, resulted in the microwave assisted synthesis of Leu-enkephalin in a much improved 81 % crude purity.

N-carboxyanhydrides

N-carboxyanhydrides (NCAs) or Leuchs' anhydrides **4** are a very interesting class of compounds as the amino group is protected whilst the carboxylate is simultaneously activated. This ultimately results in a simplified reaction scheme and a highly atom economical synthesis of a peptide bond, unlike traditional approaches to peptide synthesis. The use of NCAs for the solid-supported synthesis of peptides was first reported by De Marco et al. [27]. The NCA derivatives were first prepared in almost quantitative yields by treatment of the relevant amino acid with triphosgene using a solvent free, microwave assisted synthesis (Fig. 3). The NCAs were then used for the preparation of the opioid tetrapeptide endomorphin-1 **5** (H-Tyr-Pro-Trp-Phe-NH_2) in an aqueous borate buffer (pH 10.2) upon a PEG-based resin. Whilst the target peptide was only obtained in a moderate yield and purity, the approach represents a highly desirable one as it uses a minimal quantity of bulk chemicals, has excellent atom economy and is completely free of organic solvents.

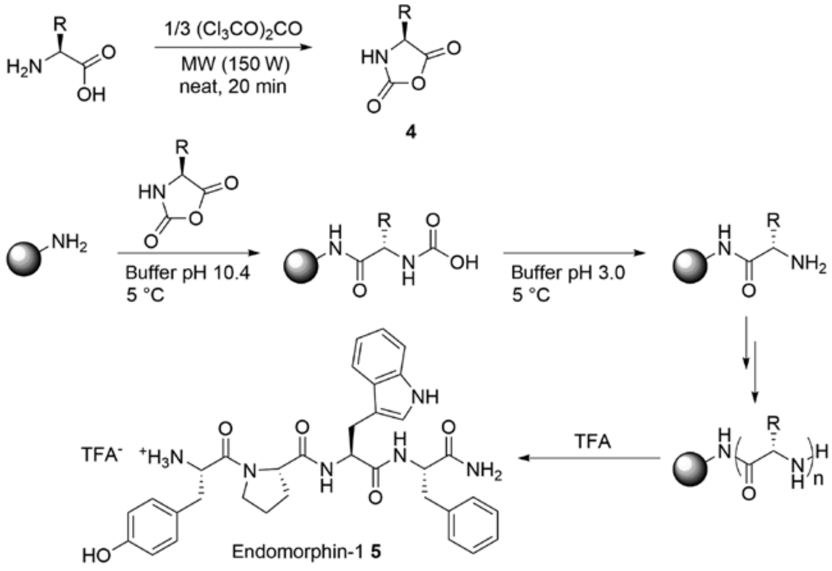

Fig. 3: SPPS of endomorphin-1 using NCAs in an aqueous media.

Alternative organic solvents

Whilst water is often considered a desirable solvent for synthetic chemistry, due to the favourable properties outlined previously, the use of water does not necessarily constitute a benign or "green" process. The contamination of aqueous waste streams with organic compounds or metal catalysts can be a substantial economic or environmental burden when it comes to its clean up or disposal, which will vary on a case-by-case basis [28, 29]. As such, there has been a recent trend towards the use of organic solvents that possess more desirable health, safety or environmental considerations to conventional organic solvents for SPOS.

This approach was first reported by Acosta et al. who investigated the use of acetonitrile as a replacement for DMF in SPPS couplings [30, 31]. Whilst acetonitrile is not often considered as a green solvent, it can be regarded as a less problematic dipolar aprotic solvent, when compared to DMF [5]. With Acosta et al. also arguing that it presents a more user friendly solvent due to its lower viscosity and boiling point. Whilst acetonitrile was unable to swell conventional PS-based resins it could adequately swell PEG-based resins. Acosta et al. then demonstrated the suitability of acetonitrile for SPPS in the preparation of the test peptides Leu-enkephalinamide and acyl carrier protein (ACP 65-74) (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2), upon PEG-based resins in excellent crude purity [30]. Subsequent reports from Albericio and co-workers have continued along the same theme of using less problematic alternatives to DMF for SPPS couplings, with the use of acetonitrile explored in more detail, along with THF, 2-MeTHF and CPME [32, 33]. Importantly, the solution-phase synthesis of Z-Phg-Pro-NH_2 indicated each of these solvents performed as well, if not better, than DMF, in suppressing racemisation. Acetonitrile and THF were then found to be fairly good solvents in the synthesis of the Aib-enkephalin pentapeptide (H-Tyr-Aib-Aib-Phe-Leu-NH_2) upon PEG-based resins, when the coupling reagents are carefully considered, producing the missed coupling product des-Aib (H-Tyr-Aib-Phe-Leu-NH_2) in minimal quantities (<10 %) [32]. 2-MeTHF and CPME performed much worse on PEG-resins using the aforementioned test sequence. They were however, found to suitably swell PS-resins and excellent results were obtained for 2-MeTHF, with only 3.0 % of the des-Aib sequence observed [33].

Whilst these represent very promising results for the replacement of DMF for SPPS they all suffer from one major drawback, being that they all still necessitate the use of piperidine in DMF (20 % *v*/*v*) for the deprotection steps and DMF/CH_2Cl_2 for washing of the resin. This has since been addressed by Jad et al. [34] who investigated a range of coupling and washing protocols using a combination of 2-MeTHF, EtOAc and IPA. Ultimately, the use of 2-MeTHF for both coupling and deprotection, combined with 2-MeTHF and EtOAc for washing the resin between steps produced the aggregation prone Aib-ACP decapeptide

(H-Val-Gln-Aib-Aib-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2) in 87.1 % crude purity. A significant improvement over the equivalent synthesis using DMF, which produced the target peptide in 70.0 % crude purity. Jad et al. [35] have also recently investigated the use of various green solvents for the Fmoc-deprotection step, identifying that γ-valerolactone shows comparable performance to DMF on both PS- and PEG-based resins.

Lawrenson et al. [36] have also recently contributed to the field of alternative organic solvents for SPOS in the use of cyclic carbonates for SPPS. Cyclic carbonates have been highlighted as highly promising replacements for conventional polar aprotic solvents, due to the fact they are non-toxic, biodegradable and produce no NO_x or SO_x upon incineration. They can also be produced *via* the 100 % atom economical reaction between epoxides and carbon dioxide, a reaction that is receiving considerable attention for waste carbon dioxide valorisation [37]. Lawrenson et al. demonstrated that propylene carbonate was a suitable solvent for both coupling and deprotection steps in solution-phase control reactions, also showing that coupling occurred with no evidence for epimerisation. The inflammatory mediator bradykinin (H-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH) was then produced using a DMF free synthesis, in 77 % crude purity, with a reference sample prepared in DMF produced in 79 % crude purity.

The use of more favorable organic solvents for SPOS has not only been limited to SPPS methodology. Coats et al. [38] have previously investigated the use of a range of very unconventional solvents for the solid-phase thionation of amides using Lawesson's reagent. The requirement for high temperatures to drive the reactions to completion when performed in parallel, due to less efficient heating and stirring, necessitated the use of a solvent with a high boiling point and low vapour pressure. In an initial screening benzyl benzoate was identified as a potentially suitable replacement for toluene or CH_2Cl_2 in this transformation. The thionation of PS-supported aryl and alkyl-derivatives of phenylalanine **6** using Lawesson's reagent **8**, and benzyl benzoate as the reaction solvent, produced the target thioamides **7** in good to excellent conversions at 100 °C after only 8 h (Fig. 4).

In an effort to promote the use of greener solvents for SPOS Lawrenson et al. [39] have recently published on the ability of a range of emerging green solvents to swell common SPOS resins. In this work, a total of nine PS-, PEG-, PS-PEG and polyamide-based resins were investigated and their swelling determined for a set of 25 green solvents, according to the general swelling method outline by Santini et al. [9]. A suitable green

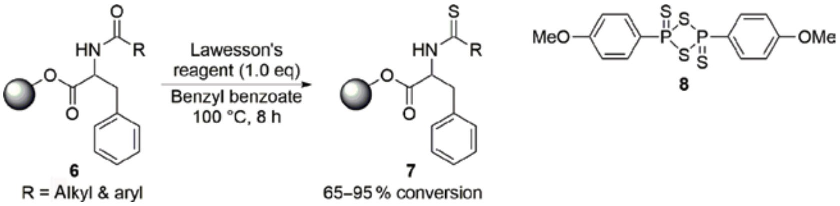

Fig. 4: Thionation of PS-supported phenylalanine using Lawesson's reagent in benzyl benzoate.

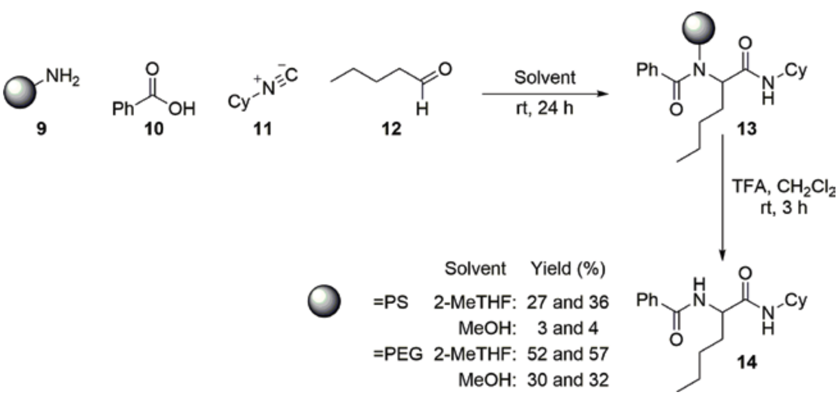

Fig. 5: Solid-phase Ugi reaction upon PS- and PEG-based resins in MeOH and 2-MeTHF.

solvent that was able to adequately swell the resin was found for eight of the nine resins investigated, with the exception being SpheriTide polyamide resin. The experimental observations were then validated through a study of the solid-supported multicomponent Ugi reaction (Fig. 5). 2-MeTHF was found to adequately swell PS based resins, producing on average isolated yields of the Ugi product **14** almost 10 times that of MeOH, which is unable to swell PS to a satisfactory level. When a solid support is used that can swell in both solvents (PEG) the results obtained are comparable to those observed in solution-phase control reactions.

Supercritical carbon dioxide

Supercritical carbon dioxide (scCO_2) is a rather unconventional reaction media that has received a lot of attention in recent years in the context of green chemistry. Being non-toxic, non-flammable and chemically inert towards many substances, it can also be simply removed by depressurisation, making it a highly desirable solvent. Additionally, the low critical point (74 bar, 31 °C) means the energy required to generate scCO_2 is relatively low [40]. The application of scCO_2 in SPOS however, is relatively unexplored, in a rather isolated example Stobrawe et al. [41] have investigated the use of compressed carbon dioxide in the solid-supported hydroformylation reaction.

As previously mentioned, solid-supported reactions often suffer from sluggish reaction kinetics due to poor mass transfer between the solid and liquid phase, this is even more of an issue in triphasic reactions (g/l/s). It was hoped that the use of scCO_2 would help overcome these limitations, leading to efficient synthesis of the target hydroformylation products on a PS support. Initial condition screening however, was rather disappointing, with the use of scCO_2 as the only reaction solvent producing the target product in only 10 % yield over 24 h. This was hypothesised to be due to the poor swelling properties of the resin in scCO_2 and subsequently the addition of small quantities of an organic co-solvent, in this case toluene, was found to greatly enhance the catalytic activity, producing the target hydroformylation products in >98 % yield.

The solid-supported hydroformylation products could then be used for the synthesis of more complex derivatives upon the solid-support, with Stobrawe et al. reporting on the Hantzsch synthesis of pyridines (Fig. 6). The solid-supported aldehydes **15**/**16** were utilised without further purification in the multicomponent coupling with acetoacetonate **17** and methyl 3-aminocrotonate **18**. The intermediates **19** and **20** were then aromatised using cerium ammonium nitrate and cleaved from the solid-support, producing the isomeric pyridines **21** and **22** in a 99 % yield and a 1.4:1 ratio.

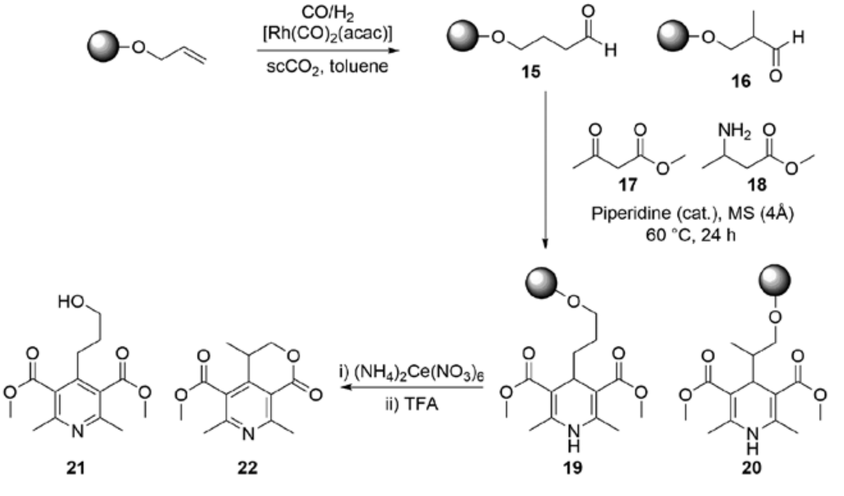

Fig. 6: Catalytic hydroformylation in scCO_2 upon PS-resin and subsequent Hantzsch pyridine synthesis.

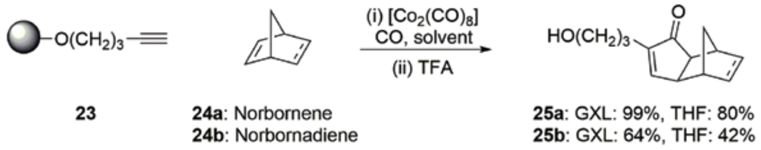

Fig. 7: Solid-supported Pauson-Khand reaction under conventional and GXL conditions.

Stobrawe et al. have also investigated the solid-supported Pauson-Khand reaction (PKR) in compressed carbon dioxide (Fig. 7) [41]. Under conventional conditions the PKR between polystyrene-supported 1-pentyn-5-ol **23**, CO (20 bar) and norbornene **24a** or norbornadiene **24b** in THF at 120 °C produced the target products **25a**/**25b** in good to moderate yields following cleavage by TFA. When repeated in the presence of compressed carbon dioxide, generating a gas expanded liquid (GXL), both **25a** and **25b** were formed in significantly improved yield, these reactions were also successful when performed in a parallel manner. The use of $scCO_2$ resulted in a decrease in yield, which is rationalised on the basis that, the increased mass-transfer to the resin ends up being offset by the substantial decrease in catalyst concentration.

Conclusions

In summary, the use of neoteric solvents and solvent technologies has been widely explored in the context of greener SPOS. Many interesting approaches to overcoming the complications that arise with synthetic transformations upon solid-supports have been described for successful SPOS in aqueous solutions, greener organic solvents and compressed carbon dioxide. By far the most significant developments have come in the field of SPPS, with greener SPPS being performed in tandem with a range of green technologies, including microwave assisted heating as well as atom economical routes to amide bond formation, such as enzymatic synthesis or use of *N*-carboxyanhydrides, for example. In contrast investigation into greener SPOS has been relatively under investigated. It is therefore hoped that this review may stimulate further interest into greener SPOS/SPPS, so that the many advantages of SPOS may be better realised with consideration for the principles of green chemistry.

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