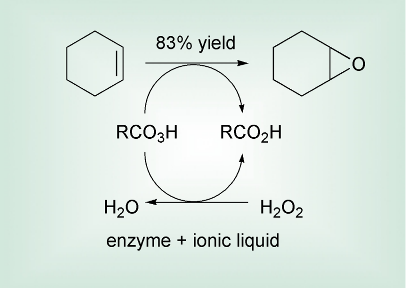
Highlights

Duncan Macquarrie reviews the latest research in green chemistry

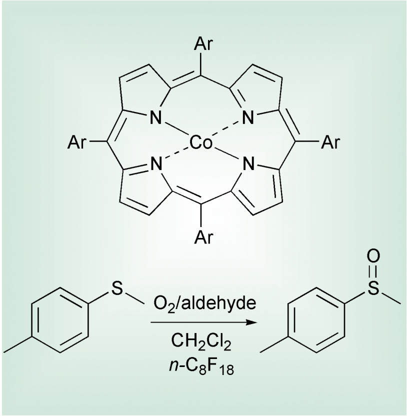
Novel solvent systems

The search for alternatives to traditional solvents continues to be an important goal, and the three papers below illustrate quite different aspects of the search for novel solvent systems.

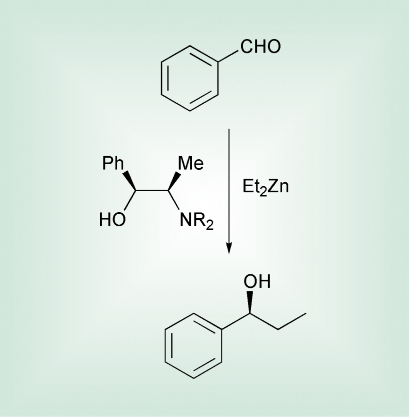
Ionic liquids represent a class of solvents which are increasingly being found to be highly versatile. Based around imidazolium salts, these solvents are liquid over a wide range, but do not have any significant vapour pressure, thus avoiding the difficulties and expense of VOC removal from waste gases. Examples of the versatility of these reaction media can be found in *Green Chemistry* (*e.g. Green Chem.*, 2000, **2,** 123; 1999, **1**, 23; 1999, **1**, 296). One of the latest examples of their utility has been published by Roger Sheldon of the Delft University of Technology (*Org. Lett.*, 2000, **2**, 4189). His group has shown that lipases are active in ionic liquids, illustrated by the transesterification and ammoniolysis of ethyl octanoate, and the epoxidation of cyclohexene by a combination of hydrogen peroxide and octanoic acid, all catalysed by *Candida antarctica* in ionic liquids. Rates and yields were generally good, in some cases better than in organic solvents.



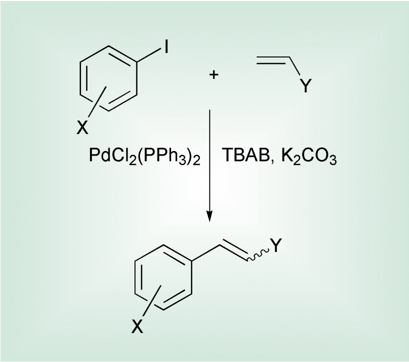
Fluorous biphasic catalysis is a second area which is receiving much attention, with the possibility of using the thermally-controlled miscibility of fluorous and organic phases to effect separation of fluorous phase-soluble catalysts from organic-soluble product. Gianluca Pozzi from the University of Milan has recently described the oxidation of sulfides using fluorous Co-phthalocyanins (*Eur. J. Org. Chem.*, 2001, 181). He found that these catalysts were capable of the efficient oxidation of sulfides to sulfoxides, with minimal over-oxidation in most cases. The oxidant system was oxygen / dimethylpropanal, taking advantage of the excellent solubility of oxygen in highly fluorinated media. Despite the excellent activity and selectivity achieved in the first run, reuse of the fluorous phase proved problematic, with either dramatic reductions in conversion, or bizarrely, extensive over-oxidation to sulfone. These changes were ascribed to oxidative changes to the catalysts, something which was not observed in earlier work on epoxidation.



Non-solvent reactions are becoming popular, and many reactions can be carried out without solvent, with obvious advantages. What is particularly rare is the successful translation of enantioselective reactions, since the choice of solvent is often critical to achieving high selectivity. Kenso Soai of the Science University of Tokyo has published details of such a system (*Chem. Commun.*, 2000, 2471). He takes a β-aminoalcohol as chiral auxiliary, in conjunction with diethylzinc, and reacts this complex with benzaldehydes, transferring the ethyl group to the carbonyl function, giving chiral alcohols. Whereas these reactions run typically in hydrocarbon solvents, Soai has shown that they can also be carried out very successfully without solvent. His group has used a series of catalysts, each of which gave yields of $\geqslant 93\%$ and ee's of 85–89% with reaction rates greater than when solvents were used.



The Heck reaction is one of the most important C–C bond forming reactions known, and many variations have been published since the initial work in the 1960s. Jin-Xiang Wang and co-workers from Northwest Normal University in Lanzhou have now published details of the Heck reaction carried out in water with microwave irradiation (*J. Chem. Res. (S)*, 2000, 484). They found that the combination of water as solvent and microwaves afforded excellent yields (86–93%) of various coupling products from the reaction of aryl iodides (nitro, carboxyl and methyl substituents) and substituted alkenes (phenyl, acid and ester substituted). Only ten minutes irradiation was sufficient to complete the reactions as compared to 3–7 hours for conventional heating.

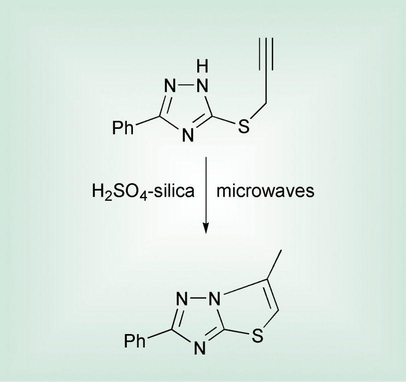


Microwave reactions

Two further papers concerning the use of microwaves have recently been published, and are summarised below:

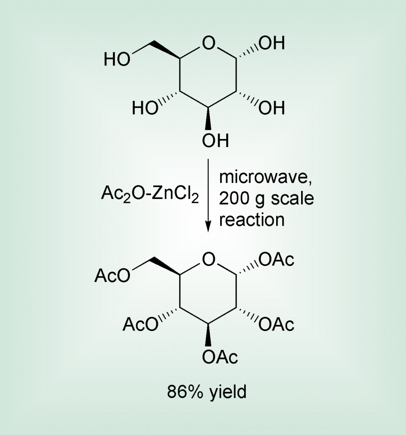
The group led by Majid Heravi at the Ferdowsi University of Mashhad in Iran have shown that microwaves can be used

DOI: 10.1039/b100267h



in conjunction with sulfuric acid / silica gel to effect the cyclisation of a series of alkynyl heterocycles to yield bi- and tricyclic thiazoles (*J. Chem. Res. (S)*, 2000, 482). Five to ten minutes reaction time were required to achieve good to excellent yields.

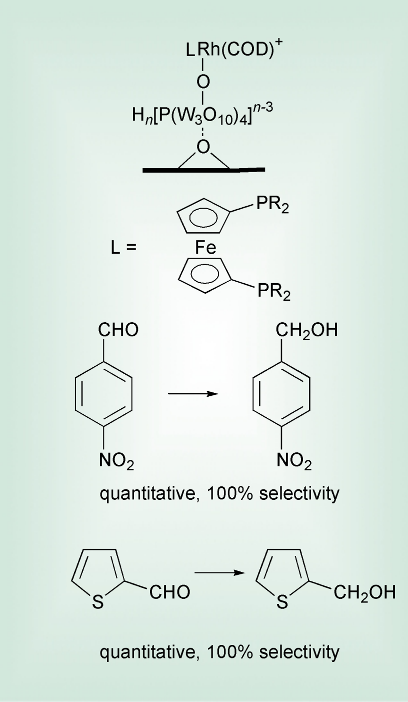
The question of scale-up of microwave reactions is an important one, and work relating to this key obstacle to commercialisation of microwave chemistry has been reported by A Loupy and co-workers from the CNRS in Gif-sur-Yvette and the Universite Paris-Sud (*Org. Proc. R+D*, 2000, **4**, 498). They have shown that, using a commercial microwave reactor, batch sizes of several hundred grams could be safely handled and rates and yields were comparable to those found in smaller (< 5 g) scale operations. A range of different reaction types (alkylation of KOAc, phenacylation of triazoles, dealkylation of 2-ethylanisole; peracetylation, glycosylation, saponification, halogenation and epoxidation of carbohydrates were also demonstrated).



For a recent review on microwaves in synthetic chemistry see *Green Chem.*, 1999, **1**, 43.

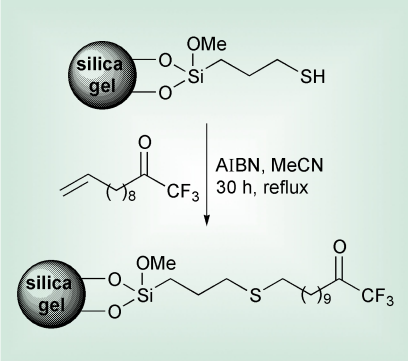
Homogeneous catalyst immobilisation

The recently developed strategy for immobilisation of charged transition metal complexes developed by Augustine (*Chem. Commun.*, 1999, 1257) has been used as the basis of a novel and highly versatile ferrocenyl-rhodium hydrogenation catalyst by researchers at Chirotech (*J. Org. Chem.*, 2000, **65**, 8933). They prepared their catalyst by combining either alumina or silica and a heteropolyacid, and then introducing the catalytic unit as a counterion to the charged heteropolyacid. The catalyst is stable to leaching unless there is a suitably competitive anion which can remove the catalyst from its interaction with the support. The catalyst was very active and selective towards a range of substrates, often displaying much greater selectivity than either homogeneous versions, or other more traditional heterogeneous hydrogenation catalysts. Sulfides are tolerated and do not poison the catalyst. A small amount of leaching was noted during the initial use of the catalyst, but none was found after this, and no reduction in activity was noted.

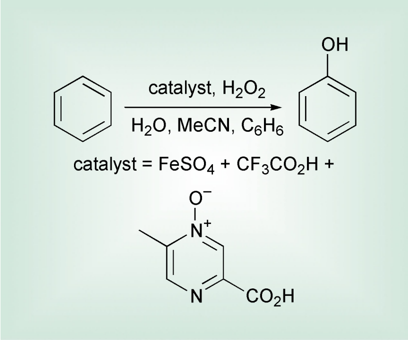


Oxidation reactions

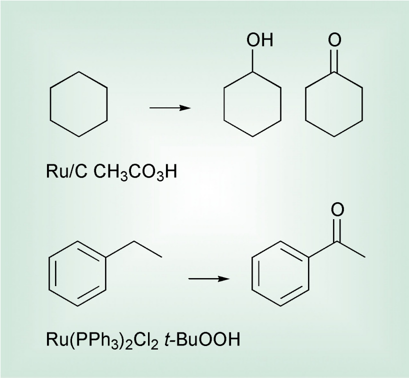
Improvements to an epoxidation catalyst have been reported by the group led by Choong Eui Song of the Korea Institute of Science and Technology (*Chem. Commun.*, 2000, 2415). They have immobilised a trifluoromethyl ketone on silica and compared its activity in the dioxirane-mediated epoxidation of alkenes. Homogeneous ketones catalyse this reaction, but are deactivated by being oxidised themselves to esters via a Baeyer–Villiger oxidation. This side reaction is suppressed, and the catalyst could be recovered and reused ten times with no loss in activity. Activity was comparable to the homogeneous version. A variety of substrates were epoxidised in yields > 90% with the catalyst.



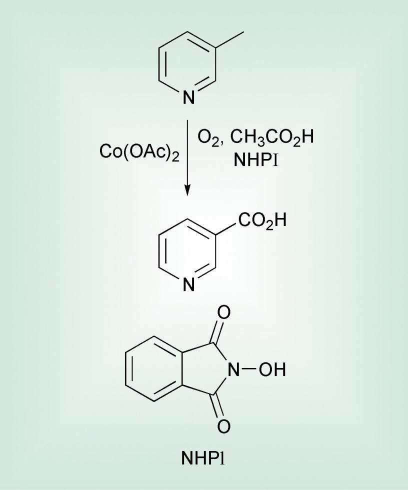
The oxidation of benzene to phenol is an important goal, but is complicated by the greater reactivity of the product phenol, leading to dihydroxybenzenes and their decomposition products. A team led by Daniele Bianchi and Rodolfo Vignola from EniChem in Novarra (*Angew. Chem., Int. Ed.*, 2000, **39**, 4321) has developed a biphasic iron-based catalyst system which give excellent selectivities to phenol at the (relatively) high conversion level of *ca.* 8%. Their catalyst is based on $FeSO_4$ with a pyrazine carboxylic acid ligand and trifluoroacetic acid as cocatalyst. Working in a benzene–water–acetonitrile biphasic system (to partition the product away from the catalyst) they achieved 97% selectivity to phenol at 35 °C. The catalyst also displays activity in the oxidation of methane to formic acid.



Shun-Ichi Murahashi and co-workers from Osaka University have published their results on the Ru catalysed oxidation of alkanes with peroxy species (*J. Org. Chem.*, 2000, **65**, 9186). They first studied the oxidation of cyclohexane to a mixture of alcohol and ketone and found that Ru-charcoal with peracetic acid gave excellent selectivities and reasonable yields. Yields could be improved substantially by the addition of trifluoroacetic acid (up to 90% conversion of cyclohexane could be achieved. A second area of investigation was the room temperature oxidation of alkyl aromatics, where the optimum system was Ru(PPh_3)$_2$$Cl_2$ and *t*-BuOOH. With this combination conversions ranging from 46–100% were achieved for a range of alkyl aromatics with selectivities of 54–95%.

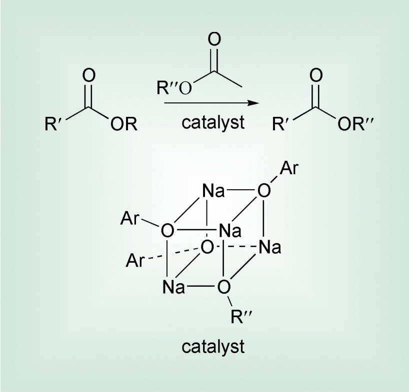


The related oxidation of methylpyridines to pyridine carboxylic acids has been investigated by Yasutaka Ishii and his group based at Kansai University in Osaka (*Org. Proc. R+D*, 2000, **4**, 505). In the latest in a series of papers on the use of *N*-hydroxyphthalimide (NHPI) as an oxidation catalyst, they report the efficient oxidation of 3-methylpyridine to the corresponding acid in 77% yield using 10 mol% NHPI, 2 mol% Co(II) acetate and 1 atmosphere of oxygen at 100 °C. The addition of 0.5 mol% Mn(II) acetate allowed the reduction of the Co level to 0.1 mol%, thus reducing the total amount of metal present. Thus, the use of NHPI allows milder conditions to be used for this type of oxidation than the normal high temperature and pressure systems currently in use.



Transesterifications

Transesterification is an important reaction type, catalysed either by strong acids or by strong bases, particularly alkoxides in the corresponding alcohol. Rebecca Kissling and Michel Gagné of the University of North Carolina have extended their previous work on alkoxides in non-protic solvents by optimising the structures of the inorganic clusters formed (*Org. Lett.*, 2000, **2**, 4209). They have found that in non-protic solvents, clusters of alkoxides form which are more reactive than the species found in alcohols. By modifying the clusters such that insoluble (and therefore inactive) clusters do not form, they have successfully extended the lifetime of these catalysts. This involved the use of both aryloxides and alkoxides to give the clusters shown in the diagram. With these clusters essentially quantitative transesterifications could be achieved with as little as 0.5 mol% catalyst, compared with the 5–10 mol% (and multiple addition strategies) normally required.



Super-efficient dyes for the coloration of cotton —the Procion® XL+ range

Dr. W. J. Ebenezer and Dr. M. G. Hutchings of DyStar UK Ltd. describe the environmental benefits available from the Procion XL+ range of reactive dyes for cotton

The discovery of the first synthetic textile dyestuffs half way through the 19th century heralded the beginning of the modern organic chemical industry. Nevertheless after a further 144 years of intensive dye research and development there still remains a need for yet more innovation in response to today's commercial, technical, and crucially environmental pressures. Over the last 5 years our team has invented and ultimately commercialised the new

Procion XL+ range of dyes for cotton. Their outstanding technocommercial properties are augmented by a combination of notable environmental advances which together have been recognised by the 2000 UK Green Chemistry Award. This article gives an overview of this technology.

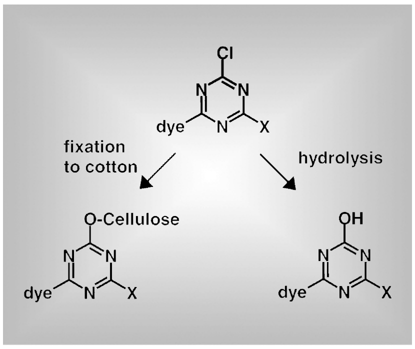
Background

Technical

Reactive dye molecules are characterised by a chromophore, to impart colour, attached to a reactive group. The latter is invariably an electrophilic species capable of reacting with cellulose, and thereby binding the chromophore to the cellulose covalently. Such dyes are water soluble by virtue of sulfonation, and are applied to cellulose from aqueous solution, under conditions which induce covalent bond formation between dye and cellulose. The subject of this innovation is a new range of dyes for application to cotton by so-called exhaust dyeing. Although the industrial technology of dye application is highly advanced and can be complex, the easiest picture of the dyeing process of relevance here is a solution of the dye plus the cotton to be dyed, to which are usually added salt to force the dye onto the fibre, and base to induce cellulose nucleophile–dye electrophile reaction. The heterogeneous mixture is heated for a period to induce reaction.

A major concern is competing hydrolysis of the dye electrophile by water at elevated pH, yielding dye which can no longer be attached permanently to the substrate, but which must nevertheless be removed in a wash-off sequence, and then discarded to effluent. Coloured effluent generated in this way can give rise to environmental problems. No commercially available reactive dye avoids the unfortunate hydrolysis problem despite some claims to the contrary. Despite this drawback, reactive dyes are attractive to the textile dyer because of their ease of use, fastness properties, brightness and the wide range of shades. In general, they are used at the higher quality end of the cellulosics market. Current main areas of commercial expansion are in sportswear, for example knitted cotton T-shirts.

An important concept to understand is that dyers rarely use a single dye when dyeing cotton with reactive dyes. Under most circumstances, a mixture of dyes is utilised to achieve the desired shade. This makes it possible to achieve an infinite number of shades with a small number of dyes. Achieving the exact shade requires some skill and re-dying is sometimes necessary with a shading addition to correct the shade. In extreme cases, the cloth may be stripped of colour and completely re-dyed, but this is both a commercial and environmental last resort. One of the root causes of problems in achieving the required shade is that if the dyes in a mixture have different dyeing profiles the shade and depth may change with time. Therefore, the timing of the dyeing process is critical.



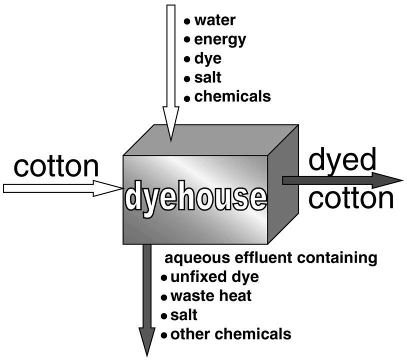
Historical – scope of the environmental problem

Reactive dyes for cotton were invented and commercialised by ICI in the mid-1950s. The superb level of wet fastness properties exhibited by these dyes led to their rapid acceptance and increasing popularity. Over the following decades research into new patented reactive dyes allowed incremental improvements in the gamut of shades available, fastness properties, and especially the fixation efficiency.

Currently, the total world-wide production of cotton is estimated at 21 × 10^6 te *p.a.* (metric tonnes *per annum*) The corresponding amount of reactive dye used for cotton coloration is estimated to be 120,000 te *p.a.* Of this about two thirds is dyed by exhaust technology. Salient statistics, which follow from these figures, include:

- 4 × 10^6 te *p.a.* of cotton is exhaust dyed with reactive dyes;
- 4 × 10^8 te *p.a.* of fresh water is used in the overall process, and all of this is ultimately discarded in a contaminated state;
- 2.8 × 10^6 te *p.a.* of salt is used in the process; and all of this is ultimately discarded in the aqueous effluent;
- 8 × 10^4 te *p.a.* of reactive dye is applied, with an average fixation yield of 70%, thus:
- 2.4 × 10^4 te *p.a.* of dye is discarded in the aqueous effluent.

Most aqueous effluent is discarded *via* local watercourses. The dyer at the dyehouse removes some colour but not salt and other additives. Nevertheless a large amount of colour finds its way to waste water treatment works and possibly further. The environmental load is therefore appreciable and has a wide impact.

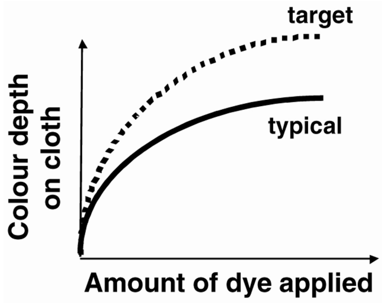


The reactive dye business, due to its maturity, is extremely competitive and price sensitive. As older dye technologies have moved out of patent, these have been taken up by manufacturers in the developing world, driving down manpower costs and total production costs. Therefore, a large proportion of cotton processing has also moved to the cheaper and currently less environmentally conscious economies of the developing world.

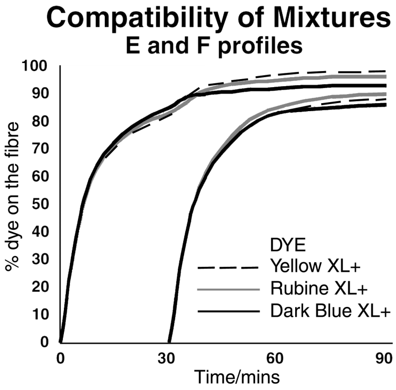
The target

In 1995 our research and technical marketing departments outlined the technical profile for a new prospective range of reactive dyes to compete effectively against cheap non-patented commodity reactive dyes. The new range should enable build-up to unprecedented depths of shade on cotton, *i.e.* the maximum depth of colour attained on the cloth should be much greater than conventionally observed. This would allow very strong colours to be obtained *using less dye*. The cost on the cloth should be at least 25% less than the market leading dyes in the individual shade ranges. In addition to the economy of coloration, the total cost of production should exhibit a step change improvement on the current state of the art.

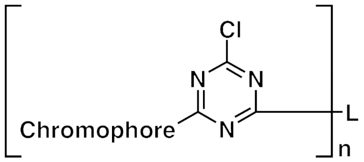
The principal method of approach toward production cost reduction was to enable *Right-First-Time* production and improve dyehouse productivity. This involved molecular engineering of the new range of dyes to exhibit almost



perfect compatibility—such that any combination of the dyes will behave *as if it were a single component*. The new range of dyes should exhibit no shade change during the course of the dyeing. The graph below shows the virtually superimposable exhaustion (upper traces; total dye, fixed and unfixed, on the fibre) and fixation (lower traces; dye covalently bound to the fibre) profiles for the new dyes on cotton versus time, during the course of a dyeing. Additionally, the dyes were required to be insensitive to changes in dyeing conditions—*i.e.* mistakes by the process operator would still yield a dyeing within specification.



The exhaust reactive dyeing market for cotton is segmented broadly into two areas, warm dyeing (60 °C) and hot dyeing (80 °C), with warm dyeing accounting for the majority (60%) share principally due to lower recipe costs. Perversely a project decision was made to target the new dye range for 90 °C dyeing; this decision subsequently yielded a large number of non-intuitive benefits.



multifunctional deactivated dyes

After 4 years of intensive effort involving cross-functional project teams, new patentable dyes had been invented and production processes developed. These products were commercialised in 1999 as the Procion XL+ range of reactive dyes. Reactive dyes consist of chromophoric units to provide the colour, plus various non-coloured functionality. The non-coloured weight consists of reactive groups, linking functionality, holding the various parts of the molecule together, and other groups which are used to alter the application properties. A major goal of our synthetic effort was to minimise the proportion of non-coloured organic weight in the dye molecules and thus use the carbon atoms within to produce colour more efficiently. The effect of this was to make dyes with high colour strength such that less dye is utilised to achieve a particular level of shade. The dyes are based on monochlorotriazine reactive groups attached to carefully designed chromophores. The reactivity of the chlorotriazine unit toward cellulose has intentionally been tuned to the desired 90 °C application profile by selection of appropriate aliphatic di- and tri-amine linking units, L. The linkers used in the various dyes also contribute to the compatibility of dye combinations. Commercial confidentiality inhibits more detailed disclosure of the chemistry underpinning the Procion XL+ dyes.

Benefits

The beauty of the Procion XL+ system is that it provides productivity benefits from two distinct sources.

The first derives from a reduction in the overall length of the dyeing process. The normal exhaust dyeing process for cotton is in three stages; preparation of the fibre (including removal of knitting oils, *i.e.* scouring); dyeing; and finally wash-off plus any after-treatment. The higher dyeing temperature allows a shorter and simpler application profile. Of particular note is the ability to combine the scouring and dyeing processes *in a single stage*. The net effect of this is a load-to-unload time of as little as 3 hours, less than half that of a conventional exhaust reactive dyeing process. This can double the productivity of a dyer, *i.e.* one dyeing machine does the work of two.

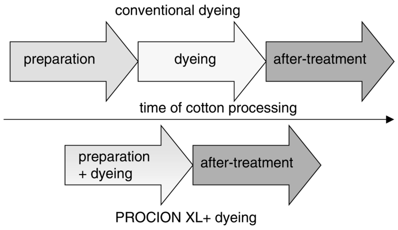
The second productivity benefit originates from the reliability of the dyes. Reproducibility levels approaching 100% (*i.e.* a *Right-First-Time* level of 100%) may be achieved, both in laboratory-to-bulk and batch-to-batch, due to the near perfect compatibility and robustness to process variables of the dyes. Customers are achieving *many months* of fault free dyeing. This eliminates the environmental drawbacks of reworking unacceptably dyed goods, such as more chemicals (including hydrosulfite for dye stripping), more energy and more water.

A reasonable estimate of the average proportion of exhaust dyed product, which falls outside the desired specification with conventional reactive dyes, is 15%. Thus, figures which follow from this include:

- 6×10^5 te *p.a.* of cotton requiring redyeing
- 6×10^7 te *p.a.* more fresh water
- 4.2×10^5 te *p.a.* more salt utilised

Use of Procion XL+ dyes negates the necessity to use these resources as well as the extra dye and associated chemical auxiliaries. In addition the time, manpower and financial resources of the dyehouse not being used in reworking can also be directed more profitably.

The combined effect of these two features is a step change in dyehouse productivity with enormous seen and unseen environmental benefits particularly around maximising the use of resources. Thus, fewer dyeing machines are needed and used in fewer dye works, requiring less manpower. The resultant increase in dyeing efficiency should mean that the most antiquated and environmentally unfriendly “low tech” dyehouses suffer disproportionately and disappear, thus having large environmental benefits although not necessarily where the technology is employed.



This new faster technology leads to up to 50% reduction in energy usage for the dyeing of cotton (independently audited), despite the use of a higher dyeing temperature.

Reactive dyeing of cotton uses a large amount of water, typically 100 litres per kg of cotton. As a result of the telescoped dyeing process, which removes the separate pre-treatment stage, coupled with efficient wash-off of unfixed dye (after-treatment step), the new dyes require up to 40% less water. Water usage and effluent discharge are a very high environmental priority, particularly in dry countries as fresh water is an increasingly scarce and valuable resource. Thus, this property is a major benefit to the dyer and surrounding community.

A typical value for salt usage is 700 g per kg of cotton. Procion XL+ dyes have been designed to have higher affinity for the cotton, in concert with superior migration properties, and therefore the total salt use is reduced by up to 33%. This impacts very favourably on aqueous effluent being discarded into local fresh watercourses.

Higher dye fixation has been designed successfully into Procion XL+ dyes. This obviously results in a reduction in colour in effluent leading to less 'coloured rivers' or less need for treatment to remove the colour from the effluent.

A related benefit is the reduced COD, BOD and TDS of the aqueous effluent, because of less dye, and also less chemical auxiliaries used to remove colour from the effluent.

An unexpected benefit of the Procion XL+ dyes was discovered through an examination of the bioadsorption of reactive dyes onto activated sewage sludge. The most important colour when considering pollution is red as the eye is very sensitive at this wavelength. It was discovered that the red Procion XL+ dye, which exhibits some novel chemical functionality, is very highly bioadsorbed, up to 20 times more than other commercial red reactive dyes. This means that any Procion Rubine XL+ dye in dyehouse effluent is efficiently removed at sewage works, virtually eliminating the possibility of colour pollution of rivers by this most visible dye.

Traditionally, very deep bright red and wine shades on cotton are dyed using azoic dyes. This very old procedure involves the synthesis of the azo dye chromophore within the cotton fibre. It is an extremely inefficient process and environmentally very undesirable. It is also notoriously difficult to control the resulting shade which exacerbates the environmental impact of this process. The exceptional build up characteristics of the Procion XL+ dyes now enable a number of deep red shades to be dyed without the use of azoic dyes. The reliability and efficiency of the Procion XL+ process has already led to a number of reactive dyers gaining business in traditional azoic shade areas and it is reasonable to assume that this trend will continue, thus contributing to the positive environmental impact.

Additionally, Procion XL+ dyes exhibit very high tolerance to the levels of calcium and magnesium ions in the water used for dyeing. This removes the need for sequestrants, which would ultimately be discharged to effluent and also improves the robustness of the process to variations in source water quality.

The Procion XL+ range also meets all of the product safety standards required of new dyestuffs.

Outlook

Within 5 years of the start of the research phase of the project, Procion XL+ dyes are already making major inroads into the cotton dyeing market and have enormous potential to reduce the visible and invisible environmental impact of one of the most basic and fundamental industrial processes used world-wide. Nevertheless there remain environmental hurdles to overcome in the colouration of cotton, and investigations at the DyStar research facility in Cheadle continue to address these issues and further improve the environmental profile of this important industry.

Focus On… Professor Keith Smith, University of Wales Swansea

The University of Wales Swansea will be the venue for the first major conference on Green Chemistry to be held in the UK (3–6 April 2001). Mike Lancaster continues the *Focus On …* series of articles by highlighting some of the work being carried out there by Professor Keith Smith

Keith Smith's initial involvement with clean technology arose almost accidentally nearly 20 years ago. At that stage Smith's main interest lay in organoboron chemistry and it was during the study of the synthesis of chloroalkanes from reaction of alkylboranes with dichloramine-T that one of his observant students noticed a strange reaction occurring during column chromatography of the reaction products. Some new products, that were not present in the crude reaction mix, were formed during column chromatography on silica. After careful examination it became evident that the silica was acting as a catalyst for chlorination. This was proven by chlorination of toluene with reagents such as *tert*-butyl hypochlorite as well as dichloramine-T in the presence of silica. These findings aroused Smith's interest in the whole area of heterogeneous catalysis and supported reagents. In particular his initial thoughts turned to improving selectivity (and hence reducing waste) of the chlorination process by using zeolites in place of silica. This in turn generated significant industrial interest and sponsorship from companies such as BP.

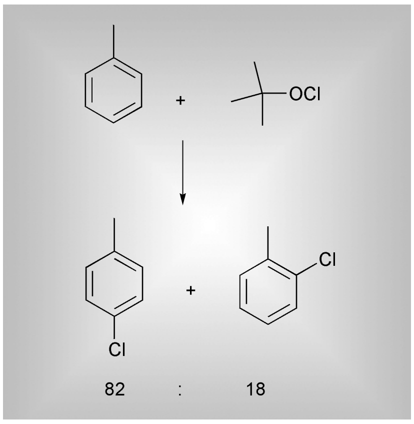
Selective halogenation

Isomerically pure chloroaromatics are valuable intermediates for fine and

Keith Smith, Professor of Organic Chemistry at the University of Wales Swansea.

pharmaceutical chemicals. However traditional synthetic methods usually suffer from lack of selectivity resulting in the production of significant amounts of unwanted products and waste *etc*. Zeolites, with their active sites embedded in well-defined pores of molecular size, should be capable of selectively delivering mono-chlorinated positional isomers from simple aromatic substrates such as toluene. Smith's group has extensively explored such reactions looking at parameters such as zeolite type, solvent and chlorinating agent. Using toluene as substrate and *tert*-butyl hypochlorite as chlorinating agent, studies showed that zeolites need to contain acidic sites in order to catalyse the ring chlorination reaction. However, the A-type zeolites, which have small pore sizes, were ineffective. The best results were obtained with the largest pore sized zeolite tested - partially proton exchanged faujasite X (HNaX) in acetonitrile solvent. In this case the *p/o* ratio was over 4.5:1. In addition the reaction occurred rapidly at 25 °C in quantitative conversion.

This reaction proved quite general, with even better selectivities being obtained with other monosubstituted benzenes. The methodology has also been adapted to the selective *para*-bromination of phenyl acetate using bromine. In this case it was observed that HBr evolved during the reaction was catalysing both *para* and *ortho* bromination leading to low selectivities. By using zeolites with low acidity, such as NaY, very high selectivities could be obtained. In addition to providing an appropriate catalyst size within the pore these zeolites also mop up HBr formed during the reaction thus preventing the more general acid catalysed process from taking place.



Aromatic nitrations

Aromatic nitro compounds are of significant commercial interest, being useful intermediates for the pharmaceutical, agrochemical, dye, and explosives industries. The technology normally employed involves use of nitric acid and stoichiometric amounts of sulfuric acid, which is required to generate the active nitronium ion. Whilst this process is economical it suffers from two major problems; the first is the generation of large amounts of spent acid for disposal and the second is poor selectivity, especially to the *para* isomer, which is often required.

Smith's initial involvement with nitration chemistry was aimed at solving the second problem using his zeolite expertise. An extensive study of the catalytic effect of zeolites of varying pore size and acidity on the nitration of toluene using acetyl nitrate (generated *in situ* from nitric acid and acetic anhydride) was undertaken. As expected zeolite activity varied enormously, the best overall results being obtained using zeolite Hβ which has a relatively large pore size to aid diffusion, but small enough to give high *para* selectivity as well as high acidity. By optimising catalyst loading, temperature and acetic anhydride quantities (stoichiometric amounts are needed) *p/o* selectivities of 4:1 could be obtained—a considerable improvement over previous methods. Smith readily admits however that this process is still not ideal, for example stoichiometric amounts of acetic acid are produced which, although easily removed by distillation and potentially reused in another process, adds to the cost and detracts somewhat from the eco-efficiency of the process.

More recently Smith has started to work on a nitration process which would largely overcome the issue of waste production. In terms of atom efficiency a process based on dinitrogen tetroxide would have many advantages as shown by the equation below.

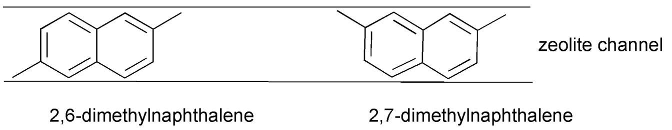
$$\mathrm{ArH} + 2\mathrm{N_2O_4} + \mathrm{O_2} \xrightarrow{\text{catalyst}} 4\mathrm{ArNO_2} + 2\mathrm{H_2O}$$

In preliminary work zeolite Hβ has again proved an effective catalyst. For example in the nitration of chlorobenzene *p/o* selectivities of over 6.5 have been achieved. This novel technology will undoubtedly be further explored and offers good potential for a highly selective, waste-free, cost-effective process that many sectors of the chemical industry would be interested in. This is one area in which Smith would like to make a commercially valuable breakthrough.

Aromatic alkylation

Smith's ability to spot commercially relevant problems is amply demonstrated by his work on the clean synthesis of 2,6-dialkylnaphthalene. Naphthalene-2,6-dicarboxylic acid is used to prepare poly(ethylene naphthalenedicarboxylate) (PEN) which is increasingly finding use in films, liquid crystal polymers, packaging and coatings for example. Although market growth is increasing the high cost of the dicarboxylic acid is preventing more rapid growth. This high cost is due to unselective and sometimes complex synthetic procedures. An ideal synthesis would involve selective dimethylation of naphthalene followed by oxidation; although this method is used the methylation procedure results in a complex mix of dimethylnaphthalenes (10 isomers are possible!) which need separating. Zeolites were again looked at to provide the answer. Although some improvements can be made there is difficulty in obtaining the 2,6-isomer in preference to the 2,7-isomer. The simplistic diagram below illustrates the problem; in a typical zeolite both isomers require roughly the same diameter of channel.

Smith is happy to point out that solving the methylation problem with current commercially available zeolites is



unlikely. Instead he has concentrated his efforts on higher alkyl derivatives. Using the synthesis of di-*tert*-butylnaphthalene as a model system, yields of the 2,6-isomer of over 60% with a 2,6 : 2,7 ratio of over 50 have been obtained with dealuminated HM zeolite as catalyst and *tert*-butanol as the alkylating agent. The ultimate aim of this approach would be to produce selectively a 2,6-dialkyl product which when oxidised would either produce another valuable co-product (*cf.* phenol production from cumene) or would produce the minimum amount of waste.

Education

Like at most universities there are a variety of chemistry courses on offer at Swansea. Of particular relevance is the *Chemistry with Environmental Chemistry* degree, which includes a module on the *Chemistry of Waste*. Typical subjects covered in this module include sources of waste, waste minimisation, waste treatment, and recycling potential. Several other modules within this course have discussion of topics relevant to green chemistry, including *Consumer Chemistry and Chemistry & Man*.

Professor Smith will be presenting a keynote lecture on aspects of his work at *Green Chemistry—Sustainable Products and Processes* (Swansea, 3–6 April 2001) (for further information contact www.rsc.org/conferences).

Further reading

K. Smith *et al.*, Selective mono-chlorination of aromatic compounds under mild conditions by *tert*-butyl hypochlorite in the presence of zeolites, *Green Chem.*, 1999, **1**, 83–90.

K. Smith *et al.*, A novel method for nitration of simple aromatic compounds, *J. Org. Chem.*, 1998, **63**, 8448–8454.

K. Smith and S. D. Roberts, Regioselective dialkylation of naphthalene, *Catal. Today*, 2000, **60**, 227–233.

K. Smith, Highly regioselective, Lewis Acid-free electrophilic aromatic substitution, *J. Chem. Tech. Biotechnol.*, 1997, **68**, 432–436.

Pipe dreams? Shifting the balance towards clean technology

September 2000 saw the launch of the UK Government's second environmental expenditure survey. Becky Allen looks at the results being generated by similar surveys elsewhere in the world and asks how industry can persuaded to spend on more on cleaner technology.

Environmental expenditure surveys

In September 2000, the UK Department of the Environment, Transport and the Regions (DETR) launched its second environmental expenditure survey. The survey—conducted by environmental consultants URS Dames & Moore—involves over 7000 UK firms and the results are due to be published in May 2001.

The survey will not only provide information that the European Union requires under its Regulation on structural business statistics. By providing an estimate of how much UK firms spend on environmental protection, the survey will also help assess the impact of this spending on the UK's competitiveness and the effect of environmental policy and regulation. According to the DETR: "We need this information . . . to see if there is a shift to using within process or 'clean' technologies to protect the environment during the production process, rather than end-of-process spending ('end-of-pipe')."

The first such survey was conducted by ECOTEC and published in 1999. Kate Martin of URS Dames & Moore told *Green Chemistry*: "We are building on the ECOTEC report and hope to improve and extend it." Despite being a rough and ready estimate of environmental expenditure by UK industries, ECOTEC's survey did reveal some interesting patterns of expenditure, particularly in the chemical sector.

The ECOTEC survey estimated total gross environmental expenditure at between £3,540 million and £5,010 million in 1997. Of this, 73% represented operating expenditure and 27% was capital expenditure, including both end-of-pipe and integrated capital expenditure. When the latter is in turn broken down, ECOTEC estimates that almost three quarters (71%) of capital spending is on end-of pipe and that only 8% of total gross environmental expenditure is on integrated processes. By far the largest spending sector was the chemical industry, accounting for 24% of the UK total, and the chemical sector spent a larger proportion (35%) of its total expenditure on capital spending.

The ECOTEC survey put environmental spending by UK industry at 0.5% of gross domestic product (GDP) which would, if accurate, be far below other European member states. However, figures from the Organisation for Economic Cooperation and Development (OECD) put the figure at 1.5% of GDP in 1996, compared with 1.4% in the USA, 1.5% in the Netherlands and 1.7% in Switzerland.

One of the major problems associated with the survey was the ability of UK

End-of-pipe equipment: UK top ten

- Effluent treatment plant equipment
- Air filters
- Extraction systems
- Solid waste compactors
- Air scrubbers
- Noise reduction
- Waste management and recycling facilities
- Bunding
- Thermal oxidation plant or incineration
- Water metering

Source: ECOTEC, 1999.

firms to supply environmental information. ECOTEC admit that: "[Our] expenditure estimates can only be indicative of broad orders of magnitude, because many firms are still unfamiliar or have difficulties with the definitions of environmental expenditure, and few firms have the information on environmental expenditure readily available." Securing improvements in this area will be an important test of the second survey, which has provided firms taking part with extensive background information. The DETR told *Green Chemistry*: "Companies are starting to be aware that environmental information in company reporting is important. In future we will be able to link into initiatives on company accounting. There are moves to identify environmental expenditure separately in company accounts, so tying the two together is the way forward."

Data aside, the question remains: how best to promote spending on clean technology instead of end-of-pipe measures? The ECOTEC survey found that regulatory compliance was by far the most influential factor driving environmental expenditure, being cited by 79% of UK companies, followed by securing health and safety improvements (35%) and saving money (21%). Most experts, however, believe that a complex mixture of policy instruments set in a stable, long-term framework, are required to stimulate clean technology.

The end of the road for end-of-pipe?

According to Reinhard Coenen and Sigrid Klein-Vielhauer of the Karlsruhe Research Centre: "End-of-pipe technologies are rapidly coming to their limits. Moreover, end-of-pipe technologies are often connected with the shifting of environmental medium to another, for example the application of control technologies for sulfur dioxide or waste water purification technologies leads to creation of solid waste and thus to waste management problems. A more ecological sustainable development requires a change of a paradigm in the engineering approach from an emission-orientated or end-of-pipe approach to a source-orientated approach."

Coenen and Klein-Vielhauer argue that although integrated environmental technology has both economic and ecological advantages over end-of-pipe technology in theory, in practice end-of-pipe technology still dominates. "Against this background, one has to raise the question of why the use of end-of-pipe technologies still dominates environmental protection," they say.

Coenen and Klein-Vielhauer believe that one of most important barriers to clean technology is the dominance of inflexible command and control regulation as instruments of environmental policy in most industrialised nations, whose standards are orientated towards performance of end-of-pipe technologies. They also point to the higher investment and transaction costs of integrated environmental technologies.

To overcome these barriers, they argue that environmental policies must be made more flexible, that economic incentives —such as eco taxes input or emission charges or emission trading—should be used to encourage a move away from end-of-pipe technologies, and that industry will need guidance for entrepreneurial planning through long-term environmental goals and norms.

The UK government appears to agree. In a report on clean technology issued in April 2000, the Parliamentary Office of Science and Technology said: "Innovation flourishes where regulation is flexible and policies stable. No one instrument on its own can stimulate companies to innovate successfully. Rather, a mixture of instruments (and flexibility in the style in which they are implemented) is needed, depending on the specific factors and circumstances of the firms and sectors involved. Also, the policy climate needs to be stable and credible over a protracted period, to minimise risks faced by industry."

Some countries seem to be moving in the right direction. In a similar pattern to the UK, 80% of German environmental spending goes on end-of-pipe technology. In Finland, however, an increasing amount is being spent on clean technology. In 1997, Finnish industries spent a total of FIM 3.3 billion on environmental protection, approximately 42% of which was capital expenditure as opposed to operating expenditure. Unlike both the UK and Germany, process-integrated environmental investment accounts for over half (52%) of capital expenditure, a proportion that has been rising steadily compared to end-of-pipe spending in Finland since 1992. Part of this may be due to structural differences in Finnish industry, says Katja Hietikko, a senior statistician at Statistics Finland: "We have a lot of forestry and basic metal industries. Their processes are quite modern and thus investments are typically process-integrated." But Hietikko suggests that the differences may also reflect attitudinal differences: "Finnish industry has a long history of done end-of-pipe investments, and if they want to minimize the environmental impacts they have to do something to the processes because the end-of-pipe investments are not good enough anymore."

References

UK Environmental Expenditure Survey, DETR, 2000, www.environment.detr.gov.uk/envsurvey/

Environmental protection expenditure by UK industry: a survey of 1997 expenditure, ECOTEC, 1999, www.environment.detr.gov.uk/expenditure97/index.htm

R. Coenen and S. Klein-Vielhauer, *The significance of environmental technology for economically and ecologically sustainable development*, www.jrc.es/iptsreport/vol14/english/ENV1E146.htm

Cleaning up? Stimulating innovation in environmental technology, Parliamentary Office of Science and Technology, 2000, www.parliament.uk/post/report.htm

Environmental protection by Finnish industry in 1997, Statistics Finland, www.stat.fi/

Environmental expenditure, Swiss Federal Statistical Office, 1997, www.statistick.admin.ch/

Statistics Canada, www.statcan.ca/

Eurostat, europa.eu.int/comm/eurostat/

Evolution and growth in 2001

The year 2001 sees a number of significant developments in the world of green chemistry. The year had an excellent start with the *IUPAC International Symposium on Green Chemistry* in Delhi in January. It is very important that developing countries with growing chemical manufacturing bases are at the forefront of the green chemistry revolution. We were delighted that IUPAC agreed to support this meeting and this helped to attract an international group of speakers from India, the USA, East and West Europe, Africa and Japan. Green chemistry conferences later in the year include the first international conference organised by the Green Chemistry Network, *Green Chemistry: Sustainable Processes and Products*, which is to be held in Swansea, Wales, in April. The 2001 *Europacat* conference in Ireland in September will also have a green chemistry theme. *Green Chemistry* hopes to include the latest information on, and reports from green chemistry meetings around the world.

The journal goes from strength to strength; institutional subscriptions have more than doubled since 1999 (the USA being the largest source of subscriptions), as have submissions. The quality of submissions continues to increase and we are pleased to have published work from many of the leading workers in this area of research and a variety of papers from institutions in so-called ‘Third World Countries’, where green chemistry may have its greatest application and impact. As a result of the increased submissions our natural rejection rate has increased to approximately 35%. Hardcopy publication times remain at an average of 120 days from receipt, with web publication even faster.

The journal now offers free contents alerts (www.rsc.org/is/journals/current/ej_update_form.htm); publication of supplementary information to your paper on the web (*e.g.*, videos, structures, related data, software) (www.rsc.org/esi); electronic submission by file upload (www.rsc.org/submissions) or e-mail attachment; and authors are sent, free of charge, electronic (.pdf) files of their papers instead of reprints allowing copies to be printed on demand. Whilst the web version of the complete journal remains free on a site-wide basis only to full-rate institutional subscribers, the web news section is free to both subscribers and non-subscribers.

Subscriptions to *Green Chemistry* were lower than we had planned for in 1999 and this led to caution and a minor cost-cutting exercise in 2000, which affected mainly the use of colour and the number of news pages we published. Colour will still be used in the back section wherever, and whenever, it is appropriate to do so. This measure had no deleterious effect on the quality of the science in the journal, in fact, the quality of work submitted has clearly improved. We are now confident of the financial viability of *Green Chemistry*, even in a very competitive market.

Nonetheless, the continued success of the journal is dependent on encouraging new subscriptions and maintaining the large volume of high quality submissions, we hope that you will continue to lend us your support in both of these areas.

We welcome articles of various types from industrial and other non-academic organisations. We have been particularly pleased to publish articles from companies about green chemistry in practice and this issue sees further examples of this—these are the most powerful arguments to support all of our efforts to persuade more and more companies that green chemistry can achieve economic as well as environmental and societal benefit. Please encourage colleagues in industry to consider publishing their case studies in *Green Chemistry*.

We should not lose sight of the fact that to represent properly what is important in the context of green chemistry, we must continue to publish more than just articles on research and industrial application. *Green Chemistry* news pages continue to provide news on awards, conferences and other activities as well as featuring highlights from the green chemistry literature. Supplementary news material will be available *via* the web —see also the Green Chemistry Network Site www.chemsoc.org/gcn for substantial information on what is happening in the world of green chemistry.

We were very pleased to publish Neil Winterton’s authoritative review on chlorine (*Green Chemistry*, 2000, **2**(5), 173). This exemplifies that, not only are we interested in publishing long (critical) reviews, but also that we welcome challenging controversial issues (though the latter would also be welcome in much shorter forms, *e.g.*, letters!). Educational issues are at least as important as any other aspect of green chemistry and we would very much like to publish more articles on innovative aspects of new courses and relevant educational material. For example, at York we are starting a new Masters (“MRes”) course in Clean Chemical Technology this year and we hope to inform the community about how the course develops and the challenges that we encounter along the way. Therefore, if you are running or planning a course, module, practical or workshop that you think may be relevant to the green chemistry community please let us know—as with industrial application, the most effective means of persuasion is by example.

We would like to extend our sincere thanks to all reviewers and authors of *Green Chemistry* papers, for their hard work and contribution(s) to the journal.

We look forward to your continued support and that of the growing community of green chemists to help ensure *Green Chemistry* is even more successful in 2001.

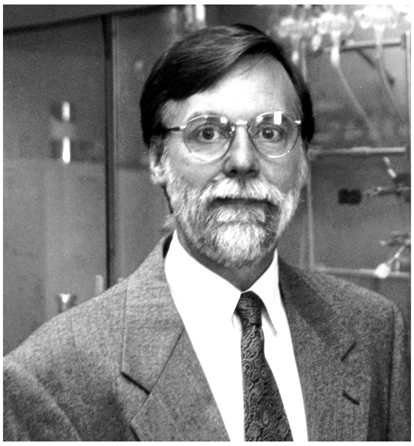
James Clark
York, January 2001

DOI: 10.1039/b100448o

Fluorous techniques for the synthesis and separation of organic molecules

Dennis Curran and Zhiyong (Robert) Lee of the Chemistry Department at the University of Pittsburgh, USA, describe how fluorous techniques provide strategic new green options for conducting organic reactions and for separating the resulting reaction mixtures. The technology is especially suitable for the preparation of combinatorial libraries.

The yield of every chemical step is limited both by the efficiency of the reaction and the ability to recover the pure product from the reaction mixture. However, most traditional solution phase synthesis methods are concerned only with conversion of starting materials to products (reactions) and not with product separations. Fluorous techniques provide strategic new options for conducting solution phase organic reactions and for separating the resulting reaction mixtures. Fluorous molecules typically contain at least one highly fluorinated domain attached to an organic domain. The fluorinated domain can be an integral part of the molecule (permanent attachment) if the intended use is as a reagent, reactant or catalyst. A temporary attachment of a removable fluorous group is required to render a reaction substrate or product fluorous. Fluorous compounds can be separated from standard organic compounds by simple workup techniques of liquid–liquid extraction (two- or three-phase) or solid–liquid extraction. Fluorous compounds can also be separated from each other based on fluorine content by fluorous chromatography.



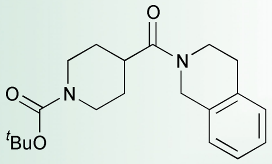
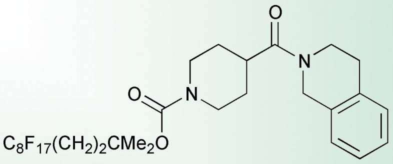
Dennis Curran, Distinguished Service Professor and Bayer Professor of Chemistry at the University of Pittsburgh, USA, and Chairman of the Scientific Advisory Board of Fluorous Technologies Inc.

Four different types of techniques are summarized: fluorous biphasic catalysis, fluorous reagents and reactants, fluorous substrates (fluorous synthesis), and fluorous mixture synthesis. The techniques differ in the size and nature of the fluorous tag, in the reaction conditions and in the separation method. Fluorous techniques are applicable to both green chemical process development and chemical discovery research. Many of these new techniques are especially suited to the preparation of combinatorial libraries by solution phase parallel synthesis.

Fluorous molecules

Fluorous molecules are designed to mimic organic molecules in terms of reactivity yet to still be readily separable from other organic molecules. In the technique of fluorous mixture synthesis, fluorous molecules are also separated from each other. Fluorous molecules typically have two domains. The organic domain resembles a standard organic parent molecule and dictates the reactivity of the molecule. The fluorous domain is a highly fluorinated group that controls the separation features of the molecule. Fluorous domains are often perfluoroalkyl groups.

Shown below are two simple examples of fluorous molecules designed after common organic parents. Fluorous tin hydrides have similar reactivity to the classical reagent tributyltin hydride. But

Organic Compounds	*Fluorous Compounds*
$(C_4H_9)_3SnH$	$(C_6F_{13}CH_2CH_2)_3SnH$
a typical organic tin hydride • mediates diverse radical reactions, but... • is difficult to separate from organic products	*a typical fluorous tin hydride* • mimics the reactivity of its organic parent, and... • is easy to separate from organic products by liquid-liquid extraction • recover and reuse are routine
	
a typical Boc protected amide • easy to prepare by amide coupling, but... • is difficult to separate from the coupling reagents	*a fluorous Boc protected amide* • prepared by the same methods as the standard Boc-amide, and... • is easy to separate from the coupling reagents by solid-liquid extraction

DOI: 10.1039/b100266j

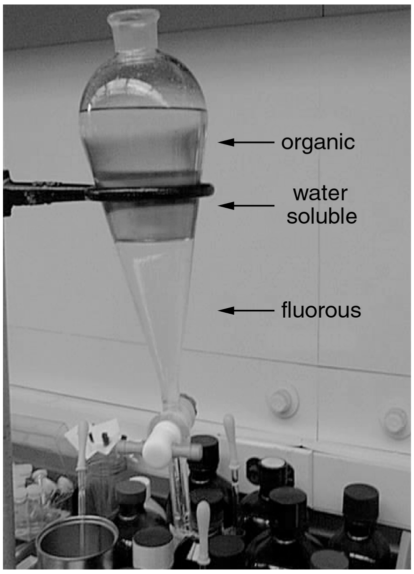
unlike tributyltin compounds, the fluorous tin compounds are readily separable from organic compounds by simple fluorous separation techniques like liquid–liquid extraction or solid–liquid extraction. The fluorous domain of the tin hydride is permanently attached because there is never any need to separate it from the organic domain. The tin compounds are simply recovered at the end of the reaction and recycled. Although only one fluorous tin hydride is shown in the table on page G3, a whole family is now available whose members differ from each other by the length and number of the fluorinated chains and the length of the spacer. This allows the separation properties and (sometimes) the reactivity properties to be tuned for particular needs.

The fluorous Boc group is a typical example of a fluorous protecting group that is designed to be attached and removed by analogy with the standard Boc group. Such fluorous protecting groups are also called ‘fluorous tags’, and they allow rapid separation of all tagged molecules from non-tagged molecules by fluorous solid phase extractions. A growing assortment of fluorous tags is now available.

Fluorous separation methods

Liquid–liquid extraction

Perfluorinated or very highly fluorinated solvents are called ‘fluorous solvents’ and they are typically immiscible with organic solvents and water. They are used in liquid–liquid extractions to quickly separate fluorous compounds from organic compounds in a two-phase liquid–liquid extraction, or from organic and inorganic (or water soluble organic) compounds in a three-phase liquid–liquid extraction. The most popular fluorous solvent is probably 3M’s FC-72™, but a number of related solvents are available and these are all comparably priced.



A photograph of a typical three-phase liquid–liquid extraction is shown above. Such extractions are readily automated, and can be used to quickly partition reaction mixtures into organic, water-soluble, and fluorous fractions. In many cases, the crude organic products are pure enough to be taken on to the next reaction, and the fluorous products can usually be recycled, if desired.

Liquid–liquid extractions work best when fluorous domains are relatively large. In the best cases, only a single separation is needed. With lower partition coefficients, the organic fraction is washed several times with the fluorous solvent. Thanks to the exceedingly low solubilities of organic compounds in fluorous solvents, the washing process can be conducted repeatedly without extractive loss of the organic product. Liquid–liquid extractive methods are typically used when the desired product is organic and some other reaction component (reactant, reagent, catalyst, scavenged product) is fluorous.

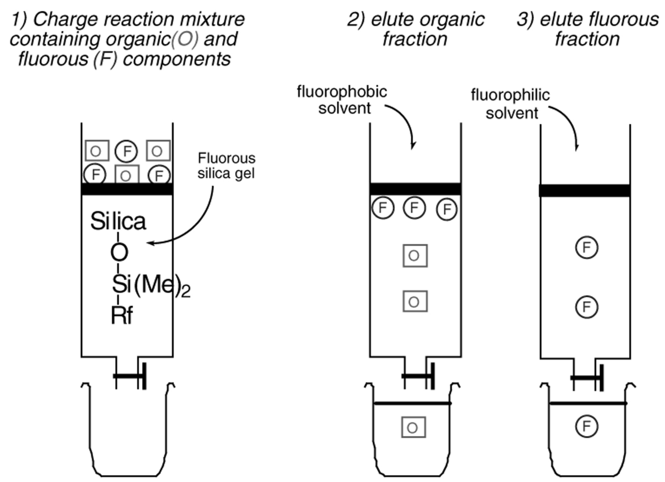
Solid–liquid extraction

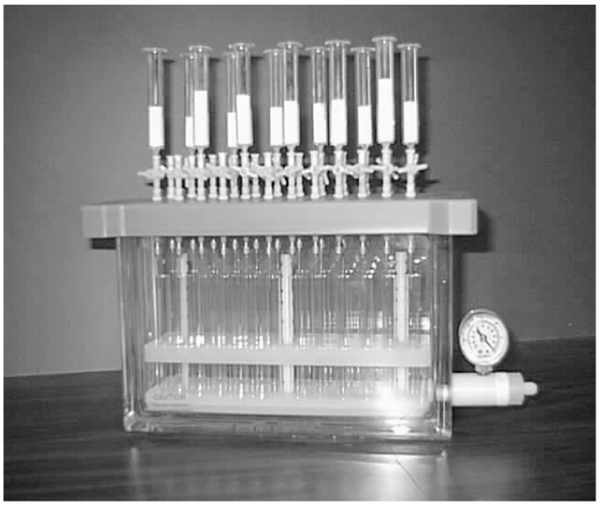
Silica gel with a fluorocarbon-bond phase (‘fluorous reverse phase silica gel’) can be used to adsorb fluorous molecules and free them from non-absorbed organic molecules by the simple process of solid–liquid extraction illustrated below. Examples of fluorocarbon bonded phases include:

–$Si(Me_2)CH_2CH_2C_6F_{13}$,
–$Si(Me_2)CH_2CH_2C_8F_{17}$, and
–$Si(Me_2)(CH_2)_3C(CF_3)_2C_3F_7$.

In the separation stage, a crude reaction mixture is charged to a suitable amount of fluorous silica gel and the silica is eluted first with a ‘fluorophobic’ solvent to remove the organic compounds while leaving the fluorous compounds adsorbed. In cases where the fluorous products are desired, a second elution with a ‘fluorophilic’ solvent then provides this material. These fluorous solid phase extractions are different from traditional chromatographies, and this is advantageous in a parallel setting. In solid phase extractions relatively high loadings of substrate/silica are used, and all of the mixtures in the synthesis behave identically. No fractionation is needed. In traditional chromatographies, each mixture behaves differently and lower loadings and carefully monitoring of fractions are needed.

The solid–liquid extractions are operationally filtrations and they are easy to conduct in parallel either manually (see the manual solid-phase extraction apparatus below) or by using various automated techniques. In addition to the





operational convenience, solid–liquid extractions succeed with many fewer fluorines in the fluorous domain compared to liquid–liquid extractions. For this reason, solid–liquid extractions are especially useful when the desired product of the reaction bears a fluorous tag. The solid phase extraction is applicable in essentially all areas from traditional synthesis through parallel synthesis, and is especially useful for parallel synthesis of intermediates.

Solid–liquid extraction is currently the most general and most easily implemented fluorous–organic phase separation technique. It is useful for the gamut of fluorous methods. Fluorous solvents are rarely needed for the extractions, and they are used only to wash the silica prior to reuse, if desired.

Fluorous chromatography

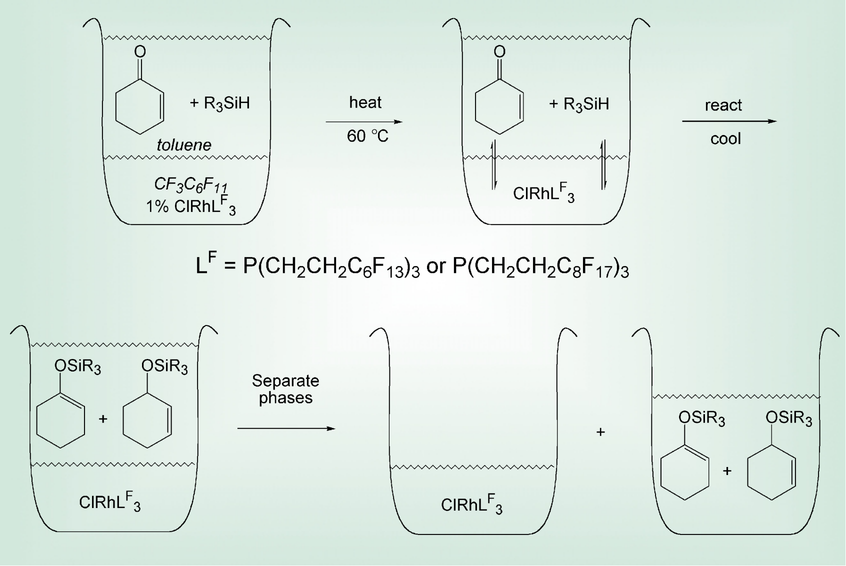
The separation of fluorous molecules from each other can sometimes be accomplished by standard chromatographic techniques, including traditional or reverse phase chromatography. However, the best way to separate fluorous compounds from each other is usually by chromatography over fluorous silica. These separations capitalize on the unique feature of fluorous solid phases, which is their ability to separate molecules primarily by fluorine content. An illustrative example of this is shown below with a family of fluoroacyl-tagged amides. The control compound lacking the fluorous tag (C_7H_{15}) comes off with the solvent front, as do most other non-fluorinated organic compounds under these conditions. The fluorinated homologs then emerge strictly in order of fluorine content, and a solvent gradient is needed to push the more highly fluorinated members of the series off the column.

Many popular fluorous techniques involve fluorous–organic separations, so preparative fluorous chromatography is not needed. However, fluorous chromatography still has two major uses. First, it can be used in methods development experiments to select suitable solvents for fluorous–organic solid phase extractions, thereby ensuring in advance that separation conditions are suitable. Second, it can be used to analyze the purity of essentially any kind of fluorous component, and it provides information that is largely complementary to traditional chromatographic analyses. In contrast to other methods, fluorous mixture synthesis techniques rely heavily on fluorous chromatography for the separation of tagged compounds by the fluorine content of the tag.

Fluorous biphasic catalysis

What we now call ‘Fluorous Biphasic Catalysis’ (FBC) was first introduced in the thesis of Dr. M. Vogt in Aachen in 1991. This work was known to almost no one, and a seminal paper by Horváth and Rábai in 1994 introduced new concepts and results along with today’s terminology. Since that time, fluorous biphasic catalytic methods have advanced rapidly, and a large number of fluorous catalysts and ligands (especially phosphines) are known. The defining feature of FBC is the use of a fluorous reaction solvent, and the technique is best viewed as a liquid phase catalyst immobilization method.

Hydroformylation with a fluorous variant of Wilkinson’s catalyst provides a typical example of fluorous biphasic catalysis below. A toluene solution of an enone and a silane is heated with a perfluoromethylcyclohexane solution of the catalyst. After the reaction is complete, the mixture is cooled and the two phases are separated to provide the organic hydrosilylation products and the recovered catalyst immobilized in the fluorous phase. In an important variant of fluorous biphasic catalysis, an organic solvent is choosen such that on warming a homogeneous (one phase) solution results. After the reaction is complete, the mixture is cooled to induce the phases to separate once again. In the hydrosilylation example, the replacement of toluene by hexane allows for one phase reaction and two phase separation.

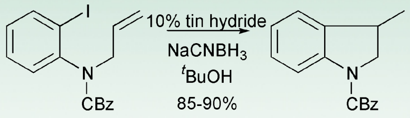


FBC and related methods are ideally suited for economical and green chemical processes. A single liquid–liquid separation provides both the product and the recovered catalyst. The safety of fluorous solvents is also an attractive feature. For the single separation to succeed, high partition coefficients are needed, so the catalysts generally have large numbers of fluorines. Fluorous catalysts have advantages over solid-supported catalysts since they can be soluble in the reaction medium. Water-based biphasic catalysis reactions are also used, but are obviously limited to water-tolerant processes. Fluorous catalysts do not share this limitation.

Fluorous reagents, reactants, catalysts

For many types of organic reactions, it is desirable to use fluorous reaction components (reagents, reactants, catalysts) with fewer fluorines. Such molecules have advantages of lower molecular weight and increased solubility in organic solvents. With these types of molecules, fluorous reaction solvents are not used, and the fluorous phase (either solid or liquid) is used only in the separation stage.

The reductive radical cyclizations with the family of fluorous tin hydrides shown below illustrate many of the features of this branch of fluorous chemistry. In general, the substrate and the product are organic molecules and one of the other reaction components (in this case, the tin hydride) is fluorous. The fluorous component can be used either catalytically or stoichiometrically and the reaction and separation stages are decoupled. After standard reactions, members of the tin hydride family with more fluorines can be separated either by liquid–liquid extraction or by solid–liquid extraction, while the solid–liquid



tin hydride	I-I extraction (no. of extractions)	s-l extraction	fluorinated rxn cosolvent?
$(C_6F_{13}CH_2CH_2)_3SnH$	yes (3)	yes	yes
$(C_4F_9CH_2CH_2)_3SnH$	yes (8–10)	yes	no
$(C_6F_{13}CH_2CH_2CH_2)_3SnH$	yes (5–8)	yes	no
$(C_4F_9CH_2CH_2CH_2)_3SnH$	yes (10–12)	yes	no
$C_{10}F_{21}CH_2CH_2SnMe_2H$	yes (3)	yes	no
$C_8F_{17}CH_2CH_2SnMe_2H$	no	yes	no

extraction is preferred for members with fewer fluorines. For the most highly fluorinated member of the series, a fluorinated reaction co-solvent like benzotrifluoride ($C_6H_5CF_3$) is needed. Benzotrifluoride is not a ‘fluorous’ solvent since it is miscible in all organic solvents (and indeed dissolves many types of organic compounds as well), but it still aids in the solubilization of fluorous compounds in the reaction medium.

These types of methods are broadly useful for all types of organic synthesis from process chemistry (fluorous catalysts preferred) through traditional synthesis to solution phase parallel synthesis and combinatorial chemistry. Tuning of preferred reaction solvents and separation methods is accomplished by selecting a reagent with an appropriate fluorine content. The reagents with fewer fluorines are especially attractive since they often have excellent solubility in organic solvents, yet can still be separated from standard organic compounds by solid–liquid extraction. Fluorous compounds are also soluble in supercritical CO_2, and can be used in green chemical reactions in that solvent. The general solubility of the fluorous reaction components is an attractive feature in comparison to reagents, quenchers, and catalysts that are immobilized on insoluble polymers.

Fluorous substrates, products

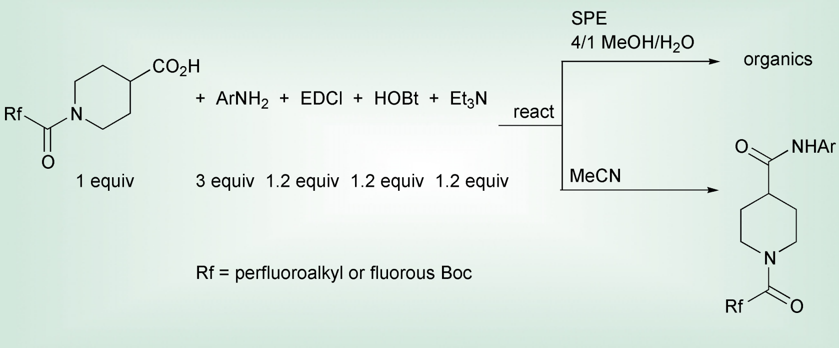
The term ‘fluorous synthesis’ is often used to describe techniques in which the substrates and/or desired products are rendered fluorous. This technique is a phase tagging strategy that is conceptually analogous to ‘solid phase synthesis’, but with major operational differences. Making substrates and products fluorous necessarily involves cleavable tags (since the final product will not be tagged), and fluorous protecting groups or traceless tags can be used. Fluorous synthesis concepts were introduced with liquid–liquid separation methods coupled with very large fluorous tags (60–120 fluorines). These early ‘heavy’ fluorous techniques are quickly being replaced by ‘light’ techniques where tags with many fewer fluorines are used coupled with solid–liquid extraction.

Amino acids are readily coupled to make amides by first tagging the amine with a fluorous acyl group or a fluorous Boc group and then coupling the acids with amines under standard conditions (below). In general, only about 15–19 fluorines are needed, and the resulting tagged molecules have solubility properties that are largely dominated by the organic domain. In other words, they are soluble in organic not fluorous solvents. However, the solid phase extraction (SPE) properties of the molecule are still dominated by the fluorous domain. The protected acids are coupled with amines under standard conditions. The desired tagged products are then retained on the column in the first pass of the solid phase extraction (MeOH/water) while all the coupling reagents, reactants and byproducts are eluted off. The coupled fluorous products are then eluted off in a second pass (MeCN) and are obtained in excellent purity.

Fluorous synthesis is attractive because a single protecting group or tag can be used to render a library of organic molecules fluorous. The resulting library of soluble molecules can then be separated from broad classes of organic and inorganic reagents, reactants, side products, *etc.* by solid phase extraction. Unlike polymer-bound molecules, the fluorous-tagged compounds are small molecules that can be analyzed and characterized by standard small molecule techniques. The tagging methods are ideal for expedited parallel synthesis and for the gram-scale preparation of chemical intermediates in parallel. Because the tagged compounds have relatively few fluorines, they can be reacted under typical conditions for non-tagged molecules and the solid phase extraction gives a fast yet substantive separation. In the final detagging step, solid phase extraction can again be used to separate the organic product from the remnant of the fluorous tag. The tag can often be recovered in a form suitable for reuse, if desired. In addition to fluorous acyl and Boc groups, there are now a number of fluorous silyl groups, fluorous THP groups, fluorous benzyl groups, *etc.*

Summary

By directly addressing the separation problems inherent in the synthesis of small organic molecules, fluorous techniques provide an array of powerful solutions that span the discipline of organic synthesis from large-scale chemical processes through traditional



Technique	Fluorine Content	Rxn Solvent	Separation	Uses
Fluorous biphasic catalysis	high	fluorous and organic	single liquid–liquid separation	green chemical processes
Fluorous reagents	low-medium	organic or hybrid	liquid–liquid or solid–liquid extraction	universal
Fluorous substrates	low	organic	solid–liquid extraction	chemical discovery, intermediate synthesis
Fluorous mixture synthesis	low, variable	organic	fluorous chromatography	leveraged chemical discovery

fine synthesis to modern chemical discovery by combinatorial methods.

The above Table summaries the four main fluorous methods outlined in this overview and compares and contrasts them.

Fluorous methods are attractive and easy to apply because the experimental techniques (solution phase reactions, liquid–liquid extractions, solid phase extractions) are familiar to practicing organic chemists. What differs from standard organic techniques are the fluorous components that are used. The application of fluorous techniques has been limited to a few specialized laboratories due to the lack of availability of fluorous reagents, reactants, tags, solvents, silica, *etc*. However, a new company, Fluorous Technologies (see box) intends to change this by providing laboratories worldwide with both the materials and the expertise that are needed to integrate fluorous methods into their ongoing discovery and production projects.

Fluorous Technologies Inc.

Fluorous Technologies Inc is a newly formed company based in Pittsburgh, PA. It has licensed from the University of Pittsburgh several patents and pending patent applications for the use of fluorous organic chemistry for chemical synthesis, isolation and purification. Investors in the company include Albany Molecular Research Inc, Alfred Bader and retired founder of Aldrich Chemical Company and the University of Pittsburgh. Denis Curran is chairman of the Scientific Advisory Board for the company. See http://www.fluorous.com for further information.

Selected references

Reviews:

D. P. Curran, Combinatorial Organic Synthesis and Phase Separation: Back to the Future, *Chemtracts—Org. Chem.*, 1996, **9**, 75–87

D. P. Curran, Strategy-level separations in organic synthesis: From planning to practice, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1175–1196.

J. J. Maul, P. J. Ostrowski, G. A. Ublacker, B. Linclau and D. P. Curran, Benzotrifluoride and Related Solvents in Organic Synthesis, In *Topic in Current Chemistry, Modern Solvents in Organic Synthesis*; P. Knochel, Ed.; Springer-Verlag: Berlin, 1999, **206**, 80–104.

D. P. Curran, Parallel Synthesis with Fluorous Reagents and Reactants, *Med. Res. Rev.*, 1999, **19**, 432–438.

D. P. Curran, S. Hadida, A. Studer, M. He, S.-Y. Kim, Z. Luo, M. Larhed, M. Hallberg and B. Linclau, Fluorous Synthesis: A User s Guide, In *Combinatorial Chemistry: A Practical Approach* (H. Fenniri, Ed.), Oxford Univ. Press, Oxford, Vol. 2., in press.

D. P. Curran, Fluorous Techniques for the Synthesis of Organic Molecules: A Unified Strategy for Reaction and Separation, in *Stimulating Concepts in Chemistry*, Wiley-VCH, in press.

Fluorous Biphasic Catalysis:

I. T. Horvath, J. Rabai, Facile catalyst separation without water: Fluorous biphase hydroformylation of olefins, *Science*, **266**, 72–75.

I. T. Horvath, Fluorous biphase chemistry, *Acc. Chem. Res.*, 1998, **31**, 641–650.

Y. Nakamura, S. Takeuchi, Y. Ohgo, D. P. Curran, Asymmetric alkylation of aromatic aldehydes with diethylzinc catalyzed by a fluorous BINOL-Ti complex in an organic and fluorous biphase system, *Tetrahedron Lett.*, 2000, **41**, 57–60.

Fluorous Reagents:

D. P. Curran, S. Hadida, Tris(2-(perfluorohexyl)ethyl)tin hydride: A new fluorous reagent for use in traditional organic synthesis and liquid phase combinatorial synthesis, *J. Am. Chem. Soc.*, 1996, **118**, 2531–2532.

D. P. Curran, S. Hadida, S. Y. Kim, Z. Y. Luo, Fluorous tin hydrides: A new family of reagents for use and reuse in radical reactions, *J. Am. Chem. Soc.*, 1999, **121**, 6607–6615.

Fluorous Synthesis:

A. Studer, S. Hadida, R. Ferritto, S. Y. Kim, P. Jeger, P. Wipf, D. P. Curran, Fluorous synthesis: A fluorous-phase strategy for improving separation efficiency in organic synthesis, *Science*, 1997, **275**, 823–826.

D. P. Curran, Z. Y. Luo, Fluorous synthesis with fewer fluorines (Light fluorous synthesis): separation of tagged from untagged products by solid-phase extraction with fluorous reverse-phase silica gel, *J. Am. Chem. Soc.*, 1999, **121**, 9069–9072.

Fluorous Mixture Synthesis:

Y, Oderaotoshi, Q. Zhang, Z. Luo, and D. P. Curran, Fluorous Mixture Synthesis: The First Strategy for the Synthesis of Mixtures of Organic Compounds that Provides Pure Individual Products through Demixing Controlled by the Fluorous Tag, in preparation.

Review

So you think your process is green, how do you know?—Using principles of sustainability to determine what is green–a corporate perspective

Alan D. Curzons,*[a] David J. C. Constable,[b] David N. Mortimer[a] and Virginia L. Cunningham[b]

[a] *GlaxoSmithKline, Southdownview Way, Worthing, West Sussex, UK BN14 8NQ.*
E-mail: alan.d.curzons@gsk.com
[b] *GlaxoSmithKline, 2200 Renaissance Boulevard, King of Prussia, PA 19406, USA*

Received 28th September 2000
First published as an Advance Article on the web 31st January 2001

An approach to quantitatively and systematically evaluate synthetic organic reactions and processes is described. This sustainability-based approach allows chemists to clearly assess whether or not chemistries and chemical processes are 'greener'. The results of this work indicate that close attention to effective use and reuse of solvents will result in the largest gains for reducing life cycle impacts in batch chemical operations.

The sustainable development context

Many people over the past decade have been discussing how to change the way humans live and behave to reduce their impacts on the environment, promote economic development, and enhance social welfare. Under the broad umbrella of Sustainable Development, different approaches to the usual way of living and behaving are being discussed, and in some instances, implemented. Sustainable Development, originally defined by the Brundtland Report in 1987,[1] is being seriously considered and debated in national and local government policy arenas, corporate boardrooms and academia. The idea that the current generation should live in a way that does not impact future generations' ability to live as well, if not better, than we do—for all living beings—is not necessarily a new idea, but one that has generally been ignored by modern industrial societies.

So why and how does a Company, who many would say has a primary objective only to add shareholder value, implement the principles of sustainable development in an area as specialized as synthetic organic chemistry, and how does this relate to the concept of green chemistry? The first question is why. Adding shareholder value and rigorously pursuing the principles of sustainable development are not mutually exclusive. Although it is beyond the scope of this article and offered without debate here, the appearance of several recent investment funds (Innovest and the SAM Sustainability Group) suggest that increased shareholder value is in fact associated with companies that pursue Sustainable Development.

Apart from adding shareholder value, why else might a company want to consider using principles of Sustainable Development as it considers what is green chemistry? There are several reasons.

First, there are risks to the business from unsustainable business practices. These include risks from greenhouse gas emissions taxes (energy, transportation), pollutants and toxic releases (energy, VOCs, various chemical compounds), shipment of highly hazardous materials (reagents, intermediates, raw materials, solvents), new and increasingly restrictive regulations (air, water, land, hazardous waste), *etc.* Second, there is the desire for competitive advantage. Companies that reduce cost by decreasing mass intensity (the total amount of mass required to produce a unit of product or service, usually on a wt/wt basis) or energy intensity (the total amount of energy required to produce a unit of product or service) will be more profitable. The more adept a company is at implementing technologies and new chemistries that simultaneously reduce mass and energy intensity, the more it will realise higher profits. They will also generally have fewer risks from unsustainable business practices. Finally, every company should be concerned about the local and business community in which it operates, and maintaining its 'right-to-operate' in these communities.

The second question of how a company implements Sustainable Development principles in the synthetic organic and green chemistry context is a bit more difficult. Over the past several years we have been considering what a company such as GlaxoSmithKline might do if it is to move towards more sustainable business practices. A logical place to start is with a consideration of our impacts to the environment. The companion dimensions of Sustainable Development, economic and social development, are admittedly longer term and more difficult issues to develop and implement at this time. This does not mean that they have no place in the green chemistry context, it is just more difficult to arrive at a consensus for the best way forward. An example of the complexity of the economic and social dimensions may be illustrated in the case of harvesting a natural product used as a synthetic precursor for an anti-cancer drug. The compound might be harvested from a plant or marine organism found in a developing country. Sorting out the various issues to ensure appropriate economic remuneration (just and sufficient for the benefit derived by the business), protection of local resources (human and environmental), impacts to the community from changes to the economy, *etc.*, can be

Green Context

We all work on green chemistry, but are we really sure about that? This is the first of two articles in this issue to discuss the development of a set of criteria designed to answer just this question. The authors describe their approach in this article by discussing the framework in which chemistry is carried out, and the necessary factors which need to be considered from an industrial perspective. The paper introduces the company's green metrics, by which an assessment of 'greenness' can be made.

DJH

DOI: 10.1039/b007871i

particularly daunting, and is certainly beyond the scope of this journal.

It has been our experience that most companies are very interested in the concept of Green Chemistry, but few have a good sense of how to move it forward. From a pragmatic standpoint, we are pursuing a largely environmental approach as a first step towards Sustainable Business Practices. This article attempts to outline in broad terms the approach that we are taking at the Corporate level within GlaxoSmithKline. It is offered in the hope that it may promote discussion and begin to build a consensus on how to know a process is Green. A companion article[2] describes how the Chemical Development Department at GlaxoSmithKline Research and Development is implementing a set of metrics to raise awareness of Green Chemistry. The R&D metrics are considered to be a 'grass-roots' complementary effort to the overall Corporate effort.

The design for the environment tool kit

Given that we are starting with the environment, what might the typical bench and management level scientist or engineer require to assist them in making the best possible decisions—those that are the most 'Green?' Current thinking suggests that the best way to make a product 'Green' is to consider what needs to be done during the design phase to ensure that the product being produced has as few adverse impacts as possible while maximizing the benefit it brings to society. This is the so-called 'Design for the Environment' approach. In the green chemistry context, we might understand this to mean producing complex molecules in just a few room-temperature atom economical (only A + B making only C) synthetic steps, using non-hazardous reagents and intermediates (derived from renewable feed stocks), in the absence of solvents or in solvents that are 100% recoverable, with no adverse safety issues. All of this is to be accomplished using the least amount of energy possible that also happens to be produced from renewable energy sources.

To meet this need, we have begun to assemble a 'Design for the Environment' Tool Kit. The first step in assembling the Tool Kit was to develop a set of fundamental and broadly applicable metrics.

Since 1997, 10–15 chemical and allied industry companies that are a part of the American Institute of Chemical Engineers' Center for Waste Reduction Technologies (AIChE/CWRT) have been working to develop a set of core and complementary sustainability metrics. The CWRT group built on the foundation of work completed by the National Roundtable on the Economy and Environment (NRTEE), a Canadian funded effort undertaken by about a dozen manufacturing companies (chemical, telecommunications, mining, utility, *etc.*). The CWRT also generally adopted the eco-efficiency framework to Sustainable Development that was developed by the World Business Council for Sustainable Development as a first step to guide the development of their metrics. A description of the CWRT efforts and the metrics that have been piloted may be found at www.aiche.org/CWRT. We (GlaxoSmithKline) have refined these metrics and are using them to organize our thinking about several programmes under development.

Beside metrics, what else do we need in the toolkit? Firstly we have embarked on a significant programme in Life Cycle Inventory/Assessment (LCI/A). The ultimate intention is to develop guidance which will enable scientists to assess the lifecycle burdens, from cradle to gate, associated with their processes and to be able to compare these during route selection. As a first step to achieve this, we have been working to create an impact inventory for one of our major drug substances. This inventory relates to about 115 chemicals and is being organized into impact categories based on our sustainability metrics; *i.e.*, mass intensity, energy, pollutants and toxics.

Secondly, especially given our business context, we have a programme for developing a Total Cost Assessment (TCA) methodology as a means of assigning a monetary value to our Life Cycle impacts and making better pollution prevention decisions. This is also a collaborative programme with the CWRT and a detailed description of the methodology and data may be obtained from the above website. Ultimately the TCA data will be used in conjunction withthe LCI database of chemicals to develop a LCI/A tool for our bench level scientists and engineers.

We have also embarked on a detailed Green Chemistry programme that is described below. The final tool we have just begun to develop is best described as Green Technology guidance. This Green Technology guidance will help scientists and engineers to choose the best technology (unit operations) from a sustainability metrics perspective.

Taken together, the 'Design for Environment' Tool Kit will provide a very powerful tool for moving GlaxoSmithKline towards more sustainable business practices. It is critically important to note that we consider all the component parts of the Tool Kit in our decision-making practices. We have found that each of these Tools informs the other tools and influences the decisions that are made. The absence of this broad approach could very well lead to perverse answers during decision making. It should also be noted that this is a long-term strategic initiative that will have an eventual but impressive business benefit.

The green chemistry programme

So how do we ensure that a series of complex synthetic organic reactions, that ultimately become a synthetic process, are 'green' and how do we measure success in achieving this? Paul Anastas and John Warner[3] produced a seminal set of twelve principles that initiated the green chemistry concept and have guided many in their pursuit of what is 'green'. In addition, the OECD Workshop on Sustainable Chemistry provided an excellent summary of sustainable chemistry (see box). The twelve principles and the OECD Sustainable Chemistry definition are very helpful in challenging chemists to consider what they might do to make their processes greener.

While the principles and the OECD definition are very good at setting the context, we desired to establish a systematic methodology and framework that would provide a means to evaluate, assess and organize our thinking. Given our work with sustainability metrics, we pursued a metrics-based approach to determining what is 'green.'

Sustainable Chemistry Defined (OECD Workshop on Sustainable Chemistry, 1998)[4]

'*Within the broad framework of Sustainable Development, we should strive to maximise resource efficiency through activities such as energy and non-renewable resource conservation, risk minimisation, pollution prevention, minimisation of waste at all stages of a product life-cycle, and the development of products that are durable and can be re-used and recycled. Sustainable Chemistry strives to accomplish these ends through the design, manufacture and use of efficient and effective, more environmentally benign chemical products and processes.*'

The first step, and a difficult one at that, was to collect descriptions of our chemistries that have been used over the past ten years. This task was aided by the regulatory requirement to produce a description of how active pharmaceutical ingredients are produced. We collected about two hundred individual chemical reactions for about 38 different products, some of which are now commercial products. Each of these reactions was categorised in several different ways in an attempt to make it easier for chemists to understand and search for the chemistry that was being evaluated, and its purpose. Table 1 contains an illustration of the approach for several categorisations. The first column defines the purpose of the synthesis, the second provides the reaction category, and the third provides the reaction name or type. While this particular approach to categorisation made sense to GlaxoSmithKline, there may be many ways to categorise reactions.

The development and use of the metrics for assessing individual reactions had two component parts. First, we have explored core and complementary metrics from a ‘green’ perspective that include safety and operational parameters. This approach helped to further our understanding of the chemistries and the most important ‘green’ factors that make them different. It is important to point out that this is an ongoing and iterative process. Second, we have developed a comprehensive set of heuristics that permits us to derive data for each metric from the available information in the process descriptions. Table 2 contains illustrative (not our final set) metrics of the type we have considered.

The next step was to assess the chemistry using our metrics and heuristics, and we developed an expert system, based in Microsoft Excel, to facilitate this complex and time-consuming process. Using this we have been able to evaluate all two hundred chemical reactions using the above metrics.

So now that we have our metrics set and we have completed our evaluation, what about the data and how do we use it? We have a vast amount of information that is providing tremendous insight across a range of areas. The following is intended to provide a snapshot of the output, with some selected examples covering some of the key learning points.

We have chosen to organise our thoughts according to a long, medium and short-term paradigm. Stated slightly more euphemistically, we can think of this as the pursuit of atom economy, the marriage of chemistry and engineering, and getting your house in order.

The idea of atom economical reactions, first introduced by Professor Barry Trost.[5] may be a useful concept in helping to promote thinking around green chemistry. Analysis of our data demonstrates that the way in which chemists build, couple molecules, introduce chirality, *etc.* often employ atom inefficient reactions. Stated differently, you can’t keep throwing away large amounts of reactants and reagents in the process of making a new compound. This is both costly and has an immense Life Cycle burden associated with it. Synthetic chemists need to pursue a new set of reactions. There are two component parts to this: (1) the need to pick the most atom efficient reactions from the currently available reactions and (2) the need to develop new chemistries or new more atom economical ways of carrying out current reactions. The latter is clearly a longer term but ongoing requirement and will require close co-operation between academia and industry.

Although the idea of atom economy may be important in focusing long-term effort towards the development of new chemistry and processes, we offer one important consideration. When considering what is ‘green’, atom economy is not the only metric to consider. A plot of atom economy *vs.* mass intensity is shown in Fig. 1 using average data for each of the chemistries.

As can be seen from this plot, our data suggest that there is no correlation between atom economy and the critical mass intensity metric. The data therefore suggests that atom economy alone will not deliver the desired ‘green’ or ‘cleaner’ processes we might use to assemble molecules.

For this reason we have developed and explored several related measures known as carbon efficiency and what we refer to as reaction mass efficiency (RME). RME takes into account yields, the actual molar quantities of reactants, and the concepts of atom efficiency.

Fig. 2 provides a calculation of RME, atom economy and mass intensity while Table 3 compares atom economy and RME for 28 different chemistries. As can be seen, RME may be a more realistic metric to illustrate how far from ‘green’ we are currently operating our processes. The information presented in Table 3 is averaged data; however, in practice there will be a range of values. While a more detailed analysis of this range of values would be essential to fully understand the relative efficiencies of individual chemistries, this is outside the scope of this article.

It is important to also consider energy use, although this is also outside the scope of this article.

This leads into the middle term objectives, or alternatively, the marriage of chemistry and engineering. Stated colloquially, if you’re a chemist, take an engineer to lunch; if you’re an engineer, take a chemist to lunch. We will not be able to move effectively towards green chemistry unless there is a very close collaboration between the chemist and engineer. We say this because our data and other experience suggests that where a reaction takes place (*i.e.*, the size, configuration, and composition of the reactor) and how the resulting intermediate or

Table 1 Categorisations of chemistries

Purpose	Reaction category	Reaction name/type
Forming a new carbon–oxygen bond	O-Alkylation	Ether synthesis
Forming a new carbon–carbon bond	C-Alkylation	Alkylation of an aromatic
Forming a new carbon–carbon bond	Addition to C=O	Knoevenagel
Forming a new carbon–nitrogen bond	N-Acylation	Amidation
Forming a new carbon–nitrogen bond	N-Alkylation	Of heterocycle
Forming a new carbon–nitrogen bond	N-Alkylation	Of amine
Forming a new carbon–sulfur bond	S-Alkylation	Thioether synthesis
Reduction	Catalytic hydrogenation/hydrogenolysis	
Reduction	Metal hydride	Lithal
Cyclisation	Heterocycle synthesis	By miscellaneous ring closure
Elimination	C=C formation	
Hydrolysis	Acid catalysed	
Hydrolysis	Base catalysed	
Halogenation	Halogenation of an alcohol	
Salt formation	Acid or base	
Neutralisation		
Resolution	Using diastereoisomers	Acid or amine

product is isolated are very important factors controlling the ‘greenness’ of a process.

For example, most chemists tend to focus on reactions rather than the technology around the reaction and virtually all reactions are undertaken in batch reactors. Thus, in general, if a reaction does not ‘work’, chemists are more inclined to change the reaction rather than investigate different equipment in which to perform the reaction. Issues of mass and energy (heat/cool) transfer, mixing, phase transfer, and general reactor design, *etc.*, are generally not as rigorously pursued by the synthetic organic chemist as by the engineer. If these issues are not adequately considered, they may result in rather large inefficiencies during development. Given increased and ever increasing pressures to reduce time to market, and the diversity of products introduced

Table 2 Selected ‘green’ metrics

Category		Units
Mass		
$\frac{\text{Total mass (kg)}}{\text{Mass of product (kg)}}$	(Mass intensity)	kg/kg
$\frac{\text{Total mass solvent (gross) (kg)}}{\text{Mass of product (kg)}}$		kg/kg
$\frac{\text{Mass of isolated product (kg)}}{\text{Total mass of reactants used in reaction (kg)}} \times 100$	(Reaction mass efficiency) RME	%
$\frac{\text{FW (g mol}^{-1}\text{) product}}{\text{FW of all reactants used in reaction}} \times 100$	(Atom economy)	% %
$\frac{\text{Mass of carbon in product (kg)}}{\text{Total mass of carbon in key reactants (kg)}} \times 100$	(Carbon efficiency)	%
Energy		
$\frac{\text{Total process energy (MJ)}}{\text{Mass of product (kg)}}$		MJ/kg
$\frac{\text{Total solvent recovery energy (MJ)}}{\text{Mass of product (kg)}}$		MJ/kg
Pollutants/toxic dispersion		
Persistent and bioaccumulative		
$\frac{\text{Total (mass persistent + bioaccumulative) (kg)}}{\text{Mass product (kg)}}$		kg/kg
Ecotoxicity		
$\frac{\text{Total (mass persistent + bioaccumulative) (kg)}}{\text{EC}_{50}{}^{a}\text{ material/EC}_{50}\text{ DDT control}}$		kg
Human health		
$\frac{\text{Total (mass of material [for all materials]) (kg)}}{\text{Permissable exposure limit (ACGIH)}^{b}\text{ (ppm)}}$		kg/ppm
POCP (photochemical ozone creation potential)		
$\frac{\text{Total [mass of solvent (kg)} \times \text{POCP value} \times \text{vapour pressure (mm)]}}{\text{mass of product (kg)} \times \text{vapour pressure [toluene]} \times \text{POCP [toluene]}}$		kg/kg (as toluene)
Greenhouse gas emissions		
$\frac{\text{Total (mass of greenhouse gas from energy [as kg CO}_2\text{ equiv.])}}{\text{mass of product (kg)}}$		kg/kg (as CO_2)
$\frac{\text{Greenhouse gas, kg CO}_2\text{ equivalent, ex energy for solvent recovery}}{\text{kg product}}$		kg/kg
Safety		
Thermal hazard		Highlight
Reagent hazard		Highlight
Pressure (high/low)		Highlight
Hazardous by-product formation		Highlight
Solvent		
Number of different solvents		Number
Overall estimated recovery efficiency		%
Energy for solvent recovery		MJ/kg
Mass intensity net of solvent recovery		kg/kg

[a] EC50 = the concentration at which 50% of the organisms in an acute toxicity test die during the fixed time period of the study. [b] ACGIH = American Conference of Governmental Industrial Hygienists. A standards setting organisation convened to set Threshold Limit Values (TLV) for chemical and physical hazards, usually expressed as the time weighted average (TWA) concentration permitted over an 8 h exposure period.

to market, chemists simply must work with engineers in a collaborative manner to solve the problems associated with mass and energy inefficiency. This will require an understanding of the alternative technologies that are available, their relative benefits and 'greenness', and the widespread availability of appropriate bench scale equipment.

The final green chemistry considerations are the short-term initiatives, or "getting your house in order." The major focus of the short term is to pay attention to solvent use. Our data demonstrates that the largest component of the mass intensity is due to reaction and work-up solvents. Solvents have a considerable life cycle impact in addition to their impacts through use and final disposal. While the market cost of solvents is quite cheap today, the broader total costs (resource depletion, life cycle and societal) are not. One illustration of the type of information we are gleaning from our evaluations is as follows:

In discussions with synthetic organic chemists, we are often told that solvent choice is dictated by the chemistry in use, and we ought not to restrict solvent choice. With a data set containing approximately 373 uses of solvents in reactions used to synthesize 38 different complex drug substances, it may be possible to draw several conclusions regarding solvent choice. Fig. 3 is a pie chart showing the mixture of solvent classes and their percentage usage. As can be seen from the chart, 50% of the solvent usage is found in two classes of solvents: alcohols and aromatics. With the addition of polar aprotics, ethers, and esters, 78% of all solvent usage is accounted for.

On the basis of the overall data, it might be argued that a choice of five 'best-of-class' solvents, one solvent in each category, may be a good starting point for running reactions when a solvent in one of these classes is called for. A simple example of this might be the case where the literature reaction calls for methanol and xylene, and the 'best-of-class' solvents are determined to be isopropyl alcohol (IPA) and toluene. The reactions then, could be run first in IPA and toluene. The elimination of multiple solvents has a profound effect in managing those solvents throughout their life cycle, and the total cost of managing 8 to 10 solvents is considerably more than managing five.

Process
React benzyl alcohol (10.81 g, 0.10 mol, FW 108.1) with *p*-toluenesulfonyl chloride (21.9 g, 0.115 mol, FW 190.65) in toluene (500 g) and triethylamine (15 g, FW 101) to give the sulfonate ester (FW 262.29) isolated in 90% yield (0.09 mol, 23.6 g)

Mass intensity $= (10.81 + 21.9 + 500 + 15)/23.6 = 23.2$ g/g
Reaction mass efficiency $= 23.6/(10.81 + 21.9) \times 100 = 70.9\%$
Atom economy $= 262.29 / (108.1 + 190.65 + 101) \times 100 = 65.8\%$

The atom economy is $<100\%$ due to formation and neutralisation of the HCl by-product. The reaction mass efficiency also takes into account the 90% yield and the need for a 15% molar excess of *p*-toluenesulfonyl chloride.

Fig. 2

One of the main outputs of our data analysis is the ability to distinguish, compare and contrast different chemistries and this will eventually form part of the guidance we intend to develop for all our scientists. While it is obvious that a Knoevenagel reaction is different and is employed for different purposes than a base hydrolysis or hydrogenation reaction, it is still of great benefit to evaluate those factors that make a particular type of chemistry 'greener' than another type. The data also provide a baseline set against which one is able to evaluate alternative

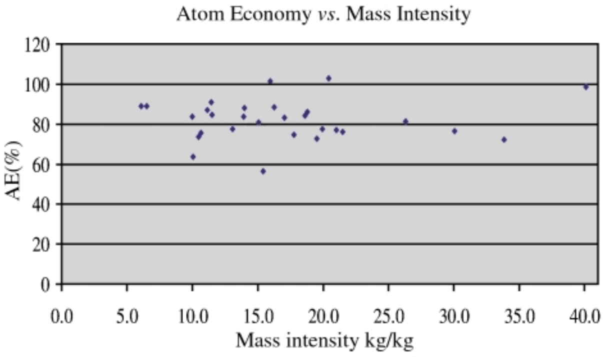


Fig. 1 Relationship of atom economy to mass intensity.

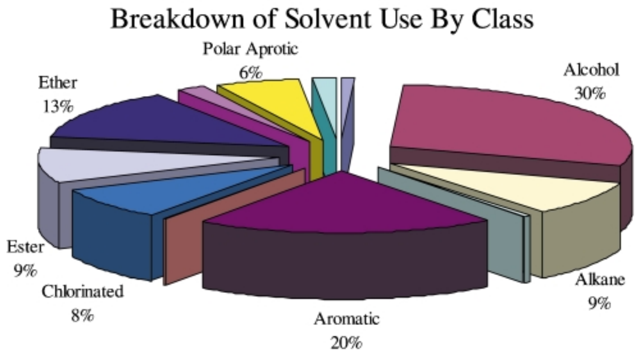


Fig. 3 Breakdown of solvent use by class

Table 3 Comparison of average atom economy with average reaction mass efficiency for 28 different chemistries

Chemistry type	Atom economy (%)	Reaction mass efficiency (%)	Chemistry type	Atom economy (%)	Reaction mass efficiency (%)
Resolution	40	31	Epoxidation	83	58
N-Dealkylation	64	27	Bromination	84	63
Elimination	72	45	Hydrogenation	84	74
N-Alkylation	73	60	S-Alkylation	84	61
Chlorination	74	46	O-Arylation	85	58
Borohydride	75	58	N-Acylation	86	62
Lithal	76	52	Amination	87	54
Grignard	76	42	C-Alkylation	88	61
Hydrolysis (acid)	76	50	Iodination	89	56
Cyclisation	77	56	Knoevenagel	89	66
Cyanation	77	65	Sulfonation	89	69
Decarboxylation	77	68	Esterification	91	67
C-Acylation	81	51	Base salt	100	80
Hydrolysis (base)	81	52	Acid Salt	100	83

chemistries to accomplish a hydrogenation, or formation of a C–C bond, or the isolation of a free acid or base.

Summary and conclusions

We believe we have developed a reliable methodology for evaluating synthetic organic reactions through the lens of sustainable practices. Our studies generally indicate that mass and energy appear to be good leading indicators of overall environmental impact, although toxicity metrics are still in great need. In the short term, rigorous management of solvent use is likely to result in the greatest improvements to making processes 'greener.' Finally, the evaluation of chemistries using our sustainability metrics framework clearly differentiates between chemistries and chemical processes.

References

1 World Commission on Environment and Development, *Our Common Future*, Oxford University Press, Oxford, 1987.
2 D. J. C. Constable, A. D. Curzons, L. M. Freitas dos Santos, G. R. Green, R. E. Hannah, J. D. Hayler, J. Kitteringhan, M. A.McGuire, J. E. Richardson, P. Smith, R. L. Webb and M. Yu, *Green Chem.*, 2001, **3**, 7.
3 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.
4 OECD Workshop on Sustainable Chemistry, 1998.
5 B. M. Trost, *Science*, 1991, **254**, 1471.

Green chemistry measures for process research and development

David J. C. Constable,[a] Alan D. Curzons,[b] Luisa M. Freitas dos Santos,[c] Graham R. Geen,*[c] Robert E. Hannah,[d] John D. Hayler,[e] John Kitteringham,[c] Michael A. McGuire,[d] John E. Richardson,[e] Paul Smith,[c] R. Lee Webb[d] and Marvin Yu[d]

[a] *GlaxoSmithKline, 2200 Renaissance Boulevard, King of Prussia, PA 19406, USA*
[b] *GlaxoSmithKline, Southdownview Way, Worthing, West Sussex, UK BN14 8NQ*
[c] *GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW. E-mail: graham_geen-1@gsk.com*
[d] *GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[e] *GlaxoSmithKline, Old Powder Mills, near Leigh, Tonbridge, Kent, UK TN11 9AN*

Received 28th September 2000
First published as an Advance Article on the web 31st January 2001

A set of metrics has been developed which enables a simple assessment to be made of batch processes in terms of waste, energy usage, and chemistry efficiency. It is intended to raise awareness of green chemistry by providing a tool to assist chemists in monitoring progress in the reduction of environmental impact as they design new routes and modify processes.

Introduction

Primary manufacturing in the pharmaceutical industry involves the use of multistage batch processes to prepare relatively small to moderate quantities (by chemical industry standards) of complex chemical compounds. As a normal part of the chemical development process for drug candidates, the route of synthesis used for the preparation of initial supplies is either optimised or, more often, replaced by an alternative route, so that the final compound is prepared more efficiently.

We wished to introduce a set of measures that would enable an assessment of the initial development process and allow environmental improvements to be monitored during the development stages. It was also intended that these measures would raise the awareness of green chemistry,[1,2] highlight key issues and provide information that would assist chemists in choosing between alternative routes. We required a relatively simple template that could be completed using readily obtainable information such as that found in typical process description reports. This information would also need to tie in with the comprehensive environmental review already conducted on compounds in the later stages of development and align with the GlaxoSmithKline Design for the Environment programme.[3]

The measures are a mixture of qualitative and quantitative assessments of inputs and outputs for a particular process.[4] The latter is a refinement of the E-factor proposed by Sheldon.[5] Although designed specifically for use within the company, these measures should find wider relevance within the pharmaceutical and chemical industries.[6]

Results and discussion

The template that has been developed is shown overleaf. It is divided into four sections.

Section 1: identification

This section provides information on the identity of the compound, the synthetic route (the scheme would normally be attached) and the basis of the assessment (usually a batch report).

Section 2: synthetic complexity

The intention of this section is to record the number and type of operations comprising the process. It has required the development of some working definitions, which are given below.

Chemistry step. This is defined as a reaction which effects a structural change and gives an isolable product, but which may or may not be isolated in practice. (This includes salt formations where isolated, but not transient formations in acid/base extractions). When making route comparisons, a higher number of steps would imply that more complex chemistry is being used to reach the target.

> Example: Reduction of RNO_2 to RNH_2 would be a single step, even though it can be argued that the reaction goes through more than one transformation, *i.e.*, through a nitroso and a hydroxylamine intermediate.

Purification step. This is a step carried out to improve the purity or form of an intermediate or final product, and includes distillations, recrystallisations, chromatography and resolutions (by chromatography or formation of diastereomeric salts, isolation and neutralisation).

Stage. This is defined as a series of operations comprising one or more chemistry and / or purification steps followed by an

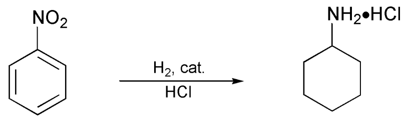
Green Context

The development of a set of simple measurements which help to assess the environmental impact of a chemical process is described. The impact of such an approach on both defining real areas for improvement, and highlighting the importance of green chemistry as an integral process development tool is highlighted. ***DJM***

Compound number	
Route designation	
Date of assessment and reference	
Number of chemistry steps	
Number of purification steps	
Number of stages	
% Overall yield	
List of solvents used	
List of extreme conditions	
List of reagents with known environmental, safety or health problems	
Overall kg solvent/kg final product	
Overall kg water/kg final product	
Overall kg input material (excluding solvent and water)/kg final product	
Total waste/kg of final product (sum of 3 boxes above)	
Overall kg input material (excluding solvent and water)/kg final product if all stage yields are 100%	
Projected peak year tonnage	
Catalytic chemistry used	
Asymmetric chemistry used	
Additional comments	

isolation procedure to give the desired intermediate or final product as a solid, oil or in solution.

Example of the difference between a stage and a step:



This may be achieved in one stage, but has three chemistry steps.

1. Reduction of nitro group
2. Reduction of aromatic ring
3. Hydrochloride salt formation

Overall yield. The overall yield of the process is included as a conventional measure of efficiency (to include all arms of the synthesis if convergent) although this provides no information on the amount or type of waste generated.

Section 3: environmental impact

This section is intended to provide information on key material usage, including solvents, quantities of waste and extreme conditions. It is used as a surrogate for energy consumption, and is a mixture of text and calculation. The assessment is made on the basis of the identity and quantity of input and auxiliary materials only and does not take into account the nature of the reaction products or the effects of side reactions.

Solvents. This is a simple list of all solvents used in the process and can be used to provide more detailed information when broken down by stages. It enables chemists to focus on the type and number of solvents. This information, when used in conjunction with the GlaxoSmithKline Solvent Selection Guide,[7] will also help to highlight separability issues and opportunities to reduce the use of solvents that have associated health and safety risks.

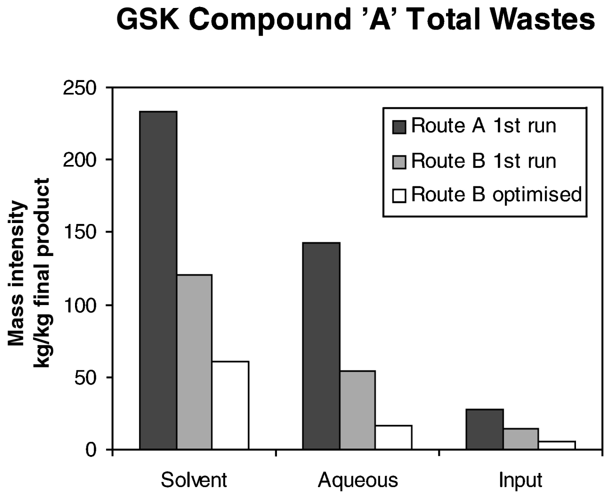


Fig. 1

Extreme conditions. This is included primarily to highlight high temperature processes, but also covers safety and solvent usage by documenting the use of high pressures or excessive dilution. For this simple template we have not implemented our systems for calculating process energy and therefore merely make a note of conditions outside those in everyday use in a typical pilot plant. These conditions include temperatures >130 or <-15 °C, pressures >50 lb in^{-2} (3.4×10^5 N m^{-2}), and reaction concentrations of $<5\%$ expressed in terms of product at 100% yield.

Reagents with known environmental, safety or health hazards. This is intended to highlight the use of reagents that have significant, recognised hazards in terms of safety (such as those with explosive properties, *e.g.*, azides), human health (*e.g.*, dimethyl sulfate), or environmental (those likely to cause waste disposal problems, *e.g.*, amines, heavy metals, cyanides).

Quantity of waste. This is calculated separately for solvents, water and all other materials, and the totals are combined to give the mass intensity or E-factor.[5] The total mass of the input material per unit weight of final product, at 100% yield, is also calculated as a simple measure of atom economy. If so desired, this may be refined by excluding auxiliary materials that are aids to product purification, and not integral to the chemistry.

Although these numbers do not provide information on waste stream composition, they provide enough information to prompt the chemist to explore opportunities for mass reduction and recycling, and to consider the potential environmental impact of the waste.

Typically, significant reductions in volumes of solvent, aqueous and input materials are experienced as more efficient routes to target compounds are introduced and optimised. An actual example of this progress is illustrated in Fig. 1.

Projected peak year tonnage. This gives an indication of the likely scale of impact and the scope for improvement on a gross basis.

Section 4: comments

This is an opportunity to highlight the use of steps involving catalytic reagents, asymmetric processes and other types of chemistry that could be more environmentally friendly. Comments may also be added about other issues that may not have been captured but that may have significant environmental impact. For example, if the chemical nature of the product is thought to restrict opportunities for environmental optimisation or where the mass of an input material appears to be high but it may be reuseable, such as in the case of chromatography packing. This section could also incorporate a description of any assumptions that have been made when preparing the assessment.

Implementation

To be of greatest value, the template must be completed at various key stages during the chemical development of the target compound. An initial assessment at the time of preparation of the first supplies (usually on a large laboratory scale) will provide a baseline. Thereafter, updates are required when preparing the first pilot plant batch using the initial chemistry, when a new route is introduced into the plant, or if there are significant process improvements made without a change of route.

We have found that it normally takes no more than 1–2 hours to complete the first template for a compound. Subsequent updates may be completed more quickly. It is important to emphasise that while these measures give a broad view of the likely environmental impact of the process, the information derived is limited. In particular, the system does not provide a breakdown of the composition of waste streams, nor does it address treatment options, or the acquisition of raw materials from sustainable sources. Key inputs to the design of the process from the process engineering and safety testing groups are also outside the scope of the current system. When processes are transferred to a manufacturing plant, it is also essential that a full environmental assessment is undertaken and this must be completed prior to the preparation of validation batches.

The introduction of the set of measures described here has raised the environmental awareness of our process chemists and has enabled us to document and highlight improvement opportunities. These opportunities will help move GlaxoSmithKline towards achieving the ultimate target of drug manufacture using 'green chemistry'. It will also enable a direct comparison of the potential environmental impact of alternative routes for a particular compound as well as between different compounds.

References

1 *Green Chemistry: Theory and Practice*, ed. P. T. Anastas and J. C. Warner, Oxford University Press, Oxford, 1998.

2 J. H. Clark, *Green. Chem.*, 1999, **1**, 1; D. J. Dale, P. J. Dunn, C. Golightly, M. L. Hughes, P. C. Levett, A. K. Pearce, P. M. Searle, G. Ward and A. S. Wood, *Org. Process Res. Dev.*, 2000, **4**, 17.

3 A. D. Curzons, D. J. C. Constable, D.N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1.

4 C. E. Berkoff, K. Kamholz, D. E. Rivard, G. Wellman and H. Winicov, *Chemtech*, 1986, **16**, 552.

5 R. A. Sheldon, *Chem. Ind. (London)*,, 1992, 903; R. A. Sheldon, *Chem. Ind. (London)*, 1997, 12.

6 Details of The Centre for Waste Reduction Technologies sustainability metrics may be found at the website, www.aiche.org.

7 A. D. Curzons, D. C. Constable and V. L. Cunningham, *Clean Products Processes*, 1999, **1**, 82.

Amphiphilic layered silicate clay for the efficient removal of organic pollutants from water

Wouter L. IJdo and Thomas J. Pinnavaia*

Department of Chemistry and Center for Fundamental Materials Research, Michigan State University, East Lansing, Michigan 28824, USA. E-mail: pinnavai@cem.msu.edu

Received 16th October 2000
First published as an Advance Article on the web 15th January 2001

An amphiphilic smectite clay, interlayered by regularly alternating galleries of organic [$C_{16}H_{33}N(C_4H_9)_3{}^+$] and inorganic ($Li^+$) exchange cations, is shown to be especially efficient for the removal of a chlorinated aromatic pollutant (2,4-dichlorophenol) from water in comparison to the fully-exchanged hydrophobic form of the same clay.

Introduction

Smectite clay minerals have a substantial capacity for the sorption of cationic organic contaminants from aqueous solution (*ca*. 100 meq g^{-1}).[1] The binding of cationic organic species occurs through ion exchange of the alkali metal and alkaline earth cations initially present in the gallery region between the silicate layers. In contrast, the sorption of non-ionic organics by native smectic minerals is generally restricted to only the external surfaces of the clay tactoids.[2] The sorptive capacity towards non-ionic organics can be greatly improved, however, if the clay interlayers are modified by ion exchange with cationic surfactants that render the gallery regions lipophilic.[3,4.] Long-chain alkylammonium ion exchange forms of smectite clays, for instance, afford especially lipophillic galleries.[5] Organic pollutants readily penetrate the onium ion interlayers and become physically adsorbed through van der Waals interactions with the hydrophobic segments of the exchange cations and the siloxane surfaces of the clay.[6–8] In this way the onium ion clay functions as a solid state partitioning medium for the removal of the pollutant from solution.[1]

The sorptive properties of organo cation exchange forms of smectite clays also can be tailored to adsorb specific organics through a judicious choice of the organic exchange cation.[7] This selectivity makes organo clays even more attractive for the removal of specific contaminants (*e.g.*, chlorinated organics) from water. However, most organo clays are exceptionally hydrophobic and cannot be wetted by an aqueous phase. This extreme hydrophobicity makes it impractical to use most organo clays for the adsorption of organic contaminants from water, because the clays rapidly segregate at the water–air interface. If an organo clay is used in packed bed form, severe channeling of the bed typically is encountered.

In the present work we describe the use of a new type of amphiphilic layered silicate clay for the removal of organic pollutants from aqueous solution. These recently reported clays are hybrid heterostructures containing regularly alternating galleries of organic [*e.g.*, $C_{16}H_{33}N(C_4H_9)_3{}^+$] and inorganic (*e.g.*, Li^+) exchange cations.[9,10] The segregation of the organic and inorganic cations into separate galleries, a behavior reminiscent of staging in graphite intercalation compounds,[11] allows for the desired amphiphilic properties.

Results and discussion

Fig. 1 schematically illustrates a 1 : 1 mixed ion smectite clay heterostructure with organic onium ions and inorganic cations segregated in alternate galleries. The segregation of the ions is driven by differences in the solvation properties of the two very different types of cations. The inorganic galleries of the heterostructure are hydrophilic and readily solvated by water, whereas the organic galleries are lipophilic and avoid hydration. This difference in the polarities of the galleries makes it possible to disperse the heterostructure in either a polar or a non-polar solvent. When the heterostructure is wetted by water, for example, the inorganic galleries become fully hydrated and exfoliate into the aqueous phase. However, as is also illustrated in Fig. 1, the lipophilic organic galleries remain sandwiched between pairs of silicate layers in the exfoliated state. These

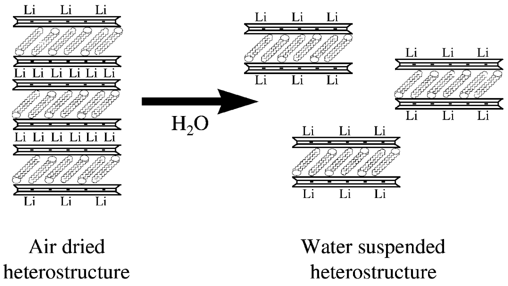


Fig. 1 A schematic illustration of the segregation of organic and inorganic cations in the galleries of a 1 : 1 mixed ion smectite clay heterostructure and the dispersion of the amphiphilic clay in water. Note that the inorganic galleries are easily wetted and exfoliated through hydration of the inorganic cations, whereas the lipophilic organic galleries remain sandwiched between pairs of silicate layers.

Green Context

Selective removal of aromatics from water is of prime importance in the clean-up of contaminated water. It is also of great importance in the development of water-based organic chemistry, an important area of research in Green Chemistry, but one where the water solvent is never completely free of organic contamination after the reaction. The research here relates to the generation of composites based on clays, made hydrophobic by surfactant molecules alternating with Li ions from layer to layer, which form an environment capable of highly selective adsorption of organics from water. These relatively cheap and accessible materials show great potential in the removal of organic molecules from water. ***DJM***

DOI: 10.1039/b008308i

dispersed packets of organophilic galleries are capable of adsorbing low concentrations of organic solutes from solution, while at the same time being dispersed in the aqueous phase. This wetting property is in contrast to the extreme hydrophobic character of a fully exchanged clay, wherein every gallery is interlayered with alkyl ammonium ions and the clay is completely non-dispersible in water.

1 : 1 Heterostructured smectite clays can be formed spontaneously upon mixing equal molar quantities of the inorganic and organic ion exchanged forms of the parent end member clays.[9,10] The redistribution of organic and inorganic ions into a mixed ion heterostructure is favored when the size of the head group on the organic cation is sufficiently large to occupy the area corresponding to one unit of charge on the clay surface.[9,10] Synthetic fluorohectorite with a layer charge density of *ca.* 1.2 e− per $O_{20}F_4$ unit cell is well suited for heterostructure formation with readily available quaternary ammonium ions and alkali metal ions. Heterostructured clays can also be formed by the direct addition of a half an exchange equivalent of alkyl ammonium ions to a suspension of the inorganic exchange form of the clay.

We first compare the adsorption properties of a 1 : 1 mixed ion clay heterostructure and a fully exchanged (homoionic) organo clay for the removal of an organic pollutant from water under equilibrium conditions. The isotherms shown in Fig. 2 were obtained for the adsorption of 2,4-dichlorophenol from water by a homoionic $C_{16}H_{33}NBu_3^+$ exchanged fluorohectorite (circles) and a 1:1 $C_{16}H_{33}NBu_3^+ : Li^+$ mixed ion heterostructured fluorohectorite clay (squares). The binding capacities of the two clays are normalized in terms of mmol 2,4-dichlorophenol adsorbed per gram of alkylammonium ion bound to the clay phase. Both clays exhibit a type I isotherm characteristic of strong adsorbate–adsorbent interactions.[12] Note that the normalized adsorption capacities are essentially equivalent. This means dichlorophenol adsorption occurs almost exclusively in the lipophilic organic galleries of both the heterostructured clay and the fully exchanged homoionic clay. Little or no adsorptive capacity can be assigned to the Li^+-exchanged surfaces of the heterostructure.

Although the normalized adsorption properties of the heterostructured clay and the fully exchanged homoionic organo clay are equivalent under equilibrium conditions, the advantage of the heterostructured clay becomes readily apparent when the adsorption of 2,4-dichlorophenol is followed as a function of time. Fig. 3 illustrates the time dependence for the adsorption of 2,4-dichlorophenol from water by homoionic $C_{16}H_{33}NBu_3^+$ exchanged fluorohectorite (circles) and by a 1 : 1 $C_{16}H_{33}NBu_3^+$ and Li^+ mixed ion heterostructured fluorohectorite clay (squares). Both clays were added to standing (unstirred) 2,4-dichlorophenol solutions in amounts containing equal quantities of onium exchange ions. The 2,4-dichlorophenol concentration reaches its final equilibrium concentration almost instantaneously when the mixed ion heterostructured clay is added to the 2,4-dichlorophenol solution. In contrast, the 2,4-dichlorophenol concentration decreases very slowly when homoionic $C_{16}H_{33}NBu_3^+$ exchanged fluorohectorite clay is added to the solution. The final equilibrium concentration was not attained even after 25 h.

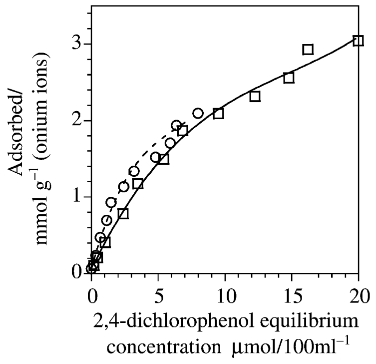


Fig. 2 Adsorption isotherms (25 °C) for the removal of 2,4-dichlorophenol from a vigorously stirred aqueous solution by homoionic $C_{16}H_{33}NBu_3^+$ exchanged fluorohectorite (circles) and a 1 : 1 $C_{16}H_{33}NBu_3^+$ and Li^+ mixed ion fluorohectorite heterostructure (squares). The clay suspensions were equilibrated for five days prior to being analyzed for 2,4-dichlorophenol uptake by the clays.

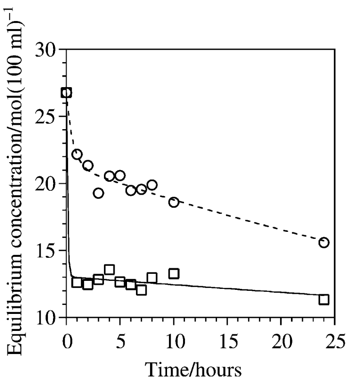


Fig. 3 Change in 2,4-dichlorophenol concentration with time when the solute is adsorbed under static conditions from water solution by a homoionic $C_{16}H_{33}NBu_3^+$ fluorohectorite clay (circles) and a 1 : 1 $C_{16}H_{33}NBu_3^+ : Li^+$ mixed ion fluorohectorite clay heterostructure (squares). The air dried clays were added to standing (unstirred) 2,4-dichlorophenol solutions at 25 °C.

The rapid uptake of 2,4-dichlorophenol by the heterostructured clay is concomitant with the almost instantaneous dispersion of the clay in the solution phase. The partitioning function of each organic interlayer is fully realized in the water–dispersed state. Consequently, the 2,4-dichlorophenol concentration decreases almost immediately upon the addition of the air-dried heterostructured clay. In contrast, the homoionic $C_{16}H_{33}NBu_3^+$ exchanged organo clay rapidly segregates at the water–air interface, depleting dichlorophenol primarily near the surface of the solution. Consequently, there initially an abrupt drop in the dichlorophenol concentration, but further access to the lipophilic galleries of the segregated homoionic organo clay is greatly limited by diffusion. As a result, the 2,4-dichlorophenol concentration decreases at a significantly reduced rate.

Amphiphilic organic–inorganic clay heterostructures can be formed from smectite clays in combination with a variety of other inorganic cations and surfactant cations containing large head groups. For instance, adsorption properties similar to those illustrated in Fig. 3 were observed for 1 : 1 heterostructures formed from Na^+ as the inorganic cation and dodecyltributylammonium as the cationic surfactant. Thus, the concept of designing amphiphilic clay heterostructures for the efficient removal of organic solutes from bodies of contaminated water or waste streams is quite general. Also, although the heterostructured clay is dispersible in water, it also can be easily recovered by filtration or, alternatively, by allowing the clay suspension to settle over time and decanting off the supernatant aqueous phase. The ability to filter the suspended particles or to remove them through settling and decanting greatly improves the potential use of these materials for environmental cleanup and pollution prevention.

Experimental

A synthetic fluorohectorite, $Li_{1.12}\cdot[Mg_{4.88}Li_{1.12}]Si_8O_{20}F_4$ (Corning, Inc.), denoted as Li^+-FH, was used as the starting smectite clay. The cation exchange capacity (CEC) of fluorohectorite, as measured by the ammonia selective electrode method,[13] was 1.21 meq g^{-1}. A portion of the Li^+-FH was converted to a homoionic clay by ion exchange reaction with $C_{16}H_{33}NBu_3^+$ ions.[10] A 10% excess of onium ions was used in the exchange reaction to ensure the complete displacement of the Li^+ ions from the galleries. The 1 : 1 heterostructured mixed cation exchanged form of fluorohectorite was prepared by a simple one-step/one-pot procedure wherein half an exchange equivalent of $C_{16}H_{33}NBu_3^+$ ions was added to a Li^+-FH suspension. Because the displacement of the inorganic cations by the onium ions was quantitative, the amount of $[C_{16}H_{33}NBu_3^+]Br^-$ surfactant added corresponded to the fraction of the onium cations present in the final mixed ion product. In a typical synthesis, 0.30 g of Li^+-FH clay was first dispersed in *ca*. 100 ml of deionized water and then the surfactant was slowly added as the bromide salt. The reaction mixtures were stirred for at least 48 h at ambient temperature. Each product was washed free of excess salt and air-dried. All exchanged forms of fluorohectorite clay were checked for phase purity by XRD.[9,10]

Adsorption isotherms (25 °C) were obtained for the adsorption of 2,4-dichlorophenol from water onto homoionic $C_{16}H_{33}NBu_3^+$ exchanged fluorohectorite and a 1 : 1 $C_{16}H_{33}NBu_3^+$ and Li^+ mixed ion heterostructured fluorohectorite clay. The adsorption isotherms were obtained by weighing known quantities of the air-dried clays into sealable polypropylene bottles. Next, precise quantities of a standard 2,4-dichlorophenol solution were added to the clay so that the amount of 2,4-dichlorophenol added was in the range 1.0–50 μmol per 100 ml of solution. The bottles were agitated on a shaker table for at least five days and then centrifuged to remove the clay. Next, the residual 2,4-dichlorophenol in solution was extracted into hexane from 5 ml of the supernatant. The 2,4-dichlorophenol concentration was then determined from the optical density of 2,4-dichlorophenol at 284 or 292 nm using an IBM 9430 UV-VIS spectrophotometer.

The change in 2,4-dichlorophenol concentration with time was followed using a static (unstirred) adsorption procedure. Air-dried powders of homoionic $C_{16}H_{33}NBu_3^+$ exchanged fluorohectorite and air-dried 1 : 1 $C_{16}H_{33}NBu_3^+ : Li^+$ mixed ion heterostructured fluorohectorite were sprinkled onto the surface of a 500 ml standing solution of 2,4-dichlorophenol in water (26.78 μmol/100 ml). A 5 ml sample was taken every hour from the center of the solution and the sample was extracted with hexane to determine the 2,4-dichlorophenol concentration.

Acknowledgment

The support of this research through NIEHS Grant ES 04911C is gratefully acknowledged.

References

1 Clay Minerals Society Workshop Lectures, *Organic Pollutants in the Environment*, ed. B. Sawhney, Clay Minerals Society, Aurora, Colorado, 1996, vol. 8.
2 R. M. Barrer, *Pure Appl. Chem.*, 1989, **61**, 1903.
3 S. H. Xu, G. Y. Sheng and S. A. Boyd, *Adv. Agron.*, 1997, **59**, 25.
4 W. F. Jaynes and G. F. Vance, *Soil Sci. Soc. Am. J.*, 1996, **60**, 1742.
5 G. Lagaly, *Solid State Ionics*, 1986, **22**, 43.
6 M. M. Mortland, S. Shaobai and S. A. Boyd, *Clays Clay Miner.*, 1986, **34**, 581.
7 S. A. Boyd, S. Shaobai, J.-F. Lee and M. M. Mortland, *Clays Clay Miner.*, 1988, **36**, 125.
8 W. F Jaynes and S. A. Boyd, *Soil Sci. Soc. Am. J.*, 1991, **55**, 43.
9 W. L. IJdo, T. Lee and T. J. Pinnavaia, *Adv. Mater.*, 1996, **8**, 79.
10 W. L. IJdo and T. J. Pinnavaia, *J. Solid State Chem.*, 1998, **139**, 281.
11 S. A. Solin, *Annu. Rev. Mater. Sci.*, 1997, **27**, 89.
12 S. J. Gregg and K. S. W. Sing, *Adsorption, Surface Area, and Porosity*, Academic Press, New York, 1982.
13 E. Busenberg and C. V. Clemency, *Clays Clay Miner.*, 1973, **21**, 213.

Integrated chemical process for green chemistry. One-pot synthesis of 3-substituted 5-(β-sulfonylvinyl)indoles by *in situ* generation of toxic vinyl sulfone

Akihiro Orita,[a] Masataka Katakami,[a] Yutaka Yasui,[a] Akio Kurihara[b] and Junzo Otera*[a]

[a] *Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700-0005, Japan. E-mail: otera@high.ous.ac.jp*
[b] *Organic Synthesis Research Laboratory, Sumitomo Chemical Co., Ltd., 10-1 2-Chome Tsukahara Takatsuki-City, Osaka 569-1093, Japan*

Received 12th July 2000
First published as an Advance Article on the web 8th January 2001

Integrated chemical processes where multi-step reactions are consolidated in one pot are effective for realizing a green chemical process. *In situ* generation followed by consumption of toxic intermediates which are formed in the process enables their complete isolation from the environment. This is so for a vinyl sulfone intermediate in the synthesis of 3-substituted 5-(β-sulfonylvinyl)indoles. The validity of this idea is further confirmed by successful one-pot operations on an automated synthesizer.

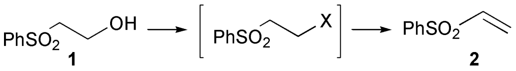
Introduction

Previously, we introduced a new concept for consolidation of multi-step reactions in one-pot, a so-called 'integrated chemical process'. In this treatment, reaction conditions which can be tolerated by all steps are established first and, then, each step is optimized within the framework of these conditions.[1] We have already disclosed that such a procedure not only effects compaction of the whole process but also gives rise to an increase in overall yield. Moreover, another advantage lies in the enclosure of relevant intermediates in the reaction flask throughout the process. This may be of great promise in terms of green chemistry because processes involving toxic intermediates can be operated without exposure of these substances to the environment.

3-Substituted 5-(β-sulfonylvinyl)indoles are useful intermediates for a variety of pharmaceuticals and are fabricated by Heck reaction between vinyl sulfone and the corresponding 5-halo indoles.[2] Phenyl vinyl sulfone, though being a versatile reagent which is used in a wide spectrum of organic syntheses,[3] is an irritant to the eyes, the respiratory system and skin on account of their facile susceptibility to the Michael reaction[4] and, thus, handling a mass of the neat compound in the open air must be avoided. We demonstrate here that the problem can be overcome by integrating two steps consisting of phenyl vinyl sulfone formation from non-toxic 2-sulfonylethanol and subsequent Heck reaction with 5-bromoindole.

Results and discussion

Initially, we assessed the validity of our concept by comparing stepwise and integrated processes using model reactions [eqns. (1) and (2)]. The preparation of phenyl vinyl sulfone **2** was screened by treating 2-phenylsulfonylethanol **1** with various dehydrating agents (Table 1). All procedures except for the benzoylation method exhibited no significant difference in the yield. Then, Heck reaction of **2** with aryl iodides or 5-halo indoles was optimized. The conditions thus determined are given in Table 2 together with the yields of the β-aryl vinyl sulfones **3**.



(1)

(2)

Next, both steps were brought together. As expected, the two reactions were virtually compatible but the overall yields were considerably dependent on the conditions for the first step. Among the procedures described above for **2**, the mesylation method gave the best outcome when aryl iodides were the reaction components in the Heck reaction. In this process,

Table 1 Preparation of phenyl vinyl sulfone **2** [eqn. (1)][a]

Entry	Reagent	Yield (%)[b]
1	$(MeSO_2)_2O$	72
2	$(CF_3SO_2)_2O$	75
3	$(p\text{-}MeC_6H_4SO_2)_2O$	70
4	$p\text{-}MeC_6H_4SO_2Cl$	73
5	$(CF_3CO)_2O$	74
6	$(PhCO)_2O$	60
7	$SOCl_2$	75

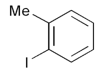
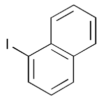
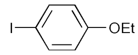
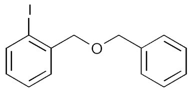
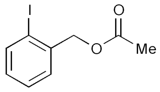
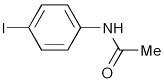
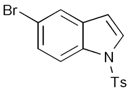
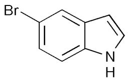
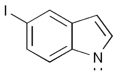
[a] *Reaction conditions*: reagent (1.1 eq); Et_3N (4.0 eq); MeCN; 50 °C, 5 h. [b] Isolated yield.

Green Context

Multi-step syntheses produce considerable amounts of waste, in part due to their complexity, but also due to a series of complex isolation procedures which must be carried out after each step. Thus, the combination of steps into a multi-step, one-pot reaction sequence can be of great value, as long as overall yield and efficiency are not negatively influenced. The chemistry described in this article is a good example of an efficient process which has been carried out over several steps without isolation of intermediates, and with excellent efficiency. Additionally, some of the toxic intermediates formed are not isolated, and thus Health and Safety aspects of the chemistry are improved. ***DJM***

DOI: 10.1039/b005645f

Table 2 Preparation of β-arylvinylsulfones **3** by Heck reaction [eqn. (2)][a]

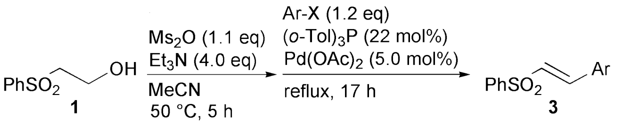
Entry	Ar-X	Product	Yield (%)[b]
1		**3a**	73
2		**3b**	74
3		**3c**	63
4		**3d**	58
5		**3e**	62
6		**3f**	60
7[c]		**3g**	20
8[c]			49
9[c]		**3h**	54
10[c]		**3h**	54

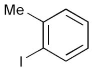
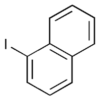
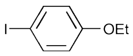
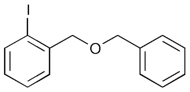
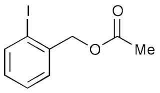
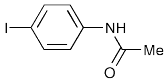
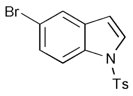
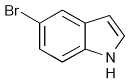
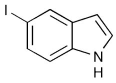
[a] *Reaction conditions*: $Pd(OAc)_2$ (5.0 mol%); (o-Tol)$_3$P (22 mol%); MeCN; reflux 17 h. [b] Isolated yield. [c] 5-Haloindole (1.5 eq) used.

acetonitrile was the solvent of choice. In Table 3, the overall yields thus obtained are shown together with those *via* the stepwise process for comparison (entries 1–6). On the other hand, trifluoroacetic anhydride (TFAA) gave better yields than the other reagents when 5-bromo- or 5-iodo-indole was subjected to the Heck reaction (entries 7–10). DMF was the common solvent for the consecutive reactions. Remarkably, the integrated protocol provided higher yields (except for entry 4) than the corresponding stepwise process regardless of the method for the generation of **2**.

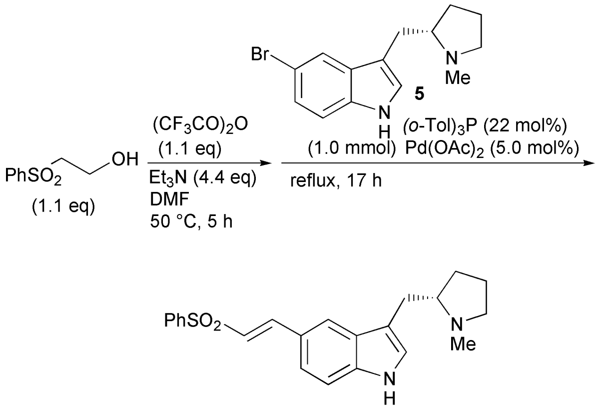
With these results in hand, we turned out attention on the one-pot synthesis of 5-(*E*)-(2-phenylsulfonylvinyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole **4**, which, upon reduction of the vinyl moiety, is converted to the corresponding 5-(2-phenylsulfonylethyl) derivative, an intermediate for drug compositions effective for treating migraine and other disorders.[2b] As shown Scheme 1, the vinyl sulfone **2** was generated by the TFAA method and subsequently treated with 5-bromo-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole **5**. When the Heck reaction was complete, a trace amount of unreacted **2** was detected in the reaction mixture by HPLC monitoring. The addition of Et_2NH completely consumed **2** without destruction of **4**. As a result, the phenyl vinyl sulfone was not exposed to the environment during the entire manipulation process. The overall yield was 58% on the basis of HPLC analysis and a 56% yield was obtained by preparative HPLC. However, the isolated yield was somewhat decreased (51%) because of the instability of **4**, yet remarkably higher than that of the stepwise process (38% = 74% × 51%). This may be attributed to the efficiency

Table 3 One-pot preparation of β-arylvinylsulfones **3**



Entry	Ar-X	Product	Yield (%)[a,b]
1		**3a**	74 (52)
2		**3b**	64 (53)
3		**3c**	49 (45)
4		**3d**	40 (42)
5		**3e**	56 (44)
6		**3f**	45 (43)
7[c]		**3g**	21 (15)
8[c,d]			58 (35)
9[c,d]		**3h**	54 (40)
10[c,d]		**3h**	52 (40)

[a] Isolated yield. [b] Overall yield for the corresponding stepwise process [% yield in eqn. (1) × % yield in eqn. (2) is given in parentheses. [c] Trifluoroacetic anhydride (1.1 eq) used in place of Ms_2O. [d] 5-Haloindole (1.5 eq) used.



4

58% (HPLC), 56% (preparative HPLC),
51% (column chromatography)

Scheme 1 One-pot synthesis of **4**.

in generation of **2** as well as in its use for the Heck reaction. Essentially, the integrated process can minimize the mechanical loss of the intermediates during manipulations for isolation and purification. Furthermore the vinyl sulfone itself is not very chemically stable[5] and, thus, the stepwise process suffers a serious decrease in the overall yield. It is also rather surprising that, despite the instability of **4**, a reasonable yield was accessible from the reaction mixture which contained various materials resulting from the two reactions, indicative of the practical usefulness of the integrated chemical process.

Finally, the validity of the present protocol as a green process was further proved by running it on an automated synthesizer (MEDLEY) which we have recently developed.[6] This machine enables successive addition of reagents in precise amounts (within ±0.01 mL) and control of the reaction temperature to ±0.1 °C. More importantly, the reaction can be run under a completely inert atmosphere to accommodate air-sensitive organometallic or transition metal compounds. We thus carried out the automated synthesis of **4** on MEDLEY. As shown in Scheme 2, a DMF solution of **1** was placed in a reaction flask and then the program was initiated. Nine operations were performed automatically and **4** was obtained in 58% yield based on HPLC analysis. This integrated chemical process is clearly environmentally benign.

$$\mathbf{1} + \mathbf{5} \longrightarrow \mathbf{4}$$

58% (HPLC), 55% (preparative HPLC)

Operations Programmed

1. addition of $(CF_3CO)_2O$ (1.1 eq) at 25 °C
2. addition of Et_3N (4.4 eq) at 25 °C
3. warming up to 50 °C
4. stirring/50 °C/5 h
5. addition of **5** (1.0 eq)/50 °C
6. addition of catalyst in THF
7. warming up to 150 °C
8. stirring/150 °C/17 h
9. addition of Et_2NH (0.15 eq)

Scheme 2 One-pot synthesis of **4** on MEDLEY.

Conclusion

An integrated chemical process has proved to be effective for realizing a green process, enabling isolation of a toxic intermediate from the environment through *in situ* generation followed by consumption. There are a number of processes in which toxic intermediates are inevitably generated and, accordingly, the concept disclosed here will find diverse applications.

Experimental

General comments

All reactions were carried out under nitrogen unless otherwise noted. Acetonitrile, dimethylformamide and triethylamine were distilled from calcium hydride. NMR spectra were recorded at 25 °C on JEOL Lambda 300 and 500 instruments and calibrated with tetramethylsilane (TMS) as an internal reference. High-performance liquid chromatography (HPLC) was performed on a Recycling Preparative HPLC LC-908 (Japan Analytical Industy Co., Ltd) equipped with GPC columns JAIGEL-1H and 2H using refractometer and UV detectors. Mass spectra were recorded on a JEOL MStation JMS-700 spectrometer. Elemental analyses were performed on a Perkin Elmer PE 2400 instrument. 2-Phenylsulfonylethanol **1** was provided by Sumitomo Chemical Co., Ltd. Silica gel (Daiso gel IR-60) was used for column chromatography.

Representative preparations

Phenyl vinyl sulfone 2. To a flame-dried flask were added **1** (186 mg, 1.0 mmol), methanesulfonic anhydride (190 mg, 1.1 mmol), triethylamine (0.56 mL, 4.0 mmol) and acetonitrile (3.0 mL), and the mixture was heated to 50 °C for 5 h. After addition of water and extraction with ethyl acetate, the organic layer was washed with brine. After drying over Na_2SO_4 and evaporation, the crude mixture was subjected to column chromatography on silica gel to afford the pure product (127 mg, 72% yield).

1-Methyl-2-(*E*)-(2-phenylsulfonylvinyl)benzene 3a (stepwise manner). To a flame-dried flask were added palladium acetate (11 mg, 0.05 mmol), tris(*o*-tolyl)phosphine (67 mg, 0.22 mmol) and acetonitrile (1 mL), and the mixture was stirred at room temperature for 10 min. To this solution were added **2** (168 mg, 1.0 mmol), *o*-iodotoluene (0.15 mL, 1.2 mmol) and triethylamine (0.28 mL, 2.0 mmol), and the mixture was heated under reflux for 7 h. After addition of water and extraction with ethyl acetate, the organic layer was washed with brine. After drying over Na_2SO_4 and evaporation, the crude mixture was subjected to column chromatography on silica gel to afford the pure product (189 mg, 73% yield).

3a (one-pot manner). To a flame-dried flask were added **2** (186 mg, 1.0 mmol), methanesulfonic anhydride (190 mg, 1.1 mmol), triethylamine (0.56 mL, 4.0 mmol) and acetonitrile (3.0 mL), and the mixture was heated at 50 °C for 5 h. After confirmation of complete consumption of **2** by TLC monitoring, palladium acetate (11 mg, 0.05 mmol) and tris(*o*-tolyl)phosphine (67 mg, 0.22 mmol) were added. Then, *o*-iodotoluene (0.15 mL, 1.2 mmol) in acetonitrile (2 mL) was added and the mixture was heated under reflux for 17 h. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine. After drying over Na_2SO_4 and evaporation, the crude mixture was subjected to column chromatography on silica gel to afford a pure product (191 mg, 74% yield).

Characterization data

1-Methyl-2-(*E*)-(2-phenylsulfonylvinyl)benzene 3a: $\delta_H(CDCl_3)$ 2.47 (s, 3H), 6.79 (d, *J* 15.3 Hz, 1H), 7.16–7.34 (m, 3H), 7.44 (d, *J* 6.7 Hz, 1H), 7.53–7.68 (m, 3H), 7.92–8.01 (m, 3H);$\delta_C(CDCl_3)$ 19.8, 126.5, 126.8, 127.6, 128.1, 129.3, 130.9, 131.0, 131.2, 133.3, 138.2, 140.1, 140.7. Anal. Calc. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.72; H, 5.43%.

1-(*E*)-(2-Phenylsulfonylvinyl)naphthalene 3b: $\delta_H(CDCl_3)$ 6.97 (d, *J* 15.0 Hz, 1H), 7.46 (t, *J* 7.6 Hz, 1H), 7.53–7.70 (m, 6H), 7.87–7.95 (m, 2H), 8.01 (d, *J* 7.6 Hz, 2H), 8.18 (d, *J* 8.3 Hz, 1H), 8.54 (d, *J* 15.0 Hz, 1H); $\delta_C(CDCl_3)$ 123.0, 125.3, 125.7, 126.5, 127.4, 127.7, 128.9, 129.4, 129.5, 129.6, 131.3, 131.5, 133.5, 133.7, 139.5, 141.0. Anal. Calc. for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79. Found: C, 73.09; H, 4.70%.

1-Ethoxy-4-(*E*)-(2-phenylsulfonylvinyl)benzene 3c): $\delta_H(CDCl_3)$ 1.42 (t, *J* 7.1 Hz, 3H), 4.06 (q, *J* 7.1 Hz, 2H), 6.70 (d, *J* 15.4 Hz, 1H), 6.89 (d, *J* 8.8 Hz, 2H), 7.43 (d, *J* 8.8 Hz, 2H), 7.50–7.65 (m, 3H), 7.63 (d, *J* 15.4 Hz, 1H), 7.94 (d, *J* 8.5 Hz, 2H); δ_C($CDCl_3$) 14.6, 63.6, 114.9, 124.1, 124.7, 127.4, 129.3, 130.3, 133.1, 141.1, 142.3, 161.4. Anal. Calc. for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.95. Found: C, 66.63; H, 5.54%.

1-Benzyloxymethyl-2-(*E*)-(2-phenylsulfonylvinyl)benzene 3d): δ_H($CDCl_3$) 4.61 (s, 2H), 4.66 (s, 2H), 6.84 (d, *J* 15.2 Hz, 1H), 7.26–7.40 (m, 8H), 7.41–7.52 (m, 3H), 7.53–7.62 (m, 1H), 7.86–7.92 (m, 2H), 8.07 (d, *J* 15.2 Hz, 1H); δ_C($CDCl_3$) 70.3, 72.7, 127.3, 127.6, 127.8, 127.9, 128.5, 128.6, 128.7, 129.2, 130.1, 130.7, 131.9, 133.2, 137.5, 137.6, 139.9, 140.6. Anal. Calc. for $C_{22}H_{20}O_3S$: C, 72.50; H, 5.53. Found: C, 72.88; H, 5.54%.

1-Acetoxymethyl-2-(*E*)-(2-phenylsulfonylvinyl)benzene 3e: δ_H($CDCl_3$) 2.08 (s, 3H), 5.23 (s, 2H), 6.84 (d, *J* 15.2 Hz, 1H), 7.30–7.45 (m, 3H), 7.50–7.69 (m, 4H), 7.95–8.02 (m, 3H); δ_C($CDCl_3$) 20.8, 63.8, 127.3, 127.7, 129.1, 129.3, 129.7, 130.6, 130.9, 132.0, 133.5, 135.2, 139.2, 140.4, 170.4; HRMS (EI): calc. for $C_{17}H_{16}O_4S$ *m/z* 316.0769, found 316.0774.

4-(*E*)-(2-Phenylsulfonylvinyl)acetanilide 3f: δ_H($CDCl_3$) 2.20 (s, 3H), 6.76 (d, *J* 15.2 Hz, 1H), 7.30–7.50 (m, 3H), 7.51–7.70 (m, 6H), 7.92–8.00 (m, 2H); δ_C($CDCl_3$) 24.6, 119.7, 125.6, 127.5, 127.7, 129.3, 129.6, 133.4, 140.7, 140.8, 141.9, 168.7. Anal. Calc. for $C_{16}H_{15}O_3NS$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.52; H, 4.93; N, 4.57%.

5-(*E*)-(2-Phenylsulfonylvinyl)-1-tosylindole 3g: δ_H($CDCl_3$) 2.34 (s, 3H), 6.66 (d, *J* 2.2 Hz, 1H), 6.83 (d, *J* 9.2 Hz, 1H), 7.23 (d, *J* 4.8 Hz, 2H), 7.43 (d, *J* 5.1 Hz, 1H), 7.52–7.59 (m, 2H), 7.59–7.62 (m, 2H), 7.66 (s, 1H), 7.72–7.76 (m, 3H), 7.93–8.00 (m, 3H); δ_C($CDCl_3$) δ 21.5, 109.0, 114.0, 122.6, 124.3, 126.2, 126.7, 127.5, 127.6, 127.7, 129.3, 130.0, 131.1, 133.3, 134.9, 136.1, 140.8, 142.6, 145.4. Anal. Calc. for $C_{23}H_{19}O_4NS_2$: C, 63.14; H, 4.38; N, 3.20. Found: C, 63.10; H, 4.40; N, 3.13%.

5-(*E*)-(2-Phenylsulfonylvinyl)-1*H*-indole 3h: δ_H($CDCl_3$) 6.59 (s, 1H), 6.80 (d, *J* 9.2 Hz, 1H), 7.31–7.40 (m, 2H), 7.52-7.62 (m, 3H), 7.78–7.88 (m, 2H), 7.95–7.98 (d, *J* 6.0 Hz, 1H), 8.35 (br, 1H); δ_C($CDCl_3$) 103.5, 111.8, 121.7, 123.2, 123.4, 124.2, 125.7, 127.4, 128.1, 129.2, 133.0, 137.4, 141.4, 144.6; HRMS (EI): calc. for $C_{16}H_{13}O_2NS$ *m/z* 283.0667, found 283.0676.

Preparation of 5-(*E*)-(2-phenylsulfonylvinyl)-3-(*N*-methylpyrrolidin-2- ylmethyl)-1*H*-indole 4 in a one-pot procedure

To a flame-dried flask were added **2** (204 mg, 1.1 mmol), trifluoroacetic anhydride (0.17 mL, 1.1 mmol), triethylamine (0.62 mL, 4.4 mmol) and DMF (1.0 mL), and the mixture was heated at 50 °C for 5 h. After confirmation of complete consumption of **2** by TLC monitoring, a DMF solution (1.0 mL) of palladium acetate (11 mg, 0.05 mmol) and tris(*o*-tolyl)phosphine (67 mg, 0.22 mmol) was added. Then, a DMF solution (1.0 mL) of **5** (293 mg, 1.0 mmol) was added and the mixture was heated under reflux for 17 h with the flask shielded from light. Et_2NH was added (0.016 mL) and the mixture was stirred at room temperature until the vinyl sulfone disappeared (HPLC monitoring). After addition of water and extraction with ethyl acetate, the organic layer was washed with brine, dried over Na_2SO_4 and evaporated. HPLC analysis of the crude mixture indicated a 58% yield of **4**. Preparative HPLC afforded 213 mg (56%) of **4** while column chromatography on silica gel [methanol–chloroform–conc. NH_3(aq) (50 : 50 : 1) → dichloromethane–methanol–conc. NH_3(aq) (90 : 10 : 1) afforded 194 mg (51% yield): δ_H($CDCl_3$) 1.50–1.90 (m, 4H), 2.24 (q, *J* 8.2 Hz, 1H), 2.37–2.53 (m, 1H), 2.46 (s, 3H), 2.54–2.67 (m, 1H), 3.10–3.20 (m, 2H), 6.79 (d, *J* 15.3 Hz, 1H), 7.07 (s, 1H), 7.30–7.40 (m, 2H), 7.51–7.65 (m, 3H), 7.74 (s, 1H), 7.84 (d, *J* 15.3 Hz, 1H), 7.98 (d, *J* 7.9 Hz, 2H), 8.26 (br, 1H); δ_C($CDCl_3$) δ 21.8, 29.7, 31.4, 40.8, 57.5, 66.5, 111.9, 115.2, 121.5, 121.8, 123.2, 123.4, 123.7, 127.4, 128.0, 133.0, 137.8, 141.4, 144.7.

Preparation of 5-(*E*)-(2-phenylsulfonylvinyl)-3-(*N*-methylpyrrolidin-2-ylmethyl)-1*H*-indole 4 on MEDLEY

A flask equipped with a reflux condenser was attached to MEDLEY and flame-dried under reduced pressure. Under a stream of nitrogen, **2** was added to the flask, and the flask was placed in an oil bath. To the storage tanks of MEDLEY were added trifluoroacetic anhydride, triethylamine, a DMF solution of **5**, a THF solution of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine and a DMF solution of Et_2NH. The reaction temperatures and periods shown in Scheme 2 were programmed, and the operations started. After the completion of the programmed operations, water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine. After drying over Na_2SO_4 and evaporation, the crude mixture was filtered through a silica gel pad [methanol–chloroform–conc. NH_3(aq) 50 : 50 : 1) → dichloromethane–methanol–conc. NH_3(aq) (90 : 10 : 1)] and HPLC separation afforded a pure product (419 mg, 55% yield).

Acknowledgements

Thanks are due to Dr Tadatoshi Aratani of Sumitomo Chemical Co. Ltd. for his helpful discussion while assistance in experimental work by H. Watanabe is gratefully acknowledged.

References

1 (*a*) A. Orita, Y. Yamashita, A. Toh and J. Otera, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 779; (*b*) A. Orita, N. Yoshioka and J. Otera, *Chem. Lett.*, 1997, 1023; (*c*) A. Orita, A. Watanabe and J. Otera, *Chem. Lett.*, 1997, 1025; (*d*) A. Orita, A. Watanabe, H. Tsuchiya and J. Otera, *Tetrahedron*, 1999, **55**, 2889; (*e*) A. Orita, N. Yoshioka, P. Struwe, A. Braier, A. Beckmann and J. Otera, *Chem. Eur. J.*, 1999, **5**, 1355; (*f*) A. Orita, J. Yaruva and J. Otera, *Angew. Chem., Int. Ed.*, 1999, **38**, 2267.

2 (*a*) P. C. North, M. R. Johnson and A. W. Oxford, *Eur. Pat. Appl.*, 90301419.9, 1990; (*b*) J. E. Macor and M. J. Wythes, *US Pat.*, 5 545 644, 1996.

3 N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, 1993, ch. 4.

4 (*a*) S. C. DeVito, *CHEMTECH*, 1996, November, 34; (*b*) Aldrich Material Safety Data Sheet, Product # 79293.

5 After the preparation of **2** [eqn. (1)], TLC monitoring exhibited a single spot attributable to the desired product, however, isolation by column chromatography always gave rise to less than 75% yields suggesting partial decomposition of **2**.

6 A. Orita, Y. Yasui and J. Otera, *Org. Process Res. Dev.*, in press.

Esterification of acetic acid with ethanol in carbon dioxide

Lynnette A. Blanchard and Joan F. Brennecke*

Department of Chemical Engineering, University of Notre Dame, Notre Dame, IN 46556, USA. E-mail: jfb@nd.edu

Received 25th September 2000
First published as an Advance Article on the web 26th January 2001

Simply applying CO_2 pressure on a liquid phase, reversible, equilibrium-limited reaction can enhance its equilibrium conversion. In particular, we show that the equilibrium conversion of the esterification of acetic acid with ethanol can be shifted from 63% in neat solution to 72% in CO_2 at 333 K and 58.6 bar.

Introduction

Supercritical carbon dioxide ($scCO_2$) has received much interest in the past several years as an alternative solvent to replace hazardous organic liquids. Most research on reactions with high-pressure CO_2 has focused on the solvent's possible effects on reaction rates, selectivities and yields.[1] For example, researchers have obtained higher enantioselectivities for an asymmetric catalytic hydrogenation reaction using $scCO_2$ as the solvent instead of conventional organic solvents.[2] CO_2 does not have to be in the supercritical state to be a viable reaction media. Recently the indium-mediated allylation of aldehydes was carried out in liquid CO_2.[3] Numerous industrial processes employing carbon dioxide as either an extraction solvent or as a reaction medium have come online in the last two decades. For instance, DuPont recently announced the construction of a plant to polymerize fluoromonomers in CO_2.[4]

This work investigates the effect of using CO_2 as a solvent for an equilibrium limited reversible reaction, the esterification of acetic acid with ethanol [eqn. (1)].

$$MeCO_2H + EtOH \rightleftharpoons MeCO_2Et + H_2O \tag{1}$$

Other recent investigations of equilibrium reactions in high-pressure CO_2 include a number of tautomerization reactions.[5–9] More significantly, Idemitsu Petrochemical Company produces butan-2-ol commercially by the reaction of butenes and water. The butanol partitions into the supercritical butenes, effectively increasing the conversion to product since the reaction occurs in the aqueous phase.[10]

The formation of ethyl acetate and water from the esterification of acetic acid with ethanol is equilibrium limited in the liquid phase for both the neat form and in various non-reactive solvents. Since this reaction progresses very slowly, a strong acid catalyst, typically sulfuric or hydrochloric acid, is generally added to increase the rate of the reaction; however, too much catalyst may cause dehydration of the alcohol or isomerization. In addition, the acids are corrosive and hazardous. It is important to note that the presence of an acid catalyst does not alter the equilibrium constant for the reaction, which is a function of temperature only, nor does it change the extent of conversion—it just enhances the reaction rate.[11] The most effective way to increase product formation is to carry out this reaction in such a manner so as to remove one of the products, usually water, during the reaction process, effectively pushing the equilibrium to the right. One option is reactive distillation; however, the components in this reaction form highly non-ideal liquid mixtures, with the possibility of forming several different azeotropes.[12,13]

The impetus for this work is to explore the effect high-pressure CO_2 may have on the uncatalyzed equilibrium-limited esterification reaction. The equilibrium constant is a function of temperature only but even for single-phase reactions the pressure can affect the conversion. The reaction equilibrium constant in the gas phase or a gas swollen liquid phase that can be modeled with an equation of state is given by eqn. (2).

$$K = \Pi\left(\frac{f_i}{f_i^{o}}\right)^{v_i} = \Pi(f_i)^{v_i} = \Pi(y_i\hat{\phi}_i P)^{v_i} \tag{2}$$

The standard state fugacity, f_i^{o}, is taken as the pure component at one bar and the fugacity, f_i, is given by the mole fraction, y_i, the fugacity coefficient, ϕ_i, and the pressure. The stoichiometric coefficients, v_i, are negative for reactants and positive for products. Thus, for reactions in which the number of moles changes during the course of the reaction, the pressure can have a dramatic effect on the equilibrium mole fractions (*i.e.*, conversion), which has been demonstrated for many reaction systems. However, the number of moles does not change in the esterification of acetic acid with ethanol so this effect is not important. On the other hand, the introduction of CO_2 can dramatically change the fugacity coefficients of the four reactants and products, thus altering the equilibrium conversion.

Another way that the introduction of high-pressure CO_2 might affect the conversion is through the formation of multiple phases. If one of the products is preferentially transferred to an additional phase, this can effectively enhance the conversion to products. For example, the formation of an aqueous-rich liquid phase would likely result in higher product yield. As a result, in this study we simultaneously investigate the reaction progression and the phase behavior. At the conditions investigated here, 333 K and 58.6 bar, we would certainly anticipate the formation of at least two phases, a liquid phase and a relatively dense gas

Green Context

The ability to push equilibrium reactions further to completion is a key factor which is often achieved by the continuous removal of one component, or the use of large excesses of another. The latter is obviously not well suited to green chemistry, whereas the former may often be technically difficult. This paper explores the ability of a novel solvent, supercritical CO_2, to influence the final position of equilibrium. In the esterification of ethanol and acetic acid, it is shown that the final equilibrium position is shifted significantly towards products compared to conventional solvents. Such an approach may help in designing more environmentally benign processes, where equilibrium position is important ***DJM***

DOI: 10.1039/b007734h

phase. There is also the possibility of forming an additional liquid phase since several ternary systems comprised of species from eqn. (1) exhibit liquid–liquid–vapor behavior:

Ethanol–ethyl acetate–H_2O at 70 °C and atmospheric pressure.[14]

CO_2–acetic acid–H_2O at 20, 30, 40 °C and 48.5–77.5 bar.[15,16]

CO_2–ethanol–H_2O at 35, 40 °C and 67.8–103.1 bar.[17–19]

This work measures the phase and reaction equilibria of an equilibrium-limited reaction under CO_2 pressure. The use of high-pressure carbon dioxide, an environmentally benign compound, provides a mechanism to shift the extent of reaction or yield. This is accomplished in the absence of corrosive, hazardous acidic catalysts, that can only affect the reaction rate and not the equilibrium conversion.

Results and discussion

The progression of the esterification of acetic acid under CO_2 pressure is shown in Fig. 1. The concentrations were normalized to the amount of ethyl acetate due to small differences in sample quantities used. The variable volume view cell was initially loaded with an approximate reactant to product mole ratio of 3 to 1. At 333 K and 58.6 bar the liquid phase present at the beginning of the reaction contained about 30 mol% CO_2. The liquid phase composition was used as the basis for the extent of reaction calculation since the concentrations of reactants and products in the vapor phase are relatively small, as described below. The formation of ethyl acetate was relatively rapid in the first 15 days, with full chemical equilibrium of the esterification reaction being reached after 42 days, as indicated by the relatively constant compositions. The reaction is slow because we chose to run the reaction in as simple a form as possible, *i.e.*, without added catalyst. The final reactant to product equilibrium mole ratio was *ca.* 1 : 2.5. This would be 72% conversion to products, if one had started with all reactants. The reaction was monitored *via* the window of the view cell, through which a vapor and liquid phase of approximately equal volumes were observed throughout the duration of the experiment. Thus we did not observe liquid–liquid–vapor equilibrium at any time during the course of the reaction.

The composition of the liquid phase as a function of time is shown in Fig. 2. Concentrations of the reactants, acetic acid (HAc) and ethanol (EtOH), decrease as a function of time from 0.23 and 0.23 mole fractions to 0.08 and 0.12, respectively. In response, the product concentrations increase from 0.12 mole fraction for both water and ethyl acetate to 0.27 and 0.25 mole fractions over the same time period. The lines in Figs. 1 and 2 representing the conversion of acetic acid and ethanol should be coincidental owing to the equimolar nature of the esterification reaction. The same is true for the water and ethyl acetate formation lines. However, as seen in Fig. 2, the mole fraction of H_2O in the liquid phase is greater than the mole fraction of ethyl acetate throughout the reaction. This may be due to the higher solubility of ethyl acetate in the CO_2-rich gas phase, as seen in Fig. 3. The mole fraction of CO_2 in the liquid phase decreased slightly from 0.30 to 0.26 over the duration of the reaction. The slight decrease of CO_2 solubility in the liquid phase can be attributed to the formation of H_2O, a compound with which CO_2 exhibits very low mutual solubilities.[20]

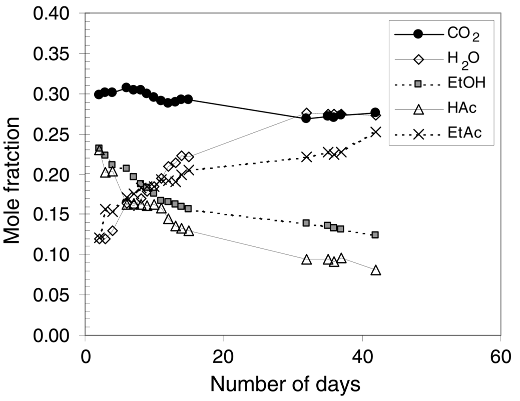


Fig. 2 Liquid-phase compositions in the esterification of acetic acid (HAc) with ethanol (EtOH) in CO_2 at 333 K and 58.6 bar.

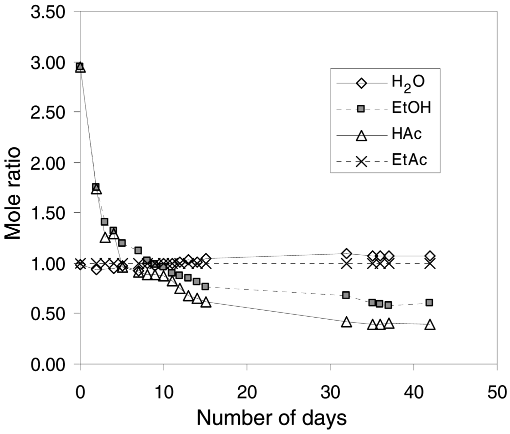


Fig. 1 Progression of the reaction of acetic acid (HAc) and ethanol (EtOH) to ethyl acetate (EtAc) and water in CO_2 at 333 K and 58.6 K bar.

Fig. 3 represents the vapor phase compositions of the esterification reaction. The concentration of CO_2 is relatively constant at 0.86 mole fraction and it comprises the majority of the vapor phase. The solubilities of the reactants and products in the vapor phase are somewhat low, the highest concentration being 0.05 mole fraction of ethyl acetate. The amount of acetic acid, ethanol and water in the vapor phase were 0.04, 0.03 and 0.02 mole fraction, respectively. The slight difference in concentrations may account for the previously mentioned discrepancies in the liquid-phase compositions. The solubilities of the two reactants in the CO_2-rich gas phase are rather similar. Conversely, the ethyl acetate has a significantly higher solubility in the gas phase than the other product, H_2O.

It should be noted that the presence of H_2O and CO_2 will inevitably result in the production of some carbonic acid. In fact, several hundred bar of CO_2 pressure applied to pure water results in the reduction of the aqueous phase pH to as low as 2.8–2.95.[21] Since the esterification of acetic acid with ethanol is acid catalyzed this might have an influence on the *rate* of the reaction. However, as pointed out above, catalysts enhance rates

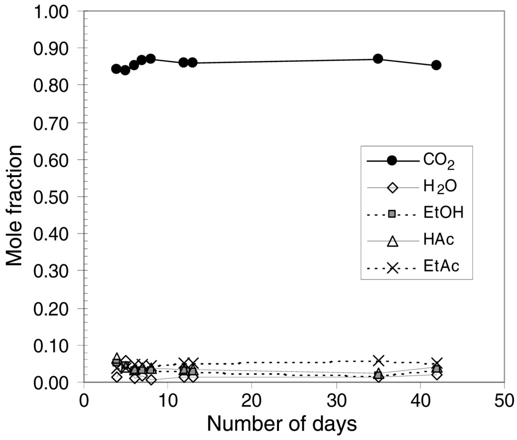


Fig. 3 Vapor-phase composition in the esterification of acetic acid (HAc) with ethanol (EtOH) in CO_2 at 333 K and 58.6 bar.

but do not affect the reaction equilibrium constant. Since the reaction was started with a reactant to product mole ratio of 3 to 1, carbonic acid would have been present from the beginning of the reaction. Since the reaction rate is quite slow, as seen from the slow change in compositions in Fig. 1, we conclude that any influence of carbonic acid on the reaction rate is small. Nonetheless, the presence of small amounts of carbonic acid in the liquid phase could have some effect on the activity (or fugacity) coefficients of the various components in the liquid phase, which determines product distribution and, ultimately, the equilibrium conversion observed experimentally.

The conversion achieved using high-pressure CO_2 as an environmentally benign solvent is a significant improvement over the neat reaction, which only proceeds to 63% conversion at 60 °C, as indicated in the literature[11] and confirmed by measurements in our laboratory. Thus, CO_2 can be used to enhance the equilibrium conversion of a reversible, equilibrium-limited reaction. For the esterification of acetic acid with ethanol, the mechanism appears to involve both the preferential solubilization of one of the products, ethyl acetate, in the CO_2-rich gas phase, and pressure effects on the non-ideality of the liquid phase.

Conclusions

The esterification of acetic acid with ethanol carried out under CO_2 pressure resulted in an increase in product formation compared to the neat reaction. At 333 K and 58.6 bar the CO_2 pressure shifted the equilibrium conversion from 63 to 72%.

Experimental

The esterification reaction of ethanol and acetic acid was carried out both in neat form and under pressure with CO_2. The chemicals used in the esterification reaction for this work are as follows:

Acetic acid, ACS grade 99.7% purity, Aldrich Chemical Company

Water, HPLC grade, Aldrich Chemical Company

Ethanol, Absolute 99.5% purity, Aaper Company

Ethyl acetate, HPLC grade 99.8% purity, Aldrich Chemical Company

Carbon dioxide, anaerobic grade, Mittler Gas Company

The neat reaction, using equimolar amounts of reactants, was allowed to proceed for eight days at 60 °C, at which time the compositions had reached steady values. The compositions at chemical equilibrium were determined by gas chromatographic analysis of samples from the liquid reaction system. GC calibration curves for the quantitative determination of each compound were first determined using a Poropak Q packed column, thermal conductivity detector and helium as the carrier gas.

The esterification reaction, using equimolar amounts of the reactants and 30.0 mol% CO_2, was performed in CO_2 at 58.6 ± 0.5 bar and 60 ± 1 °C. This reaction was measured in a high-pressure variable volume view cell equipped with a quartz window to allow for the visible inspection of the number of phases present (Fig. 4). Two Valco four-port sampling valves allowed for the direct sampling of the top (vapor) and bottom (liquid) phases. Compositions in each phase were determined by injection of isolated liquid and vapor samples into the gas chromatography. Estimated uncertainties in the liquid and gas phase compositions are ±0.005 and ±0.006, respectively. Although samples were drawn from the reaction system, a piston located within the view cell maintained constant pressure within the vessel.

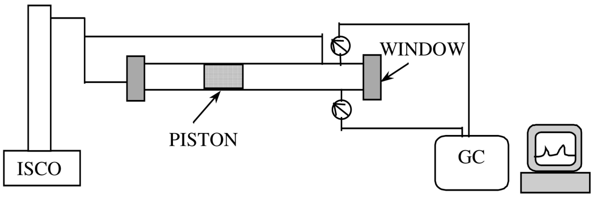


Fig. 4 Variable volume view cell.

Acknowledgements

Financial support from the Environmental Protection Agency (grant R826734-01-0), the National Science Foundation (grant EE697-00537-CRCD), and Clare Booth Luce Fellowship are gratefully acknowledged.

References

1 B. Subramaniam and M. A. McHugh, *Ind. Eng. Chem. Process Des. Dev.*, 1986, **25**, 1.
2 M. J. Burk, S. Feng, M. F. Gross and W. Tumas, *J. Am. Chem. Soc.*, 1995, **117**, 8277.
3 J. X. Haberman, G. C. Irvin, V. T. John and C. J. Li, *Green Chem.*, 1999, **1**, 265.
4 M. McCoy, *Chem. Eng. News*, 1999, **77**(**17**), 10.
5 K. Akao and Y. Yoshimura, *J. Chem. Phys.*, 1991, **94**, 52433.
6 K. P. O'Shea, K. M. Kirmse, M. A. Fox and K. P. Johnston, *J. Phys. Chem.*, 1991, **95**, 7863.
7 D. L. Tomasko, B. L. Knutson, F. Pouillot, C. L. Liotta and C. A. Eckert, *J. Phys. Chem.*, 1993, **97**, 11823.
8 Y. Yagi, S. Saito and H. Inomata, *J. Chem. Eng. Jpn.*, 1993, **26**, 116.
9 K. Yamasaki and O. Kajimoto, *Chem. Phys. Lett.*, 1990, **172**, 271.
10 *Chemical Synthesis Using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, FRG, 1999.
11 E. E. Reid, *Unit Processes in Organic Synthesis*, ed. P. H. Groggins, McGraw-Hill Book Co. Inc., NY, 1938.
12 H. Bock, M. Jimoh and G. Wozny, *Chem. Eng. Technol.*, 1997, **20**, 182.
13 R. P. Stateva and W. A. Wakeham, *Ind. Eng. Chem. Res.*, 1997, **36**, 5474.
14 L. S. Lee, W. C. Chen and J. F. Huang, *J. Chem. Eng. Jpn.*, 1996, **29**, 427.
15 A. Z. Panagiotopoulos, R. C. Willson and R. C. Reid, *J. Chem. Eng. Data*, 1988, **33**, 321.
16 S. Laugier, D. Richon and H. Renon, *Fluid Phase Equilibria*, 1990, **54**, 19.
17 S. Takishima, K. Saiki, K. Arai and S. Saito, *J. Chem. Eng. Jpn.*, 1986, **19**, 48.
18 J. H. Yoon, H. Lee and B. H. Chung, *Fluid Phase Equilibria*, 1994, **102**, 287.
19 A. V. Shvarts and G. D. Efremova, *Russ. J. Phys. Chem.*, 1970, **44**, 614.
20 A. Zawisza and B. Malesinska, *J. Chem. Eng. Data*, 1981, **26**, 388.
21 K. L. Toews, R. M. Shroll, C. M. Wai and N. G. Smart, *Anal. Chem.*, 1995, **67**, 4040.

Highly selective molybdenum phosphate catalyst for the ammoxidation of 2-methylpyrazine to 2-cyanopyrazine†

K. Narasimha Rao, Rajesh Gopinath and P. S. Sai Prasad*

Catalysis and Physical Chemistry Division, Indian Institute of Chemical Technology,
Hyderabad - 500 007, India. E-mail:saiprasad@iict.ap.nic.in

Received 12th July 2000
First published as an Advance Article on the web 18th January 2001

A catalyst containing the ammonium salt of a 12-molybdophosphoric acid, prepared *in situ*, is found to be highly selective for the ammoxidation of 2-methylpyrazine to 2-cyanopyrazine.

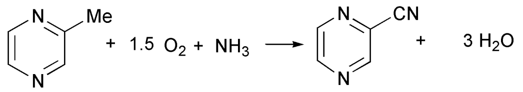
Introduction

2-Amidopyrazine, often termed pyrazinamide, is an important anti-tubercular drug. It is conventionally prepared by a non-catalytic multi-step process starting from 1,2-phenylenediamine and glyoxol, in which substantial quantities of waste products are generated, which is economically as well as environmentally disadvantageous. Recently, ammoxidation of 2-methylpyrazine (MP) to 2-cyanopyrazine (CP) and its subsequent simple hydrolysis to amidopyrazine have been recognized as an alternative and highly competitive catalytic route.[1] Ammoxidation of MP to CP is very crucial in this process, since the reaction carried out in the vapor phase is highly exothermic and the selectivity is affected by the facile formation of pyrazine as the main byproduct (due to oxidative dealkylation) as well as oxides of carbon (due to total combustion). Among the catalysts employed, the V–Sb oxide system proposed by Forni[1] and Bondareva *et al*.[2,3] is found to be very active for the ammoxidation. V–P–O based catalyst systems have been extensively studied for the ammoxidation of methylaromatics and heteroaromatics, particularly methylpyridines.[4,5] Despite this, reports on the applicability of VPO catalysts for the ammoxidation of MP are scarce, although it may be inferred that vanadium based catalysts which operate at high reaction temperatures (close to 430 °C) could lead to thermal runaway since the highly exothermic oxidation of ammonia starts dominating under these conditions. Very recently, molybdenum based catalysts have also been adopted for this reaction. Bondareva *et al*[6] have employed a V-containing 12-molybdophosphate heteropoly compound at lower reaction temperatures (380–390 °C) and achieved about a yield of CP of *ca*. 75%. This catalyst, however, produces 10–25% byproducts (pyrazine and others) depending on the process conditions. A recent American patent[7] also proposes an Mo-based phosphate catalytic system for achieving higher selectivity. However, the structural details of the catalyst are not disclosed in this case. It appears from the open literature that attention has been focused on obtaining maximum activity rather than maximum selectivity. We now report the synthesis of a highly selective molybdenum phosphate based heteropolyacid catalyst, which offers maximum selectivity to CP so that the process could be environmentally acceptable.

Results and discussion

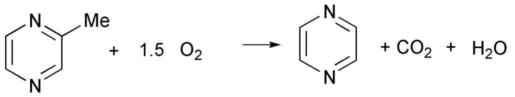
During the ammoxidation of MP, apart from the main reaction [eqn. (1)], two byproduct reactions [eqns. (2) and (3)] also take place depending on the nature of the catalyst and the process conditions. Hence it is important to study the physico-chemical properties of the catalyst and to optimize the reaction conditions to reduce byproduct formation.

1. Ammoxidation:



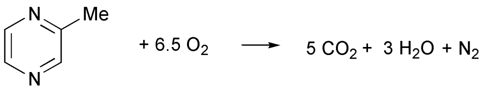
(1)

2. Oxidative Dealkylation:



(2)

3. Total Combustion:



(3)

In the present investigation the performance of the *in situ* generated ammonium salt of 12-molybdophosphoric acid (referred to as salt catalyst) was examined during the ammoxidation of MP. A commercially available 12-molybdophosphoric acid (referred to as acid catalyst) was also used as a catalyst for comparison.

The X-ray powder diffraction (XRD) pattern of the fresh salt catalyst is shown in Fig. 1A. Formation of the ammonium salt of the 12-molybdophosphoric acid [$(NH_4)_3PO_4$-$(MoO_3)_{12}\cdot 4H_2O$, ASTM File No. 9-412] is clearly seen along with traces of $(NH_4)_2H_2P_2O_7$. The salt catalyst, after use at a reaction temperature of 420 °C, also displays the presence of the ammonium salt. However, the formation of basic molybdenum phosphate, $MoPO_4(OH)_3$, predominates. This could be due to exposure of the catalyst to higher reaction temperature for a reasonably longer period (> 20 h). The XRD pattern (Fig. 1B) of the fresh acid catalyst corresponds to the 12-molybdophosphoric acid and that of the used catalyst indicates the formation of the ammonium salt of the 12-molybdophosphoric acid.

Green Context

Catalytic ammoxidation of 2-methylpyrazine to 2-cyanopyrazine (2-CP) at low conversions using the *in situ* generated ammonium salt of 12-molybdophosphoric acid, offers the highest selectivity, reducing byproduct formation considerably.

DJM

---

† IICT Communication number: 4576.

DOI: 10.1039/b005643j

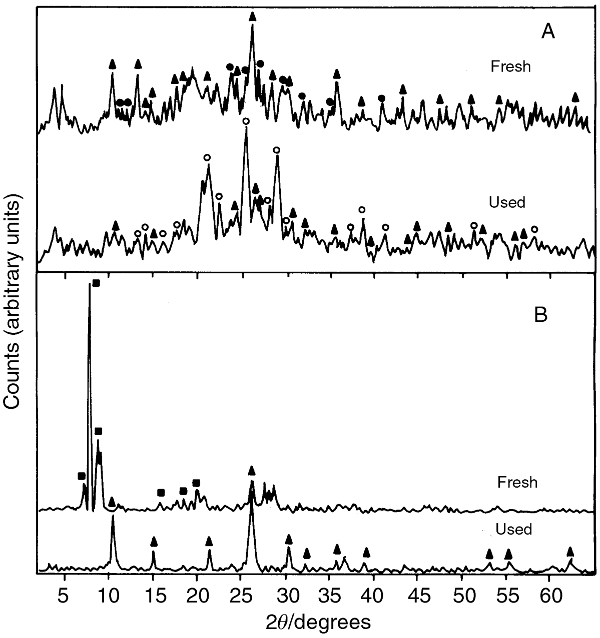


Fig. 1 XRD patterns of the fresh and used salt (A) and acid (B) catalysts: (▲)[$(NH_4)_3PO_4(MoO_3)_{12}\cdot 4H_2O$, (●) $(NH_4)_2H_2P_2O_7$, (○) $MoPO_4(OH)_3$, (■) $H_3PMo_{12}O_{40}\cdot xH_2O$.

FTIR spectra of the fresh and used salt catalysts are shown in Fig. 2A with bands in the region 1500–600 cm^{-1} shown as an inset. The spectra reveal the presence of ammonium salt of the acid by a clear band appearing at 1410 cm^{-1} as reported by Albonetti *et al.*[8] Characteristic bands of the fresh catalyst are observed at 1060, 960, 855, 775 and 722 cm^{-1} due to the Keggin ion these values being almost the same as those reported by Narasimha Rao *et al.*[9] The spectrum of the used salt catalyst also demonstrates the presence of ammonium ions with a characteristic band at 1410 cm^{-1}, though bands due to the Keggin ions are obscured by the dominance of bands corresponding to the phosphate ion.[10] Well resolved bands due to the Keggin ion are observed in the FTIR spectrum (Fig. 2B) of the fresh acid catalyst at 1070, 965, 870 and 590 cm^{-1}, in agreement with the values reported by Bielanski *et al.*[10] Formation of the ammonium species could be observed from the band at 1410 cm^{-1} in the used acid catalyst, in addition to the peaks due to the Keggin structure. Bondareva *et al.*[6] have also observed formation of a band corresponding to the ammonium ion in their used catalysts; their fresh catalysts, however, did not exhibit this band, possibly due to a different method of preparation. Berndt *et al.*[11] have also reported formation of an ammonium salt of the form α-$(NH_4)_2[(VO)_3(P_2O_7)_2]$ during their studies on ammoxidation of toluene to benzonitrile using different vanadium phosphate precursors. The importance of the present investigation lies in the *in situ* preparation of the ammonium salt.

The effect of reaction temperature on the activity and selectivity of the salt as well as acid catalysts is shown in Fig. 3A and B, respectively. Both catalysts show a continuous increase in conversion with reaction temperature in the range 360–420 °C. A comparison of the activity and selectivity of the salt catalyst with that of the acid catalyst reveals some interesting observations. The acid catalyst is more active under the conditions of evaluation, however, it only demonstrates a maximum CP selectivity of *ca*. 80% and the corresponding selectivity towards pyrazine is as high as 20%. The salt catalyst, though less active, demonstrates a maximum selectivity towards CP of about 100%. Formation of a byproduct, pyrazine, is negligibly small; only above 400 °C does the selectivity to CP start to decrease and that of pyrazine increase.

Almost all the studies on the ammoxidation of MP[12] appear to concentrate on achieving high MP conversion despite the expense of considerable byproduct formation, perhaps owing to a high demand for the product. The present results indicate that at lower conversions the formation of the byproducts can be almost eliminated. This is also advantageous from the process point of view, in terms of better controllability of reaction temperature of an exothermic reaction. Besides, the reactant can be separated and recycled which could improve the overall yield. However, the economics of the process needs to be studied to estimate an acceptable conversion level.

It is interesting to understand why the salt catalyst shows higher selectivity towards CP. From the XRD and the FTIR

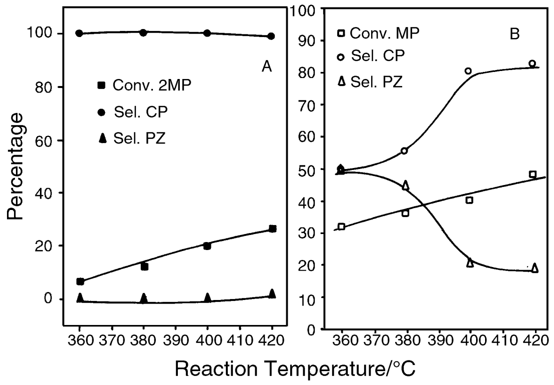


Fig. 3 Influence of reaction temperature on the conversion of MP and the selectivities to CP and pyrazine.

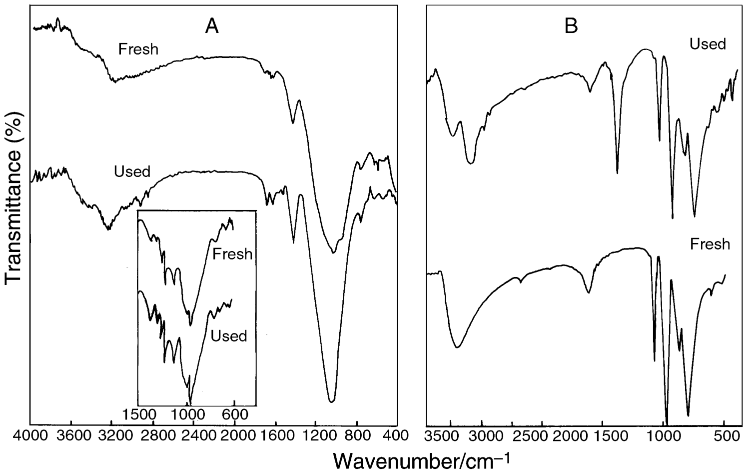


Fig. 2 FTIR spectra of fresh and used salt and acid catalysts.

results, it is known that this catalyst consists of the ammonium salt of the heteropolyacid. Hence, it appears that the high selectivity is related to the presence of the ammonium salt. Our observations indicate that by adopting the present method of preparation, the ammonium salt of the 12-molybdophosphoric acid can be prepared *in situ*, which could lead to higher selectivity. It has already been reported[13] that the heteropolyacid $H_3PMoO_{12}O_{40}$ in the solid state is a Brönsted acid which is stronger than conventional solid acids such as SiO_2–Al_2O_3. The strength and the number of acid centres on the heteropolyacid can be controlled by its structure, composition, the extent of hydration, the type of support and the extent of thermal treatment.[14] Though the exact mechanism is not yet understood, it might be expected that the formation of the ammonium salt substantially reduces the number of Brönsted acid sites on the heteropolyacid and thus formation of pyrazine on the acid sites by oxidative dealkylation is minimized. Pyrazine may also be formed by the after-oxidation of cyanopyrazine at high conversions of MP (> 80%), as reported by Bondareva *et al.*[6] In the present investigation the conversion of MP is restricted to a lower value, thus obviating this possibility as well.

It may be concluded that under conditions of low conversion of MP and in the presence of the ammonium salt of a molybdophosphoric acid, maximum selectivity towards CP can be obtained.

Experimental

The salt catalyst was prepared by dissolving ammonium heptamolybdate [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$] and ammonium dihydrogen orthophosphate [$NH_4H_2(PO_4)$], in a stoichiometric ratio 1 : 1, in water. This solution was then evaporated in a water bath and dried first at 120 °C (6 h) and then at 180 °C (6 h). The catalyst mass was subsequently activated in air at 400 °C. Commercially available (Loba Chemie, GR) phosphomolybdic acid was used as catalyst for comparison studies. X-Ray diffraction (XRD) patterns of the catalysts were obtained on a Siemens D-5000 diffractometer using Cu-Kα radiation. FTIR spectra were recorded on a Biorad–175 C (USA) spectrometer using the KBr disc method.

The reaction was studied taking 5 g (18/25 BSS mesh size) of catalyst in a tubular reactor and passing a mixture of MP, water, ammonia and air in the molar ratio 1 : 13 : 7 : 38, respectively (at a liquid flow rate of 2 ml h^{-1}), in the temperature range 360–420 °C. The liquid product collected, after the catalyst had attained steady state, was analyzed by gas chromatography. From the analysis of the non-condensable exit gas mixture it was confirmed that the presence of any organic species or oxides of carbon was negligible.

Acknowledgements

We are indebted to Dr K. V. Raghavan, Director, IICT, Hyderabad, for his encouragement and useful suggestions. Thanks are due to Dr I. Suryanarayana, Scientist, IICT, for his help in the FTIR analysis.

References

1 L. Forni, *Appl. Catal.*, 1986, **20**, 219.
2 V. M.Bondareva, T. V. Andrushkevich and G. A. Zenkovets, *Kinet. Catal.*, 1997, **38**, 657.
3 V. M. Bondareva, T. V. Andrushkevich, L. M. Plyasova, E. B. Burgina, O. B. Lapina and A. A. Altynnikov, *Kinet. Catal.*, 1997, **38**, 662.
4 A. Martin, B. Lucke, H. Seeboth, G. Ladwig and E. Fischer, *React. Kinet. Catal. Lett.*, 1989, **38**, 33.
5 B. Lucke and A. Martin, *Catalysis of Organic Reactions*, Marcel Dekker, New York, 1995, p. 479.
6 V. M. Bondareva, T. V. Andrushkevich, L. G. Detusheva and G. S. Litvak, *Catal. Lett.*, 1996, **42**, 113.
7 K.-Y. Lee, C.-H. Shin, T.-S. Chang, D.-K. Lee and D.-H. Cho, *US Pat.*, 5 786 478, Korean Institute of Chemical Technology, August, 1995.
8 S. Albonetti, F. Cavani, F. Triffiro, M. Gazzano, M. Koutyrev, F. C. Aissi, A. Aboukais and M. Guelton, *J. Catal.*, 1994, **146**, 491.
9 K. L. Narasimha Rao, K. S. Sarma, C.Mathew, A. V. Jadav, J. P. Shukla, V. Natarajan, T. K. Seshagiri, S. K. Sali, K. I. Dhiwar, B. Pande and B. Venkataramani, *J. Chem. Soc., Faraday Trans.*, 1998, **94**, 1641.
10 A. Bielanski and A. Malecka, *J. Chem. Soc., Faraday Trans. 1*, 1989, **85**, 2847.
11 H. Berndt, K. Buker, A. Martin, S. Rabe, Y. Zhang and M. Meisel, *Catal. Today*, 1996, **32**, 285.
12 L. Forni, C. Oliva and C. Rebuschini, *J. Chem. Soc., Faraday Trans. 1*, 1988, **84**, 2397.
13 M. Furuta, K. Sakata, M. Misino and Y. Yoneda, *Chem. Lett.*, 1979, 31.
14 N. Mizuno and M. Misono, *Chem. Rev.*, 1998, **98**, 198.

A novel Suzuki reaction system based on a supported palladium catalyst

Egid B. Mubofu, James H. Clark* and Duncan J. Macquarrie

Clean Technology Centre, Department of Chemistry, University of York, York UK YO10 5DD.
E-mail: jhc1@york.ac.uk

Received 7th July 2000
First published as an Advance Article on the web 18th January 2001

A range of supported palladium complex-catalysed Suzuki reactions is described with notable features including fast and efficient reactions, excellent catalyst recyclability, and total catalyst stability under the reaction conditions. We have achieved turnover numbers of several thousand based on ten re-use experiments from batch reactions in air. Our system not only solves the basic problems of catalyst separation and recovery but also avoids the use of phosphine ligands.

Introduction

The Suzuki reaction is proving to be an increasingly popular method for forming carbon–carbon bonds both in the laboratory and in commercial manufacturing; it has quickly become an integral part of modern organic synthesis.[1,2] The reaction represents an attractive alternative over other methods using organometallics because organoboranes are air- and moisture-stable with relatively low toxicity.[1] However, like many organic reactions using inorganic reagents and catalysts, the standard procedures suffer from wasted inorganics which are too difficult to recover and are lost in an aqueous work-up stage.[3] For Suzuki reactions soluble complex palladium catalysts are normally employed alongside bases such as soluble amines; these are rarely recoverable without elaborate and wasteful procedures that are commercially unacceptable. Some progress has been made with the use of solid reagents, for example the combination of alumina-supported fluorides and palladium powder has been recently shown to be effective in the Suzuki coupling of phenyl boronic acids with iodobenzenes.[4,5] However, the reaction is much less effective with bromobenzenes and there is no evidence for the recyclability of the palladium, an essential aspect of the process on environmental and economic grounds. The use of an efficient heterogeneously supported palladium catalyst (Pd/C) in Suzuki cross-coupling has been used to produce biphenylacetic acid.[6] In other reported cases supported palladium catalysts have suffered on application from diffusion limitations and dissolution of the palladium complex in the reaction medium. Here we describe an entirely novel heterogeneous palladium-catalysed Suzuki reaction system that is very effective with the less expensive bromobenzenes, uses only hydrocarbon solvents, and requires very small amounts of the solid palladium catalysts which are entirely recoverable and reusable; there is no contribution to the reaction due to homogeneous catalysis from any leached metal complex. One salient feature of our catalyst is that it does not require addition of phosphines (commonly introduced into palladium-catalysed reactions) thus improving the atom economy of the reaction. While reducing process costs, it also eliminates side reactions that may occur between arylphosphines and arylboronic acid.[7] The overall outcome of these improvements may lead to cost effective industrial processes and to the reduction of unwanted wastes.

Results and discussion

The organically modified silica (Merck Kieselgel 100) and micelle templated silicas (MTS) materials used for preparing the catalysts were prepared by a one-pot method.[8] They were studied for the presence and stability of bound organics by diffuse reflectance infrared spectroscopy (DRIFTS) and simultaneous thermal analysis (STA). The DRIFTS of 3-aminopropyl-MTS for example, displays the characteristic $C–H_2$ stretching bands at 2938 and 2867 cm^{-1} and aliphatic CH_2 deformation bands at 1471 and 1439 cm^{-1}. The IR spectrum of the chemically modified 3-aminopropyl-MTS and 3-aminopropyl-silica prior to complexation with the metal had a peak at 1647 cm^{-1} due to the C=N stretching vibration of the imine. The peak disappears on complexation with palladium, changing into bands at 1525 and 1593 cm^{-1} consistent with strong binding between the metal and the ligand. Simultaneous thermal analysis shows a loss of residual solvent at *ca*. 80 °C followed by a gradual minor weight loss of $< 1\%$ up to *ca*. 505 °C where a sudden major loss (*ca*. 10%) is observed. The major weight loss at such high temperatures in the MTS material is characteristic of chemisorbed material and shows that the 3-aminopropyl is chemically bound. The thermal stability of the organically modifed Kieselgel 100 is less, with decomposition occuring between 205 and 385 °C.

The palladium catalysts bound on these materials have been tested in the Suzuki reaction between phenylboronic acid and bromobenzene in xylene in the presence of potassium carbonate as the base. Catalysts based on the solid carboxylic acids[9] [$TMS–(CH_2)_nCO_2H$ leading to catalyst 1] are active but quickly lose activity (turnover number ArBr/Pd = *ca*. 100) although washing the catalyst after use (with dichloromethane and then water) restored some of the original activity, giving up to 76% yields (Table 1, cycle 3). Catalysts 2 and 3 are based on reaction

Green Context

These Suzuki reactions combine the efficiency and high turnover number typical of palladium catalysis, with the recoverability and reusability offered by heterogeneous systems, to give high yields in short times without the need for phosphine ligands. ***ST***

DOI: 10.1039/b009190l

of aminopropyl–TMS (leading to catalyst 2) and aminopropylsilica (leading to catalyst 3) with pyridinecarbaldehyde,[10] followed by complexation of palladium acetate (Fig. 1) are more active and have excellent recyclability (Table 1). With these catalysts, we have achieved turnover numbers of several thousand based on ten filtrations and reuse experiments from batch reactions. The other advantage of our systems, compared to work up procedure,[1a] is that high yields of the biaryls are obtained in air at the lower temperature of 95 °C, at shorter times and without using phosphine ligands.

The stability of the supported complex towards dissolution during the reaction is a problem of great concern for most anchored catalysts.[11] In view of the leaching problems observed with palladium supported on polymer beads,[12] quantitative analysis using atomic absorption spectroscopy (AAS) was employed to determine the amount of metal in the final reaction solution. We also performed the hot filtration test.[13] No palladium could be detected in the liquid reaction mixtures by AAS and more significantly, hot filtration of the reaction mixture at an early stage of the reaction followed by taking the mixture back to reaction temperature completely stopped the reaction, effectively proving heterogeneous catalysis and no measurable contribution from homogeneous catalysis (Fig. 2).[13] Very good to excellent yields of biphenyl in short reaction times for reactions run using catalysts 2 and 3 were achieved with the latter having the better lifetime. The study was then extended to substituted bromobenzenes involving electronically activating and deactivating groups. A favourable effect of electron-withdrawing substituents is normally observed in palladium catalysed reactions.[14] With our catalysts however, electron withdrawing groups have relatively little effect on the reaction rate or selectivity (Table 2). Substituted chlorobenzenes are inert under the standard conditions giving a cross-coupling product (<2% yield) and a 4% yield of biphenyl from homocoupling of the phenylboronic acid. To further illustrate that chloroarenes are inert in the reaction system, *p*-chlorobiphenyl was selectivity produced in the reaction of phenylboronic acid with *p*-bromochlorobenzene (Table 2, entries 6, 14). The importance of the base is illustrated by the lack of

Table 1 Comparison of the activities on reuse of different supported palladium catalysts on the Suzuki reaction between phenylboronic acid and bromobenzene at 95 °C in xylene and K_2CO_3 as base[a]

Catalyst cycle[b]	Catalyst	*t*/min	GC Yield[b] (%)[c]
1	1	60	75
2	1	180	4.4
3	1	180	76
4	1	180	25
1	2	60	75
2	2	60	98
3	2	60	97
4	2	60	98
5	2	60	96
6	2	60	45
1	3	60	90
2	3	60	98
3	3	60	97
4	3	60	96
5	3	60	95
6	3	60	85
7	3	60	64
8	3	60	70
9	3	60 (120)	36 (44)
10	3	60 (180)	17 (20)

[a] The reactions were carried out in xylene (13 ml) with 5 mmol of bromobenzene, 7.3 mmol of phenylboronic acid, 10 mmol of K_2CO_3 base and 0.2 g palladium catalyst (loading 0.3 mmol g^{-1}) at 95 °C. [b] The used catalysts were thoroughly washed with dichloromethane then water before reuse. [c] GC yields obtained using *n*-dodecane as an internal standard and is based on the amount of haloarene employed in relation to authentic standard biphenyl.

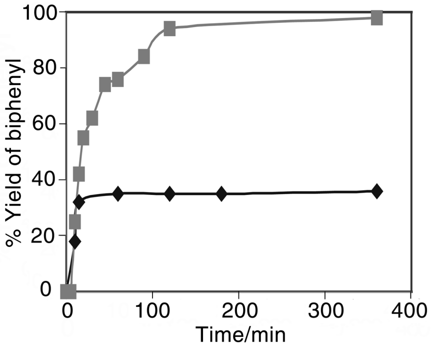


Fig. 2 Effect of removing the supported palladium catalyst from the reaction of phenylboronic acid and bromobenzene (hot filtration test, see text).

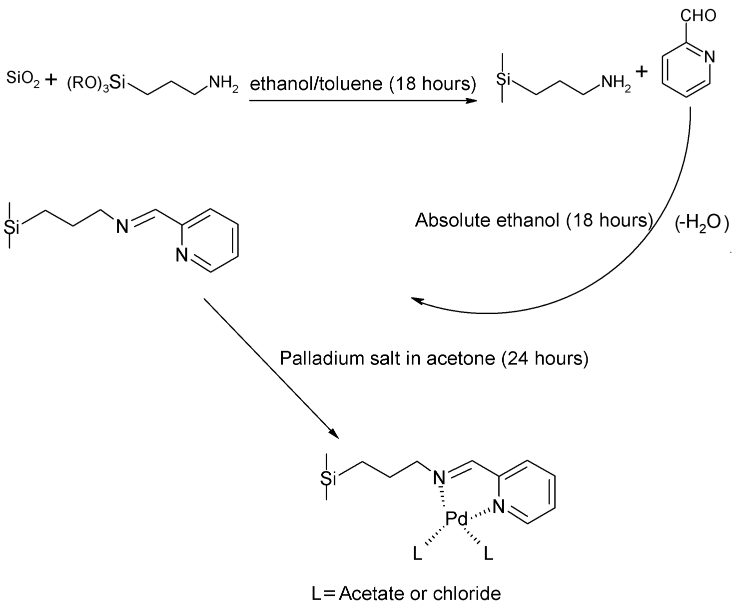
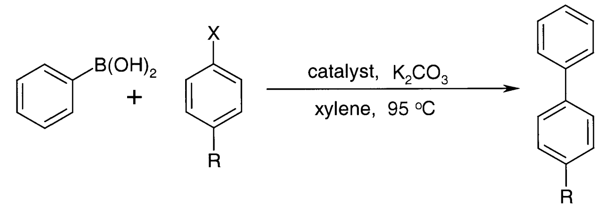


Fig. 1 Preparation of the active and reusable supported palladium catalysts (catalysts 2 and 3) based on chemically modified aminopropyl mesoporous silicas.

Table 2 Suzuki reactions of substituted bromobenzenes catalysed by supported phosphine free palladium catalysts



Entry	X, R	Catalyst	t/min	Yield (%)	Catalyst: substrate ratio
1	Br, H	1	180	81	1:833
2	Br, H	2	180	98	1:833
3	Br, H	3	180	98	1:167
4	Br, H	4	180	90	1:833
5	Br, CN	2	120	98	1:167
6	Br, Cl	2	180	98	1:167
7	Br, OMe	2	360	82	1:167
8	Br, CH$_2$Br	2	360	79	1:167
9	Br, H	3	180	97	1:833
10	Br, H	3	180	95	1:167
11	Br, CN	3	120	92	1:167
12	Cl, CN	3	180	<2	1:167
13	Cl, CHO	3	180	<2	1:167
14	Br, Cl	3	180	88	1:167
15	Br, OMe	3	360	79	1:167
16	Br, CH$_2$Br	3	360	60	1:167

desired cross-coupling product when the reaction is run in the absence of base.

Experimental

Chemicals were obtained from Aldrich and Merck and were used as received. The detailed preparation schemes of the catalysts have already been published.[9,10] In this instance however, the organically modified MTS was prepared by a one-pot synthesis method[8] using a long-chain neutral templating amine (5.10 g *n*-dodecylamine in this case) in aqueous ethanol (46 ml ethanol–53 ml water). To this solution, 8.36 g (40 mmol) of tetraethoxysilane (TEOS) and 1.79 g (10 mmol) of 3-aminopropyl(trimethoxy)silane were separately but simultaneously added and stirred together at room temperature for 18 h. After this solution, the mixture is initially turbid, then turns milky after about 10 min and finally forms a thick white paste after 18 h. The thick white paste was filtered off and the template was extracted from the white solid by Soxhlet extraction with ethanol for 10 h. The template-extracted white 3-aminopropyl-MTS solid was dried in air at 90 °C overnight before further reactions appropriate for metal complex anchoring were carried out. The dried 3-aminopropyl-MTS (or silica) was reacted with an equivalent of 2-pyridinecarbaldehyde in ethanol at room temperature. The resulting modified material was dried overnight in air at 90 °C before reacting with a solution of palladium acetate in acetone. The mixture was magnetically stirred for 24 h, and the catalyst paste was filtered off and washed thoroughly with acetone until the washings were colourless. The catalyst was dried overnight in air at 90 °C to result into a brown palladium supported catalyst. The catalyst was conditioned for a total of 27 h by refluxing in ethanol, toluene and then acetonitrile before being tested for activity. The condition was done to remove any physisorbed palladium. The final conditioned catalyst was filtered off and dried overnight in air at 90 °C to be ready for use.

The IR spectra of the final materials were measured on a Bruker Equinox 55 spectrometer fitted with an environmental chamber diffuse reflectance unit. Simultaneous thermal analysis (thermal analysis coupled with differential thermal analysis, STA) was carried out to determine the thermal stability of the bound organics. The pore size distribution and BET surface areas were determined by using Coulter SA2100 porosimeter with dinitrogen as an adsorbate.

A variety of silica supported palladium catalysts were evaluated in the Suzuki cross-coupling reactions. In a typical reaction, phenylboronic acid (914 mg, 7.3 mmol), bromobenzene (785 mg, 5 mmol), potassium carbonate (1381 mg, 10 mmol), dodecane (1 ml, internal standard) and the supported catalyst (0.2 g at 0.3 mmol Pd per gram) were stirred together in *o*-xylene (or *m*-xylene) (13 ml) at 95 °C. Samples were withdrawn periodically and analysed by GC/GC–MS. The isolated products were analysed by GC/GC–MS and NMR and compared with authentic samples.

Conclusion

These new supported palladium catalysts show remarkable versatility as they are capable of catalysing Suzuki and Heck reactions to high yields of coupling products at lower temperatures than conventional systems in air. Further catalyst reuse studies on other Suzuki cross-coupling reactions are being investigated.

Acknowledgements

The financial support of the Norwegian Agency for International Development (NORAD) through the University of Dar es Salaam, Tanzania (to E. B. M.) is gratefully acknowledged. We also thank the Royal Academy of Engineering and EPSRC for a Clean Technology Fellowship (to J. H. C.) and the Royal Society for a University Research Fellowship (to D. J. M.).

References

1 (*a*) N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513; (*b*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
2 A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.
3 J. H. Clark, *Green Chem.*, 1999, **1**, 1.
4 G. W. Kabalka, R. M. Pagni and C. M. Hair, *Org. Lett.*, 1999, **1**, 1423.
5 G. W. Kabalka, R. M. Pagni, L. Wang, V. Namboodiri and C. M. Hair, *Green. Chem.*, 2000, **2**, 120.
6 D. Gala, A. Stamford, J. Jenkins and M. Kugelman, *Org. Proc. Res. Dev.*, 1997, **1**, 163.
7 D. O'Keefe, M. Dannock and S. Marcuccio, *Tetrahedron Lett.*, 1992, **33**, 6679; K.-C. Kong and C.-H. Cheng, *J. Am. Chem. Soc.*, 1991, **113**, 6313.
8 D. J. Macquarrie, *Chem. Commun.*, 1996, 1961; D. J. Macquarrie and D. B. Jackson, *Chem. Commun.*, 1997, 1781.
9 A. Butterworth, J. H. Clark, P. H. Walton and S. J. Barlow, *Chem. Commun.*, 1996, 1859; J. A. Elings, R. Ait-Meddour, J. H. Clark and D. J. Macquarrie, *Chem. Commun.*, 1998, 2707.
10 J. H. Clark, D. J. Macquarrie and E. B. Mubofu, *Green Chem.*, 2000, **2**, 53.
11 W. M. H. Sachtler, *Acc. Chem. Res.*, 1993, **26**, 383, D. Brunel, *Coord. Chem. Rev.*, 1998, **178–180**, 1085.
12 M. S. Anson, M. P. Leese, L. Tonks and J. M. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 3529.
13 H. E. B. Lempers and R. A. Sheldon, *J. Catal.*, 1998, **175**, 62.
14 V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047.

Conjugate additions of heteronucleophiles to enones and alkynoates. A ‘benign by design’ functionalization of heteroaromatics

Martín Avalos, Reyes Babiano, José L. Bravo, Pedro Cintas, José L. Jiménez, Juan C. Palacios* and María A. Silva

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain. E-mail: palacios@unex.es

Received 1st November 2000
First published as an Advance Article on the web 17th January 2001

A simple and convenient functionalization of pyrrole and thiophene nuclei has been accomplished by one-step clay-catalyzed conjugate addition reactions of these heteroaromatics with some enones and alkynoates under very mild conditions. The experimental protocol can be easily modified to accommodate one or two alkyl groups.

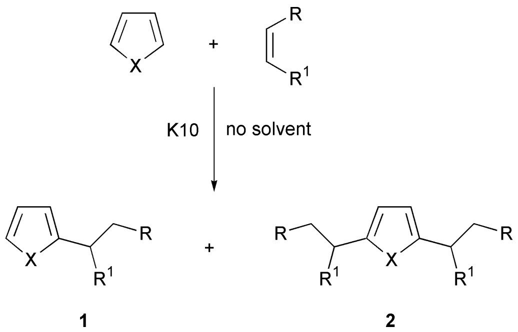
Introduction

In a series of recent investigations we have disclosed that homo-Diels–Alder reactions can be conducted under solvent-free conditions using inexpensive and innocuous mineral solids as catalysts.[1] Furans undergo competitive cycloaddition and Michael-type reactions, and the product distribution is largely dependent on the stoichiometry and experimental conditions.[2] The incessant demand for increasingly green technologies is encouraging scientists to think more on environmentally friendly chemical processes.[3] In this context, important generic areas of chemistry such as acid-catalyzed reactions need to be rethought and modified. Besides furan, the π-excessive heteroaromatics pyrrole and thiophene react with electrophiles *via* Friedel–Crafts-type reactions to give useful precursors for natural product syntheses. However, these reactions often require acid catalysts and/or high temperatures to be achieved,[4–6] and oligomeric side products are also obtained. Remarkably, polypyrrole and polythiophene films are currently being explored in applications such as biosensores, organic semiconductors, or addressable gene-chips.[7,8] It may be possible to substitute the above-mentioned forcing conditions for solid catalysts (*e.g.* clays, zeolites) or supported reagents, thereby making unnecessary the use of solvents and separation agents.[9] We now report a facile functionalization of these important heterocycles involving their solventless condensation with enones adsorbed on montmorillonite K10 to afford mono- and bis-alkylated products in moderate to good overall yields.

Results and discussion

Our results with pyrrole and thiophene have been collectively summarized in Schemes 1 and 2, and Table 1. Condensations with *N*-phenylmaleimide proceed slowly, presumably due to steric reasons. Reactions can either be stirred or irradiated with focused microwaves, thereby resulting in shorter reaction times especially with thiophene derivatives (Scheme 2). These fast reaction conditions also favor the formation of monoalkylated products, although lower yields are often obtained owing to the volatility of the products (Table 1, entry 6). It should be noted that irradiated reactions can equally be conducted in a domestic oven with similar results. Nevertheless, our reactions employing a monomode reactor (see Experimental section) exhibited increased efficiency and reproducibility. In addition, and unlike domestic ovens, the reaction temperature can be controlled by power modulation within a wide range of Watts and measured with accuracy by IR detection. Furthermore, this device offers a homogeneous distribution of the electric field inside the cavity.[10]

The reaction of pyrrole with maleic anhydride gives rise to a mixture of **6** and the dicarboxylic derivative **7**, the latter arising from ring opening of the anhydride moiety at the catalytically active acid sites of montmorillonite, and is the exclusive product after a prolonged reaction time (Scheme 3). The distinctive identification between compounds **6** and **7** could be accomplished on the basis of their IR data, as **7** exhibits characteristic bands at *ca.* 3000–2500 cm^{-1} due to OH stretching. Likewise, and unlike **6**, compound **7** was insoluble in chloroform. No reaction was observed between thiophene derivatives and *N*-phenylmaleimide or maleic anhydride.

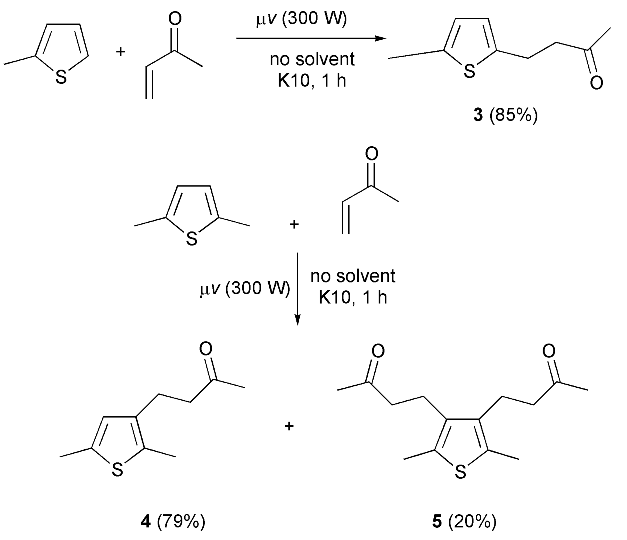


Scheme 1

Green Context

Pyrroles and thiophenes are extremely useful compounds with applicability in numerous areas including bioactive compounds, organic semiconductors and addressable gene-chips. Thus their functionalisation is of considerable interest though traditionally reliant on hazardous and wasteful procedures. Here novel facile functionalisation procedures are described. These are solvent-free, employ safe and reusable solid acids and subject to microwave acceleration. A variety of mono- and bis-alkylated products have been prepared using this procedure. ***DJM***

DOI: 10.1039/b008795p

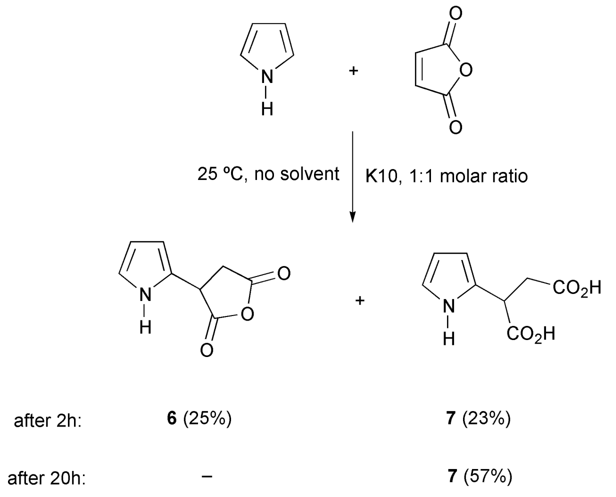


Scheme 2

This clay-catalyzed protocol could also be extended to alkynic substrates such as dimethyl acetylenedicarboxylate providing an interesting reaction mixture of double addition products (**8** and **9**) accompanied by a *Z/E* mixture of alkenes (**10**, Scheme 4), which could be purified by flash chromatography and identified by spectroscopic methods. It is well known that simple pyrroles or thiophenes show little tendency to react as 4π components in cycloadditions owing to their enhanced aromaticity. In fact, Diels–Alder reaction between pyrrole and methyl vinyl ketone catalyzed by Cr(III)-exchanged montmorillonite in organic solvents has been observed, although the cycloadduct was obtained in 35% yield, but no reaction could be detected for thiophene under these Lewis-acid conditions.[11] On the other hand, conjugate addition reactions with electrophilic alkynes are accelerated by high pressure or by Lewis-acid catalysts.[4]

Compound **9** was obtained as a single diastereomer as evidenced by its NMR spectra which showed only one signal set. Likewise, it was difficult to establish a spectroscopic distinction between isomers **10*Z*** and **10*E***, because of the similarity of their coupling pattern.

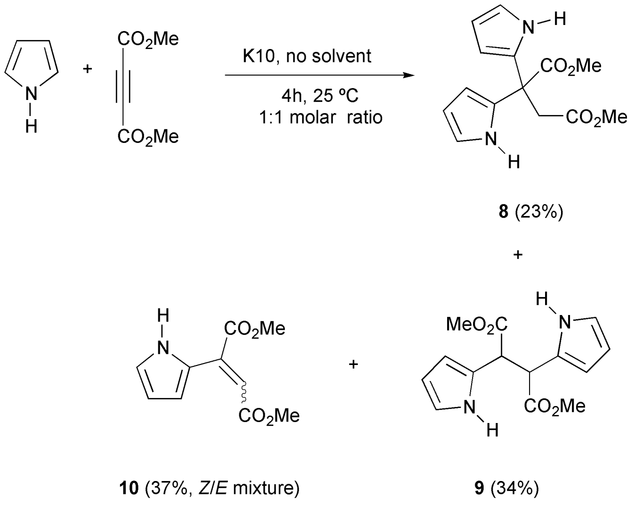
No alkene derivatives could be detected in the reaction between pyrrole and methyl propiolate, but rather products **11** and **12** resulting from successive Michael-type additions (Scheme 5). The latter results are especially attractive because they represent a facile entry to polypyrrolic fragments and porphyrin precursors,[12] which are currently accessible *via* the classical reaction of pyrroles with aldehydes[13] or the self-condensation of dipyrromethanes.[14] It should also be pointed out that compound **12**, as well as the symmetrical compounds **2** (X = NH), show H-3 signals as doublets (*J* = 2.8 Hz) as a consequence of a long range coupling between H-3 and the NH proton which could further be determined by selective spin–spin decoupling. In fact, it is well documented that the NH proton of a pyrrole or an amide is coupled to vicinal protons, even though the NH absorption may be broad as result of partial decoupling by the nitrogen electrical quadrupole moment.[15]



Scheme 3

With a few exceptions, such as **1** (X = NH, R = R¹ = CONPhCO), **8** and **9** which could be obtained as crystalline solids and gave satisfactory combustion analyses, most samples were homogeneous oils by TLC analysis. Finally, the mechanism associated with these processes is a subject of an ongoing investigation, since it is unclear if the conjugate addition follows a concerted[16] or stepwise pathway,[17] and a theoretical study is under way.

In conclusion, we have shown that a clay material drives conjugate addition reactions of heteroaromatics to enones and alkynes in absence of organic solvents. The protocol combines atom economy, efficiency and provides access to mono- and di-

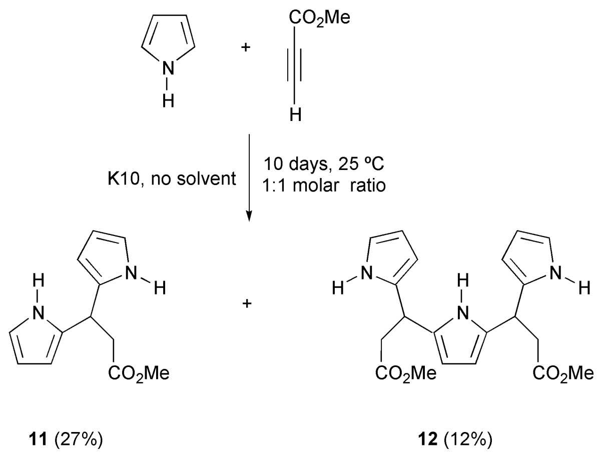


Scheme 4

Table 1 Pyrrole and thiophene functionization reactions

Entry	X	R	R¹	Substrates (Molar ratio)	Conditions	*t*	Yield (%)[a]
1	NH	COMe	H	1:2	0 °C	45 min	**2** (100)
2	NH	COMe	H	1:1	0 °C	1 h	**1** (15), **2** (68)
3	NH	COMe	H	2:1	0 °C	1 h	**1** (30), **2** (50)
4	NH	–CONPhCO–		1:1	25 °C	12 h	**1** (16)
5	NH	–CONPhCO–		2:1	25 °C	48 h	**1** (30)
6	NH	–CONPhCO–		1:1	*μν* (300 W)[b]	1 h	**1** (16)
7	S	COMe	H	1:1	25 °C	3 d	**1** (14), **2** (64)

[a] Isolated yields of flash-chromatographed products. [b] Using monomode reactor with focused microwaves (2.45 GHz, 5% relative intensity).



Scheme 5

alkylated products under mild conditions. Although this procedure will require further exploration of its scope, it is hoped that the above results will be of benefit to the scientific community engaged in solvent-free condensations.

Experimental

All commercial reagents and solvents were used without further purification. Montmorillonite K10 was purchased from Aldrich. Column chromatography and TLC analyses were performed on Merck silica gel 60 (400–230 mesh) and GF$_{254}$, respectively. NMR spectra were recorded on a 400 MHz Bruker spectrometer in CDCl$_3$. Microwave-irradiated reactions were conducted in a Synthewave® 402 reactor from Prolabo.

Typical procedure

To commercially available montmorillonite K10 (2.5 g), cooled previously at 0 °C, was added dropwise the corresponding heterocycle (5.0 mmol) and methyl vinyl ketone (5.0 mmol) with vigorous stirring, and the reaction mixture was kept at 0 °C (or 25 °C). Upon standing for an appropirate reaction time, the mixture was extracted with CH$_2$Cl$_2$ (20 mL) and MeOH (20 mL), filtered, and concentrated to give a residue, which was purified by flash chromatography (diethyl ether–hexane or ethyl acetate–hexane eluent systems).

Reaction of pyrrole and methyl vinyl ketone

2-(3′-Oxobutyl)pyrrole: δ_H(CDCl$_3$) 8.51 (br s, NH), 6.62 (m, H-5), 6.06 (dd, J = 2.9, 2.3 Hz, H-4), 5.86 (br s, H-3), 2.83 (2H, t, J = 6.0 Hz, H-1′, H-1″), 2.76 (2H, t, J = 6.0 Hz, H-2′, H-2″), 2.14 (3H, s, CH$_3$), δ_C(CDCl$_3$) 209.7 (C=O), 131.4 (C-2), 116.7 (C-5), 107.8 (C-4), 105.2 (C-3), 44.1 (C-2′), 30.0 (CH$_3$), 21.2 (C-1′). 2,3-Bis(3′-oxobutyl)pyrrole: δ_H(CDCl$_3$) 8.47 (1H, br s, NH), 5.71 (2H, d, J = 2.8 Hz, H-3, H-4). 2.73–2.81 (8H, m, H-1′, H-1″, H-2′, H-2″), 2.16 (6H, s, 2 × CH$_3$), δ_C(CDCl$_3$) 209.1 (C=O), 130.4 (C-2), 104.7 (C-3), 43.9 (C-2′), 27.0 (CH$_3$), 21.4 (C-1′).

Reaction of pyrrole and *N*-phenylmaleimide

3-(2′-Pyrroyl)-*N*-phenylsuccinimide: Mp 176.5 °C. δ_H(CDCl$_3$) 9.11 (br s, NH), 7.48 (2H, t, J = 7.2 Hz, Ar), 7.40 (1H, t, J = 7.2 Hz, Ar), 7.26 (2H, d, J = 7.2 Hz, Ar), 6.82 (br s, H-5′), 6.20 (dd, J = 3.2, 2.8 Hz, H-4′), 6.00 (m, H-3′). 4.24 (dd, J = 9.2, 5.6 Hz, H-3), 3.35 (dd, J = 18.0, 9.2 Hz, H-4b), 3.20 (dd, J = 18.0, 5.6 Hz, H-4a). δ_C(CDCl$_3$) 176.7, 174.7, (C=O), 131.6, 129.2, 128.8, 126.4 (Ar), 125.2 (C-2′), 119.0 (C-5′), 108.5 (C-4′), 105.7 (C-3′), 38.5 (C-3), 34.2 (C-4). Anal. Calc. for C$_{14}$H$_{12}$N$_2$O$_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.45; H, 4.84; N, 11.60%.

Reaction of thiophene and methyl vinyl ketone

2-(3′-Oxobutyl)thiophene: δ_H(CDCl$_3$) 7.11 (dd, J = 5.2, 1.2 Hz, H-5), 6.90 (dd, J = 5.2, 3.6 Hz, H-4), 6.79 (dd, J = 3.6, 1.2 Hz, H-3), 3.11 (2H, t, J = 7.6 Hz, H-1′, H-1″), 2.82 (2H, t, J = 7.6 Hz, H-2′, H-2″), 2.16 (3H, s, CH$_3$). δ_C(CDCl$_3$) 207.2 (C=O), 143.5 (C-2), 126.8 (C-5), 124.5 (C-4), 123.3 (C-3), 45.2 (C-1′), 30.0 (CH$_3$), 23.8 (C-2′). 2,5-Bis(3′-oxobutyl)thiophene: δ_H(CDCl$_3$) 6.56 (2H, s, H-3, H-4), 3.01 (4H, t, J = 7.3 Hz, H-1′, H-1″), 2.78 (4H, t, J = 7.3 Hz, H-2′, H-2″), 2.15 (6H, s, 2 × CH$_3$). δ_C(CDCl$_3$) 207.0 (C=O), 141.4 (C-2), 123.9 (C-3), 44.8 (C-1′), 29.8 (CH$_3$), 23.8 (C-2′).

Reaction of 2-methyl thiophene and methyl vinyl ketone

The preparation of **3**, 2-methyl-5-(3′-oxobutyl)thiophene, constitutes a representative example: An equimolar mixture of 2-methylthiophene (10 mmol) and methyl vinyl ketone (10 mmol) was adsorbed on montmorillonite K10 (5.0 g) with stirring for 5 min. The homogenized mixture was then irradiated in a microwave reactor with focused electromagnetic radiation (2.45 GHz, 300 W, 5% relative intensity) for 1 h. Extraction with CH$_2$Cl$_2$, followed by filtration and evaporation gave **3** as a yellowish oil in 85% yield. δ_H(CDCl$_3$) 6.53 (m, 2H, H-2, H-3), 3.01 (t, J = 7.3 Hz, 2H, CH$_2$), 2.77 (t, J = 7.3 Hz, 2H, CH$_2$), 2.41 (s, 3H, CH$_3$CO), 2.12 (s, 3H, CH$_3$); δ_C(CDCl$_3$) 207.2 (C=O), 141.2 (C-2), 137.6 (C-5), 124.6 (C-3), 124.1 (C-4), 45.1 (CH$_2$), 29.9 (*C*H$_3$CO), 23.9 (CH$_2$), 15.1 (CH$_3$).

Reaction of 2,5-dimethyl thiophene and methyl vinyl ketone

2,5-Dimethyl-3-(3′-oxobutyl)thiophene **4**: δ_H(CDCl$_3$) 6.42 (1H, s, H-4), 2.65 (4H, m, H-1′, H-1″, H-2′, H-2″), 2.36 [3H, s, CH$_3$(C-5)], 2.28 [3H, s, CH$_3$(C-2)], 2.13 (3H, s, COCH$_3$). δ_C(CDCl$_3$) 208.12 (C=O), 135.8 (C-5), 135.3 (C-2), 130.6 (C-3), 126.4 (C-4), 44.1 (C-1′), 30.0 [(C=O)CH$_3$], 22.2 (C-2′), 12.7 [CH$_3$(C-2)], 15.1 [CH$_3$(C-5)]. 2,5-Dimethyl-3,4-bis(3′-oxobutyl)thiophene **5**: δ_H(CDCl$_3$) 2.67 (4H, t, J = 7.3 Hz, H-1′, H-1″), 2.54 (4H, t, J = 7.3 Hz, H-2′, H-2″), 2.27 (6H, s, 2 × CH$_3$), 2.16 [6H, s, 2 × CH$_3$(CO)]. δ_C(CDCl$_3$) 207.9 (C=O), 135.2 (C-2), 129.8 (C-3), 43.8 (C-1′), 29.9 (CH$_3$), 20.9 (C-2′), 12.9 [*C*H$_3$(CO)].

Reaction of pyrrole and maleic anhydride

2-(2′-Pyrroyl)succinic anhydride **6**: δ_H(CDCl$_3$) 8.82 (br s, NH), 6.84 (m, H-5′), 6.19 (dd, J = 2.9, 2.7 Hz, H-4′), 6.05 (br s, H-3′), 4.39 (dd, J = 9.6, 7.2 Hz, H-2), 3.43 (dd, J = 18.8, 9.6 Hz, H-3b), 3.30 (dd, J = 18.8, 7.2 Hz, H-3a). δ_C(CDCl$_3$) 171.6, 168.9 (C=O), 122.5 (C-2′), 119.6 (C-5′), 108.9 (C-4′), 106.5 (C-3′), 39.5 (C-2), 34.2 (C-3). 2-(2′-Pyrroyl)etanodioic acid **7**: mp 126.5 °C. δ_H(DMSO-d_6) 10.72 (s, NH), 6.61 (m, H-5′), 5.90 (dd, J = 2.8, 2.4 Hz, H-4′), 5.82 (br s, H-3′), 3.88 (dd, J = 10.4, 4.8 Hz, H-2), 2.92 (dd, J = 17.2, 10.4 Hz, H-3b), 2.54 (dd, J = 17.2, 4.8 Hz, H-3a). δ_C(DMSO-d_6) 173.7, 173.0 (C=O), 128.1 (C-2′), 117.4 (C-5′), 107.5 (C-4′), 105.2 (C-3′), 40.5 (C-2), 36.5 (C-3).

Reaction of pyrrole and dimethyl acetylenedicarboxylate

Dimethyl 2,2-bis(2′-pyrroyl)butanodioate **8**: mp 98 °C. $\delta_H(CDCl_3)$ 8.79 (2H, br s, NH), 6.71 (2H, m, H-5′), 6.12 (2H, m, H-4′), 5.92 (2H, m, H-3′), 3.78 (3H, s, CH_3), 3.64 (3H, s, CH_3), 3.43 (2H, s, H-3). $\delta_C(CDCl_3)$ 173.0, 172.0 (C=O), 130.3 (C-2′), 118.0 (C-5′), 108.1 (C-3′), 106.6 (C-4′), 53.0 (CH_3), 52.0 (CH_3), 48.5 (C-2), 43.1 (C-3). Anal. Calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.16; H, 6.04; N, 9.68%. Dimethyl 2,3-bis(2′-pyrroyl)butanodioate **9**: mp 216 °C. $\delta_H(CDCl_3)$: 8.62 (2H, br s, NH), 6.72 (2H, m, H-5′), 6.09 (2H, m, H-4′), 6.04 (2H, m, H-3′), 4.30 (2H, s, H-2), 3.56 (6H, s, 2 × CH_3). $\delta_C(CDCl_3)$ 172.2 (C=O), 124.8 (C-2′), 118.4 (C-5′), 108.4 (C-3′), 108.2 (C-4′), 52.4 (CH_3). 48.8 (C-2). Anal. Calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.20; H, 5.66; N, 9.98%. *trans*-Dimethyl 2-(2′-pyrroyl)butenodioate *E*-**10**: $\delta_H(CDCl_3)$ 9.05 (br s, NH), 6.91 (dd, *J* = 2.4, 1.2 Hz, H-5′), 6.48 (dd, *J* = 3.6, 2.4 Hz, H-4′), 6.25 (dd, *J* = 3.6, 1.2 Hz, H-3′), 6.00 (s, H-3), 3.93 (3H, s, CH_3), 3.72 (3H, s, CH_3). $\delta_C(CDCl_3)$ 168.2, 166.2 (C=O), 140.0 (C-2), 123.5 (C-3), 125.9 (C-2′), 113.7 (C-5′), 111.2 (C-3′), 108.8 (C-4′), 52.9 (CH_3), 51.9 (CH_3). *cis*-Dimethyl 2-(2′-pyrroyl)butenodioate *Z*-**10**: $\delta_H(CDCl_3)$ 8.78 (br s, NH), 7.05 (dd, *J* = 2.4, 1.2 Hz, H-5′), 6.73 (dd, *J* = 3.6, 2.4 Hz, H-4′), 6.30 (dd, *J* = 3.6, 1.2 Hz, H-3′), 5.96 (1H, s, H-3), 3.90 (3H, s, CH_3), 3.80 (3H, s, CH_3). $\delta_C(CDCl_3)$ 168.9, 168.1 (C=O), 138.7 (C-2), 125.8 (C-2′), 123.7 (C-3), 118.1 (C-5′), 110.5 (C-3′), 109.7 (C-4′), 52.8 (CH_3), 52.1 (CH_3).

Reaction of pyrrole and methyl propiolate

Methyl 3,3-bis(2′-pyrroyl)propanoate **11**: $\delta_H(CDCl_3)$ 8.24 (2H, br s, NH), 6.67 (2H, m, H-5′), 6.13 (2H, m, H-4′), 5.98 (2H, m, H-3′), 4.58 (1H, t, *J* = 7.2 Hz, H-3), 3.67 (3H, s, CH_3), 3.01 (2H, d, *J* = 7.2 Hz, H-2). $\delta_C(CDCl_3)$ 173.1 (C=O), 131.7 (C-2′), 117.2 (C-5′), 108.1 (C-4′), 105.3 (C-3′), 51.9 (CH_3), 40.0 (C-2), 33.8 (C-3). 2,5-Bis(1′-(2-pyrroyl)-2′-carbomethoxyethyl)pyrrole **12**: $\delta_H(CDCl_3)$ 8.27, 8.19 (3H, m, NH), 6.64 (2H, m, H-5″), 6.08 (2H, m, H-4″), 5.91 (2H, br s, H-3″), 5.85 (2H, d, *J* = 2.8 Hz, H-3), 4.48 (2H, t, *J* = 7.2 Hz, H-1′), 3.64 (6H, s, 2 × CH_3), 2.92 (4H, d, *J* = 7.2 Hz, H-2′). $\delta_C(CDCl_3)$ 173.1 (C=O), 132.1 (C-2), 131.7 (C-2″), 117.2 (C-5″), 108.2 (C-4″), 105.4 (C-3), 105.3 (C-3″), 51.9 (CH_3), 40.0 (C-2′), 33.7 (C-1′).

Acknowledgements

Financial support from the Spanish Ministry of Science and Technology (DGICYT, PB98-0997 and AMB99-0591) and the Junta de Extremadura-Fondo Social Europeo (IPR98-A065) is gratefully acknowledged.

References

1 M. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jiménez, J. C. Palacios and B. C. Ranu, *Tetrahedron Lett.*, 1998, **39**, 2013.

2 M. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jiménez and J. C. Palacios, *Tetrahedron Lett.*, 1998, **39**, 9301.

3 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; P. T. Anastas and T. C. Williamson, *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processes*, Oxford University Press, Oxford, 1998.

4 J. A. Joule, K. Mills and G. F. Smith, *Heterocyclic Chemistry*, Chapman & Hall, London, 1995, pp. 231–242.

5 K. Hayakawa, M. Yodo, S. Ohsuki and K. Kanematsu, *J. Am. Chem. Soc.*, 1984, **106**, 6735.

6 Y. Kamitori, M. Hojo, R. Masuda, T. Izumi and S. Tsukamoto, *J. Org. Chem.*, 1984, **49**, 4161.

7 V. R. Shastri and M. V. Pishko, in *Electrical and Optical Polymer Systems*, ed. D. L. Wise, G. E. Wnek, D. J. Trantolo, T. M. Cooper and J. D. Gresser, Marcel Dekker, New York, 1998.

8 J. Roncali, *Chem. Rev.*, 1992, **92**, 711; G. Schopf and G. Kossmehl, *Polythiophenes—Electrically Conductive Polymers*, Springer, Berlin, 1997; R. D. McCullough, *Adv. Mater.*, 1998, **10**, 93.

9 J. H. Clark and C. N. Rhodes, *Clean Synthesis Using Porous Inorganic Solid Catalysts and Supported Reagents*, Royal Society of Chemistry, Cambridge, 2000.

10 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacqualt and D. Mathé, *Synthesis*, 1998, 1213.

11 J. M. Adams, S. Dyer, K. Martin, W. A. Matear and R. W. McCabe, *J. Chem. Soc., Perkin Trans. 1*, 1994, 761.

12 J. L. Sessler and S. J. Weghorn, *Expanded, Contracted and Isomeric Porphyrins*, Elsevier, Oxford, 1997.

13 M. Onaka, T. Shinoda, Y. Izumi and E. Nolen, *Tetrahedron Lett.*, 1993, **34**, 2625.

14 C. Pichon and A. I. Scott, *Tetrahedron Lett.*, 1994, **35**, 4497.

15 R. M. Silverstein, G. C. Bassler and T. C. Morrill, *Spectrometric Identification of Organic Compounds*, Wiley, New York, 1974, p. 192.

16 D. Niu and K. Zhao, *J. Am. Chem. Soc.*, 1999, **121**, 2456.

17 L. R. Domingo, M. T. Picher and R. J. Zaragoza, *J. Org. Chem.*, 1998, **63**, 9183.

The synthesis and reaction of zinc reagents in ionic liquids

Tomoya Kitazume* and Kana Kasai

Department of Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku
Yokohama 226-8501, Japan. E-mail: tkitazum@bio.titech.ac.jp

Received 11th October 2000
First published as an Advance Article on the web 31st January 2001

The syntheses and reactions of alkynyl zinc reagents and Reformatsky-type reactions in ionic liquids as a safe recyclable reaction medium are described.

The challenge in chemistry to develop practical processes, reaction media, conditions and/or utility of materials based on the idea of green chemistry is one of the most important issues in the scientific society.[1] Recently, in synthetic chemistry, studies of reusable media such as fluorous fluids[2] and molten salts (ionic liquids)[3] have been having an important impact on organic reactions. Especially, studies of ionic liquids are having an important impact on organic reactions such as Friedel–Crafts reactions,[4] alkylation reactions,[5] Diels–Alder reactions,[6] palladium catalyzed allylation,[7] asymmetric hydrogenation,[8] and the Horner–Wadsworth–Emmons reaction.[9] While organometallic reagents have been recognized to be useful for organic synthesis,[10] and usually, their reactions are carried out in polar organic solvents (such as THF, Et_2O etc), their synthetic value in ionic liquids still appears to be grossly underestimated. Obviously, practical generation and synthetic applications for organometallic reagents in ionic liquids remains an important synthetic challenge.

Here, we describe the utility of reusable molten salts for Reformatsky reactions and the synthesis and reaction of alkynyl zinc reagents.

Table 1 Reformatsky reaction

$$\underset{\mathbf{1}}{\text{RCHO}} + \underset{\mathbf{2}}{\text{BrCX}_2\text{COY}} \xrightarrow[\text{Zn}]{\text{ionic liquid}} \underset{\mathbf{3}}{\text{RCH(OH)CX}_2\text{COY}}$$

Entry	RCHO R	$BrCX_2COY$	Ionic liquid[a]	Yield (%)
1	Ph	$BrCF_2CO_2Et$	[EtDBU][OTf][b]	52
2			[EtDBU][OTf]	76
3			[EtDBU][OTf]	93[c]
4			[bmim][PF_6]	61
5			[bmim][BF_4]	69
6		$BrCH_2CO_2Et$	[EtDBU][OTf]	63[d]
7	$PhCH_2CH_2$	$BrCF_2CO_2Et$	[EtDBU][OTf]	45
8		$BrCH_2CO_2Et$	[EtDBU][OTf]	53[e]
9	(*E*)-PhCH=CH	$BrCF_2CO_2Et$	[EtDBU][OTf]	52
		$BrCH_2CO_2Et$	[EtDBU][OTf]	45

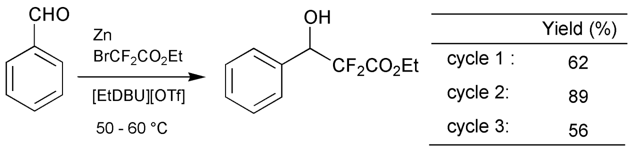
[a] Ionic liquids: [EtDBU][OTf]; 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate: [bmim][BF_4]; 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate: [bmim][PF_6}; 1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate. [b] Reaction temperature: rt, other entries were carried out at 50–60 °C. [c] Molar ratio of PhCHO : Zn : $BrCF_2CO_2Et$ = 1 : 3 : 3. [d] Ref. 11. [e] Ref. 15.

Reformatsky reaction

The first synthetic application to generate organometallic reagents are Reformatsky-type reagents[11] based on the addition of α-halo esters and carbonyl substrates to a suspension of zinc powder in an ionic liquid. It is known that the preparation of Reformatsky reagents derived from ethyl bromodifluoroacetate in tetrahydrofuran proceeds at 50–55 °C in 70–85% yield.[12–14]

In the present reaction, when the reaction was attempted in tetrahydrofuran and in an ionic liquid ([EtDBu][OTf]) at room temperature, the yields of the Reformatsky reaction were 65 and 52% (entry 1), respectively. However, under heating at 50–60 °C the reaction (entry 2) smoothly proceeded to give the target material in 76% yield. Table 1 summarises the results from the reactions of various types of Reformatsky-type reagents with carbonyl materials. The reaction of ethyl bromodifluoroacetate with benzaldehyde proceeded under the applied conditions {bromodifluoroacetate (2 equiv.), benzaldehyde (1 equiv.) and zinc powder (2 equiv.) in an ionic liquid ([EtDBU][OTf], 1 g) at 50–60 °C} to give the corresponding carbinol. Furthermore, in this system, since the reaction intermediates (zinc reaction intermediates) were converted to the carbinols (along with a small amount of water containing diethyl ether), ionic liquids were recovered smoothly after extracting the target material with commercially available diethyl ether. Moreover, in this reaction system, the yield was increased to 93% when increasing the molar ration of PhCHO : $BrCF_2CO_2Et$ (1 : 3; entry 3).

Reuse of the recovered ionic liquid in the same reaction yielded amounts of product almost as high as in the first cycle as shown in Fig. 1.



	Yield (%)
cycle 1 :	62
cycle 2:	89
cycle 3:	56

Fig. 1 Recycling ionic liquids

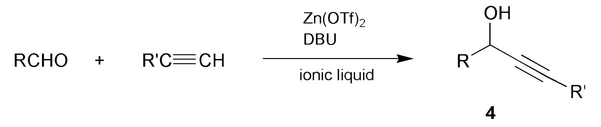
Green Context

The utility of ionic liquids in a range of reaction types continues to expand. This contribution describes the ability of ionic liquids as an environment for organozinc reagents, and describes their preparation and use in the Reformatsky reaction. Yields are at least as good as with conventional solvents, product extraction is straightforward, and no VOC problem is encountered. ***DJM***

Alkynyl zinc reagent

Recently, the preparation of propargylic alcohols by direct addition of teminal alkynes to aldehydes in the system Et$_3$N–toluene at 23 °C, has been reported with yields of these reactions being 50–99%.[15] To clarify the generation and/or synthetic scope of alkynyl zinc reagents in ionic liquids, we examined the direct addition of terminal alkynes to aldehydes in the presence of zinc trifluoromethanesulfonate and base. The reactions proceeded smoothly under the applied conditions {terminal alkyne (3 equiv.), aldehyde (1.5 equiv.), zinc trifluoromethanesulfonate (2 equiv.), and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU, 3 equiv.) in an ionic liquid ([EtDBU][OTf], 1 g) at room temperature}, giving the corresponding propargylic alcohols. The present reaction (summarized in Table 2) proceeded smoothly at room temperature in molten salt.

Table 2 Preparation of propargylic alcohols



Entry	RCHO	R′C≡CH R′	Ionic liquid[a]	Reaction time/h	Yield (%)
10	PhCHO	Ph	[EtDBU][OTf]	48	47
11			[bmim][BF$_4$]	48	59
12			[bmim][BF$_6$]	48	35
13		C$_4$H$_9$	[EtDBU][OTf]	48	51
14			[bmim][PF$_6$]	48	60
15		C$_6$H$_{13}$	[EtDBU][OTf]	48	75
16			[bmim][BF$_4$]	48	62
17	4-FC$_6$H$_4$CHO	Ph	[EtDBU][OTf]	48	47
18		C$_4$H$_9$	[EtDBU][OTf]	48	50
19		C$_6$H$_{13}$	[EtDBU][OTf]	48	55
20	4-NO$_2$C$_6$H$_4$CHO	Ph	[EtDBU][OTf]	24	70
21	PhCH=CHCHO	Ph	[EtDBU][OTf]	48	55

[a] Ionic liquids: [EtDBU][OTf]; 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate: [bmim][BF$_4$]; 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate: [bmim][PF$_6$}; 1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate.

In this reaction system, no reaction occurred in the absence of base and/or Zn(OTf)$_2$. The alkynylzinc reagents were prepared *in situ* from the reaction of terminal alkynes and Zn(OTf)$_2$ in the presence of base in an ionic liquid for the reaction of the zinc reagents with the aldehydes proceeding slowly. After 24–48 h of stirring at room temperature, the cerresponding propargyl alcohol was obtained upon extraction with diethyl ether, and the ionic liquid was recovered. Before the use and reuse of ionic liquids, ionic liquids were purified under dynamic vacuum at 70–80 °C for 1 h, and their purity checked by ^{1}H and ^{19}F NMR spectroscopy (no other peaks except those of the ionic liquid).

In conclusion, we have shown that ionic liquids are a good alternative reaction media for the generation and synthesis of zinc reagents.

Experimental

General

All commercially available reagents were used without further purification. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in ppm (δ) downfield from the internal standard (Me$_4$Si, δ 0.00) in CDCl$_3$. The ^{19}F (282 MHz) NMR spectra were recorded in ppm downfield from the intenral standard C$_6$F$_6$ in CDCl$_3$ using a VXR 300 instrument.

Ethyl 2,2-difluoro-3-hydroxy-3-phenylpropionate[13,14]

A mixed solution of benzaldehyde (321 mg, 3.02 mmol), ethyl bromodifluoroacetate (1.29 g, 6 mmol) and zinc powder (392 mg) in 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate (1 g) was stirred for 3 h in oil bath (50–60 °C). The product was extracted with crude diethyl ether (10 × 20 ml), and the ionic liquid recovered. The organic layer was dried over anhydrous MgSO$_4$ and on removal of the solvent, the yield (76%) was determined by the ^{19}F NMR integral intensities using trifluoroacetic acid as an internal standard. Ethyl 3-hydroxy-3-phenyl-2,2-difluoropropionate **1a** was purified by column chromatography on silica gel using hexane–ethyl acetate (10:1) as eluent.

^{1}H NMR (CDCl$_3$): δ 1.29 (3H, t, J = 7.15 Hz), 2.84 (1 H, s), 4.30 (2 H, q, J = 7.14 Hz), 5.17 (1 H, dd, J = 15.4, 7.97 Hz), 7.37–7.50 (Ar-H). ^{13}C NMR (CDCl$_3$): δ 13.76, 63.10, 73.54 (dd, J = 24.33, 27.48 Hz), 113.72 (dd, J = 250.8, 254.64 Hz), 127.54, 128.16, 128.95, 134.42 (d, J = 1.72 Hz), 163.46 (t, J = 32.4 Hz).^{19}F NMR (CDCl$_3$): δ 41.3 (dd, J = 261.9, 14.65 Hz), 47.9 (dd, J = 261.9, 7.75 Hz). IR: 3480 (OH), 1770 (C=O) cm^{-1}.

Ethyl 2,2-difluoro-3-hydroxy-5-phenylbutyrate[15]

In the above reaction 3-phenylpropanal (402 mg, 3 mmol), ethyl bromodifluoroacetate (1.29 g, 6 mmol) and zinc powder (392 mg) in 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate (1 g) were used, and then worked-up similarly.

^{1}H NMR (CDCl$_3$): δ 1.34 (3H, t, J = 7.14 Hz), 2.52 (OH), 4.36 (2 H, q, J = 7.14 Hz), 4.75 (1 H, m), 6.24 (1 H, dd, J = 15.9, 6.59 Hz), 6.81 (1 H, d, J = 15.9 Hz), 7.26–7.43 (Ar-H). ^{19}F NMR (CDCl$_3$): δ 40.5 (d, J = 13.8 Hz), 41.7 (dd, J = 13.8 Hz).

1,3-Diphenylhydroxyprop-2-yne[12]

(a) To a mixed solution of benzaldehyde (318 mg, 3 mmol), phenylacetylene (612 mg, 6 mmol) and 1,8-diazabicyclo[5,4,0]-7-undecene (912 mg, 6 mmol) in 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1** (1 g), zinc trifluoromethanesulfonate (1.45 g, 4 mmol) was added at room temperature. After 48 h of stirring at room temperature, the product was extracted with diethyl ether (10 × 20 ml) and the ionic liquid was recoved. The organic layer was dried over anhydrous MgSO$_4$, and then the solvent was removed. The yield (47%) was determiend by the ^{1}H NMR integral intensities using nitromethane as an internal standard. 1,3-Diphenyl-1-hydroxypropyne was purified by column chromatography on silica agel using a mixture of hexane–ethyl acetate (10:1) as an elutent.

^{1}H NMR (CDCl$_3$): δ 2.34 (OH, d), 5.69 (1 H, d, J = 6.05 Hz), 7.31–7.61 (Ar-H). ^{13}C NMR (CDCl$_3$): δ 64.868, 86.427, 88.704, 122.213, 126.565, 128.090, 128.166, 128.363, 128.424, 131.531, 140.396. IR: 3350 (OH), 2229 (C≡C) cm^{-1}.

(b) In the above reaction, 1-butyl-3-methyl-1*H*-imidozolium tetrafluoroborate (1 g) was used and worked up similarly, giving 1,3-diphenyl-1-hydroxypropyne in 59% yield. (c) In the above reaction, 1-butyl-3-methyl-1*H*-imidozolium hexafluorophosphate (1 g) was used and worked up similarly, giving 1,3-diphenyl-1-hydroxypropyne in 35% yield.

1-Phenyl-1-hydroxyhept-2-yne

^{1}H NMR (CDCl$_3$): δ 0.92 (3 H, t, J = 7.32 Hz), 1.39–1.46 (2 H, m), 1.48–1.53 (2 H, m), 2.17 (1 H, s), 2.28 (2 H, td, J = 7.08, 1.95 Hz), 7.2–7.64 (Ar-H). ^{13}C NMR (CDCl$_3$): δ 13.672, 18.554, 22.056, 30.664, 64.132, 79.701, 87.884, 115.074, 115.358, 128.272, 128.382. IR: 3349 (OH), 2229 (C≡C) cm^{-1}.

1-Phenyl-1-hydroxynon-2-yne

^{1}H NMR (CDCl$_3$): δ 0.89 (3 H, t, J = 6.87 Hz), 1.23–1.60 (8 H, m), 2.27 (2 H, td J = 7.15, 1.92 Hz), 5.45, 7.35–7.53 (Ar-H). ^{13}C NMR (CDCl$_3$): δ 14.108. 18.865, 22.587, 28.570, 28.600, 31.335, 64.746, 79.872, 87.626, 126.485, 128.006, 128.340, 141.091. IR: 3386 (OH), 2226 cm^{-1}.

1-(4-Fluorophenyl)-3-phenyl-1-hydroxyprop-2-yne

^{1}H NMR (CDCl$_3$): δ 2.99 (OH, s), 5.63 (1 H, s), 7.00–7.57 (Ar-H). ^{19}F NMR (CDCl$_3$): δ 48.02 (1 F, m) from internal C_6F_6. ^{13}C NMR (CDCl$_3$): δ 64.215, 86.674, 88.411, 115.288 (J_{C-F} = 21.47 Hz), 122.016, 128.169, 128.412 (J_{C-F} = 8.59 Hz), 128.541, 131.534, 136.23 (J_{C-F} = 3.44 Hz), 162.385 (J_{C-F} = 246.2 Hz). IR: 3350 (OH), 2199 (C≡C) cm^{-1}.

1-(4-Fluorophenyl)-1-hydroxyhept-2-yne

^{1}H NMR (CDCl$_3$): δ 0.92 (3 H, t J = 7.14 Hz), 1.43–1.53 (4 H, m), 2.77 (2 H, td, J = 7.14, 2.20 Hz), 5.44 (OH), 7.02–7.54 (Ar-H). ^{19}F NMR (CDCl$_3$): δ 47.51 (1 F, m) from internal C_6F_6. ^{13}C NMR (CDCl$_3$): δ 13.613, 18.476, 21.993, 30.593, 63.947, 79.665, 87.730, 115.108 (d, J_{C-F} = 21.47 Hz), 128.268 (d, J_{C-F} = 8.25 Hz), 136.883 (d, J_{C-F} = 3.15 Hz), 162.267 (d, J_{C-F} = 245.92 Hz). IR: 3375 (OH), 2226 (C≡C) cm^{-1}.

1-(4-Fluorophenyl)-1-hydroxynon-2-yne

^{1}H NMR (CDCl$_3$): δ 0.90 (3 H, m), 1.25–1.60 (6 H, m), 2.20–2.30 (2 H, m), 5.42 (1 H, d, J = Hz), 7.08, 7.58 (Ar-H). ^{19}F NMR (CDCl$_3$): δ 47.51 (1 F, m) from internal C_6F_6. ^{13}C NMR (CDCl$_3$): δ 14.135, 18.854, 22.606, 28.551, 28.623, 31.343, 64.101, 79.686, 87.949, 115.201 (d, J_{C-F} = 21.47 Hz), 128.329 (d, J_{C-F} = 8.59 Hz), 136.937, 162.358 (d, J_{C-F} = 245.92 Hz). IR: 3361 (OH), 2225 (C≡C) cm^{-1}.

1-(4-Nitrophenyl)-3-phenyl-1-hydroxyprop-2-yne

^{1}H NMR (CDCl$_3$): δ 2.47 (OH, d, J = 5.77 Hz), 5.80 (1 H, d, J = 5.76 Hz), 7.36–8.39 (Ar-H). ^{13}C NMR (CDCl$_3$): δ 63.991, 87.361, 86.558, 121.599, 123.708, 127.304, 128.298, 128.472, 128.924, 130.313, 131.622, 133.154, 147.271.

(*E*)-1,5-Diphenyl-3-hydroxypent-4-enyl-1-yne

^{1}H NMR (CDCl$_3$): δ 5.29 (CHOH, dd, J = 5.77 Hz), 6.39 (1 H, dd, J = 15.65, 6.05 Hz), 6.85 (1 H, dd, J = 17.66, 1.10 Hz), 7.27–7.50 (Ar-H). ^{13}C NMR (CDCl$_3$): δ 63.400, 74.432, 87.861, 110.096, 122.213, 126.310, 126.682, 127.881, 127.968, 128.177, 128.461, 131.348, 131.599, 131.849, 135.901, 141.607, 144.148. IR: 3385 (OH), 2203 cm^{-1}.

References

1 P. Tundo and P. T. Anastas, *Green Chemistry: Challenging Perspectives*, Oxford Science, Oxford, 1999.

2 I. T. Horváth and J. Rábai, *Science*, 1994, **266**, 72; H. Nakano and T. Kitazume, *Green Chem.*, 1999, **1**, 21 and references therein; H. Nakano and T. Kitazume, *Green Chem.*, 1999, **1**, 179.

3 M. J. Earle, P. B. McCormac and K. R. Seddon, *Chem. Commun.*, 1999, 2245; C. L. Adams, M. J. Earle, G. Roberts and K. R. Seddon, *Chem. Commun.*, 1998, 2097; T. Kitazume, F. Zulfiqar and G. Tanaka, *Green Chem.*, 2000, **4**, 133 and references therein; F. Zulfiqar and T. Kitazume, *Green Chem.*, 2000, **4**, 137; F. Zulfiqar and T. Kitazume, *Green Chem.*, 2000, **6**, 296.

4 J. K. D. Surette, L. Green and R. D. Singer, *Chem. Commun.*, 1996, 2753; J. A. Boon, J. A. Levisky, J. L. Pflug and J. S. Wilkes, *J. Org. Chem.*, 1986, **51**, 480.

5 V. R. Koch, L. L. Miller and R. A. Osteryoung, *J. Am. Chem. Soc.*, 1976, **98**, 5277; Y. Chauvin, A. Hirschauer and H. Olivier, *J. Mol. Catal.*, 1994, **92**, 155.

6 C. W. Lee, *Tetrahedron Lett.*, 1999, **40**, 2461; M. J. Earle, P. B. McCormac and K. R. Seddon, *Green Chem.*, 1999, **1**, 23.

7 W. Chen, L. Xu, C. Chatterton and J. Xiao, *Chem. Commun.*, 1999, 1247; A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac and K. R. Seddon, *Org. Lett.*, 1999, **1**, 997.

8 A. L. Monteiro, F. K. Zinn, R. F. de Souza and J. Dupont, *Tetrahedron: Asymmetry*, 1997, **8**, 177.

9 T. Kitazume and G. Tanaka, *J. Fluorine Chem.*, 2000, **106**, 211.

10 *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, Pergamon Press, Oxford, 1982, vol. 1–8.

11 M. W. Rathke and P. Weipert, *Comprehensive Organic Synthesis*, Pergamon Press, Oxford, 1991, vol. 2, p. 277.

12 J. Fried and E. A. Hallinan, *Tetrahedron Lett.*, 1984, **25**, 2301.

13 H. Fukuda and T. Kitazume, *J. Fluorine Chem.*, 1995, **74**, 171; R. Pedrosa, *Synthesis*, 1996, 1070; T. Kitazume and T. Yamazaki, *Experimental Methods in Organic Fluorine Chemistry*, Gordon & Breach Science Publishers and Kodansha, Tokyo, 1998.

14 S. Watanabe, T. Fujita, M. Sakamoto, H. Takeda, T. Kitazume and T. Yamazaki, *J. Fluorine Chem.*, 1977, **82**, 1.

15 D. E. Frantz, R. Fässler and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 806.

A simple colorimetric method for the quality control of 1-alkyl-3-methylimidazolium ionic liquid precursors

John D. Holbrey,[a] Kenneth R. Seddon[a] and Roger Wareing[b]

[a] *The QUILL Centre, The Queen's University of Belfast, David Keir Building, Stranmillis Road, Belfast, Northern Ireland, UK BT9 5AG. E-mail: k.seddon@qub.ac.uk*
[b] *Elementis Specialties, Birtley, Chester-le-Street, Co. Durham, UK DH3 1QX*

Received 27th November 2000
First published as an Advance Article on the web 31st January 2001

A simple colorimetric method to monitor the production of ionic liquid precursors is developed, which is based on the determination of 1-methylimidazole with copper(II) chloride. The synthesis of 1-ethyl-3-methylimidazolium chloride, an industrially important ionic liquid precursor, can be followed and the purity of the final product can be readily assessed in a quick and convenient manner.

Introduction

Room-temperature ionic liquids[1–5] have been widely studied as solvents for electrochemical technologies and more recently as clean, environmentally benign solvents for industrial chemical processes.[6–8] Room-temperature ionic liquids typically comprise an organic cation and weakly coordinating anion;[3] systems of greatest current interest contain 1-alkyl-3-methylimidazolium cations (Fig. 1). Most ionic liquid systems are derived from chloride salts (of the 1-alkyl-3-methylimidazolium cation) either by mixing [*i.e.* tetrachloroaluminate(III) ionic liquids[9]] or *via* metathesis;[10] direct alkylation routes have also been applied[11] The chloride salts may be prepared by alkylation of 1-methylimidazole with the corresponding chloroalkane.[9,12]

However, despite the current level of interest in ionic liquids, from both academic groups and industry,[13–15] these materials are not readily available on a commercial basis. The key to the synthesis of ionic liquids is the relatively simple preparation of 1-alkyl-3-methylimidazolium chloride salts by alkylation of 1-methylimidazole with the corresponding 1-chloroalkane, in particular, the synthesis of 1-ethyl-3-methylimidazolium chloride ([emim]Cl). As part of a development program in the scale-up of ionic liquid production, it was necessary to monitor the synthesis of [emim]Cl and determine the purity of the final product using a procedure that could be applied at both a laboratory scale and under industrial production conditions as a quality control method. In particular, the presence of unreacted 1-methylimidazole starting material in the ionic liquids from incomplete alkylation poses potential downstream problems from catalyst poisoning and introduction of protic impurities. 1-Methylimidazole is a coordinating base, and has proved difficult to remove from ionic liquids at a later stage.

We present here a method to monitor the end-point of the alkylation reaction and determine the levels of unreacted 1-methylimidazole contamination to < 0.2 mol%, based on the complexation of 1-methylimidazole with copper(II) chloride in ethanol to form the $[Cu(mim)_4]^{2+}$ ion[16] (mim = 1-methylimidazole), which has an intense blue colour. In contrast, the interaction of copper(II) chloride with [emim]Cl in ethanolic solution gives a yellow solution in the absence of 1-methylimidazole and provides the necessary spectral shift to allow a colorimetric determination based on the position of λ_{max} of the absorption band in the electronic absorption spectrum.

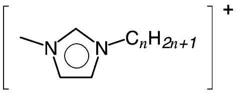


Fig. 1 The structure of the 1-alkyl-3-methylimidazolium cation ($n = 2$ is conventionally designated as $[emim]^+$).

Experimental

1-Methylimidazole (*ex* Aldrich) was distilled from CaH_2 prior to use; ethanol (spectroscopic grade) and copper(II) chloride dihydrate (Analar) were used as received. Electronic absorption spectra of samples in 1 mm or 1 cm quartz cells were obtained using a Perkin Elmer Lambda-9 spectrometer over the range 500–1500 nm. A 3 l autoclave, equipped with overhead, magnetically coupled stirrer was manufactured by Strata Technology Ltd, Sunbury-on-Thames, UK.

Preparation of 1-ethyl-3-methylimidazolium chloride

1-Ethyl-3-methylimidazolium chloride ([emim]Cl) was prepared on a bulk scale from 1-methylimidazole and chloroethane. Samples were then taken and recrystallised twice from ethanenitrile–ethyl ethanoate and then stored under dinitrogen in a dry-box. Purity was confirmed by ^1H, and ^{13}C NMR spectroscopy, CHN microanalysis, and determination of Cl^- content.

An autoclave (3 l) was charged with 1-methylimidazole (1030 g, 12.54 mol, 1000 cm^3; freshly distilled from CaH_2) and cooled to 0 °C under dinitrogen. Chloroethane (1000 g, 19.8 mol) was condensed into a partially evacuated 2 l Schlenk tube and transferred to the autoclave, which was then sealed and pressurised to 5 bar with dinitrogen. The autoclave was then

Green Context

Ionic liquids are attracting a lot of attention as novel, VOC-free solvent systems. One of the barriers to acceptance industrially is the assurance of quality and reproducibility. A contribution to this is the development of a simple and rapid technique to monitor levels of the parent imidazole in the final product. The method is rapid, sensitive and requires only standard lab equipment. ***DJM***

DOI: 10.1039/b009459p

heated and stirred at 75 °C for 48 h. The reactor contents were transferred to a round-bottomed flask under dinitrogen and the excess of chloroethane was removed with heating at 70 °C under reduced pressure and finally *in vacuo* to give a colourless, viscous oil. The molten product was then transferred to a dry-box and poured into a shallow tray, where it crystallised on cooling as a white solid (yield 1818 g, 99%; $C_6H_{11}ClN_2$: found (calc.): C, 48.96 (49.15); H, 7.49 (7.56); N, 18.89 (19.10%); Mp 87 °C (*lit*. 84 °C[9]).

Job plot analysis and calibration curves

For the Job plot analysis, a standard solution (1000 cm^3) of [emim]Cl (77.70 g, 0.530 mol) in ethanol was prepared ([emim]Cl concentration, 0.530 mol l^{-1}). Two stock solutions (250 cm^3) were then prepared from copper(II) chloride $CuCl_2{\cdot}2H_2O$ (2.26 g, 13.3 mmol) with the standard ethanolic [emim]Cl solution, (53.2 mmol l^{-1} in [Cu(II)]) and from 1-methylimidazole (1.09 g, 13.3 mol) with the standard ethanolic [emim]Cl solution (1-methylimidazole concentration 53.2 mmol l^{-1}).

Samples of 10 cm^3 volume, in each case with constant overall [Cu(II)] + [mim] concentration, were prepared from the two stock solutions (**1–10**, Table 1) using the quantities indicated in Table 1; overall concentrations were 0.530 mol l^{-1} in [emim]Cl and 53.2 mmol l^{-1} in combined copper(II) chloride and 1-methylimidazole. Electronic absorption spectra were obtained over the range 500–1500 nm using 1 mm path length quartz cuvettes.

For the calibration curve, a standard ethanolic solution (100 cm^3) of copper(II) chloride solution ($CuCl_2{\cdot}2H_2O$, 1.00 g, 5.87 mmol) and a stock solution (1000 cm^3) of pure [emim]Cl (51.210 g, 0.3493 mol) in ethanol were prepared. Solutions (**11**–**19**, Table 2) of known [emim]Cl:[mim] concentration ratios were prepared from 1-methylimidazole (accurately measured in the range 0–0.2500 g, *ca*. 0–3 mmol) and the stock solution of [emim]Cl (100 cm^3). Finally a 10 cm^3 aliquot of the [emim]Cl/[mim] solutions in ethanol was taken and copper(II) chloride solution (1.0 cm^3) was added, to give an immediate colour change. The overall copper concentration was 6.73 mmol l^{-1}, which was calculated to be sufficient to completely complex 1-methylimidazole at concentrations up to 27 mmol l^{-1}. Under the conditions chosen, this corresponds to *ca*. 8 mol% 1-methylimidazole in a sample of [emim]Cl. Electronic absorption spectra were obtained of the samples over the range 500–1500 nm using 1 cm path length quartz cuvettes.

Table 1 Solutions prepared for Job plot composition analysis, indicating the volume of the standard solutions of $Cu(II)Cl_2$ and 1-methylimidazole (in ethanolic [emim]Cl) used, concentration of each component in the final solution and position of λ_{max} in the electronic absorption spectrum. Total [Cu(II)] + [mim] concentration was 53.2 mmol l^{-1} and 0.530 mol^{-1} in [emim]Cl for each solution

	$Cu(II)Cl_2$		mim		
Solution	Volume/ cm^3	Conc./ mmol l^{-1}	Volume/ cm^3	Conc./ mmol l^{-1}	λ_{max}/nm
1	10.0	53.2	0	0.0	1090
2	9.0	47.7	1.0	5.3	1046
3	8.0	42.4	2.0	10.6	996
4	7.0	37.1	3.0	15.9	939
5	6.0	31.8	4.0	21.2	898
6	5.0	26.5	5.0	26.5	856
7	4.0	21.2	6.0	31.8	856
8	3.0	15.9	7.0	37.1	773
9	2.0	10.6	8.0	42.4	735
10	1.0	5.3	9.0	47.7	648

Results and discussion

The change in the electronic absorbtion spectrum of the composite mixture [Cu(II)]–[emim]Cl–mim (Table 1) was investigated as a function of [Cu(II)]:[mim] ratio using a Job plot analysis[17] to characterise the copper–imidazole species as a function of composition (Fig. 2). Electronic absorption spectra of **1–10** with constant overall concentration and varying [Cu(II)]:[mim] ratios were obtained. The [Cu(II)]:[mim] molar ratio was varied in the range 10–100 mol% Cu(II) while maintaining constant overall ionic concentration with a ten-fold excess of [emim]Cl and the electronic spectra taken over the range 500–1500 nm.

The maximum values (λ_{max}) in the absorption spectra vary continuously and linearly with copper:[mim] concentration and are independent of the excess of [emim]Cl. This indicates a continuous gradual transition from a solvated copper(II) chromophore to a mononuclear $[Cu(mim)_4]^{2+}$ chromophore on increasing [mim]:[Cu] ratio. This is in agreement with electron paramagnetic resonance (EPR) measurements on mixtures of copper(II) nitrate and 1-methylimidazole.[18] The spectrum obtained at 4 : 1 [mim]:[Cu(II)] (20% copper content) is identical to the spectrum of $[Cu(mim)_4]Cl_2$ dissolved in ethanol containing an excess of [emim]Cl.

The Job plot analysis shows that there is a continuous, gradual change in the absorption spectrum as a function of composition. The positions of the absorption maxima depend only on the relative Cu(II):mim ratio, and are independent of the [emim]Cl:mim ratio. Thus, by monitoring the change in λ_{max} with 1-methylimidazole concentration while maintaining con-

Table 2 The maxima in the electronic absorbance spectra (λ_{max}) with concentration of 1-methylimidazole in the calibration solutions, containing fixed concentration of copper(II) (5.336 mmol l^{-1}) and an excess of [emim]Cl (317.8 mmol l^{-1}).

Solution	[mim]/mmol l^{-1}	λ_{max}/nm
11	0.000	1093
12	0.000	1096
13	0.886	1065
14	2.768	963
15	3.875	945
16	6.864	873
17	11.072	796
18	14.725	777
19	25.686	754

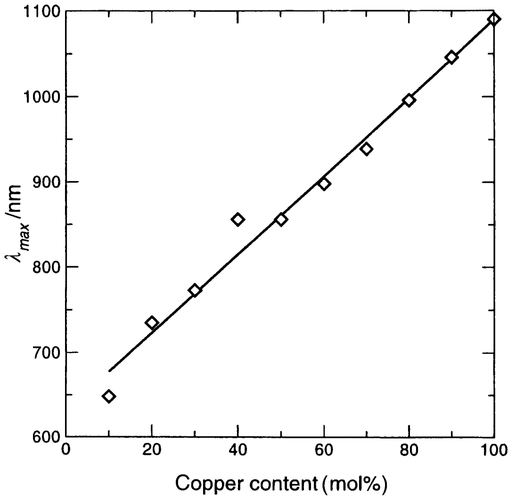


Fig. 2 Variation in the absorption maxima (λ_{max}) of the electronic spectra of solutions **1**–**10** with copper(II)–1-methylimidazole molar composition in ethanol. The solutions (Table 1) have a constant combined [Cu(II)] + [mim] concentration (53.2 mmol l^{-1}) and constant [emim]Cl concentration (0.530 mol l^{-1}).

stant copper concentration, a calibration curve can be constructed which will enable the 1-methylimidazole component of mixed [emim]Cl/1-methylimidazole samples to be determined by reference to the calibration curve, and the overall composition calculated from the initial weight of sample taken.

The absorption spectra of solutions of known composition with [mim]:[emim]Cl ratio in the range 0–5 mol% and methylimidazole concentration in the range 0–30 mmol l^{-1}, (**11–19**) with constant copper(II) concentration (Table 2) were measured, and λ_{max} plotted as a function of 1-methylimidazole concentration (Fig. 3). The copper concentration used was calculated to be sufficient to complex all the 1-methylimidazole over the composition range studied [up to *ca*. 27 mmol l^{-1}, equivalent to *ca*. 8 mol% in the samples **11–19** (Table 2)]. The solutions prepared varied from yellow (in the absence of 1-methylimidazole, [mim] = 0) progressively to blue–green as the 1-methylimidazole concentration was increased, with a shift in λ_{max} from 1100 to 750 nm (Figs. 4 and 5).

The absorption maximum with 1-methylimidazole composition varies following an exponential curve (Fig. 3) and demonstrates a very high sensitivity to 1-methylimidazole concentration. Under the experimental conditions chosen for this study, λ_{max} varies by 300 nm for a change in 1-methylimidazole concentration in the range 0–10 mmol l^{-1}. By changing the concentration of [Cu(II)] used, the sensitivity of the method can be tuned to different concentration ranges of 1-methylimidazole. Under the conditions described here, the upper limit in 1-methylimidazole concentration determination in the sample is *ca*. 27 mmol, at which point, all of the available copper ions are complexed to 1-methylimidazole as the blue, square-planar $[Cu(mim)_4]^{2+}$ species.[16] It is notable that the sensitivity of this method for determining the purity of [emim]Cl is greatest at low [mim] concentration, which is ideal for industrial process monitoring.

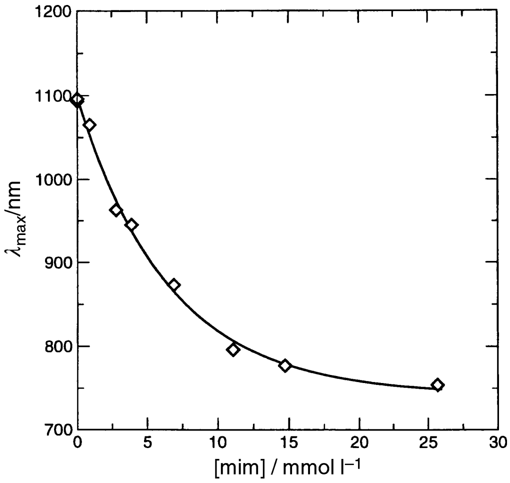


Fig. 3 The absorption maxima (λ_{max}) as a function of 1-methylimidazole concentration from Table 2. Data were fitted with an exponential curve $y = a + b^{(-x/c)}$, $a = 742.47$, $b = 355.89$, $c = 6.46$; $R^2 = 0.996$.

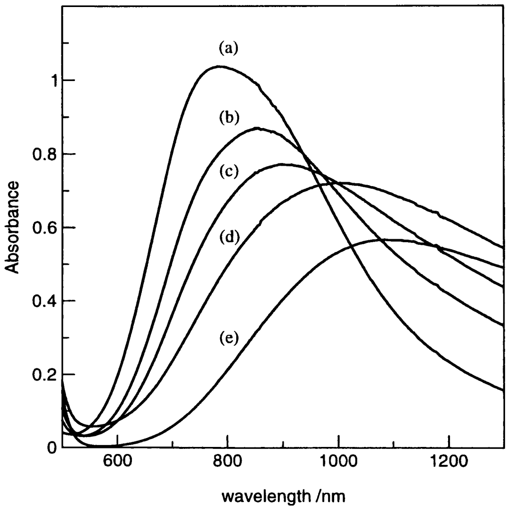


Fig. 4 Change in the electronic absorption spectra of the calibration standards (from Table 2) with 1-methylimidazole concentration; (a) 25.0 mmol l^{-1}, (b) 6.8 mmol l^{-1}, (c) 3.9 mmol l^{-1}, (d) 0.9 mmol l^{-1}, (e) 0 mmol l^{-1}. In each case, [Cu(II)] concentration is 5.336 mmol l^{-1} and [emim]Cl concentration is 317.8 mmol l^{-1}.

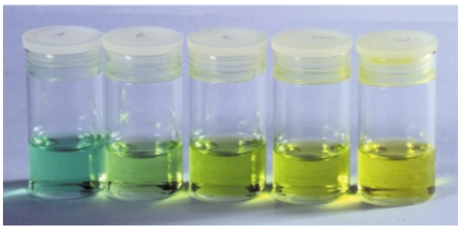


Fig. 5 The progressive, visual change in colour of test solutions, on decreasing [mim] concentration, from blue–green (8 mmol l^{-1}) to yellow (0 mmol l^{-1}).

These results demonstrate that, under the range of conditions used, the response of the absorption maximum to 1-methylimidazole concentration is independent of the [emim]Cl concentration. This both confirms the conclusions drawn from the Job analysis and shows that the calibration plot can be used to determine the 1-methylimidazole content of unknown (*i.e.* experimental) samples of [emim]Cl of accurately known, but varying, weights. This, then, is the basis of the analytical procedure described below.

Analytical procedure

A standard procedure was developed to measure the 1-methylimidazole content of 1-ethyl-3-methylimidazolium chloride samples taken from the alkylation reaction. A sample of the reaction mixture (approximately 0.5 g, assumed to contain at least 95% [emim]Cl) was accurately weighed into a 10 cm^3 volumetric flask and dissolved in ethanol, taking precautions to limit absorbance of moisture from the environment. A 1 cm^3 aliquot of the standard ethanolic copper(II) solution (containing 1.0 g, 5.87 mmol in 100 cm^3 ethanol) was then added and the absorption spectra recorded in the range 500–1500 nm using 1 cm path length cuvettes. The maximum, λ_{max}, was measured and compared to the standard calibration plot (Fig. 3) to determine the total concentration of 1-methylimidazole in the test solution. The molar ratio of 1-methylimidazole to [emim]Cl in the reaction mixture can then be calculated from this result and the weight of the sample.

Under the conditions used ([emim]Cl samples of *ca*. 0.5 g), 1-methylimidazole content can be determined in the range 0–3 mol%, corresponding to a concentration in the range 0–10 mmol l^{-1} in the test solution. Over this concentration range, the position of λ_{max} changes by almost 300 nm and provides a very sensitive technique to monitor 1-methylimidazole content to better than ±0.2 mol% in [emim]Cl.

Conclusion

In conclusion, we present a quick, simple reliable method for following the important reaction between 1-methylimidazole and chloroethane and determining the purity of the product, [emim]Cl. The general method has been shown to also be applicable in general to the formation of other 1,3-dialkylimidazolium salts by alkylation of a functionalised imidazole with chloro- and bromo-alkanes. The procedure is equally applicable to a small scale laboratory synthesis, or to a multi-ton commercial process.

Acknowledgements

We would like to thank the ERDF Technology Development Programme and the QUESTOR Centre (J. D. H.) for financial support and the EPSRC and Royal Academy of Engineering for the award of a Clean Technology Fellowship (to K. R. S.). This research was also partially funded under a Brite-Euram III framework project (BRPR-CT97-0431/BE-96-3745).

References

1 C. L. Hussey, *Adv. Molten Salt Chem.*, 1983, **5**, 185.
2 C. L. Hussey, *Pure Appl. Chem.*, 1988, **60**, 1763.
3 Y. Chauvin and H. Olivier-Bourbigou, *Chemtech*, 1995, **25**, 26.
4 K. R. Seddon, *Kinet. Catal.*, 1996, **37**, 693.
5 K. R. Seddon, *J. Chem. Tech. Biotech.*, 1997, **68**, 351.
6 J. D. Holbrey and K. R. Seddon, *Clean Prod. Proc.*, 1999, **1**, 233.
7 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
8 W. Keim and P. Wasserscheid, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772.
9 J. S. Wilkes, J. A. Levisky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263.
10 J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965.
11 P. Bonhôte, A. P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168.
12 A. K. Abdul-Sada, P. W. Ambler, P. K. G. Hodgson, K. R. Seddon and N. J. Stewart, *World Pat.*, WO95/21871, 1995.
13 M. Freemantle, *Chem. Eng. News*, 2000, **78** (May 15), 37.
14 D. Adam, *Nature*, 2000, **407**, 938.
15 R. D. Rogers, *Green Chem.*, 2000, **2**, G94.
16 W. Clegg, J. R. Nicholson, D. Collison and C. D. Garner, *Acta Crystallogr., Sect. C*, 1988, **44**, 453.
17 P. Job, *Ann. Chim.*, 1928, **9**, 113.
18 P. J. Baesjou, W. L. Driessen, G. Challa and J. Reedijk, *J. Mol. Catal. A*, 1996, **110**, 195.

Organic reaction in water. Part 5.[1] Novel synthesis of anilines by zinc metal-mediated chemoselective reduction of nitroarenes

Takehito Tsukinoki* and Hirohisa Tsuzuki

Tohwa Institute for Science, Tohwa University, 1-1-1 Chikushigaoka Minami-ku, Fukuoka 815-8510, Japan. E-mail: takehito@tohwa-u.ac.jp

Received 12th October 2000
First published as an Advance Article on the web 22nd January 2001

Nitroarenes can be reduced in high yields to the corresponding anilines using zinc metal and NH_4Cl in water without any organic solvent at 80 °C with a simple procedure at low cost. The procedure is powerful enough to reduce sterically hindered 2,6-dimethylnitrobenzene and is chemoselective for nitro groups; ester, amide and halide substituents on aromatic rings are unaffected.

Introduction

Reduction of nitroarenes leading to aromatic amines is an important key step in the industrial syntheses of dyes, medicinal supplies and agricultural chemicals. Furthermore, the primary aromatic amines are readily converted into diazonium salts, which can be substituted for many other functional groups. Therefore, a variety of methods for the reduction of nitro groups have been developed.[2] The methods employed generally are catalytic hydrogenation[3] such as with Raney Ni, Pd/C and PtO_2, or dissolving metal reduction, for example, with Fe/HCl[4] and Sn/HCl.[5] In addition, recently, chemoselective reduction of nitro groups using metallic reducing reagents such as Sm,[6] In[7] and $B_{10}H_{14}$[8] was reported. However, these reactions require an expensive and/or a moisture-sensitive reagent and an organic solvent, and for catalytic hydrogenation, it is necessary to pressurize the reactor with hydrogen gas. In these methods, there is little consideration given to the environment, cost, safety, or simplicity of operation. On the other hand, recently, in view of human health and environmental concerns, much attention is being paid to 'Green Chemistry', which is a chemical methodology to decrease or eliminate the use or generation of hazardous substances in the design, preparation and application of chemical production.[9] In this area of investigation, there is growing interest in synthetic organic reactions in environmentally friendly water.[10] We have demonstrated a facile reductive coupling of aromatic imines by zinc metal and NH_4Cl in water.[1] In continuation of our progressive investigation into the application of this methodology, we are strongly interested in the development of the chemoselective reduction of nitro groups using a cheap reagent with easy operation in water without any organic solvent, a methodology which would have some advantages in terms of cost, safety, simple operation, human health and environmental concerns as compared with use of an organic solvent. Here, we wish to report that in water without any organic solvent, aromatic amines can be obtained in high yields by an operationally easy chemoselective reduction of aromatic nitro compounds facilitated by cheap zinc metal.

Results and discussion

In preliminary work, we investigated the influence of additives and solvent on reduction of nitrobenzene **1** using zinc metal (Scheme 1 and Table 1). Some zinc and ammonium salts, except for ammonium nitrate, were effective for the reduction of nitrobenzene using zinc metal in water to give aniline **2** in high yield without any other coupling products such as azo- and hydrazo-benzenes (runs 1–9).[11] Furthermore, when using α-amino acids as an additive, the reduction of **1** proceeds readily at a neutral pH (runs 10 and 11). We found that an additive was

$$\underset{\mathbf{1}}{\text{Ph-NO}_2} \xrightarrow[\text{Solvent, 80°C}]{\text{Zn, additives}} \underset{\mathbf{2}}{\text{Ph-NH}_2}$$

Scheme 1

Table 1 Reduction of nitrobenzene under various conditions[a]

Run	Additive	Solvent	Reaction time/h	Isolated yield(%)
1	NH_4Cl	MeOH	1	79
2	NH_4Cl	EtOH	6	80
3	NH_4Cl	Water	0.5	84
4	NH_4NO_3	Water	No reaction	—
5	$(NH_4)_2SO_4$	Water	1	87
6	$MeCO_2NH_4$	Water	0.5	89
7	$HCOONH_4$	Water	0.5	81
8	$ZnCl_2$	Water	0.5	81
9	$ZnSO_4$	Water	1	82
10	L-Alanine	Water	0.5	87
11	L-Glutamine	Water	0.5	78

[a] **1**: 2 mmol, Zn: 14.5 mmol, additive: 4 mmol, solvent: 15 ml.

Green Context

The reduction of aromatic nitro compounds to anilines is a very important synthetic transformation since the nitro group is often used to activate the aromatic nucleus to nucleophilic substitution but the amino group is often used for further derivitisation towards valuable products such as pharmaceuticals. There are many methods for carrying out this reaction and these are generally hazardous to the environment due to the use of organic solvents and can suffer from the need for expensive and sensitive metallic reagents. Here both of these problems are dealt with by using water as the solvent and the relatively benign and inexpensive reagents zinc with ammonium chloride. The procedure is versatile, quick and enables easy separation of the products from the inorganic reagents.

JHC

DOI: 10.1039/b008219h

Table 2 Reduction of nitroarenes with Zn/NH_4Cl in water[a]

Entry	Substrate	Reaction time/h	Product	Isolated yield(%)
1	2-$MeC_6H_4NO_2$	0.5	2-$MeC_6H_4NH_2$	94
2	4-$MeC_6H_4NO_2$	0.5	4-$MeC_6H_4NH_2$	93
3	2,6-$Me_2C_6H_3NO_2$	1	2,6-$Me_2C_6H_3NH_2$	95
4	4-$MeCO_2C_6H_4NO_2$	0.5	4-$MeCO_2C_6H_4NH_2$	97
5	4-$MeCONHC_6H_4NO_2$	1	4-$MeCONHC_6H_4NH_2$	82
6	4-$FC_6H_4NO_2$	0.5	4-$FC_6H_4NH_2$	81
7	4-$ClC_6H_4NO_2$	0.5	4-$ClC_6H_4NH_2$	92
8	4-$BrC_6H_4NO_2$	0.5	4-$BrC_6H_4NH_2$	90

[a] Substrate: 2 mmol, Zn: 14.5 mmol, NH_4Cl: 4 mmol, water: 15 ml.

necessary because the reduction did not occur in the presence of zinc metal and methanol, ethanol, or water only. As a solvent for the reduction of **1**, water was superior to alcohols such as methanol and ethanol in terms of reaction time (runs 1–3). Reduction of **1** occurred with other metals such as bismuth and magnesium; however, these methods were inferior in terms of the yield of **2** or reaction times compared with that using zinc metal.[12]

On the basis of these results, reduction of other nitroarenes were carried out by using zinc metal and NH_4Cl in water without any organic solvent at 80 °C under atmospheric pressure (Table 2). We found that the reduction of nitroarenes took place smoothly and chemoselectively to afford the corresponding anilines in high yields (entries 4–8). These results demonstrate that reduction-sensitive substituents such as ester (entry 4), amido (entry 5), and halide (entries 6–8) groups are unaffected during this reaction. In addition, the sterically hindered 2,6-dimethylnitrobenzene was readily reduced to the 2,6-dimethylaniline in excellent yield (95%) by this method, which did not require any drastic conditions (entry 3).

For reduction of nitroarenes leading to aromatic amines with zinc metal, methods employing Zn/HCl,[13] Zn/aq. NaOH/EtOH,[14] Zn/NH_3,[15] Zn/$CaCl_2$/EtOH[16] and Zn/near-critical H_2O[17] have been reported. However, since the conventional methods require an organic solvent and/or drastic conditions using an irritant reagent such as NH_3, concentrated HCl or 20% aq. NaOH, it is difficult to contend that these methods are environmentally harmonious. In addition, the reaction time is prolonged (24 h) for Zn/NH_3, whilst using Zn/$CaCl_2$/EtOH, a substantial amount of zinc metal is required (39 equiv.). On the other hand, special apparatus is required when using near-critical water. The greatest advantage of our method compared with other methods is that handling is very easy, and the reaction in water is safe, and cost is low because zinc metal and water as a solvent are cheap.

In conclusion, we have demonstrated an environmentally friendly method for the synthesis of anilines by the chemoselective reduction of nitroarenes with zinc metal in water.

Notes and references

1 Part 4, see: T. Tsukinoki, S. Nagashima, Y. Mitoma and M. Tashiro, *Green Chem.*, 2000, **2**, 117.

2 R. C. Larock, *Comprehensive Organic Transformations: a Guide to Functional Group Preparations*, Wiley-VCH, New York, 2nd edn., 1999, pp. 823–827.

3 G. V. Smith and F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry*, Academic Press, New York, 1999, pp. 71–79.

4 C. A. Merlic, S. Motamed and B. Quinn, *J. Org. Chem.*, 1995, **60**, 3365.

5 K. M. Doxsee, M. Feigel, K. D. Stewart, J. W. Canary, C. B. Knobler and D. J. Cram, *J. Am. Chem. Soc.*, 1987, **109**, 3098.

6 B. K. Banik, C. Mukhopadhyay, M. S. Venkattaman and F. F. Becker, *Tetrahedron Lett.*, 1998, **39**, 7243; L. Wang, L. Zhou and Y. Zhang, *Synlett*, 1999, 1065.

7 C. J. Moody and M. R. Pitts, *Synlett*, 1998, 1028.

8 J. W. Bae, Y. J. Cho, S. H. Lee and C. M. Yoon, *Tetrahedron Lett.*, 2000, **41**, 175.

9 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford, New York, 1998, pp. 1–129; P. T. Anastas and T. C. Williamson, *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*, Oxford, New York, 1998, pp. 1–360.

10 C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997, pp. 1–189; P. A. Grieco, *Organic Synthesis in Water*, Blackie Academic & Professional, London, 1998, pp. 1–305; *Mordern Solvents in Organic Synthesis*, ed. P. Knochel, Springer, Berlin, 1999, pp. 41–59.

11 *General procedure*: to a stirred mixture of nitrobenzene (246 mg, 2 mmol) and water (15 ml), NH_4Cl (214 mg, 4 mmol) and zinc metal (950 mg, 14.5 mmol, powder) were added at room temperature. After the reaction mixture was stirred for 30 min at 80 °C, the insoluble materials were filtered off and the filtrate was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give a residue, which was distilled on a Kugelrohr apparatus (oven temperature: 94–95 °C) under reduced pressure (16 Torr), to afford aniline (156 mg, 84%).

12 Bi (14.5 mmol): reaction time: 24 h, yield: 33%; Mg (39 mmol): reaction time: 6 h, yield: 28%.

13 E. Kock, *Chem. Ber.*, 1887, **20**, 1567.

14 E. L. Martin, *Org. Synth.*, 1943, **Coll. Vol. II**, 501.

15 A. Burawoy and J. P. Critchley, *Tetrahedron*, 1959, **5**, 340.

16 R. Shundberg and W. Pitts, *J. Org. Chem.*, 1991, **56**, 3048.

17 C. Boix and M. Poliakoff, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1487.

Envirocat EPZG and natural clay as efficient catalysts for transesterification of β-keto esters

B. P. Bandgar,* L. S. Uppalla and V. S. Sadavarte

Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431 606, India. E-mail: upekam@hotmail.com

Received 25th August 2000
First published as an Advance Article on the web 9th January 2001

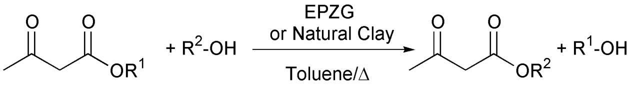
Ethyl/methyl β-keto esters react with various alcohols in the presence of a catalytic amount of Envirocat EPZG or natural clay and undergo transesterification effectively.

Introduction

Transesterification reactions, one of the most effective and useful methods of ester synthesis has wide applications in academic and industrial research.[1] It is accelerated by protic acids,[2] Lewis acids[2] and basic catalysts.[2] Various methods are reported for transesterification. However most of them are not general as far as β-keto esters are concerned. More recently various catalysts have been developed for transesterification.[2,3] Normal methods of transesterification of β-keto esters are equilibrium driven reactions where usage of excess of one of the reactants is mandatory to obtain good yields. Toxic and expensive 4-(dimethylamino)pyridine[4] which catalyzes transesterification requires a large amount of catalyst whereas use of *tert*-butyl acetoacetate[5] leads to restriction to *tert*-butyl esters, thus lacking generality. Distannoxanes[6] gave good yields of β-keto esters but such catalysts are difficult to prepare while transesterification of β-keto esters with propargylic alcohols in general is not trivial. Conventional transesterification reactions with propargylic alcohols provided in most cases low yields of the propargylic β-keto esters; furthermore the Taber procedure,[4] as well as a modified version,[7] produce considerable tarring. As can be clearly seen, there is an obvious need to develop a satisfactory method for transesterification of β-ketoesters using eco-friendly catalysts.

In recent years, there has been considerable growth in interest in the catalysis of organic reactions by inorganic reagents supported on high surface area inorganic materials.[8] Envirocats, a new family of solid supported reagents have led to a significant breakthrough in environmentally friendly chemistry.[9] These solid supported catalysts are non toxic powders which can be filtered easily from the process and may be reused after activation. Envirocat EPZG^R is a solid supported catalyst which exhibits both Bronsted and Lewis acid characteristics.[9] Envirocat EPZG^R represents a major step forward in the development of truly heterogeneous catalysis in acid catalyzed reactions,[10] reducing gaseous emission and eliminating liquid effluent. There is a 10-fold reduction in the quantity of catalyst required when it is substituted for aluminium trichloride.[9] This catalysis is also possible to use Envirocat EPZG^R in non-polar or solvent-free reaction systems. It is synthesized and supplied by Contract Chemicals, UK and is a free flowing yellow–green powder having a bulk density of 0.76 g cm^{-3}. The pH of a 2% (w/v) aqueous suspension is 2.2 and the surface area is *ca.* 250 m^2 g^{-1}. Generally, it requires activation by azeotropic drying overnight or heating at 300–350 °C for 1 h (and cooling) in a flow of nitrogen (heating or cooling EPZG in air can denature the catalyst, rendering it inactive).

Clays have many advantages such as ease of handling, non-corrosiveness, low cost and regeneration. Owing their Brönsted and Lewis acidities, clays, both in their natural and ion-exchanged forms, function as efficient catalysts for various organic transformations.[11] We have recently reported the catalytic property of natural kaolinitic clay for selective deprotection of thioacetals[12] and aryl acetates.[13] In this report we demonstrate that Envirocat EPZG and natural Kaolinitic clay are novel, efficient catalysts for transesterification of β-keto esters (Scheme 1).



Scheme 1

Results and discussion

Natural kaolinitic clay was procured from the Padappakara mine of Quilon district, Kerala, India and it was subsequently purified and characterized by FTIR, XRD, UV, EPR, SEM, EDX and chemical analysis (AAS). The composition of clay has been determined (i) by wet chemical analysis (%): SiO_2 = 67.45, Al_2O_3 = 22.2, Fe_2O_3 = 6.1, TiO_2 = 3.45, K = 0.8 and (ii) by electron dispersive X-ray (EDX) analysis (%) SiO_2 = 62.8, Al_2O_3 = 24.92, Fe_2O_3 = 7.5, TiO_2 = 3.79 and K = 0.4. Natural kaolinitic clay was supplied by Dr Lalithambika, RRL, Trivandrum, India and used as obtained without any pretreatment or activation.

Treatment of ethyl or methyl β-keto ester with alcohols along with a catalytic amount of EPZG or natural clay in refluxing toluene with a distillation condenser to remove methanol or

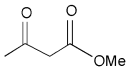
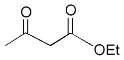
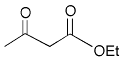
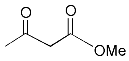
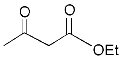
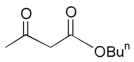
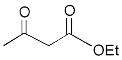
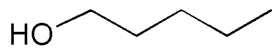
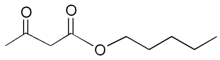
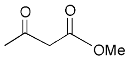
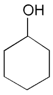
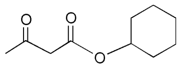
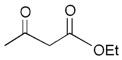
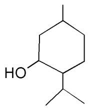
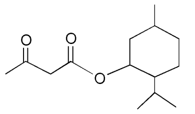
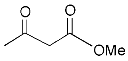
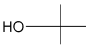
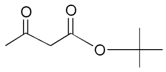
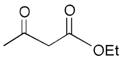
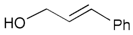
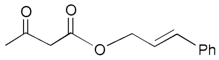
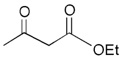
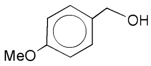
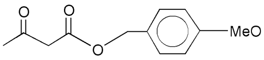
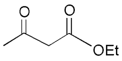
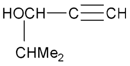
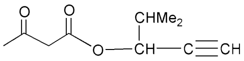
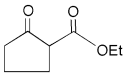
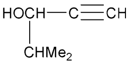
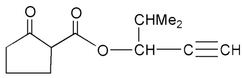
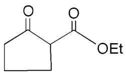
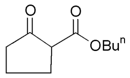
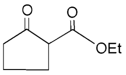
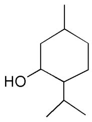
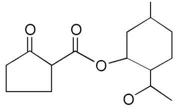
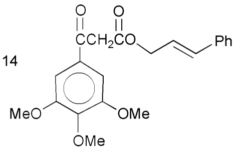
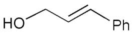
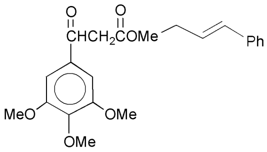
Green Context

Transesterifications are important reactions in many sectors of the chemical industry. They are traditionally carried out using soluble strong acids which need to be washed from the product mixture and are lost as waste. The transesterification of β-ketoesters is especially problematic and while numerous methods have been reported, none are entirely satisfactory. Here, the use of a commercial clay-based catalyst is described. The new method is widely applicable giving good product yields but since the catalyst can be easily separated and reused, there is no acidic waste and catalyst lifetime can be maximised. *JHC*

DOI: 10.1039/b006946i

ethanol afforded the β-keto ester in excellent to high yields. Various alcohols used (primary, secondary, tertiary, benzylic, allylic) underwent smooth transesterification to give the β-keto esters (Table 1). At the temperature used, only a very small amount of toluene was collected along with liberated ethanol or methanol and there was no need to add additional toluene. Transesterification with tertiary alcohols is often problematic in acid catalyzed reactions and indeed fail to undergo transesterification with $Ti(OEt)_4$.[3e] However, with the present catalysts even the less reactive *tert*-butyl alcohol afforded the corresponding β-keto ester in low to moderate yield depending on the reaction time (entry 7) It should be pointed out that transesterification of β-keto esters with unsaturated alcohols is rather difficult as it is offset by facile decarboxylation rearrangment;[14] however β-keto esters underwent smooth transesterification using this method even with unsaturated alcohols (entries 8,10,11,14). The superiority of this procedure can be clearly visualized in transesterifications leading to the synthesis of β-keto esters containing an aromatic moiety in good yields (entry 14). In this connection it should be mentioned that a recent literature report[15] which describes the synthesis of alkyl β-keto esters employing a tin-based super-acid catalyst, (sulfated tin oxide) failed with aromatic substrates. The important feature of our method is that the conversion of the methyl ester to a higher homologue appears to be efficient (entry 1) and the reverse transformation could be achieved equally well in excellent yield (entry 2). It is important to note that the chiral integrity of the alcohol (−)-menthol is maintained under these reaction conditions (chiral alcohol is recovered by base hydrolysis of the ester and measuring its optical rotation) (entries 6, 13). Very little

Table 1 EPZG and natural clay transesterification of β-ketoesters

Entry	β-Ketoester	Alcohol	t/h	Product	Catalyst	Yield[a,b] (%)
1		EtOH	2 2		EPZG NC	91 93
2		MeOH	2 2		EPZG NC	91 92
3		Bu^nOH	2 2		EPZG NC	98 95
4			2 2		EPZG NC	94 89
5			3 3.5		EPZG NC	88 89
6			2.5 3		EPZG NC	88 89
7			8 8		EPZG NC	52 48
8			2 2		EPZG NC	63 60
9			2 2		EPZG NC	82 84
10			3 3		EPZG NC	75 78
11			4 4		EPZG NC	82 77
12		Bu^nOH	2.5 3		EPZG NC	76 72
13			3.5 3		EPZG NC	83 80
14			6 6		EPZG NC	72 79

[a] Yields of pure isolated products. [b] Products characterised by IR and ^1H NMR spectroscopy and comparison with authentic samples.

attention has been paid to transestrifications of β-keto esters required for the synthesis of lignans including podophylotoxin.[3a,d] In this connection it should be mentioned that the present protocol is successfully used for transesterification of these types of β-keto esters (entry 14).

The effectiveness of this protocol is manifested in its selectivity towards β-keto esters whereas normal esters are found to be unreactive. Selective transesterification of ß-keto esters suggests that the role of the carbonyl group in enhancing the reactivity by chelation with the catalyst is crucial for success of the reaction.

In conclusion, the present results demonstrate that natural kaolinitic clay and Envirocat EPZG serve as efficient, convenient and general catalysts to effect transesterification of β-keto esters. The superiority and flexibility of this method over the existing methods coupled with the ease of operation and the simplicity of work-up makes such catalysts potentially very useful. Both catalysts can be recovered and reused at least three times without appreciable loss of activity.

Experimental

IR spectra were recorded on a Bomem MB 104 FTIR spectrometer and ^{1}H NMR spectra were recorded on a Brucker AC 300F NMR spectrometer (300 MHz).

Typical procedure

Ethyl acetoacetate (5 mmol), *n*-butyl alcohol (5 mmol) and catalyst (100 mg) in toluene (20 ml) were heated to 110 °C in a round bottom flask equipped with distillation condenser to remove ethanol. After completion (TLC) the reaction mixture was cooled, filtered and the filtrate concentrated and chromatographed on silica [hexane–ethyl acetate (9 : 1)] to afford the ester, butyl acetocetate, in excellent yield.

Acknowledgement

We thank Contract Chemicals, England and Dr Lalithambika, RRL, Trivandrum, India for generous gifts of Envirocat EPZG and natural Kaolinitic Clay respectively. V.S.S. thanks CSIR, New Delhi for a Junior Research Fellowship.

References

1 T. Fujoita, M. Tanak, Y. Norimine and H. Suemunc, *J. Org. Chem.*, 1997, **62**, 3824; G. Shapiro and M. Marli, *J. Org. Chem.*, 1997, **62**, 7096.

2 P. Kumar and R. K. Pandey, *Synlett*, 2000, **2**, 251 and references therein.

3 (*a*) B. S. Balaji, M. Sasidharan, R. Kumar and B. Chanda, *Chem. Commun.*, 1996, 707; (*b*) B. C. Ranu, P. Dutta and A. Sarkar, *J. Org. Chem.*, 1998, **63**, 6027; (*c*) B. M. Reddy, V R. Reddy and B. Manohar, *Synth. Commun.*, 1999, **29**, 1235; (*d*) B. S. Balaji and B. M. Chanda, *Tetrahedron*, 1998, **54**, 13 227; (*e*) P. Krasik, *Tetrahedron Lett.*, 1998, **39**, 4223; (*f*) S. Fukuzawa and Y. Hongo, *Tetrahedron Lett.*, 1998, **39**, 3521.

4 D. F. Taber, J. C. Amedio, Jr. and Y. K. Patte, *J. Org. Chem.*, 1985, **50**, 3618.

5 J. S. Witzeman and W. D. Nottingham, *J. Org. Chem.*, 1991, **56**, 1713.

6 J. Otera, N. Danoh and H. Nozaki, *J. Org. Chem.*, 1991, **56**, 5301.

7 J. C. Gilbert and T. A. Kelly, *J. Org. Chem.*, 1988, **53**, 449.

8 J. H. Clark, A. P. Kybett and D. J. Macquarrie, *Supported reagents: Preparation, Analysis and Applications*, VCH, New York, 1992; P. Laszlo, *Preparative Chemistry Using Supported Reagents*, Academic Press, Inc., London, 1987.

9 *Envirocats-Supported Reagents : Product information*, Contract Chemicals, UK, 1994.

10 B. P. Bandgar, S. P. Kasture, K. Tidake and S. S. Makone, *Green Chem.*, 2000, **2**, 152 and references therein.

11 D. Ponde, H. B. Borate, A. Sudlai, T. Ravindranathan and V. H. Deshpande, *Tetrahedron Lett.*, 1996, **37**, 4605; T. T. Upadhya, T. Daniel, A. Sudlai, T. Ravindranathan and K. R. Sabu, *Synth. Commun.*, 1996, **26**, 4539; G. K. Janeshwara, N. B. Barhate, A. Sudlai, V. H. Deshpande, A. S. Gajare, M. S. Shingare and R. Sukumar, *J. Chem. Soc., Perkin Trans. 1*, 1998, 965; N. S. Shaikh, A. S. Gajare, V. H. Deshpande and A. V. Bedekar, *Tetrahedron. Lett.*, 2000, **41**, 385.

12 B. P. Bandgar and S. P. Kasture, *Green Chem.*, 2000, **2**, 154.

13 B. P. Bandgar, L. S. Upalla, A. D. Sagar and V. S. Sadavarte, *Tetrahedron Lett.*, in press.

14 M. F. Carrol, *J. Am. Chem. Soc.*, 1940, 704; W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, 1943, **65**, 1992.

15 S. P. Chavan, P. K. Zubaidha, S. W. Dantale, A. Keshvraja, A. V. Ramaswami and T. Ravindranathan, *Tetrahedron Lett.*, 1996, **37**, 233.

Photocatalytic properties of iron porphyrins revisited in aqueous micellar environment: oxygenation of alkenes and reductive degradation of carbon tetrachloride

A. Maldotti,*[a] L. Andreotti,[a] A. Molinari,[a] G. Varani,[a] G. Cerichelli[b] and M. Chiarini[b]

[a] *Dipartimento di Chimica, Centro di Studio su Fotoreattività e Catalisi del C.N.R.,*
Università degli Studi di Ferrara, Via L. Borsari 46, 44100 Ferrara, Italy.
E-mail: mla@dns.unife.it
[b] *Dipartimento di Chimica, Ingegneria Chimica e Materiali, Universita' dell'Aquila, Via*
Vetoio Coppito II 67010 L'Aquila, Italy

Received 3rd August 2000
First published as an Advance Article on the web 6th December 2000

N,*N*-Dimethyltetradecylamine *N*-oxide (DTAO) is an appropriate surfactant to form micelles able to host the iron(III) *meso*-tetrakis(2,6-dichlorophenyl)porphyrin [Fe(III)(TDCPP)]. The so obtained microheterogeneous catalyst can induce biomimetic redox processes on organic substrates in aqueous medium, using sunlight and oxygen as clean reagents. The primary photochemical process consists in the photoinduced reduction of Fe(III) to Fe(II) with the contemporaneous oxidation of the axial ligand to radical species. The micelle environment may control some main parameters affecting the reactivity of these intermediates and, therefore, the chemoselectivity of the hydrocarbon oxidation processes. In contrast to what is observed in homogeneous organic solution, both cyclohexene and cyclooctene can be oxidised to the corresponding epoxides, with a selectivity higher than 90% in the case of cyclooctene. On the other hand, the main oxidation product of cyclohexene is cyclohex-2-en-1-one as expected in a hydrophobic micellar environment. The Fe(III)(TDCPP)/DTAO photocatalyst is very promising also in view of obtaining catalytic systems capable of converting small amounts of toxic halogenated alkanes present in water into less dangerous products. In particular, CCl_4 can be reduced by ethanol or cyclohexanol with high quantum yields ($>10^{-1}$), with good conversion (*ca.* 75%) and turnover values (>1500).

Introduction

The use of water as an alternative reaction medium, instead of toxic and expensive organic compounds, is a very attractive challenge to reduce the environmental impact of chemical processes. In this framework, a possible approach is the use of appropriate, water soluble, surfactants able to form micelles with hydrophobic cores. Herein, this strategy is followed in order to induce biomimetic redox processes based on the use of iron porphyrins catalysts and of clean reagents such as molecular oxygen and sunlight.

In the last two decades, the catalytic activity of iron porphyrin complexes has attracted the attention of many researchers in view to build up model systems of cytochrome P-450 oxygenases, accounting for both monooxygenation of organic substrates[1–6] and reduction of halogenated compounds.[7–12] These models are investigated for two main reasons: (i) better understanding of the essential steps of the enzyme mechanism in living organisms; (ii) the growing demand of both fine and industrial chemistry for new active catalysts, working with high efficiency and selectivity under mild temperature and pressure conditions.

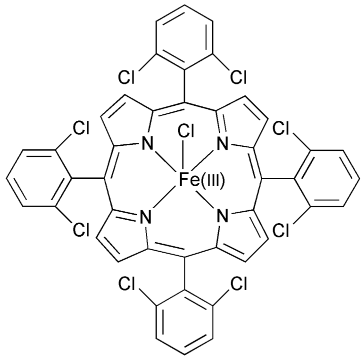
There is a similarity between the photochemical technique and other more conventional methods of activation of oxygenase model systems based on the use of chemical reagents. In particular, it has been demonstrated that the biomimetic catalytic activity of Fe(III) porphyrins may originate by intramolecular photoreactions at suitable wavelengths (λ = 300–400 nm) which lead to the reduction of the metal center as well as to the formation of reactive radical species. These primary photoproducts can induce the subsequent reductive activation of O_2 to give hydrocarbon oxidation[13–19] as well as the reductive degradation of carbon tetrachloride.[20,21]

In this work we use *N*,*N*-dimethyltetradecylamine *N*-oxide as surfactant [$(C_{14}H_{29})Me_2NO$, DTAO] to create water soluble micelles where the synthetic iron(III) *meso*-tetrakis(2,6-dichlorophenyl)porphyrin chloride [Fe(III)(TDCPP)Cl] and different organic substrates may reside. An interesting peculiarity of this iron porphyrin is that the chlorine atoms in its *meso*-aryl groups provide a steric protection of the porphyrin ring against its radical induced oxidative degradation.[22]

Green Context

There is an increasing trend towards the use of water as a medium for carrying out organic transformations. There are obvious advantages to the environment through the avoidance of volatile organic compounds and process costs can be reduced since highly effective solvent recovery steps are unnecessary. However, the incompatibility of water with many organic compounds hinders this approach and additives may often be necessary to enable effective reactions. Here the use of a surfactant to form micelles with a highly useful iron porphyrin catalyst is described. By doing this the authors demonstrate a very interesting new oxidation system that can for example, give high yields of epoxides from the direct reaction of alkenes with oxygen using surfactant–iron porphyrin catalysts and irradiation only. *JHC*

DOI: 10.1039/b006330o



Fe(III)(TDCPP)

Results and discussion

Photoreduction of the DTAO/Fe(III)(TDCPP) system under anaerobic conditions

Aqueous mixtures of DTAO (5×10^{-2} M) and Fe(III)(TDCPP) (2×10^{-5} M) containing pyridine (4×10^{-2} M) were irradiated ($\lambda > 350$ nm) under anaerobic conditions. The UV–VIS spectral variations displayed in Fig. 1 showed that the Soret band was progressively red shifted while the growth of a band at 540 nm occurred. Addition of the reducing agent, sodium dithionite, reinforced the spectral variations seen under irradiation. These results are analogous to those previously obtained irradiating iron porphyrin complexes in homogeneous solution containing pyridine[23] and are a clear indication that Fe(III)(TDCPP) inside the micelle is photochemically reduced to Fe(II)[TDCPP(py)$_2$] (bis-pyridine hemochrome). There is a major difference between the photochemical behaviour of Fe(III)(TDCPP) inside DTAO micelles and in homogeneous organic solution, where we found that the iron(II) porphyrin could be accumulated also in the absence of pyridine.[20]

A number of workers has demonstrated the ability of non-emitting iron porphyrins to undergo intramolecular redox photochemistry according to the first equilibrium of Scheme 1.[14,20,21,23,24] Irradiation in axial-ligand-to-metal charge transfer bands in the near-UV can bring about the reduction of the metal centre with the concomitant oxidation of the axial ligand to a radical species. In the system investigated here the axial ligand Cl^- may be oxidised to the $Cl^{\bullet}$ radical. The efficiency of this process depends on: (i) the efficiency of the charge separation that occurs in competition with radiationless deactivation of the excited state; (ii) the possibility for the radical to diffuse away from the first coordination sphere of the metal; (iii) the presence of species able to trap either Fe(II) porphyrin or the oxidised ligand. The results reported indicate that the diffusion of the primary photoproducts is strongly inhibited when the iron porphyrin is confined inside the micelle. Therefore, we observe reduction of Fe(III)(TDCPP) only in the presence of a large excess of pyridine, which effectively reacts with the iron(II) porphyrin to give the relatively stable bis-pyridine hemochrome Fe(II)[TDCPP(py)$_2$].

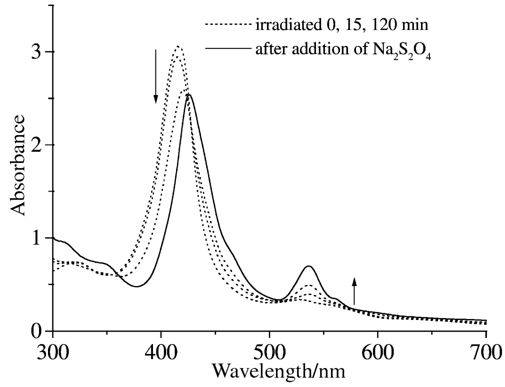
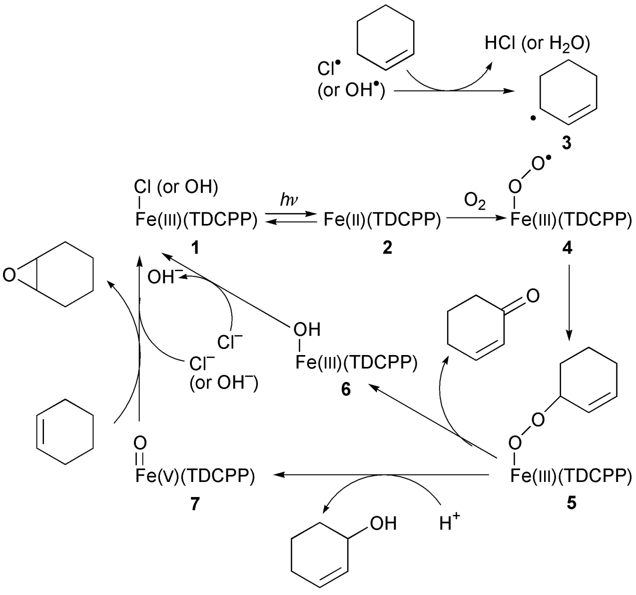


Fig. 1 UV–VIS spectral variations of a de-aerated aqueous mixture of Fe(III)(TDCPP) (2×10^{-5} M)/DTAO (5×10^{-2} M) containing pyridine (4×10^{-2} M) irradiated with $\lambda > 350$ nm. Dotted lines: during irradiation; solid line: after addition of sodium dithionite.

Photooxygenation of cycloalkenes

Water solutions of DTAO (5×10^{-2} M) and Fe(III)(TDCPP) (2×10^{-5} M) were able to dissolve considerable amounts of cyclohexene or cyclooctene (5×10^{-2} M). Irradiation of the so-obtained mixtures ($\lambda > 350$ nm) in the presence of oxygen led to the oxidation of the two cycloalkenes to give the products reported in Table 1, which also shows the ratio between the total substrate oxidised and the Fe(III)(TDCPP) destroyed during the photochemical experiment (total turnover).

The nature and distribution of the products obtained from the oxidation of cyclohexene may be explained on the basis of previous work carried out in homogeneous organic solutions.[13,16,18,19] As shown in Scheme 1, the photogenerated $Cl^{\bullet}$ radicals may easily abstract the allylic hydrogen atom from cyclohexene to give the resonance-stabilised radical **3**. The very fast reaction of O_2 with Fe(II)(TDCPP) in the presence of cyclohexenyl radicals should lead to the formation of the Fe(III)porphyrin–peroxide complex **5**, which, in non-polar environments, is known to undergo an intramolecular decomposition, giving the starting Fe(III) porphyrin–hydroxy complex **6** and the corresponding ketone.[25] Since cyclohex-2-en-1-one represents about 60% of the overall oxidised cyclohexene, we infer that the photocatalytic process occurs to a significant level



Scheme 1 Catalytic cycle for the monooxygenation of cyclohexene by photoexcited Fe(III)(TDCPP) in DTAO micelles.

Table 1 Photooxygenation of alkenes[a]

Substrate	Product	Conc.[b]/μM	Total turnover[c]
Cyclohexene	Cyclohex-2-en-1-one	77	34
	Cyclohex-2-en-1-ol	23	
	Cyclohexene oxide	25	
Cyclooctene	Cyclooctene oxide	40	40

[a] Samples of 3 ml of aqueous solutions containing Fe(III)(TDCPP) (2×10^{-5} M), DTAO (5×10^{-2} M) and the alkene (5×10^{-2} M) were irradiated for 4 h under 1 atm 100% O_2 at 22 ± 1 °C ($\lambda > 350$ nm). [b] Relative error on reported values is 20%. [c] Mol of total oxidised substrate/mol of consumed Fe(III)(TDCPP).

in the non-polar region of the micelles. In the proximity of the polar interface, **5** should undergo a heterolytic cleavage of the O–O bond, with formation of cyclohex-2-en-1-ol as well as of the high-valence iron–oxo–porphyrin complex **7**, which is able to insert directly its oxygen atom in double bonds to yield cyclohexene oxide, regenerating the initial complex **1**.[1,26–28] This statement is confirmed by the observation that cyclohex-2-en-1-ol and cyclohexene oxide are obtained in a 1 : 1 molar ratio. It is of note that some of the reactive iron complex intermediates reported in Scheme 1 resemble those formed during the catalytic cycle of cytochrome P-450, especially the high valence iron–oxo species **7**.[1–4] It is possible that at the end of the cycle, the starting axial ligand Cl^- is replaced by OH^-. This axial ligand, however, is expected to undergo photooxidation to give $OH^\bullet$ radicals able to induce the formation of **3** as well as $Cl^\bullet$.

The above results confirm our previous finding indicating that the control of the reaction environment through the employment of heterogeneous or organized systems can direct the selectivity of hydrocarbon photooxidation process.[13,19,29] In particular, proper conditions have been found here that are connected to the unusual reaction environment inside the DTAO micelles. Therefore, at variance with the above behaviour, photooxidation of cyclohexene by Fe(III)(TDCPP) dissolved in ethanol–cyclohexene (3 : 2, v/v) mixed solvent led to the formation of a mixture of various oxygenation products which, however, did not include the epoxide.[13,30]

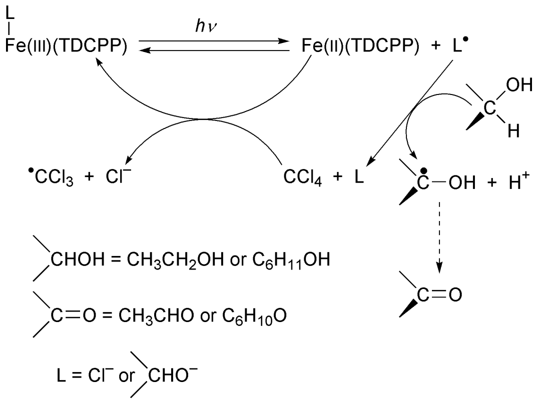
When the DTAO/Fe(III)(TDCPP) system was photoexcited in the presence of cyclooctene, the only oxidation product was the corresponding epoxide (Table 1). These findings are in line with the fact that, in contrast to cyclohexene, cyclooctene is not able to form resonance-stabilised radicals analogous to **3** because ring tensions prevent a coplanar disposition of C=C and a neighbouring radical carbon.[31] Therefore, extraction of the allylic hydrogen atom by $Cl^\bullet$ is not favoured and allylic oxidation products are not formed. In accord with previous work concerning the oxidation of cyclooctene by peroxy radicals,[31] we propose that this alkene gave large proportions of epoxide in the experiment described here *via* addition of the iron peroxo intermediate **4** to its double bond.

Photoreduction of carbon tetrachloride

The ability of photoexcited Fe(III)(TDCPP) to induce the reduction of CCl_4 has been previously demonstrated.[20] This process occurs when the porphyrin complex is irradiated in the near-UV in the mixed solvent ethanol–CCl_4 (2 : 3 v/v) according to eqn. (1)

$$CCl_4 + CH_3CH_2OH \rightarrow CHCl_3 + HCl + CH_3CHO \quad (1)$$

The proposed mechanism for eqn. (1) is summarised in Scheme 2. The primary photochemical act leads to the reduction of Fe(III) to Fe(II) and to the oxidation of the axial ligand L to $L^\bullet$, which, in turn, oxidises CH_3CH_2OH to $CH_3CH^\bullet OH$ and H^+. The iron(II) porphyrin, mimicking the catalytic cycle of cytochrome P450 under anaerobic conditions, is able to reduce the coordinated CCl_4 yielding Cl^- and $^\bullet CCl_3$.[7–12] The two radicals $CH_3CH^\bullet OH$ and $^\bullet CCl_3$ can initiate a chain process leading to the formation of $CHCl_3$, CH_3CHO and HCl with a quantum yield of *ca.* 3×10^{-2}.[20] As described in the following, the employment of DTAO–water micellar solution significantly increases the photochemical efficiency of Fe(III)(TDCPP) and allows the initial concentration of CCl_4 to be reduced and to use the water incompatible $C_6H_{11}OH$ as reducing species.



Scheme 2 Catalytic cycle for the reductive degradation of CCl_4 by photoexcited Fe(III)(TDCPP) in DTAO micelles.

The aqueous system DTAO/Fe(III)(TDCPP) (5×10^{-2} M/ 2×10^{-5} M) in the presence of ethanol (10% v/v) and CCl_4 (2×10^{-2} M) was prepared as described in the Experimental section and irradiated with wavelengths > 350 nm for 4 h. Table 2 shows that ethanol was oxidised to acetaldehyde while CCl_4 underwent a reduction process leading to the formation of Cl^- ion. Some experiments were also carried out with monochromatic light at 365 nm in order to obtain the quantum yield value for the photoreduction of CCl_4, given as the ratio of the number of mol of Cl^- ions to the number of mol of absorbed photons. We calculated a value of $(3 \pm 0.2) \times 10^{-1}$, which, interestingly, was one order of magnitude higher than that previously obtained in an analogous experiment carried out by dissolving the iron porphyrin in the mixed solvent ethanol–CCl_4 (2 : 3 v/v).[20] Finally, the good stability of Fe(III)(TDCPP) inside DTAO micelles is demonstrated by a turnover value, calculated as mol of reduced CCl_4 per mol of consumed porphyrin, of *ca.* 2500.

Table 2 also reports the results obtained when cyclohexanol was used in the place of ethanol for the reduction of CCl_4. This alcohol, almost insoluble in water, must largely reside at the micellar interface. Therefore the microheterogeneous environment is able to maintain high concentrations of cyclohexanol in proximity to the metal centre also when it is dissolved in small amounts, comparable to those of carbon tetrachloride (7×10^{-2} M and 2×10^{-2} M, respectively).

Irradiation of the Fe(TDCPP)DTAO system in the presence of cyclohexanol and CCl_4 induced a catalytic cycle analogous to that already discussed for ethanol (Scheme 2), leading to the formation of cyclohexanone. The photoreduction of CCl_4 to Cl^- was characterized by a quantum yield of $(1 \pm 0.1) \times 10^{-1}$ at 365 nm and a turnover value of 1600. Table 2 shows that the amount of ketone produced was significantly less than that of chloride anion, indicating that CCl_4 may be reduced with the involvement of species other than cyclohexanol. Possible candidates are cyclohexanone and the surfactant aliphatic chains, which may be involved in the radical chain process initiated by $^\bullet CCl_3$ and $L^\bullet$.

In order to investigate deeper into the application perspectives of the described photocatalytic system in water detoxification, we carried out some experiments decreasing the concentration of both DTAO and Fe(TDCPP) by on order of magnitude. Interestingly, irradiation (λ = 365 nm) of aqueous solutions of DTAO (5×10^{-3} M) and Fe(TDCPP) (2.5×10^{-6}

Table 2 Photoreduction of carbon tetrachloride[a]

Electron donor	Detected product	Conc./mM	Turnover[b]
Ethanol (co-solvent, 10% v/v)	Chloride anion Acetaldehyde	16[c] 11[d]	2500 1700
Cyclohexanol (7×10^{-2} M)	Chloride anion Cyclohexanone	5.6[c] 2.4[d]	1600 700

[a] Samples of 3 ml aqueous solutions containing Fe(III)(TDCPP) (2×10^{-5} M), DTAO (5×10^{-2} M), CCl_4 (2×10^{-2} M) and the electron donor were irradiated for 4 h at 22 ± 1 °C (λ > 350 nm). [b] Mol of product/mol of consumed Fe(III)(TDCPP). [c] Relative error on reported values is 5%. [d] Relative error on reported values is 20%.

M) containing cyclohexanol (1.5×10^{-2} M) and CCl_4 (5×10^{-3} M) still led to the reduction of CCl_4 to Cl^- with a quantum yield of $(2.5 \pm 0.2) \times 10^{-2}$, which is the same as that previously obtained in a homogeneous solution of EtOH and CCl_4.

Conclusions and perspectives

We have demonstrated that DTAO micelles are able to host the catalyst Fe(III)(TDCPP) and several organic substrates. In this way, it is possible to realise biomimetic redox processes in aqueous media utilising sunlight and oxygen as clean reagents. Inside the micelles, irradiation induces the homolytic cleavage of the Fe(III)–axial ligand bond as well as the subsequent oxygenation of cyclohexene and cyclooctene. In contrast to what is observed in homogeneous organic solution, both cyclohexene and cyclooctene can be oxidised to the corresponding epoxides, with a selectivity >90% in the case of cyclooctene. On the other hand, the main oxidation product of cyclohexene is cyclohex-2-en-1-one, as expected in the hydrophobic micellar environment inside the micelle core. The Fe(III)(TDCPP)/DTAO photocatalytic system appears to be very promising also in view of obtaining catalytic systems capable of converting small amounts of toxic halogenated alkanes present in water into less dangerous products. In particular, CCl_4 can be reduced either by ethanol or cyclohexanol with high quantum yields ($>10^{-1}$), with good conversion (*ca.* 75% with ethanol) and turnover values (>1500).

Experimental

Materials

Iron(III) *meso*-tetrakis(2,6-dichlorophenyl)porphyrin chloride [Fe(III)(TDCPP)Cl] was kindly supplied by Drs D. Mansuy and P. Battioni of the Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, Ura 400 CNRS Université Paris V. All the solvents were spectroscopic grade products (Fluka). Cyclohexene, cyclooctene, cyclohexanol and carbon tetrachloride were reagent grade and were distilled before use.

N,*N*-Dimethyltetradecylamine *N*-oxide was prepared modifying a literature procedure;[32] 0.1 mol of *N*,*N*-dimethyltetradecylamine (Fluka, purified by vacuum distillation) and 0.15 mol of hydrogen peroxide (35% w/w solution in water by Carlo Erba) were dissolved in 60 ml of ethanol and stirred (room temperature) in a flask for *ca.* 24 h. Addition of 10 mg of MnO_2 destroyed the excess hydrogen peroxide. The solution was filtered and evaporated under vacuum. The obtained crude solid was dissolved in benzene and dehydrated using a Dean–Stark apparatus; the benzene was evaporated under vacuum. The obtained solid was dissolved in methylene chloride, filtered off and evaporated under vacuum. The crude solid was recrystallised twice from acetone and from acetone–diethyl ether, filtered and dried in vacuum over P_4O_{10}. The critical micellar concentration of DTAO, determined by surface tension, is 3.2×10^{-4} M.

Apparatus

Irradiation with wavelengths >350 nm was carried out using a medium-pressure mercury lamp (GR.E 400, Helios Italquartz) and a glass cut-off filter. Irradiation at 365 nm was performed with a 250 W xenon source equipped with a f/3.4 grating monochromator (Applied Photophysics). All photochemical experiments were carried out in a thermostable cell holder at 22 ± 1 °C. UV–VIS spectra were measured with a Kontron Uvikon 940 spectrophotometer and with a Lambda 6 spectrophotometer from Perkin-Elmer equipped with an integrating sphere.

Gas chromatographic analysis were carried out with a DANI 8521-a equipped with a column, packed with Carbowax 20 M 5% on Chromosorb W-AW, and a flame ionization detector.

Potentiometric titrations were performed using an electronic voltmeter AMEL 337 connected to a reference calomel electrode and a working Ag/AgCl electrode.

Procedures

Preparation of the DTAO/Fe(III)(TDCPP) system. Aqueous solutions of DTAO (5×10^{-2} M) and Fe(TDCPP) (2×10^{-5} M) were prepared as follows. Weighted amounts of surfactant and porphyrin were dissolved in CH_2Cl_2. The solvent was allowed to evaporate under stirring and water was added to re-dissolve the two components giving a transparent, liquid, microheterogeneous mixture. The substrates were added directly to the aqueous system in the desired amount. Irradiations were carried out in a 3 ml quartz cell, 1 cm path length (22 ± 1 °C).

Irradiation of de-aerated samples. The aqueous mixture of DTAO and Fe(III)(TDCPP) containing pyridine (4×10^{-2} M) was irradiated ($\lambda > 350$ nm) after de-aeration by four vacuum-line freeze–thaw–pump cycles.

Photooxidation of alkenes. The aqueous system DTAO/Fe(III)(TDCPP) containing cyclohexene or cyclooctene (5×10^{-2} M) was irradiated ($\lambda > 350$ nm) for 4 h under 1 atm of O_2. The degradation of Fe(III)(TDCPP) was followed through the decrease of its Soret band. The photooxidation products were detected by gas chromatographic analysis. Blank experiments in the absence of light or iron porphyrin gave no detectable products.

Photoreduction of CCl_4. Three aqueous systems were irradiated ($\lambda > 350$ nm) for 4 h: (i) DTAO/Fe(III)(TDCPP)/CCl_4/ethanol (5×10^{-2} M/ 2×10^{-5} M/ 2×10^{-2} M/ 10% v/v), (ii) DTAO/Fe(III)(TDCPP)/CCl_4/cyclohexanol (5×10^{-2} M/ 2×10^{-5} M/ 2×10^{-2} M/ 7×10^{-2} M), (iii) DTAO/Fe(III)(TDCPP)/CCl_4/cyclohexanol (5×10^{-3} M/ 2×10^{-6} M/ 5×10^{-3} M/ 1.5×10^{-2} M). Irradiation of the first two systems were carried out in a 3 ml quartz cell, 1 cm path length. By contrast, we were compelled to use a 12 ml quartz cell, 4 cm path length in order to absorb completely the incident light in the experiment carried out in the presence of lower amounts of both DTAO and Fe(III)(TDCPP). After irradiation, the products derived from alcohol oxidation were determined through gas chromatographic analysis. To determine Cl^-, 0.5 ml of the irradiated mixtures (i) and (ii) (diluted to 10 ml) and 10 ml of (iii) were titrated with $AgNO_3$. No reactivity was observed in the absence of light or Fe(III)(TDCPP).

The above described systems were also irradiated with monochromatic light at 365 nm (±2 nm) in order to obtain the quantum yield values for the photoreduction of CCl_4, given as the ratio of the number of mol of Cl^- ions to the number of mol of absorbed photons.

Acknowledgements

This research was supported by MURST (Programmi di ricerca scientifica di rilevante interesse nazionale) and by CNR.

References

1 M. Sono, M. P. Roach, E. D. Coulter and J. H. Dawson, *Chem. Rev.*, 1996, **96**, 2841.
2 D. Dolphin, T. G. Traylor and L. Y. Xie, *Acc. Chem. Res.*, 1997, **30**, 251.
3 P. R. Ortiz de Montellano, in *Cytochrome P-450, Structure, Mechanism and Biochemistry*, Plenum Press, New York, 2nd edn., 1995.
4 B. Meunier, *Chem. Rev.*, 1992, **92**, 1411.
5 D. Mansuy, *Pure Appl. Chem.*, 1990, **62**, 741.
6 P. E. Ellis and J. E. Lyons, *Coord. Chem. Rev.*, 1990, **105**, 181.
7 D. Brault, C. Bizet, P. Morliere, M. Rougee, E. J. Land, R. Santus and A. J. Swallow, *J. Am. Chem. Soc.*, 1980, **102**, 1015.
8 D. Brault and P. Neta, *J. Phys. Chem.*, 1982, **86**, 3405.
9 D. Brault, *Environ. Health Perspect.*, 1985, **64**, 53.
10 D. Mansuy, M. Lange, J. C. Chottard, P. Guerin, P. Morliere, D. Brault and M. Rougee, *J. Chem. Soc. Chem. Commun.*, 1977, 648.
11 D. Mansuy and M. Fontecave, *Biochem. Biophys. Res. Comm.*, 1982, **104**, 1651.
12 D. Mansuy and M. Fontecave, *Biochem. Pharm.*, 1983, **32**, 1871.
13 A. Maldotti, L. Andreotti, A. Molinari and V. Carassiti, *J. Biol. Inorg. Chem.*, 1999, **4**, 154.
14 D. N. Hendrickson, M. G. Kinnaird and K. S. Suslick, *J. Am. Chem. Soc.*, 1987, **109**, 1243.
15 M. W. Peterson, D. S. Rivers and R. M. Richman, *J. Am. Chem. Soc.*, 1985, **107**, 2907.
16 A. Maldotti, C. Bartocci, R. Amadelli, E. Polo, P. Battioni and D. Mansuy, *J. Chem. Soc. Chem. Commun.*, 1991, 1487.
17 L. Weber, R. Hommel, J. Behling, G. Haufe and H. Hennig, *J. Am. Chem. Soc.*, 1994, **116**, 2400.
18 A. Maldotti, C. Bartocci, G. Varani, A. Molinari, P. Battioni and D. Mansuy, *Inorg. Chem.*, 1996, **35**, 1126.
19 A. Maldotti, A. Molinari, L. Andreotti, M. Fogagnolo and R. Amadelli, *Chem. Commun.*, 1998, **4**, 507.
20 C. Bartocci, A. Maldotti, G. Varani, P. Battioni, V. Carassiti and D. Mansuy, *Inorg. Chem.*, 1991, **30**, 1255.
21 A. Maldotti, C. Bartocci, R. Amadelli and V. Carassiti, *J. Chem. Soc., Dalton Trans.*, 1989, 1197.
22 T. G. Traylor and S. Tshuchiya, *Inorg. Chem.*, 1987, **26**, 1338.
23 C. Bartocci, F. Scandola, A. Ferri and V. Carassiti, *J. Am. Chem. Soc.*, 1980, **102**, 7067.
24 J. Sima and J. Makanova, *Coord. Chem. Rev.*, 1997, **160**, 161.
25 R. D. Arasingham, A. L. Balch, C. R. Cornman and L. Latos-Grazynski, *J. Am. Chem. Soc.*, 1989, **111**, 4357.
26 T. G. Traylor and F. Xu, *J. Am. Chem. Soc.*, 1990, **112**, 178.
27 J. T. Groves and Y. Watanabe, *J. Am. Chem. Soc.*, 1988, **110**, 8443.
28 K. Yamaguchi, Y. Watanabe and I. Morishima, *J. Am. Chem. Soc.*, 1993, **115**, 4058.
29 A. Maldotti, R. Amadelli, A. Molinari and V. Carassiti, in *Green Chemistry: Challenging Perspectives*, ed. P. Tundo and P. Anastas, Oxford University Press, New York, 2000, p. 125.
30 A. Maldotti, C. Bartocci, R. Amadelli, G. Varani, E. Polo and V. Carassiti, in *Chemistry and Properties of Biomolecular Systems*, ed. E. Rizzarelli and T. Theophanides, Kluwer Academic Press, Dordrecht, The Netherlands, 1991, p. 103.
31 D. E. Van Sickle, F. R. Mayo and R. M. Arluck, *J. Am. Chem. Soc.*, 1965, **87**, 4824.
32 A. C. Cope and H. H. Lee, *J. Am. Chem. Soc.*, 1957, **79**, 964.

Dechlorination of pentachlorophenol in supercritical carbon dioxide with a zero-valent silver–iron bimetallic mixture

Anwar Kabir and William D. Marshall

Dept. of Food Science and Agricultural Chemistry, Macdonald Campus of McGill, 21,111
Lakeshore Road, Ste-Anne-de-Bellevue, Qué., Canada H9X 3V9.
E-mail: marshall@agradm.lan.mcgill.ca

Received 9th October 2000
First published as an Advance Article on the web 26th January 2001

A continuous stream of pentachlorophenol (PCP, 10–20 mg min^{-1}) in supercritical carbon dioxide (scCO$_2$) was dechlorinated efficiently by a heated column (25 × 1 cm diameter) of a zero-valent silver–iron (Ag^0/Fe^0) bimetallic mixture. Dechlorination efficiencies in successive 10 min fractions of reactor eluate were influenced appreciably by the temperature and pressure within the reactor column(s), the flow rate of the mobile phase and especially by the composition of the feedstock solvent. During 1 h of operation at 450 °C, organically-bound chlorine was liberated, virtually quantitatively, from a 20% (w/v) feedstock stream (0.1 ml min^{-1} merged with 4 ml min^{-1} scCO$_2$), and deposited as chloride ion on the surfaces of the metal particles. Sea sand, maintained under identical conditions, was capable of dechlorinating the substrate only partially (50% loss of the GC peak area for substrate; only partially dechlorinated products). By contrast, the dechlorination was virtually quantitative with the Ag^0/Fe^0 support. There was no evidence of PCP substrate or chlorinated aromatics among the products. In addition to approximately equal quantities of phenol and methylated phenols [*o*-and *m*-cresol; dimethyl- (2,4-, 2,6-, 3,4-, 3,5-, 3,5-dimethyl)phenol and trimethyl-(2,3,6-, 2,4,6-trimethyl)phenol] the remaining 5% of the product mixture consisted of methylated benzenes (*m*- and *p*-xylene, 1,2,4-trimethyl-, pentamethyl- and hexamethyl-benzene). If the feedstock solvent was changed from methanol to propan-2-ol, the product distribution was changed to *ca.* 50% phenol, 36% 1,2,4-trimethylbenzene and the remainder methylated phenols. In extended operation the reactor was run continuously for 14 h without apparent loss of activity provided that the chloride was washed from the Ag^0/Fe^0 metal surfaces at *ca.* 3 h intervals.

Introduction

The abiotic dehalogenation of aromatic organochlorine (OC) toxicants continues to attract a great deal of attention among researchers. A broad array of different techniques have been proposed to accelerate transformation(s) that reduce the number of substituent chlorine atoms on aromatic rings. Many of the methods for the treatment of chlorophenol-containing waters and waste streams are oxidative and include near-critical water oxidation[1,2] wet air oxidation[3,4] and various oxidation processes that use UV photolysis[5–7] and/or Fenton's reagent.[8,9] Yet other approaches have involved the use of ultrasound[10,11] γ-radiolysis,[12] electrochemical oxidation[13] or microwaves.[14] In addition, separation based on catalytic adsorption has also been used.[15]

Catalytic hydroprocessing over hydrogen that mediate the reduction of aryl-chlorine substituents to chloride at relatively low temperatures has been reported with Ni, Pd-, Pt- and Rh-based catalysts.[16–20] The liquid phase catalytic hydrodechlorination of chlorophenols over Pd/C[21] and in the gas phase over Ni^0/Mo^0/Al$_2$O$_3$,[22] Ni^0/ Al$_2$O$_3$[16] and Ni^0/SiO$_2$[23,24] has been assessed. Similarly, steam at high temperature has been used to efficiently dechlorinate aromatic chlorocompounds[25] and in an earlier report,[26] the hydrogenation/hydrogenolysis of phenol was described. Static water-based systems have also been studied with a bimetallic Pd^0/Fe^0 catalyst.[27,28]

Hydrogen treatment of HOArCl$_x$ isomers in the range 423–573 K, yielded phenol as the only appreciable product. Hoke *et al.*, using commercial Pd/C in the presence of base, reported HOAr as the only organic product[21] whereas Chon and Allen[22] recovered benzene and chlorobenzenes from hydrodechlorinations of chlorophenols over NiMo/Al$_2$O$_3$. The benzene ring however, remained intact. Under these conditions, phenol was hydrogenated to cyclohexanol and cyclohexanone with benzene being formed at $T > 523$ K.

Whereas extraction methods can transfer and concentrate target toxicants from one medium to another, they do not detoxify the toxicants *per se*. It would be more efficient to combine the extraction/mobilization of aryl-organochlorine compounds with an *on line* dechlorination step. Such a dechlorination stage that could be combined with an extraction into supercritical carbon dioxide (scCO$_2$) has been reported[29] for polychlorinated biphenyl (Aroclor 1242 and 1248) mixtures.

Green Context

While the destruction of toxic compounds *per se* does not fall under the green chemistry umbrella, we do recognise that chemical detoxification processes are currently necessary and should be subject to the principle of green chemistry. In this paper, the authors describe the use of an environmentally benign solvent and a very efficient bimetallic mixture to optimise the efficiency and minimise the environmental impact of a dechlorination reaction. It is also interesting to read this article alongside the authoritative review on organochlorine compounds and their role in the environment published in a previous issue of this journal (*Green Chem.*, 2000, 2, 173). We cannot and should not consider all organochlorine compounds as being harmful to the environment but we must also recognise that some of these compounds are harmful and must be dealt with by using our greenest technologies.

JHC

DOI: 10.1039/b008122l

With the current report, the dechlorination method is extended to pentachlorophenol (PCP).

Experimental

Chemicals

Sodium dispersion [40% (*w/v*) in oil] was purchased from Alfa Aesar, Ward Hill, MA, acetic anhydride (Ac_2O), ethylene glycol dimethyl ether (1,2-DME), hexane, and silver nitrate were purchased from Fisher Scientific, Ottawa, ON and were used as received. Ag/Fe^0 was prepared from ~40-mesh iron that had been washed copiously with 6 M HCl and rinsed with distilled water. Sufficient aqueous $AgNO_3$ to result in a 2% (w/w) surface coverage of the iron, was added to the aqueous iron suspension that was gently mixed on a rotary evaporator for 12 h. Ag^0/Ni^0 was prepared in similar fashion by reaction of aqueous $AgNO_3$ [sufficient to provide a 2% (w/w) surface coverage] with an aqueous suspension of pre-washed 50–100 mesh nickel granules during 12 h.

Reactor

The dechlorination assembly[29] consisted of source of pressurized $scCO_2$, (Prepmaster, Isco Corporation, Lincoln, NE), a mixing tee and a reactor unit. Target substrate chemical in a suitable solvent, was delivered at 0.1 ml min^{-1} to the mixing tee (1/16" i.d.), merged with a $scCO_2$ stream (*ca.* 4 ml min^{-1}) and fed to one or two stainless steel (ss) HPLC column assemblies [10 mm inner diameter (i.d.) × 25 cm] connected in series, that were filled with test zero-valent metal (or metal mixture) encased in an insulating alumina jacket (fashioned from a thin walled alumina tube (Alfa Aesar, Danvers, MA), that had been cut lengthwise to provide two semi-cylinders). The ss column-alumina jacketed assemblies were heated separately with 80-turn coils of high resistance heating wire that were energized from variable transformers. Pressure within the reactor was maintained with a terminal restrictor made of capillary quartz (25 cm × 0.050 mm) tubing (Chromatographic Specialties, Brockville, ON).

Reactor operation

After a short delay to purge residues of air from the system (during which time only $scCO_2$ was fed to the reactor), feedstock, 0.1 ml min^{-1}, was added continuously *via* the HPLC pump to the $scCO_2$ stream and transported to the reactor. Measurements at the exit of the capillary restrictor indicated a flow rate corresponding to 200–850 ml min^{-1} of decompressed gas. The exit tip of the capillary restrictor was immersed in hexane (25 ml) to trap products from the reactor eluate. Each experiment was continued until five or six consecutive traps had been collected, each corresponding to 30 or 10 min of cumulative trapping of reactor eluate. The course of the dechlorination was monitored by gas chromatography–mass spectrometry (GC–MS) and by titration to measure levels of residual organically bound chlorine in the eluate.

Organically bound chlorine

The general procedure outlined in ref. 30 was followed. Residual organically bound chlorine in the organic trapping solution was determined by titration with standardized $AgNO_3$ (*ca.* 0.01 M). Sodium dispersion, 2 ml, was added to a vigorously stirred 10 ml aliquot of hexane trapping solution that had been further diluted 5-fold with fresh hexane. Methanol, 2 ml, was added dropwise; the reaction was continued for 5 min then quenched by the addition of propan-2-ol (15 ml) followed by 90 ml water. The aqueous phase was diluted to 100 ml in a volumetric flask. A 20 ml aliquot of the reaction mixture was acidified to pH 6–7 with nitric acid (7 M), supplemented with 5 drops of potassium chromate indicator solution then titrated with $AgNO_3$. Blank determinations for chloride in reactor eluate consisted of an identical procedure in the absence of added sodium dispersion.

Gas chromatography–mass spectrometry

GC–MS was performed on an Agilent Technologies model 5890 series II gas chromatograph fitted with a model 5970 mass selective detector. The HP1 capillary column (30 m × 0.25 mm i.d.) was eluted with helium at 0.5 ml min^{-1}. After an initial hold for 2.5 min at 40 °C, the column was ramped, at 25 °C min^{-1}, to 100 °C, held for 1 min, followed by heating to 210 °C at 10 °C min^{-1} and held for a further 1 min prior to cooling. The temperature of the injector and detector were maintained at 250 and 280 °C, respectively. Eluting components were identified tentatively by comparison of experimental mass spectra with spectra catalogued in the National Institute of Standards and Technology (NIST) or Wiley 318 spectral libraries and corroborated by co-chromatography and spectral matching with authentic standards.

Results and discussion

The addition of 0.1 ml methanolic solution to the $scCO_2$ mobile phase is considered to result in a single supercritical phase[31] that possesses attractive features including increased solvent strength while the viscosities and fluidities approach those of supercritical carbon dioxide ($scCO_2$).[32]

The extent of loss of the gas chromatography (GC) peak for pentachlorophenol (PCP) in the reactor eluate was influenced appreciably by the identity of the zero-valent (ZV) metal, by the temperature and pressure within the reactor column(s) and by the composition of the feedstock solvent. As had been observed previously,[29] higher reactor column operating temperatures favoured the dechlorination of PCP. With a single column of zero-valent silver–iron (Ag^0/Fe^0) bimetallic mixture and moderate operating temperature, increasing quantities of PCP were detected in successive trapping solutions. However, at higher operating temperatures, the reaction was more complete and more persistent (shorter range of PCP recoveries) over the six successive traps that constituted each trial (Table 1). At 450 °C, the disappearance of PCP from a 20% (w/v) PCP solution in methanol (fed to the reactor at 0.1 ml min^{-1}) was virtually complete over the course of the 1 h trial.

The dechlorination efficiency (percentage yield), defined as (1 − the ratio of the quantity of organically bound chlorine in the reactor eluate divided by the content of organically bound chlorine in an equivalent quantity of feedstock) × 100, was monitored by argentiometric titration. The dechlorination yields among consecutive 10 min trapping solutions and the range of dechlorination efficiencies (for the six traps) are also recorded in Table 1. Whereas PCP was reacted virtually completely and the reactor could be run for 1 h, residual organically bound chlorine remained in each trap. By connecting two reactor columns in series, the dechlorination became more efficient (Table 2). The flow rate of mobile phase $scCO_2$ also influenced the dechlorination yield (Table 3). Increased mobile phase flow rates that resulted in a decreased contact time of substrate with the metal surface, decreased the dechlorination efficiency somewhat. With 52.4 g of *ca.* 40 mesh Ag^0/Fe^0 bimetallic mixture required to fill the column completely, the void volume was estimated to be < 1 cm^3.

The course of the reaction was probed further by measuring the quantity of chloride that could be extracted from the Ag/Fe bimetallic mixture contained in one column. After continuous reaction of a 20% (w/v) methanolic PCP solution during 1 h (corresponding to the addition of 799.0 mg Cl to the column), the packing material was washed copiously with water. The percentage loss of the PCP peak (GC) and the dechlorination yield (titration) are recorded in Table 4. The combined water washes contained 737 mg of chloride in close agreement with the mean percent dechlorination in the eluate of 94.7% of the organically bound chlorine (corresponding to the release of 757 mg of chloride). The chlorine content of PCP was converted efficiently to chloride and was deposited on the surfaces of the metal particles.

Table 1 Percentage losses of pentachlorophenol (PCP) with the concomitant release of chloride in six sequential trapping solutions collected at the exit during 10 min for a single reactor column containing zero-valent silver–iron bimetallic mixture

Feedstock solvent[a]	PCP in feedstock (%)	Reactor temp/°C	Loss[b] of PCP (%)	Yield of Cl^- [c] (%)
MeOH	5	350	75–96	
MeOH	5	350	77–95	
DGDE	5	400	95–99	88–91
MeOH	10	400	95–100	89–95
Ac_2O–DME (1/8)	10	400	97–100	76–81
IBMK	10	450	89–96	72–85
MeOH	20	450	88–99	96–97
MeOH	20	450	100	91–94
MeOH	20	450	100	93–95

[a] MeOH, methanol; DGDE, diethyleneglycol diethyl ether; Ac_2O, acetic anhydride; DME, ethylene glycol dimethyl ether; IBMK, isobutyl methyl ketone. [b] Percentage loss of PCP in the reactor eluate (as determined by GC) relative to 1 ml (0.1 ml min^{-1} × 10 min) of feedstock. [c] [1 − (ratio of organically bound chlorine in the trapping solution/organically bound chlorine in an equivalent quantity of feedstock)] × 100.

Table 2 Observations with two sequential Fe^0 reactor columns connected in series or a single reactor column for a 20% (w/v) methanolic feedstock delivered, at 0.1 ml min^{-1}, to the reactor maintained at 450 °C under 250 atm of $scCO_2$

	Trap					
	1	2	3	4	5	6
Two columns						
PCP loss[a] (%)	100	100	100	100	100	100
Loss org Cl[b] (%)	98.0	98.0	98.3	98.5	98.5	98.5
One column						
PCP loss[a] (%)	96.9	98.9	99.6	99.3	99.8	99.8
Loss org Cl[b] (%)	92.9	94.3	94.8	95.3	95.3	95.3

[a] Percentage reduction in the gas chromatography peak for PCP. [b] Percentage reduction in the quantity of organically bound chlorine.

Table 3 Influence of the $scCO_2$ flow rate at constant pressure (250 atm) on the percentage reduction in the peak area of pentachlorophenol for a single reactor column of Fe^0 operated at 450 °C

Trial number	Decompressed CO_2 flow rate/ ml min^{-1}	Loss of PCP peak[a] (%)
1	220	96.5–97.8
2	300	94.5–95.8
3	350	92.0–94.5
4	450	89.6–92.0
5	600	87.1–91.0

[a] Range observed for the six sequential traps of reactor eluate that had been collected during 10 min.

To evaluate the magnitude of thermally induced dechlorinations, a companion experiment was conducted using silica (sea sand) to fill the reactor column. With the optimized reaction conditions (450 °C/250 atm, 1.5 ml min^{-1} $scCO_2$), a feedstock of 10% (w/v) PCP in 1,2-DME delivered at 0.1 ml min^{-1} was used to collect six traps of eluate. The resulting chromatograms indicated the loss of *ca.* 50% of the PCP peak area and the formation of 4-chlorophenol, 3,5-dichlorophenol, 2,3,5-trichlorophenol, 2,3,4-trichlorophenol and 2,3,4,5-tetrachlorophenol that comprised the remainder of the products. Only a trace of phenol was detected in any of the eluate solutions. Thus, thermally induced dechlorination is inefficient relative to the action of the Ag^0/Fe^0 particles.

A variety of products were detected by GC–MS (Table 5) from trials using a 15% (w/v) methanolic PCP feedstock. Conditions were as before (0.1 ml min^{-1} feedstock delivered to the reactor at 450 °C/250 atm) except that successive traps were collected during 30 min. In addition to the anticipated phenol (46.9 ± 1.0%), methylated products, principally methylated phenols (47.5 ± 1.5) and methylated benzenes (5.1 ± 0.5%) dominated the remaining products. Table 5 also provides a measure of the levels of repeatability that was achieved in these studies and indicates that 74.6 ± 2.7% of the substrate (mean mass balance) was accounted for among the products. Presumably other products were not detected because they co-eluted from the GC with the solvent.

It was of interest to evaluate the reactor under conditions of extended operation. A further 23 traps were collected during the total of 14 h of continued operation. At selected intervals (2.5 or 3 h), the flow of feedstock was interrupted and the column was washed with 30 ml of water–methanol (1/1) to remove accumulated chloride from the particle surfaces. The reactor column was subsequently dried with $scCO_2$ for 30 min prior to continuing the addition of substrate. Chlorinated product was detected (albeit in low yield) in traps 3–5 of this experiment (Table 5). The results of monitoring the course of the reaction by GC–MS (28 successive traps) are summarized in Table 6. For clarity, the different products have been grouped into methylated phenols, methylated benzenes and chlorinated phenols. Over the course of the extended trial, there were no major differences in the distributions of products [mean percentage phenol in traps 6–28, 54.6 ± 3.9; mean percentage methylated phenols, 42.3 ± 4.4; mean percentage methylated benzenes, 3.1 ± 0.8]. Substrate PCP was not detected in any of the traps and chlorinated phenols (4-chlorophenol and 2,4-dichlorophenol that collectively accounted for a maximum of 0.36–1.26% yield) were detected only intermittently (in traps 3, 4, 5, 16, 17, 20, 21 and 22). Chlorinated products were first detected in trap 3 and increased in concentration in traps 4 and 5 (Table 5). Similar concentrations were detected in traps 15 and 16 and in traps 20, 21 and 22. However, as summarized in Table 6, the appearance of chlorinated phenols among the products was eliminated by the 30 ml methanol–water wash. It is postulated that chloride partially blocked access of the substrate to active sites on the catalyst. The activity of the reactor column apparently was restored completely by this washing procedure. There was no reason why the experiment could not have been prolonged appreciably.

Table 4 Substrate losses and dechlorination yields observed in six sequential traps for a 20% (w/v) methanolic PCP feedstock delivered, at 0.1 ml min^{-1}, to a single Ag^0/Fe^0 column maintained at 450 °C/250 atm

	Trap					
	1	2	3	4	5	6
PCP peak loss (GC) (%)	96.9	98.9	99.6	99.3	99.8	99.8
Dechlorination (titration) (%)	92.9	94.3	94.8	95.3	95.3	95.3

It was also of interest to gain insight into the source of the methyl substituents in the dechlorinated products. Several patents have described the *ortho/para* methylation of phenolic substrates by methanol over metal oxide catalysts at elevated temperature.[33–35] An alternate source of the methyl groups in the products might be the scCO$_2$ mobile phase. Carbon dioxide can be reduced at iron surfaces in the presence of water to form short chain alkanes. Approximately 90% of the products

Table 5 Percentage distributions of products in successive 30-min traps collected at the exit of a single reactor column of silver–iron (2% w/w) bimetallic mixture from a methanolic PCP [15% (w/v)] feedstock delivered to the reactor (450 °C/250 atm) at 0.1 ml min^{-1}

	Trap				
Product	1	2	3	4	5
p-Xylene	1.2	1.3	1.2	1.3	0.9
m-Xylene	1.8	1.7	1.8	1.8	1.6
1,2,4-Trimethylbenzene	N.D.	1.7	1.5	1.8	1.6
Pentamethylbenzene	0.2	N.D.	N.D.	N.D.	N.D.
Hexamethylbenzene	1.3	0.8	0.7	0.7	0.5
Phenol	45.2	46.9	47.5	47.4	47.6
o-Cresol	33.6	31.3	30.7	29.9	30.3
m-Cresol	12.0	12.2	12.3	11.9	12.6
2,6-Dimethylphenol	1.7	1.6	1.6	1.7	1.8
2,4-Dimethylphenol	1.3	1.4	1.4	1.4	1.4
3,4-Dimethylphenol	N.D.	N.D.	N.D.	N.D.	N.D.
3,5-Dimethylphenol	N.D.	0.2	0.3	0.3	0.3
2,4,6-Trimethylphenol	0.8	0.7	0.7	0.5	0.4
2,3,6-Trimethylphenol	0.5	0.4	0.3	0.2	0.2
4-Chlorophenol	N.D.	N.D.	0.5	0.8	1.0
Mass balance	0.706	0.751	0.777	0.761	0.736

	Trap					
Product	1	2	3	4	5	Mean
Methylated phenols	49.9	47.8	47.4	45.9	47.0	47.5 ± 1.5
Phenol	45.2	46.9	47.5	47.4	47.6	46.9 ± 1.0
Methylated benzenes	4.5	5.5	5.2	5.6	4.6	5.1 ± 0.5
Chlorinated phenols	N.D.	N.D.	0.5	0.8	1.0	

Table 6 Percentage distributions of recovered products in 30 min cumulative fractions of reactor eluate either prior to (traps 5, 11, 17, 22 or 28) or post (traps 6, 12, 18 or 23) an on-column wash with 30 ml methanol–water (1 : 1)

	Trap								
Product	5	6	11	12	17	18	22	23	28
Methylated benzenes	4.8	2.6	3.4	3.7	3.8	3.8	3.2	3.0	1.8
Phenol	48.4	47.8	50.2	52.5	58.4	57.0	53.4	40.2	58.8
Methylated phenols	45.9	49.6	46.3	43.8	36.9	39.3	42.2	56.5	39.3
Chlorinated phenols	0.9	N.D.	N.D.	N.D.	1.8	N.D.	1.2	N.D.	N.D.
Mass balance	0.737	0.703	0.761	0.722	0.737	0.738	0.687	0.711	0.702

Table 7 Dechlorination of PCP, 10% (w/v) in propan-2-ol, delivered at 0.1 ml min^{-1}, to a single reactor column of silver–iron (2% w/w) bimetallic mixture maintained at 450 °C/250 atm

	Trap					
	1	2	3	4	5	6
Loss PCP peak (%)	100	100	100	100	100	100
Dechlorination (%)	98.0	98.7	98.7	99.3	99.3	99.3
Phenol/µmol	162	160	168	170	168	167
1,2,4-Trimethylbenzene/µmol	118	120	120	122	120	121
o-Cresol	23	15	22	22	20	22
m-Cresol	17	9	10	14	14	17
2,4-Dimethylphenol	13	9	9	8	8	8
Total mass/µmol	333	313	335	332	330	332
Mass balance	0.887	0.833	0.892	0.884	0.878	0.887

	Trap						
Distribution of products (%)	1	2	3	4	5	6	Mean
Methylated phenols	15.9	10.6	12.3	13.2	13.3	14.1	13.3 ± 1.7
Phenol	48.6	51.1	50.1	51.2	50.9	50.3	50.4 ± 1.0
Methylated benzenes	35.4	38.3	35.8	36.7	36.4	36.4	36.5 ± 1.0
Chlorophenols	N.D.	N.D.	N.D.	N.D.	N.D.	1.6	

consisted of methane.[36] A possible probe might be to use a different solvent to dissolve the substrate PCP. Table 7 records the product distribution when substrate PCP, in propan-2-ol, was delivered to the reactor (450 °C/250 atm) at 0.1 ml min^{-1}. Although there were no differences in the product identities and the mean mass balance over the six traps accounted for 87.7 ± 2.1% of the PCP substrate, the distribution of products were appreciably different from those observed in methanol (Table 5). Whereas phenol accounted for 50.4 ± 1.0% of the products in propan-2-ol, (not appreciably different from the 46.9 ± 1.0% observed in methanol), methylated phenols accounted for only 13.3 ± 1.7% *vs.* 47.5 ± 1.5% in the methanol carrier. The remainder of the products in the propan-2-ol carrier was 1,2,4-trimethylbenzene (36.5 ± 1.0%). Propan-2-ol solvent has been used a source of thermally induced hydrogen radicals and was anticipated to lower the contribution of methyl groups from the solvent. This unanticipated reaction is under investigation.

The ability to influence the selectivity/direction of the reaction would be helpful. The loss of the hydroxyl group from the substrate is considered undesirable as a detoxification route since the lipophilicity of the product is increased and a functional group, that can facilitate metabolic transformations, is lost. Thus, methanol is favoured as a solvent because of the formation of phenol and methylated phenols at the expense of substituted benzenes.

Acknowledgements

Financial support from the Natural Science and Engineering Research Council of Canada is gratefully acknowledged.

References

1 K. C. Shallow and W. R. Killilea, *Environ. Sci. Technol.*, 1992, **26**, 1849.
2 C. A. Eckert, G. W. Leman and H. H. Yang, *Hazard. Mater. Control*, 1990, **3**, 20.
3 M. J. Dietrich, T. L. Randall and P. J. Canney, *Environ. Prog.*, 1985, **4**, 171.
4 H. S. Joglekar, S. D. Samant and J. B. Joashi, *Water Res.*, 1991, **25**, 135.
5 M. Barbeni, C. Minero, E. Pelizzetti, E. Borgarello and N. Serpone, *Chemosphere*, 1987, **16**, 2225.
6 J. M. Tseng and C. P. Huang, *Water Sci. Technol.*, 1991, **23**, 377.
7 S. Vollmuth, A. Zajc and R. Niessner, *Environ. Sci. Technol.*, 1994, **28**, 1145.
8 J. X. Ravikumar and M. D. Gurol, *Environ. Sci. Technol.*, 1994, **28**, 394.
9 T. Viraraghavan and R. Sapach, *Hazard. Ind. Wastes*, 1998, **30**, 775.
10 C. Petrier, M. Micolle, G. Merlin, J. L. Luche and G. Reverdy, *Environ. Sci. Technol.*, 1992, **26**, 1639.
11 N. Gondrexon, V. Renaudin, C. Petrier, P. Boldo, A. Bernis and Y. Gonthier, *Ultrason. Sonochem.*, 1999, **5**, 125.
12 X. Fang, Y. He, J. Liu and J. Wu, *Radiat. Phys. Chem.*, 1998, **53**, 411.
13 J. J. Lee, C. P. Yao, Y. Y. Wang and C. C. Wan, *Environ. Sci. Technol.*, 1992, **26**, 553.
14 R. A. Abramovitch, H. BangZhou, M. Davis and L. Peters, *Chemosphere*, 1998, **37**, 1427.
15 T. G. Danis, T. A. Albanis, D. E. Petrakis and P. J. Pomonis, *Water Res.*, 1998, **32**, 295.
16 A. R. Suzdorf, S. V. Morozov, N. N. Anshits, S. I. Tsiganova and A. G. Anshits, *Catal. Lett.*, 1994, **29**, 49.
17 F. Gioia, E. J. Gallagher and V. J. Famiglietti, *Hazard. Mater.*, 1994, **38**, 277.
18 R. B. Lapierre, L. Guczi, W. L. Kranich and A. H. Weiss, *J. Catal.*, 1978, **52**, 230.
19 B. Coq, G. Ferrat and F. Figueras, *J. Catal.*, 1986, **101**, 434.
20 E. J. Creyghton, M. H. W. Burgers, J. C. Jansen and H. van Bekkum, *Appl. Catal. A*, 1995, **128**, 275.
21 J. B. Hoke, G. A. Gramiccioni and E. N. Balko, *Appl. Catal. B*, 1992, **1**, 285.
22 S. Chon and D. T. Allen, *AIChE J.*, 1991, **37**, 1730.
23 M. A. Keane and E.-J. Shin, *Appl. Catal. B*, 1998, **18**, 241.
24 E.-J. Shin and M. A. Keane, *Catal. Lett.*, 1999, **58**, 141.
25 N. Couté and J. T. Richardson, *Appl. Catal. B*, 2000, **26**, 217.
26 E.-J. Shin and M. A. Keane, *J. Catal.*, 1998, **173**, 450.
27 C. Grittini, Ph.D. Dissertation, Univ. of Arizona, Tucson, AZ, USA; C. Grittini, *Diss. Abstr. Int. B*, 1997, **58**, 1851.
28 C. Grittini, G. A. Romeo Jr., Q. Fernando and N. E. Korte, *Complete Dechlorination of Pentachlorophenol*, Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25–29, ENVR-049, American Chemical Society, Washington, D.C., 1996.
29 Q. Wu, A. Majid and W. D. Marshall, *Green Chem.*, 2000, **2**, 127.
30 M. L. Ware, M. D. Argentine and G. W. Rice, *Anal. Chem.*, 1988, **60**, 383.
31 Y. Cui and S. V. Olesik, *Anal. Chem.*, 1991, **63**, 1812.
32 Q. Sun and S. V. Olesik, *Anal. Chem.*, 1999, **71**, 2139.
33 G. A. Valiullina, L. N. Kishkan, B. M. Khlebnikov, A. P. Krysin, T. G. Egorova and T. F. Titova, *Method of preparing a mixture of 2-methyl-1-naphthol and 2,4-dimethyl-1-naphthol, Russ. Pat. Appl.*, 91-4948001, 19910624, 1991.
34 M. Imanari, M. Inaba and Y. Inui, *Methylated phenols, Jap. Pat. Appl.*, JP 84-147592, 19840718, 1984.
35 K. A. Adey, F. S. Yates and J. H. Young, *Ortho-alkylation of phenols, US Pat. Appl.*, US 83-493407 19830511, 1984.
36 R. W. Gillham and L. I. Hardy, *Environ. Sci. Technol.*, 1996, **57**, 30.

Potassium exchanged zirconium hydrogen phosphate $Zr(O_3POK)_2$: a heterogeneous basic catalyst for Knoevenagel reaction without solvent

David Fildes,[a] Vincent Caignaert,[b] Didier Villemin*[a] and Paul-Alain Jaffrès*[a]

[a] LCMT, UMR, CNRS 6507, Ecole Nationale Supérieure d'Ingénieur de Caen, Université de Caen, ISMRA, 6Bd du Maréchal Juin, F-14050 Caen, France. E-mail: jaffres@ismra.fr
[b] CRISMAT, UMR CNRS 6508 Ecole Nationale Supérieure d'Ingénieur de Caen, Université de Caen, ISMRA, 6Bd du Maréchal Juin, F-14050 Caen, France

Received 16th November 2000
First published as an Advance Article on the web 31st January 2001

A simple work-up to prepare crystalline potassium exchanged zirconium hydrogen phosphate $Zr(O_3POK)_2$ is proposed. In addition the synthesis of amorphous potassium exchanged zirconium hydrogen phosphate $Zr(O_3POK)_2$, obtained from an amorphous sample of $Zr(O_3POH)_2 \cdot H_2O$ is reported. All these exchanged materials $Zr(O_3POK)_2$ are powerful catalysts for the Knoevenagel reaction. Furthermore the absence of solvent increases the rate of the reaction. Products can be separated from the catalyst by sublimation thus avoiding the use of solvent in the purification step. The catalyst, which is thus easily recovered, shows no appreciable loss of activity when recycled three times.

Introduction

The use of heterogeneous catalysts allows a simplification of the purification step to a simple filtration, separating the catalyst from the reaction media. Heterogeneous basic catalysis is an area of growing interest which has been recently reviewed.[1] The structure of inorganic catalysts may be amorphous (silica, alumina) or organised (Al-MCM, zeolite, clay, *etc.*).[2] Even in the latter class of inorganic basic catalysts, their structures are frequently unknown on the atomic scale. This increases the difficulty of characterising the accurate structure of the catalytic centre. Metal–phosphate materials $M(O_3POH)_n$ are a class of compounds that has been widely studied as proton conductors,[3] ionic exchangers,[4] catalysts[5] or as supports for ionic chromatography.[6] The protons of these materials may be exchanged to yield potentially basic materials. Furthermore the structure of these exchanged metal–phosphate materials may be determined at the atomic level. The potassium exchanged zirconium hydrogen phosphate $Zr(O_3POK)_2$ has already been used as a basic catalyst for Michael addition,[7] Henry reaction,[8] cyanosilylation of carbonyl compounds[9] and more recently for the desilylation of phenol silyl ethers.[10] $Zr(O_3POK)_2$, is a layered material which possesses ionic oxygen pointing towards the interlayer space. This compound may be obtained either from zirconium hydrogen phosphate $Zr(O_3POH)_2 \cdot H_2O$ *via* an exchange with potassium hydroxide[7] or directly from a solid-phase synthesis at high temperature.[11]

The Knoevenagel condensation is a useful reaction for the generation of double bonds from a carbonyl compound and an active methylene compound. Many homogeneous catalysts have been used to promote this reaction (triethylamine, pyridine–$TiCl_4$, secondary amines *etc*…).[12] More recently the use of heterogeneous basic catalysts have been employed to facilitate the separation of the catalyst from the reaction media. Furthermore in many cases the catalyst may be reused. Metal oxides supported on silica gel, barium hydroxide, zeolites, montmorillonite, magnesium and aluminium oxides, hydrotalcite,[13] Cs-MCM-41,[14] modified silicagel,[15] and more recently Ga/Al-containing layered double hydroxides[16] are just a few examples of effective materials which may be used for the Knoevenagel condensation. In some cases, the reaction can be achieved under dry conditions thus decreasing both the cost of the synthesis and the amount of waste flow.[17]

Here, a simplification of the literature procedure to synthesise crystalline $Zr(O_3POK)_2$ is reported as well as the synthesis of amorphous samples of $Zr(O_3POK)_2$. The basic properties of these materials are used to catalyse Knoevenagel condensations.

Results and discussion

The synthesis of potassium exchanged zirconium phosphate $Zr(O_3POK)_2$ according to the literature [from $Zr(O_3POH)_2 \cdot H_2O$] is quite laborious as it needs several steps. Nevertheless this method is more convenient for organic chemists, compared to the solid-phase synthesis,[11] since it does not need special equipment (high temperature oven). The first step, as reported in the literature, is to increase the specific surface area of the parent material $Zr(O_3POH)_2 \cdot H_2O$. Exfoliation with *n*-butylamine followed by a reprecipitation leads to an increase in the specific surface of the parent material from 0.5 to 17 $m^2\ g^{-1}$. In order to reduce the number of steps to produce $Zr(O_3POK)_2$ we have utilized crystalline α-zirconium hydrogen phosphate directly in the exchange process. α-Zirconium

Green Context

Heterogeneous basic catalysts are of importance in the fine chemicals area, and several have been investigated in reactions such as the Knoevenagel reaction, an important reaction with pronounced solvent dependency. This paper deals with a simplified preparation of one such catalyst, and shows that it is active in the condensation of aromatic aldehydes with C-acids. Of particular interest is the ability to run the reactions without solvent, and to isolate the products by sublimation, so also avoiding the need for solvents in the purification step.

DJM

hydrogen phosphate $Zr(O_3POH)_2·H_2O$ **1a** was obtained according to a modification of the literature procedure[18] (the BET specific surface area of $Zr(O_3POH)·H_2O$ thus obtained was 7.8 $m^2\ g^{-1}$). In order to produce a large amount of $Zr(O_3POK)_2$ **2a** the concentration of the KOH and KCl solutions in ultra-pure water was dramatically increased (1 M instead of 0.1 M). Thus 8 g of $Zr(O_3POK)_2$ **2a** were produced with a reasonable volume of solution. The X-ray powder diffraction pattern of $Zr(O_3POK)_2$ thus synthesised is compared (Fig. 1) to the structure obtained by Dörffel and Liebertz[11] from a single-crystal X-ray diffraction study. The only notable differences concern the cell parameters which are slightly larger in our study (average 0.18%; see Experimental section). As expected from the crystal structure, a singlet is observed for the ^{31}P MAS NMR spectrum of $Zr(O_3POK)_2$ (Fig. 2) indicating the equivalence of all the phosphorus atoms in the structure and thus demonstrating the efficiency of the exchange. The chemical shift of $Zr(O_3POK)_2$ **2a** is displaced towards low field ($\delta_{iso} = -11.4$ ppm) compared to the parent material $Zr(O_3POH)_2·H_2O$ ($\delta_{iso} = -18.7$ ppm). Previous work describing the high-resolution ^{31}P MAS NMR in some antimony phosphates reported that the ^{31}P chemical shift (δ_{iso}) was closely dependent on the P–O bond length.[19] In compounds which possess a non-coordinated oxygen, the shorter the P–O bond is the larger the shielding effect is on the phosphorus. It is of note that in the present example, that the opposite behavior is observed. Indeed, the P–O bond length (the bond pointing to the interlayer space) in compounds **1a** and **2a** are 1.542 Å[25] and 1.508 Å,[11] respectively. This behaviour could arise from the three P–O bonds connected to zirconium that are longer in compound **2a** (1.548 Å) than in compound **1a** (average: 1.515 Å). The excellent thermal stability of $Zr(O_3POK)_2$ **2a**, which is stable up to 1200 °C as reported earlier,[7] was confirmed by TDA analysis which revealed no transition upto 1000 °C except a transition at 150 °C due to the loss of residual water [Fig. 5(c)]. FTIR analysis [Fig. 6(a)] clearly indicates two P–O stretching vibrations: one at 1174 cm^{-1} arising from the shortest P–O bond (1.508 Å) and one at 976 cm^{-1} which may be attributed to the three P–O bonds with a length of 1.548 Å. It is worth noting that compound **2a** absorbs water from the atmosphere leading to an increase in the broad band at 3450 cm^{-1} thus decreasing the resolution of the two bands at 974 and 1174 cm^{-1}. The two bands at 552 and 614 cm^{-1} disappear in the amorphous sample **2c** supporting the assumption that these two bands correspond to the vibrations of the network that can be observed only in a well organised structure.

The amorphous samples of $Zr(O_3POK)_2$, **2b** and **2c**, were obtained by an exchange process of $Zr(O_3POH)_2·H_2O$ **1b** and **1c** in the presence of KCl and KOH aqueous solutions. Compounds **1b** and **1c** were synthesised by the reaction of $ZrOCl_2·8H_2O$ with H_3PO_4 in water without HF and were obtained, owing to the different conditions of reaction (**1b**: 14 h at reflux; **1c**, 4 h at room temperature), with different specific surface areas (BET), 9 and 226 $m^2\ g^{-1}$, respectively. The specific surface area (BET) of the potassium exchanged material **2b** is 7 $m^2\ g^{-1}$ while that of compound **2c** is dramatically reduced (55.9 $m^2\ g^{-1}$) compared to the specific surface area of the parent material **1c** (226 $m^2\ g^{-1}$). The FTIR spectra of these exchanged amorphous samples [Fig. 6(c)] clearly indicates the bands corresponding to the P–O stretching (950–1180 cm^{-1}). Figs. 3 and 4 show the ^{31}P MAS NMR of the parent materials $Zr(O_3POH)_2·H_2O$ **1b** and **1c** and materials **2b** and **2c** resulting from the exchange of the hydrogen atoms by potassium. In agreement with previous

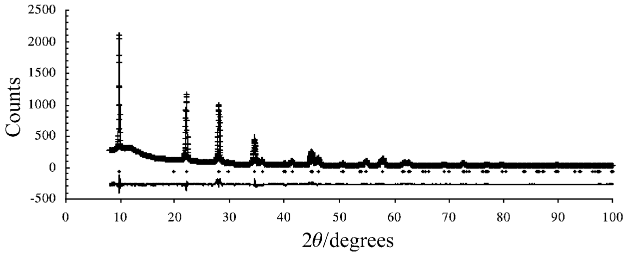


Fig. 1 Calculated (×), observed (—) and difference X-ray profiles for $Zr(O_3POK)_2$. Reflection marks are shown for the $P\bar{3}$ space group.

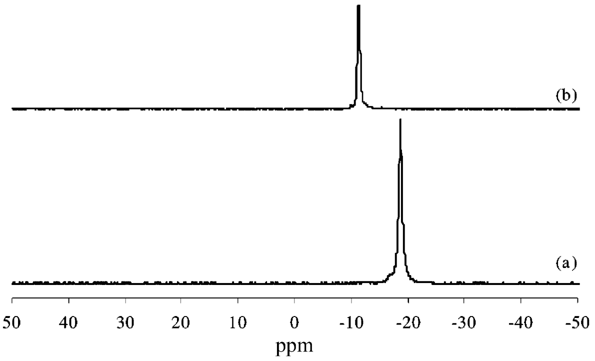


Fig. 2 ^{31}P MAS NMR spectra (12 kHz, NS = 4; d1 = 60 s): (a) $Zr(O_3POH)_2·H_2O$ **1a**: (b) $Zr(O_3POK)_2$ **2a**.

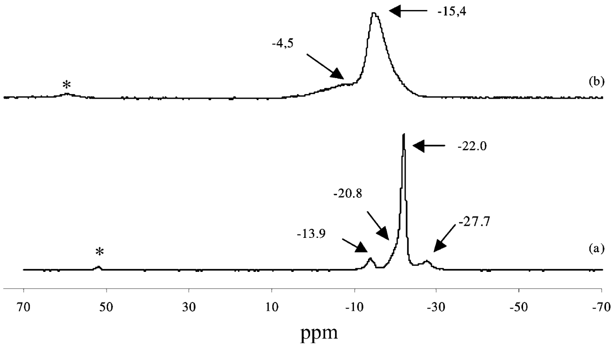


Fig. 3 ^{31}P MAS NMR spectra (12 kHz): (a) $Zr(O_3POH)_2·H_2O$ **1b**; (b) $Zr(O_3POK)_2$ **2b** (peaks marked with * are rotation bands).

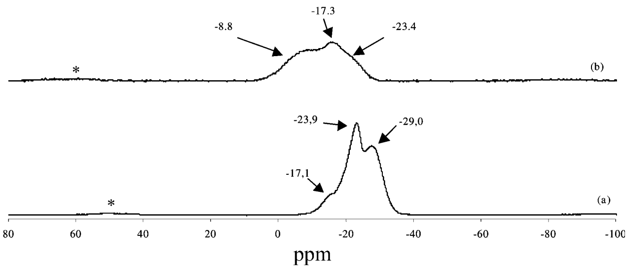


Fig. 4 ^{31}P MAS NMR spectra (12 kHz): (a) $Zr(O_3POH)_2·H_2O$ **1c**; (b) $Zr(O_3POK)_2$ **2c** (peaks marked with * are rotation bands).

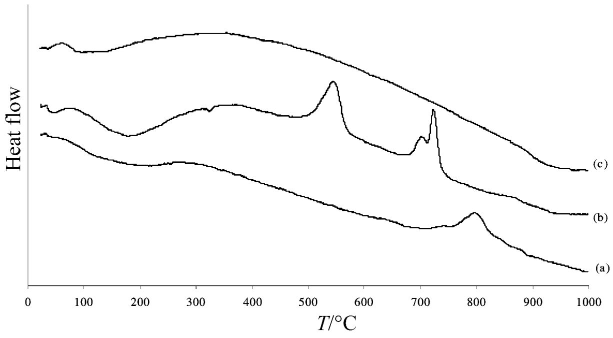


Fig. 5 DTA analyses under argon (heating rate: 10 °C min^{-1}): (a) compound **2c**; (b) compound **2b**; (c) compound **2a**.

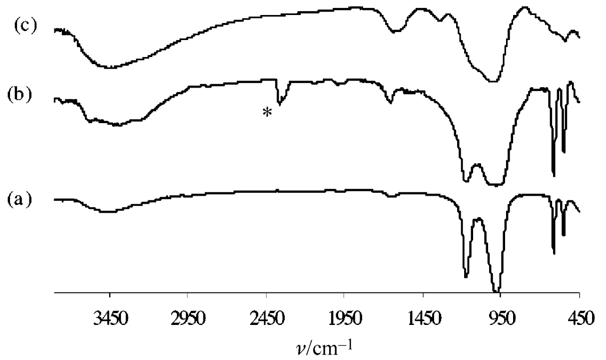


Fig. 6 FTIR spectra of $Zr(O_3POK)_2$ in KBr: (a) anhydrous crystalline sample **2a**; (b) wet crystalline sample **2a** (sample left in an open flask for 1 month); (c) anhydrous amorphous sample **2c** (peak marked as * is an artefact due to the presence of CO_2).

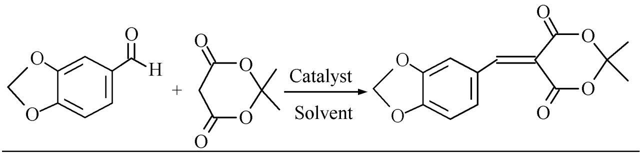
work,[20] the amorphous samples of $Zr(O_3POH)_2{\cdot}H_2O$ **1b** and **1c** show several signals while the crystalline sample simply shows a singlet (Fig. 2). Both the relative intensities of the signals and the specific surface area depend on the advancement of the crystallisation. The chemical shifts of the exchanged compounds **2b** and **2c** are displaced towards lower field as found for the crystalline sample **2a** (Fig. 2) indicating the efficiency of the exchange.

Thermal analysis of these two amorphous exchanged materials **2b** and **2c** (DTA) reveals an endothermic transition from 80 to 250 °C which is due to the loss of residual water [Fig. 5(a) and 5(b)]. Two (740 and 795 °C) and three (545, 701 and 722 °C) exothermic transitions, respectively are observed for compounds **2c** [Fig. 5(a)] and **2b** [Fig. 5(b)]. Partial hydrogen exchange in compound **2b** could explain its thermal behaviour. Indeed, the first transition (545 °C) could be attributed to the condensation of phosphate groups into pyrophosphates as was previously reported for the non-exchanged materials $Zr(O_3POH)_2$ (transition observed at 550 °C[20]). The two transitions observed for compounds **2b** (701 and 722 °C) and **2c** (740 and 795 °C), that have almost the same relative intensity, could arise from the same transformation. These transitions were previously reported for a copper salt intercalated in α-zirconium phosphate.[21] The different position of these transitions could arise from a partial exchange in compound **2b**. Furthermore the absence of a transition around 550 °C for compound **2c** indicates a fully exchanged material.

$Zr(O_3POK)_2$ was first tested as a basic catalyst for the Knoevenagel condensation of piperonal and Meldrum's acid. According to the kinetic data obtained using the amorphous catalyst **2b** (Table 1, entries 1 and 3), THF was the best solvent while the use of ethanol (Table 1, entry 5) inhibited the reaction. The superiority of THF over CH_2Cl_2 may be explained by the fact that Knovenagel condensation produces one mol of water per mol of product. Owing to the non-miscibility of water and dichlorormethane and taking into account the polar character of the catalyst, water produced by this condensation could be readily localised on the catalyst when dichloromethane is used as a solvent. Thus the efficiency of the catalyst could be affected. Nevertheless, when the reaction is carried out without solvent the reaction time is even shorter (Table 1, entries 7 and 9). Noteworthy is that the reaction times and yields are identical whatever the structure (amorphous or crystalline) of the catalyst used for the reaction (Table 1, entries 2 and 4). This is the first example of the use of amorphous potassium exchanged zirconium phosphate as a basic catalyst. In absence of solvent a total conversion is reached after only 14 minutes. Interestingly, no difference (yield, reaction times) was observed by the use of microwave heating or classical heating (isomantle). Nevertheless for the expediancy of the procedure, microwave heating (commercial microwave oven Whirlpool) was chosen. The powder X-ray diffraction of the catalyst after the condensation of piperonal with Meldrum's acid, and before the elimination of the product, did not reveal any modifications of the d_{001} peak (9.02 Å), indicating that neither the substrate nor the product are present in the interlayer space. This observation indicates that the catalytic process is only located on the surface of the catalyst. Nevertheless the kinetics of the Knoevenagel condensation of piperonal with Meldrum's acid (experiments carried out in THF, Table 1 entries 2–4) did not show any significant difference between catalysts **2a**, **2b** and **2c** despite their different specific surface areas.

Taking into account the fact that reactions carried out without solvent contribute to a reduction in costs and waste flow it is of note that all the following reactions were achieved without solvent. The mixing step of the catalyst with substrates can affect the reproducibility of the results. The first method, which is completely solvent-free, is to mechanically mix for the catalyst with the substrates for several minutes. The second method is less laborious and consists of dissolving the substrates in a minimum of solvent followed by the addition of this solution to the catalyst. Finally the solvent is removed *in vacuo* leading to the substrates being absorbed on the catalyst. Although the results of these two methods were identical, we chose the second method due to the rapidity of the work up. Selected data corresponding to the condensation of piperonal with different active methylene compounds are reported in Table 2. The mechanism of the Knoevenagel condensation (under basic conditions) is that one proton from the acidic methylene compound is removed by the base to generate a nucleophile that will react with the aldehyde. In view of the results of Table 2, it appears that the catalyst **2a** is efficient for methylene compounds which possess a pK_a (determined in water) in the range 4–12. Surprisingly, the use of tetronic acid as the methylenic acid compound (Table 2, entry 6 ; pK_a = 3.76) does not yield the condensation product. Despite the coloration of the catalyst almost all the piperonal is recovered; this coloration might be due to the auto-condensation of tetronic acid. Despite the lack of reactivity of tetronic acid it is worth mentioning that other methods are able to catalyse the aldol type condensation of tetronic acid with aldehyde in a 1 : 1[22] or 2 : 1[23] ratio. On the other hand, catalysts **2a** are not sufficiently basic to be efficient when methylenic compounds possessing a pK_a > 13 are used. To illustrate the reusability of the catalyst, catalyst **2a** was engaged three times in the condensation of piperonal with Meldrum's acid (Table 3). After each reaction the product was separated from the catalyst by sublimation. After three cycles the catalyst was still efficient as reported in Table 3.

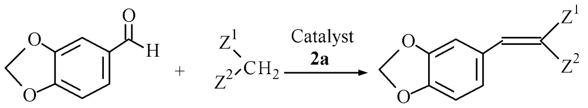
Table 1 Knoevenagel condensation of piperonal to Meldrum's acid

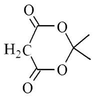
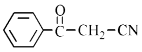
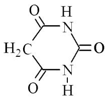
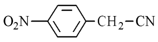
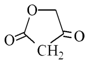


Entry	mg (Catalyst)	Solvent	Temp./°C	Time	Conversion[a] (%)
1	400 (**2b**)	CH_2Cl_2	39	10.5 h	100
2	400 (**2a**)	THF	66	4 ± 1 h	100
3	400 (**2b**)	THF	66	4 ± 1 h	100
4	400 (**2c**)	THF	66	4 ± 1 h	100
5	400 (**2b**)	EtOH	78	2 days	0
6	200 (**2a**)	None	M.W.[b]	7 × 2 min[c]	>98
7	200 (**2b**)	None	M.W.[b]	7 × 2 min[c]	>98
8	200 (**2c**)	None	M.W.[b]	7 × 2 min[c]	>98
9	200 (**2b**)	None	Δ[d]	14 min[e]	>98

[a] Determined by CPG. [b] Irradiation in an open flask. [c] After each heating cycle, the solid was mixed. [d] An open flask was placed in an isomantle. [e] The solid was mixed regularly (every 2 min).

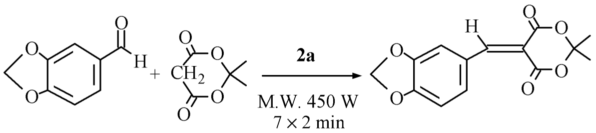
Table 2 Condensation of piperonal to methylene acid compounds using microwave heating (450 W, 7 × 2 min)



Entry	$Z^1Z^2CH_2$	pK_a[30]	Mp/°C of product (lit.)	Yield (%) (lit.)
1		4.83	179 (178.5–179.5[29])	100^a(93)
2	NC–CH$_2$–CN	11.2	199 (199–200[31])	100^a(80)
3		> 9	137 (138[32])	97^a(—)
4		4.0	> 260 (270[33])	85^a(85)
5		> 12	None	0^b
6		3.76	None	0^b

[a] Isolated yield. [b] Determined by CPG.

Table 3 Illustration of the reusability of catalyst **2a**



Number of reaction	Yield (%)
1	100
2	98
3	95

Conclusion

The present article deals with the simplification of the synthesis of crystalline potassium exchanged zirconium hydrogen phosphate **2a**. Furthermore the synthesis of the amorphous equivalent of compound **2a** is described. The basic properties of these materials, which are readily available in large amounts, were used to catalyse the Knoevenagel condensation. Interestingly, both amorphous and crystalline potassium exchanged zirconium hydrogen phosphate are able to catalyse the Knoevenagel reaction. These catalysts are efficient for methylenic compounds possessing pK_a values in the range of 4–12. It is noteworthy the efficiency of these catalysts is increased by the absence of solvent. The yields reported and the reaction times are identical to or better than those previously reported. Furthermore the catalyst is easily recovered and can be reused without significant loss of its efficiency.

Experimental

Catalyst preparation

α-Zr(O_3POH)$_2$·H_2O 1a. A modification of the method of slow decomposition of a zirconium fluoro complex was used.[24] 8.2 ml of 40% aqueous HF solution (188 mmol) was added to a solution of $ZrOCl_2\cdot8H_2O$ (15.01 g, 46.6 mmol) in 217 ml of ultra-pure water placed in a 1 l round bottomed-flask fitted with an air condenser. 75% aqueous H_3PO_4 (163.3 ml; 1.97 mol) was added to this solution. The homogeneous solution was heated at 90–95 °C for 7 days. The precipitate was recovered by filtration, washed with ultra-pure water (150 ml), acetone (20 ml) and dried at room temperature for 48 h. According to powder X-ray diffraction, the structure of the product is in excellent agreement with literature data.[25] ^{31}P MAS NMR (12 KHz; d1 = 60 s; NS = 4): −18.7 ppm (lit.,[26] −18.7 ppm); BET surface area 7.8 m^2 g^{-1} (lit.,[27] 0.5 m^2 g^{-1}).

Amorphous zirconium phosphate Zr(O_3POH)$_2$·H_2O 1b. The literature procedure[28] was modified as follows: a solution of $ZrOCl_2\cdot8H_2O$ (10 g, 31 mmol) in water (55 ml) was added to a solution of 85% aqueous H_3PO_4 (7.15 g; 62 mmol) in 30 ml of water. The solution was refluxed for 14 h, the solid filtered off, and washed with ultra-pure water (50 ml), acetone (20 ml) and dried at 100 °C for 5 h to yield a white solid (9.3 g; 100%). The specific surface area (BET) of the resulting compound was 9.0 m^2 g^{-1}.

Amorphous zirconium phosphate Zr(O_3POH)$_2$·H_2O 1c. The literature procedure[25] was modified as follows: a solution of $ZrOCl_2\cdot8H_2O$ (10 g, 31 mmol) in water (55 ml) was added to a solution of 85% aqueous H_3PO_4 (7.15 g; 62 mmol) in water (30 ml). The solution was stirred at room temperature for 4 h, the solid filtered off, and washed with ultra-pure water (50 ml) and acetone (20 ml) and then dried at 100 °C for 10 h to yield a white solid (9.3 g; 100%). The specific surface area (BET) of the resulting compound was 226.0 m^2 g^{-1}.

Crystalline potassium exchanged zirconium phosphate Zr(O_3POK)$_2$ 2a. A modification of the method described by Costantino *et al.*[7] was used: 50 ml of KOH (1 M in ultra pure water) and 50 ml of KCl (1 M in ultra pure water) was added to 6.9 g of crystalline α-Zr(O_3POH)$_2$·H_2O **1a** (21.6 mmol). After 24 h of slow stirring KCl (7 ml; 1 M) and KOH (7 ml; 1 M) were added. The heterogeneous solution was stirred for a further 6 days. The precipitate was filtered off, washed with potassium hydrogenphosphate (20 ml; 1 M in ultra pure water) and dried at room temperature for 2 days. The product was dried further at 190 °C for 24 h to yield 7.75 g of white solid (100%). The specific surface area (BET) of the product was 11.0 m^2 g^{-1}. ^{31}P MAS NMR (12 kHz ; d1 = 60s ; NS = 4) δ_{iso} = −11.3 ppm; powder X-ray diffraction (see Fig. 1): trigonal, space group $P\bar{3}$ a = 5.188(9) [lit.,[11] a = b = 5.176(1)], c = 9.022(2) [lit.,[11] c = 9.012(8)], number of reflections: 162; GOF = 1.7, R_p = 0.067; R_{Wp} = 0.093; R_I = 0.08.

Amorphous potassium exchanged zirconium phosphate Zr(O_3POK)$_2$ 2b and 2c. The same procedure described for compound **2a** was used. The starting compounds were **1b** and **1c**, respectively. The specific surface area of the exchanged materials **2b** and **2c** were 7.0 and 55.9 m^2 g^{-1}, respectively.

Knoevenagel condensations

In a typical experiment 200 mg of compound **2a** were added to a solution of piperonal (75 mg; 5 mmol) and Meldrum's acid (72 mg ; 5 mmol) in dichloromethane (2 ml) placed in a 100 ml round bottomed flask. The solvent was removed under reduced pressure. The round bottomed flask was placed in a microwave oven (Whirlpool, M430, Jet 900) and irradiated (450 W) for a total of 14 min and in 2 min intervals. After cooling, the crude product was purified by sublimation (10 mTorr, isomantle at a temperature between 180 and 220 °C) to give 5-(3,4-methylenedioxyphenyl)methylene-2,2-dimethyl[1,3]dioxane-4,6-dione (0.14 g; 100%). mp 179 °C (lit.,[29] 178.5–179.5 °C). The results of other experiments are summarised in Table 2.

Acknowledgements

We thank Valérie Montouillout and Christian Fernandez (Laboratoire de Catalyse et Spectroscopie, L.C.S. UMR CNRS 6506) for assistance in the solid-state NMR experiments.

References

1 J. M. Fraile, J. I. Garcia and J. A. Mayoral, *Catal. Today*, 2000, **57**, 3.
2 A. Corma, *Chem. Rev.*, 1997, **97**, 2373.
3 G. Alberti, M. Casciola, S. Cavalaglio and R. Vivani, *Solid State Ionics*, 1999, **125**, 91.
4 A. Clearfield, *Chem. Rev.*, 1988, **88**, 125.
5 A. Clearfield and D.S. Thakur, *Appl. Catal.*, 1986, **26**, 1.
6 L. Maya, *J. Inorg. Nucl. Chem.*, 1981, **43**, 400.
7 U. Costantino, F. Marmottini, M. Curini and O. Rosati, *Catal. Lett.*, 1993, **22**, 333.
8 U. Costantino, M. Curini, F. Marmottini, O. Rosati and E. Pisani, *Chem. Lett.*, 1994, 2215.
9 M. Curini, F. Epifano, M.C. Marcotullio, O. Rosati and M. Rossi, *Synlett*, 1999, 315.
10 M. Curini, F. Epifano, M.C. Marcotullio, O. Rosati, M. Rossi and A. Tsadjout, *Synth. Commun.*, 2000, **30**, 3181.
11 M. Dörffel and J. Liebertz, *Z. Kristallogr.*, 1990, **193**, 155.
12 L. F. Tietze and U. Beifuss, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 2, p. 341.
13 A. Corma, S. Iborra, J. Primo and F. Rey, *Appl. Catal.*, 1994, **114**, 215.
14 K. R. Kloestra and H. Van Bekkum, *J. Chem. Soc., Chem. Commun.*, 1995, 1005.
15 P. M. Price, J. H. Clark and D. J. Macquarrie, *J. Chem. Soc., Dalton Trans.*, 2000, 101.
16 I. Rousselot, C. Taviot-Guého and J. P. Besse, *Int. J. Inorg. Mater.*, 1999, 165.
17 D. Villemin, *Chem. Ind.*, 1983, 478.
18 G. Alberti and E. Torracca, *J. Inorg. Nucl. Chem.*, 1968, **30**, 317.
19 F. Taulelle, C. Sanchez, J. Livage, A. Lachgard and Y. Piffard, *J. Phys. Chem. Solids*, 1988, **49**, 299.
20 H. Benhamza, P. Barboux, A. Bouhaouss, F.-A. Josien and J. Livage, *J. Mater. Chem.*, 1991, **1**, 681.
21 C. Ferragia, A. La Ginestra, M. A. Massucci, P. Cafarelli and R. Di Rocco, *J. Therm. Anal.*, 1994, **41**, 1469.
22 H. Zimmer, W. W. Hillstrom, J. C. Schmidt, P. D. Seemuth and R. Vögeli, *J. Org. Chem.*, 1978, **43**, 1541; D. Villemin and B. Labiad, *Synth. Commun.*, 1990, **20**, 3207.
23 L. Wolff and C. Schwabe, *Justus Liebigs Ann. Chem.*, 1896, **291**, 231; N. Olthoff, R. Huttenrauch and H. Brauniger, *Z. Chem.*, 1970, **10**, 341.
24 G. Alberti and E. Torracca, *J. Inorg. Nucl. Chem.*, 1968, **30**, 317.
25 A. Clearfield and G. D. Smith, *Inorg. Chem.*, 1969, **8**, 431.
26 N. J. Clayden, *J. Chem. Soc., Dalton Trans.*, 1987, 1877.
27 U. Costantino, F. Marmottini, M. Curini and O. Rosati, *Catal. Lett.*, 1993, **22**, 333.
28 A. Clearfield, A. Oskarsson and C. Oskarsson, *Ion Exch. Membr.*, 1972, **1**, 91.
29 G. A. Kraus and M. E. Krolski, *J. Org. Chem.*, 1986, **51**, 3347.
30 H. F. Ebel, *CH-Acidität*, (Houben-Weyl), Georg Thieme Verlag, Stuttgart, 1970, vol. 13/1, p. 31.
31 B. B. Corson and R. W. Staughton, *J. Am. Chem. Soc.*, 1928, **50**, 2829.
32 Kauffmann, *Chem. Ber.*, 1919, 1435.
33 D. Villemin and B. Labiad, *Synth. Commun.*, 1990, 3333.