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Recent advances in solventless organic reactions: towards benign synthesis with remarkable versatility

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A paradigm shift away from using solvents in organic synthesis as solventless reactions can lead to improved outcomes, and more benign synthetic procedures, in for example aldol condensation reactions, sequential aldol and Michael addition reactions *en route* to Kröhnke type pyridines, reactions leading to 3-carboxycoumarins, benzylidenes, 4-aryl-1,4-dihydropyridines and 2-aryl-1,2,3,4-tetrahydroquinazolines, and oligomerisation reactions for the synthesis of cavitands; kinetic considerations for the reaction of two solids can only be explained if a eutectic melt is formed during the reaction.

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Introduction

Sustainability is increasingly an important issue in the wider context dealing with population, health, the environment, energy, technology, renewable resources, and, in the sciences, as an integral part of the rapidly emerging field called Green Chemistry.[1,2] This is a multidisciplinary field, requiring integrated study in the chemical, biological and physical sciences as well as many aspects of engineering. Even nanotechnology is important in Green Chemistry, providing a way of dematerialising society while providing the benefits of technology.[3] The twelve principles of Green Chemistry, as defined by Anastas and Warner,[1] and generally accepted internationally, cover complex issues including waste minimisation, reduction in energy usage, and the use of renewable resources rather than depleting natural resources such as oil, coal and gas. Biocatalysis is an important area of Green Chemistry providing a means of converting biomass, a renewable resource, into commodity chemicals.[1–3] In the chemical sciences there is a need to develop benign synthetic pathways which, in addition to being high yielding (historically the most important measure of the success of a reaction), are simple and exhibit high atom efficiency, hence a reduced number of steps and no waste, are safe, and are environmentally acceptable.[2] Another measure of the 'greenness' of a reaction is the *E* factor (= waste (kg)/1 kg product),[4] which, for pharmaceuticals, is typically >100. The emergence of Green Chemistry has resulted in a paradigm shift in the way chemists develop processes and products, and requires the development of a Green Chemistry toolbox.

Removing organic solvents in chemical synthesis is important in the drive towards benign chemical technologies. Organic solvents are high on the list of toxic or otherwise damaging compounds because of the large volumes used in industry, and difficulties in containing volatile compounds. Replacement reaction media include ionic liquids[5–7] (which have extremely low vapour pressure and can be recycled), liquid and supercritical CO_2,[8] water (often at high temperature under microwave irradiation),[1,9,10] and polyethylene and polypropylene glycol[11] (Fig. 1). Another alternative is not to use a reaction medium, the so called solventless reactions, which is the main focus of this article.[7,11–20] The choice of solventless or specific non-organic solvent reaction medium will depend on several issues, including selectivity, stereochemistry, yield, waste, viscosity, ease of recycling, energy usage, ease of isolation of product(s), competing reactions, and heat of reaction. In using a reaction medium, there are many choices within each system, for example using ionic liquids with the appropriate hydrophobic–hydrophilic balance, and varying the density of liquid and supercritical CO_2, which can affect the stereochemical outcome of addition reactions.[8]

Advantages in using solventless reactions, particularly those described herein, relative to using organic or other reaction

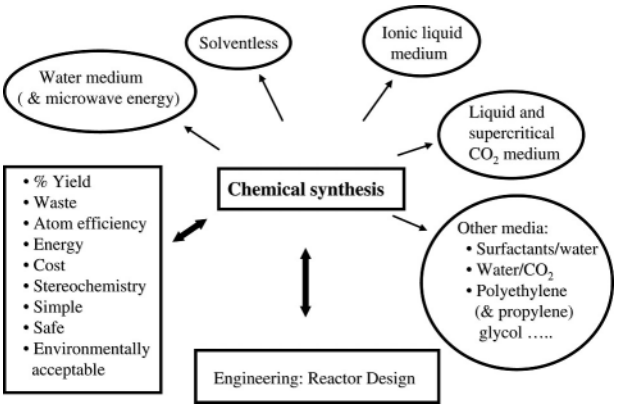


Fig. 1 Non-organic solvent reaction medium linking into reactor design.

media include: (i) there is no reaction medium to collect, purify and recycle, (ii) the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography, and indeed in some cases the need for recrystallisation, (iii) sequential solventless reactions are possible in high yielding systems, (iv) the reactions can be rapid, often reaching substantial completion in several minutes compared to hours in organic solvents, (v) there is often no need for specialised equipment (see below), (vi) energy usage can be much lower, (vii) the need for pre-formed salts and metal–metalloid complexes may often be dispensed with, (viii) functional group protection–deprotection can be avoided, (ix) lower capital outlay for equipment in setting up industrial processes, and (x) considerable batch size reduction and processing cost savings are achievable such that such solvent-free protocols are not only more environmentally benign but are also more economically feasible. This is one of the original considerations in bringing Green Chemistry to the fore.[1]

There are some disadvantages in solventless reactions but these are solvable using developments in engineering reactor technology[21] (Fig. 1). Objections to the use of solventless reaction conditions include the formation of hot spots and the possibility of runaway reactions. Instead of operating in the old paradigm, notably the use of a reaction medium or solvent as a heat sink or heat transfer agent, consideration could be given to applying developments in reactor design either for continuous flow or batch systems. Our recent paper on the solventless aldol condensation reaction,[15] attracted attention in *Chem. Brit.* (June 2000, p. 18) with a subsequent letter to the editor drawing attention to the potential for run away reactions (January 2001, p. 14). Clearly measurement of heat of reaction in solventless systems is important as is effective heat dissipation. If highly exothermic reactions are identified which are otherwise suited to solventless conditions the problem could be addressed through advanced reactor design. Another objection can be difficulties in handling solid or highly viscous material. Again this can be overcome by advances in engineering and innovative reactor design. Solventless reactions may be more appropriate for small volume commodity chemicals rather than high throughput although it is possible to envisage extrusion type continuous reactors. Though the concept of grinding (including ultra high energy grinding) to promote chemical reactions has been known for some time, there have been few reports of applications of high intensity grinding in organic synthesis.[22–24]

Historically organic synthesis was carried out in organic solvents even in the absence of apparent reasons to do so (other than heat transfer considerations). In moving towards sustainable technologies the issue now becomes either carrying out solventless reactions, or using alternative reaction media, or (for a multi-step synthesis) a combination of these. In covering recent advances in solventless reactions, we will compare (where information is available) reactions in organic solvents and in other media. We initially entered Green Chemistry as a challenge to establish solventless procedures for reactions which traditionally play a pivotal role in organic synthesis. We also targeted solventless reactions, and reactions in ionic liquids, for preparing building molecules which feature extensively in supramolecular chemistry leading to advances in materials chemistry and nano-technology. This is based on the premise that any developments in supramolecular chemistry are more likely to have downstream applications if the building molecules are readily available using benign synthetic protocols. Specific reactions studied include solventless aldol reactions,[15] sequential aldol and Michael addition reactions as a route to symmetrical and unsymmetrical 1,5-diketones leading to Kröhnke type pyridines,[17–19] synthesis of 3-carboxycoumarins (and a comparison with using an aqueous slurry),[16] oligomerisation reactions affording cavitands, notably cyclotriveratrylene and related compounds (and a comparison with an ionic liquid reaction medium),[7] calix[4]resorcinarenes,[11] and 4-substituted-1,4-dihydropyridine compounds such as the commonly used cardiovascular drug Felodipine.[25] All these reactions have a common theme of dehydration, and most exhibit high atom efficiency. We note that Kröhnke type pyridines and cavitands have 'high technology' applications, for example in devices, materials chemistry, and liquid crystals, and ultimately in developing sustainable technologies, Fig. 2, but this is not

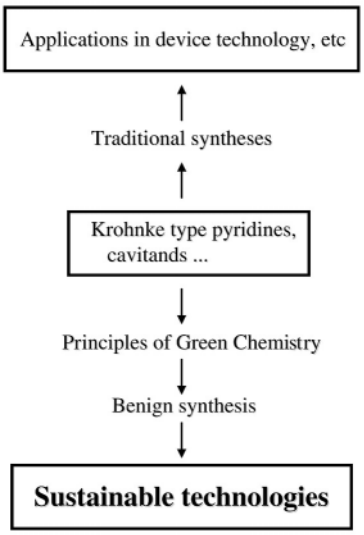
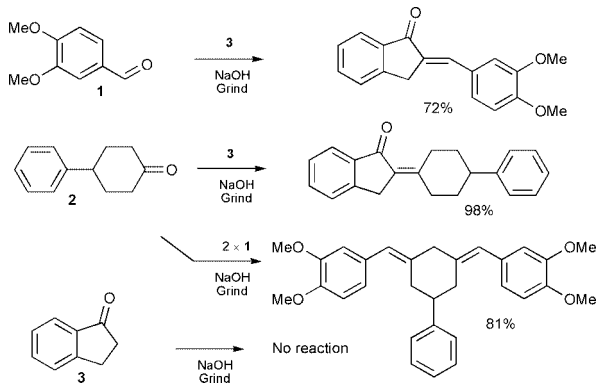


Fig. 2 Relationship between compounds with materials applications and sustainable technologies.

matched by their syntheses. We have also studied the kinetics of these solventless reactions, to help understand the chemistry at the molecular level which is important in developing tools for Green Chemistry.

Chemoselective, aldol condensation reactions

The aldol reaction, the formation of a β-hydroxycarbonyl compound from two carbonyl compounds with at least one being enolisable, which on dehydration becomes an α,β-unsaturated carbonyl compound, can be carried out by simply grinding together solid (or liquid) aldehydes and ketones in the presence of solid NaOH followed by washing with a dilute aqueous acid solution, Scheme 1.[15] No preformed enolates are used, no heating or cooling is required, no organic solvent is utilised in the reaction (unless product recrystallisation is required), and the only waste produced is a small amount of acidic aqueous waste. Single crossed aldol condensation products are produced in high yield even in reactions where a mixture of products is possible. Solvent free aldol condensation reactions of benzaldehyde and acetophenone derivatives have been reported by Toda *et al.*,[26] although in all cases the



Scheme 1

aldehydes are devoid of α-hydrogen atoms, thereby ensuring that only a single aldol condensation product is possible.

Interestingly, the first reports of aldol reactions utilised underivatised ketones and aldehydes with simple acid[27] or base[28] catalysis. The trend has been towards reactions using pre-formed enolates, which serve both to increase the driving force of the reaction and to ensure that the desired chemoselectivity is achieved. Numerous elegant procedures have been developed to this end[29] but they frequently require the use of reagents which are themselves somewhat noxious and result in the generation of significant quantities of waste containing metal salts such as Li^+ salts. Some routes use enol esters or silyl enol ethers but these are poor performers with regard to atom efficiency and often require the use of potentially polluting solvents and low temperatures.

In highlighting the solventless approach, the solids veratraldehyde, **1**, 4-phenylcyclohexanone, **2**, and indan-1-one, **3**, are reacted in various combinations affording aldol condensation products, with a high degree of conversion and a single major product, Scheme 1.[15] In the case of **1** and **3** a single condensation product is obtained as expected, since the aldehyde bears no α-hydrogen atoms and cannot therefore act as a carbon nucleophile. Compounds **1** and **2** may yield two products (a mono- and bis-adduct). The combination of **2** and **3** is less straightforward and a number of possible products may be envisioned including crossed aldol products with either ketone acting as a nucleophile, self condensation products of the ketones and a mixture of these two. Under solventless conditions, only one crossed aldol product is isolated. In stark contrast, for the reaction of compounds **2** and **3** in solution, without the use of a pre-formed enolate, a complex mixture of products results.[30] Attempted self-condensation of **3** under solventless conditions fails to give the condensation product.

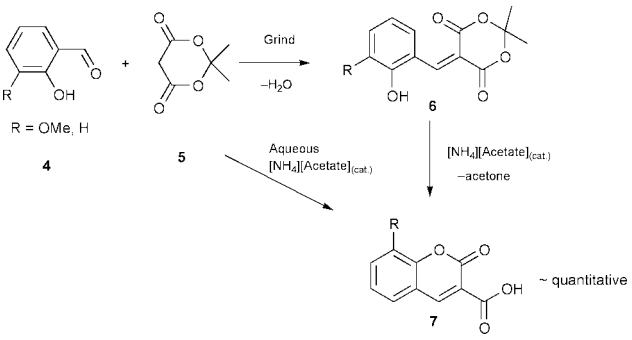
Where reaction occurs, a eutectic mixture, with melting point lower than the ambient temperature, results and the reaction mixture is in fact a *mutual solution* of the carbonyl compounds reacting together to yield a solid product which separates from this solution as the reaction proceeds.[20] This observation may provide insight into the remarkable selectivity of the ketone–ketone reaction involving **2** and **3** under these conditions, with the product arising from attack by a carbanion formed by indan-1-one on the electrophilic carbonyl carbon of 4-phenylcyclohexanone followed by spontaneous dehydration and sequestration of the product as a separate solid phase.

If dehydration occurs immediately and is *irreversible under the conditions of the reaction* the product is trapped and no equilibration occurs. The solid product appears to be insoluble in the reaction mixture and is effectively removed by this change in phase driving the reaction rapidly to completion. Stabilisation of the indanon-1-one carbanion intermediate leads to higher acidity of the α-hydrogen atoms and, as no equilibration is possible (as the product is removed from the 'reaction solution'), no products due to attack of 4-phenylcyclohexanone carbanions are noted.

Adopting the principles of Green Chemistry for the aldol condensation reaction, has resulted in establishing a new benchmark for minimising waste in these reactions while allowing for a greater degree of chemoselectivity than in solution. These are distinct advantages over the classical reactions in organic solvent. Moreover, intermediates formed by grinding together two solids and the base catalyst may be stored for months without impact on product quality, and this issue alone may be attractive in industrial applications of the solventless aldol reaction.

3-Carboxycoumarins

These compounds, **7**, can be readily prepared from 2-hydroxybenzaldehydes, **4**, and Meldrum's acid, **5**, by a room temperature reaction involving two solids or a solid and a liquid with a catalytic amount of ammonium acetate, Scheme 2.[16] The



Scheme 2

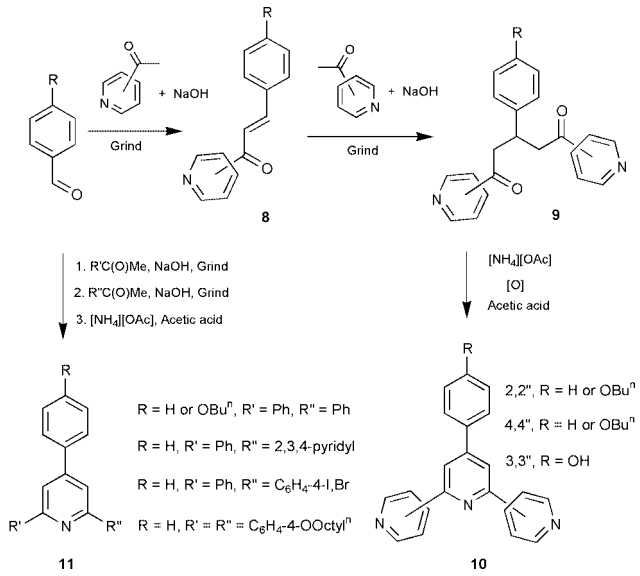
yields of **7** are quantitative, with no heating, and no use of organic solvent, with purification achieved by an aqueous wash. Alternatively the reactions can be carried out as slurries in aqueous solutions of ammonium acetate, despite the extremely low solubility of Meldrum's acid, **5**. As for the solventless reaction, the ammonium acetate solution can be reused without affecting product quality. The Knoevenagel reaction product (the benzylidene intermediate, **6**) can be isolated from a reaction mixture devoid of catalyst and further reacted, in the presence of the catalyst, either as a solid or in aqueous slurry to effect ring closure to the coumarin. Remarkably, the reaction of **4** and **5** to produce **7** proceeds *more* rapidly when carried out under aqueous slurry conditions. It is generally accepted that the 1,2-elimination in the Knoevenagel reaction is inhibited in protic solvents[31] and this provides a clue to an increase in the rate of the reactions in aqueous slurries. If the 1,2-elimination is inhibited and hydrolysis of Meldrum's acid and ring closure proceeds once the β-hydroxydiketone is formed, *i.e.* before or concomitantly with 1,2-elimination of water, then the longer lived the flexible β-hydroxydiketone, the more favourable are the conditions for coumarin formation and the more rapid the reaction.[16]

3-Carboxycoumarins represent an important class of biologically active compounds, and their synthesis is now more convenient, clean and efficient. There is no need for the use of polar aprotic solvents such as DMF or solvents in general, no heating is required, and minimal waste is generated.[16] The procedure becomes almost facile in its simplicity and equipment use is limited to vessels for stirring and suitable filtration devices. The Knoevenagel reaction of active methylene compounds with 2-hydroxybenzaldehdes has been extensively used in the first step in the synthesis of 3-carboxycoumarins. Knoevenagel himself described the solution phase condensation of 2-hydroxybenzaldehydes with malonic acid more than 100 years ago.[32] Numerous routes to 3-substituted coumarins have been published, including the use of noxious compounds such as $POCl_3$,[33] bases such as piperidine,[34] solvents such as DMF,[35] and, recently, a low-yielding 'solid phase' synthesis, utilising

ethyl malonate tethered to a Wang resin and suspended in pyridine.[36] A more benign method is a one pot microwave mediated synthesis which entails the use of a solid catalyst,[37] but this is not solvent free, unlike in our methods, Scheme 2, requiring removal of the product from the catalyst using a solvent, followed by extensive use of solvent for chromatographic purification.[37]

Synthesis of Kröhnke type pyridines

Despite the continual research and applications surrounding Kröhnke type pyridines and related compounds, the methodologies used to synthesise these compounds have changed little since a review article by Kröhnke in 1976,[38] which involves volatile organic solvents and displays only moderate to low yields with low atom efficiency. In applying the principles of Green Chemistry a new and indeed more versatile protocol has been established.[17–19] The aldol condensation of an enolisable ketone and a benzaldehyde followed by Michael addition of the enone, **8**, with a second enolisable ketone, both steps under solvent free conditions involving grinding with solid NaOH, leads to the quantitative formation of a 1,5-diketone, **9**, either symmetrical or unsymmetrical with respect to the aromatic rings, depending on the ratio of reactants and order of addition.[17–19] A Kröhnke type pyridine, either a terpyridyl **10**, or a bipyridyl or pyridine **11**, is then readily formed in high yield *via* a double condensation in the presence of ammonium acetate in acetic acid. Some of the types of compounds prepared using this new approach are shown in Scheme 3. Overall, this



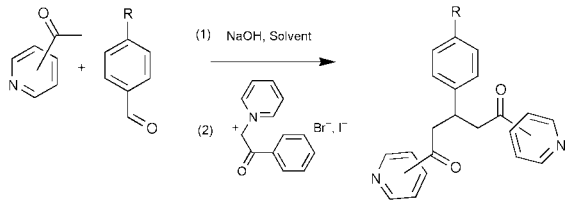
Scheme 3

solventless approach coupled with the ring closure in acetic acid allows access to a diverse range of oligopyridyls, including bipyridyls and terpyridyls (symmetrical and unsymetrical) which in many cases are not accessible using traditional methods, or are accessible only in low yields. Thus the Green Chemistry approach not only reduces the use of organic solvents and minimises other waste,[1] it allows access to new classes of compounds and associated applications. It is noteworthy that the new method is simple, occurs under mild conditions (improved energy usage), and has inherently lower costs.[18] In keeping with our 'green' approach we have also synthesised all non-commercially available starting alkoxybenzaldehydes and alkoxyacetophenones for **10** and **11** using recyclable polypropylene glycol as a low vapour pressure reaction medium.[11]

It is noteworthy that Kröhnke type pyridines and other substituted pyridines, including the related terpyridines, with their π-stacking ability, directional H-bonding and coordination properties, are prominent building blocks in both organic and inorganic supramolecular chemistry.[19,39–41] They also have luminescence properties,[42] with applications in liquid crystals,[43] photosensitisers,[44] and biochemical DNA binding reaction mechanisms.[45] Studies into the possible medical applications of substituted terpyridines have shown promising results, attributed to their ability to form complexes with metals, although the toxicity of previously synthesised materials has hampered clinical trials.[46] The significance of being able to synthesise such substituted terpyridines for use in pharmacological testing alone is reflected in the increasing number of associated international patents in recent years.[47]

The solventless reactions, Scheme 3, occur for combinations of liquids, liquids and solids, and solids. In a typical experiment, benzaldhyde and acetophenone are both colourless liquids at room temperature and upon addition of the NaOH the liquids immediately turn yellow indicating the formation of the enolate. By aggregating the reaction mixture in a mortar and pestle, the viscosity rapidly increases to form a tacky solid after *ca.* 5 min of constant mixing, which hardens after *ca.* 30 minutes as the solid aldol product, **8**. During the reaction between two solids the reaction mixture undergoes a phase transition into a eutectic melt. Grinding the solid starting materials in the absence of base, this eutectic phase can be reproduced, however, there is no observed conversion to the aldol product.

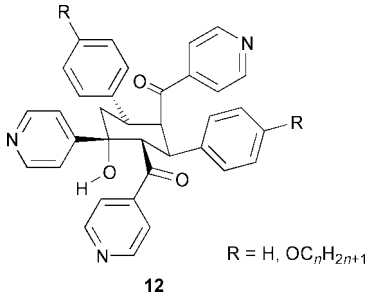
A conventional Kröhnke synthesis proceeds by treating an unsaturated ketone with the pyridinium salt formed by reacting halogenated-methyl ketone with pyridine, Scheme 4, to produce



Scheme 4

the Michael addition product **9**. Although this step is reported to be high yielding, the byproducts of the reaction generate significant waste and the reagents are expensive (see below). The direct reaction of the enone with an enolisable aryl methyl ketone in a basic solution proceeds to the 1,5-diketone,[48] thus eliminating the preliminary pyridinium salt formation. In the case of unsymmetrical compounds, there is no need to isolate the intermediate enone which is essentially formed quantitatively, thereby eliminating an intermediate purification step, and without the need to add more NaOH.

When the solvent based methods were adopted in an attempt to prepare **10**, 4,4″, R = *O*-alkyl, only the cyclohexyl product



12

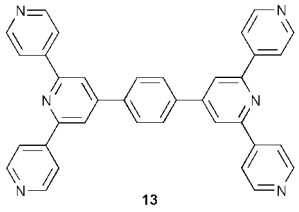
12 could be isolated from the complex reaction mixture which was devoid of target molecules. A recent paper describes the synthesis of **10**, 4,4″, R = H, under somewhat harsh conditions with a moderate 6% overall yield,[49] compared with 84% using the solventless approach.[17–19]

After the final ring closure reaction in acetic acid, addition of water results in precipitation of the product which can be collected and washed with ethanol. Although this stage of the

synthesis requires the use of a solvent, it should be noted that the low vapor-pressure of the acetic acid allows the use of an air condenser during the reflux, following the workup process the acetic acid can be efficiently regenerated and used as a batch process. The chosen solvent is also a naturally renewable source in alignment with the principals of Green Chemistry. Typically the traditional methods to prepare Kröhnke type pyridines generates as much as 29 times more solid waste than the 'greener' route to the same compound.[50] Moreover, even for a compound available in modest yield using traditional methods,[50] the 'greener' route is estimated to be 600% more cost effective, not taking into account the cost of energy usage and waste disposal, which is rapidly escalating. Then there is the new chemistry which is accessible, for example the synthesis of the complex molecules **13** and **14**.[50]

By utilising the above techniques, we have synthesised several novel building blocks, including **13** and **14**,[50] which have potential as supramolecular synthons, polymeric monomers, coordination ligands, mono- and di-cyclometallation ligands, and as molecules with pharmacological properties. The added halogen functionality on the terminal carbon of the alkyl chains in compounds also allows for great scope. As an example of the utility of the new pyridines now available in supramolecular chemistry, compound **10**, 4,4″, R = *O*-Octyl^n, forms hetero-multi-component molecular capsules with *C*-methylcalix[4]resorcinarene, Scheme 5.[19] The calix[4]resorcinarene is also readily prepared in high yield as the cavitand C_{4v} isomer under solvent free conditions[19] which dispenses with the need for using large volumes of acid and solvent (see below).[51] Overall, supramolecular chemistry is part of the drive towards sustainable technologies in nano-chemistry and beyond. Molecular capsules in general find applications in clean chemical synthesis,[52] drug delivery, materials and separation sciences,[53] and they are structurally related to components in biological systems such as those in viruses.[54]

The molecular capsules contain microenvironments of solvent, either four toluene molecules, or if a trace of diethyl ether is present, two diethyl ether molecules and two toluene molecules, which has implications in separation technology. Both capsules have been structurally authenticated, with the structure of the latter shown in Fig. 3, and are held together by



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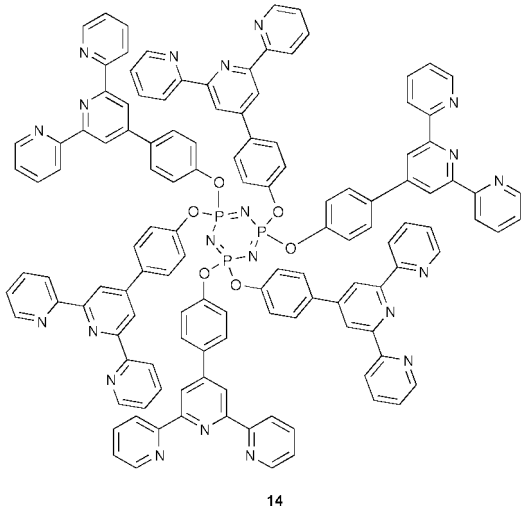
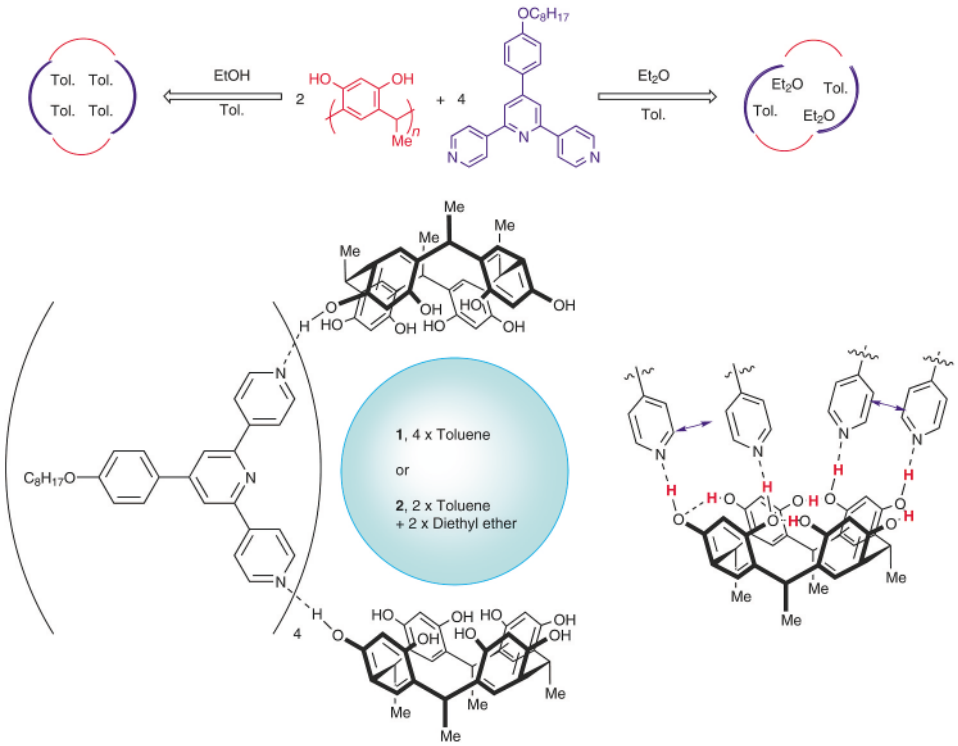


14

a total of 8 N···HO hydrogen bonds, and π-stacking associated with pairs of terpyridines.

Cavitands: calix[4]resorcinarenes, cyclotriveratrylene (CTV) and related molecules

The synthesis of *calix[4]resorcinarenes* was first reported in the late 19th century by Baeyer[55] and in spite of the increased interest in such compounds the synthetic methodology used has changed little. This typically involves heating resorcinol and the appropriate aldehyde to reflux for hours to days in a mixture of mineral acid and alcohol (usually a 2 : 2 : 1 ratio of ethanol, water



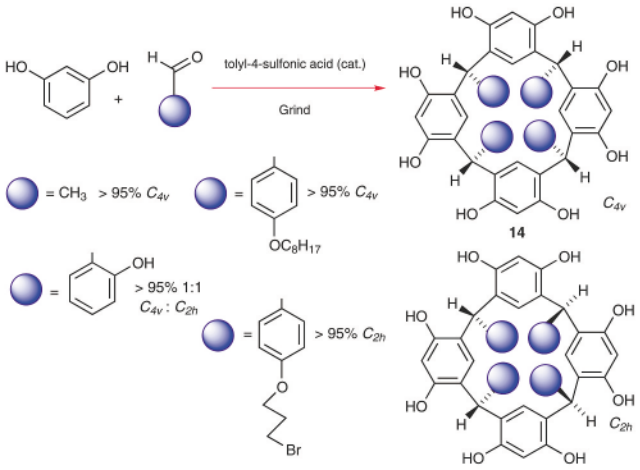
Scheme 5

and concentrated HCl).[56] In applying the principles of Green Chemistry *C*-aryl and *C*-methylcalix[4]resorcinarenes are now accessible in substantially higher yields and high purity by the direct reaction of resorcinol and aldehyde in the presence of a catalytic amount of solid acid, tolyl-*p*-sulfonic acid, at ambient temperature, under solvent-free conditions with grinding for a few minutes, Scheme 6.[11,19] This represents a significant improvement on the traditional solution phase methodology with respect to energy usage, solvent wastes and associated hazards, reaction time and yield. In addition, and again applying the principles of Green Chemistry, the relevant benzaldehyde derivatives are prepared in polypropylene glycol, which is readily recycled. Calix[4]resorcinarenes find applications as supramolecular tectons[19,57] and host molecules,[58] as components in liquid crystals,[59] photoresists,[60] selective membranes,[61] surface reforming agents,[62] HPLC stationary phases,[63] as ion channel mimics[64] and metal ion extraction agents.[65]

As noted previously,[7,20] the reaction mixtures are viscous liquids or pastes even where all reagents are solids; the melt formed on mixing the reagents stiffens within minutes to yield a sticky solid that hardens further on standing. This material is mainly the product **14** and purification involves washing with water to effect removal of the catalyst, followed by recrystallisation from hot methanol where required.

Calix[4]resorcinarenes commonly occur in two isomeric forms, namely the *rccc* or C_{4v} and the *rctt* or C_{2h} isomers.[66] For *C*-methyl- and *C*-C_6H_4-4-*O*-Octyl^n–calix[4]resorcinarenes the C_{4v} isomer results, whereas for *C*-C_6H_4-2-OH–calix[4]resorcinarene the C_{2h} isomer predominates and, for *C*-C_6H_4-4-O$(CH_2)_4$Br–calix[4]resorcinarene, a mixture of the two isomers is obtained (Scheme 6). The predominance of the C_{2h} isomer contrasts with molecular modelling calculations,[11] which indicate that the C_{4v} isomer in the crown conformer is favoured over the C_{2h} isomer in the chair conformer (in the absence of solvent effects) by 6.3 and 14.4 kcal mol^{-1} for *C*-C_6H_4-4-*O*-Octyl^n–calix[4]resorcinarenes and *C*-C_6H_4-4-O$(CH_2)_4$Br–calix[4]resorcinarene respectively. Altering the reaction time does not lead to an increase in the formation of the C_{4v} isomer.

CTV and related molecules, **16**, are versatile supramolecular host molecules, recently gaining prominence in forming complexes with large globular molecules such as fullerenes and



Scheme 6

carboranes,[67,68] yet the synthesis of these host molecules has changed little since their discovery earlier last century.[69] CTV is formed by the harsh acid catalysed condensation of veratryl alcohol **15**, or veratrole and formaldehyde. In focusing on more benign syntheses, two new methods have been developed, solventless and the use of an ionic liquid as a reaction medium, both providing reasonable yields yet being low waste generating, Scheme 7.[7] The solvent free method is particularly well suited to the analogues of CTV derived from the corresponding benzyl alcohol which are sensitive to strongly acidic conditions, while condensation in the ionic liquid N_{6444} Amide facilitates the condensation of liquid or molten benzyl alcohol monomers to the cyclic trimers. While the yields from the solventless reactions carried out at room temperature are modest, 41–59%, these are readily improved by the use of elevated temperatures.[70] The trimer is more easily isolated than in traditional syntheses, and only a catalytic amount of acid is required, the volume of solvent used is hugely reduced and is only associated with product purification. Phosphoric acid proved the best catalyst as solid tolyl-*p*-sulfonic acid results in the formation of solid product shells around the catalyst, effectively rendering the catalyst inactive.[7] Organic solvents used in product isolation are not heated above ambient temperature, thus reducing the difficulties associated with containment of vapours.

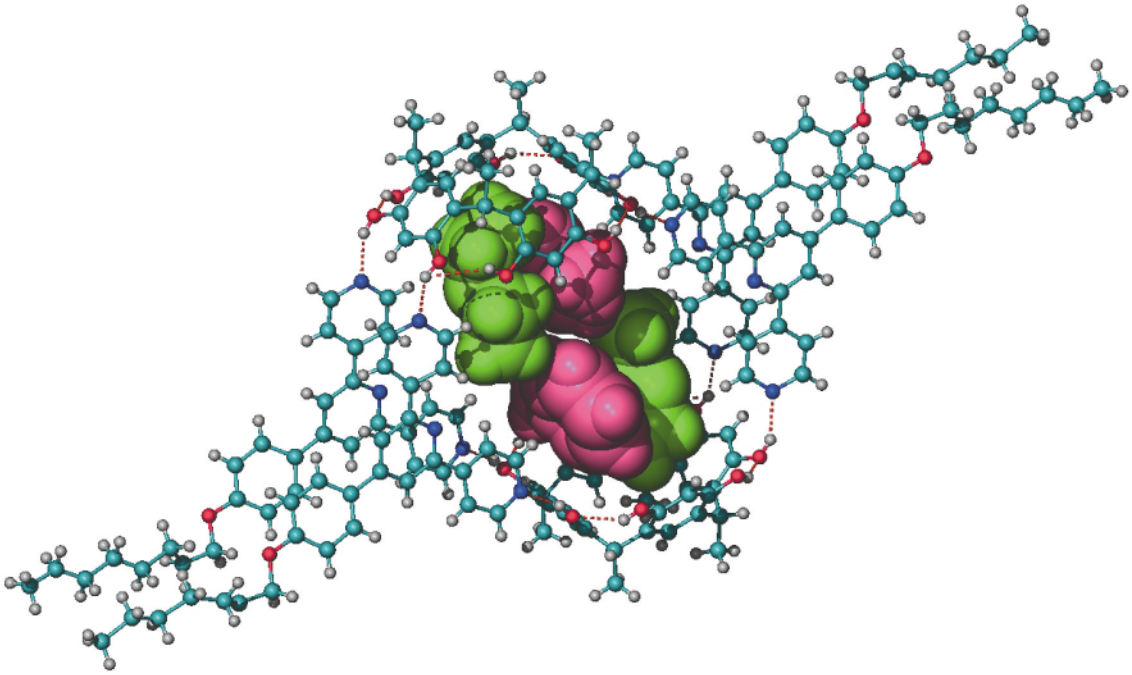
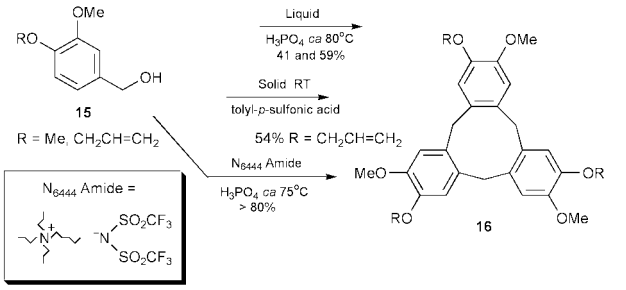


Fig. 3 Structure of [{$(OEt_2)_2$(toluene)$_2$}⊂(*C*-Methylcalix[4]resorcinarane)$_2$ (**10**, 4,4″, R = –*O*-Octyl^n)$_4$].



Scheme 7

In the case of the ionic liquid method, the reaction of **15** with a catalytic amount of phosphoric acid affords the trimer in very high yield, >82%, and the non-volatility of the ionic liquid provides unique recycling possibilities. Indeed it can be recycled five times before product quality is compromised and the scheme for recycling the ionic liquid is shown in Fig. 4. The

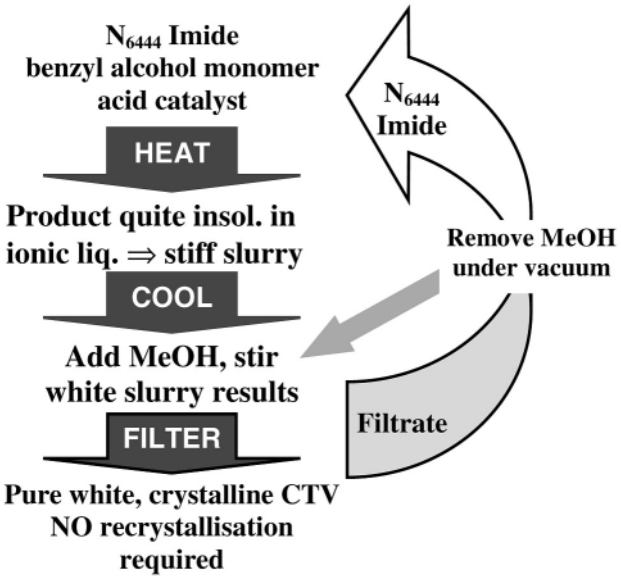
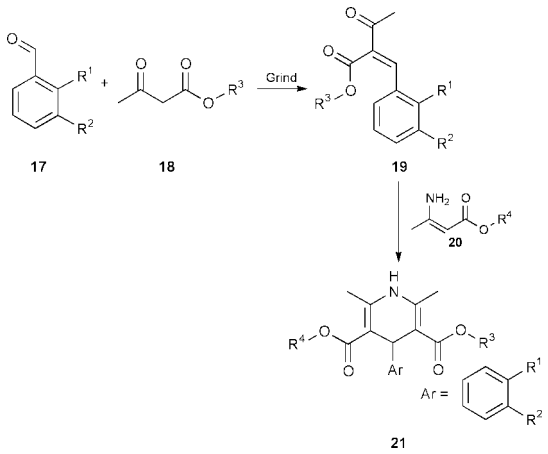


Fig. 4 Procedure for recycling of ionic liquid N_{6444} Amide in the synthesis of CTV. This anion is also commonly described in the materials and electrochemistry literature as the bis(trifluoromethylsulfonyl)*imide* ion, hence the abbreviation N_{xyyy}*Imide*.

methanol used in the scheme can be removed by distillation and recycled. The high yielding reaction occurs in an ionic liquid which is strongly hydrophobic and with the negative charge on the anion diffuse and partially protected.[7] The low equilibrium concentration of water in the reaction mixture assists in driving the reaction to high yield, the excess water being continuously lost as vapour. The properties of the ionic liquid which favour the trimerisation reaction underscores the need to develop a wide range of ionic liquids of varying properties, and this is an important part of the rapidly expanding research in ionic liquids.[5–7]

Therapeutic agents

4-Aryl-1,4-dihydropyridines such as **21** are potent calcium channels agonists and antagonists and are extensively used in the treatment of cardiovascular disease (CVD),[71] which is one of the leading causes of death the world over (for example, 41.4% of deaths in the USA in 1996 were a result of CVD).[72] Following the two step regime illustrated in Scheme 8 (and similar to most industrially used synthetic routes to such unsymmetrically substituted dihydropyridine derivatives), but using solventless reaction conditions, leads to a vast improvement in extent of conversion and isolated yield while delivering significantly shortened reaction times, batch sizes that are defined only by the quantity of drug to be produced and



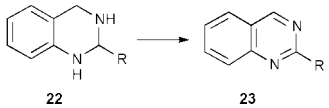
Scheme 8

concomitant improvements in energy utilisation.[73] Volatile organic compound (VOC) use is restricted to product recrystallisation, in turn facilitated by the high degree of conversion achieved which results in low quantities of residual starting materials or impurities.

The simplicity and efficacy of the solventless methodology may again be contrasted with the various strategies that have been employed to maximise conversion and minimise reaction time in traditional solvent-phase syntheses. These include azeotropic removal of water,[76–76] catalyst optimisation,[74,77] and selective deesterification of diesters using acid catalysts.[78] Reaction times are of the order of 2 to 40 hours and overall yields for the two step synthesis are significantly lower than quantitative (30 to 65%). Extractive workups[79] and the need to separate symmetrical diester byproducts from the desired product[74] serve to increase the usage of volatile organic compounds and decrease efficiency with respect to yield and number of process steps.

These reactions proceed at ambient temperature but, in common with the solution phase methods, more rapid conversion is achieved at elevated temperatures. To gain further understanding of these reactions, we have studied the rate of formation of the products **19** and **21** and find that it is possible to optimise reaction conditions with respect to maximum rate of conversion *vs*. energy use.[73]

Remarkable improvements in yield, energy use and waste minimisation are also achieved in the synthesis of 1,2,3,4-tetrahydroquinazolines **22** and the related fully aromatised quinazolines **23** (Scheme 9).[80] These compounds are biologically



Scheme 9

active[81] and derivatives are of interest as dihydrofolate reductase inhibitors,[82] antitubercular[83] and antibacterial agents.[84]

Mechanistic considerations

That many of the solventless reactions discussed above involve the reaction of macroscopic solid organic particles, yet proceed *via* a liquid or melt phase is intriguing and has formed the basis of a detailed study of several organic reactions.[20] Some of these reactions have been reported to proceed 'in the solid phase' but clearly involve the formation of a liquid phase. Catalytic transformations, including aldol condensations and oligomerisation of benzylic compounds to form cavitands, proceed *via* a liquid phase, as do many non-catalytic reactions including Baeyer–Villiger oxidations, oxidative coupling of naphthols using iron chloride, condensation of amines and aldehydes to

form azomethines, homo-etherification of benzylic alcohols using tolyl-*p*-sulfonic acid, and nuclear aromatic bromination with NBS.[20] This liquefaction implies the existence of a eutectic mixture with T_{fusion} below ambient temperature (although both reagents have higher than ambient melting points). In cases where heating is required, it is again clear that a phase change (from solid to liquid) occurs, explaining the observed reaction kinetics. We have previously examined a number of experimental examples,[20] and these along with the examples described above provide the basis for a description of such reactive systems involving intervention of a liquid phase resulting from the occurrence of a eutectic (or peritectic) melt phase. When considering reactions between solids it is important to distinguish between **solid phase synthesis** (the reaction of molecules from a fluid phase with a solid substrate as in the polymer-supported peptide syntheses); **solvent-free synthesis** (any system in which neat reagents react together, in the absence of a solvent); and **solid-state synthesis** or **solid-solid reactions**, in which two macroscopic solids interact *directly* and form a third, solid product *without intervention of a liquid or vapour phase*. A cartoon of these three processes is shown in Fig. 5. Numerous reactions such as those resulting in

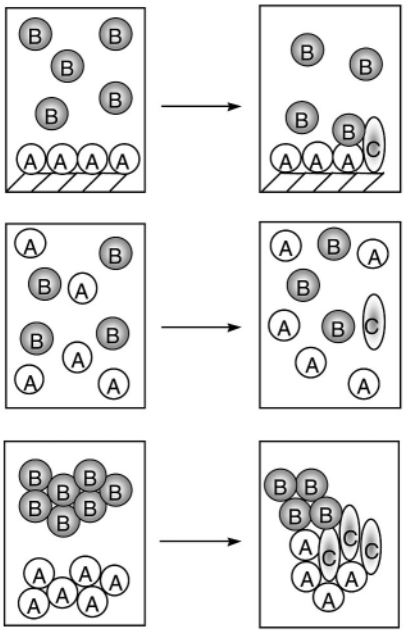


Fig. 5 Cartoon of solid phase reaction (top), solvent-free reaction (middle), and solid-state reaction (bottom).

the formation of a complex such as a charge-transfer or molecular complex,[85] reactions in a single crystalline phase such as photochemically induced solid-state transformations,[86] or the reaction of two components that crystallise together to form a discrete stoichiometric co-crystal (or inclusion compound), may be considered to occur in the solid phase.[87] However, it may be demonstrated that many reactions between discrete solid particles are actually reactions in a liquid melt phase.[20]

In the aldol condensation, observation of the phase resulting on grinding together the solid aldehydes or ketones *without* addition of the base catalyst, reveals that in some cases a liquid melt forms while in others the solid reagents occur as mechanically mixed, discrete crystalline phases (as verified by powder X-ray diffraction studies). More importantly, upon addition of the solid base catalyst, reaction is *only* observed in those systems that exhibit a phase change to a melt.[15] Thus, *the existence of a liquid phase is a prerequisite for reaction in these systems!* In systems such as these, which require addition of an acid or base catalyst, it is possible to construct the phase diagram for the two component reagent mixture. Measurement of thaw and liquidus points for the system indan-1-one **2** and 4-phenylcyclohexanone **3** yields Fig. 6. The eutectic temperature of 19 °C is below the ambient temperature of the reaction experiments. However, it is interesting to note that at a 1 : 1 mole ratio of **1** : **2** the liquidus temperature is above ambient *T*, implying that some unmelted solid **2** would be present. This is not observed in the bulk samples and may indicate the tendency of the system to supercool.[88] In addition, this implies that some heat is released on grinding of the two components which leads to complete melting of the mixture. Such heat may be generated by the occurrence of 'hot spots'[89] during initial grinding of the solids and this phenomenon should be carefully considered when high intensity grinding techniques, such as ball milling, are employed (even in cases where temperature-controlled apparatus is used).

Similar melt behaviour is noted in a number of reactions and, for example, trimerisation of benzylic alcohols, achieved by grinding 4-allyloxy-3-methoxybenzylalcohol with one equivalent of tolyl-*p*-sulfonic acid, yields a viscous melt that solidifies over a period of days yielding **16**, R = allyl (Scheme 7), which separates as a microcrystalline solid. Once again, this solvent-free reaction is not a solid–solid reaction in spite of the relatively high melting points (86 °C and 103–105 °C, respectively) of both reagents. One mole of water is produced for each mole of benzyl alcohol condensed, but this does not account for the apparent liquefaction of the reaction mixture. Although the viscosity of the monomer–acid mixture is lowest directly after the grinding of the two components, TLC analysis reveals < 5% product at this point. Thus, the water present is derived chiefly from the monohydrate catalyst and would be insufficient to achieve dissolution of the very sparingly soluble benzyl alcohol monomer.

Highly efficient solventless transformations of benzaldehyde and aniline derivatives have been reported previously,[90] and the reaction between *o*-vanillin **24** and *p*-toluidine **25** to yield the azomethine product **26** (Scheme 10), provides a striking example of a melt phase on mixing of the solid reagents.

Mixing of the finely powdered reagents (without grinding) immediately yields a bright orange fluid that has a low viscocity and may be drawn into a pasteur pipette as illustrated in Fig. 7. This liquid rapidly solidifies yielding a bright orange crystalline solid that is slightly wetted (presumably by the water produced in the condensation reaction). As with many solventless reactions, reaction is rapid and conversion virtually quantitative. Aside from drying, no further purification is required.

Clearly many of the so-called 'solid–solid' reactions are not reactions in the solid-state. Solid–solid reactions occurring between two discrete crystalline solids, without intervention of

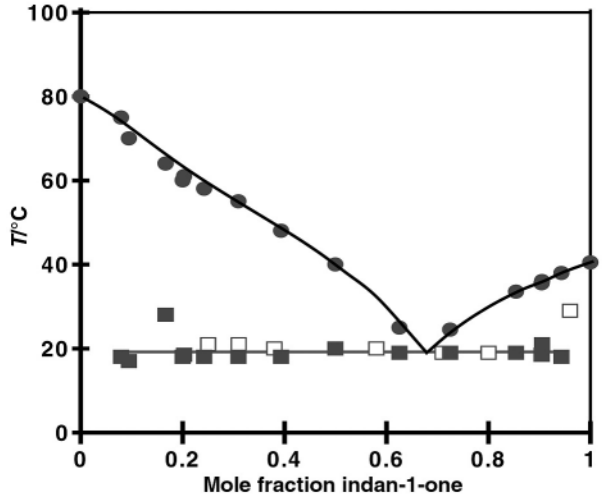
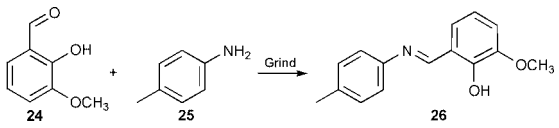


Fig. 6 Phase diagram of indan-1-one **1** and 4-phenylcyclohexanone **2** at constant (ambient) pressure. Filled circles represent liquidus temperatures, filled squares, thaw points, and open squares the onset temperature of the first endotherm measured by DSC analysis.



Scheme 10

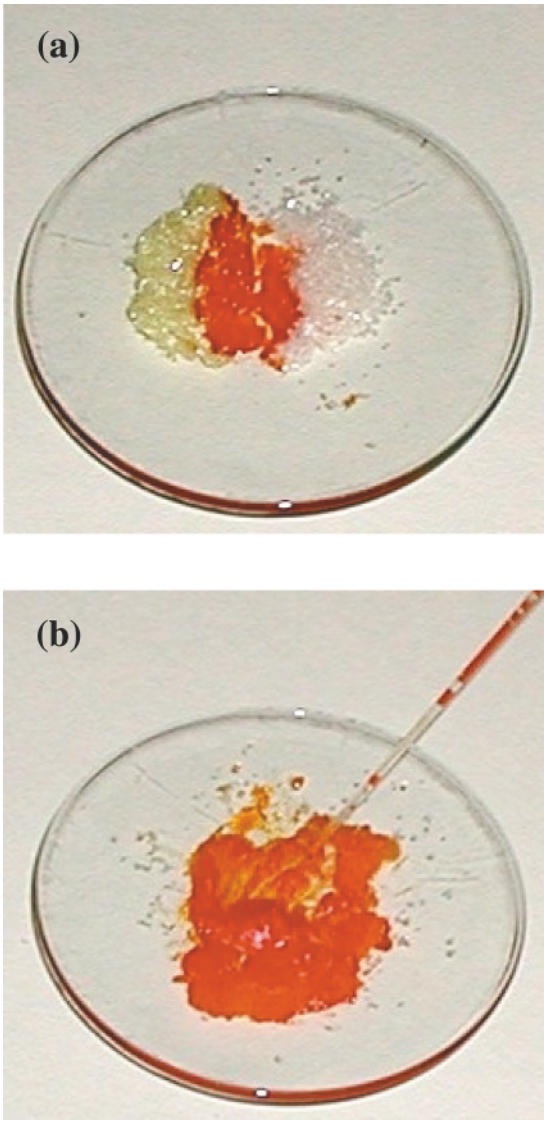


Fig. 7 Photographs of liquid phase formed upon mixing of *o*-vanillin and *p*-toluidine. (a) Pale yellow crystalline *o*-vanillin (left) and white crystalline *p*-toluidine (right) form an orange liquid phase upon contact. (b) The orange liquid phase is fluid enough to be drawn into a Pasteur pipette and solidifies rapidly to form the orange crystalline solid azomethine product.

a mobile phase (which allows a large number of productive molecular collisions) would be expected to exhibit diffusion-controlled kinetics.[91] Thus, the rapid rates noted do not support the theory of two solids reacting together without intervention of a new (liquid) phase that enables higher substrate mobility.[20]

A description of the behaviour noted is described: upon mixing of the reagents, a melt of mutually miscible A and B exists, so that these may be considered to be *mutually soluble*. In the reaction A + B ⇒ C, the overall phase equilibria may be represented by a triangular prism as shown in Fig. 8a. In this prism each rectangular face represents one binary diagram (AB, AC *etc*.).[92] Since the reactions are not thermally isolated these approximate systems at constant *T*, and the chemical and phase composition may be represented by triangular cross sections of the prism such as the central triangle in Fig. 8(b) which represent a cross-section at *T*1. This figure illustrates the situation where the temperature is above that of the binary eutectic formed by A and B (and above the binary eutectics formed by A and C, B and C and the ternary eutectic formed by A, B and C). Thus as A and B react in 1 : 1 stoichiometry to form product C the composition changes along the line qC. The liquid phase, initially composed of 1 : 1 A : B, becomes enriched in C until the liquidus line is crossed and C begins to crystallise out of the melt. At complete conversion the only phase present will be a solid, crystalline C. As the quantities of A and B, relative to each other, remain constant throughout the reaction, a vertical section of the triangular prism such as Fig. 8c can be used to depict the phase equilibria occurring. Each face of the prism is in fact a two component diagram such as that appended to the base of the triangular cross section in Fig. 8b. It may be illustrated that a number of reactive systems exhibit 2 component phase diagrams AC and BC such as those represented as dotted rectangles appended to the sides of the triangle (Fig. 8b).

Overall, these reactions should therefore be classified together with classical liquid–liquid and liquid–solid systems that react in the absence of an added solvent such as many of the solid–liquid or liquid–liquid systems presented above.

Future trends

The remarkable versatility and success of using solventless reactions to prepare several classes of compounds demonstrates that this methodology has an important place in the toolbox arsenal for Green Chemistry. In accepting the enormous challenge of Green Chemistry in the march towards sustainability, new chemistry can emerge as well as access to compounds not possible using traditional methods, and on this

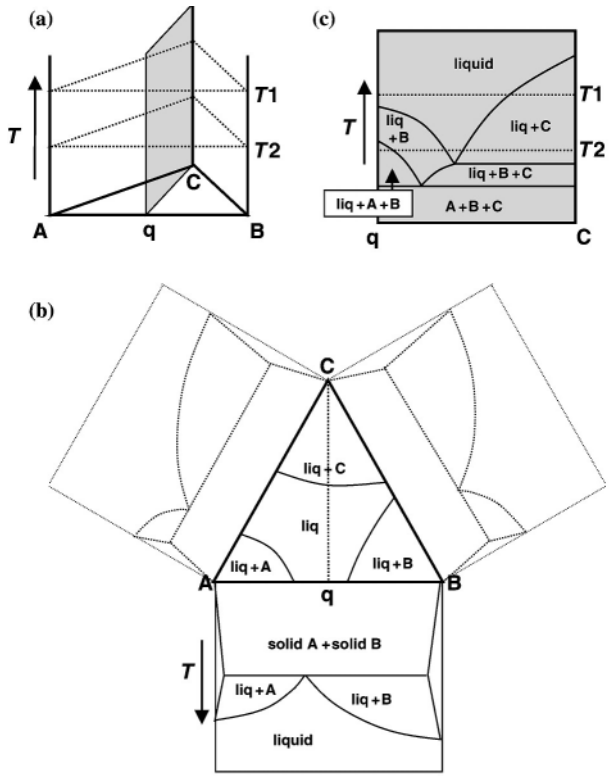


Fig. 8 (a) Triangular prism basis for a 3 component phase diagram at constant *P* (vertical axis represents increasing *T*). Consideration of cross sections such as *T*1 and *T*2 allow analysis of the phases occurring at various component concentrations at a specific, constant temperature. (b) Represents a cross section of this prism at a particular temperature (central triangle) greater than the AB, BC, AC or ABC eutectic temperature (note liquid phase at *C* = 0). (c) Diagram representing constant A and B composition of 1 : 1 mole ratio with increasing *T*. Moving along the dotted lines marked *T*1 and *T*2 indicates the phase changes occurring as *C* increases.

issue alone, the results challenge the classical approach of using volatile organic solvents in synthesis. Green Chemistry is an area of chemistry where applied and fundamental research collapses with a common thread of sustainability. It also challenges the description of certain classes of reactions between organic solids as being solid state reactions. Applying the principles of Green Chemistry has led us into developing new building blocks for supramolecular chemistry, and establishing protocol for organic synthesis. In this context then the question is: 'why wouldn't you want to embark on research in Green Chemistry?'

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