Looking forward to 2003

In the recent International Assessment of University Research in Chemistry in the UK, Green and Sustainable Chemistry was highlighted as a "far reaching opportunity for chemistry" and one where "active involvement of chemistry in environmental and sustainable technologies is crucially important societally" (see http://www.epsrc.ac.uk)

The assessment was carried out by an international panel of experts and it is pleasing to see yet another endorsement of the importance of applying the principles of green chemistry to all aspects of the chemical sciences. The panel also noted that the establishment of the journal *Green Chemistry* by the RSC was a useful step. We can be justifiably proud of the recognition of this journal which was also evident in the excellent 2002 impact factor of 2.6 and a large increase in the number of manuscripts received (more than double that in 2000).

The panel also noted the good work of the UK's main green chemistry networking and technology transfer organisation, the Green Chemistry Network (GCN) (http://www.chemsoc.org/gcn) and the CRYSTAL Faraday partnership (http://www.crystal.org) respectively. The success of these organisations is a further indication of the progress we have made in the years since the pioneering work of Joe Breen and Paul Anastas set the scene for the green chemistry revolution. Much of the good work in green chemistry started with the establishment of the Green Chemistry Institute (GCI) in the USA in 1997. The GCI is now a partnership with the American Chemical Society with the goal of "working today to prevent pollution tomorrow through chemistry research and education". The GCI is now under the directorship of Dr Dennis Hjeresen and we hope to publish an update on their activities in a later issue.

The GCI and the GCN have organised and supported several successful green chemistry related symposia in recent years and a highlight of 2003 will be the first international conference on green and sustainable chemistry organised by their sister organisation in Japan, the Green and Sustainable Chemistry Network. This major event is being run in co-operation with a number of organisations around the world including the GCI, the GCN and the Centre for Green Chemistry in Australia. We can look forward to reading papers from this conference in this journal.

We have made progress in the five years since Joe Breen set up the GCI but we cannot afford to be complacent! As the international assessment panel has pointed out "…there is no country that can be said to have a broad, vigorous community in academic chemistry that is focussed on management and reduction of pollution and waste." It is vital that we engage some of the most able academic research groups. It is equally important their efforts are integrated through multidisciplinary and collaborative research involving multiple departments and universities as well as across national boundaries. We intend to promote this in *Green Chemistry* through the publication of the highest quality research including the work of multidisciplinary and multi-organisational groups.

I wish you all a prosperous and successful 2003 and I look forward to seeing a continued increase in the quality and quantity of articles submitted to *Green Chemistry*.

James Clark
York
Scientific Editor, *Green Chemistry*

DOI: 10.1039/b300498h

EDITORIAL

Phenomenal growth, but technology keeps *Green Chemistry* at the cutting edge

Green Chemistry enters its fifth year of publication, with confidence in the science it is currently publishing and optimism for even better quality material in the future. The number of articles received in 2002 was a new all-time high (Fig. 1), and the journal continues to grow in size. All issues in 2002 were the maximum size this type of binding would allow, thus in 2003 *Green Chemistry* will have a spine allowing greater flexibility. However, this increase in size has not been allowed to affect our impressively quick publication times which still average less than four months from receipt (Fig. 2).

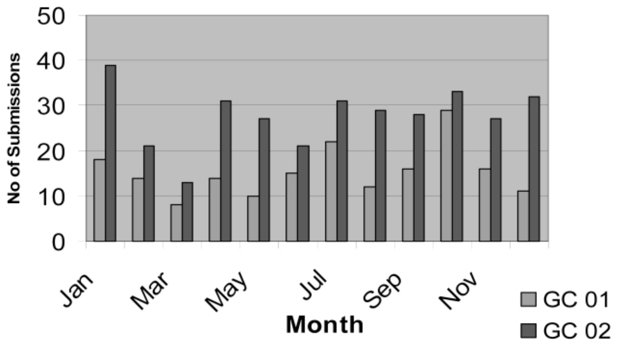


Fig. 1 **Green Chemistry** ***submissions 2002 vs. 2001.***

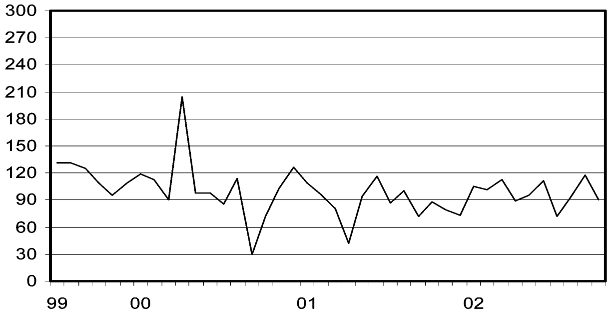


Fig. 2 **Green Chemistry** ***receipt to publication times (t(50%)/days).***

I would like to express my thanks to all *Green Chemistry* Board Members on both the Editorial and Advisory Boards as they play a crucial role in promoting *Green Chemistry* across the globe, in supptimerorting the journal with high quality submissions from their own groups, and in the refereeing and adjudication of articles submitted by others. There are a number of developments, some new, which *Green Chemistry* readers should be aware of as follows:

1. Electronic publishing continues to grow in impact, and *Green Chemistry* continues to be at the forefront of such developments. Electronic files of papers can now be uploaded directly onto our web site at www.rsc.org/submissions.
2. Abstracts of all *Green Chemistry* papers have been freely available on the web since mid-2002 and access to online *Green Chemistry* papers is now **free to all just two years after publication**.
3. E-mail alerts now include direct links to articles—please sign up at http://www.rsc.org/is/journals/current/ej_update_form.htm to take advantage of this service.
4. Access to the electronic form of any RSC print journal comes free with a 2003 institutional subscription, while those institutional subscribers who wish to receive just the electronic version can now subscribe and save 10%. One institutional print subscription, or online-only subscription, allows site-wide access to the electronic version of that journal at no further cost.
5. Users of RSC journals online can now benefit from a new Reference Linking facility. This citation linking backbone is a collaborative reference linking service that allows a user to click on a citation and be taken directly to the target content. Facilities include: free access to the Chemical Abstracts Service abstract for the reference *via* ChemPort (http://www.chemport.org) and links to the full text of the reference, where available online, on the publisher's server (a subscription or pay-per-view may be required to access the article), *via* CrossRef. Future enhancements will include a mechanism to purchase a printed copy of the cited article *via* the RSC Library and Information Centre's Document Delivery Service and links to other resources.
6. Where a primary article contains chemical biology, it will be available free of charge for one month following publication in an issue through the Chemical Biology Virtual Journal (www.rsc.org/chemicalbiology). This provides an easy-to-use point of access to chemical biology literature in all RSC publications.

Finally, I would like to express my sincere thanks and gratitude to everyone who has reviewed material for *Green Chemistry* in 2002 and responded so magnificently to allow us to maintain the fastest publication times in this sector. The reputation of the journal and, ultimately its success or failure is dependent on the reports provided by dedicated reviewers. Thus, their input cannot be underestimated. We continue to expand our database of reviewers and hope to lighten the load, a little, for many reviewers in 2003.

As always, Editorial Board members and staff welcome suggestions as to how the journal might be improved or enhanced further. I wish you all every success in 2003.

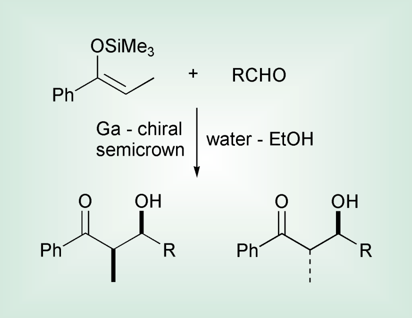
Harp Minhas
Managing Editor, *Green Chemistry*

Highlights

Duncan Macquarrie highlights some of the recent literature in green chemistry

Lewis acids

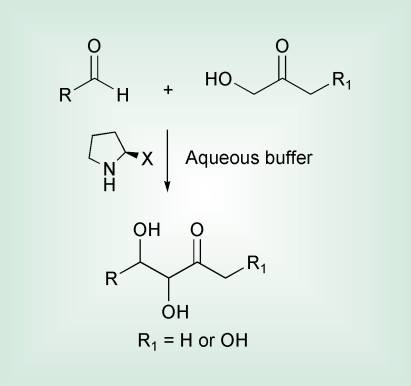
Lewis acids capable of functioning in aqueous environments are interesting as potentially recoverable and reusable Lewis acids, in contrast to the more traditional metal halides which are very prone to hydrolysis. Thus lanthanides have been widely researched in the last few years, since they function well in aqueous and protic environments. Chao-Jun Li from Tulane University, USA, and colleagues at the Chinese Academy of Science in Beijing have now shown that a chiral gallium complex can function as an efficient enantioselective catalyst in aqueous ethanol (*Chem. Commun.*, 2002, 2994).



They found that the complex shown was an efficient catalyst for the Mukaiyama aldol reaction, giving high yields, good *syn*/*anti* selectivities and very good enantioselectivities under mild conditions and reasonable times. While several metal centres were of similar activity, gallium was the only one which afforded enantioselectivity.

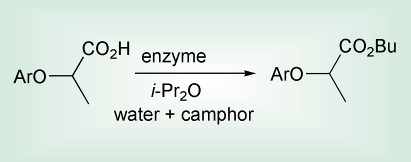
Aldol reactions

A further aqueous system for the aldol reaction has been uncovered by Carlos F Barbar III and his groups at the Scripps Institute, USA (*Chem. Commun.*, 2002, 3024). They have found that cyclic amines such as L-proline are excellent catalysts for the aldol condensation of acetone and several aldehydes, especially in a phosphate buffered system. In aqueous systems no diastereoselectivity or enantioselectivity were noted; diastereoselectivity was found in DMSO as solvent. In many cases yields were very high and conditions were mild. Interestingly, the authors propose that this system might represent a prebiotic route to sugars.



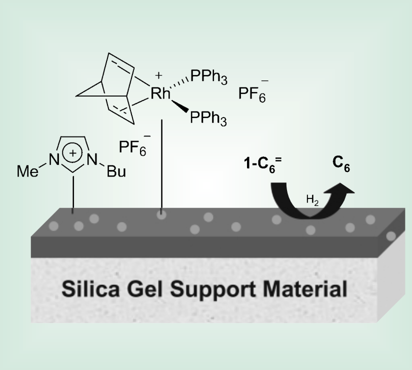
Enzyme-catalysed reactions

Enzyme-catalysed reactions are attractive options for many reactions. However, enantioselectivity is often disappointingly low, and strategies to improve this are being investigated. One approach is the use of a chiral additive in small amounts—this can sometimes have a substantial impact on selectivity. A paper from Shin-ichi Ueji and colleagues at Kobe University, Japan, now shows that two additives can be much better than one (*Bull. Chem. Soc. Japan.*, 2002, **75**, 2239). They found that the enantioselectivity obtained in the esterification of phenoxypropanoic acids with 1-butanol could be improved to some extent (85–90%) by the addition of camphor; water had a similar effect (85–91%). By adding both water and camphor, the enantioselectivity jumped to 96%.



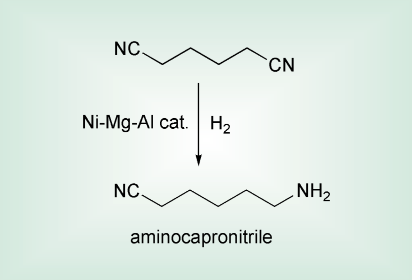
Supported aqueous phase catalysis

Supported aqueous phase catalysis (SAP) was put forward as a novel mode of heterogeneous catalysis by Mark Davis over a decade ago. Now Christian Mehnert and colleagues from ExxonMobil in Annandale, USA, have extended the concept to supported ionic liquid phases on a silica gel support (*Chem. Commun.*, 2002, 3010). They have immobilised a layer of an ionic liquid onto a silica and used it as a host for a Rh catalyst. This approach led to a catalyst which was significantly more active that an equivalent homogeneous system, and which could also be used in fixed bed reactors. Catalyst stability was excellent, with no loss of Rh being found, and 18 runs with the same catalyst proved consistency over several cycles.



Nylon

Alternative routes for the production of nylon include the use of aminocapronitrile as a precursor to caprolactam. There is considerable industrial effort in this area, and catalysts for the tricky partial hydrogenation of adiponitrile to aminocapronitrile are sought. Bernard Coq and his team at the CNRS in Montpellier, France, have recently published details of a Ni–Mg–Al hydrotalcite catalyst which displays very good selectivity at relatively high conversions (*e.g.* 66% selectivity at 70% conversion) (*J. Catal.*, 2002, **211**, 511).



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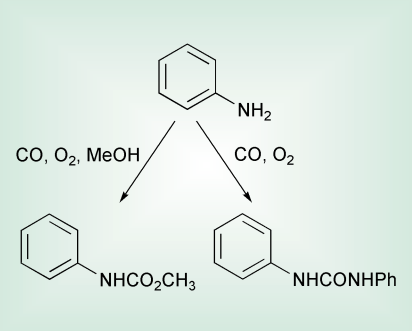
This is attributed to the combination of the faster desorption from the catalyst surface which reduces over-hydrogenation and the catalysts ability to maintain intact the very small Ni assemblies found—the formation over time of larger Ni assemblies is known to lead to deleterious side reactions in many systems.

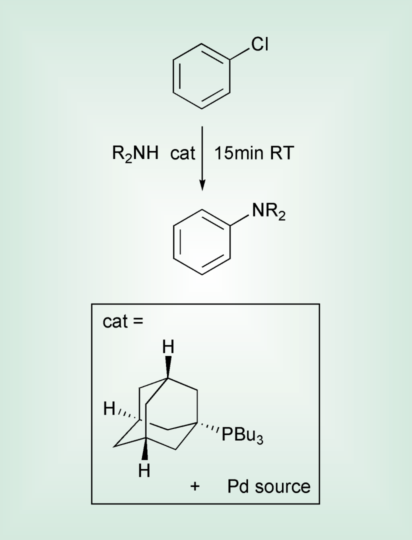
Carbamates

Carbamates are very important intermediates in many reactions systems, and a clean synthesis of this class of compounds would obviate the use of dangerous reagents such as phosgene in many processes. Feng Shi and Youquan Deng from the Centre for Green Chemistry at the Chinese Academy of Sciences in Langzhou have now demonstrated that the oxidative carbonylation of anilines is indeed possible and can be applied to the synthesis of carbamates from anilines, CO, oxygen and methanol in high yields and excellent selectivity (*J. Catal.*, 2002, **211**, 548). Their catalyst is a gold species immobilised on an ion-exchange polymer. The system can also be utilised in the related conversion of an aniline to a symmetrical urea.



Aromatic halide couplings

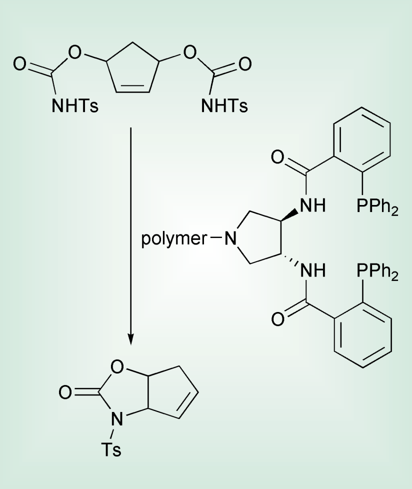
The coupling of aromatic halides with amines and aryl boronic acids is a highly active field. The search for an effective catalyst which will work under mild conditions with aryl chlorides is still ongoing. A remarkably active system has just been disclosed by John Hartwig and his group at Yale University, USA (*Angew. Chem. Int. Ed.*, 2002, **41**, 4746). They have found that the air stable complexes of Pd with bulky phosphines such as alkyl di-*t*-butyl phosphane are capable of the coupling of a range of aryl chlorides with amines in 15 min at room temperature and catalyst levels of 0.5mol%. Excellent yields were obtained.



The system was also extremely active for the Suzuki coupling of *o,o*-disubstituted aryl bromides.

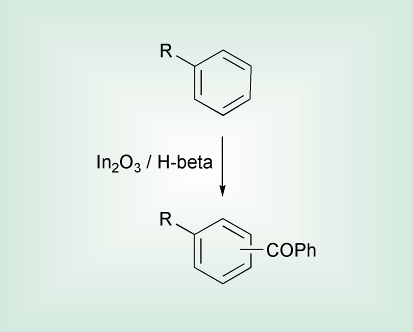
Asymmetric allylic alkylation

Barry Trost and his team at Stanford, USA, have published details of a study on the development of a highly efficient polymer-bound palladium complex for the asymmetric allylic alkylation reaction (*Angew. Chem., Int. Ed.*, 2002, **41**, 4691). They have supported the ligand system shown above on a variety of polymeric backbones using different linkers, and found that a combination of ArgoGel and an amide-linked ligand system. With this catalyst, excellent ee's were obtained in THF at high conversions. Recycling was also effective with the catalyst performing constantly over four cycles.



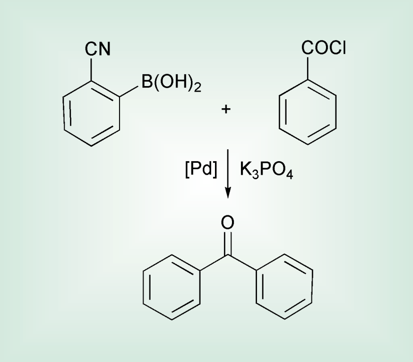
Friedel–Crafts reactions

The Friedel–Crafts reaction of unactivated aromatics with alkylating agents and, less commonly, with acylating agents is an area of intense activity. While the alkylation is relatively facile (with selectivity being the main issue) the acylation of unactivated aromatics remains a major challenge. A contribution to this field has been made by researchers at the National Chemical Laboratory in Pune, India, and at RMIT University in Melbourne, Australia, led by V. R. Choudary (*Microp. Mesop. Mater.*, 2003, **57**, 21). They have found that indium oxide-doped H-beta is a very active catalyst for the acylation of toluene and similar aromatics with benzoyl chloride. While the amount of catalyst was relatively high (*ca.* 35 wt%), the activity was impressive (80% conversion of benzoyl chloride in 1 h at 80 °C in the reaction with toluene) and the alkyl aromatics reacted almost as rapidly as anisole. A trace of moisture was found to be beneficial.



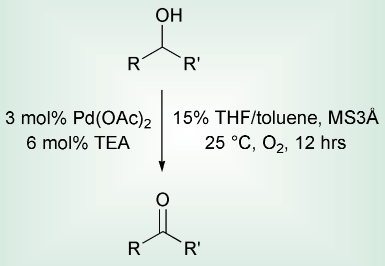
Aromatic ketones

An alternative route to aromatic ketones (which is applicable to electron-poor aromatics) has been investigated by Yoshio Urawa and Katsuyuki Ogura (*Tetrahedron Lett.*, 2003, **44**, 271). They have shown that Pd-catalysed coupling of acyl halides with aryl boronic acids can be readily achieved in excellent yield using toluene and hydrated potassium phosphate as base. Reaction times are relatively short and yields are high.



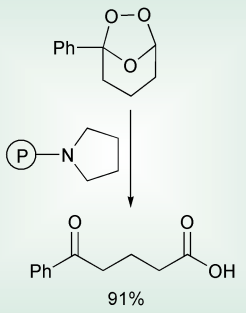
Oxidations

Oxidation of molecules using clean oxidants is still a challenge. A contribution to this field has been published by Matthew Sigman and co-workers from the University of Utah, USA (*Chem. Commun.*, 2002, 3034). They have shown that oxygen will oxidise primary and secondary alcohols to aldehydes or ketones at room temperature with palladium acetate and a small amount of a base such as triethylamine. They show that a range of alcohols can be easily oxidised under these very mild conditions to the ketone in very good yield. The mixed solvent system of THF and toluene is perhaps not ideal from a green perspective, but the implication is that THF could be used, giving excellent yields but taking longer to complete.



Ozonolysis

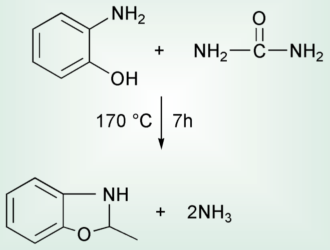
Ozonolysis is a potentially clean route to carbonyl compounds, especially from symmetrical or cyclic alkenes. However, the usual drawback is the reduction of the ozonide formed, often requiring O-acceptors such as phosphines and sulfides in stoichiometric amounts (although Pd/H_2 is a very attractive option giving very low residual peroxide levels). An alternative method has been published by Yung-Son Hon from the National Chung Cheng University and Kun-Chan Wu of the Academia Sinica, China (*Tetrahedron*, 2003, **59**, 493), they have shown that treatment of the ozonide with a polymer supported tertiary amine can give very good yields of the carbonyl compound. The polymer can be successfully regenerated and reused at least four times.



Greening the manufacture of pesticides for developing countries

R. J. Krupadam, a scientist based at the National Environmental Engineering Research Institute in Nagpur in India (email rkjoshua@rediffmail.com) and Y. Anjaneyulu and K. Babu Rao, based at the Centre for Environment at the Jawaharlal Nehru Technological University in Hyderabad, also in India, discuss

The manufacture of the pesticide phosalone for use in developing countries involves the reaction of *o*-aminophenol with urea to form benzoxazolone and ammonia as a key step in the process:



In a typical factory manufacturing 10 tons per day, 7000 l of effluent are produced which contain *ca*. 500 kg of ammonia.

Aeration is used as a common method for removal of dissolved gases in wastewater. Ammonium ions in wastewater exist in equilibrium with ammonia. As the pH of wastewater is increased above 7, the equilibrium is shifted to the left and the ammonium ion is converted to ammonia, which may be removed as a gas by agitating the wastewater in the presence of air. With a view to utilizing the ammonia present in the liquid effluents of the phosalone process, it has been shown that it is possible to recover it as a value-added byproduct. It was observed that the recovery of ammonia is accomplished in a steam stripper column. It is thus possible to make 25% solutions of aqueous ammonia, which is used for indigenous purposes and also offered on the open market.

The process (Fig. 1) is performed in the temperature range of 80–120 °C. The liquid effluent containing ammonia after pH adjustment by sodium hydroxide solution (25%) is transported to a steam stripper column. The top vapour consisting of ammonia, water and organic impurities is cooled down by a partial condenser. In this condenser most of the water and organic impurities are condensed while crude ammonia vapour leaves the condenser. The condensate passes through a separator and the top

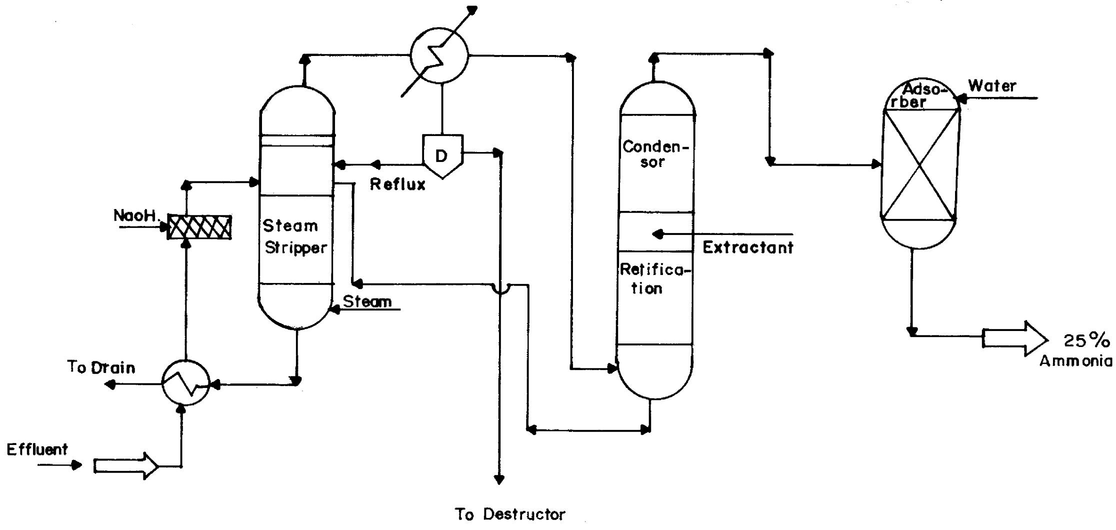


Fig. 1 Set-up for ammonia recovery.

Table 1 Ammonia recovery / treatment effluent pollution characteristics.

			Final ammonia solution					
S.No	Qty. of Effluent (L)	Initial Assay (%)	Initial COD (mg/L)	Qty. (L)	Density (g/mL)	Assay (%)	COD (mg/L)	Cost of NH_3/ ton Effluent Rs.
1	286	7.01	6000	80	0.896	25.0	5000	2237
2	1500	7.20	7500	424	0.895	25.2	5200	2261
3	1500	7.20	7600	421	0.893	25.4	5100	2245
4	1500	7.1	7800	418	0.893	25.3	5200	2229

layer, comprising organic fluid is sent to a destructor (incinerator). The bottom layer is a mixture of water and ammonia, and is recirculated into the steam stripped column.

The crude ammonia vapour leaving the condenser is sent to a rectification column containing a condenser and is cooled to below 0 °C. The ammonia vapour condenses in the top condenser and is then re-circulated in the column in order to remove impurities. When pure ammonia is needed, a small amount of a suitable extractant such as toluene is dosed into the rectification column. This helps in removing impurities which tend to form azeotropes with ammonia. It also helps in extracting organic impurities from the ammonia vapour.

The top vapour leaving the column is purified ammonia and this is absorbed to make 25% aqueous ammonia solution. The bottom product emerging from the rectification column consists of extractant organic impurities and traces of ammonia which is recirculated into the top of the steam stripper.

The recovered aqueous ammonia solution (25%) is utilized for indigenous purposes. It is used in making the ammonium salt of *O*,*O*-diethyl phosphoric acid which is an important intermediate in producing phosalone and ethion products. Highly satisfactory results are achieved by using the ammonia salt of such pesticides in place of sodium salts.

The ammonium output is analyzed by both chemical and ion-selective electrode methods and reproducible results are obtained by using both methods.

The process enables the production of ammonia with a high degree of purity from effluents contaminated with volatile and non-volatile organic impurities. Typical results are given in the Table 1.

Furthermore in the actual manufacturing process by introducing the reflux column BDB as shown in Fig. 1, the non-ammonical COD is significantly reduced by introducing an extra partial condensor where the phenolic compounds will be also separated. The recovered ammonia (25%) is suitable for integrated ammonia based pesticides manufacturing in the plant.

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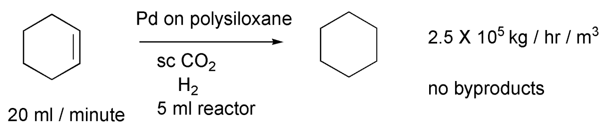
Some recent trends and problems in green chemistry

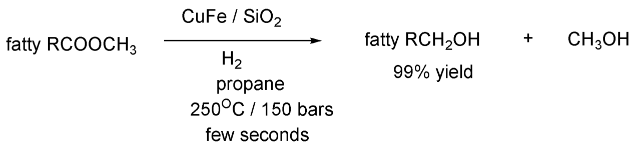
Albert Matlack has been one of the pioneers in green chemistry education and his book Introduction to *Green Chemistry* (reviewed on the Green Chemistry website) was based on a one semester course at the senior-graduate level interface. Here he critically considers some of the recent developments in green chemistry and some possibilities for improvements especially in areas of solvent replacement, intensive processing, electrochemical synthesis, and catalysis

Green chemistry is coming of age with interest in it increasing in both academic and industrial laboratories.[1] Progress has been made in the search for processes that use fewer toxic chemicals and produce less waste while using less energy. However, many challenges remain in the shift to a sustainable future.[2]

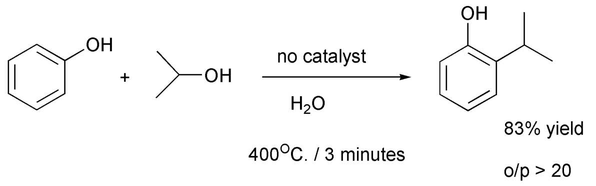
The elimination of toxic and / or flammable organic solvents continues to be an area of intense interest.[3] A wide variety of reactions have been run in sc carbon dioxide,[4] including enzymatic ones. This medium is now being used commercially for the polymerization of tetrafluoroethylene by DuPont, dry cleaning of clothes, cleaning of semiconductor chips, hydrogenations and the extraction of caffeine from coffee. It offers promise for non-aqueous dyeing of textiles and the preparation of fine particles.[5] Cheap polyethercarbonates[6] might be used instead of the earlier fluorinated surfactants to bring other uses closer to commercialization.

The rates of hydrogenations are limited by the low solubility of hydrogen in the usual solvents. Much higher rates can be obtained in supercritical fluids in which hydrogen is miscible. The first example uses sc carbon dioxide[7] and the second uses sc propane.[8] The work-up in the second reaction consisted of flashing off the hydrogen, propane and methanol.

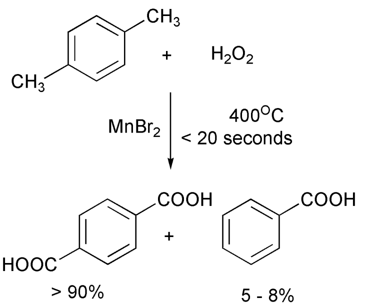



$$\text{fatty RCOOCH}_3 \xrightarrow[\text{H}_2\text{, propane, 250°C / 150 bars, few seconds}]{\text{CuFe / SiO}_2} \text{fatty RCH}_2\text{OH} + \text{CH}_3\text{OH}$$

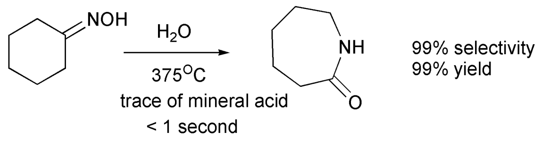
Supercritical water (with a critical temperature of 374 °C.) is too hot for many organic compounds to be stable. Batch reactions with sc water have usually led to mediocre yields and poor selectivity, but recent reactions in sc water with short contact times have been more successful. Phenol has been alkylated with isopropyl alcohol in three minutes in 83% yield.[9]



Terephthalic acid has been produced by the oxidation of *p*-xylene in > 90% yield in < 20 seconds in a continuous process.[10]



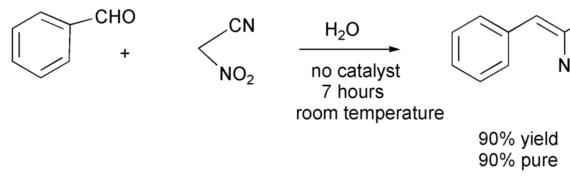
Caprolactam has been made from cyclohexanone oxime in sc water containing a trace of sulfuric acid with 99% selectivity using a continuous flow microreactor in 0.7 second.[11]



The limitation on the use of supercritical fluids is that they require equipment for use at 2000 p.s.i. or more. Many labs may not be set up for this.

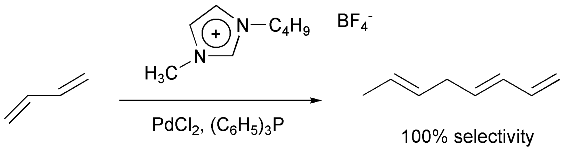
It should be possible to run many more reactions in water at lower temperatures, especially if hydrotropic agents such as sodium xylenesulfonates or cyclodextrins are used to solubilize the organic compounds, or if surfactants are used to form emulsions. Recently, starch, gum arabic and glucosamine have been used to solubilize carbon nanotubes in water.[12] Some Knoevenagel reactions have been run in water without catalyst.[13] The work-up consisted of filtration of the product after cooling to 0 °C. The filtrate could be used again in additional runs, the

DOI: 10.1039/b300501c

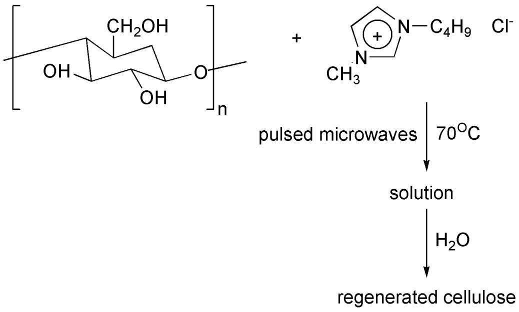


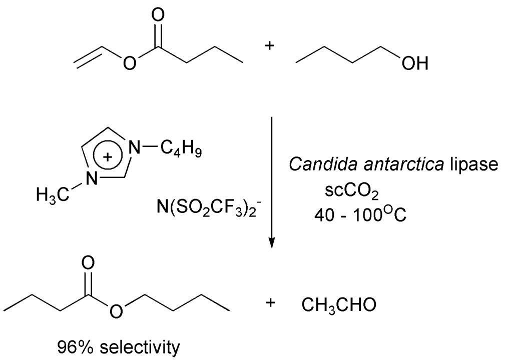
yield being the same as in the first and fifth runs. The product could be recrystallized from ethanol (a benign solvent).

Ionic liquids are being tested as media for a wide variety of reactions.[14] In some cases, the organic product can be recovered as a separate layer. However, in far too many cases, workers resort to solvents such as ethyl ether or methylene chloride to recover the product, which obviates the advantage of the ionic liquid as a replacement for an organic solvent.



Sometimes the addition of carbon dioxide can promote separation or the product may be removed by vacuum distillation.[15] Two recent results are important: The first is the ability to dissolve cellulose in an ionic liquid and to then run reactions on it.[16]

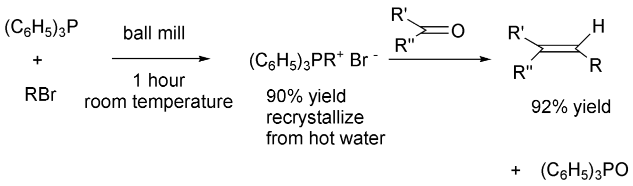




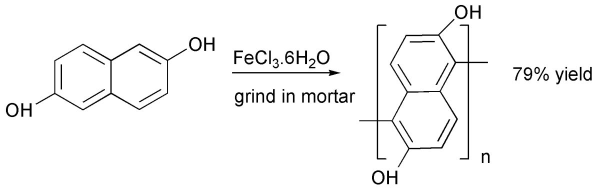
The second combines an ionic liquid with sc carbon dioxide in an enzymatic esterification in which the enzyme is more stable thermally than it is in water.[17] The substrate and the product are in the sc carbon dioxide layer and the enzyme is in the ionic liquid.

The big questions are about the cost and toxicity of ionic liquids. These will vary depending on the structure and the anion. Quaternary ammonium salts used now as bactericides, fabric softeners, hair conditioners and detergents are neither too expensive nor too toxic for general use. For most structures, the LD50 is 100–5000 mg/kg.[18] In addition, almost no material is too expensive to use if none is lost and there is a simple method to recycle it for reuse, *e.g.* the rhodium catalyst in the hydroformylation of propylene.

More reactions should be run without solvent in the gas, liquid or solid phases, but only after testing by thermal analysis to see how exothermic they are. Just grinding the reactants together has worked well in some cases. High yields of olefins from the Wittig reaction have been obtained by grinding the reactants in ball mills.[19]



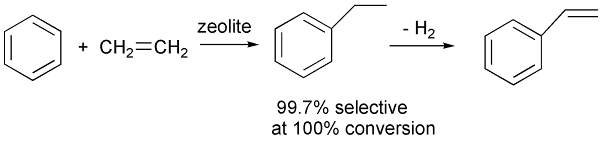
Grinding in a ball mill with iron(III) chloride hexahydrate converted 2,5-napthalenediol to a polymer that cannot be made by a comparable reaction in solution.[20]



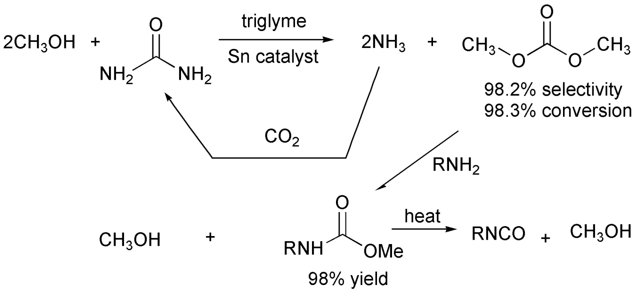
While grinding to perform reactions in the laboratory is not common, grinding is done on a huge scale in the processing of mineral ores prior to benefication.

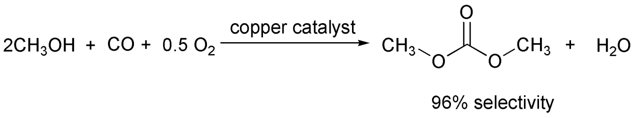
The vast majority of the reactions that are run without solvent, and are called green, are worked up with solvents such as ethyl ether and methylene chloride. This means that a plant employing such a process still has to handle toxic and/or flammable solvents as well as recycle them. There is an urgent need to study nonsolvent work-ups by means such as vacuum distillation, membrane separations, extraction with hot water (with or without hydrotropic reagents), melt recrystallisation *etc*—or at least shift to more benign solvents.

Yields and purity can often be increased by separating products continuously as they are formed. A variety of techniques are available for this, including reactive distillation, continuous extractions, membrane reactors, biphasic reactions, adsorption, crystallizing out as formed and nanoreactors such as zeolites or other molecular sieves. These methods can shift equilibria, and avoid further reaction, isomerization or decomposition. Short contact times in continuous flowing systems are often useful. In a typical reactive distillation, benzene and ethylene are passed into a vertical column of a solid acid catalyst. Any ethylbenzene that forms drops into the pot below, with 99.7% selectivity at 100% conversion in the reaction.



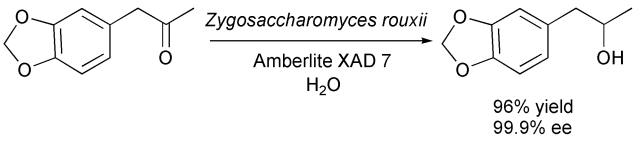
In similar processes, benzene can be alkylated by propylene with 99.6% selectivity and methyl tert-butyl ether can be produced from isobutylene with methanol with nearly 100% selectivity. Dimethyl carbonate can be prepared from urea with 98.2% selectivity.



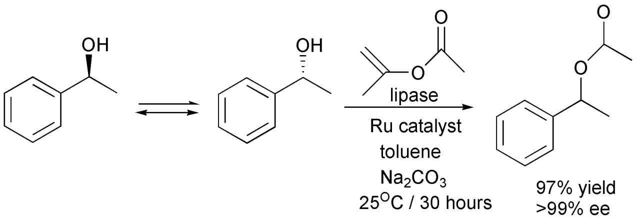


Dimethyl carbonate can be reacted with amines to produce methylcarbamates which can be pyrolyzed to isocyanates. The ammonia and methanol side products can both be recycled, so that the total sequence from urea to isocyanate uses only the amine and carbon dioxide and produces water as the only useable byproduct. The sequence uses carbon dioxide instead of the toxic carbon monoxide. It should be possible to reduce toxicity further by substituting ethanol for methanol in the synthesis.

The reduction below is possible only because the inhibition of the yeast by the starting material and the product is removed by adsorbing both on a resin:

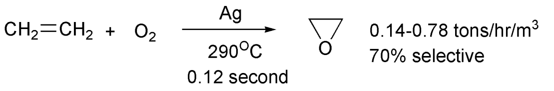


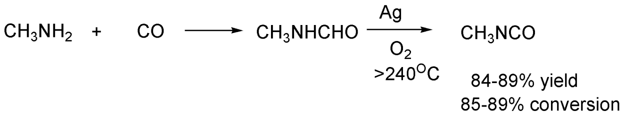
The maximum yield in the resolution of a racemate is 50%. However, an increasing number of resolutions which achieve higher yields by *in situ* racemization of the unwanted isomer are being done. The following example uses a ruthenium catalyst for the racemization:[21]



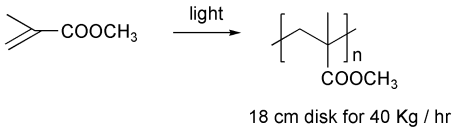
The techniques for separating a product as formed should be tried in any case where an initial product can react a second time. They should be tried in a reaction where % selectivity declines with increasing % conversion. For example, they might increase yields in the reaction of ethylene oxide with water or ammonia and in the base-catalyzed self condensation of acetone. Reactive distillation should be tried in the reaction of isobutane with butenes using solid acid catalysts.

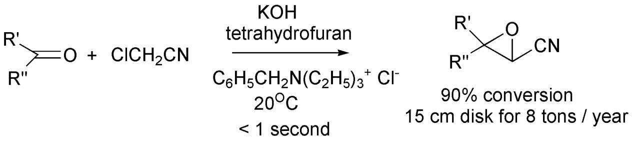
Process intensification offers the prospects of higher yields and purities with less capital expense and smaller plants.[22] Problems of scale-up, heat transfer, mass transfer and safety are reduced greatly in these continuous flow systems. The techniques include microreactors with channels, spinning disc reactors, spinning tube in tube reactors, use of microwaves, extruders with or without ultrasound or microwaves and hydrogenation in sc carbon dioxide. Channeled microreactors have been used in the preparation of ethylene oxide[23] and in the synthesis of methyl isocyanate.





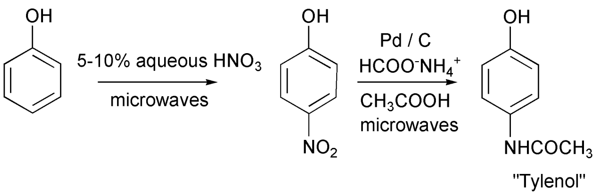
Spinning disc reactors, in which the reagents drop on to a disc spinning at several hundred r.p.m., have been used for the polymerization of methyl methacrylate[24] and in a Darzens Reaction.[25] In the second reaction, the reaction time was reduced by 99.9%, the inventory by 99% and the impurity level by 93%.

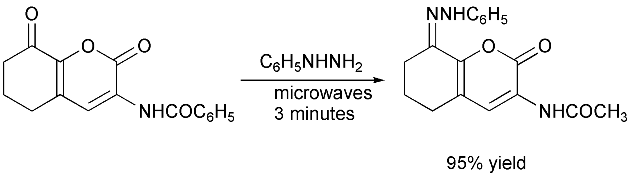




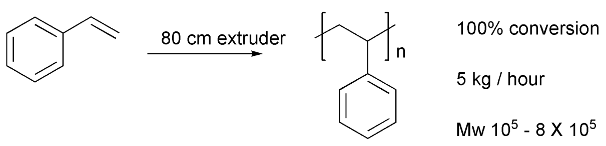
The spinning tube in tube reactor of Holl Technologies consists of a rotor spinning at 3000 r.p.m. inside a stator with an annular gap of 0.25–1.5 mm. which ensures excellent mixing of reagents.[6] Sizes vary from desktop units that can process pounds per day to one about 15 feet long that can handle a ton per hour.

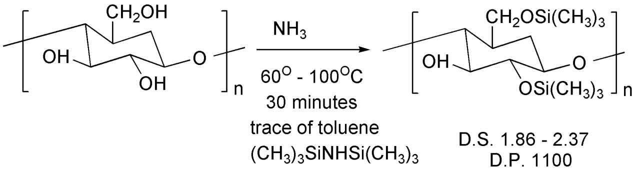
Reactions that take several hours under conventional conditions can be done in a few minutes with microwaves.[26] Examples include the preparation of "Tylenol"[27] and phenylhydrazones.[28] The work-up in the second case consisted of cooling, addition of methanol and filtration.



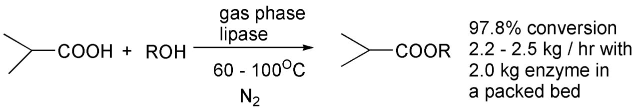


Extruders offer another route to continuous processing. Styrene can be polymerised in an extruder[29] and cellulose can be derivatized in one.[30] Polymers based on renewable cellulose cost more than those derived from petrochemicals. If it can be made more general, derivatization in extruders should lower the cost of the former appreciably. For reactions without ammonia, it may be possible to achieve higher rates by going to higher temperatures.

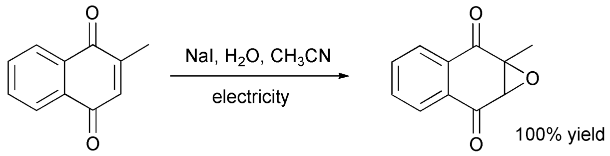


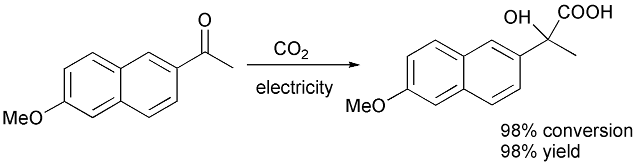


Gas phase biocatalysis in a tubular reactor offers possible reductions in plant size of up to 1000 times. Enzymes are more stable thermally when restricted amounts of water are present.[31]



Electricity is a cheap and potentially very clean reagent ($0.06 per "mole"). There is no catalyst to remove or recycle. It can also be used to regenerate expensive reagents in situ. It deserves to be used more often in organic chemistry.



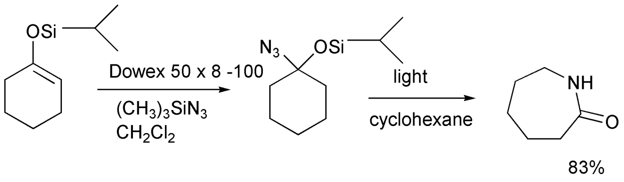


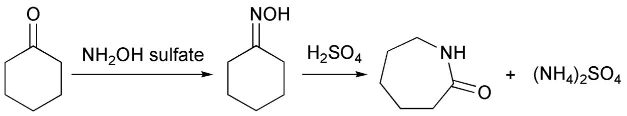
There are some cases where the desired result can be accomplished by doing without a chemical with a cost saving. Scale inhibitors are often added to cooling water to prevent deposition of calcium carbonate. Application of pulsed ultrasound or electric fields outside the pipe causes the calcium carbonate to form in fine crystals that sweep through with the water.[32] Machining can be done without cutting oils when the tool is coated with a nanocomposite film of $Ti_{1-x}Al_x/a–Si_3N_4$ put on by plasma deposition.[33] Vacuum pumps that use no oil are now in use by the semiconductor industry.[34] They are also suitable for mass spectrometry. It has been possible to produce 140 nm features by irradiating a silicon chip through a quartz mold with a laser pulse of 20 nanoseconds.[35] The mold sinks into the molten surface of the chip and is then removed. This may eliminate the need for many photoresists and the cleaning needed with them.

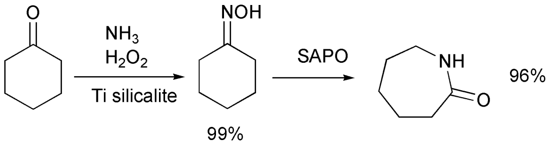
Refrigeration can be done without refrigerants using thermoelectric, magnetocaloric or thermoacoustic systems. The solid state devices have no moving parts, no emission of toxic gases, low maintenance, high reliability and long life. The energy consumption of the thermoelectric devices is too high for general use, but efforts are underway to increase ZT, the figure of merit, by choice of compounds other than the conventional ones such as Bi_2Te_3.[36] Thermoacoustic systems are being scaled up by Praxair and Los Alamos labs.[37]

Drinking water can be sterilized by heat, high pressure, ultraviolet light, membrane microfiltration, electron beam or pulsed electric fields without the need for chemicals.

Not all syntheses are as green as the authors say they are. A recent synthesis of caprolactam is said to be convenient and environmentally benign.[38] The starting silylenol ether is made from cyclohexanone.

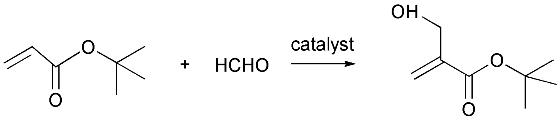






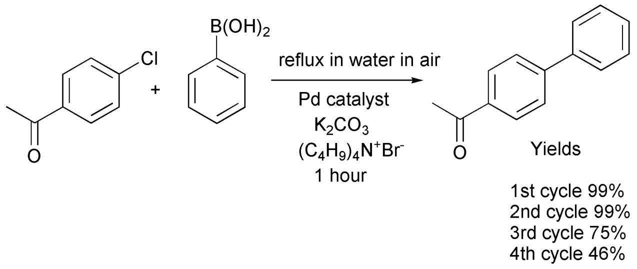
Methylene chloride is cancer-suspect. Azidotrimethylsilane is highly toxic. The first step requires 2–5 days. Both intermediate and product are purified by chromatography, the first in hexane and the second in ethylacetate–hexane. In contrast, the usual commercial process converts cyclohexanone to its oxime and rearranges it to caprolactam with sulfuric acid. The principal disadvantage is that 4.4 pounds of ammonium sulfate are produced for each pound of caprolactam. The new Enichem–Sumitomo process gives high yields and produces no ammonium sulfate. Caprolactam is availabe commercially for $0.77 per pound.

A Bayliss–Hillman Reaction has been described as green and atom-economical with no aqueous or organic waste streams in an environmentally friendly drug synthesis.[39] The catalyst can be recycled.

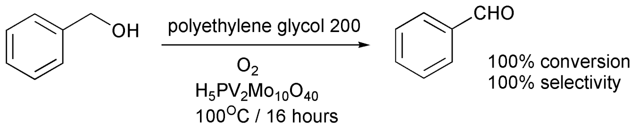


However, formaldehyde is a carcinogen and while this one step in the synthesis of the drug is atom-economical, the reaction sequence is not since the tert-butyl blocking group is removed in a later step in the synthesis.

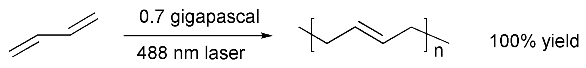
An aqueous Suzuki Reaction gives 99% yields in the first and second cycles, but the yield drops to 75% in the third cycle and to 46% in the fourth cycle, indicating deactivation or loss of the catalyst.[40] This is a common problem in many reactions, especially those with supported catalysts. The reaction also produces waste salts. Elimination of the usual organic solvent is a step forward.



An oxidation of benzyl alcohol to benzaldehyde by oxygen uses polyethylene glycol 200 as a non-toxic, cheap, non-volatile solvent.[41] The product can be recovered by vacuum distillation. There is no organic ligand in the catalyst to oxidize. The solvent-catalyst phase can be reused in the next run. The problem is that 5% of the solvent is lost in each cycle. Could it be run without a solvent?



1,3-Butadiene can be polymerized to a stereoregular polymer by a combination of light and pressure.[42] This is "potentially leading to practical green chemistry without the use of solvents, catalysts and radical initiators". The problem is that the pressure used is too high for most commercial processes.



It is better to green some than not to green at all. Some of these syntheses do represent steps forward. The caprolactam synthesis reminds one of the comment of one reviewer of a book on green chemistry who said that he didn't want "green chemistry" to be a synonym for more complicated chemistry.[43]

The biggest problem with green chemistry is the slowness with which it is being adopted. We need to move toward a sustainable future.[44] History is replete with predictions of the future that failed. However the future in the area of green chemistry may bring:

- Smaller chemical plants
- Less storage of toxic chemicals and more made on demand
- More in line monitoring of reactions
- More leakless valves
- Liquid acid catalysts replaced by solid ones
- More reactions run without organic solvents
- A shift of emphasis from oxidation of hydrocarbons to deoxygenation of sugars
- Novel reactions catalyzed by antibodies
- Hydrogen peroxide made commercially from hydrogen and oxygen in microreactors
- More organic electrochemistry
- More reactions catalyzed by sunlight
- More surfactants made from renewable raw materials
- Washing clothes at room temperature
- Useful plastics from lignin.
- Useful plastics from proteins plus fatty acids
- Cheap cellulose derivatives made in extruders
- More genetically-engineered organisms
- More chemicals and vaccines produced in crop plants
- More chemicals from plant and animal tissure culture
- More biocatalysis using wood, biomass and agricultural wastes
- More physical methods to replace chemicals—cutting oils, scale inhibitors, refrigerants, electroplating and photoresists
- Coloring fabrics without water and cars without organic solvents
- The demise of the cathode ray tube—replaced by flat screens that contain no mercury or lead
- The demise of the fluorescent lamp containing mercury—replaced by light emitting diodes or filament lamps more energy-efficient than the fluorescent ones
- The taxing of waste
- The outlawing or taxing of some plastic items e.g. poly(vinyl chloride) packaging
- More regulations
- More leasing, less buying
- More interdisciplinary courses?
- Green chemistry in all chemistry, physics and biology courses?
- Broader techniques shown in chemistry laboratory courses?

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Review

Recent developments on the epoxidation of alkenes using hydrogen peroxide as an oxidant

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Received 12th September 2002
First published as an Advance Article on the web 20th December 2002

This paper reviews recent developments on the epoxidation of alkenes using hydrogen peroxide as an environmentally friendly oxidant. The activation of hydrogen peroxide takes place in the presence of a homogeneous metal catalyst such as tungten, manganese, iron and rhenium or through addition of stoichiometric amounts of auxiliaries, which convert hydrogen peroxide to a more active oxidant. Hydrogen peroxide has also been used with solids catalysts such as mixed oxides, redox zeolites, layered materials and supported metal catalysts. Heterogeneous catalysts, however, suffer generally from lower activity and stability compared to the homogeneous catalysts.

Introduction

Epoxides are highly useful intermediates for the manufacture of a range of important commercial products.[1] Their selective synthesis is a subject of considerable academic and industrial interest. Olefin epoxidation is one of the main routes, which leads to the production of epoxides on both a laboratory and industrial scale.[2]

The use of oxygen, peroxides and peracids for direct oxidation of alkenes is the main method for industrial applications. Ethylene is commercially epoxidised by vapour-phase oxidation with oxygen or air using a supported silver catalyst.[3] However, this catalytic method is not efficient for alkenes with allylic C–H bonds due to oxidation at this position. Propylene oxide is produced by the metal catalysed liquid phase oxidation of propylene using organic hydroperoxides produced by hydrocarbon autoxidation.[4] Homogeneous[5] Mo^{VI} and heterogeneous[6] Ti^{IV} are used efficiently as catalysts and *tert*-butyl hydroperoxide or ethylbenzene hydroperoxide as the oxidants. Even though, the method has been widely used for the production of epoxides, it suffers from the formation of the alcohol co-product (*tert*-butanol or 1-phenylethanol).

Epoxidation of substituted alkenes widely used in the fine chemicals industry can be successfully achieved by using stoichiometric amounts of peracids such as peracetic acid and *m*-chlorobenzoic acid.[7] However, the employment of peracids is not a clean method as equivalent amounts of acid waste are produced. The safety issues associated with handling peracids is also a matter for concern.

There is a strong need for the development of new epoxidation methods which employ safer oxidants and produce little waste. The employment of hydrogen peroxide is an attractive option both on environmental and economic grounds. It is cheap, readily available and gives water as the only by-product. Many catalytic systems based on different metals such as tungsten, manganese, rhenium and titanium have been reported for the epoxidation of a wide range of alkenes using hydrogen peroxide. Furthermore, immobilisation of active homogeneous catalysts on solid supports has attracted a lot of interest as heterogeneous catalysts are easily separated from the product mixture and can possibly be recycled. Here, we critically review recent literature on the synthesis of epoxides using hydrogen peroxide as the terminal oxidant.

Heteropolyoxometalates

Transition metal substituted polyoxometalates have attracted considerable interest as oxidatively stable catalysts, [8–10] however, chlorinated solvents are normally required in order to obtain high reaction rates and yields of epoxides.

An improved catalytic system was developed by Noyori and co-workers[11,12] containing sodium tungstate dihydrate, aminomethylphosphonic acid and a quaternary ammonium salt hydrogen sulfate with 30% hydrogen peroxide in the absence of solvent or alternatively in toluene (Fig. 1). Lipophilic quaternary ammonium hydrogen sulfate significantly enhances the yield to epoxide. This catalytic system is effective for the epoxidation of terminal and cyclic olefins. The reaction, however, fails to produce acid sensitive epoxides due to their hydrolytic decomposition under the acidic conditions.

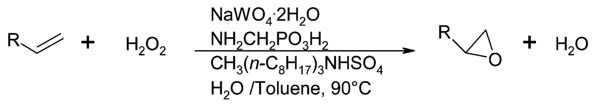


Fig. 1 Epoxidation of alkenes by phosphotungstate catalysts under PTC conditions.

A quaternary ammonium cetylpyridinium heteropolyoxotungstate $\pi\text{-}[C_5H_5NC_{16}H_{33}]_3[PO_4(WO_3)_4]$ based catalyst with special solubility characteristics has recently been reported[13] for the catalysis of the epoxidation of 1-hexene and cyclohexene at

Green Context

The epoxidation of alkenes is one of the key steps in functionalising hydrocarbons, as well as rapidly building functionality into a range of molecules, often with excellent control over selectivity. This review covers the development of clean epoxidation chemistry, in particular focussing on those methods which involve hydrogen peroxide, which is arguably the 'greenest' terminal oxidant in the continued absence of a general direct method to directly utilise oxygen in this transformation. ***DJM***

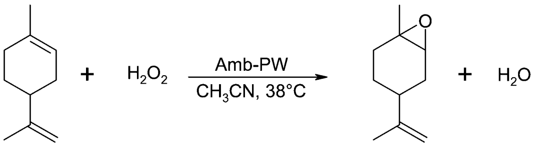
DOI: 10.1039/b208925b

high selectivities (>87%). The catalyst becomes soluble in aqueous hydrogen peroxide–toluene due to the *in situ* formation of π-$[C_5H_5NC_{16}H_{33}]_3\{PO_4[W(O)_2(O_2)]_4\}$. At the end of the reaction in the absence of hydrogen peroxide, the catalyst precipitates out, facilitating its recovery from the reaction mixture. The catalyst is stable and can be recycled without loss of activity.

The catalytic efficiency of a series of 'sandwich' type transition metal substituted polyoxometalates of the general formula $Na_xM_2Zn_3W_{19}O_{68}$ (M = Ru, Mn, Zn, Pd, Pt, Co, Fe, Rh) has been examined in the epoxidation of different alkenes using hydrogen peroxide as a terminal oxidant under biphasic conditions in the presence of tricaprylammonium chloride as a phase transfer catalyst.[14] $[WZnMn^{II}_2(ZnW_9O_{34})_2]^{12-}$ efficiently catalyses the epoxidation of a wide range of alkenes such as acyclic and cyclic alkenes, and alkenols with high chemoselectivity and stereospecificity. The other transition metal substituted polyoxometalates degrade in the presence of aqueous hydrogen peroxide and the active species formed efficiently catalyses the epoxidation of primary alkenols only. Therefore, those catalysts suffer from a significant loss of their activity and low recyclability due to their degradation.

Even though most of the polyoxometalates catalysed epoxidations are limited to alkenes containing one double bond, novel manganese containing heteropolyanions have been efficiently applied to the regioselective epoxidation of (*R*)-(+)-limonene.[15] A series of manganese(II) substituted polyoxometalates such as $[(Mn^{II}(H_2O)_3)_2(WO_2)_2(BiW_9O_{33})_2]^{10-}$, $[(Mn^{II}(H_2O))_3(SbW_9O_{33})_2]^{12-}$ and $[(Mn^{II}(H_2O)_3)_2(Mn^{II}(H_2O)_2)_2(TeW_9O_{33})_2]^{8-}$ have been synthesised and gave high yields of 1,2-limonene oxide at ambient temperature. Furthermore, remarkably high turnovers (>2500 after 24 h) at higher ratios of substrate–oxidant–catalyst (5000 : 10000 : 1) have been achieved. The use of dichloromethane as a solvent is critical for the reaction, as the catalysts are not soluble enough in other solvents such as acetonitrile, acetone and ethanol.

Epoxidation of terpenes such as α-pinene, 3-carene and linalool has been effectively catalysed by a heterogeneous tungsten based catalyst[16] which was obtained by the exchange of a commercial, macroreticular Amberlite IRA-900 with the Venturello anion $\{PO_4[WO(O_2)_2]_4\}^{3-}$. The catalyst is very active and highly selective (>90%) towards the epoxide in the oxidation of limonene (Fig. 2), unsaturated C_{10} alcohols and their esters. However, the epoxidation of acid sensitive terpene epoxides such as α-pinene oxide was only achieved under homogeneous conditions at 83% conversion and 92% selectivity by adding a preformed Venturello complex $[(C_8H_{17})_3NCH_3]_3[PW_4O_{24}]$ to the reaction mixture. In the latter case, benzene or toluene has been used as solvent instead of halogenated solvent which is normally used under Venturello conditions.[17]



84% Conversion, 85% Selectivity

Fig. 2 Epoxidation of limonene by Amberlite-supported tungsten catalyst.

The immobilisation of tungsten and phosphotungsten (PW) catalytic species on both organic resins such as Amberlite IRA-900 and hybrid silica materials has been examined in the epoxidation of bulky olefins.[18] Silica supports modified with quaternary ammonium functionalities provide a stable charged support where PW species are supported by electrostatic interactions. Alternatively, PW species were covalently supported on a phosphoramide modified silica. The ion exchange of the preformed Venturello complex $\{PO_4[WO(O_2)_2]_4\}^{3-}$ on the Amberlite support leads to efficient catalysts. However, *in situ* formation of peroxo–W species bound to the immobilised P groups results in the most active catalyst and epoxidises bulky olefins such as cyclooctene, norbornene and geraniol with good conversions and high selectivities (>93%).

Another interesting report[19] of heterogeneous tungsten catalysts has demonstrated the immobilisation of peroxotungsten complexes on porous polymers modified with organophosphorous ligands. Peroxotungstic complexes linked to polystyrene grafted phosphoramides (**1**) (Fig. 3) catalyse the epoxidation of cyclohexene with high conversion (90%) and a high TOF of 400 (turnover frequency = mole of epoxide formed per mole of tungsten per h), but moderate selectivity (70%). Higher catalytic efficiency has been obtained for the polymethacrylate-grafted phosphotriamides (**2**) (Fig. 3) supported peroxotungstic complexes (TOF = 1000) in the epoxidation of cyclohexene. Those catalysts show not only higher activities but also better selectivities than the soluble complexes.

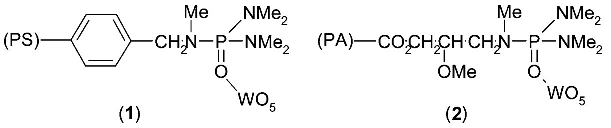


Fig. 3 Polystyrene-grafted phosphoramides and polymethacrylate-grafted phosphotriamide.

The new concept of triphase catalysis has been reported recently[20] involving incorporating inorganic species in an amphiphilic chain polymer to form a self-assembled and networked supramolecular complex in water. A mixture of phosphotungstic acid and poly(*N*-isopropylacrylamide) copolymer containing quaternary ammonium salts has been used to prepare the triphasic catalyst where the quaternary ammonium salt moiety is possibly cross-linked by trivalent $[PW_{12}O_{40}]^-$. The insoluble catalyst is very efficient in the epoxidation of allylic alcohols at room temperature and in the absence of solvent.

Polyoxometalates of the formula $[ZnWMn_2{}^{II}(ZnW_9O_{34})_2]^{12-}$ have been supported[21] on a modified silica containing quaternary ammonium functionalities introduced using the sol–gel technique (Fig. 4). The catalytic activity is significantly increased when the silica surface is modified with polyethylene oxide (PEO) and polypropylene oxide (PPO). An intermediate 10% PEO, 10% PPO silica provides the highest activity due to the optimal contact of the organic substrate and the aqueous oxidant at the balanced

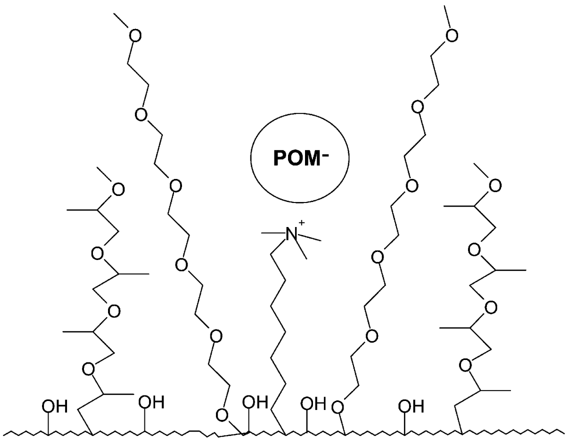


Fig. 4 Schematic representation of the $[ZnWMn_2{}^{II}(ZnW_9O_{34})_2]^{12-}$ polyoxometalate immobilised on functionalised silica Q^+–PE(P)O–SiO_2.

hydrophobic/hydrophilic catalyst surface. Cyclooctene epoxidation using 30% H_2O_2 has been obtained in higher yields compared to the homogeneous conditions under solvent free conditions.

Hydrophobic mesoporous silica gel chemically modified with Ph_3SiOEt and $Me_2NCH(OCH_2Ph)_2$ in a 1 : 1 ratio has been recently reported[22] as an effective support for tris(cetylpyridinium)(12-tungstophospate) $[\pi\text{-}C_5H_5N(CH_2)_{15}CH_3]_3\text{-}(PW_{12}O_{40})]$ polyoxometalate catalyst. A variety of terminal, cyclic, highly substituted and aromatic olefins have been selectively epoxidised with high yields using this catalyst (> 97%).

New heterogeneous catalysts, containing tungstate WO_4^{2-} ions exchanged onto Ni,Al-layered double hydroxides, have been applied to the bromide-assisted epoxidation with H_2O_2.[23] Initially, oxidative bromination of olefins takes place to form the bromohydrin intermediate followed by its dehydrobromination to give the epoxide product (Fig. 5) under mild reaction conditions (pH 6–7). Carrying out the reaction under monophasic conditions in a mixed $CH_3CN–H_2O$ (3 : 7) solvent system favours the epoxidation reaction. Even though turnover frequencies are higher than classical W-catalysed epoxidations, the catalyst efficiency is limited to the epoxidation of geminally di-, tri- and tetrasubstituted olefins.

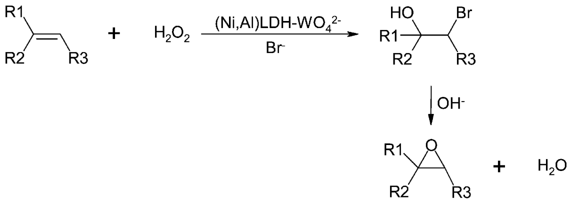


Fig. 5 Bromide-assisted epoxidation of olefins with H_2O_2 catalysed by WO_4^{2-}–Ni,Al-layered double hydroxides.

Metalloporphyrins and metal salen complexes

The high activity of biological metalloporhyrins containing enzymes like cytochrome P450 has led to the development of porphyrin based catalysts for the enantioselective epoxidation of alkenes.[24] The extensive research of metalloporphyrins catalysed epoxidation reactions has concentrated on using iron(III) and manganese(III) and the role of pyridine or imidazole ligands.[25] The proposed mechanism for the reaction proceeds through the formation of a high valent metal–oxo species.[26]

The use of hydrogen peroxide as an oxidant in metalloporphyrin catalysed epoxidations causes fast destruction of the catalysts, resulting in the dismutation of the oxidant. Furthermore, the structure of the catalyst has an important effect on its activity. A lot of work has been done to investigate the effect of the electronic and steric characteristics of the tetraphenylporphyrin on the stability and activity of those catalysts.[27–30] In addition, the use of co-catalysts significantly affects the catalyst activity.

Addition of carboxylic acids to the manganese–porphyrin/hydrogen peroxide epoxidations leads to a remarkable increase in the reaction rates.[31] A metal–acylperoxo complex, as shown in Fig. 6, was proposed to be a possible intermediate when acid was added in excess. Reaction rates strongly depend on both the amount of the acid and its acidity.

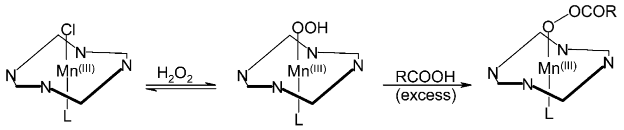


Fig. 6 Proposed mechanism for the formation of a metallo–acylperoxo intermediate in the presence of an excess of the acid co-catalyst.

Unsaturated monoterpenes have been efficiently epoxidised with hydrogen peroxide and ammonium acetate as a co-catalyst in the presence of Mn^{III} porphyrin complexes.[32]

Enantioselective epoxidation of non-functionalised alkenes catalysed by a dimeric homochiral Mn^{III} –Schiff base complex and urea–hydrogen peroxide as an oxidant has been recently reported[33] in a DCM–MeOH solvent system and with ammonium acetate as a co-catalyst (Fig. 7). Complete conversions were obtained for a series of chromenes and the chiral induction increases for the electron deficient alkenes. The reaction rate decreases in the presence of other nitrogen or oxygen coordinating co-catalysts compared to ammonium acetate. Recycling of the catalyst reduces reaction rates while enantioselectivities remain constant.

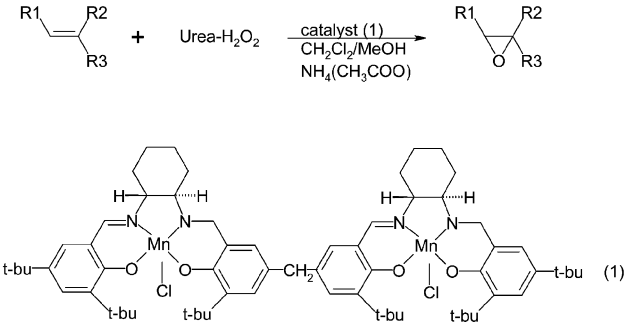


Fig. 7 Manganese–salen catalysed epoxidation of olefins with urea–hydrogen peroxide as terminal oxidant and ammonium acetate as a co-catalyst.

Catalytic epoxidation of olefins by an electron-rich Fe^{III} porphyrin complex and hydrogen peroxide in aprotic solvents can be carried out effectively in the presence of 5-chloro-1-methylimidazole.[34] The role of this electron poor imidazole is critical for the reaction as it decelerates the O–O bond cleavage of the reactive intermediate $(Por)Fe^{III}(OOR)$ complex.

The employment of micellar catalysis is advantageous for the manganese complexes catalysed epoxidation of terminal alkenes using hydrogen peroxide as the terminal oxidant.[35] The homogeneous manganese porphyrin complex chloro(5,10,15,20-tetrakis(*o*-chlorophenyl)porphyrinato)manganese(III) solubilised in Triton X-100 $(C(CH_3)_3CH_2C(CH_3)_2C_6H_4(\text{polyethylene oxide})_{9-10})$ in the presence of imidazole as a co-catalyst showed very good stability and selectivity in the epoxidation of 1-octene, however the conversion is quite low (25%).

The effect of different carboxylate salts on the epoxidation of 1,2-dihydronaphthalene with a manganese chiral salen complex and aqueous hydrogen peroxide was investigated.[36] The highest reactivity was obtained for ammonium acetate. The exact role of the carboxylate in the system is not clear: promoting the formation of HO_2^-, acting as an axial ligand or forming peroxyacylmanganese species. It is evident however, that these salts significantly promote the reaction rates and selectivities of the reaction.

A significant increase of reaction reactivity and selectivity can be obtained by the addition of carboxylic acid anhydrides to a manganese salen complex–*N*-methylmorpholine *N*-oxide catalytic system.[37] Peroxycarboxylic acids are formed *in situ* from anhydrous $Ph_3PO–H_2O_2$ and carboxylic acid anhydrides while the highest enantioselectivity has been obtained with maleic anhydride as a co-catalyst.

Furthermore, even simple manganese salts such as $MnSO_4$ have been reported[38] to catalyse the epoxidation of a range of disubstituted alkenes with good yields in a hydrogen peroxide buffer solution (0.2 M, pH 8.0, $NaHCO_3$). Percarbonate is formed *in situ* and combines with manganese to give the active intermediate, reducing the reaction times. However the method suffers from the use of DMF as a solvent and the large amount

(10 equiv.) of hydrogen peroxide solution needed, which requires slow and careful addition.

Much effort has been made on immobilising manganese complexes on a solid support, as the homogeneous catalysts can not be recycled and they are rather expensive and unstable in contact with the oxidant. Catalysts covalently attached to silica have been prepared[39] by grafting (5-(pentafluorophenyl)-10,15,20-tris(2,6-dichlorophenyl)porphyrinato)manganese(III) or (2,3,7,8,12,13,17,18-octachloro-5-(pentafluorophenyl)-10,15-20-tris(2.6-dichlorophenyl)porphyrinato)manganese(II) (Fig. 8) on aminopropylated silica. High yields for the epoxidation of cyclooctene with iodosylbenzene were obtained using those heterogeneous catalysts (95% and 67% respectively) and the first catalyst can be recycled giving a somewhat reduced but reproducible yield of 70%. Epoxidation of cyclohexene is less selective but it still gives the epoxide as the main product. Use of hydrogen peroxide as an oxidant shows very low yields in the epoxidation of cyclooctene, however, the reaction is enhanced by the addition of a weak base such as imidazole or ammonium acetate.

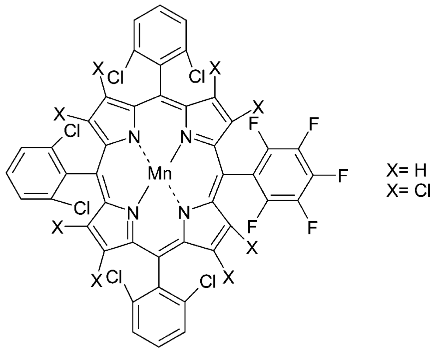


Fig. 8 Manganese–porphyrin catalysts.

Another active catalyst for the epoxidation of alkenes with hydrogen peroxide is the manganese(IV) complex based on the *N,N′,N″*-trimethyl-1,4,7-triazacyclononane (tmtacn) ligand. The use of this catalyst initially suffered from decomposition of hydrogen peroxide into water and O_2.[40] A significant improvement in the system came by the addition of catalytic amounts of ligands.[41] A 1 : 1 mixture of oxalic acid–oxalate buffer added to the system results in high conversions (95%) and selectivities of the epoxidation of terminal alkenes. Electron deficient alkenes react slightly faster than electron rich alkenes and the system can be used for the double epoxidation of (non)-conjugated dienes (Fig. 9).

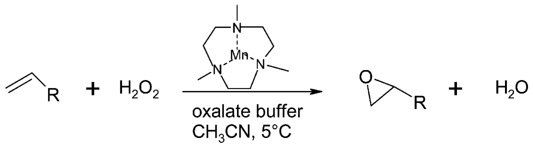


Fig. 9 Mn–trimethyltriazacyclonane catalysed epoxidation of terminal olefins in the presence of an oxalate buffer.

A very efficient manganese catalyst $[Mn_2O_3(tmtacn)_2](PF_6)_2$ has been recently reported[42] with hydroxymethoxyacetic acid methyl ester as a co-catalyst. High conversions have been obtained for the epoxidation of different cyclic olefins and turnover numbers to the epoxides were up to 600. However, substantial *cis*-diol products are formed depending on the ring size of alkene.

Novel dinucleating ligands incorporating the three N-donor atoms for each Mn atom have been synthesised[43] and showed high turnovers of up to 900 for cyclohexene epoxidation. The catalyst is more reactive for disubstituted olefins than terminal alkenes. Even though reaction conditions are mild (ambient temperature), the employment of acetone as a solvent is hazardous due to the possible formation of acetone peroxide.

Non-heme iron complexes based on a tetradentate ligand (*N,N′*-dimethyl-*N,N′*-bis(pyridylmethyl)ethane-1,2-diamine), have been recently reported[44] to epoxidise aliphatic alkenes at high yields (60–90%) with 50% hydrogen peroxide. The iron-complex mimics the oxidative enzyme methane monooxygenase. The addition of acetic acid (30 mol%) significantly favours the epoxide production due to the formation of a μ-oxo, carboxylate-bridged diiron(III) complex. This complex is easily formed *in situ* and produces a very active system, in which the epoxidation reaction occurs within 5 min.

Metal oxides

Methyltrioxorhenium (MTO) is an active catalyst for the epoxidation of alkenes using hydrogen peroxide as an oxidant. Initially, anhydrous hydrogen peroxide in Bu^tOH was used as the oxidant but low selectivities were reported for acid sensitive epoxides due to the high acidity of the MTO–H_2O_2 system.[45]

The addition of a base, such as pyridine,[46] in large excess to MTO ($>10:1$) enhances the rate and selectivity of the epoxidation of di-, tri- and tetra-substituted alkenes, as it protects the epoxide from ring opening. Commercially available aqueous 30% H_2O_2 can be used as an oxidant.

Epoxidation of unreactive terminal alkenes is achieved in the presence of the less basic 3-cyanopyridine or 3-fluoropyridine at high yields.[47,48] Nevertheless, epoxidation of styrene requires a mixture of pyridine and 3-cyanopyridine to obtain both high conversion and protection of the styrene oxide. Use of pyrazole (24 : 1 ratio) as the basic ligand and dichloromethane as solvent was reported to give even better results than the other bases.[49]

The system can be improved further by the use of fluorinated alcohols as solvents.[50] The use of trifluoroethanol and MTO–pyrazole system with a low catalyst loading (1%), is very effective for the epoxidation a range of alkenes (yields $>98\%$), with the exception of the very apolar ones (C_{12} or higher alkenes and stilbenes) which are insoluble in the reaction medium.

While hydrogen peroxide is typically used in the MTO catalysed epoxidation, other oxidants such as sodium percarbonate have been reported[51] to act as an oxygen source. High yields were obtained for a range of alkene epoxidations catalysed by MTO–pyrazole and in the presence of trifluoroacetic acid. No external cooling is required as the interaction between the sodium percarbonate and the acid ensures the slow release of hydrogen peroxide.

MTO is a very active epoxidation catalyst, however, its difficult, hazardous and environmentally unfriendly synthesis involving organotin reagents[52] makes it an unattractive option for epoxidation reactions.

Epoxidations in the absence of metals

The activation of hyrogen peroxide in the absence of metals by converting it in a more reactive oxidant has been the subject of many studies.

Potassium peroxomonosulfate has mainly been used for the generation of dioxirane, as the sulfate moiety is a good leaving group, which facilitates the ring closure for the formation of dioxirane.[53,54] However, hydrogen peroxide has been demonstrated[55] to be an effective oxidant for the fructose derived dioxirane catalysed epoxidation of a number of olefins at high yields and ee's. The use of acetonitrile is critical for the reaction, suggesting that the actual oxidant responsible for the *in situ* formation of dioxirane, is the corresponding peroxyimidic acid as shown in Fig. 10.

The use of H_2O_2–CH_3CN as an oxidative system has been explored[56] in the presence of different achiral ketones. Among them, trifluoroacetone is the most active one (used in small

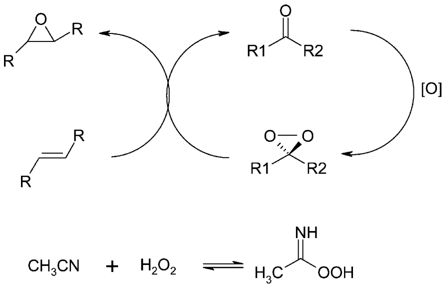


Fig. 10 Epoxidation of alkenes by dioxiranes likely formed by peroxyimidic acid.

amounts 10–30 mol%), for the epoxidation of a variety of terminal, cyclic, acyclic, *trans*, *cis* and trisubstituted olefins with good yields. The pH has a major effect on the reaction and the maximum epoxide yield was obtained at pH 10.

Another example of promoting the activity of hydrogen peroxide is by using carbodiimide with mildly basic or acidic catalysts. A peroxyisourea is possibly formed as a reactive intermediate by the reaction of hydrogen peroxide with an excess of of dicyclohexylcarbodiimide (DCC) (2 equiv.)[57] as shown in Fig. 11. Hydroxyl containing solvents such as methanol or ethanol are preferable for the reaction. Disubstituted olefins are epoxidised in good yields, however reaction times are long and the selectivity of the reaction for substrates containing two double bonds is very poor. Furthermore after the reaction, equivalent amounts of urea compounds are formed which can not be easily recycled.

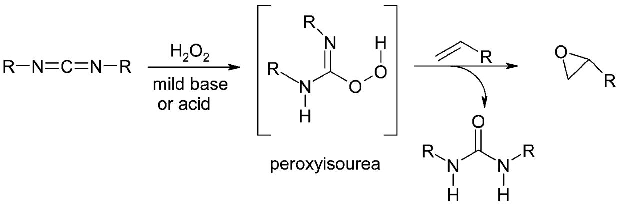


Fig. 11 Activation of hydrogen peroxide in the presence of DCC by the formation of the intermediate peroxyisourea.

An interesting method for activating hydrogen peroxide is through the presence of the hydrogen carbonate ion which forms the active oxidant peroxomonocarbonate ion, HCO_4^-.[58] Water-soluble alkenes were epoxidised with stoichiometric amounts of hydrogen peroxide (1.5–6 equiv.) with good yields. Water insoluble alkenes can react under the same conditions if an acetonitrile–water (3 : 2 v : v) mixture is used as the solvent. The reaction conditions are mild, however conversions are low for less nucleophilic substrates and sensitive epoxides are readily hydrolysed under the reaction conditions.

Recently, a 'green epoxidation system' has been reported[59] based on the use of CO_2 as a solvent and hydrogen peroxide as the terminal oxidant in the presence of a base. Percarbonate is believed to be the active species and transfer limitation problems between the H_2O/CO_2 phases were overcome by the employment of surfactants. However, product yields are quite low, especially for *n*-alkenes.

Perfluorinated ketones combined with hydrogen peroxide have been demonstrated to enable epoxidation reactions. Perfluoroheptadecan-9-one is a very active catalyst,[60] however a mixture of refluxing 1,2-dichloroethane–ethyl acetate is required to ensure its reasonable solubility in the system. Good product yields are obtained for a range of substrates and moderate yields are obtained for acid sensitive epoxides when the reaction mixture was buffered. Trifluoroethanol can be used as a solvent for the reaction but the recovery of the catalyst is poorer than in dichloroethane.

The use of fluorinated ketones suffers from environmental issues due to the high toxicity of these compounds. Immobilisation of fluorinated ketones is advantageous and a heterogeneous silicate synthesised by the sol–gel method containing hexafluoroketone has been efficiently used in the epoxidation of nucleophilic alkenes.[61]

Fluorinated alcohols such as trifluoroethanol and hexafluoro-2-propanol have been used as solvents[62] for the uncatalysed epoxidation of a range of alkenes with an aqueous hydrogen peroxide buffered solution (Fig. 12). Trisubstituted alkenes were obtained in high yields (80–90%) by reflux in trifluoroethanol, except for hydrolysis-sensitive alkenes. Hexafluoro-2-propanol can be used at room temperature, giving the same rates as in boiling trifluoroethanol and in good yields for electron rich alkenes.

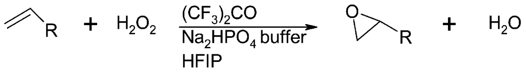


Fig. 12 Epoxidation of olefins by the hexafluoroacetone–hydrogen peroxide system in hexafluoro-2-propanol.

Heterogeneous catalysts

Heterogeneous catalysts offer the advantages of easy catalyst separation and sometimes higher selectivity, however most of these catalysts suffer from lower activity, instability in the epoxidation systems and limited recyclability.

Titanium containing silicates, including amorphous titania–silica materials and Ti-substituted molecular sieves are the most efficient heterogeneous catalysts for epoxidation reactions.

A well-known solid epoxidation catalyst is the molecular sieve, type Ti Silicate-1 (TS-1)[63] which can activate hydrogen peroxide as an oxidant and catalyse the epoxidation of different alkenes. The main drawback of this catalyst is its small pore dimensions of 5.6 × 5.3 Å, which makes it accessible to only relatively small reactants[64] and restricts this catalyst to epoxidation of linear alkenes.

To overcome the steric limitation of TS-1, other mesoporous and macroporous, titanium containing zeolitic-materials have been developed, such as Ti,Al-beta, which has a three-dimensional pore structure. The presence of aluminium causes Brønsted acidity, which can lead to acid catalysed side reactions[65] which thus decreases the selectivity of epoxide production.

Therefore, an aluminium-free Ti-beta catalyst has been developed[66] which has been shown to efficiently catalyse the epoxidation of bulky substrates such as norbornene, substituted cyclohexenes, cyclic terpenes and allylic alcohols with hydrogen peroxide. For linear alkenes, the catalyst activity is lower than that of TS-1 and internal alkenes react faster than alkenes with a terminal double bond. For bulky substrates however, steric effects play an important role and contribute to the reactivity of the substrates, suggesting that the hindered formation of the transition state at the titanium site is an important factor in the activity of the catalyst.

Improvement of the activity and stability of Ti–silicate catalysts can be obtained by enhancing their hydrophobicity. Trimethylsilation of micro- and mesoporous titanosilicates by *N*,*O*-bis(trimethylsilyl)trifluoroacetamide increases the activity of the catalyst, particularly for the MCM and mixed SiO_2/TiO_2 aerogels. [67]

Hydrophobic mesoporous titanosilicates can be prepared by the sol–gel technique using hexadecyltrimethylammonium chloride as a templating surfactant under acidic conditions during long gelation times. Temperatures lower than room temperature and a 0.014 H^+/Si ratio proved to be beneficial for higher surface area and pore size of the material and a 2.5% Ti loading can be obtained.[68] The catalysts enable the epoxidation of cyclohexene and norbornene at high selectivities (>95%) using TBHP or hydrogen peroxide as an oxidant.

Ti has been supported on amphiphilic NaY zeolite which have been partially modified with alkylsilyl groups.[69] The surface of this catalyst contains both hydroxyl and alkylsilyl groups which results in their placement between hydrogen peroxide and the organic phase in the liquid–liquid phase boundary. Epoxidation of linear alkenes is efficiently catalysed and epoxide yields are higher under static conditions.

A unique *trans*-selectivity in the epoxidation of *cis*, *trans* alkenes has been shown[70] for Ti-MWW zeolite (known as MCM-22) heterogeneous catalyst compared to the TS-1 and Ti-Beta. Selectivities reach up to 80% for the corresponding *trans* epoxide from a 50:50 *cis*/*trans* ratio of the alkene. The increased *trans* selectivity is attributed to the structure of the Ti-MWW, specifically, the 10-MR (membered ring) sinusoidal channels whose shape promote the epoxidation of *trans* alkenes.

Rhenium oxides Re_2O_7 and ReO_4^- have been supported on zeolite Y, mixed alumina–silica and pure alumina as epoxidation catalysts with anhydrous hydrogen peroxide.[71] Stable catalysts are formed in the case of the alumina support and ReO_4^-. The schematic representation of the activation of the immobilised MTO in alumina by hydrogen peroxide is shown in Fig. 13. Low conversions (40%) were obtained for the epoxidation of cyclooctene, while selectivity is high (>96%). Epoxidation of cyclohexene using these catalysts failed as cyclohexane diol is obtained as the major product.

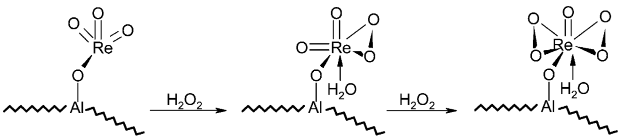


Fig. 13 Reaction of hydrogen peroxide with the immobilised ReO_3 to form the active complexes.

Ordinary chromatographic alumina has been shown to have good catalytic activity in the epoxidation of a range of 1-alkylcyclohexenes using hydrogen peroxide which is dried *in situ* by performing the reaction under reflux with Dean–Stark water separation.[72] Completely anhydrous conditions result in lower selectivity, as the alumina catalysed decomposition of the epoxide and hydrogen peroxide is prevented by the presence of only a small amount of water. The system is not very reactive however, for the epoxidation of cycloalkenes.[73]

Hydrotalcites $Mg_{10}Al_2(OH)_{24}(CO_3)$ have been reported[74] as efficient heterogeneous base catalysts for the epoxidation of various olefins using hydrogen peroxide as an oxidant and isobutyramide as a co-catalyst. Addition of an anionic surfactant, sodium dodecyl sulfate, remarkably enhances the rate of the reaction, while cationic surfactants inhibit the reaction and non-ionic surfactants have no effect. Hydrocarbons can be used as solvents, even though 1,2-dichloroethane gives higher conversions for cyclooctene epoxidation. The catalyst can be reused without a significant loss of catalytic activity. However, the method suffers due to the use of equivalent amounts of amide, which are consumed during the reaction to the corresponding acids.

Electron deficient α,β-unsaturated ketones have been efficiently (>90%) epoxidised under mild conditions by hydrogen peroxide in the presence of basic hydrotalcite $Mg_{10}Al_2(OH)_{24}(CO_3)$.[75] Methanol can be used as a solvent and excellent hydrogen peroxide utilisation can be attained. The presence of quaternary ammonium salts as phase transfer catalysts enhance the reaction, especially for hydrophobic ketones. The catalyst actually promotes the transformation of hydrogen peroxide into the perhydroxyl anion as the active species and can easily be recycled and reused without the loss of their activity. Heating by microwave radiation in the hydrotalcite catalysed epoxidation of olefins with hydrogen peroxide and a nitrile, accelerates significantly the reaction rates and results in higher yields of epoxides.[76]

Furthermore, the intercalation of anionic surfactants, such as dodecyl sulfate and dodecyl benzenesulfonate, into double layered hydroxide hydrotalcite results in a more selective catalyst for the epoxidation of limonene to its 1,2-epoxide. However, conversions are lower in comparison with the carbonate analogue and an excess of nitrile is necessary in order to activate the hydrogen peroxide.[77]

Conclusions

The development of new epoxidation methods based on the use of hydrogen peroxide as an oxidant in order to achieve the cleaner synthesis of epoxides has been described in this review. The use of metal catalysts is very important, however further development in order to replace the often-used chlorinated solvents and to more efficiently separate the catalysts is needed (possibly, through the use of nanofiltration membranes). Activation of hydrogen peroxide in the absence of metals results in the production of large amounts of waste due to the need for auxiliaries.

The use of heterogenised homogeneous catalysts has had limited success due to poor product yields and catalyst stability, which leads to leaching during reactions and thus limits the potential for recyclability. While the use of hydrogen peroxide as an oxidant in epoxide reactions is an attractive method in the context of green chemistry, the employment of redox zeolites catalysts such as titanium–silicates (TS-1) is limited to linear alkenes.

Improving the stability of supported metal catalysts is generally an important goal in oxidation catalysis and the difficulty is increased by the necessity of an aqueous oxidant. Further research in the synthesis of new catalytic materials by maximising their accessible surface area and tuning their surface polarity and organophilicity is required to achieve more active epoxidation catalysts.

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Origin of the mediator losses in electrochemical delignification processes: primary and secondary reactions of violuric acid and *N*,*N*′-dimethylvioluric acid radicals with lignin model compounds

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Received 9th September 2002
First published as an Advance Article on the web 16th January 2003

The use of mediator-based processes for the delignification of wood pulps is of great interest as they promise to be environmentally as well as economically interesting alternatives to the currently dominating chlorine-based processes. Mediator-based processes suffer from the fact that substantial amounts of the mediator molecules are irreversibly lost during the reactions. We have now analyzed in detail the primary and in addition the secondary reactions of the oxime type mediators violuric acid and dimethylvioluric acid with lignin model compounds and softwood pulp in order to find the reasons for the repeatedly reported loss of mediator molecules during enzymatic and electrochemical delignification processes. Using a set of lignin model compounds, representing the various structural subunits in the lignin network, we were able to demonstrate that the loss of mediator is not due to the primary reaction of the mediator radicals with the lignin but occurs in a secondary reaction where the activated lignin subunits react with the mediators in the solution. The primary reaction of the mediator radicals is hydrogen abstraction from phenols and activated aromatic rings which leads to the formation of phenoxyl and phenyl radicals. The secondary reaction is the formation of colored semi-stable covalent adduct molecules from an activated lignin subunit with a mediator molecule in the solution leading to polycyclic *N*-hydroxy compounds. Only in this secondary reaction mediator molecules are removed from the solution due to covalent attachment to the lignin network. No reaction with the cellulose content in the pulp is observed. The findings reported in this paper point the way to an improved mediator design and appropriately modified processes, where the secondary mediator reactions are suppressed, and removes a major road block towards a technical application of the mediator-based delignification procedures.

Introduction

In the late eighties the principle of mediator-based pulp bleaching processes was proposed, where enzymatically oxidized mediator molecules cause a delignification, *i.e.* an oxidation of the brown colored lignin in the pulp.[1] The redox mediators used first for this purpose were ABTS (2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonic acid)) and HBT (1-H-hydroxybenzotriazole). Later *N*-hydroxy-compounds[2,3] and recently also transition metal complexes[4–6] were proposed as mediators for pulp delignification. The enzymatic oxidation of these compounds leads to radicals[1,3,6–8] or highly oxidized states which are the active agents. The radicals are generated by the enzymes, released and diffuse into the pulp fibers where they react with the lignin. Theoretically there should be no consumption of the mediator at all as it is fully recovered and permanently recycled in the process. However, a significant loss of mediator was observed in cases where radicals are used as oxidizing agent but up to now no analysis of the molecular mechanisms causing this loss has been reported. We found that the mediator loss is not due to the primary reaction of the radicals with the lignin but due to a secondary reaction of the activated lignin network with mediator molecules in the aqueous solution. With the findings reported the use of catalytic amounts of chlorine-, sulfur- and heavy metal-free mediators instead of the stoichiometric use of chlorine in delignification becomes somewhat more realistic. This is a contribution to the environmentally friendly use of sustainable resources.

Results and discussion

Electrochemical mediator-based delignification

Many of the mediators proposed in the literature react also with the enzymes required for activation and cause their deactivation. In addition the use of enzymes to produce the required radicals implies a number of restrictions for the processes as pH as well as temperature of the pulp during the enzymatic treatment need to be controlled properly to match the physiological requirements of the enzyme.

Green Context

The development of more environmentally benign alternatives to chlorine in pulp bleaching processes is an important large scale industrial challenge—Redox mediators and more recently *N*-hydroxy compounds have been proposed for this purpose. They generate radicals in the presence of enzymes, and these in turn cause pulp delignification. Unfortunately, significant quantities of these ‘mediators’ are lost in the delignification process. This paper analyses this loss, explains its cause and thus opens the door to improved mediator design. Thus electrochemical mediator-based delignification is shown to be an attractive alternative to existing chlorine-based processes. *JHC*

DOI: 10.1039/b208812f

To overcome these restrictions we introduced an electrochemical process where the enzymatic mediator oxidation is replaced by an electrochemical oxidation at the anode of an electrolyzer cell.[5,9] The use of an electrolyzer cell removes the restriction to physiological conditions (pH, temperature) implied by the use of enzymes.

For the electrochemical process described the cyclic oximes violuric acid (Vio) and dimethylvioluric acid (dmVio) are suitable mediators. The molecules are electrochemically as well as enzymatically oxidizable to the corresponding iminoxy radicals[5] which are extraordinarily stable in the pH range 2–10 and show a half-life of more than 30 min. It has been shown that the radicals undergo a fast reaction with the lignin portion in the pulp leading to a delignification of up to 50% in a single step.[9,10] The redox systems of Vio as well as dmVio show a single electron oxidation peak at 1.02 V *vs.* NHE. The redox system is completely reversible in water as derived from cyclovoltammetric experiments.[9,10]

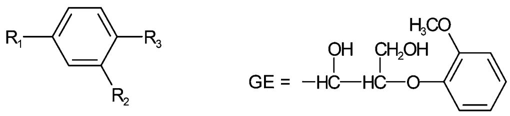
However, like in the enzymatic systems a loss of mediator during the electrochemical delignification is observed with Vio and dmVio. This loss limits the efficiency of the total process. We have now analyzed the primary molecular mechanisms of the radical catalyzed depolymerization of lignin in more detail.

Reaction of violuric acid and *N*,*N*′-dimethylvioluric acid radicals with lignin model compounds

In the following the reactions of violuric acid (Vio·) and *N*,*N*′-dimethylvioluric acid (dmVio·) radicals with lignin containing pulp is analyzed by means of lignin model compounds. The goal of the investigation is to detect the reaction sites as well as to determine the reaction rates of the Vio· and dmVio· radicals with the various structural groups in lignin.[11]

For the investigations the model compounds shown in Table 1 were used. The compounds tested comprise classical lignin model compounds as well as monofunctional aromatic molecules. A focus is on guaiacol (Gua) and veratryl alcohol (VA) as representatives for phenolic and for non-phenolic structural lignin subunits. The dimeric lignin models are representatives of the O-4 linkage type, which frequently occurs in lignin, and show similar reactions but due to the multi-functionality of these compounds several chemical reactions occur in parallel and lead to a more complex analysis.

Table 1 Lignin model compounds



R_1	R_2	R_3	Compound
OH	OCH_3	H	Guaiacol
OH	OCH_3	CH_2OH	Vanillyl alcohol
OH	OCH_3	GE	Guaiacolglyceryl-β-guaiacyl ether
OCH_3	OCH_3	H	Veratrole
OCH_3	H	H	Anisole
OCH_3	H	CH_2OH	Anisyl alcohol
OCH_3	OCH_3	CH_2OH	Veratryl alcohol
OCH_3	OCH_3	GE	Veratrolglyceryl-β-guaiacyl ether
OCH_3	$OCH(OH)CH_2OH$	H	Guaiacolglyceryl ether
CH_2OH	H	H	Benzyl alcohol

Violuric acid (Vio) as well as *N*,*N*′-dimethylvioluric acid (dmVio) form almost identical radicals upon electrochemical oxidation (Fig. 1). From the EPR spectra their radical structure is derived with the unpaired electron localized on the NO group.[12] The lifetime of these radicals in water at room temperature is on the order of several tens of minutes.[9]

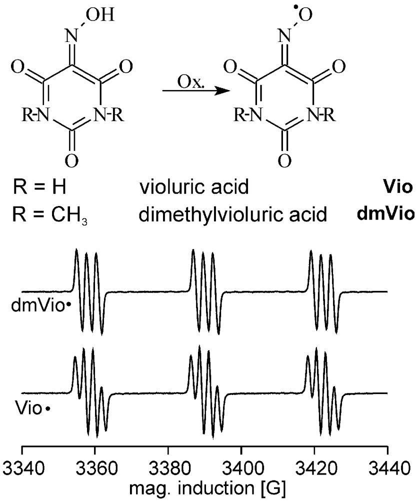


Fig. 1 Structure of violuric acid (Vio) and dimethyl violuric acid (dmVio) and EPR-spectra of the corresponding iminoxy radicals. The radicals are the reactive species in the so-called delignification process.

The reaction of Vio· with a number of test compounds is shown in Fig. 2. EPR was employed to monitor the time-dependence of the radical concentration in the reactions with different lignin model compounds. 50 mL of 100 mmol L^{-1} aqueous solutions (or suspensions where required) of the model compounds were added to 1 L of 0.5 mmol L^{-1} Vio solution (containing about 40% as Vio·). The at least 10-fold excess of the model compound guarantees that the kinetics observed is corresponding to the different reactivities of the model compounds. No reaction is observed upon addition of cellobiose (**1**) but phenolic lignin model compounds (**8–10**) cause an immediate radical consumption. With non-phenolic aromatic model compounds (**2–7**) a slower reaction kinetics is observed.

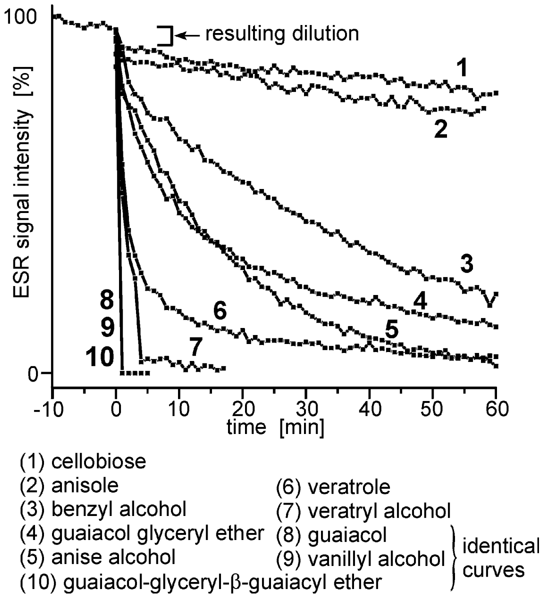


Fig. 2 Time dependent decrease of the EPR radical signal of Vio· after the addition of different lignin model compounds. Before $t = 0$ the thermal decay of the Vio· radical in water is seen. At $t = 0$ the model compounds are added and a small change in the signal intensity due to dilution of the radical is observed for all compounds.

The electrochemical formation of the mediator radicals Vio· and dmVio· is equivalent to the abstraction of a hydrogen atom from the oxime group. The fast reaction of Vio· with phenolic groups is due to hydrogen abstraction from the phenolic group which leads to the formation of a phenoxyl radical and recovery of Vio. The slower reaction of Vio· with the different aromatic model compounds is due to an oxidation of the aromatic ring. The rate constants correspond to the activation of the ring by its substituents and its thermodynamic oxidation potentials (U_{ox}). This is seen from the initially same reaction rates of veratryl alcohol (U_{ox} = 1.35 V *vs.* SCE) **7**, a benzyl alcoholic compound, and veratrole (U_{ox} = 1.27 V *vs.* SCE) **6**, an activated aromatic compound. The comparison of the reaction rates of veratrole **6** and anise alcohol (U_{ox} = 1.45 V *vs.* SCE) **5** show a clearly higher reaction rate with veratrol which proves that abstraction of benzylic hydrogen atoms is of minor importance. The structural unit where lignin is attacked with Vio·/dmVio· is an aromatic system activated by two methoxy groups, a benzyl alcohol function or a phenolic group (U_{ox} = 0.7 V *vs.* SCE). The spontaneous radical decrease observed with EPR after addition of pulp is related to the reaction with the phenolic subunits[9] because they show the fastest reaction due to the acidic hydrogen atom.

In order to prove the selectivity of the radical the reaction with cellobiose **1** was tested which is a soluble model compound for the carbohydrate content in pulp. By adding cellobiose to a Vio· solution no reduction of the radical signal is observed. Thus no reaction takes place with the cellulose part of the pulp, which guarantees a high quality of the pulp produced. Viscosity investigations at electrochemically delignified pulp confirm the very good selectivity of the reaction.

Mediator recovery

As long as the reactions of the mediators would only comprise the above described mechanisms no mediator consumption should be observed. However, in the literature the irreversible loss of mediator is repeatedly reported [*e.g.* refs. 2 and 13]. The mediators analyzed in pure form by cyclovoltammetry reveal to be nicely reversible. The loss of mediator must be dependent on and due to the reaction partners during the delignification reaction.

We have analyzed the recovery rate of Vio· for the reaction with equimolar solutions of the model compounds guaiacol and veratryl alcohol as well as for softwood Kraft pulp. RDE-voltammetry is a suitable tool to measure simultaneously the amount of Vio and Vio· with acceptable time resolution. The decrease of radical as well as the recovery of Vio from Vio· after the addition of lignin model compounds or pulp is quantitatively determined. The initial amount of mediator radical (Vio·) should be theoretically 100% be converted back to mediator (Vio). The amount of mediator recovered in the experiment is given by the difference of mediator at the time where no more radical is detected (Vio_{end}) minus the initial amount of mediator (Vio_{start}). The recovery rate RR is then calculated from RR = ($[Vio]_{end} - [Vio]_{start}$)/$[Vio^{\cdot}]_{start}$. Recovery rates of Vio· to Vio with the lignin model compounds veratryl alcohol and guaiacol (Fig. 3) of 52% and 61%, respectively, are obtained. For softwood pulp a recovery rate of 66% is found. The reactions are completed within several minutes.

A more detailed analysis is required to investigate which processes occur in parallel. The turnover of each mediator molecule of Vio and dmVio may be calculated to range between two and three cycles in a real experiment. These values are in contradiction to the earlier finding that the mediators show an excellent electrochemical reversibility in aqueous solution. If the primary mediator reaction is not responsible for the apparently low mediator cyclicity then secondary reactions must occur which cause that mediator is removed from the solution and chemically attached to the model compounds or the pulp.

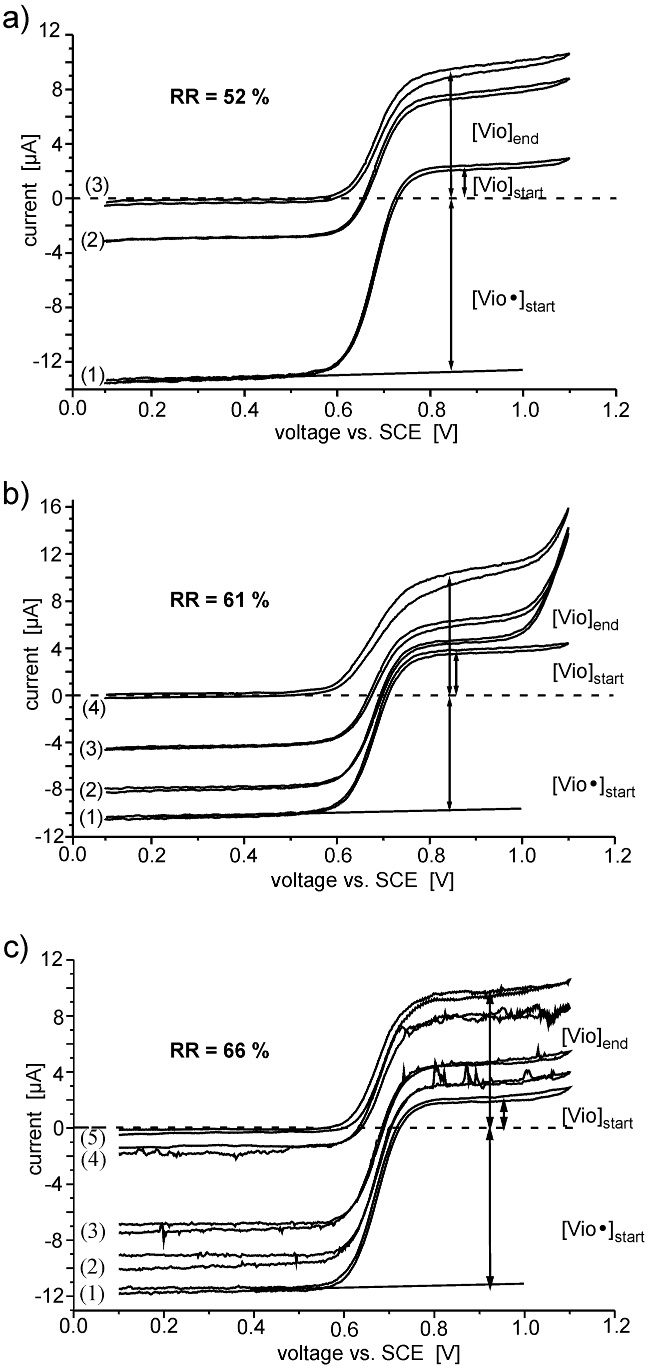


Fig. 3 Recovery of violuric acid from its radical upon reaction with the model compounds guaiacol and veratryl alcohol as well as softwood kraft pulp. The diagrams show the RDE-analyses of the reaction of Vio· with a = guaiacol, b = veratryl alcohol and c = pulp, respectively. The numbering corresponds to measurements at different times: (1) before (2) 30 s; (3) 3 min; (4) 7 min; (5) 11 min after the adding of the model compounds. The recovery rate RR is calculated from RR(t) = ($[Vio]_{end} - [Vio]_{start}$)/$[Vio^{\cdot}]_{start}$. The end of the reaction is reached as soon as no remaining Vio· is detected.

Formation of mediator-model compound adducts

We have analyzed the soluble reaction products of Vio· and dmVio· radicals with lignin model compounds by time-dependent LC-MS analysis. It was found that in the case of Vio· an equimolar coupling product between Vio· and the substrate was formed (Fig. 4). The retention time indicates an increased polarity of the adduct in comparison to the lignin model substance. The molecular mass of the detected coupling product was 280 u which corresponds to the sum of Vio· (156 u) and guaiacol (124 u). In order to verify this result an analogous reaction with dmVio· was performed and a similar product with

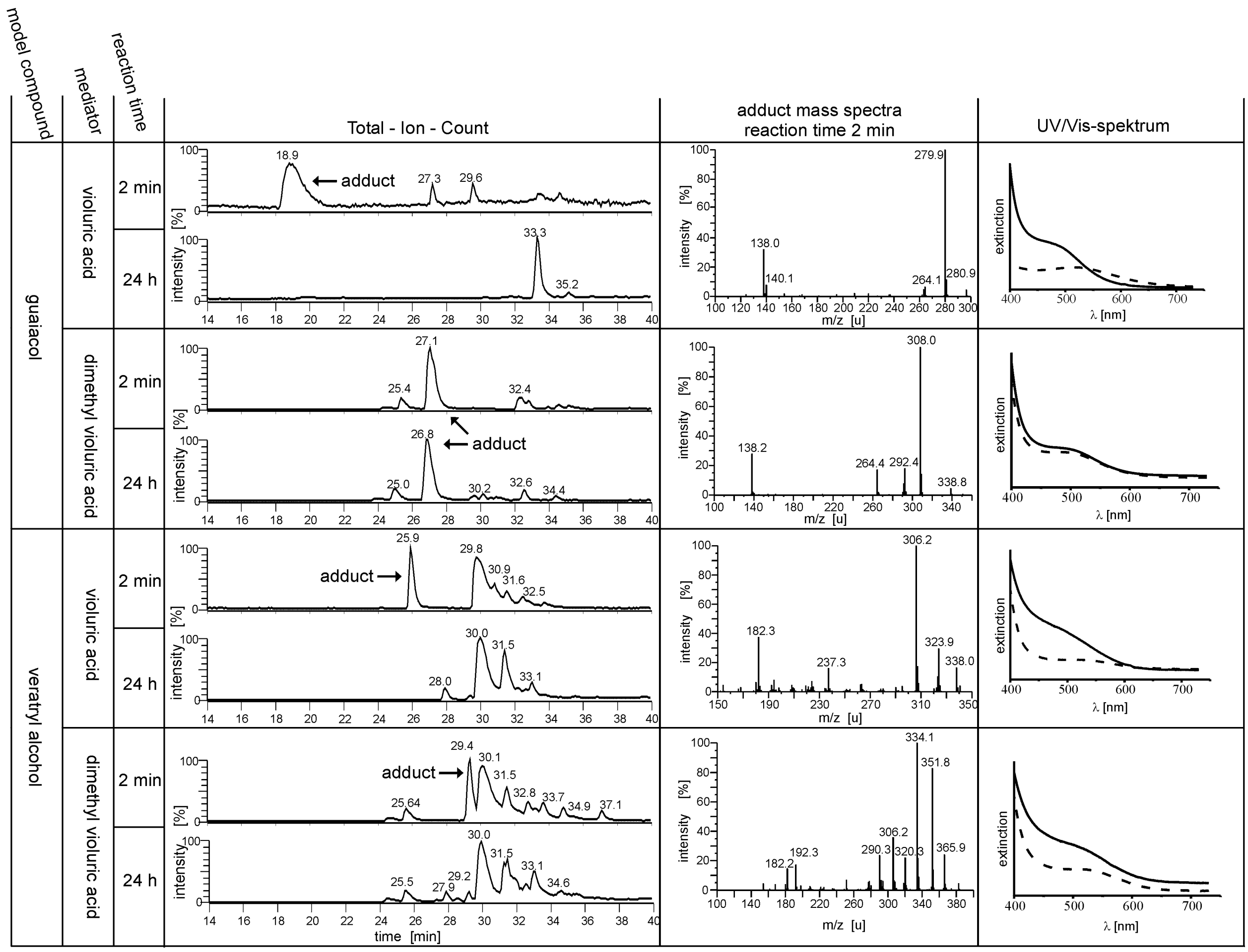


Fig. 4 Analysis of the products obtained from the reactions of mediator radicals Vio· and dmVio· with the model compounds guaiacol and veratryl alcohol. Shown is the total ion count (positive mode) chromatogram after 2 min and 24 h reaction time and the mass spectra of the formed adduct molecules after 2 min reaction time. In the last column the time dependent UV/Vis (solid line: 2 min reaction time, broken line 24 h reaction time) spectra are shown.

a molecular weight increased by 28 u (due to the two additional methyl groups) was obtained at 308 u. Both experiments indicate the formation of a 1 : 1 adduct between mediator and guaiacol.

However, also a striking difference is observed in that while the Vio adduct disappears after 24 h reaction time, the corresponding dmVio product is stable.

The formation of a covalent adduct is not only observed with the phenolic model compound guaiacol, but also with benzyl alcoholic model compounds like veratryl alcohol and also with activated aromatics like veratrole (not shown). In the case of veratryl alcohol the expected mass of the adduct molecule is 324 u with Vio and 352 u with dmVio. Both signals are observed, but the most intense ion signals correspond to an ion after an internal condensation reaction (308 u and 334 u).

After 24 h reaction time with both mediators (Vio and dmVio) no residual adduct molecules are detected which is in contrast to the phenolic lignin model compounds. In the Experimental section a more detailed summery of the reactant and product peaks and their identification is given (Table 2).

The formation of a semi-stable adduct also can be monitored by UV/Vis spectroscopy. From reaction of the radicals with the model compounds intensely redish colored solutions result, with an absorption maximum found at around 500 nm (Fig. 4). A continuous reduction of the absorption is observed which conforms to the semi-stability of the adducts found by LC-MS measurements.

From these experiments it is concluded that the reaction of mediators and model compounds lead to 1 : 1 covalent adduct molecules. In most cases this adduct molecule is not stable and the adduct complex hydrolyses (type a), but in some cases, here *e.g.* dmVio and guaiacol, a stable adduct is formed (type b). The first mechanism (type a) could explain a transient loss of mediator, but the latter mechanism (type b) also may hold for an irreversible loss of mediator due to chemical attachment to the pulp.

Table 2 Identified LC-MS peaks

	Retention time/ min	Mass/u	Substance
Reactants	9.2	156	Vio (not shown)
	25.5	184	dmVio
	20.9 (UV)	No ion	Gua
	29.8	167, 151[a]	VA
Gua + Vio	18.9	280,[a] 138	Adduct
	33.3 (24 h)	276,[a] 260	Quinoid dimer
Gua + dmVio	25.7	184	dmVio
	27.1	308,[a] 292, 138	Adduct
	32.6 924 h)	276,[a] 260	Quinoid dimer
VA + Vio	25.9	324, 306,[a] 182	Adduct
	29.8	168, 151[a]	VA
	32.5	167,[a] 151	Veratric aldehyde
VA + dmVio	25.7	184	dmVio
	29.4	352, 334[a]	Adduct
	30.1	168, 151[a]	VA
	32.8	167,[a] 151	Veratric aldehyde

[a] Most abundant ion.

Formation of model compound dimers

The next question to analyze is whether the observed reactions are due to the direct reaction of mediator radicals with model compounds or whether other mechanisms are involved. A good indicator for concomitant reactions is that the solutions (see Fig. 4) do not become completely colorless, because other colored compounds develop.

The mass spectra indicate the formation of dimeric quinoid compounds from the lignin model compounds (Fig. 5). The same product is formed from reactions involving the different mediators Vio and dmVio. This corresponds with the reaction scheme that in a first step the model compound reacts with the Vio· under formation of an aromatic radical and in a second step a dimerisation with another model compound molecule occurs. Oxygen-rich quinoid systems are formed *via* reactions with the oxygen content of the aqueous solution.[14–16] Performing MS/MS experiments with the product ion of mass 276 u leads to a major fragment with 244 u which correlates to the loss of molecular oxygen (Fig. 5) which proves the above mentioned mechanism.

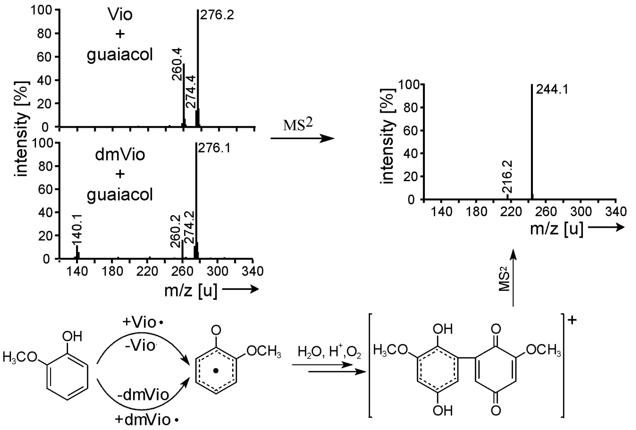


Fig. 5 Formation of mediator type independent guaiacol dimers. The MS and MS/MS spectra of the molecule and a proposed reaction scheme is shown.

The reaction mechanism found here is only triggered by the reaction of the mediator radical with the lignin model compound but the mediator does not take part in the second reaction step. Such type of reactions will cause undesired products but it would not cause any loss of mediator. Firthermore the dimerisation reaction is of little importance for the lignin in the pulp, as there is no free mobility of the aromatic subunits.

Reaction of model compound radicals with mediator molecules

From the experiments described the only possible conclusion is that the mediator radical is not covalently attached to the model compound but rather a second mediator molecule is reacting with the activated model compound.

Hydrogen abstraction of the mediator-radical from lignin or the model compounds leads to the formation of secondary radicals which should be detectable by EPR spectroscopy as long as they have a sufficient lifetime. In non-protic organic solvents an extended lifetime of the secondary radicals is expected. For the detection of these secondary model compound radicals lyophilized Vio· and dmVio· was prepared and dissolved in cold acetonitrile (−40 °C). As a suitable lignin model compound the dimeric phenolic guaiacolglyceryl-β-guaiacyl ether was chosen. A small amount of the ether dissolved in cold acetonitrile was added to the mediator radical solution in acetonitrile. When Vio· was used no secondary radical signal could be detected after the addition of the model compound. Using dmVio· led to the formation a new radical signal, which clearly indicates a disappearance of the oxime structure (Fig. 6). The EPR signal of iminoxy radicals is split into three groups with a hyperfine constant ranging from 28 to 32 G due to an interaction with the oxime nitrogen atom (Fig. 6, upper curve).[17] After the addition of guaiacolglyceryl-β-guaiacyl ether a radical signal is detected, which shows splitting into three groups of lines of same intensity. This indicates a coupling with a spin $I = 1$ atom like nitrogen. However, now the hyperfine constant is only approx. 10 G typical of *N*-hydroxy radicals.[18] The further splitting of each group of lines into a doublet with a hyperfine constant of 2 G is caused by a proton at the α-carbon or a proton from a hydroxy group at the nitrogen atom. The detected radical signal belongs to the primary radical adduct between dmVio and the model substance guaiacolglyceryl-β-guaiacyl ether. With the formation of a covalent bond the oxime structure is lost.

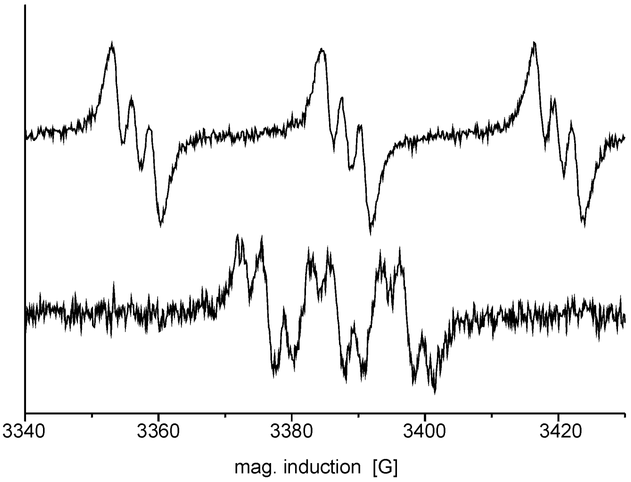


Fig. 6 Radical reaction monitored by EPR in acetonitrile (−40 °C). (Upper curve) The EPR-signal of dmVio· with its large coupling constant is typical for an oxime radical. (Lower curve) After reaction of dmVio· with guaiacolglyceryl-β-guaiacyl ether the dmVio· signal disappears and a new radical signal with a much smaller coupling constant appears.

In Fig. 7 a model for the structure of the adducts as well as their development is proposed on the basis of veratrol and guaiacol. Primarily a radical adduct is formed from the model compound radical obtained in the first step with a mediator molecule which leads to the formation of a *N*-hydroxy radical structure as seen in EPR. Due to the radical structure it is assumed that further internal reactions will occur, in particular ring-closure, before the radical character is lost *via* an inhibitor.

The reactions cause the formation of semi-stable molecules. Using the proposed reaction model (Fig. 7) the fragmentation pattern of the APCI mass spectrum of the veratryl alcohol–Vio adduct may be interpreted (Fig. 8). The formed adduct releases H_2O during ionization and a break down of the mediator part of the adduct is induced. Similar reactions occur in the reaction solution. They are responsible for the disappearance of the adduct signal within 24 h reaction time.

Summary

Electrochemical mediator-based (EMB) delignification is an attractive alternative to existing delignification processes based on chlorine. Theoretically this process should be possible without any consumption of chemicals. Thus it has the potential to be economically as well as environmentally attractive. Very little was known about the reaction of the activated mediator radicals with the lignin content in the pulp. We have investigated the key reactions of Vio· and dmVio· with lignin model compounds as well as native lignin by electrochemical, chromatographic and spectroscopic methods.

It was found that the mediator radicals in aqueous solution react very rapidly with phenolic groups, and more slowly with

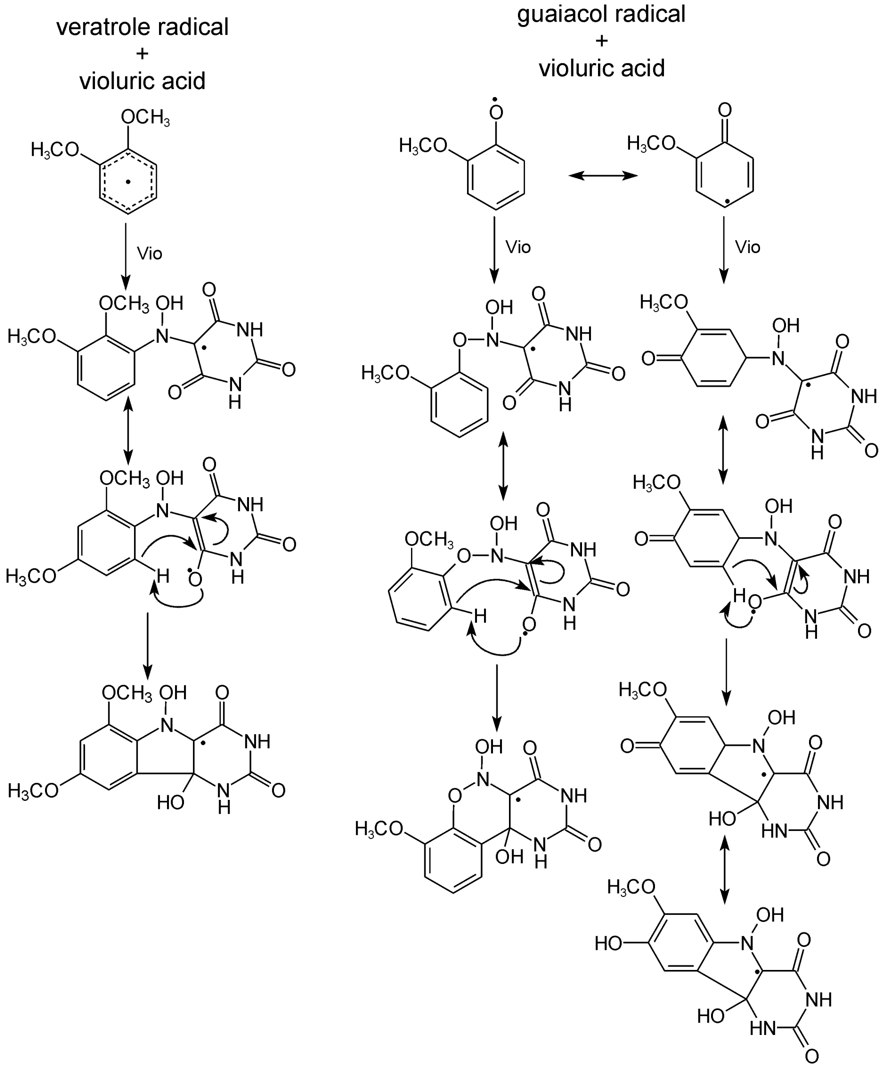


Fig. 7 Proposed mechanism for the mediator–substrate adduct formation. From the LC-MS measurements a one-to-one stoichiometry between radical and lignin model compound is derived.

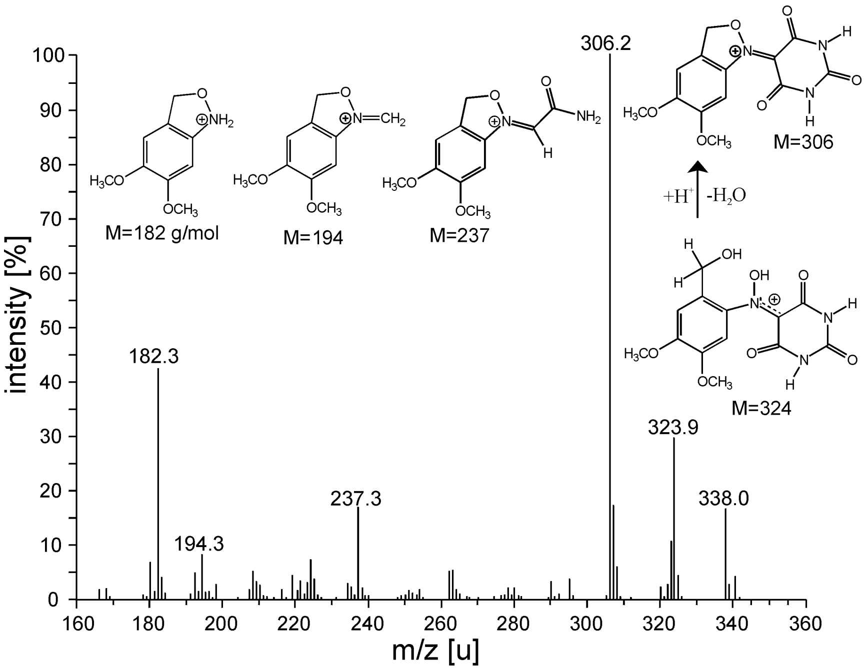


Fig. 8 Shown is the APCI mass spectrum of the adduct of Vio˙ and veratryl alcohol. The fragmentation pattern observed fully corresponds with the ring formation theory.

activated aromatic rings under abstraction of hydrogen atoms. Hydrogen abstraction from the benzyl alcoholic carbon is of minor importance. No reaction with the cellulose content of pulp is expected as experiments with cellobiose have shown.

The reaction stoichiometry between the mediator radicals and the model compounds was found to be one to one.

The molecular cause for the loss of mediator is due to the formation of covalent adducts from mediator-activated model compound radicals (and their counterparts in the lignin network, respectively) with mediator molecules. The adduct molecules predicted by this model have been identified by LC-MS spectrometry. The adducts are colored semi-stable compounds. Primary radical *N*-hydroxy type adducts were identified by EPR measurements. As a consequence of the radical character further internal reactions are assumed which stabilize the adduct.

The findings reported in this paper point the way to an optimization of mediator-based enzymatic as well as electrochemical processes for pulp delignification. The interception of the induced secondary radicals by additives will increase the cyclicity of the mediator.

Experimental

Chemicals

Commercially available chemicals were purchased from Fluka–Sigma–Aldrich and used without further purification. Guaiacolglyceryl-β-guaiacyl ether was synthesized according to ref. 19. Veratrolglyceryl-β-guaiacyl ether was synthesized by reaction of guaiacolglyceryl-β-guaiacyl ether with dimethyl sulfate. The mediator dmVio was synthesized from dimethylbarbituric acid by oxidation with selenium dioxide followed by a reaction with hydroxylamine hydrochloride. All described reactions were performed in 0.1 M acetate buffer (pH 4.5).

Methods

The X-band EPR-measurements were performed on a EPR spectrometer ESP 300 E from Bruker. A resonator from Varian equipped with a thin layer flow cell was used. The modulation amplitude was 2 G at a modulation frequency of 12.5 kHz. The mediator concentrations used were 2 mmol L^{-1}. The solutions were circulated through the spectrometer by a peristaltic pump. The solution was pre-electrolyzed with Pt-electrodes at 1.5 V for 45 min at room temperature in order to achieve a radical content of about 40%. The radical concentration was determined by EPR which was calibrated by RDE-voltammetry. The half-life of the radicals under the conditions used here (room temperature, 0.1 M acetate-buffer pH 4.5) is more than one hour. After the electrolysation the very slow thermal decay of the radical population was measured ($t = -10$ to 0). Then the model compounds were added as a solution or suspension. In order to determine the reaction kinetics a reactivation of the mediator was not intended.

For rotating disk electrode (RDE) measurements a BM-EDI101 electrode and CTV 101 speed control module from Radiometer Analytical were used. As a working electrode a glassy carbon disk with 3 mm diameter, as a counter electrode a glassy carbon rod with 5 mm diameter and a saturated calomel electrode (SCE) as a reference electrode were used. The electrode was rotated at 1000 rpm and the scan rate was 20 mV s^{-1} in the potential range from 0.1 to 1.1 V *vs.* SCE. All experiments were performed in 0.1 M acetate buffer (pH 4.5). For the determination of the mediator recovery rate for the reaction with guaiacol (U_{Ox} = 0.7 V *vs.* SCE) it is important to add only a small excess of guaiacol to minimize the error due to direct electrochemical oxidation of guaiacol. The RDE-measurements with pulp were done at a pulp consistency of 3% (1.3 g dried pulp in 40 ml 0.1 M acetate buffer pH 4.5). A direct oxidation of the pulp is not observable due to the fact that a direct contact of electrode and pulp scarcely occurs in the experiment.

LC-MS/MS measurements were done on a LCQduo from Thermoquest Finnigan equipped with an LC-system comprising of a P4000 gradient pump, a UV2000 UV/Vis detector and a RP18 Nucleosil column from Bischoff (Germany) (length 250 mm, 2 mm diameter, particle size 5μm). The mobile phase was a linear gradient from water containing 0.5% formic acid (**A**) and methanol, containing 10% water and 0.5% formic acid (**B**) (0–10 min: 100% **A**; 10–30 min: linear gradient 0% to 100% **B**; 30–60 min: 100% **B**). The concentration of the samples was 1–5 mmol L^{-1}. APCI ionization (positive mode) with nitrogen as shooting gas was used. The radical solution in 0.1 M acetate buffer pH 4.5 was prepared electrochemically, and the radical concentration was determined by RDE-voltammetry. An excess of the model compounds in 0.1 M acetate buffer (pH 4.5) was added. Samples were taken from the reaction solution at different times and immediately frozen in liquid nitrogen. Then the samples were successively measured by LC-MS. In Table 2 the retention times and masses of the different peaks are given. The main peaks were identified by their mass spectra apart from the peak with the retention time 31.5 min when reacting Vio and dmVio with VA. The peak consists of a major ion with 182 u and a fragment with 151 u. The signal does not fit in its retention time and fragmentation pattern of veratric acid (m/z = 200, 183 (100%), 139, 117).

UV/Vis spectra were measured on a UV900 from Kontron. The probe was a diluted sample (1 to 1000) from the LC-MS investigations.

Acknowledgements

Stimulating discussions with D. Braga and N. Vlachopoulos as well as financial support from the Fond der Chemischen Industrie are gratefully acknowledged.

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Adsorption and separation of water-soluble aromatic molecules by cyclodextrin-functionalized mesoporous silica†

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Received 20th September 2002
First published as an Advance Article on the web 5th December 2002

The adsorption properties of various water-soluble aromatic molecules (*p*-nitrophenol, *p*-nitroaniline, *m*-nitrophenol, *p*-chlorophenol and phenol), with CD-HMS, a new class of cyclodextrin-containing materials with uniform framework mesoporosity, has been investigated. The adsorption isotherms, uptake kinetics and distribution coefficients of the various solutes with the adsorbents were measured and the results interpreted based on the physicochemical properties of the adsorbents, the chemical structure of the adsorbates, and the inclusion thermodynamics between the adsorbates and the cyclodextrin binding sites. The CD-HMS adsorbents were thus shown to be promising materials for the selective separation of aromatic molecules from water.

Introduction

Cyclodextrins are cyclic oligosaccharides consisting of six or more linked D-glucopyranose units. The most widely studied cyclodextrins are those composed of six, seven and eight of these units, denoted α-, β- and γ-cyclodextrin, respectively. The conical shape of these molecules results in well-defined hydrophobic central cavities (with top and bottom diameters of 5.3 and 4.7 Å for α-cyclodextrin, 6.5 and 6.0 Å for β-cyclodextrin, and 8.3 and 7.5 Å for γ-cyclodextrin) that can accommodate the inclusion of various organic molecules with suitable geometry and function.[1] Fig. 1 shows the chemical structure of β-cyclodextrin and the depicts the formation of an inclusion complex with the cavity of the molecule. Cyclodextrins therefore behave as receptors for the selective binding of organic molecules, forming weak inclusion complexes with bound guest species.[1]

The unique host–guest chemistry of cyclodextrins is highly conducive to the selective uptake of organic molecules from aqueous systems.[2–5] Moreover, the chiral nature of the cavity in these molecules makes them useful for enantiomeric separation applications.[1] These macromolecules thus demonstrate potential usefulness in a wide variety of applications, such as for chromatography, for the remediation of contaminated water, and for the purification of organic products. Because product/reagent separation, waste minimization and trace component analysis are important objectives of green chemistry and clean technology, cyclodextrins may be useful towards the achievement of these goals.

Cyclodextrins themselves, however, are highly water soluble, and must therefore be processed into solid forms before they can be implemented into usable separation technology. Thus, three different approaches for the preparation of cyclodextrin-functionalized solid materials have up until now been developed. The first of these involve the incorporation of cyclodextrins into polymers by attaching the moieties *via* chemical linkers to the backbone of polymer chains (Fig. 2(a)).[2–8] The second approach involves the coating or grafting of cyclodextrin moieties onto stationary phases such as organic polymers[9,10] or silica gel[11–18] (Fig. 2(b)). Most recently, a third type of cyclodextrin-modified materials, denoted CD-HMS, was developed in which the cyclodextrin groups are located within the framework of nanoporous oxides (Fig. 2(c)).[19]

CD-containing polymers are useful materials for organic molecule separation because they possess high CD group content and can easily be processed into various forms for

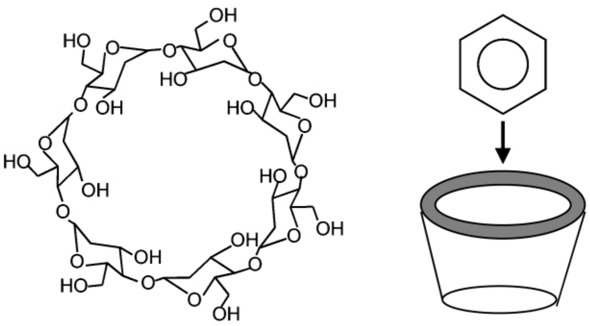

Fig. 1 (left) Molecular structure of β-cyclodextrin and (right) depiction of the macromolecule's inclusion cavity into which organic molecules can bind.

Green Context

Green chemistry encompasses reductions in the environmental impact of all chemical processes including remediation processes. The separation and isolation of organic compounds from aqueous process streams in a way that does not add to the environmental footprint of the whole process is an important goal in this context. Here we see how by utilising the excellent host–guest chemistry of cyclodextrins within easily accessible mesoporous silica structure, we can achieve efficient adsorption of organic molecules from water. The supported reagents can be prepared in a quite environmentally friendly way and they are effective under the typically harsh conditions (above ambient temperature, low pH, presence of bacteria, *etc*) found in industrial and waste water treatment plants. ***JHC***

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† Electronic supplementary information (ESI) available: Figs. S1–5: distribution coefficient profiles. See http://www.rsc.org/suppdata/gc/b2/b209251b/

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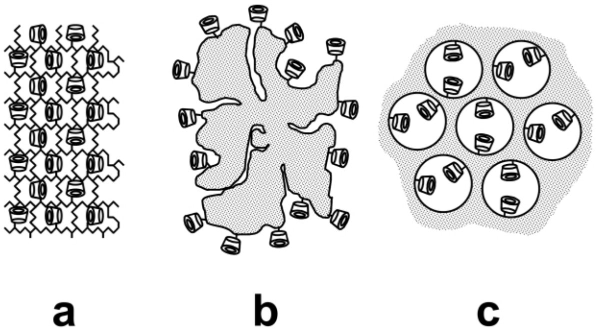

Fig. 2 Schematic representations of diverse cyclodextrin-functionalized materials: (a) polymer matrices, (b) coated substrates and (c) nanoporous frameworks.

practical applications (*i.e.*, resin beads, membranes, *etc.*). These polymers, however, are plagued by their very low specific surface areas and absence of framework nanoporosity,[2–8] drawbacks that impede the access of adsorbate molecules to the crowded cyclodextrin sites within the network of polymer chains (Fig. 2(a)), and subsequently result in incomplete sorption to the binding sites and slow diffusion kinetics. In addition, the lack of thermal and chemical stability of polymers often make them incompatible with the harsh conditions used in many industrial processes. In contrast, CD-coated (or grafted) materials such as silica offer improved access to the binding sites because the moieties are located on the external surface of the support, and the structure has improved stability owing to the robustness of the substrate (Fig. 2(a)). Unfortunately, the low CD loading of these materials impart them with greatly limited adsorption capacities. Our recently reported success in incorporating CD groups inside the pore channels of mesoporous silica with uniform channel structure (denoted CD-HMS) has resulted in a new class of CD-functionalized materials with both high CD group loadings and chemically robust structures (Fig. 2(c)).[19] Preliminary adsorption studies on CD-HMS materials have shown that their open-framework structures promote unhindered interactions of organic guests with their CD binding sites because they easily permeate the material and reach the abundant CD groups inside the adsorbent (Fig. 2(c)).[19]

CD-HMS materials are prepared using an entirely aqueous/ethanolic synthesis procedure involving surfactant structure-directing agents (alkylamines), pore expanding additives (trimethylbenzene, TMB) and ethoxysilane precursors (for an extensive description of the CD-HMS synthesis process, see ref. 19). Once the materials are formed, the surfactant and TMS are removed from their framework by ethanol extraction, and can therefore be recycled for further use. The environmentally friendly aspects of CD-HMS preparation are therefore compatible with the principles of 'green synthesis', avoiding the use and disposal of toxic solvents and precursors which are often necessitated in the preparation of organic polymers and coated silicas.

Mesoporous silicas related to CD-HMS but functionalized with ligand groups have in recent years been extensively investigated for their ability to bind toxic inorganic species such as heavy metal ions from solution.[20–28] In contrast, similar efforts to apply ordered mesoporous silicas for the selective adsorption of *organic* molecules have up until now remained virtually non-existant. This report investigates and compares the sorption properties of various soluble aromatic compounds by a series of mesoporous CD-HMS adsorbents having varying loadings of cyclodextrin groups. To the best of our knowledge, CD-HMS represents the first class of mesoporous materials which can selectively separate organic molecules by using the shape- and function-specific inclusion properties of receptor binding sites such as those of cyclodextrin. Because the designed of tailored solid adsorbents (silica-based materials in particular) applied towards the separation and isolation of reagents, products and wastes from process streams constitutes one of the primary objectives of green chemistry,[29,30] CD-HMS materials represent an important advancement in this area.

Experimental

Adsorbents and solutions

Nanoporous CD-HMS materials containing various loadings of CD groups were synthesized by the crosslinking of a silylated derivative of β-cyclodextrin with tetraethoxysilane (TEOS) in the presence of a structure-directing surfactant, following previously described processes.[19] The CD-containing nanoporous materials thus formed were designated as CD-HMS-*X*%, where *X* refers to the molar percentage of CD groups in the materials with respect to their Si content. The adsorbents were structurally and chemically characterized according to the methods described in ref. 19. Aqueous solutions with varying concentrations (in the range 0–0.4 mM) of the following aromatic compounds (Aldrich) were prepared using deionized water: *p*-nitrophenol ($O_2NC_6H_4OH$, pNP), *p*-nitroaniline ($O_2NC_6H_4NH_2$, pNA), *m*-nitrophenol ($O_2NC_6H_4OH$, mNP), *p*-chlorophenol (ClC_6H_4OH, pCP) and phenol (C_6H_5OH, PhOH).

Aromatic molecule adsorption

For each CD-HMS adsorbent, 5 mg samples were stirred with 25 ml of the adsorbate solutions for 24 h. The suspension was then filtered and the residual solute concentration in the filtrate was measured using UV–vis spectroscopy (using the intensity of the λ_{max} peak for each aromatic solute: pNP = 405 nm, pNA = 405 nm, mNP = 288 nm, pCP = 281 nm and PhOH = 400 nm). The amount of aromatic solute adsorbed by the CD-HMS was then determined by subtracting the concentration in the supernatent from that of the initial untreated solution.

Adsorption kinetics

5 mg samples of each adsorbent were slurried in 20 ml water. 20 ml of aromatic molecule solution (0.22 mM) were then rapidly added to the slurry, after which the suspensions were stirred for specific time periods (up to 600 s), then rapidly vacuum filtered through a Whatmann paper filter. The residual solute concentrations in the filtrates was measured by UV–vis spectroscopy. The amount of aromatic solute adsorbed by the CD-HMS was then determined by subtracting the concentration in the supernatent from that of the initial untreated solution.

Results and discussion

Adsorbent characteristics

The nomenclature and physico-chemical properties of the CD-HMS materials are shown in Table 1. The adsorbents had high surface areas (200–550 m^2 g^{-1}) and pore volumes (0.21–0.51 cm^3 g^{-1}), and uniform pore channels with diameters in the range 38–42 Å (Table 1).[19] The CD contents in the materials (up to 0.39 mmol g^{-1}, or about 30% by weight) were comparable to

Table 1 Physical and surface properties of CD-HMS materials

Material	Surface area/m^2 g^{-1}	Pore volume/ cm^3 g^{-1}	Pore diameter/Å	CD content/ mmol g^{-1}
CD-HMS-2%	547	0.51	38	0.14
CD-HMS-4%	319	0.26	39	0.32
CD-HMS-6%	197	0.21	40	0.33
CD-HMS-8%	235	0.27	42	0.39

those of typical CD-containing polymers,[2–8] and clearly superior to those of CD-coated adsorbents.[19]

Adsorption isotherms

Representative adsorption isotherms for CD-HMS-8% with each of the aromatic guests are shown in Fig. 3. The aromatic solutes were taken up by the adsorbents until a maximum saturation capacity was reached, the magnitude of which being related to both the amount of cyclodextrin groups incorporated within the CD-HMS materials and to the type of aromatic solute, as shown in Table 2. Control adsorption experiment in which non-functionalized HMS silica was used under otherwise identical experimental conditions revealed negligible uptake of the aromatic solutes. This shows that the uptake of the aromatic molecules results exclusively from their inclusion within the CD groups of the materials, and not through non-specific binding interactions with the silica support.

Interestingly, the maximum adsorption capacity for the different solutes, expressed in mmol g^{-1}, were very dissimilar for each CD-HMS adsorbent investigated. For instance, the maximum adsorption capacity for pNP was found to mirror that of the cyclodextrin content in each of the CD-HMS materials (Table 2), suggesting that 1:1 complexation of the solute is occurring with virtually every cyclodextrin group present. The decreasing adsorption capacity of the adsorbents towards other aromatic solutes, however (Table 2), denoted weakened binding affinity of the materials for aromatic molecules with different chemical structures. The affinity of the CD-HMS adsorbents for the aromatic molecules showed the following trend: pNP > mNP > pCP ≈ pNA > PhOH (Table 2), which is found to correlate with the magnitude of the free energies measured for solution-phase complexation of the solutes with β-cyclodextrin (pNP: −14.5 kJ mol^{-1}, pNA: −14.3 kJ mol^{-1}, mNP: −13.9 kJ mol^{-1}, pCP: −13.7 kJ mol^{-1}, PhOH: −11.3 kJ mol^{-1}).[1] The degree of access of the CD binding sites within the adsorbents is thus related to the complexation affinity of these sites towards the different aromatic solutes. The ability of the CD sites to bind with certain aromatic molecules while completely exclude others demonstrates the ability of CD-HMS to selectively adsorb and separate different water-soluble aromatic molecules.

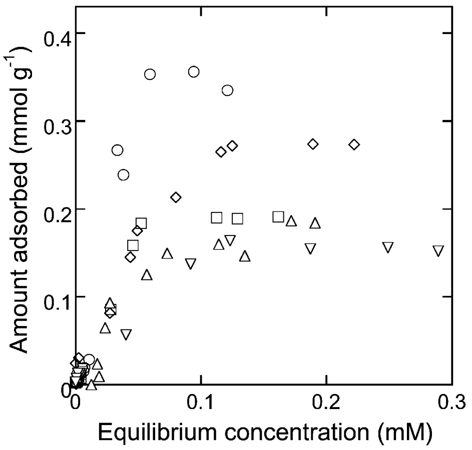

Fig. 3 Aromatic molecule adsorption isotherms for CD-HMS-8% (pNP = ○, pNA = □, mNP = ◇, pCP = △, PhOH = ▽). Expressed in ppm concentration units, 0.1 mM corresponds to 13.9 ppm for pNP and mNP, 13.8 ppm for pNA, 12.9 ppm for pCP, and 9.4 ppm for PhOH.

Table 2 Adsorption capacities of CD-HMS materials for various aromatic molecules. The values indicated in parentheses denote the percentage of CD groups in the adsorbents that bind with each aromatic solute

	Adsorption capacities/mmol g^{-1}			
Adsorbate	CD-HMS-2%	CD-HMS-4%	CD-HMS-6%	CD-HMS-8%
(theoretical maxima)[a]	*0.14*	*0.32*	*0.33*	*0.39*
pNP	0.13 (93%)	0.24 (75%)	0.30 (91%)	0.36 (92%)
mNP	0.13 (93%)	0.17 (53%)	0.23 (70%)	0.28 (72%)
pCP	0.10 (71%)	0.14 (44%)	0.16 (48%)	0.18 (46%)
pNA	0.10 (71%)	0.13 (41%)	0.15 (45%)	0.19 (49%)
PhOH	0.06 (43%)	0.10 (31%)	0.12 (36%)	0.15 (38%)

[a] Amount of CD groups in adsorbent (mmol g^{-1}).

A close inspection of the adsorption isotherms at very low equilibrium solute concentrations reveals that the uptake of the aromatic molecules is efficient, but the amount adsorbed levels off at values well below that of the maximum adsorption capacity of the materials (up to about 0.03 mmol g^{-1}). This signifies that, although the materials can act as effective adsorbents for low levels of aromatic molecules, significant uptake of the solutes only occurs at comparatively high concentrations (greater that about 3 × 10^{-4} M). Such adsorption behaviour attests the inherently weak interactions which exist between the cyclodextrin binding sites and the targeted aromatic guests. Previous studies have also found that, as in the case of CD-HMS, the adsorption capacity of CD-functionalized polymers is highly dependent on the solute concentration of the treated solutions.[2,3]

Adsorption kinetics

Representative kinetic uptake curves for each solute with CD-HMS-8% are shown in Fig. 4. The uptake of aromatic molecules by the CD-HMS materials were generally very rapid, reaching the maximum adsorption capacity of the adsorbents after about 5 min of solution exposure. In particular, pNP demonstrated exceptionally rapid uptake at the early stages of the adsorption process, with almost half of the CD sites being accessed within the first minute of exposure (Fig. 4). The sorption kinetics of the CD-HMS materials were vastly improved compared to those reported for CD-containing polymers, which under similar treatment conditions reached saturation only after 30 min of exposure.[2,3] The fast adsorptivity exhibited by these materials can be attributed to the open-framework nature of the

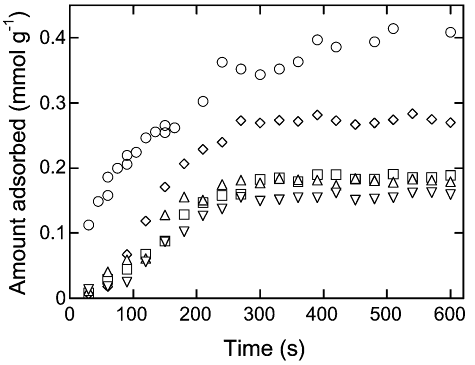

Fig. 4 Kinetic uptake plots of aromatic molecules (pNP = ○, pNA = □, mNP = ◇, pCP = △, PhOH = ▽) for CD-HMS-8%.

mesoporous adsorbents, resulting in greatly improved access of the targeted adsorbate molecules to the cyclodextrin binding sites.

Uptake effectiveness

The effectiveness of the CD-HMS materials towards the removal and separation of aromatic molecules from water was gauged by comparing the distribution coefficients, K_d, of the adsorbents at different solute concentrations with respect to the various solutes investigated. The value of K_d for each adsorbent–adsorbate system were obtained from eqn. (1)[27,28] using their respective equilibrium adsorption data:

$$K_d = (C_i - C_f)V_{sol}/(C_f m_{ads}) \qquad (1)$$

where C_i is the initial metal ion concentration of the solution, C_f is the metal ion concentrations after adsorption, V_{sol} is the volume of the solution (mL) and m_{ads} is the amount of adsorbent used (g). Fig. 5 shows representative concentration-dependent K_d profiles for each aromatic solute. Overall, the K_d values measured for the CD-HMS materials were in the range of 10^3–10^5 mL g^{-1}, consistent with values reported for highly effective adsorbents, such as those found for ligand-functionalized metal-ion adsorbents.[27,28]

The K_d values for pNP and pNA generally followed a decreasing trend as a function of increasing solute concentrations (Fig. 5). This type of separation behaviour is typical for materials that have appreciable binding interactions with targeted guest compounds (especially in the case of heavy metal ions)[27,28] because adsorbents with adsorbate-specific binding sites (such as in CD-HMS) are usually most effective at binding when these sites are largely unoccupied (or uncomplexed) by the adsorbate. As saturation of these sites is approached (*i.e*, at higher adsorbate concentration), the binding affinity of the materials decrease.

The decreasing values of K_d , however, is not systematic for most solutes. For instance, the K_d values for pNP and pNA adsorption with CD-HMS decreased in the low adsorbate concentrations range (below 1 ppm) (Fig. 5(a) and (b)), but the values subsequently increased thereafter, reaching a second maximum values at adsorbate concentrations near 10 ppm (beyond which the values once again resume their decreasing trend).[31] The presence of this second K_d maximum suggests the presence of two distinct types of CD binding sites within the adsorbents. The first of these respond well to the adsorption of low concentrations of the adsorbates, and likely represents the complexation of the aromatic molecules with the most readily accessible CD groups found either on the perifery of the adsorbate particles, or near the openings of the pore channels.

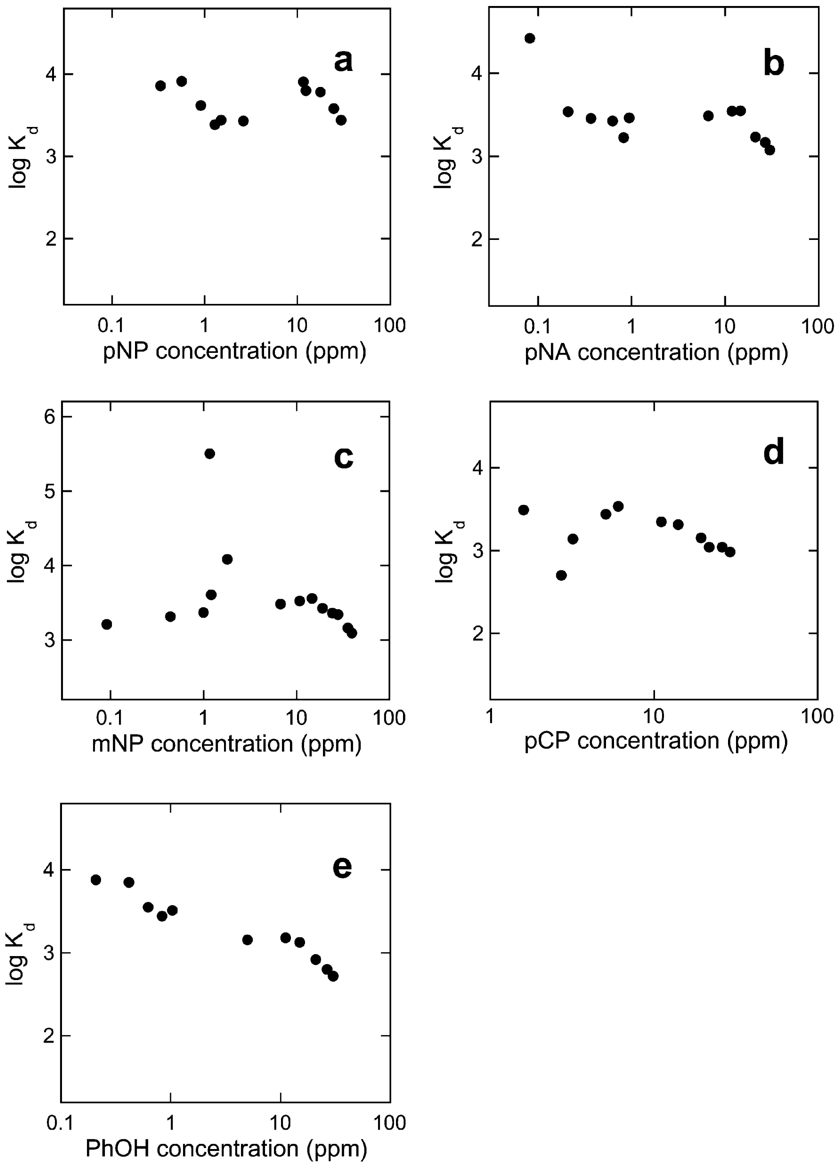

Fig. 5 Distribution coefficient (K_d) profiles of CD-HMS-8% towards (a) pNP, (b) pNA, (c) mNP, (d) pCP and (e) PhOH.[31]

The second type of site, which only interact with the adsorbate molecules at higher concentrations (*ca.* 10 ppm) can be assigned to the interaction of the adsorbates with CD groups located deeper within the pore channels of the materials (requiring a higher adsorbate concentration so that these can be driven to interact with these more sterically impeded sites). This interpretation is consistent with the shape of the adsorption isotherms (Fig. 3, *vide supra*), in which two distinct adsorption inflexions were also reported (denoting two distinct types of binding environments).

Unlike those of pNP and pNA, which showed optimal adsorption effectiveness at low concentrations (below 0.3 ppm), the K_d values for mNP, pCP and PhOH were in general significantly reduced in this concentration range. This discrepancy can be rationalized by comparing the free energies for the solution-phase complexation for pNP and pNA with β-cyclodextrin (measured at -14.5 and -14.3 kJ mol^{-1}, respectively)[1] with those of mNP, pCP and PhOH (-13.9, -13.7 and -11.3 kJ mol^{-1}, respectively).[1] The ability of the CD-HMS materials to effectively adsorb pNP and pNA at low concentrations can therefore be attributed to the inherently higher free energies of complexation of these solutes with the most accessible (peripheral) binding sites compared to that of the other aromatic species. The K_d values for mNP, pCP and PhOH reach maximum values at higher adsorbate concentrations (between 1 and 10 ppm), where the adsorbate molecules interact with the CD groups located inside the pore channels of the adsorbent framework.

Conclusions

Mesoporous CD-HMS materials have been shown to be an effective new class of adsorbents for the selective adsorption of organic molecules from water. The open-framework structure of the adsorbents and their high CD content allowed for the rapid and unimpeded access of the targeted adsorbate molecules to potentially every binding site within the structure. The chemical and biological robustness of the silica framework encapsulating the cyclodextrin groups make CD-HMS materials particularly promising for use under the harsh conditions often encountered in industrial and wastewater treatment applications (*i.e.*, temperature, pH, presence of bacteria or algae, *etc.*).[19] Finally, that CD-HMS can be prepared in an environmentally-friendly manner makes these materials of particular interest for green chemistry applications. All of these beneficial characteristics therefore make CD-HMS materials clearly superior to other related adsorbents materials (such as polymers and coated silicas) from both industrial process and green chemistry points of view.

The results of the experiments presented in this work demonstrate that mesoporous CD-containing materials such as CD-HMS represent a promising emerging technology for a wide variety of environmental and separation applications, including pesticide remediation, VOC capture, reagent/product isolation, chiral drug separations and liquid chromatography.

Acknowledgements

The authors would like to thank the Natural Science and Engineering Research Council of Canada (NSERC) and Laurentian University for financial support.

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31 The distribution coefficient profiles of the other adsorbents (*viz.*, CD-HMS-2%, CD-HMS-4% and CD-HMS-6%) for each solute were virtually identical to each other, attesting to the reproducibility of the results. The complete distribution coefficient profiles for all CD-HMS materials has been provided as ESI†.

On-board hydrogen production in a hybrid electric vehicle by bio-ethanol oxidative steam reforming over Ni and noble metal based catalysts

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Received 21st August 2002
First published as an Advance Article on the web 16th December 2002

In this work we present the optimisation of the oxidative steam reforming of ethanol for hydrogen production in order to feed a Solid Polymer Fuel Cell (SPFC) over a Ni–Cu/SiO_2 catalyst at on-board conditions. The optimised experimental conditions involve a reforming temperature close to 700 °C, a molar ratio of H_2O/EtOH equal to 1.6 and a molar ratio of O_2/EtOH equal to 0.68. These conditions were also used to test noble metal (Pt, Pd, Ru and Rh) based catalysts. Ni and Rh based catalysts were tested in ageing experiments for up to 140 h at the optimised operating conditions. Ni–Cu/SiO_2 and Rh/Al_2O_3 catalysts allowed a high hydrogen mixture as well as a constant selectivity to the reaction products, moreover the ethanol was totally converted during this time. In contrast, the Ni/SiO_2 catalyst showed a continuous decrease in hydrogen production during ageing. An explanation to the differences between Ni and Ni–Cu catalysts is given in terms of the lower coke deposition on Ni–Cu catalyst due to the alloy formed. The rich hydrogen content in the outlet flow from the reformer obtained with the Ni–Cu, Ru and Rh based catalysts can be considered of high interest for fuel cells (FC) in mobile applications.

1 Introduction

Fuel cells (FCs) forego the traditional extraction of energy in the form of combustion heat, conversion of heat energy to mechanical energy and finally turning mechanical energy into electricity. FCs operate like continuous batteries when supplied with fuel (hydrogen) to the anode and oxidant (oxygen or air) to the cathode. Encouraged by a catalyst, the hydrogen atom splits into a proton and an electron, which take different paths to the cathode. Protons pass through the electrolyte and electrons create a separate current that can be utilised before they return to the cathode, to be reunited with the hydrogen and oxygen in a molecule of water. Therefore, FCs chemically combine the molecules of a fuel and oxidiser without burning but converting them directly to electrical energy and so dispensing with the inefficiencies and pollution of traditional combustion.

According to the U.S. Department of Energy, 'Solid Polymer Fuel Cells (SPFC) are the primary candidates for light-duty vehicles, for buildings, and potentially for much smaller applications such as replacements for rechargeable batteries'. These cells have high power density, can vary their output quickly to meet shifts in power demand, and so are suited for automobiles where quick startup is required.

Ideally, vehicles would store hydrogen fuel onboard in high-pressure tanks. However, because current technology does not permit storage of enough H_2 to deliver the driving range to which motorists are accustomed, hydrogen may initially be supplied from liquid fuels. Fuels containing hydrogen generally require a 'fuel reformer' that extracts the hydrogen. Generally, the reformate gas include H_2, CO, CO_2, H_2O and a small amount of CH_4. Carbon monoxide needs to be completely converted both because it is a criterion pollutant and also because it poisons the platinum electrodes, limited to 100 ppm.[1] Therefore other processes are required:[2–4] water gas shift (WGS) reactions, and/or selective oxidation (SELOX). After energy production in SPFC, the residual amounts of hydrogen and byproducts are converted into carbon dioxide and water in the catalytic burner.

Hydrogen sources include fossil fuels as methanol, ethanol, natural gas, petroleum distillates, liquid propane and gasified coal and even gas from landfills and wastewater treatment plants. Alcohols exhibit high qualities as H_2 generators, since they are easily decomposed in the presence of water (steam reforming reaction) and generate a H_2-rich mixture suitable for feeding fuel cells. Ethanol appears as an attractive alternative to methanol since it is much less toxic and is already used as versatile transportation fuel that offers a high octane number, a high heat of vaporisation and a low photochemical reactivity. Moreover, bio-ethanol can be produced in large quantities from biomass fermentation, therefore as a renewable energy source. This alcohol has also a significant advantage over fossil-fuel based systems: it is CO_2 neutral, since the carbon dioxide that is produced in the process is consumed by biomass growth and a closed carbon cycle is operated.

Several works have been recently published on ethanol steam reforming over Ni, Co, Ni/Cu and noble metals (Pd, Pt, Rh) on various supports.[5–14] In contrast, little work has been done on oxidative steam reforming despite the fact that it has been

Green Context

The development of fuel cells for automotive use relies on the on-board production of hydrogen in the vehicle. Most effort has been put into the development of methods for the extraction of hydrogen from methanol, which has a H : C ratio of 4, but less work has been published on the use of the less hydrogen rich ethanol. This paper shows that ethanol can be produced efficiently under conditions where no NOx or SOx emissions take place, and thus (bio) ethanol could be an appropriate fuel for fuel cell applications. *DJM*

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DOI: 10.1039/b208201m

shown as a very convenient method for the selective production of hydrogen from methane[15] and methanol[16] and that the process can be made more energy-efficient and the hardware can be smaller and lighter.[17] In a previous work we presented the optimisation of oxidative steam reforming of ethanol at diluted conditions over a Ni–Cu/SiO$_2$ catalyst.[18] The objective of the present study is to investigate in detail the effect of operating variables of the oxidative steam reforming of ethanol over the same catalyst under on-board conditions. Moreover, the hydrogen yield and the reaction selectivities obtained with this catalyst are compared with those obtained with noble metal (Pt, Pd, Ru and Rh) based catalysts.

2 Experimental

2.1 Catalyst

The active and selective materials selected for ethanol steam reforming were two Ni based catalysts supported on SiO$_2$, one of them doped with Cu, and several 5% noble metal (Pt, Pd, Ru, Rh) based catalysts supported on Al$_2$O$_3$ and supplied by Engelhardt. The Ni/SO$_2$ and Ni–Cu/SiO$_2$ catalysts were prepared on a silica support (Degussa) with a BET surface of 200 m^2 g^{-1} and by ionic exchange using Ni(NO$_3$)$_2$·6H$_2$O and Cu(NO$_3$)$_2$·3H$_2$O as precursors. The Ni/SiO$_2$ catalyst has a Ni content of 19.4%. The Ni–Cu/SiO$_2$catalyst has a Cu/(Ni + Cu) weight ratio of 10 and a total metal content of 18.4%. After calcination at 650 °C for 15 h, the Ni based catalysts were sieved to 0.2–0.3 mm.

2.2 Catalytic tests

Prior to catalytic testing, the catalyst was placed in a fixed bed reactor and reduced under flowing hydrogen (30 ml min^{-1}) at 650 °C for 8 h with a heating rate of 2 °C min^{-1}. After reduction the catalyst was cooled down to reaction temperature under helium atmosphere. The runs were performed under on-board conditions with helium instead of nitrogen at atmospheric pressure in a fixed bed reactor (ID = 4 mm and h_{bed} = 7 mm) where 50 mg of the catalyst are introduced. Catalyst was dispersed with SiC to minimise hot spot effects.

Two parallel reactors and a system of valves allow pretreating a catalyst while a second one is being tested. There are two lines of gases to the reactors providing an ethanol–water–air-like (79% He and 21% O$_2$) mixture from a gaseous He–O$_2$ mixture and a liquid H$_2$O–EtOH blend or a gas flow to pre-treat the catalyst with H$_2$. The H$_2$O–EtOH blend is regulated by a HPLC pump, the liquid is vaporised at 130 °C and then mixed with the gas flow before being fed to the fixed bed reactor or being sent to analysis before reaction. Gases were analysed on line by mass spectrometry and by gas chromatography. Wet gases were analysed by means of a Hewlett-Packard gas chromatograph model 6890, equipped with a TCD detector and a HP-PlotQ column that analyses CO$_2$, CO, CH$_4$ and other hydrocarbons as C$_2$H$_6$, C$_2$H$_4$ as well as EtOH and H$_2$O. Helium was used as the internal standard and the variation of its concentration measured by gas spectrometry allows the evaluation of the volume correction factor and of the ethanol conversion and selectivities to the reaction products.

2.3 Kinetic parameter formulae

Since this work was carried out at on-board conditions a volume correction factor (CF) that takes into account the volume change as a result of reactions was considered to calculate conversions and selectivities.

$$\mathrm{CF} = \frac{\mathrm{He_{in}}}{\mathrm{He_{out}}} = \frac{V_{\mathrm{out}}}{V_{\mathrm{in}}} \qquad (1)$$

where He$_{\mathrm{in}}$ and He$_{\mathrm{out}}$ are the He concentration at the inlet and at the outlet of the reactor respectively. The reactants conversion (ethanol, water or oxygen), denoted X_{reactant} is calculated according to eqn. (2) where $F_{\mathrm{i,\,in}}$ and $F_{\mathrm{i,\,out}}$ represents the molar flow rate of the i species measured at the inlet and at the outlet of the reactor respectively.

$$X_{\mathrm{reactant}} = \frac{[F_{\mathrm{reactant}}]_{\mathrm{in}} - [F_{\mathrm{reactant}}]_{\mathrm{out}}\mathrm{CF}}{[F_{\mathrm{reactant}}]_{\mathrm{in}}} \qquad (2)$$

and selectivities to carbon containing products (Cn) are calculated by the following equation:

$$S_{\mathrm{Cn}} = \frac{\lfloor F_{\mathrm{Cn}} \rfloor_{\mathrm{out}}\mathrm{CF}}{n\left[[F_{\mathrm{EtOH}}]_{\mathrm{in}} - [F_{\mathrm{EtOH}}]_{\mathrm{out}}\mathrm{CF}\right]} \qquad (3)$$

where n is the number of atoms of carbon in the product (n = 1 for CO, CO$_2$ and CH$_4$ and n = 2 for C$_2$H$_6$, C$_2$H$_4$ and CH$_3$CHO). The carbon deposited on the catalyst can be calculated [eqn. (4)] or determined experimentally by TPO experiments.

$$C_{\mathrm{deposited}} = ([F_{\mathrm{carbon\ in}}V_{\mathrm{in}} - F_{\mathrm{carbon\ out}}V_{\mathrm{out}}] \times 12)/m_{\mathrm{catalyst}} \qquad (4)$$

Selectivity towards hydrogen is calculated taking into account the variation of ethanol and water concentrations.

$$S_{\mathrm{H_2}} = \frac{[F_{\mathrm{H_2}}]_{\mathrm{out}}\mathrm{CF}}{3\left[[F_{\mathrm{EtOH}}]_{\mathrm{in}} - [F_{\mathrm{EtOH}}]_{\mathrm{out}}\mathrm{CF}\right] - \left[[F_{\mathrm{H_2O}}]_{\mathrm{in}} - [F_{\mathrm{H_2O}}]_{\mathrm{out}}\mathrm{CF}\right]} \qquad (5)$$

The contact time (t_{c}) is defined as the ratio between the mass of catalyst and the molar flow of the inlet ethanol. Though contact time is usually defined as the ratio between the mass of catalyst and the total inlet flow rate, the present definition focuses on the ethanol contact time for a direct evaluation of the link between the active sites concentration and the number of ethanol moles to convert.

$$t_{\mathrm{c}} = m_{\mathrm{catal}}\ (\mathrm{kg})/\mathrm{EtOH}\ (\mathrm{mol\ min^{-1}}) \qquad (6)$$

2.4 Ageing experiments

Ageing experiments were carried out using 50 mg of catalyst, a H$_2$O–EtOH molar ratio of 1.6 and O$_2$/EtOH molar ratio of 0.68 at 700 °C and a total volume flow of 80 ml min^{-1}. Three catalysts were tested under these conditions, the two Ni catalysts prepared in our laboratory and the 5% Rh/Al$_2$O$_3$ commercial catalyst.

3 Results and discussion

The oxidative steam reforming of ethanol is an intermediate step of a global process that allows electricity production. The optimisation criteria of the operating parameters must take into account the technologic limitations fixed by the system: (1) limitation of H$_2$O/EtOH molar to minimise the volume and weight of the system; (2) reduction of carbon deposition on the catalyst to prolong the lifetime of the catalyst and (3) reduction of the CO concentration to limit the importance (weight and volume) of the WGS and SELOX steps downstream.

Homogeneous reactions are very important when studying the oxidative steam reforming of ethanol and special attention must be paid to reduce the dead volume to avoid them. Fig. 1 shows the selectivity of the ethanol reforming in absence of

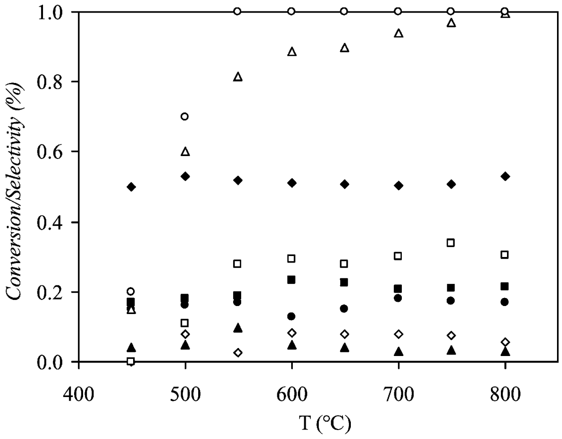

Fig. 1 Conversion of ethanol and oxygen and product selectivity of ethanol reforming reaction *versus* temperature at homogenous conditions; O_2/EtOH = 0.68, H_2O/EtOH = 1.6 and flow rate = 80 cm³ min⁻¹: (◆) S_{CO}, (■) S_{CH_4}, (▲) S_{CO_2}, (●) $S_{C_2H_4}$, (◇) $S_{C_2H_6}$, (□) S_{H_2}, (△) X_{EtOH}, (○) X_{O_2}.

catalyst at temperatures from 450 to 800 °C, with a H_2O/EtOH molar ratio of 1.6 and a O_2/EtOH molar ratio of 0.68. Ethanol decomposes at temperatures higher than 450 °C reaching a conversion of 95% at 700 °C with a total oxygen conversion from 550 °C. The selectivity to the reaction products is nearly constant at temperatures higher than 500 °C. There is a high selectivity to CO ($\approx$50%) and the selectivity to hydrogen remains very low ($\approx$30%) due to the high reaction selectivities to hydrogenated products as methane, ethane and ethylene and the production of water by the EtOH combustion. The selectivity to C_2H_4 ($\approx$18%) is also rather important, ethylene acts as a very strong promoter of carbon formation and probably an important quantity of ethanol is converted to coke.

In a previous work we optimised the operating variables for ethanol oxidative reforming at diluted conditions. A temperature close to 600 °C, a H_2O/EtOH molar ratio 1.55 and a O_2/EtOH molar ratio of 0.5 with a contact time close to 1 min kg mol^{-1} resulted in the highest selectivity to hydrogen (92.5%) reducing in turn the amount of water introduced and the carbon deposition.

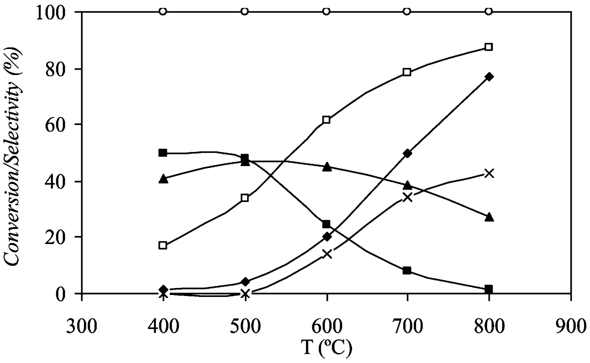

Fig. 2 Effect of temperature on reactants conversion and products selectivity at on-board conditions; H_2O/EtOH = 1.55 and O_2/EtOH = 0.5: (◆) S_{CO}, (■) S_{CH_4}, (▲) S_{CO_2}, (□) S_{H_2}, (×) X_{H_2O}, (○) X_{O_2}.

Fig. 2 shows the effect of temperature on reactants conversion and products selectivity at on-board conditions using the H_2O/EtOH and O_2/EtOH molar ratios optimised at diluted conditions, 1.55 and 0.5, respectively. Ethanol is completely converted over the whole studied temperature range and the conversion of water increases with temperature. The selectivity toward H_2 and CO increases with temperature, whereas the selectivity toward CH_4 decreases. Selectivity to hydrogen is only of 61.6%, this change (compared with 92.5% at diluted conditions) probably indicates a complex kinetic law with positive and negative partial reaction orders that are changed due to the higher partial pressures of the reactants at on-board conditions. Therefore, reaction temperature has to be increased in order to recover an important hydrogen production at on-board conditions. A reaction temperature close to 700 °C allows having an important production of hydrogen keeping the CO_2/CO_x ratio high enough for the downstream processes of the on-board system.

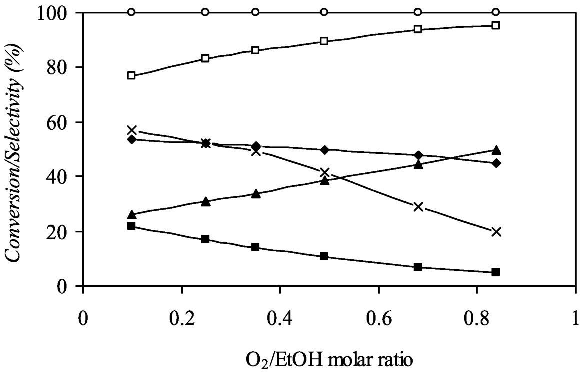

Fig. 3 Evolution of reactant conversions and reaction selectivities *versus* O_2/EtOH molar ratio at 700 °C: (◆) S_{CO}, (■) S_{CH_4}, (▲) S_{CO_2}, (□) S_{H_2}, (×) X_{H_2O}, (○) X_{O_2}.

Fig. 3 shows the evolution of reactant conversions and reaction selectivities as the O_2/EtOH molar ratio increases at 700 °C. The introduction of a larger amount of oxygen reduces selectivities to CH_4 and CO whereas CO_2 and H_2O are produced in a larger extent. It appears as if increasing the O_2/EtOH ratio, O_2 is used to oxidise CH_4 and part of the CO. Selectivity to hydrogen is also improved (96.8%) by increasing air feeding to the system. Moreover the introduction of a higher quantity of oxygen reduces the carbon deposition and so increases the lifetime of the catalyst. Under these more realistic conditions the optimised experimental conditions involve a reforming temperature close to 700 °C, a molar ratio of H_2O/EtOH equal to 1.6, a molar ratio of O_2/EtOH equal to 0.68 and a contact time close to 0.2 min kg mol^{-1}.[19] The composition of the outlet flow from the reformer was H_2/CO/CO_2/CH_4/H_2O/N_2 = 33/13/9/1/13/31.

3.1 Noble metal catalysts

5% Pd, Pt, Ru and Rh on Al_2O_3 were tested at temperatures from 650 to 800 °C, a molar ratio of H_2O/EtOH equal to 1.6, a molar ratio of O_2/EtOH equal to 0.68 and a total volume flow of 80 cm³ min⁻¹. We have already discussed the mechanism of the ethanol reforming as a function of the temperature domain with a Ni–Cu catalyst.[18] We showed that the acetaldehyde formation results from ethanol dehydrogenation at 300 °C and in the absence of oxygen. However, when catalysts based on Pd and Pt were tested there was a very high selectivity to acetaldehyde and high yields to CH_4 even at high temperatures. The amounts of C_2H_6 and C_2H_4 were also important and so the selectivity of ethanol reforming to hydrogen was rather small, never higher than 50–60%. Fig. 4(a) shows the product selectivities and the ethanol conversion for the oxidative ethanol reforming when using a 5% Pt/Al_2O_3 catalyst. The oxidative-dehydrogenation of ethanol on Pd and Pt based catalysts has an important role up to 750 °C. Selectivity to acetaldehyde (S_{acet}) decreases as reaction temperature increases being 50 and 20% at 650 and 700 °C, respectively. At 750 °C the decomposition of acetaldehyde is complete and CH_4 reforming and the water gas shift (WGS) reactions control the selectivities of the reaction.

Ru and Rh based catalysts showed much better performances. Fig. 4(b) shows the product selectivities and the ethanol

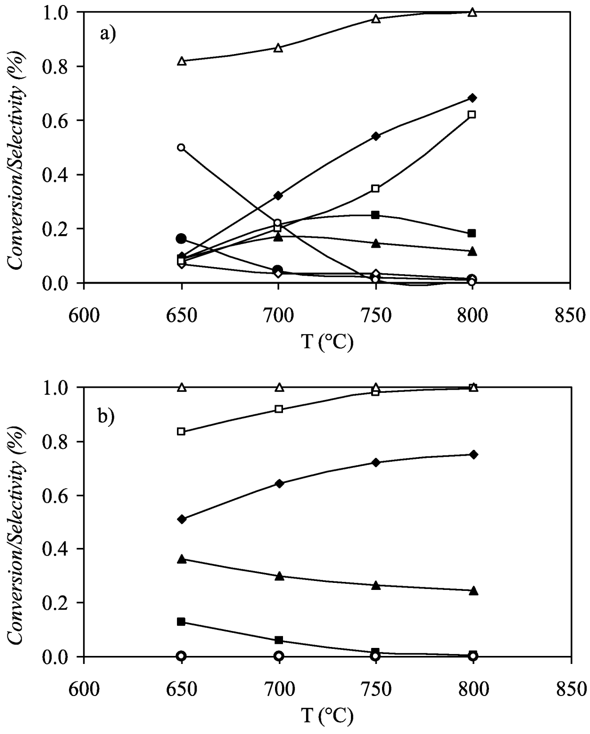

Fig. 4 Product selectivity reforming reaction and conversion of ethanol *versus* temperature (a) for 5% Pt/Al_2O_3 catalyst and (b) for 5% Rh/Al_2O_3 catalyst; $O_2/EtOH = 0.68$, $H_2O/EtOH = 1.6$ and $t_c = 0.084$ min kg mol^{-1}: (◆) S_{CO}, (■) S_{CH_4}, (▲) S_{CO_2}, (●) $S_{C_2H_4}$, (◇) $S_{C_2H_6}$, (□) S_{H_2}, (△) X_{EtOH}, (○) S_{acet}.

conversion for the oxidative ethanol reforming when using a 5% Rh/Al_2O_3 catalyst. Selectivities to hydrogen higher than 70% were already reached at 650 °C. Performances improved with reaction temperature and selectivity to CH_4 was negligible at 750 °C. No ethylene production was observed in the temperature range of study and so a lower deposition of coke can be expected.

An order in the performance of the noble metal based catalysts can be established based on the experiments carried

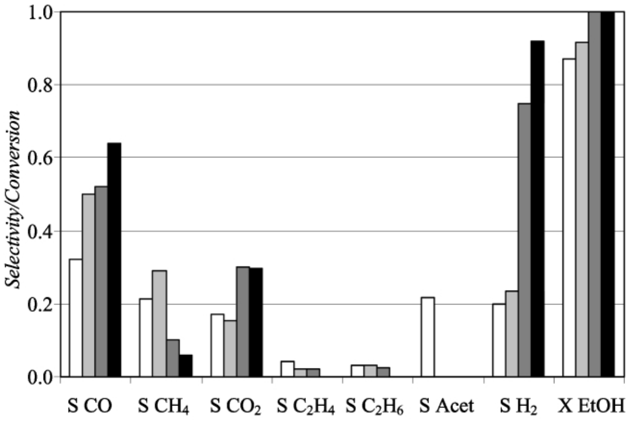

Fig. 5 Product selectivities of the reforming reaction and conversion of ethanol at 700 °C for noble metal based catalysts on Al_2O_3; $O_2/EtOH = 0.68$, $H_2O/EtOH = 1.6$ and $t_c = 0.084$ min kg mol^{-1}: (□) 5% Pt, (▨) 5% Pd, (▩); 5% Ru, (■) 5% Rh.

out at the standard conditions: Pt < Pd ≪ Ru < Rh. Fig. 5 shows the results observed with the 5% noble metal/Al_2O_3 at 700 °C. On the one hand Pt and Pd show similar performances and low selectivities to H_2 (0.20 and 0.23%, respectively), whilst Ru and Rh showed much higher selectivities to H_2 (0.75 and 0.90%, respectively). The very different results observed from Pd and Pt to Ru and Rh could be explained by the existence of a different reaction mechanism. In this sense, a detailed mechanism study by IR-DRIFT is in progress in our group.

3.2 Ageing experiments

Since the commercial development of oxidative reforming of ethanol requires a good stability of the catalyst, the most promising catalysts Ni–Cu/SiO_2 and 5% Rh/Al_2O_3 catalysts were tested for 140 h at the optimised operating conditions. Their selectivity toward hydrogen initially decreased with time-on-stream and stabilised after 10 h at values at 89 and 88% for Ni–Cu/SiO_2 and 5% Rh/Al_2O_3, respectively. These catalysts exhibited also a constant selectivity to the rest of reaction products and the ethanol was totally converted during this time.

Most workers agree on a metastable metal carbide being an intermediate stage in the growth of filamentary carbon. Formation of this metal carbide can be avoided by alloying the active metal with a metal not forming a carbide of significant stability. The doping of copper adjusts the properties of nickel particles, alters their existing state and also changes their affinity with carbon. The melting points of Ni and Cu are 1455 and 1084 °C, respectively, and that of Ni–Cu alloy is between that of Ni and Cu. Rostrup-Nielsen *et al.*[20] stated that small amounts of Cu alloying promotes while larger amounts (Cu : Ni = 0.1) inhibits carbon formation and changes the morphology of the filaments.

A Ni/SiO_2 catalyst was also tested and results compared with the Ni–Cu/SiO_2 catalyst in order to study the efficiency of Cu addition. This catalyst deactivated progressively with time-on-stream and the ageing experiment was stopped after 100 h when selectivity towards hydrogen was 65%. As selectivity towards H_2 decreased C_2 species such as acetaldehyde and ethylene increased and deposition of coke became significant due either to direct ethanol dissociation or to the Boudard reaction. Although catalyst performance is initially reduced by Cu addition, we have shown that it considerably increases the lifetime of the catalyst for the oxidative steam reforming of ethanol at on-board conditions. Furthermore, copper allows total conversion of ethanol and constant selectivity towards hydrogen.

4 Conclusions

Results reported here clearly indicate that high efficiency and nearly zero emissions characterise oxidative steam reforming of bioethanol. Ni–Cu/SiO_2 and Rh/Al_2O_3 catalysts show high activities and selectivities toward hydrogen production in contrast to Ni/SiO_2 catalyst that deactivates rapidly due to coke deposition. The outlet reformer composition obtained over Ni–Cu/SiO_2 and Rh/Al_2O_3 catalysts presents a selectivity to hydrogen of approximately 30% with long term stability of the catalysts. This hydrogen rich gas stream can be even improved by WGS and SELOX and it can be considered of high interest to produce electricity for mobile applications by means of fuel cells.

Acknowledgements

We are pleased to acknowledge the financial support of the European Commission through contract number ERK6-CT-1999-00012.

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Detoxification of aryl-organochlorine compounds by catalytic reduction in supercritical carbon dioxide

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Received 29th August 2002
First published as an Advance Article on the web 14th November 2002

Pentachlorophenol, octachloronaphthalene and decachlorobiphenyl were smoothly converted to cyclohexanol, decalin and dicyclohexyl, respectively, by reaction, during 0.5–2 h, with excess hydrogen over alumina-supported palladium (5% w/w) in the presence/absence of supercritical carbon dioxide (50–90 °C). With these conditions, dechlorinations and dearomatization to their cyclic analogs were complete but no carbon–carbon bond scission was observed and only traces of partial deoxygenation/dimerization of the pentachlorophenol substrate (to form 1,1′-oxybiscyclohexane) was seen. The $scCO_2$ medium functioned as an inert support for the reactions; differences in rates of reaction between chlorinated compounds and their aromatic hydrocarbon homologs were not observed. These results suggest that environmentally recalcitrant chlorinated aromatic compounds can be detoxified facilely by catalytic reduction with H_2 under mild conditions.

Introduction

$scCO_2$ Reaction media

The use of mixtures of molecular hydrogen with supercritical carbon dioxide ($scCO_2$) as a medium to perform reductive dechlorinations has remained less extensively explored, yet this phase possesses several attractive properties. The use of $scCO_2$ has often been considered to be an ideal phase because of its mild critical properties (T_C = 31 °C, P_C = 7.4 MPa), non-toxicity, non-flammability, modest cost and a lack of restrictive regulations. Molecular hydrogen is completely miscible in near-critical CO_2,[1] and can result in a very high initial rate of reaction—up to 1400 mol of formic acid have been produced from CO_2 per mol of catalyst per h[2]). The same reaction under identical conditions but in liquid organic solvents is much slower principally the result of decreased diffusion rates and the limited solubility of H_2 in most organic solvents. Solvent polarity of the reaction medium can be fine tuned with ease in the near-critical region (generally 1.05–1.2T_C[3]) by simply changing the pressure. To achieve suitable substrate solubility, the reaction medium can be modified by adding an inert co-solvent. As an example, ethanol can be volume expanded several fold with dense-phase CO_2 in which this solvent becomes totally miscible. Moreover, the reactants/products can be separated readily from the reaction medium by pressure reduction. Because aromatic hydrogenations are highly exothermic,[4] reaction is favoured and selectivities can be increased by operation at lower temperatures yet for hydrogenations on a larger scale some means of heat dissipation can become necessary. The heat capacities of $scCO_2$ can also be pressure-tuned to be more liquid-like[5] and to minimize product hold up. For porous solid catalysts, product selectivity can also be optimized to mitigate pore-diffusion limitations and the accumulation of coke-forming precursors that can inactivate catalytic sites. Clark and Subramaniam[6] have reported that in $scCO_2$, 1-butene/isobutane alkylation resultied in virtually steady alkylate (trimethylpentanes and dimethylhexanes) production during two days. The ability of the carbon dioxide based supercritical reaction mixtures to mitigate coking and thereby to maintain better pore accessibilities was evident from the narrow product spectrum (confined to C_8 products), the lighter color of the spent catalyst samples, and relatively low surface-area and pore-volume losses (<25%) in the spent catalysts. For identical 1-butene space-velocity and feed isobutane/olefin ratios in the absence of CO_2, alkylate formation declined continuously with time. At the high temperatures (>135 °C) required for supercritical operation without carbon dioxide, cracking and coking reactions were dominant.

Catalytic inactivation has been reported during hydrogenations over Pt^0/Al_2O_3 in near-critical CO_2[7] that might have resulted from the possible formation of one or more surface species including formates, carbonates and/or CO in the presence of $CO_2 + H_2$. A variety of fats and oils have been reduced successfully in near-critical CO_2 over Ni,[8] Pd or Pt.[9] As well, as the reduction of double bonds of unsaturated ketones over Pd/Al_2O_3 has been reported.[10] Several insightful reviews,[11–13] have been published recently.

Green Context

The destruction of problematic pollutants such as polychlorinated aromatics is an urgent task, which falls at the fringes of green chemistry. When the destruction is replaced by a method which detoxifies and simultaneously converts the pollutant into useful molecules this represents a distinctly green process. Here, the catalytic reduction of some chloroarenes is demonstrated which leads to the efficient production of *e.g.* cyclohexanol, a useful industrial intermediate. The process proceeds smoothly in supercritical CO_2 under relatively mild conditions ***DJM***

Hydrodechlorinations

The gas phase hydrodechlorination of chlorophenols [dichlorophenols (DCPs), trichlorophenols (TCPs) and pentachlorophenol (PCP)] in H_2 over Ni (1.5%, w/w and 15.2%) loaded silica and Ni (2.2%, w/w) exchanged Y zeolite catalysts were evaluated over the temperature range 200–300 °C. In every instance, the Ni catalysts were 100% selective in cleaving the Cl component from the ring, leaving the aromatic nucleus and OH substituent intact.[14] Similarly, the gas phase hydrodechlorination of methanolic and mixed methanol–water solutions of 2-chlorophenol, 2,6-dichlorophenol, 2,4,5-trichlorophenol and pentachlorophenol has been studied at 300 °C over Ni/SiO_2 catalysts of varying (1.5–20.3 wt% Ni) nickel loading.[15] Each catalyst was again 100% selective in promoting hydrodechlorination.

Hydrogen temperature programmed desorption (TPD) revealed the existence of three forms of surface hydrogen: (i) hydrogen bound to the surface nickel; (ii) hydrogen at the nickel/silica interface; (iii) spillover hydrogen on the silica support.[16] The spillover hydrogen appeared to be hydrogenolytic in nature and was responsible for promoting hydrodechlorination while the hydrogen that was chemisorbed on, and remained associated with, the surface nickel metal participates in aromatic hydrogenation. Hydrodechlorination proceeded *via* an electrophilic mechanism, possibly involving spillover hydronium ions. The gas-phase hydrogenation/hydrogenolysis of alcoholic solutions of phenol was studied at 150–300 °C using a Y zeolite-supported Ni catalyst and a Ni/SiO_2 catalyst.[17] Phenol hydrogenation proceeded in a stepwise fashion giving cyclohexanone as a reactive intermediate while a combination of hydrogenolysis and hydrogenation yielded cyclohexane. Hydrogenolysis to benzene was favored by high Ni loadings and elevated temperatures. The gas-phase hydrogenation of PhOH at 150–300 °C has also been studied over Pd^0/Mg^0 (1% , w/w). Hydrogenation proceeded in a stepwise fashion with cyclohexanone as the partially hydrogenated product and cyclohexanol as the fully hydrogenated product.[18] The catalyst provided 96% selectivity with respect to cyclohexanone at 150 °C, but the cyclohexanone yield decreases at higher temperatures as conversion declined and cyclohexanol was increasingly preferred. Conversion and selectivity were both stable with prolonged catalyst use (*i.e.*, time on stream >55 h). The catalytic hydrodechlorination of chlorobenzene in ethanol over Ni^0/C, Pd^0/C and Ni^0/Pd^0 was studied at 50 °C, 1 atm H_2. All three catalysts had mediated efficient dechlorination after 3 h.[19]

Dechlorinations in $scCO_2$ of polychlorinated biphenyl (PCB) compounds or pentachlorophenol (PCP) have been performed in a flow-through reactor filled with zero-valent metal (Fe^0 or Mg^0) or bimetallic mixture (Ag^0/Fe^0, Pd^0/Fe^0 or Pd^0/Mg^0). Substrate (20–30 mg min^{-1}) was dechlorinated very efficiently (but not quantitatively) within a 25 × 1 cm reactor column operated at ~ 450 °C. The only appreciable products were biphenyl (or phenol) and chloride ion that remained on the ZV metal surface.[20–22] Aqueous slurries of four surfactant formulations were evaluated for the mobilisation of PCB compounds from contaminated soil[23] and coupled with *on line* dechlorination.[24] The objectives of the current study were to evaluate mixtures of H_2 with $scCO_2$ for their ability to mediate the catalytic dechlorination of aromatic organochlorine compounds.

Experimental

Reactor

The dechlorination assembly consisted of source of pressurized $scCO_2$, [a K-type cylinder of compressed CO_2 that was further pressurized with an diaphragm compressor (Newport Scientific, Jessop, MD)], and a reactor unit. The supercritical fluid reactor consisted of a 50 ml high-pressure cylindrical vessel with a demountable top that had been modified with the addition of two 1/16″ stainless steel (ss) tubes that served as gas inlet and outlet. The tubes were each terminated with a high pressure needle valve. In operation, the vessel was equilibrated in a water bath to the desired operating temperature of the experiment then charged with substrate (1 or 10 mg) in 0.2 ml hexane, test catalyst (25 mg), and a Teflon-coated stirring bar. The mixture was then pressurised to 345 or 690 kPa with H_2 gas. For certain runs, the reaction medium was overpressured with CO_2 (to 0.69–30.34 MPa). Post reaction for 0.5–2 h, the pressure was vented gradually by release through a capillary restrictor (5 μm × 20 cm) into ethanolic trapping solvent (10 ml). All trials were performed in triplicate [each entry in the Tables represent the mean recovery (mol%) ± 1 relative standard deviation]. The course each trial was monitored by gas chromatography–mass spectrometry (GC–MS).

Chemicals

Biphenyl, cyclohexanol, cyclohexanone, *o*-chlorophenol, *p*-chlorophenol, decachlorobiphenyl, 2,3-dichlorophenol, methanol, naphthalene, octachloronaphthalene, phenol, 2,3,4,5-tetrachlorophenol, 2,3,4,6-tetrachlorophernol, 2,3,5,6-tetrachlorophenol, 2,3,5-trichlorophenol and 2,3,6-trichlorophenol were purchased from Aldrich Chemical Co., Oakville, ON, Canada. Chemicals were ACS Reagent Grade or better and were used as received. Catalysts, $Ni^0/SiO_2–Al_2O_3$ (66 ± 3% w/w, catalog #31276), Pd^0/γ-Al_2O_3, reduced (5% w/w, catalog #11713) and Pt^0/γ-Al_2O_3 reduced (1% w/w, catalog #11797) were purchased from Alfa Aesar, Ward Hill, MA, USA whereas Fe^0/γ-Al_2O_3 (0.3% w/w) and $Ag^0/Fe^0/\gamma$-Al_2O_3 (0.3%/1.7% w/w) were synthesized by A. Majid.

Gas chromatography–mass spectrometry

GC–MS was performed on a Varian model 3900 gas chromatograph fitted with a model 8400 autosampler and a model 2100T ion trap detector. The DB-5 capillary column (30 m × 0.25 mm i.d.) was eluted with helium at 1.0 ml min^{-1}. After an initial hold for 1 min at 50 °C, the column was ramped, at 10 °C min^{-1}, to 300 °C and held for a further 3 min prior to cool down. The temperature of the injector and detector were maintained at 250 and 150 °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 the Saturn spectral libraries and corroborated by co-chromatography and spectral matching with authentic standards.

Results and discussion

It was envisaged that the overall process of decontamination of natural media (soils/sediments) would become more appealing if supercritical carbon dioxide ($scCO_2$) extractions of organochlorine (OC) contaminants from polluted media were to be coupled with an on line detoxification sequence. Generally, OC compounds have been considered to be environmentally recalcitrant due principally to their relatively non-polar nature (that decrease aqueous solubility and hinder physical dispersal processes) and the general lack of functional groups (that can facilitate metabolic transformations). Toxicities of both alkyl and aryl OC compounds, that generally increase with increasing chlorine content,[25] can be reduced appreciably by reductive dechlorination to form relatively innocuous hydrocarbon and chloride ion. It was further anticipated that once mobilized into supercritical carbon dioxide ($scCO_2$), dechlorination might be accelerated further by contact of the solution with molecular hydrogen in the presence of a catalyst.

It was also anticipated that operation above the boiling point of hexane would assure a single supercritical phase for the solution. In initial experiments, the capacities of five alumina supported catalysts to accelerate the dechlorination of pentachlorophenol (PCP) in the presence of a large excess of hydrogen were evaluated (Table 1). With 0.5 h of reaction at 80 °C, the bare alumina support material mediated only partial dechlorination to tetrachlorophenol species (~5 mol% conversion) that was only marginally more efficient than trials in the absence of either catalyst or hydrogen for which no reaction was observed. The zero-valent iron (Fe^0) loaded support was not more efficient at mediating dechlorination than was the bare alumina. Product distributions for reactions in the presence of Ag^0/Fe^0 supported bimetallic mixture contained only totally dechlorinated product that had also been ring reduced to cyclohexanol (~11 mol%) in addition to unreacted substrate (~67 mol%). The Pt^0 and the Ni^0 supported catalysts did not produce more cyclohexanol (~12 and 14 mol%, respectively) than the bimetallic catalyst but less substrate remained after reaction (~47 and 37 mol%, respectively) and smaller quantities of tetrachlorophenols (~7 and 18 mol%) and 1,1′-oxybiscyclohexane (~3 and ~5 mol%, respectively) were formed. The Pd^0/Al_2O_3 formulation was appreciably more efficient again. Chlorinated materials were absent, cyclohexanol was the one appreciable product (~71 mol%) and small quantities of cyclohexanone (~2 mol%) and 1,1′-oxybiscyclohexane (~2 mol%) were also detected. Thus, for this catalyst, dechlorination and de-aromatization were complete and only ~1 mol% of the substrate had lost an oxygen substituent.

In subsequent studies (Table 2(a)), the pressure was maintained at 22 MPa while the temperature of the reaction of PCP with H_2 over Pd^0/Al_2O_3 was varied between 50 and 90 °C without any appreciable change in the product distribution after 2 h of reaction. Both the cyclohexanone and the 1,1′-oxybiscyclohexane were present in the product mixture only at trace quantities so that quantitation was somewhat less repeatable for these products. The reaction mixture was also over-pressured with CO_2 (to 0.69–30.34 MPa) while the temperature was maintained at 60 °C (Table 2(b)). Again, there was no perceptible effect on the product distribution. With these conditions, the $scCO_2$ functioned as an inert medium for the reaction and apparently did not influence the course of the reaction. Table 3(a) summarizes efforts to detect time–pressure interactions. The product distributions remained unchanged by increasing the total pressure from 8.3 to 13.8 MPa and the duration of reaction from 1 to 2 h. In subsequent trials in H_2 alone (Table 3(b)), the quantity of PCP was increased 10-fold [3.75 μmol PCP or aqueous phenolate ($NaOC_6Cl_5$)] while the solvent was maintained at 0.2 ml. Hydrodechlorination and ring reduction were complete for PCP, however, the quantity of 1,1′-oxybiscyclohexane was elevated (~20 mol%) relative to the mean of Table 3(a) (6.6 mol%). By contrast, the reaction was incomplete for the phenolate (~33 mol% as cyclohexone/cyclohexanol) but the remainder (~40 mol%) was unreacted substrate. Apparently, conversion to phenolate influenced the rate of reaction but the course of the reaction was essentially unchanged. It had been anticipated that introducing anionic character to the substrate might have accelerated electrophilic hydrodechlorination but it is also probable that the H_2 was only sparingly soluble in this medium so that the rates of substrate reduction were compromised.

The variations among replicate trials, performed under the same operating conditions, was superior to the variations among trials at different operating conditions. A possible explanation for the variations in recoveries resides in the differences in the total pressure at which the various trials were performed. In general, the recoveries of products were greater for release from relatively lower pressure (0.69 MPa) than from higher operating pressures (8.27–30.34 MPa). The products were considered to

Table 1 Variations in product yield (mol% ± 1 relative standard deviation) with catalyst identity for the reaction of 0.375 μmol PCP in the presence of 25 mg catalyst and ~1% H_2 (0.69 MPa, ~570 μmol) in $scCO_2$ (22.1 MPa) at 80 °C

Product	$Ag^0/Fe^0/Al_2O_3$	$Pd^0/\gamma\text{-}Al_2O_3$	Fe^0/Al_2O_3	$Pt^0/\gamma\text{-}Al_2O_3$	$Ni^0/SiO_2\text{-}Al_2O_3$	Al_2O_3	No catalyst	no H_2
Cyclohexanone	N.D.[a]	2.0 ± 7.6	N.D.	2.5 ± 60.7	1.0 ± 20.8	N.D.	N.D.	N.D.
Cyclohexanol	11.4 ± 1.6	71.1 ± 2.6	N.D.	12.2 ± 15.8	14.5 ± 4.3	N.D.	N.D.	N.D.
1,1′-Oxybiscyclohexane	N.D.	2.0 ± 1.5	N.D.	3.4 ± 0.6	4.8 ± 13.2	N.D.	N.D.	N.D.
Tetrachlorophenols	N.D.	N.D.	3.8 ± 5.9	6.6 ± 17.6	17.5 ± 11.4	4.9 ± 21.3	N.D.	N.D.
PCP	66.9 ± 5.2	N.D.	76.4 ± 2.4	46.9 ± 11.7	37.4 ± 0.9	71.7 ± 8.8	75.5 ± 2.2	76.2 ± 16.3
Mass balance	0.773 ± 0.043	0.751 ± 0.027	0.802 ± 0.024	0.716 ± 0.052	0.752 ± 0.036	0.766 ± 0.094	0.755 ± 0.022	0.762 ± 0.163

[a] N.D., none detected (<0.05 mol%).

Table 2 Variations of product recoveries (mol% ± 1 relative standard deviation) with (a) temperature (50–90 °C) at 22 MPa or (b) pressure (0.69–30.3 MPa) at 60 °C for 2 h of reaction of PCP (0.375 μmol) with H_2 (0.69 MPa) in $scCO_2$ in the presence of 25 mg of 5% (w/w) $Pd^0/\gamma\text{-}Al_2O_3$.

(a)	Temperature/°C				
Product	50	60	70	80	90
Cyclohexanone	1.0 ± 8.4	2.9 ± 7.0	3.6 ± 29.3	3.7 ± 10.1	7.8 ± 10.1
Cyclohexanol	66.8 ± 0.4	70.1 ± 3.3	66.8 ± 6.1	78.4 ± 0.8	75.1 ± 0.2
1,1′-Oxybiscyclohexane	5.9 ± 6.7	4.7 ± 1.4	6.4 ± 9.4	7.0 ± 0.6	6.8 ± 1.2
Mass balance	0.736 ± 0.044	0.777 ± 0.033	0.768 ± 0.048	0.891 ± 0.004	0.898 ± 0.009

(b)	Pressure/MPa						
Product	0.69	8.27	13.79	18.62	22.06	26.20	30.34
Cyclohexanone	24.4 ± 0.5	7.0 ± 69.8	5.9 ± 52.9	1.5 ± 0.4	0.8 ± 4.3	7.4 ± 3.6	4.4 ± 81.6
Cyclohexanol	64.7 ± 0.2	59.5 ± 5.7	59.4 ± 2.3	62.9 ± 3.6	71.0 ± 8.0	58.4 ± 1.1	55.7 ± 10.1
1,1′-Oxybiscyclohexane	6.5 ± 0.1	7.2 ± 5.9	6.4 ± 4.5	6.3 ± 0.1	7.2 ± 1.0	5.3 ± 0.4	5.3 ± 6.0
Mass balance	0.966 ± 0.002	0.732 ± 0.081	0.717 ± 0.035	0.708 ± 0.034	0.790 ± 0.053	0.711 ± 0.021	0.654 ± 0.046

be somewhat volatile so that trapping of products from the CO_2 was more efficient when released from lower operating pressures than release from higher operating pressures. A more efficient trapping procedure might have solved this problem.

Other highly chlorinated aromatic compounds were also subjected to reaction under similar conditions. Octachloronaphthalene (~70% chlorine by weight) was reacted with H_2 (0.69 MPa) in the presence/absence of 25 mg Pd/Al_2O_3 for 0.5 or 2 h. Only decalin ($C_{10}H_{18}$) was observed in the crude product mixture (Table 4). Interestingly, the ratio of *trans*- to *cis*-product that was approximately 3:1 after 0.5 h had been decreased to 2.3:1 after 2 h of reaction and might have become nearly equal after extended equilibration. In companion trials, reaction to decalin, in the presence of sufficient hexane (5 ml) to cover the catalyst surface completely, was also virtually complete at 80 or at 60 °C but at 50 °C, tetralin was the major product (~75 mol%). The other products were decalin (ratio *trans* to *cis*, 3.2:1) and traces of substrate. A possible explanation is a two-phase system (at 50 °C but perhaps not at 60 °C) that hindered H_2 access to the catalyst surface. A doubling of reaction rate for a 10 degree increase in reaction temperature would seem to be insufficient to account for the observed differences between 50 and 60 °C. Naphthalene also served as substrate for reaction during 0.5 h. In this case, the ratio of *trans*- to *cis*-decalin was different again (~0.8:1). There was no tendency for dehydrogenation with these reaction conditions. Neither *trans*- nor *cis*-decalin, when pressurised to 690 kPa with nitrogen in the presence of Pd^0/Al_2O_3 and reacted at 70 °C for 0.5–1 h, provided evidence for dehydrogenation to tetralin or naphthalene or for configurational isomerization.

In a final series of trials, decachlorobiphenyl (~71% Cl by weight) served as substrate (Table 5). Post 0.5 h reaction at 70 °C/0.69 MPa, only dicyclohexyl was observed in the crude product mixture. The reaction was complete; chlorine was removed from the substrate and the product had been de-aromatized but no carbon–carbon bond scission had occurred.

In summary, highly chlorinated aromatic compounds were dechlorinated quantitatively when exposed to alumina supported palladium in hydrogen atmospheres under mild conditions. With these conditions, perchlorinated phenol, naphthalene or biphenyl substrates as well as their hydrocarbon homologs were also smoothly dearomatized to their cyclic analogs but no carbon–carbon bond rupture was observed and in the case of PCP only small quantities of partial deoxygenation

Table 3 Variations in the distribution of products (mol% ± 1 relative standard deviation) for (a) the reduction of PCP (0.375 µmol) with H_2 (575 µmol) in $scCO_2$ (8.3 or 13.8 MPa) or (b) with substrate (3.75 µmol)/solvent combination for reactions at 60 °C for 1 or 2 h

(a)	Reaction time/h ($scCO_2$ pressure/MPa)			
Product	1 (8.3)	1 (13.8)	2 (8.3)	2 (13.8)
Cyclohexanone	9.9 ± 1.7	8.6 ± 3.7	7.0 ± 69.8	5.9 ± 52.9
Cyclohexanol	53.2 ± 0.05	54.1 ± 4.8	59.1 ± 5.7	59.4 ± 2.3
1,1′-Oxybiscyclohexane	6.3 ± 1.7	6.3 ± 3.3	7.2 ± 5.9	6.4 ± 4.5
Tetrachlorophenols	N.D.[a]	N.D.	N.D.	N.D.
PCP	N.D.	N.D.	N.D.	N.D.
Mass balance	0.694 ± 0.050	0.690 ± 0.039	0.732 ± 0.081	0.717 ± 0.035
(b)	PCP (3.75 µmol) in 0.2 ml hexane		Na-PCP (3.75 µmol) in 0.2 ml water	
Cyclohexanone	2.7 ± 12.4		23.1 ± 2.6	
Cyclohexanol	67.8 ± 1.9		9.6 ± 0.8	
1,1′-Oxybiscyclohexane	20.1 ± 1.9		N.D.	
Tetrachlorophenols	N.D.		N.D.	
PCP	N.D.		39.6 ± 12.1	
Mass balance	0.906 ± 0.015		0.723 ± 0.074	

[a] N.D. = none detected (<0.05 mol%).

Table 4 Variations in decalin recoveries (mol% ± 1 relative standard deviation) after 0.5 or 2 h of hydrogenation (70 °C/0.69 MPa) of 1 mg octachloronaphthalene or naphthalene in the presence/absence of 25 mg of 5% (*w/w*) $Pd^0/\gamma\text{-}Al_2O_3$

	$C_{10}Cl_8$			$C_{10}H_8$	
Products	2 h, no cat.	0.5 h	2 h	2 h, no cat.	0.5 h
$C_{10}Cl_8$	95.2 ± 5.1	N.D.[a]	N.D.		
$C_{10}H_8$	N.D.	N.D.	N.D.	93.1 ± 5.5	N.D.
cis-$C_{10}H_{18}$	N.D.	23.3 ± 4.8	29.8 ± 6,6	N.D.	54.6 ± 6.4
trans-$C_{10}H_{18}$	N.D.	71.7 ± 3.5	67.7 ± 3.4	N.D.	44.5 ± 3.4
Mass balance	0.952 ± 0.051	0.950 ± 0.020	0.975 ± 0.042	0.931 ± 0.055	0.991 ± 0.051

[a] N.D. = none detected (<0.05 mol%).

Table 5 Variations in dicyclohexyl recoveries (mol% ± 1 relative standard deviation) after 0.5 h of hydrogenation (70 °C/0.69 MPa) of 1 mg decachlorobiphenyl or biphenyl in the presence/absence of 25 mg of 5% (w/w) $Pd^0/\gamma\text{-}Al_2O_3$

	$C_{12}Cl_{10}$		$C_{12}H_{10}$	
Product	0.5 h, no cat.	0.5 h	0.5 h, no cat.	0.5 h
$C_{12}Cl_{10}$	102.7 ± 5.8	N.D.[a]		
$C_{12}H_{10}$	N.D.	N.D.	93.1 ± 3.4	N.D.
Dicyclohexyl		101.6 ± 1.4		96.9 ± 9.6
Mass balance	1.027 ± 0.058	1.016 ± 0.014	0.931 ± 0.034	0.969 ± 0.096

[a] N.D. = none detected (less than 0.05 mol%).

was observed. These observations, under mild reaction conditions, suggest that they might be applied to other aromatic compounmds including environmentally recalcitrant polyaromatic hydrocarbons (PAHs).

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A thermodynamic investigation of solvent-free reactions

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Received 17th October 2002
First published as an Advance Article on the web 18th November 2002

A series of solvent-free condensation reactions have been studied calorimetrically, with the goal of determining feasibility of scale-up in the realisation of potentially greener processes, in which the use of auxiliary compounds, such as solvents, are obviated. Knoevenagel reactions leading to intermediates used in the production of 1,4-dihydropyridine drugs, and in drug libraries currently under testing, exhibit a reaction exotherm ascribed almost entirely to the formation of the imminium 'Knoevenagel' intermediate, which may be controlled by regulation of the quantity of catalyst. Reactions to form stable imines and cyanoamide products are also demonstrated to be exothermic.

Introduction

A number of authors have described protocols for the solvent-free synthesis of a wide range of organic compounds and the number of reports of rapid, selective and efficient transformations, occurring with a high degree of conversion of reactants to products, grows daily.[1,2] Such protocols bear further investigation as they may offer distinct advantages such as: improved atom utilisation[3] or atom economy[4] by avoidance of common derivatisation procedures;[5] decreased by-product formation and hence decreased waste (improved E-factors[6]) resulting from purification procedures required to separate the desired product from the impurities; and, in many cases, reduced energy utilization both in the reaction and purification stages as well as opportunities for process intensification. Some specific reactions targeted include solventless aldol reactions,[5] sequential aldol and Michael addition as a route to symmetrical and unsymmetrical 1,5-diketones leading to Krohnke type pyridines,[7] synthesis of 3-carboxycoumarins[8] and tetrahydroquinazolines,[9] oligomerisation reactions,[10] calix[4]resorcinarene[11] synthesis and, the focus of this paper, the 4-substituted-1,4-dihydropyridine compounds,[12] such as the commonly used cardiovascular drug Felodipine, and some highly functionalized cyanoamido benzaldehyde derivatives of interest as dynamin inhibitors.[13]

These (and numerous other) examples indicate that solvent-free reaction conditions may provide one tool for addressing waste-reduction and energy efficiency, but there are obvious and important questions to be asked about whether or not such procedures are hazard-free. One of the reasons that solvent use has become ubiquitous in organic synthetic chemistry relates to the very effective role of solvents (usually present in huge excess compared to reagents) as heat transfer media and, more specifically, as heat sinks in exothermic reactions. The consequences of loss of control of exothermic reactions are well known: thermal runaways, resulting from the mismatch between rate of heat evolution (which increases exponentially) and rate of heat removal (which increases linearly) may result in a rapidly rising temperature, leaving little time for correction. Reaction vessels may be at risk from over-pressurisation due to violent boiling or rapid gas generation and elevated temperatures may initiate secondary, more hazardous runaway reactions or decompositions. Clearly a greater understanding of the thermal characteristics of solvent-free reactions is required. Thus, suitable import must be given to the phrase 'fundamental knowledge of chemical processes' in the definition of green chemistry.

To this end we have undertaken studies of phase changes and the role of eutectic melts in solvent-free reactions between solid reactants,[14,15] used combined differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) to detect reaction endotherms or exotherms and thus optimize the temperature of reaction[12] and we now report a microcalorimetric investigation designed to allow rational, informed decision-making in determining the feasibility of scale-up of some useful solvent-free transformations.

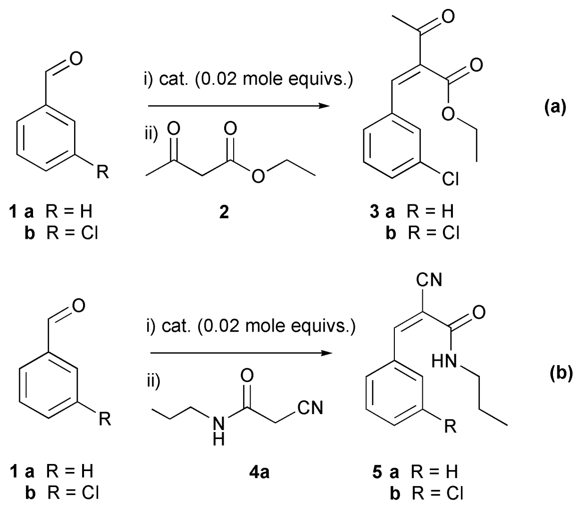
Results and discussion

The Knoevenagel reactions of benzaldehydes **1** with ethyl acetoacetate **2** or cyanoamide derivatives **4**, leading to intermediates of known[12] or potential[13] drug substances (Scheme 1), were chosen as model reactions for this study as there are a large

Green Context

The safe elimination of solvents from reactions implies an alternative heat sink is required to keep the reaction under control. How major a factor this is is obviously dependent on the thermodynamics and kinetics of the reaction. This paper provides details of heat flows and thermodynamic information for a range of Knoevenagel reactions, allowing a better understanding of the likely heat evolution, and thus providing a basis for proper design and scale-up of these processes. ***DJM***

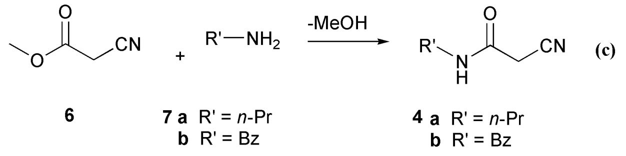
DOI: 10.1039/b210220j



Scheme 1

number of 1,4-dihydropyridine drugs currently produced in tonne quantities[16] and, should any of our library compounds prove to have promising activity, larger quantities would be needed and effective scale-up of these reactions required.

Reaction (b) is the second of two solvent-free reactions in the synthesis of these potential dynamin inhibitors **5** and thus reaction (c) (Scheme 2) was included in the study.



Scheme 2

The first exploratory calorimetric experiment revealed the occurrence of a rapid exothermic reaction on addition of premixed ethylacetoacetate **2** and catalyst to benzaldehyde **1a** (mol ratio 1 : 0.02 : 1). Quantities of reagents were scaled down significantly to achieve a heat flow deflection within the measurement range of the microcalorimeter and benchtop experiments confirmed the exothermic nature of the reaction. The shape of the heat flow curve, depicted in Fig. 1, implies a rapid, highly exothermic event followed by (or overlaid on) a slower process. The time taken for the initial process is comparable to the instantaneous reaction between HCl and NaOH used to calibrate the instrument.

The Knoevenagel reaction is a two-step process[18] and, since two distinct processes were detected in the heat flow curve, reaction (d) (Scheme 3), the formation of the active imminium intermediate, was investigated and compared to the formation of stable imines, reaction (e). (The facile and almost completely waste-free solventless synthesis of such stable imines has been reported by Kaupp *et al.*[19] and we have found this a suitable method for preparation of, otherwise difficult to isolate, imines.[20] Thus, this too, represents a useful chemical transformation worthy of investigation of scale-up feasibility.)

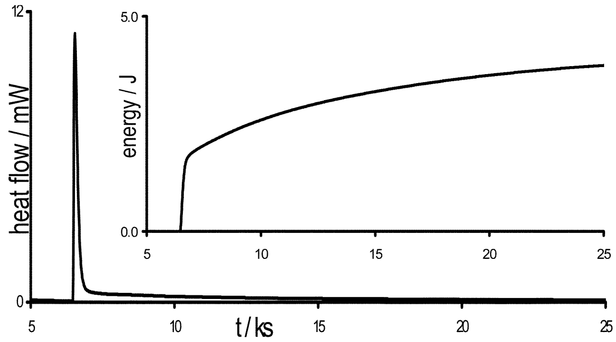
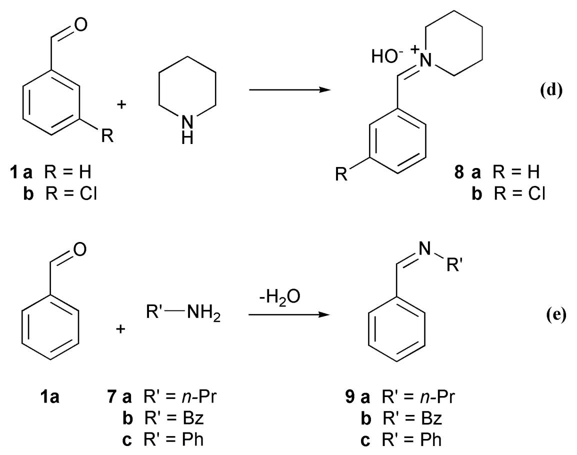


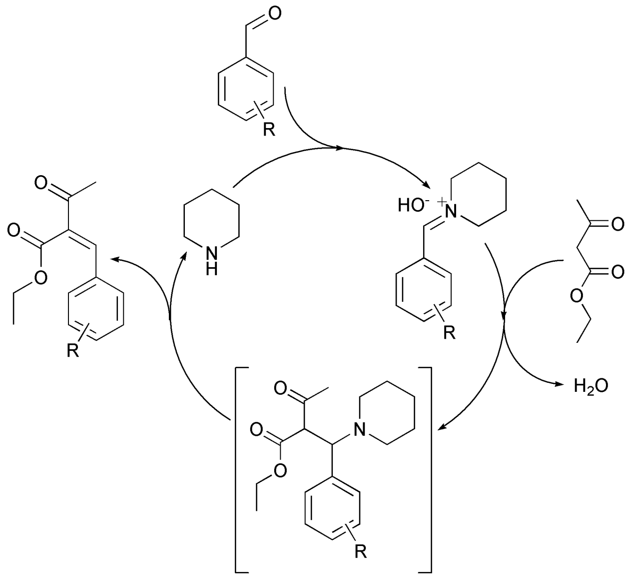
Fig. 1 Heat flow trace for benzaldehyde added to premixed catalyst and ethyl acetoacetate (mol ratio 1 : 0.02 : 1; t_{mixing} = 6.5 ks). Inset, integrated curve clearly showing a rapid first process overlaid on a slower second process.[17]



Scheme 3

Values of the measured enthalpies of reaction obtained in each case are listed in Table 1. Clearly these are *net* reaction enthalpies, incorporating contributions from all processes including mixing, formation of active intermediates and reaction. In all cases quantities of excess reactant are chosen such that no precipitation or crystallisation of product occurs, although, in the stoichiometric reactions described previously,[12,13,19] this may provide an added contribution.

The major contribution to the exothermic nature of the Knoevenagel reactions studied ((a) and (b)) is from the preliminary reaction between benzaldehyde or 3-chlorobenzaldehyde and the piperidine catalyst to form the 'imminium' intermediate **8**. This imminium species subsequently reacts with the ethyl ester to form the benzylidene product, as described by Knoevenagel in one of the original publications on the topic.[18] The piperidine catalytic cycle, depicted in Scheme 4, is traversed a number of times in the experiments described here. Reexpressing the measured enthalpy in terms of the number of



Scheme 4 Catalytic cycle with respect to piperidine. The reaction proceeds *via* the Knoevenagel mechanism and the formation of the imminium intermediate from piperidine and the benzaldehyde derivative accounts for significant quantities of heat evolved during the reaction.

Table 1 Enthalpies of reaction

	Reactants				
Reaction	Limiting	Excess	Product	Catalyst	ΔH/kJ mol^{-1}
(a)	**2**	**1a**	**3a**	pip[a]	−26.3 ± 0.9
	2	**1b**	**3b**	pip	−31.0 ± 1.7
	2	**1a**	**3a**	pip/CH_3COOH	−26.7 ± 0.6
	2	**1b**	**3b**	pip/CH_3COOH	−30.1 ± 1.1
(b)	**4a**	**1a**	—		15.5[b]
	4a	**1a**	**5a**	pip	−31.5[c]
	4a	**1b**	—		22.3[b]
	4a	**1b**	**5b**	pip	−36.0[c]
(c)	**6**	**7a**	**4a**	—	−11.7 ± 0.5
	6	**7b**	**4b**	—	−68.8 ± 1.4
(d)	pip	**1a**	**8a**	—	−46.9 ± 1.6
	pip	**1b**	**8b**	—	−47.5 ± 2.5
(e)	**7a**	**1a**	**9a**	—	−5.1 ± 0.2
	7b	**1a**	**9b**	—	−30.4 ± 1.5
	7c	**1a**	**9c**	—	−24.8 ± 2.3

[a] piperidine; [b] single determination; [c] calculated value (difference)

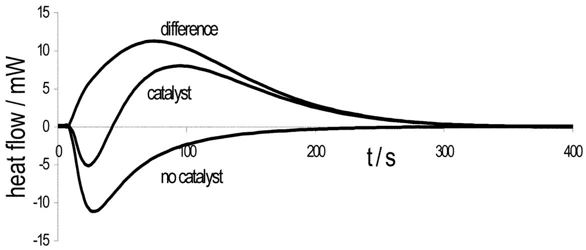


Fig. 2 Heat flow traces for the reaction of **1b** and **4a**. Bottom: without catalyst *i.e.* heat of mixing of reactants only; middle: with piperidine catalyst, showing exothermic process overlaid on endothermic process and top: the result of subtracting the heat of mixing from the heat flow measured during the reaction, allowing an estimate of the reaction exotherm. (Note: $t_{\text{mixing}} \neq 0$ s.)

moles of piperidine[21] undergoing reaction (d) during the process of reaction (a), R = H and R = Cl yields values of −38 kJ mol^{-1} and −39 kJ mol^{-1}, respectively, indicating that the second process *i.e.* addition of ethylacetoacetate and elimination of piperidine is, if anything, endothermic. The choice of catalyst (piperidine or piperidine acetate) has no apparent affect on the enthalpy of reaction and benchtop experiments confirm that the product produced is identical in each case.

The second Knoevenagel reaction studied involves reaction of a solid cyanoamide derivative **4a** with liquid benzaldehydes **1a** and **1b** and this, not surprisingly, yields a thermal trace indicative of an exothermic process overlaid on an endothermic one as illustrated in Fig. 2.

The endothermic process is ascribed to the dissolution of solid **4a** in **1b** and measurement of the heat flow upon mixing of **4a** in **1a** or **1b** indeed yields a distinct endotherm (and no product on the timescale of the measurement). This allows estimation of the ΔH of dissolution and subtraction of this (after correction for specific experimental quantities) from the measured heat flow during reaction yields a calculated heat flow curve representing the reaction exotherm as illustrated in Fig. 2. While these values are determined for one experiment only, it is gratifying to note that the ΔH of reaction for reaction (b) is similar to that determined for reaction (a).

If the measured exotherm is due largely to the heat generated upon formation of the imminium intermediate then control of the reaction exotherm may be effected by regulation of the quantity of piperidine added. Thermal control of reaction (c) would be effected by slow addition of one reactant and, in this case the use of reactors engineered to have small mixing chambers, such as extrusion reactors, which would be preferable to bulk batch processes. The same is true of the formation of stable imines, reaction (e), as these processes are also exothermic. In all cases the formation of the more stable product, leads, not surprisingly to a higher measured reaction exotherm.

This microcalorimetric study of solvent-free reactions demonstrates that it is possible to determine, by quite simple experiments, using readily available equipment, the overall ΔH of reaction to allow sensible decisions relating to scale-up and exotherm control. In addition, while this is not intended to comprise a comprehensive study of the mechanism of the Knoevenagel reaction or the thermochemistry of each discrete process, information gained about the source of the reaction exotherm allows one to effect control by controlling the order and rate of addition of reactants. Such studies are required if solvent-free reactions are to become useful tools in the green chemistry toolbox.

Experimental

Instrumentation

All calorimetry measurements for this work were carried out using a SETARAM micro DSC III calorimeter. The instrument incorporates the use of two mixing batch vessel one of which acts as a reference during a trace. The vessels comprise a cylinder with two separate chambers which are separated by parts mounted on a rod which pass through the cylinder. The upper chamber has a capacity of 0.2 cm^3 and the lower chamber has a capacity of 0.55 cm^3. A composite o-ring on the obturator ensures the tightness of the upper chamber. These were removed after each experiment as in almost each case the o-rings would swell. The upper viton stopper ensures the tightness of the vessel and these did not need to be replaced as frequently. This method allows for non-invasive and non-destructive analysis of the samples and their interactions.

All volumes were delivered using calibrated micro-syringes. All reagents were of 98% purity or greater and used as purchased from the supplier unless noted otherwise.

The multi-task software package provided by SETARAM recorded heat flow (thermal power) as a function of time from which ΔH values were determined by integration.

General procedure for determination of $\Delta H_{\text{reaction}}$ for reactions (a)–(e)

For each set of experiments, the limiting reagent was injected into the lower chamber of the mixing vessel to ensure good mixing and completeness of reaction. Care was taken to avoid premature mixing of reactants (manufacturer supplied o-rings were replaced with o-rings of larger diameter) and, once a steady baseline was achieved, reaction was initiated by mixing of reactants on plunger depression. Baselines were modelled as either constant or sloping straight lines as appropriate. All experiments were conducted at 25 °C. On average all traces were completed within 3 h and each repeated at least three times.

2-Acetyl-3-phenylacrylic acid ethyl ester 3a. 150 μL (1.47×10^{-3} mol) of benzaldehyde and 2.5 μL (0.017 mol equivalents) of piperidine were mixed and injected into the top chamber. This was added to 18.7 μl (1.48×10^{-4}) of ethyl acetoacetate in the bottom chamber.

2-Acetyl-3-(3′-chlorophenyl)acrylic acid ethyl ester 3b. 150 μL (1.32×10^{-3} mol) of 3-chlorobenzaldehyde and 2.5 μL (0.019 mol equivalents) of piperidine were mixed and injected into the top chamber. This was added to 16.6 μL (1.31×10^{-4} mol) of ethyl acetoacetate in the bottom chamber.

2-Acetyl-3-phenylacrylic acid ethyl ester 3a. 150 μL (1.47×10^{-3} mol) of benzaldehyde and 2.5 μL (0.017 mol equivalents) of an equimolar mixture of piperidine and glacial acetic acid were mixed and injected into the top chamber. This was added to 18.6 μL (1.47×10^{-4} mol) of ethyl acetoacetate in the bottom chamber.

2-Acetyl,3-(3′-chlorophenyl)acrylic acid ethyl ester 3b. 150 μL (1.32×10^{-3} mol) of 3-chlorobenzaldehyde and 2.5 μL (0.019 mol equivalents) of an equimolar mixture of piperidine and glacial acetic acid were mixed and injected into the top chamber. This was added to 16.6 μL (1.31×10^{-4} mol) of ethyl acetoacetate in the bottom chamber.

2-Cyano-3-phenyl-*N*-propylacrylamide 5a. 150 μL (1.47×10^{-3} mol) of benzaldehyde and 1 μL (0.0069 mol equivalents) of piperidine were injected into the top chamber of the mixing batch vessel. This mixture was then dropped into the bottom chamber which contained 0.0080 g (6.34×10^{-5} mol) *n*-propyl cyanoamide.

3-(3′-Chlorophenyl)-2-cyano-*N*-propylacrylamide 5b. 150 μL (1.32×10^{-3} mol) of 3-chlorobenzaldehyde and 1 μL (1.01×10^{-5} mol) of piperidine were injected into the top chamber of the mixing batch vessel. This mixture was then dropped into the bottom chamber which contained 0.0079 g (6.26×10^{-5} mol) *n*-propyl cyanoamide.

2-Cyano-*N*-phenylacetamide 4a. 150 μL (1.82×10^{-3} mol) of *n*-propylamine was injected into the top chamber and added to 5 μL (5.67×10^{-5} mol) of methyl cyanoacetate in the bottom chamber.

***N*-Benzyl-2-cyanoacetamide 4b**. 150 μL (1.37×10^{-3} mol) of benzylamine was injected into the top chamber and added to 5 μL (5.67×10^{-5} mol) of methyl cyanoacetate in the bottom chamber.

1-Benzylidene piperidinium hydroxide 8a. 150 μL (1.47×10^{-3} mol) of benzaldehyde in the top chamber was added to 2.5 μL (2.52×10^{-5} mol) of piperidine in the bottom chamber.

1-(3-Chlorobenzylidene) piperidinium hydroxide 8b. 150 μL (1.32×10^{-3} mol) of 3-chlorobenzaldehyde in the top chamber was added to 1.5 μL (1.51×10^{-5} mol) of piperidine in the bottom chamber.

Benzylidene proylamine 9a. 150 μL (1.47×10^{-3} mol) of benzaldehyde in the top chamber was added to 2 μL (2.42×10^{-5} mol) of *n*-propylamine in the bottom chamber.

Benzylidene phenylamine 9b. 150 μL (1.47×10^{-3} mol) of benzaldehyde in the top chamber was added to 2 μL (1.83×10^{-5} mol) of benzylamine in the bottom chamber.

Benzylidene benzylamine 9c. 150 μL (1.47×10^{-3} mol) of benzaldehyde in the top chamber was added to 2 μL (2.19×10^{-5} mol) of aniline in the bottom chamber.

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16 Common cardiovascular drugs such as Felodipine, Nifedipine, Amlodipine and numerous others fall within this category.

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21 Note that the ratios of reactants are 1 : 0.02 : 0.1 benzaldehyde : catalyst : ethyl acetoacetate. Thus, the ratio of ethyl acetoacetate to piperidine is *ca.* 5 : 1, but 1 mol of piperidine is already reacted with benzaldehyde thus the piperidine added will traverse the catalytic cycle *ca.* 4 times, hence one may reexpress the reaction enthalpy in terms of piperidine traversing the catalytic cycles as follows: (mol **2**/(mol **2** − mol piperidine) × ΔH and specifically for the two substrates tested in reaction (a): R = H: $1.48 \times 10^{-4}/(1.48 \times 10^{-4} - 2.79 \times 10^{-5}) = -38$ kJ mol^{-1}; R = Cl: $1.31 \times 10^{-4}/(1.31 \times 10^{-4} - 2.24 \times 10^{-5}) = -39$ kJ mol^{-1}.

Dimethyl carbonate–water: an environmentally friendly solvent system for ruthenium tetraoxide oxidations

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Received 5th November 2002
First published as an Advance Article on the web 12th December 2002

Dimethyl carbonate (DMC)–water is an environmentally benign solvent system for ruthenium tetraoxide oxidations of various substrates including alkenes, alkynes, arenes, alcohols, ethers and aldehydes. Either hydrated ruthenium trichloride or hydrated ruthenium dioxide can be used as sources of ruthenium, while suitable cooxidants include sodium periodate, bleach and Oxone®.

Introduction

Ruthenium tetraoxide oxidation is a powerful method for oxidation of organic compounds. The reaction is fast and the products are usually isolated in a high yield. In the course of an oxidation, ruthenium tetraoxide is prepared *in situ* by addition of a suitable cooxidant to a solution or a suspension of either hydrated ruthenium trichloride or hydrated ruthenium dioxide in a mixture of solvents. As the reaction proceeds, ruthenium tetraoxide is reduced to lower valent species. In turn, those lower valent ruthenium species are reoxidized by a cooxidant to ruthenium tetraoxide. Thus, the cooxidant is used up, while the actual oxidizing agent is ruthenium tetraoxide. The main problem in ruthenium tetraoxide catalyzed oxidations is complexation of lower valent ruthenium species by the oxidation products, in particular carboxylic acids, to give insoluble complexes. This causes the reaction to slow down and eventually cease.[1,2] The problem has been addressed by Sharpless and coworkers, who added acetonitrile to the reaction mixture.[1] Acetonitrile is stable under the reaction conditions and is capable of complexing lower valent ruthenium species, thus keeping them in solution and allowing them to be reoxidized to ruthenium tetraoxide. However, in addition to acetonitrile, water has to be added to dissolve the cooxidant and yet another solvent is necessary to dissolve the formed ruthenium tetraoxide. That solvent is usually a chlorinated solvent, with carbon tetrachloride being the most commonly used. Since carbon tetrachloride has been identified as a solvent responsible for destruction of the stratospheric ozone, further use of carbon tetrachloride in the USA has been banned by the Environmental Protection Agency.[3] Use of solvent systems consisting of water and acetonitrile was reported.[4] However, it gave poor results in our hands. The solvent system that was successfully used in RuO_4-catalysed oxidative cyclisations ($EtOAc–CH_3CN–H_2O$)[5] was also unsatisfactory.† In order to improve the reaction system we investigated dimethyl carbonate (DMC)–water as a solvent system. We speculated that DMC, as a highly oxygenated compound, would have an ability to complex ruthenium ion thus allowing the reoxidation of lower valent ruthenium species back to ruthenium tetraoxide. This solvent system has an advantage that it is environmentally friendly.[6]

Results and discussion

Either hydrated ruthenium trichloride or hydrated ruthenium dioxide can be used as a source of ruthenium. Suitable cooxidants are sodium periodate,[7] sodium hypochlorite (household bleach)[8] or Oxone® (potassium hydrogen persulfate).[9] Oxidations with Oxone® as a cooxidant proceeded at a slightly lower rate compared to periodate as a cooxidant and a larger amount of precipitate formed in the course of a reaction. Nevertheless, Oxone® is an inexpensive alternative to periodate cooxidants. Potassium bromate[10] did not appear to be a suitable cooxidant. Reaction rates were slower and the yields were lower compared to periodate or hypochlorite cooxidants.

Examples of oxidation of organic substrates by ruthenium tetraoxide with sodium periodate as a stochiometric reagent in DMC–water solvent system are shown in Table 1. Most organic substrates are soluble in DMC. However, 1-octadecanol (Table 1, entry 2) was insoluble and was added to the reaction mixture as a powder. After about 1 h, it completely dissolved and the oxidation was completed after 2 h. It was reported that ruthenium tetraoxide oxidation of ethers proceeds cleanly and in good yields.[1,11] Ruthenium tetraoxide oxidation of tetrahydrofuran in DMC–water provided only a modest yield of the γ-butyrolactone as evidenced by GLC (Table 1, entry 7). The GLC yield peaked at 48% after 1.5 h. Apparently, the lactone hydrolyzed and was further oxidized to glutaric acid. It was

Green Context

The clean oxidation of organics is a pressing problem which is being addressed in many ways. This paper is about the development of a benign solvent system for Ru catalysed oxidations, which often utilise a mixed solvent system containing carbon tetrachloride, making it impossible to use industrially in several countries. It is shown that the use of aqueous dimethyl carbonate leads to the ready reoxidation of Ru species, without the need for complex solvent mixtures. While this is a significant step towards a green oxidation process, further improvements in the stoichiometric oxidant would make this an extremely attractive methodology for a number of oxidations. ***DJM***

DOI: 10.1039/b210880c

Table 1 Catalytic RuO_4 oxidation with $NaIO_4$ as a stochiometric oxidant in DMC–water solvent system

Entry	Starting material	Equiv. of $NaIO_4$	Reaction time/h	Product (yield,[a] %)
1	Benzyl alcohol	4.1	3	Benzoic acid (86)
2	1-Octadecanol	4.1	2	Stearic acid (92)
3	Cyclododecanol	2.05	2.5	Cyclododecanone (87)
4	4-Methoxybenzaldehyde	2.05	2.5	4-Methoxybenzoic acid (86)
5	1-Iodooctadecane	4.1	4	Stearic acid (79)[b]
6	1-Hexyne	8.2	1	Pentanoic acid (88)
7	Tetrahydrofuran	4.1	1.5	γ-Butyrolactone (48)[c]
8	Hexadecylbenzene	16.4	22	Heptadecanoic acid (91)
9	1,2,3,4-Tetrahydronaphthalene	16.4	18	Adipic acid (88)
10	Cyclopropylphenylmethane	8.2	20	Cyclopropyl phenyl ketone (56),[c] cyclopropylacetic acid (9)[c]

[a] Isolated yield. [b] $RuO_2{\cdot}xH_2O$ (4.5 mol%) was used as the ruthenium source. [c] GLC yield.

recently reported that ethyl acetate–bleach may be a suitable solvent–cooxidant system for oxidation of ethers.[12] Aromatic compounds were oxidized by a catalytic amount of ruthenium tetraoxide with sodium periodate as a stochiometric oxidant in CCl_4–CH_3CN–H_2O solvent system in 60–91% yields.[13] Oxidation of simple aromatic compounds in the DMC–water solvent system gave the corresponding carboxylic acids in good yields (Table 1, entries 8, 9). Oxidation of cyclopropylphenylmethane gave cyclopropyl phenyl ketone as the major product (Table 1, entry 10). The cyclopropyl group is known to activate the neighboring methylene group towards ruthenium tetraoxide oxidation.[14]

We used 2.05–16.4 equivalents of $NaIO_4$, for the reaction on 1–2 mmol of substrate (Table 1). The solvent was a mixture of 10 mL of DMC (5 mL of DMC was added initially to the reaction mixture and remaining 5 mL was used to dissolve the substrate prior to addition) and 5 mL of water. Vigorous stirring that ensured mixing of the two layers was essential. If the stirring was not vigorous enough, ruthenium compounds precipitated, as was indicated by black color of the solution, and the oxidation stopped. In such a system it was enough to increase the rate of stirring for oxidation to resume (yellow or red color of ruthenium tetraoxide returned within seconds). In contrast to ruthenium tetraoxide oxidations prepared in the presence of acetonitrile where a chlorinated solvent was necessary, addition of a chlorinated solvent such as dichloromethane or carbon tetrachloride was detrimental to the oxidation in DMC–water. Thus, addition of 0.184 g (1 mmol) of cyclododecanol dissolved in 5 mL of dichloromethane to the reaction mixture containing 5 mL of water, 5 mL of dimethylcarbonate, 5 mg of hydrated ruthenium tetraoxide and 0.877 g (4.1 mmol) sodium periodate resulted in precipitation of ruthenium species and termination of the reaction. Addition of either ethyl acetate or acetone, two other solvents commonly used in ruthenium tetraoxide oxidations, was also detrimental to the oxidation as evidenced by a reduced reaction rate. Addition of acetonitrile to the DMC–water solvent mixture was not detrimental to the ruthenium tetraoxide oxidation. However, it did not appear to provide any benefits either. The reaction rate and isolated yields of the oxidation products were similar in both cases.

Ruthenium tetraoxide oxidations with bleach (6% aqueous solution of NaClO) as a stochiometric oxidant gave good to excellent results in oxidation of alcohols, aldehydes, ethers and aromatic rings (Table 2). We obtained the best results by adding a solution of bleach to the reaction mixture in small portions over a period of time. Bleach was particularly suitable in degradation of aromatic rings. The oxidation was fast (1 h) compared to the $RuCl_3$–$NaIO_4$ oxidation system (18–22 h) and proceeded in a high yield. This method was successful in oxidative degradation of 2,4,6-trichlorophenol (Table 2, entry 9), a compound that has been identified as a persistent chlorinated pollutant. A drawback of the $RuCl_3$–NaClO oxidation system is that oxidation of aromatic substrates in which the benzene ring should be preserved proceeded in somewhat lower yields. Thus, oxidation of 4-methoxybenzaldehyde (Table 2, entry 4) proceeded in only 50% yield due to competing degradation of benzene ring. Even oxidation of 4-nitrobenzaldehyde (Table 2, entry 5) proceeded in only 72% yield. Attempts to improve the reaction by reducing reaction times or amounts of the cooxidant failed to improve the yield (Table 2, entry 6). Oxidation of tetrahydrofuran to γ-butyrolactone with $RuCl_3$–NaClO oxidation system proceded in 69% yield (Table 2, entry 7) and was superior to both $RuCl_3$–$NaIO_4$ (Table 1, entry 7) and $RuCl_3$–Oxone® (Table 3, entry 5). It was recently reported that oxidation of tetrahydrofuran to γ-butyrolactone with $RuCl_3$–NaClO in ethyl acetate–water as solvent proceeded in only 44% yield.[8] Further research on oxidation of ethers with $RuCl_3$–NaClO in DMC is in progress.

With Oxone® as a cooxidant, most of the oxidation products were obtained in good yields (Table 3). However, often a somewhat larger excess of reagent was required, compared to $RuCl_3$–NaClO and $RuCl_3$–$NaIO_4$ systems. A lower amount of the reagent was needed to complete the oxidation when an aqueous solution of Oxone® was added to the reaction mixture in small portions over a period of time.

The largest difference among the three stochiometric oxidants was encountered in oxidation of alkenes (Table 4). As

Table 2 Catalytic RuO_4 oxidation with NaClO as a stochiometric oxidant in DMC–water solvent system

Entry	Starting material	Equiv. of NaClO	Reaction time/h	Product (yield,[a] %)
1	Benzyl alcohol	6	1	Benzoic acid (61)
2	1-Octadecanol	6	1	Stearic acid (81)
3	Cyclododecanol	3	1	Cyclododecanone (95)
4	4-Methoxybenzaldehyde	3	1	4-Methoxybenzoic acid (50)
5	4-Nitrobenzaldehyde	3	1	4-Nitrobenzoic acid (72)
6	4-Nitrobenzaldehyde	2.6	0.33	4-Nitrobenzoic acid (46)
7	Tetrahydrofuran	3.33	1	γ-Butyrolactone (69)[b]
8	Hexadecylbenzene	20	1	Heptadecanoic acid (86)
9	2,4,6-Trichlorophenol	20	24	—

[a] Isolated yield. [b] GLC yield.

Table 3 Catalytic RuO_4 oxidation with Oxone® as a stochiometric oxidant in DMC–water solvent system

Entry	Starting material	Equiv. of Oxone®	Reaction time/h	Product (yield,[a] %)
1	Benzyl alcohol	8	2	Benzoic acid (72)
2	Cyclododecanol	4	1	Cyclododecanone (94)
3	4-Methoxybenzaldehyde	7	25	4-Methoxybenzoic acid (69)
5	Tetrahydrofuran	6	4	γ-Butyrolactone (35)[b]
6	Hexadecylbenzene	20	1	Heptadecanoic acid (88)

[a] Isolated yield. [b] GLC yield.

Table 4 Catalytic RuO_4 oxidation of alkenes

Entry	Starting material	Stochiometric oxidant/eqiuv.	Reaction time/h	Product (yield,[a] %)
1	Cyclooctene	$NaIO_4$ (8.2)	4	Suberic acid (91)[b]
2	Cyclododecene	$NaIO_4$ (8.2)	4	Dodecanedioic acid (87)[b]
3	Cyclooctene	Bleach (10)	2	Suberic acid (2)
4	Cyclooctene	Bleach (10)	1	Suberic acid (43)[c]
5	Cyclododecene	Bleach (10)	2	Dodecanedioic acid (12)
6	Cyclododecene	Bleach (10)	1	Dodecanedioic acid (15)[c]
7	Cyclododecene	Bleach (10)	1	Dodecanedioic acid (73)[d]
8	Cyclooctene	Oxone® (10)	6	Suberic acid (44)
9	Cyclododecene	Oxone® (10)	4.5	Dodecanedioic acid (63)

[a] Isolated yield. [b] Solvent system consisted of 20 mL of DMC and 10 mL of water. [c] Acid was obtained by $NaIO_4$ oxidation of the aqueous phase. [d] DMC (10 mL) and acetonitrile (10 ml) were used as the reaction solvent.

expected, the $RuCl_3$–$NaIO_4$ system oxidized alkenes to the corresponding dicarboxylic acids in high yields (Table 4, entries 1 and 2). In order to avoid deactivation of the catalyst, a somewhat larger amount of DMC (20 mL instead of the usual 10 mL) was used. The $RuCl_3$–NaClO system in DMC failed to oxidize alkenes. The reaction was rapid and the alkenes were consumed quickly. However, only low yields of the corresponding diacids were isolated (Table 4, entries 3 and 5). Upon addition of bleach to the reaction mixture containing an alkene, a ruthenium catalyst and DMC, instead of a yellow–orange color of ruthenium tetraoxide, a black solution with greenish tint, reminiscent of the color of a deactivated ruthenium catalyst, was obtained. We speculated that, since oxidation of alkenes proceeds *via* the intermediate vicinal diols,[15] the diols were water soluble and in the aqueous phase were not oxidized further by ruthenium tetraoxide, which was dissolved in the DMC phase. The fact that oxidation of alkenes proceeded in high yields when sodium periodate, which is capable of cleaving vicinal diols, was used as a stochiometric oxidant, and that yields were somewhat lower with Oxone® (Table 4, entries 8 and 9), which does not oxidize diols in the aqueous phase, supports this hypothesis. To confirm the hypothesis, we run a $RuCl_3$–NaClO oxidation of an alkene (cyclooctene or cyclododecanone) for 1 h, separated the aqueous phase, extracted the aqueous phase with DMC in order to remove any ruthenium compounds that may have remained in it, and treated it with an aqueous solution of sodium periodate. Suberic and dodecanedioic acids were isolated in 43 and 15% yields, respectively (Table 4, entries 4 and 6). The results indicate that, at least in the case of lower molecular weight diols, the solubility of a diol in the aqueous phase presents a problem. Since the color of the solution indicated that the ruthenium catalyst was deactivated in the course of $RuCl_3$–NaClO oxidation of an alkene, we attempted to reactivate it. Addition of a larger amount of DMC to the reaction mixture did not provide an improvement. However, addition of 10 mL of acetonitrile to the reaction mixture resulted in a rapid color change from black-green to yellow. Thus $RuCl_3$–NaClO, in a solvent system consisting of DMC–acetonitrile (1 : 1 by volume), oxidized cyclododecanone to decanedioic acid in a good yield (Table 4, entry 7). It is also possible to perform the oxidation in acetonitrile only (without DMC). However, in such a case a larger amount of acetonitrile was needed (50 mL).

The described method represents a simpler, environmentally friendly, solvent system for a ruthenium tetraoxide oxidation of a wide range of substrates. Furthermore, together with bleach as a cooxidant, it may be have an application in ruthenium tetraoxide oxidative degradation of pollutants such as chlorophenols as well as polychlorinated biphenyls.

Experimental

The isolated products were identified by comparison with commercially available authentic samples. Compounds analyzed by GLC were identified by coinjection with authentic samples using a HP 5890 Gas Chromatograph equipped with a 0.53 mm × 30 m RTX-35 (Restek Corp.) column and FID.

Oxidation with sodium periodate as a stochiometric oxidant

In a typical experiment, 0.877 g (4.1 mmol, 2.05 equiv.) of sodium peroidate was dissolved in 5 mL of water. Hydrated ruthenium trichloride (5 mg, 1.2 mol%) was added followed by 5 mL dimethyl carbonate. A solution of cyclododecanol (369 mg, 2 mmol, 1 equiv.) in 5 mL dimethyl carbonate was added and the reaction mixture was stirred vigorously for 1 h. The layers were separated, and aqueous layer was extracted with ethyl acetate. Organic phases were combined, the excess of ruthenium tetraoxide was destroyed by addition of 2 mL of diethyl ether, and the solution was dried over anhydrous $MgSO_4$. The solution was filtered through a short column of Celite and evaporated to give 335.1 mg (92%) of cyclododecanone.

Oxidation with bleach as a stochiometric oxidant

In a typical experiment, to hydrated ruthenium trichloride (5 mg, 2.5 mol%) was added 10 mL dimethyl carbonate followed by hexadecylbenzene (355 μL, 1 mmol, 1 equiv.). Bleach was added in small portions over the course of the reaction. The color of the reaction mixture became black upon addition of bleach and, after a few seconds, turned yellow. An exothermic reaction ensued and the temperature of the solution rose to 45 °C. The reaction mixture was stirred for 1 h. The pH of the reaction mixture was adjusted to 2 by addition of 10 M hydrochloric acid. The layers were separated and the aqueous layer was extracted with diethyl ether. Organic phases were combined and the solution was dried over anhydrous $MgSO_4$. The solution was filtered through a short column of Celite and evaporated. Recrystallization (water–methanol) of the crude product gave 251.3 mg (86%) of heptadecanoic acid.

Oxidation with Oxone® as a stochiometric oxidant

In a typical experiment, to hydrated ruthenium trichloride (5 mg, 2.5 mol%) was added 10 mL dimethyl carbonate followed by cyclododecene (190 μL, 1 mmol, 1 equiv.). An aqueous solution of Oxone® (1 mmol or 0.615 g per 3 mL water) was added in small portions over the course of the reaction until a total of 10 mmol were added. The reaction mixture was stirred vigorously for 4.5 h. The layers were separated and aqueous layer was extracted with ethyl acetate. Organic phases were combined, the excess of ruthenium tetraoxide was destroyed by addition of 2 mL of diethyl ether, and the solution was dried over anhydrous $MgSO_4$. The solution was filtered through a short column of Celite and evaporated. Recrystallization (ethanol–water) of the crude product gave 208.5 mg (63%) of dodecanedioic acid.

Acknowledgement

We thank Nova Southeastern University for support in form of President's Faculty Scholarship Award (Grant no. 338 319) to V. D.

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Brønsted acidic ionic liquid 1-methylimidazolium tetrafluoroborate: a green catalyst and recyclable medium for esterification

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Received (in Cambridge, UK) 20th September 2002
First published as an Advance Article on the web 11th December 2002

Esterification of carboxylic acids with alcohols could be carried out in a Brønsted acidic ionic liquid 1-methylimidazolium tetrafluoroborate ($[Hmim]^+BF_4^-$). Good yields were obtained, and the esters produced could be easily separated from the reaction mixture without any volatile organic solvents. The ionic liquid $[Hmim]^+BF_4^-$ could be reused after removal of water.

Introduction

Organic esters are important products or intermediates in the chemical and pharmaceutical industries.[1] Esterification of carboxylic acids using liquid inorganic acid catalysts is well known.[2–4] However, removal of water or/and use of excess amount of the reactants is generally needed for satisfactory conversion, and a large volume of volatile organic solvents is often required. Meanwhile, it is very difficult to recycle the liquid inorganic acid catalysts, which need to be neutralized after the reaction. Large amounts of volatile organic solvents and liquid inorganic acids may result in pollution to the environment.

Ionic liquids are emerging as green reaction media for a variety of organic transformations.[5] Recently, it has been reported that esterification could be carried out in ionic liquids, such as 1-hexyl-3-methylimidazolium hydrogen sulfate and 1-[2-(2-hydroxyethoxy)ethyl]-3-methylimidazolium hydrogen sulfate.[6] However, the preparation of these ionic liquids was not convenient, and volatile organic solvents were also used for the preparation and reuse of the ionic liquids. Furthermore, the conversions were lower than 60% for most of the substrates.

In this paper a practical and efficient procedure for esterification of carboxylic acids with alcohols is reported, using a Brønsted acidic ionic liquid, 1-methylimidazolium tetrafluoroborate ($[Hmim]^+BF_4^-$), as recyclable catalyst and solvent (Scheme 1).

$$\mathrm{RCOOH} + \mathrm{R'OH} \xrightarrow[110\ ^\circ\mathrm{C}]{[\mathrm{Hmim}]^+\mathrm{BF}_4^-} \mathrm{RCOOR'}$$

Scheme 1

Experimental

General remarks

All commercial chemicals were used as received. The reactions were carried out in a glass reactor fitted with a reflux condenser and oil-bath. The reacting acids and alcohols (indicated in Table 1) were added to the ionic liquid $[Hmim]^+BF_4^-$. The esterification reactions proceed for a period of time ranging from 2 to 10 h with vigorous stirring and using an oil-bath at 110 °C. Reaction progress was monitored by GC-MS (Agilent GC: 6890 MS: 5973N). After the reaction, the ester and ionic liquid $[Hmim]^+BF_4^-$ were separated conveniently by decanting. The ionic liquid $[Hmim]^+BF_4^-$ was reused after removal of water under vacuum (0.01 Torr) at 70 °C for 1 h.

Preparation of ionic liquid 1-methylimidazolium tetrafluoroborate ($[Hmim]^+BF_4^-$)[7]

1-Methylimidazole (61.5 g, 0.75 mol) was placed in a three-necked flask, which was provided with a stirrer and cooled to 0 °C. Then tetrafluoroboric acid (0.75 mol, 40% solution in water) was added slowly over a period of 30 min while stirring and cooling to maintain the temperature at 0–5 °C. The reaction mixture was stirred for an additional period of 2 h. Water was removed in vacuum to give the product as a colorless liquid, which solidified on cooling.

Typical esterification procedure

1-Butanol (2 ml, 0.02 mol), equivalent acetic acid (1.6 ml, 0.02 mol) and ionic liquid $[Hmim]^+BF_4^-$ (2 ml) were added in a flask with a reflux condenser and oil-bath. The reaction mixture was stirred for 2 h with the oil-bath at 110 °C. Reaction progress was monitored by GC-MS. After reaction, the mixture was decanted, the ester was isolated, and the ionic liquid $[Hmim]^+BF_4^-$ was reused after removal of water under vacuum (0.01 Torr) at 70 °C for 1 h.

Results and discussion

The preparation of the ionic liquid $[Hmim]^+BF_4^-$ was very convenient being obtained by simply mixing 1-methylimida-

Green Context

Esterification is a simple process, yet there are still many challenges to produce a simple and clean route to esters from acids and alcohols. One particularly attractive method uses a Brønsted acidic ionic liquid to carry out the reaction. The product ester is insoluble and separates from the ionic liquid as the reaction proceeds, presumably helping to drive the equilibrium towards products. Very high yields can be achieved with a simple separation, and the ionic liquid can be reused several times. ***DJM***

Table 1 Results of esterification for different acids and alcohols in ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ at 110 °C

Entry	Acid	Alcohol	Conversion[a] (%)	Selectivity to ester (%)	Time/h
1	Acetic acid	1-Butanol	97	100	2
2	Acetic acid	1-Octanol	>99	100	2
3	*n*-Decanoic acid	1-Butanol	96	100	3
4	*n*-Decanoic acid	1-Ocatanol	97	100	3
5	*n*-Decanoic acid	Methanol	97	100	5
6	Stearic acid	1-Butanol	>99	100	3
7	Stearic acid	1-Octanol	>99	100	3
8	Stearic acid	Methanol	>99	100	6
9	Undecanoic acid	1-Butanol	>99	100	3
10	Undecylenic acid	1-Butanol	>99	100	3
11	Lactic acid	1-Butanol	>99	100	2
12	Crotonic acid	Methanol	93	100	6
13	Oxalic acid	Ethanol	>99	100[b]	4
14	Oxalic acid	1-Octanol	>99	100[b]	4
15	Benzoic acid	1-Butanol	80	100	10
16	3-Hydroxybenzoic acid	1-Butanol	93	100	10

[a] The conversion of acid or alcohol (ratio of acid to alcohol = 1 : 1). [b] The esters are all double esterification products. No monoesterification product was detected; ratio of acid to alcohol = 1 : 2.

zole with tetrafluoroboric acid (40% aq.) at 0–5 °C and stirring for 2 h at room temperature, followed by removal of water. The ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ was obtained in quantitative yield.

Esterification of a variety of acids with four common alcohols was carried out in $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$. The results are listed in Table 1. Good to excellent yields and perfect selectivity were obtained in all cases. No by-products such as olefins were detected. And all of the esters produced could be easily separated due to their immiscibility with the ionic liquid. It is noteworthy that removal of water or using an excess of reactant is not necessary. No volatile organic solvents are required during the work-up and recycle of the ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$.

The results in Table 1 showed that the esterification of aliphatic acids with primary alcohols was very satisfactory, and the length of alkyl chains did not affect the conversion and the selectivity. Olefinic bonds of aliphatic acids were not changed under these reaction conditions (Table 1, entries 10 and 12). The hydroxy group of lactic acid did not take part in the esterification with only *n*-butyl lactate being obtained (Table 1, entry 11).

In the reaction of oxalic acid, no monoesterification products were detected when the molar ratio of acid to alcohols was 1 : 2 (Table 1, entries 13 and 14).

Esterification of aromatic acids gave lower yields compared with those of aliphatic acids, further substituent groups on the aryl ring affected the reactions (Table 1, entries 15 and 16).

The esterification of methanol (Table 1, entries 5, 8 and 12) was not very easy due to its low boiling point and the required reaction time was longer than that of the other alcohols. However, satisfactory results were obtained.

The water produced in the reactions did not need to be removed because the ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ was miscible with water while the esters were immiscible with the ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$. Hence the esterification proceeded smoothly to completion. Liquid esters could be separated conveniently by decanting. Some esters (Table 1, entries 6–8, 15 and 16) have to be isolated above their melting point since they solidify at room temperature.

The ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ could be easily recycled. After reaction, with the mixture decanted, the ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ was separated and reused after drying in vacuum. The $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ was utilized repeatedly over eight times in the esterifacation of acetic acid with 1-butanol with the conversion and selectivity being unchanged (Table 2).

Table 2 Recycling of $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ in the synthesis of butyl acetate

Run	Conversion (%)	Selectivity to ester (%)	Time/h
1	97	100	2
2	96	100	2
3	97	100	2
4	95	100	2
5	96	100	2
6	95	100	2
7	94	100	2
8	94	100	2

In summary, the esterification of carboxylic acid with alcohol, using the ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ as catalyst and solvent, has several advantages: (1) the ionic liquid $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$, as a strong Brønsted acid, shows superior catalytic activity than the systems reported by Fraga-Dubreuil *et al.*[6] (2) The preparation of $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ was very simpe. (3) $[\mathrm{Hmim}]^+\mathrm{BF}_4^-$ could be directly reused after removal of water since no by-products were produced in the reaction. (4) The esters produced can be isolated conveniently in high yields and purity.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (No. 20172016), Shanghai Phosphor Project of Science & Technology for Excellent Young Research (No. 01QA14017), the Foundation of Shanghai Science and Technology Development.

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Exhaustive hydrodechlorination of chlorinated aromatic environmental pollutants to alicyclic compounds

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Received (in Cambridge, UK) 17th July 2002
First published as an Advance Article on the web 6th January 2003

A combined Pd–Rh catalyst obtained by co-entrapment of metallic palladium and soluble $[Rh(cod)Cl]_2$ within a silica sol–gel matrix exhaustively detoxifies chlorinated aromatic pollutants not only by total removal of the chlorine, but also by the total reduction of the aromatic moieties to alicyclic rings. The list of chloroarenes which have been successfully destroyed by the catalysts includes most of the major pollutants which are of public concern, namely chlorinated dibenzo[*b,e*]dioxin and dibenzofuran, PCBs, DDT, Hexachlorophene and 2,4,5-T. The reactions take place under the relatively mild conditions of 80–100 °C under 27 atm H_2. The immobilised catalyst is leach proof in a variety of solvents and can be reused in several runs. The high activity of the combined Pd–Rh system is attributed to synergism between the two different metal atoms.

Introduction

Public concern over chlorinated organic pollutants[1] has fueled many efforts to develop efficient and clean destruction methods of these chemicals. Several processes have been developed towards this goal, most of which are reductive procedures that remove the chlorine but leave the aromatic hydrocarbons unaffected.[2] However, as benzene and some of its derivatives, as well as polycyclic aromatic hydrocarbons (PAH) are by themselves hazardous carcinogenic substances, it seems imperative to develop detoxification processes that destroy the aromatic moieties as well. So far only a few studies in this direction, leading from chlorinated benzene derivatives to cyclohexanes, have been announced.[3,4] However, to the best of our knowledge, no general efficient catalyst that transfers all major pollutants—polychlorinated dibenzo[*b,e*]dioxin (PCDDs), dibenzofuran (PCDFs), and biphenyl (PCBs), as well as 1,1′-(2,2,2-trichloroethylidene)bis(4-chlorobenzene) (DDT), 2,2′-methylenebis(3,4,6-trichlorophenol) (Hexachlorophene) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)—directly to HCl and totally reduced aromatics, has been reported. Here we describe such a catalyst, namely a sol–gel-entrapped combined Pd–$[Rh(cod)Cl]_2$ system. This recyclable system has already been shown to promote the hydrogenation of aromatic C–C bonds,[5] as well as the direct transformation of benzylic CO to CH_2 moieties.[6]

Results and discussion

Our initial hydrogenation experiments of some simple chloroarenes in the presence of the sol–gel entrapped Pd-$[Rh(cod)Cl]_2$ catalyst are listed in Table 1. Under our experimental conditions (80–100 °C and 27 atm H_2) the Pd–Rh catalyst system is stable and recyclable. Several of the reactions listed in Table 1 were repeated 3–4 times with the same catalyst without significant loss in its activity. The same catalyst has also been used occasionally for the hydrogenation of different substrates. It is notable that the HCl eliminated in these reactions does not accumulate in the sol–gel matrix. The chlorine content of the HF-treated immobilized catalyst prior to the catalytic process and after it was found to be identical. Although the hydrogenation process both eliminates the ring-bound chlorine atom and saturates the aromatic C–C bonds, simple alkyl chlorides are not affected. Therefore, it is possible to carry out the reactions in 1,2-dichloroethane in which many chloroarenes are highly soluble. The hydrodechlorination process can however, be performed equally well in chlorine-free alkanes. Other common solvents such as methanol or THF have also been used, but the reaction proceeded at a lower rate (see Table 1, entries 4 and 5). In water, in which the chloroarenes are usually only sparingly soluble the reaction proceeded even slower. Although steric hindrance seems to have some effect on the combined dechlorination and aromatic ring hydrogenation, the various vicinal di-, tri- and tetrachlorobenzenes, listed in Table 1 gave, under our standard conditions, solely cyclohexane, free of chlorinated side products. Only the reaction mixture of pentachlorobenzene consisted after 6 h of the fully hydrogenated cyclohexane together with 10% of tetrachlorobenzene which gradually disappeared upon extension of the reaction time. Hexachlorobenzene, however did not react at all. We presume that the unreactivity of hexachlorobenzene and the slow reaction of tetrachlorobenzene are associated with steric effects. 1-Chloronaphthalene (entry 11), was found to form a mixture of tetralin and *cis*- and *trans*-decalin. Although linear chloroalkanes are not dechlorinated, entries 12 and 13 indicate that chlorine atoms at the benzylic position undergo hydro-

Green Context

While green chemistry seeks to avoid the formation of pollutants through highly efficient clean processes and the production of benign products, we will always have pollutants to deal with. Chlorinated organic pollutants represent one of the major targets for treatment. It is important that in carrying out such treatments we do not add to the overall environmental burden through unreasonable use of additional resource (including energy) or through the production of secondary pollutants. Here we see described a new hetergeneous catalyst for the hydrodechlorination of chlorinated aromatic pollutants. The reactions take place under quite mild conditions (minimum energy demands) and the precious metal catalyst is reusable (minimum resource demands). ***JHC***

Table 1 Hydrogenation of some chlorinated aromatic compounds in the presence of the sol–gel entrapped Pd–[Rh(cod)Cl]$_2$ catalyst[a]

Entry	Substrate	Solvent	Reaction time/h	Product (yield, %)[b]
1	C_6H_5Cl	1,2-$C_2H_4Cl_2$	3	C_6H_{12} (87)
2	1,2-$C_6H_4Cl_2$	1,2-$C_2H_4Cl_2$	3	C_6H_{12} (91)
3	1,2-$C_6H_4Cl_2$	Hexane[c]	3	C_6H_{12} (100)
4	1,2-$C_6H_4Cl_2$	MeOH	3	C_6H_{12} (70)
5	1,2-$C_6H_4Cl_2$	THF	3	C_6H_{12} (20)
6	1,3-$C_6H_4Cl_2$	1,2-$C_2H_4Cl_2$	3	C_6H_{12} (78)
7	1,4-$C_6H_4Cl_2$	Hexane[c]	3	C_6H_{12} (100)
8	1,2,4-$C_6H_3Cl_3$	1,2-$C_2H_4Cl_2$	6	C_6H_{12} (32)
9	1,2,3,4-$C_6H_2Cl_4$	1,2-$C_2H_4Cl_2$	6	C_6H_{12} (43)
10	1,2,3,4,5-C_6HCl_5	1,2-$C_2H_4Cl_2$	6	C_6H_{12} (63), 1,2,4,5-$C_6H_2Cl_4$ (10)
11	1-$C_{10}H_7Cl$	Hexane[c]	3	$C_{10}H_{12}$ (71), *c*-$C_{10}H_{18}$ (11), *t*-$C_{10}H_{18}$ (17)
12	$C_6H_5CH_2Cl$	1,2-$C_2H_4Cl_2$	6	$C_6H_{11}CH_3$ (95)
13	$C_6H_5CCl_3$	Hexane[c]	6	$C_6H_{11}CH_3$ (96)
14	3-ClC_6H_4OH	H_2O	6	$C_6H_{11}OH$ (44), $C_6H_{10}O$ (26)
15	4-ClC_6H_4OH	1,2-$C_2H_4Cl_2$	4	C_6H_{12} (37), $C_6H_{11}OH$ (25), $C_6H_{10}O$ (28)
16	4-ClC_6H_4OH	H_2O	4	$C_6H_{11}OH$ (49), $C_6H_{10}O$ (21)

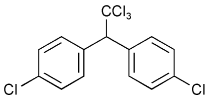
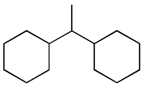
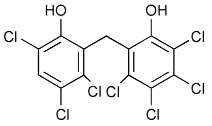
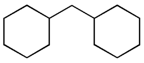
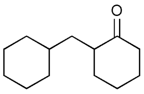
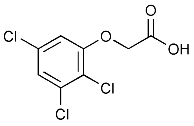
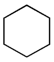
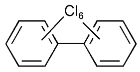
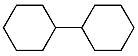
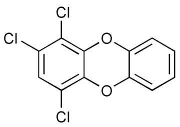
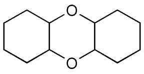
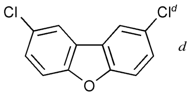
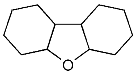
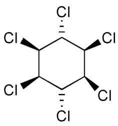
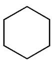
[a] *Reaction conditions*: 2 mmol substrate, ceramic catalyst containing 2 × 10^{-2} [Rh(cod)Cl]$_2$ and 0.1 mmol Pd, 5 ml solvent, 100 °C, 27 atm. H_2., stirring rate 150 rpm. [b] The yield is an average of at least two runs that did not differ by more than 5%. The missing percentage is usually accounted for by unreacted starting material. [c] Mixture of hexanes containing ~85% of *n*-hexane.

genolysis similar to aryl chlorides. It is remarkable that under the conditions of Table 1, the chlorobenzenes do not yield detectable amounts of chlorine-free reaction intermediates (*i.e.*, benzene, cyclohexadienes or cyclohexene). However, the hydrogenation of 3- and 4-chlorophenol forms, apart from cyclohexanol, considerable amounts of cyclohexanone which can be regarded as the keto tautomer of 1-cyclohexenol.

Interestingly, while the hydrogenation of chlorophenols in 1,2-dichloroethane yields, apart from the carbinol and the ketone also cyclohexane, in water the oxygen functions do not undergo hydrogenolysis.

Next we studied the hydrogenation of some major pollutants in the presence of the sol–gel entrapped Pd–[Rh(cod)Cl]$_2$ catalyst. The results are summarised in Table 2. The Table

Table 2 Hydrogenation of some major chlorinated aromatic industrial products and industrial wastes in the presence of the sol–gel entrapped Pd–[Rh(cod)Cl]$_2$ catalyst[a]

Entry	Substrate	Solvent	Product	Yield[b] (%)
1		Hexane		90
2		1,2-$C_2H_4Cl_2$		58
				32
3		1,2-$C_2H_4Cl_2$		75[c]
4		Hexane		99
5		1,2-$C_2H_4Cl_2$		93
6	 [d]	1,2-$C_2H_4Cl_2$		81[e]
7		1,2-$C_2H_4Cl_2$		18

[a] Reaction conditions as in Table 1. Time 24 h. The hexane used contained ~85% *n*-hexane. [b] Average of at least 2 runs. Except for entry 6, the missing percentage is accounted for by unreacted starting material. [c] The amount of chloroacetyl chloride in the reaction mixture was not determined. [d] Mixed with 16% of 2,3,8-trichlorodibenzofuran. [e] Contaminated with 19% of chlorine- and oxygen-free non-aromatic hydrocarbons.

indicates that in the banned insecticide DDT[7] both the ring-bound, as well as the chlorine atoms at the homobenzylic position undergo hydrogenolysis and 1,1-dicyclohexylethane is formed in a high yield (Table 2, entry 1). The former bactericide and antiseptic agent Hexcachlorophene which turned out to be neurotoxic[8] yields mainly dicyclohexylmethane, but in analogy to the chlorophenols listed in Table 1, gives also a ketone, 2-cyclohexylmethyl(cyclohexanone)[9] (entry 2). The infamous plant growth regulator and herbecide, 2,4,5-T[10] proved to give under our standard conditions only chloroacetyl chloride and cyclohexane (entry 3). As a representative example for the polychlorinated biphenyls (PCBs)[11,12] we hydrogenated a commercial mixture of 2,2′,3,3′,4,4′-, 2,2′,3,4,4′5- and 2,2′4,4′,5,5′-hexachloro-1,1′-biphenyl (PCB-128, PCB-138 and PCB-153, respectively). In this experiment (Table 2, entry 4) chlorine-free bicyclohexyl was obtained in quantitative yield. Using 1,2,4-trichlorodibenzo[*b*,*e*][1,4]dioxin[13] and chlorinated dibenzofuran[14] as model compounds, for polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) the high efficiency of our catalyst was demonstrated again through exhaustive hydrogenation of these compounds (entries 5 and 6). While the dioxin derivative yielded almost entirely pure dodecahydrodibenzo[*b*,*e*][1,4]dioxin,[15] the dodecahydrodibenzofuran[16] was contaminated with up to 18% of a mixture of chlorine- and oxygen-free non-aromatic hydrocarbons.

As noted above the refractory behaviour of aliphatic chloroalkanes toward hydrogenation, under our experimental conditions, enabled us to carry out the reactions in 1,2-dichloroethane. Some *cyclic* chlorohydrocarbons could however be dechlorinated. Of particular interest is the hydrodechlorination of the hexachlorocyclohexanes. The γ-isomer, Lindane, which is sold worldwide under many different trademarks as an insecticide is reduced slowly (18% within 24 h) under the conditions of Table 2 (entry 7). Chlorinated intermediates were not detected in the reaction mixture.

In contrast to some other catalytic hydrogenations of chloroarenes (*e.g.*, see references 2*e* and 2*s*), the liberated hydrogen chloride seems neither to interfere nor to enhance the progress of the process. However, attempts to trap the HCl gas by running the reaction in an autoclave beaded with $Ba(OH)_2$ resulted in a decrease of the reaction rate.

The pronounced catalytic activity of the combined Pd–Rh system is attributed to synergism that may exist between the sol–gel entrapped palladium and the metal of the encaged $[Rh(cod)Cl]_2$ complex. While the combined catalyst system promoted the conversion of 1,2-dichlorobenzene in $1,2\text{-}C_2H_4Cl_2$ to give 91% of cyclohexane within 3 h (Table 1, entry 2), the reaction with rhodium-free entrapped palladium afforded only 30% of cyclohexane and the heterogenized $[Rh(cod)Cl]_2$ gave under the same conditions 19% of the alicyclic product.

Although this study is concerned with the hydrodehalogenation of chloroarenes, it is notable that fluoroarenes undergo similar defluorination albeit at somewhat lower rates. Under the conditions of Table 1, fluorobenzene is converted into cyclohexane in 50% yield within 3 h (as compared with the yield of 87% obtained from chlorobenzene under the same conditions). Bromoarenes are hydrodehalogenated to give chiefly halogen-free aromatic products. Under the aforementioned conditions, bromobenzene gives after 3 h 80% of benzene and 18% of cyclohexane. We attribute the partial poisoning of the catalyst to the formation of HBr. A similar phenomenon has already been observed in a previous study on hydrogenation of haloarenes by the sol–gel entrapped ion pair $RhCl_3$–Aliquat 336.[4]

In conclusion, we propose that this general catalytic process by the immobilised Pd–Rh catalyst may also serve as a facile way for disposal of other unwanted chloroarenes that form unfavoured benzene derivatives by the conventional hydrodechlorination methods.

Experimental

General procedure for hydrodechlorination of aromatic chlorine compounds

Typically, a glass lined autoclave, equipped with a mechanical stirrer, a sampler and a temperature controller was charged with the chlorinated substrate (2 mmol), the appropriate solvent (5 ml) and a sol–gel entrapped catalyst[5] prepared from Na_2PdCl_4 (32 mg, 0.11 mmol), $NaBH_4$ (22 mg), $H_2N(CH_2)_3Si(OCH_3)_3$ (0.27 ml), $[Rh(cod)Cl]_2$ (10 mg, 0.02 mmol) and $Si(OCH_3)_4$ (1.7 ml). The Pd and Rh loading in the heterogenized catalyst so formed, was 1.45 and 0.52% respectively, the diameters of the Pd particles were 2–4 nm, and the N_2-Langmiur surface area of the ceramic materials was 730 $m^2\ g^{-1}$ with a narrow pore size distribution centered around 15 Å. The sealed autoclave was flushed three times with hydrogen and pressurized to 27 atm. The reaction mixture was stirred at a rate of 150 rpm at 100 °C for the required length of time. After cooling to room temperature the autoclave was opened, the catalyst separated by filtration, washed and sonicated with dichloromethane, dried and reused in a second run. The filtrate was concentrated and the reaction products separated, if necessary by GC, and analyzed by comparing their IR, NMR and MS spectra with those of authentic samples.

Acknowledgements

We thank Roy Jackson and the staff of the Centre of Green Chemistry at Monash University, Melbourne for most helpful discussions, and the Israel Science Foundation, as well as the Ministry of Science, Culture and Sport for financial support of this study.

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Highly efficient acylation of alcohols, amines and thiols under solvent-free and catalyst-free conditions

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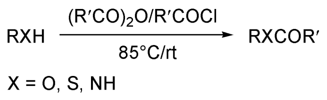
Received 13th November 2002
First published as an Advance Article on the web 14th January 2003

A general, simple, efficient, cost-effective and green procedure for acylation of alcohols, amines and thiols has been developed by treatment with acid anhydride or acid chloride at 80–85 °C under solvent and catalyst-free conditions.

Introduction

The acylation of functional groups, especially hydroxyl and amino groups is one of the most basic and frequently used transformations in organic synthesis as it provides a useful and efficient protection protocol in a multistep synthetic process.[1] Moreover, this reaction has a biomimetic importance as acylation of xenobiotics is a metabolic pathway that increases lipophilicity. Acylation is usually carried out by treatment of an alcohol or amine with acetyl chloride or acetic anhydride in the presence of an acid or a base catalyst in a suitable organic solvent, although acetic anhydride is the most commonly used being less toxic.[1] The most efficient base catalysts are 4-(dimethylamino)pyridine (DMAP),[2a] and phosphines,[2b,c] and the powerful acid catalysts employed include $CoCl_2$,[3a] $TaCl_5$,[3b] $Cu(OTf)_2$,[3c] Me_3SiOTf,[3d] $Sc(OTf)_3$,[3e,f] $In(OTf)_3$,[3g] $Bi(OTf)_3$,[3h] $LiClO_4$[3i] and yttria-zirconica based Lewis acid.[3j] The solvents commonly chosen for these reactions are methylene chloride, acetonitrile and tetrahydrofuran. Thus, apart from some operational disadvantages like moisture-sensitivity and high cost of many of these catalysts these procedures using toxic metal derivatives and chlorinated hydrocarbons as solvents also do not satisfy the requirements of green synthesis. Thus, a need for a practical, efficient and greener alternative for this important transformation prompted us to disclose here a simple procedure for acylation without any solvent and catalyst (Scheme 1).



$$RXH \xrightarrow[85°C/rt]{(R'CO)_2O/R'COCl} RXCOR'$$

X = O, S, NH

Scheme 1

Although there are a few examples of solvent-free acylation in the presence of an acid or a base particularly for amides and imides[4] to the best of our knowledge, no generalized and systematic study for acylation of alcohols, amines and thiols has been made under solvent- and catalyst-free conditions with a view to developing a practical methodology.

Results and discussion

In a typical general procedure, a neat mixture of an alcohol and an acid anhydride was heated at 80–85 °C without any solvent and catalyst under nitrogen for a certain period of time as required to complete the reaction. The acetate was distilled out directly from the reaction vessel under reduced pressure.

A wide range of structurally diverse and functionalised alcohols underwent acylation by this procedure to provide the corresponding acetates in excellent yields. The results are reported in Table 1. As evident from the results, this procedure is uniformly effective for acylation of primary (including saturated, allylic, propargylic and benzylic) and secondary alcohols, phenols and diols. Acylations of hindered secondary alcohol (entry 34) and tertiary alcohol (entry 36) which are often considered difficult, are also accomplished in reasonably good yields. Carbohydrate molecules such as glucose, galactose and sucrose undergo complete acylation of all the hydroxyl groups (entries 39–41). This procedure is also applicable for efficient acylation of thiols, amines and oximes (entries 48–54). Although most of the reactions were carried out with acetic anhydride other acid anhydrides such as propionic and benzoic anhydride are also equally effective (entries 5, 6, 15, 16, 30 and 31). Acid chlorides can also be used for acylation under similar experimental conditions at room temperature (entries 7, 8, 17, 18, 32 and 33). Most significantly, tolerance to several acid-sensitive functionalities such as acetal (entry 23), methylenedioxy (entry 22), carboxylic ester (entries 37 and 45) shows the superiority of this methodology over many existing procedures using strong Lewis acids.

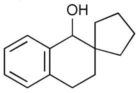
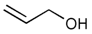
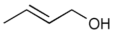
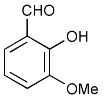
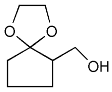
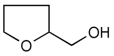
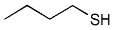
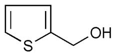
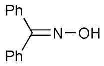
The acylations are, in general reasonably fast and clean. No side product has been isolated in any reaction. The products obtained by direct distillation from the reaction vessel are of high purity and do not require further purification. As a test case, a couple of reactions are scaled up to the extent of a batch with 10 g of alcohol (amount not optimised) without any difficulty avoiding use of any organic solvent in any step.

Green Context

Green chemistry can be considered as a set of reductions and for chemical processes a reduction in the complexity of that process is fundamentally important. This means reducing the use of auxiliaries (solvent, reagent, catalyst, *etc.*) and reducing the waste. Here we see an example of green chemistry reductions applied to the widely used acylation of functional groups. The methodology described here employs substrates only, with no solvent or catalyst and the product can be removed directly from the process by distillation. ***JHC***

DOI: 10.1039/b211238h

Table 1 Acylation of alcohols, amines and thiols under solvent- and catalyst-free condition

Entry	Substrate	Anhydride/acid chloride	Time/h	Yield of acetate^a (%)	Entry	Substrate	Anhydride/acid chloride	Time/h	Yield of acetate^a (%)
1	$CH_3(CH_2)_5OH$	$(MeCO)_2O$	1.5	92	28	Cyclopentanol	$(MeCO)_2O$	2	90
2	$CH_3OCH_2CH_2OH$	$(MeCO)_2O$	1.5	94	29	Cyclohexanol	$(MeCO)_2O$	2	92
3	$CH_3CH_2OCH_2CH_2OH$	$(MeCO)_2O$	1.5	93	30	Cyclohexanol	$(EtCO)_2O$	2	90
4	$PhCH_2OH$	$(MeCO)_2O$	2	95	31	Cyclohexanol	$(PhCO)_2O$	1.5	89
5	$PhCH_2OH$	$(EtCO)_2O$	1.5	88	32	Cyclohexanol	MeCOCl	0.75	89^b
6	$PhCH_2OH$	$(PhCO)_2O$	1.5	90	33	Cyclohexanol	EtCOCl	0.75	88^b
7	$PhCH_2OH$	MeCOCl	0.5	91^b	34		$(MeCO)_2O$	2	84
8	$PhCH_2OH$	EtCOCl	0.5	92^b	35	(−)-Menthol	$(MeCO)_2O$	2	89
9	$PhCH_2CH_2OH$	$(MeCO)_2O$	1.75	91	36	*t*-Butanol	$(MeCO)_2O$	3	78
10	$PhCH_2CH_2OH$	$(PhCO)_2O$	1.5	91	37	Diethyl L-tartarate	$(MeCO)_2O$	2.5	76
11		$(MeCO)_2O$	1.25	89	38	Glycerol	$(MeCO)_2O$	2.5	70
12	$HC{\equiv}CCH_2OH$	$(MeCO)_2O$	1.5	91	39	D-Glucose	$(MeCO)_2O$	2.5	70
13		$(MeCO)_2O$	1.25	87	40	D-Galactose	$(MeCO)_2O$	2.5	75
14	$PhCH{=}CHCH_2OH$	$(MeCO)_2O$	1.5	92	41	Sucrose	$(MeCO)_2O$	2.5	73
15	$PhCH{=}CHCH_2OH$	$(EtCO)_2O$	1.5	85	42	Phenol	$(MeCO)_2O$	1.5	80
16	$PhCH{=}CHCH_2OH$	$(PhCO)_2O$	2	86^b	43	$4\text{-}(OMe)C_6H_4OH$	$(MeCO)_2O$	1.5	82
17	$PhCH{=}CHCH_2OH$	MeCOCl	0.75	90^b	44	$4\text{-}(NO_2)C_6H_4OH$	$(MeCO)_2O$	1.5	84
18	$PhCH{=}CHCH_2OH$	EtCOCl	0.75	91	45	Ethyl salicylate	$(MeCO)_2O$	1.5	89
19	$4\text{-}(O\text{-}Allyl)C_6H_4CH_2OH$	$(MeCO)_2O$	2	91	46		$(MeCO)_2O$	2	74
20	$4\text{-}(OBz)C_6H_4CH_2OH$	$(MeCO)_2O$	2	89	47	Catechol	$(MeCO)_2O$	1.5	75
21	$4\text{-}(NO_2)C_6H_4CH_2OH$	$(MeCO)_2O$	2	88	48	PhSH	$(MeCO)_2O$	1.5	82
22	Piperonyl alcohol	$(MeCO)_2O$	2	90	49	PhSH	$(EtCO)_2O$	1	90
23		$(MeCO)_2O$	1.75	92	50	PhSH	MeCOCl	0.5	93^b
24		$(MeCO)_2O$	1.75	74	51		$(MeCO)_2O$	1.5	85
25		$(MeCO)_2O$	1.5	79	52	$PhNH_2$	$(MeCO)_2O$	0.5	93
26	$CH_3CH_2CH(OH)CH_3$	$(MeCO)_2O$	2	90	53	Cyclohexyl amine	$(MeCO)_2O$	1	79
27	$PhCH(OH)CH_3$	$(MeCO)_2O$	2	91	54		$(MeCO)_2O$	1.5	80

[a] Yields refer to those of pure isolated products characterized by spetral data (IR, ^1H, ^{13}C NMR). [b] Reaction carried out at room temperature.

Conclusion

The present solvent-free and catalyst-free procedure provides a powerful and versatile acylation method for alcohols, thiols, amines and oximes. This method is endowed with several unique merits, namely, simplicity in operation, mild reaction conditions tolerable to acid sensitive functionalities, wide applicability and cost-efficiency. Moreover, this protocol introduces a practical and viable green technology of solvent-free and catalyst-free reactions.[5] Further investigations to broaden the scope of this technology are in progress.

Experimental

General

All alcohols, thiols and amines are commercial materials and are distilled before use. Acetic, propionic and benzoic anhydrides and acid chlorides were freshly distilled and stored over anhydrous potassium carbonate.

General experimental procedure for acylation

A neat mixture of an alcohol (thiol or amine) (5 mmol) and an acid anhydride (or acid chloride) (6 mmol) was gently heated with stirring at 80–85 °C (oil-bath) without any solvent and catalyst under nitrogen for a certain period of time as required for a complete reaction (monitored by TLC). The resulting acetate was distilled out directly from the reaction vessel under reduced pressure. Alternatively, for a lower scale reaction if distillation is not convenient, the product was extracted with diethyl ether. The ether extract was washed with aqueous sodium bicarbonate solution followed by brine and evaporated to leave the crude product which was purified by short column chromatography over silica gel.

The acetates are all well known compounds and are easily identified by their IR, ^1H NMR and ^{13}C NMR spectral data in comparison to those reported.

Acknowledgement

This investigation has enjoyed the financial support from CSIR, New Delhi [Grant No. 01(1739)/02]. S. S. D. and A. H. are also thankful to CSIR for their fellowships.

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New food antioxidant additive based on hydrolysis products of lactose

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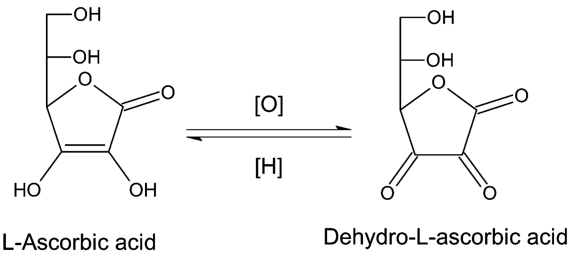
Received 7th August 2002
First published as an Advance Article on the web 16th January 2003

The hydrolysis products of lactose, D-glucose and D-galactose, were oxidized in two consecutive steps using appropriate bimetallic catalysts (Bi–Pd, Bi–Pt on charcoal) to the corresponding 2-ketoaldonic acids. The latter were further processed to provide two stereoisomers of L-ascorbic acid (vitamin C), D-ascorbic acid (D-lyxoascorbic acid) and erythorbic acid (D-araboascorbic acid). The antioxidant activity of these two isomers as well as that of the equimolar mixture thereof was evaluated by measuring their reducing activity against DPPH (2,2-diphenyl-1-picrylhydrazyl) and their scavenging activity of O_2^- species in the presence of NBT (Nitro Blue Tetrazolium). The compounds and their equimolar mixture were found to exhibit the same antioxidant activity as L-ascorbic acid suggesting that they may be used as cheap alternatives to L-ascorbic acid as food antioxidant additives when the vitamin C activity is not required.

Introduction

The industrial production of L-ascorbic acid has now reached a volume of *ca.* 60000 t/a. The industrial process is a five-step synthesis starting from D-glucose and involves a regioselective biocatalytic oxidation of sorbitol. The overall yield of L-ascorbic acid from D-glucose is presently *ca.* 60% and its current price is about 14€/kg. About one-third of the total production is used for vitamin preparations in the pharmaceutical industry. The remainder is mainly applied as an antioxidant additive to food and feed to enhance product quality and stability.[1]

The most significant characteristic of L-ascorbic acid is its oxidation to dehydro-L-ascorbic acid with which it forms a reversible redox system (Scheme 1). L-Ascorbic acid is a strong reducing agent due to its enediol structure. The oxidation of L-ascorbic acid proceeds in two steps *via* the intermediate radical anion, semidehydro-L-ascorbic acid, to provide dehydro-L-ascorbic acid. Semidehydro-L-ascorbic acid is a strong acid with a pK_a of 0.45 and acts as a good radical scavenger.[2]



Scheme 1 L-Ascorbic acid/dehydro-L-ascorbic acid reversible redox system.

The vitamin C activity of L-ascorbic acid is related to the enediol lactone group, the *R*-configuration for the C-4 chiral center, the presence of at least two carbon substituents on C-4 and the L-configuration for the C-5 hydroxyl group. The primary C-6 hydroxyl group has a minor impact on the biological activity. Of the other three diastereomers of L-ascorbic acid only erythorbic acid (D-araboascorbic acid) shows some antiscorbutic activity, *ca.* 5% of that of vitamin C.[3]

In applications where the vitamin C activity is not important, erythorbic acid, possessing the required enediol structure to act as an antioxidant, is often used as a cheaper alternative to L-ascorbic acid. Some of the applications of the antioxidant and reducing properties of L-ascorbic acid are:[1]

- inhibition of nitrosamine formation in cured meat products
- protection toward enzymatic browning of processed fruits and vegetables
- improvement of flour baking qualities of dough and the appearance of baked goods
- retardation of oxidative rancidity in fats and oils
- increased clarity of wine and beer
- synergetic activity in applications with other antioxidants (*e.g.*, tocopherols)
- as a developing agent in photography, *etc*…

The potential use of L-ascorbic acid in agriculture (improvement of seed germination, ozone protection, harvesting aid) is limited by its price. In this work we have applied the present

Green Context

L-Ascorbic acid is now a large volume chemical product with applications in vitamin preparations and as an antioxidant in food. The current industrial manufacturing process is multi-step and the high cost of the product limits the scope of its applications. Here it is shown that the equimolar mixture of D-glucose and D-galactose derived stereoisomers of L-ascorbic acid is a promising alternative antioxidant where vitamin C is not required. The substitute mixture is cheaper and can be prepared directly by the hydrolysis of lactose. Thus a useful environmentally benign product can be prepared by an efficient simple route in a way that enables its more widespread application. *JHC*

DOI: 10.1039/b207752n

state of art in the selective catalytic oxidation of carbohydrates[4] to prepare a cheaper antioxidant and reducing agent mixture from the less expensive and readily available and also renewable raw material lactose (Scheme 2).

Lactose, or milk sugar, is among the most abundant of carbohydrates and its principal source is (sweet) whey, the main by-product in cheese and casein production in the dairy industry.[5] Due to the size of the dairy industry in the EU, only a part of the whey is further processed to lactose. The EU production of lactose is currently 250000 t/a. One third of the lactose produced is used in the pharmaceutical industry while the remainder is consumed in the manufacture of various foods and infant nutrition products. Much effort has been made to develop new processes and products based on lactose to enlarge its total market.[6–16] Among the commercial products derived from lactose are lactitol (*ca.* 6000 t/a), lactulose (*ca.* 20.000 t/a) and Ca–lactobionate (*ca.* 200 t/a) obtained by hydrogenation, isomerization and oxidation, respectively. This work is also aimed toward an enlargement of the lactose market by developing new products based on this raw material. Upon hydrolysis of lactose an equimolar mixture of D-glucose and D-galactose is obtained. These two monosaccharides were submitted to consecutive known catalytic reactions to provide a cheaper antioxidant and reducing agent based on the L-ascorbic acid stereoisomers, D-ascorbic acid (D-lyxoascorbic acid) and erythorbic acid (D-araboascorbic acid). The antioxidant/reducing properties of these stereoisomers as well as their 1 : 1 mixture have been compared with those of L-ascorbic acid.

Results and discussion

The aim of this work was to develop new cheap food antioxidant additives by further processing of the D-glucose/D-galactose equimolar mixture obtained upon hydrolysis of lactose. The resulting product after processing is a 1 : 1 mixture of stereoisomers of L-ascorbic acid with antioxidant/reducing properties. Prior to studying the preparation of this antioxidant mixture directly from lactose, we have undertaken the synthesis of each stereoisomer of L-ascorbic acid separately by starting from the corresponding monosaccharide. Furthermore, we have evaluated the antioxidant activity of these stereoisomers as well as the activity of their equimolar mixture. Their performance was compared to that of L-ascorbic acid. Two methods were applied for the evaluation of the antioxidant activity:

i. measurement of the antioxidant reducing activity against DPPH (2,2-diphenyl-1-picrylhydrazyl).[17]

ii. measurement of the antioxidant scavenging activity of O_2^- species in the presence of the dye NBT (Nitro Blue Tetrazolium).[18,19]

Synthesis of D-glucose and D-galactose derived stereoisomers of L-ascorbic acid

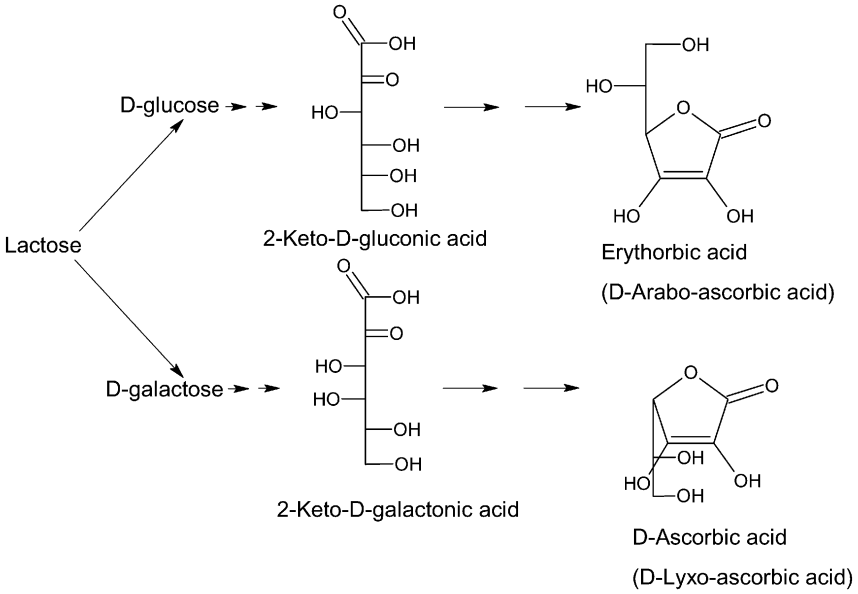
The monosaccharide (aldose) was first oxidized to the corresponding aldonic acid using a Bi–Pd on carbon catalyst with oxygen acting as the oxidant. The oxidation reaction was carried out under alkaline conditions (pH = 9) as described in the literature.[20,21] The pH was kept constant during the oxidation by addition of a solution of 2 M NaOH using a Dosimat. Under these reaction conditions a total conversion of the aldose to aldonic acid was achieved with a selectivity higher than 98%.

The sodium aldonate obtained was further submitted to oxygen-catalyzed oxidation over a Bi–Pt on carbon catalyst to provide the corresponding sodium 2-ketoaldonate. The oxidation reaction was conducted as described previously[22] without pH control with a conversion and selectivity higher than 98%.

The sodium 2-ketoaldonate was then converted to its corresponding acid form by treatment with a cation exchange resin and the free acid was esterified with methanol in the presence of 5 wt% dry HCl as the catalyst. The methyl ester was finally treated with sodium methoxide to provide the corresponding isomer of L-ascorbic acid by cyclo-transesterification. Details in connection with the synthetic procedures are reported in the Experimental section.

Evaluation of the antioxidant activity

We have applied DPPH and NBT as reagents for the evaluation of the antioxidant activity of the D-galactose and the D-glucose derived stereoisomers of L-ascorbic acid as well as the equimolar mixture of these two compounds. The activity measured was compared to that of L-ascorbic acid. The results are reported below.



Scheme 2 Synthetic pathway for the formation of the two stereoisomers of L-ascorbic acid, erythorbic acid (D-araboascorbic acid) and D-ascorbic acid (D-lyxoascorbic acid) from lactose.

Measurement of the antioxidant reducing activity against DPPH. This rapid method for appraising the antioxidant activity is based on the reduction of DPPH (2,2-diphenyl-1-picrylhydrazyl).[16] Due to the odd electron the DPPH radical shows a strong absorption band in ethanol at 517 nm. Upon reduction, this absorption vanishes and the resulting decolorization is stoichiometric with respect to the number of electrons taken up. According to earlier studies, solutions of DPPH appear to be decolorized in the ratio of two molecules of DPPH per molecule of L-ascorbic acid.[16] The reducing activity of L-ascorbic acid, its D-galactose and D-glucose stereoisomers, as well as their equimolar mixture is summarized in Table 1. The results reported show that the antioxidants studied exhibit the same reducing activity against DPPH. Each molecule of the antioxidant reduces two molecules of DPPH in agreement with the previous results reported for L-ascorbic acid.

Table 1 Measurement of the reducing capacity of the studied antioxidants against a 10^{-4} M solution of DPPH in ethanol

Antioxidant	Concentration/M	Reduced DPPH (%)
L-Ascorbic acid	1×10^{-5}	16.6
	5×10^{-5}	94.8
	1×10^{-4}	98.6
Erythorbic acid (D-araboascorbic acid)	1×10^{-5}	17.2
	5×10^{-5}	93.4
	1×10^{-4}	99.4
D-Ascorbic acid (D-lyxoascorbic acid)	1×10^{-5}	17.7
	5×10^{-5}	94.1
	1×10^{-4}	99.4
1 : 1 mixture[a] of erythorbic acid/D-ascorbic acid	1×10^{-5}	17.1
	5×10^{-5}	93.7
	1×10^{-4}	99.2

[a] The listed concentrations are the sum of the concentrations of the two stereoisomers.

Measurement of the antioxidant scavenging activity of O_2^- species in the presence of Nitro Blue Tetrazolium (NBT). This method is based on the generation of the active species O_2^- by the action of xanthine oxidase on xanthine under aerobic conditions. The *in-situ* generated O_2^- reacts with NBT forming Blue Formazan and leads to an increase in the absorbance of the sample solution at 560 nm.[18,19] In the presence of a scavenger of O_2^- the conversion of NBT to Blue Formazan is inhibited. Thus, the scavenging activity could be estimated by measuring the difference in the optical density (OD) between the solution containing the scavenger and the blank.

We have applied this method to compare the O_2^- scavenging activity of L-ascorbic acid with its stereoisomers obtained from D-glucose, D-galactose as well as their equimolar mixture. The sample mixture was left for 30 min at 25 °C whereby the enzymatic reaction was stopped by addition of $CuCl_2$ (see Experimental section). The results are summarized in Table 2.

From these results we can conclude that the O_2^- scavenging activity of the two stereoisomers studied as well as that of their equimolar mixture is comparable to that of L-ascorbic acid. The formation of Blue Formazan was totally inhibited by a concentration of 10^{-4} M of the antioxidant in the reaction mixture, suggesting that all O_2^- species generated by the xanthine oxidase/xanthine system were scavenged prior to any reaction with NBT.

Conclusion

The D-glucose and D-galactose derived stereoisomers of L-ascorbic acid as well as their equimolar mixture exhibit the same activity as L-ascorbic acid toward the reduction of DPPH and the scavenging of the *in situ*-generated active O_2^- species.

Table 2 Evaluation of the antioxidant scavenging activity of the O_2^- species generated *in-situ* by xanthine oxidase/xanthine system in the presence of NBT. Measurement of Blue Formazan formed from NBT for various amounts of the antioxidant

Antioxidant	Concentration	Formazan formed (%)
L-Ascorbic acid	1×10^{-6}	93.3
	1×10^{-5}	35.6
	1×10^{-4}	n.f[b]
Erythorbic acid (D-araboascorbic acid)	1×10^{-6}	94.6
	1×10^{-5}	40.7
	1×10^{-4}	n.f
D-Ascorbic acid (D-lyxoascorbic acid)	1×10^{-6}	95
	1×10^{-5}	35.6
	1×10^{-4}	n.f
1 : 1 mixture[a] of erythorbic acid/D-ascorbic acid	1×10^{-6}	95.5
	1×10^{-5}	38
	1×10^{-4}	n.f

[a] The listed concentrations are the sum of the concentrations of the two stereoisomers. [b] No formazan is formed.

The equimolar mixture of D-glucose and D-galactose derived stereoisomers of L-ascorbic acid is a promising and inexpensive antioxidant that may be used as a cheaper alternative to L-ascorbic acid when the vitamin C activity is not required.

The optimization of the different steps of the process to prepare this antioxidant mixture directly from the D-glucose/D-galactose equimolar mixture, readily obtained by hydrolysis of lactose, is in progress to evaluate the feasibility and the economy of this new food antioxidant additive.

Experimental

Materials

L-Ascorbic acid, DPPH, NBT, xanthine, the disodium salt of EDTA, 5% Pt/C and bismuth(III) nitrate were purchased from Aldrich. Xanthine oxidase and a 5% solution of albumin (BSA) were obtained from Sigma. Solvents, all of analytical grade, D-glucose, D-galactose and 5% Pd/C were purchased from Acros Organics. All the reagents were used without further purification.

Synthesis of D-glucose and D-galactose derived stereoisomers of L-ascorbic acid

The apparatus used, the analysis procedures, as well as the start-up of the oxidation reactions have already been described.[22,23] The preparation of the 5% Bi/5% Pd/C catalyst has been reported in the literature.[20,21]

i. Oxidation of the aldose to sodium D-aldonate

Preparation of the catalyst. To a suspension of 5 g of the 5% Pd/C catalyst in 60 mL of deionized water was added under nitrogen 0.8 ml of hydrochloric acid (37%). The mixture was stirred for 15 min whereupon a solution of bismuth(III) (0.43 g of $Bi(NO_3)_3 \cdot 5H_2O$ dissolved in 2.9 mL of 37% hydrochloric acid and 7.1 mL of deionized water) was added to this suspension and the stirring was continued for 2 h at room temperature. Thereafter a solution of sodium hydroxide (5.7 g of sodium hydroxide in 43 mL deionized water) was added to the catalyst suspension and the mixture was heated with stirring under nitrogen to 40–50 °C for 4 h. 2.2 mL of formaldehyde (37–38%) was then added and the suspension was further stirred for 1 h at 85 °C. Finally, the suspension was cooled to room temperature, filtered and the catalyst washed several times with deionized water, and then dried.

Oxidation procedure. 1 g of the catalyst was introduced into the reactor containing 50 mL of deionized water and the system was flushed with nitrogen for 5 min to remove oxygen from the reactor. Thereafter hydrogen was bubbled through the reactor for 5 min at a high flow rate and low stirring speed, and then for an additional 25 min at low flow rate and high stirring speed. Finally, the hydrogen was removed from the gas phase by flushing with nitrogen for 5 min. 10 g of the aldose was dissolved in 50 mL deionized water and this solution was added to the reduced catalyst under low nitrogen flow. The system was equilibrated at 50 °C and the pH was set at 9 with a solution of 2 M NaOH. Oxygen was then introduced to the reactor to start the reaction. The partial pressure of oxygen in the reactor as well as the pH of the reaction mixture were kept constant during the oxidation by an automatic oxygen supply system and a Dosimat, respectively.[23] The consumption of oxygen and sodium hydroxide were monitored during the oxidation. After 4 h, the theoretical amount of NaOH was consumed and the reaction was stopped. HPLC analysis showed that only the corresponding aldonic acid was present in the solution and the aldose was completely consumed. The catalyst was removed by filtration and the filtrate was concentrated in vacuum and left to crystallize overnight at 0 °C to provide the desired sodium aldonate.

Sodium D-galactonate. Isolated yield = 94%, mp = 181 °C (decomp.).

^{13}C NMR (75 MHz, D_2O): δ 181.1, 73.1, 72.9, 71.6, 71.3, 64.9.

Sodium D-gluconate. Isolated yield = 90%, mp = 203 °C (decomp.).

^{13}C NMR (75 MHz, D_2O): δ 180.2, 75.6, 74.1, 72.7, 72.5, 64.1.

ii. Oxidation of sodium aldonate to sodium 2-ketoaldonate

The 5% Bi/5% Pt/C catalyst was prepared in the same manner as the 5% Bi/5% Pd/C catalyst. The start-up procedure for the heterogeneous selective catalytic oxidation of aldose was applied for the preparation of the sodium 2-ketoaldonate derivatives. The oxidation reaction was carried out at 50 °C but without pH control[22] using 1 g of the catalyst for 5 g of sodium aldonate. After 2.5 h the consumption of oxygen ceased and a sample was taken from the reaction mixture and analyzed by HPLC. A total conversion of sodium aldonate to the corresponding 2-ketoaldonic acid with a selectivity >98% was observed. The oxidation reaction was then stopped, the catalyst was removed by filtration and the filtrate was concentrated to provide sodium 2-keto-D-adonate on standing at 0 °C.

Sodium 2-keto-D-galactonate. Isolated yield = 86%, mp = 132 °C.

^{13}C NMR (75 MHz, D_2O): δ 173.6, 98.2, 72.6, 72.1, 67.5, 64.2.

Sodium 2-keto-D-gluconate. Isolated yield = 82%, mp = 109 °C

^{13}C NMR (75 MHz, D_2O): δ 176.2, 96.7, 71.5, 70.8, 65.9, 63.6.

iii. Synthesis of 2-keto-aldonic acid methyl ester

Sodium 2-keto-D-aldonate, obtained from the previous oxidation, was dissolved in deionized water, treated with a cation exchange resin (type Dowex in the H$^+$ form) and freeze-dried to offer the corresponding 2-keto-D-aldonic acid.

8 g of 2-keto-D-aldonic acid was suspended in 100 mL of methanol containing 5 wt% dry HCl and the mixture was refluxed under nitrogen for 4 h. The reaction mixture was then cooled to room temperature under nitrogen and concentrated in vacuum. The syrup obtained was allowed to crystallize overnight at 0 °C to provide the methyl ester of 2-keto-D-aldonic acid. The crude product was further purified by crystallization from methanol.

Methyl ester of 2-keto-D-galactonic acid. Isolated yield = 81%, mp = 142 °C.

^{13}C NMR (75 MHz, D_2O): δ 172.2, 98.3, 72.6, 72.0, 67.3, 64.2, 54.9.

Methyl ester of 2-keto-D-gluconic acid. Isolated yield = 73%, mp = 184 °C.

^{13}C NMR (75 MHz, D_2O): δ 171.9, 98.3, 73.1, 72.5, 67.6, 64.3, 55.3.

iv. Cyclization of the methyl ester of 2-ketoaldonic acid

5 g of the methyl ester was dissolved under nitrogen in 50 mL of methanol and the temperature of the solution was set at 68 °C. To this solution was added 1 equivalent of sodium methoxide whereupon an instantaneous reaction took place and a precipitate of the sodium salt of the corresponding stereoisomer of L-ascorbic acid was formed. The reaction was allowed to proceed for 5 min then the reaction mixture was cooled in an ice-bath. The suspension was treated with a previously dried cation exchange resin to prepare the free form of the L-ascorbic acid stereoisomer. After 15 min, the cation exchange resin was removed by filtration and the clear solution was evaporated in vacuum. The residue obtained was crystallized at 0 °C from small amount of methanol to provide the desired antioxidant.

D-Ascorbic acid (D-lyxoascorbic acid). Isolated yield = 71%, mp = 190 °C.

^{13}C NMR (75 MHz, D_2O): δ 172.1, 153.6, 115.8, 79.4, 70.9, 64.0.

^{1}H NMR (300 MHz, D_2O): δ 4.5 (d, 1H), 4.0 (m, 1H), 3.7 (q, 2H).

Erythorbic acid (D-araboascorbic acid):. isolated yield = 68%, mp = 171 °C.

^{13}C NMR(75 MHz, D_2O): δ 174.9, 157.2, 119.4, 77.8, 70.5, 63.6.

^{1}H NMR (300 MHz, D_2O): δ 4.9 (d, 1H), 4.0 (m, 1H), 3.7 (t, 2H).

Measurement of the antioxidant reducing activity against DPPH

Weighed amounts of the test compound was dissolved in 5 mL of DMF and diluted to 100 mL with ethanol to give 10^{-5}, 10^{-4}, 10^{-3} and 10^{-2} M solutions. To 5 mL of a 2×10^{-4} M solution of DPPH in ethanol was added 4 mL of ethanol and 1 mL of the test compound solution. After standing for 20 min at 25 °C the absorbance of the sample was measured at 517 nm. The difference in absorbance from the control (no test compound added) was taken as a measure of the reducing activity.

Measurement of the antioxidant scavenging activity of O_2^- species in the presence of Nitro Blue Tetrazolium (NBT)

To 50 mL of sodium carbonate buffer solution (pH = 10.2) was added 22.81 mg of xanthine (3×10^{-4} M), 31.33 mg of NBT (7.5×10^{-5} M), 55.83 mg of Na_2H_2EDTA (3×10^{-4} M) and a weighed amount of the test compound to prepare sample solutions with concentrations of 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} M. Further, in a separate flask, a mixture was prepared containing a 1% (v/v) xanthine oxidase suspension from buttermilk (>0.5 units/mg protein) in an aqueous solution of 0.15% (v/v) albumin from bovine serum (BSA).

To 5 mL of the buffered mixture was added 0.16 mL of the solution containing xanthine oxidase. The mixture was incubated at 25 °C for 30 min. The enzymatic reaction was stopped by addition of 1 mL of a 6 mM aqueous solution of $CuCl_2$ and the absorbance of the reaction mixture was measured at 560 nm (the maximum absorbancy of Blue Formazan). The decrease in the absorbance relative to the control was taken as a measure for the scavenging activity.

Acknowledgement

The authors wish to express their gratitude to Glucona B.V., Veendam, The Netherlands, for financial support.

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Anti-microbial activities of ionic liquids

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Received 1st August 2002
First published as an Advance Article on the web 2nd December 2002

Ionic liquids (ILs) are shown to display anti-microbial activity with the activities being greatly affected by alkyl chain lengths. Shorter substituents on the cation result in a lack of activity against cocci, rods and fungi. ILs containing 10, 11, 12 and 14 carbon atoms in an alkoxy group show very high anti-microbial activities. The use of microorganisms in the IL require consideration of their minimum inhibitory concentration (MIC) values.

Introduction

Ionic liquids (ILs), a class of neoteric solvent, have attracted increasing interest over recent years as excellent alternatives to organic solvents in homogeneous and biphasic processes. These solvents can be used as media for a wide range of chemical reactions which have been the subject of several excellent reviews.[1–7] ILs are non-volatile, non-flammable, have low melting points, high thermal stability in a wide temperature range and relatively low viscosity. They can be used as replacements for selected organic solvents and have shown promise toward important applications such as synthesis,[1–10] separation and extraction processes.[11–14] Investigation of this group of compounds as solvents is in its very early stages. Before the full potential of these ILs are realized, much more information about them as solvent systems must be obtained. The polarity,[15–17] physical[18–20] and thermodynamic[21,22] properties of ILs have been investigated. ILs have been proposed as green solvents for organic synthesis due to the ease with which they can be recycled and reused whilst offering inert, dipolar media compatible with much of conventional chemistry.[1]

One of the most exciting recent developments is the use of enzymes and other types of biotransformations in ILs. Reactions have been carried out in a biphasic H_2O–IL system[23,24] and show higher final yields; also an anhydrous system has been reported.[25–32] The lipase reaction in ILs can be scaled up without major difficulty.[27] The enzyme suspended in the IL could be reused three times with less than 10% loss of activity per cycle and the enantioselectivity was not influenced.[26] The enzymes are stable in solvents such as 3-butyl-1-methylimidazolium hexafluorophosphate or tetrafluroborate. Based on these initial studies the use of enzymes in ionic liquids would appear to open up a new field of non-aqueous enzymonology. The most important finding of the preliminary reports is the fact that many enzymes retain their activity in ILs. In the literature there are examples of the use of a whole-cell biotransformation in an IL for the bacterium *Rhodococcus* R312 that contains the nitrile hydratase enzyme[23] or Baker's yeast.[33] The studies of ABE fermentation with 3-octyl-1-methylimidazolium hexafluorophosphate present at saturation level suggest that the IL suppresses biological activity in the system.[34]

In this paper we report our results of the investigation of anti-microbial activities of ILs.

Results and discussion

A series of 3-alkoxymethyl-1-methylimidazolium salts of $[Cl]^-$ (**1**), $[BF_4]^-$ (**2**) and $[PF_6]^-$ (**3**) were prepared (Table 1). All chlorides synthesized were very hygroscopic. The $[BF_4]^-$ and $[PF_6]^-$ salts were obtained by simple metathesis reactions from the corresponding chlorides using aqueous KBF_4 or KPF_6. The $[BF_4]^-$ salts have a greater miscibility with water than the corresponding $[PF_6]^-$ salts. The water miscibility of 3-alkoxymethyl-1-methylimidazolium $[BF_4]^-$ and $[PF_6]^-$ depends on the length of the alkoxymethyl chain. The water soluble ones are those salts with short chains (propoxymethyl, butoxymethyl and pentyloxymethyl). Water was present in all salts of the type we studied even after a moderate drying procedure (drying at 70 °C for 4 h on a vacuum line). The water content in the dried ILs depends on the length of the alkyl chain and was found to be between 2200 and 400 ppm.[19] All the salts prepared are air-stable under ambient conditions and may be handled under

Table 1 3-Alkoxymethyl-1-methylimidazolium salts **1–3**

Chlorides			Tetrafluoroborates			Hexafluorophosphates		
	R	Mp/°C		R	Mp/°C		R	Mp/°C
1a	C_3H_7	Oil	**2a**	C_3H_7	Liquid	**3a**	C_3H_7	Liquid
1b	C_4H_9	Oil	**2b**	C_4H_9	Liquid	**3b**	C_4H_9	Liquid
1c	C_5H_{11}	Oil	**2c**	C_5H_{11}	Liquid	**3c**	C_5H_{11}	Liquid
1d	C_6H_{13}	Grease	**2d**	C_6H_{13}	Liquid	**3d**	C_6H_{13}	Liquid
1e	C_7H_{15}	Grease	**2e**	C_7H_{15}	Liquid	**3e**	C_7H_{15}	37–38
1f	C_8H_{17}	Grease	**2f**	C_8H_{17}	Liquid	**3f**	C_8H_{17}	48–50
1g	C_9H_{19}	Grease	**2g**	C_9H_{19}	Liquid	**3g**	C_9H_{19}	47–49
1h	$C_{10}H_{21}$	Grease	**2h**	$C_{10}H_{21}$	56–57	**3h**	$C_{10}H_{21}$	46–47
1i	$C_{11}H_{23}$	66–68	**2i**	$C_{11}H_{23}$	61–62	**3i**	$C_{11}H_{23}$	52–53
1j	$C_{12}H_{25}$	67–70	**2j**	$C_{12}H_{25}$	62–64	**3j**	$C_{12}H_{25}$	61–63
1k	$C_{14}H_{29}$	70–73	**2k**	$C_{14}H_{29}$	65–67	**3k**	$C_{14}H_{29}$	67–69
1l	$C_{16}H_{33}$	73–75	**2l**	$C_{16}H_{33}$	68–69	**3l**	$C_{16}H_{33}$	71–73

Grease = heavy oil.

Green Context

As often is the case with more interesting new areas of technology a high level of research activity leads to spin-off benefits outside of the main focus of effort. The dramatic growth in interest is the use of ionic liquids as alternative 'greener' solvents has led to such added benefits with somewhat unexpected applications being reported in synthesis and in biotechnology. Here we can read about their use as anti-microbial agents. The ILs studied are shown to be active against cocci, rods and fungi. The research reveals a relationship between the structure of the cation and the anti-microbial activities. ***JHC***

DOI: 10.1039/b207543c

normal laboratory conditions. Molecular states of water in ILs have been investigated based on the 1-alkyl-3-methylimidazolium salts.[35] It has been shown that in these ILs water moleculas absorbed from the air are present mostly in the 'free' state, bound *via* H-bonding with $[PF_6]^-$ and $[BF_4]^-$ with the concentration of dissolved water in the range 0.2–1.0 mol L^{-1}. It has been concluded that most of the water molecules at these concentrations exist as 1:2 H-bonded complexes: anion···HOH···anion.

All synthesized imidazolium salts were tested for anti-microbial activity against cocci, rods and fungi. Minimum inhibitory concentration (MIC) values and minimum bactericidal or fungicidal concentration (MBC) values are given in Tables 2–4. Also the MIC and MBC values of benzalkonium chloride (**BAC**) were determined and shown in Table 2. The calculated average MIC and MBC values for cocci, rods and fungi are presented in Figs. 1–3 as a relationship between the alkyl chain length and anti-microbial activity. As shown by the

Table 2 MIC[a] and MBC[a] values of 3-alkoxymethyl-1-methylimidazolium chlorides (**1a–l**) and of **BAC**

		Chloride										
Strain		**1a–1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**	**1j**	**1k**	**1l**	**BAC**[b]
Cocci												
M. luteus	MIC	> 8600	4300	2030	960	230	108	52	25	—[c]	—[c]	7
	MBC	> 8600	4300	4060	3800	910	217	207	49	91	336	11
S. epidermidis	MIC	> 8600	4300	1000	480	110	54	52	25	—[c]	—[c]	3
	MBC	> 8600	4300	2030	1900	1820	867	103	49	91	1340	3
S. aureus	MIC	> 8600	4300	500	480	228	54	52	25	—[c]	—[c]	7
	MBC	> 8600	8600	1000	960	1820	867	826	99	91	168	7
S. aureus MRSA	MIC	> 8600	8600	4060	3800	1820	433	207	99	—[c]	—[c]	7
	MBC	> 8600	8600	8100	7680	3640	867	413	395	363	671	11
E. hirae	MIC	> 8600	8600	8100	1900	228	108	103	99	—[c]	—[c]	11
	MBC	> 8600	8600	8100	7680	3640	433	207	197	91	168	22
Rods												
E. coli	MIC	> 8600	8600	8100	3800	1820	433	413	99	181	671	7
	MBC	> 8600	8600	8100	7680	1820	867	413	395	363	2680	11
P. vulgaris	MIC	> 8600	8600	4060	3800	1820	217	207	197	181	336	22
	MBC	> 8600	8600	8100	3800	1820	867	413	197	363	336	22
K. pneumoniae	MIC	> 8600	8600	8100	3800	1820	433	207	197	181	168	11
	MBC	> 8600	8600	8100	7680	3640	1733	413	395	181	336	11
P. aeruginosa	MIC	> 8600	8600	4060	3800	1820	867	826	395	726	2680	54
	MBC	> 8600	8600	8100	7680	3640	1733	1653	790	5800	> 5370	205
Fungi												
C. albicans	MIC	> 8600	8600	4060	1900	1820	433	413	197	91	84	7
	MBC	> 8600	8600	8100	3800	3640	867	413	395	181	84	11
R. rubra	MIC	> 8600	8600	2030	1900	910	217	103	99	45	42	11
	MBC	> 8600	8600	4060	3800	3640	867	207	197	91	42	11

[a] In μM, the number of microorganisms in 1 mL range from 10^4 to 10^5. [b] BAC, benzalkonium chloride. [c] No data available (opacity of solution).

Table 3 MIC[a] and MBC[a] values of 3-alkoxymethyl-1-methylimidazolium tetrafluoroborates (**2a–2k**)

		Tetraflouroborates								
Strain		**2a–c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**	**2k**
Cocci										
M. luteus	MIC	> 7000	3500	3360	800	192	46	44	21	—[b]
	MBC	> 7000	7000	3360	1600	1540	368	88	21	39
S. epidermidis	MIC	> 7000	3500	1680	400	192	46	44	21	—[b]
	MBC	> 7000	7000	3360	800	1540	368	177	85	158
S. aureus	MIC	> 7000	7000	840	800	384	92	22	21	—[b]
	MBC	> 7000	7000	1680	3200	1540	736	353	85	79
S. aureus MRSA	MIC	> 7000	7000	3360	3200	1540	368	177	85	—[b]
	MBC	> 7000	7000	6700	6400	3070	736	353	680	632
E. hirae	MIC	> 7000	3500	3360	1600	384	92	88	85	—[b]
	MBC	> 7000	7000	6700	6400	3070	1471	177	340	158
Rods										
E. coli	MIC	> 7000	7000	6700	3200	1540	368	177	170	316
	MBC	> 7000	7000	6700	6400	3070	1471	177	170	158
P. vulgaris	MIC	> 7000	7000	6700	3200	1540	184	177	170	158
	MBC	> 7000	7000	6700	3200	3070	736	353	170	316
K. pneumoniae	MIC	> 7000	7000	6700	1600	3070	368	177	170	158
	MBC	> 7000	7000	6700	6400	3070	736	353	340	158
P. aeruginosa	MIC	> 7000	7000	6700	3200	1540	1471	707	340	632
	MBC	> 7000	7000	6700	6400	3070	1471	1413	680	1260
Fungi										
C. albicans	MIC	> 7000	7000	3360	1600	770	736	707	340	158
	MBC	> 7000	7000	6700	3200	1540	1471	1413	340	158
R. rubra	MIC	> 7000	7000	3360	1600	192	184	177	21	20
	MBC	> 7000	7000	6700	3200	1540	736	177	85	39

[a] In μM, the number of microorganisms in 1 mL range from 10^4 to 10^5. [b] No data available (opacity of solution)

Table 4 MIC[a] and MBC[a] values of 1-alkoxymethyl-3-methylimidazolium hexafluorophosphates (**3a–3k**)

		Hexafluorophosphates								
Strain		**3a–c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**
Cocci										
M. luteus	MIC	> 5850	2900	2800	1350	330	160	152	37	—[b]
	MBC	> 5850	5850	5600	2700	1300	630	152	73	138
S. epidermidis	MIC	> 5850	2900	1400	680	330	80	76	18	—[b]
	MBC	> 5850	5850	5600	2700	1300	1250	303	147	138
S. aureus	MIC	> 5850	2900	2800	1350	650	160	19	18	—[b]
	MBC	> 5850	5850	5600	2700	2600	1250	607	73	69
S. aureus MRSA	MIC	> 5850	5850	2800	2700	1300	630	607	73	—[b]
	MBC	> 5850	5850	5600	5400	2600	2500	1214	587	551
E. hirae	MIC	> 5850	2900	2800	2700	330	630	152	37	—[b]
	MBC	> 5850	5850	5600	5400	2600	2500	607	587	275
Rods										
E. coli	MIC	> 5850	5850	5600	2700	1300	1250	607	73	138
	MBC	> 5850	5850	5600	5400	2600	1250	607	293	275
P. vulgaris	MIC	> 5850	5850	5600	2700	1300	314	303	147	138
	MBC	> 5850	5850	5600	5400	2600	2500	1214	293	551
K. pneumoniae	MIC	> 5850	5850	5600	2700	2600	630	152	147	138
	MBC	> 5850	5850	5600	5400	2600	2500	1214	147	138
P. aeruginosa	MIC	> 5850	5850	5600	2700	2600	1250	1214	587	1100
	MBC	> 5850	5850	5600	5400	2600	2500	1214	587	2200
Fungi										
C. albicans	MIC	> 5850	5850	2800	1350	1300	630	607	587	138
	MBC	> 5850	5850	5600	2700	2600	1250	1214	587	275
R. rubra	MIC	> 5850	5850	2800	1350	650	314	152	37	17
	MBC	> 5850	5850	5600	2700	2600	630	303	587	138

[a] In μM, the number of microorganisms in 1 mL range from 10^4 to 10^5. [b] No data available (opacity of solution)

results, the salts studied are active against cocci, rods and fungi. Some of them exhibited strong activity and wide anti-bacterial action. Their activities are greatly affected by the alkyl chain length in the alkoxymethyl substituent but do not depend on the type of anion. The MIC values of imidazolium chlorides indicate the anti-microbial activities for the same imidazolium salts with $[BF_4]^-$ or $[PF_6]^-$. For the studied salts the same correlation is observed for the MIC and MBC values. The most active salts against cocci and rods have an alkoxy group which contains 10, 11, 12 or 14 carbon atoms. The curves in Figs. 1 and 2 demonstrate the optimum anti-microbial efficiency, the most effective group being dodecyloxymethyl. Activity against fungi is significantly different with the curves in Fig. 3 indicating that no optimum activity was clear with the salts

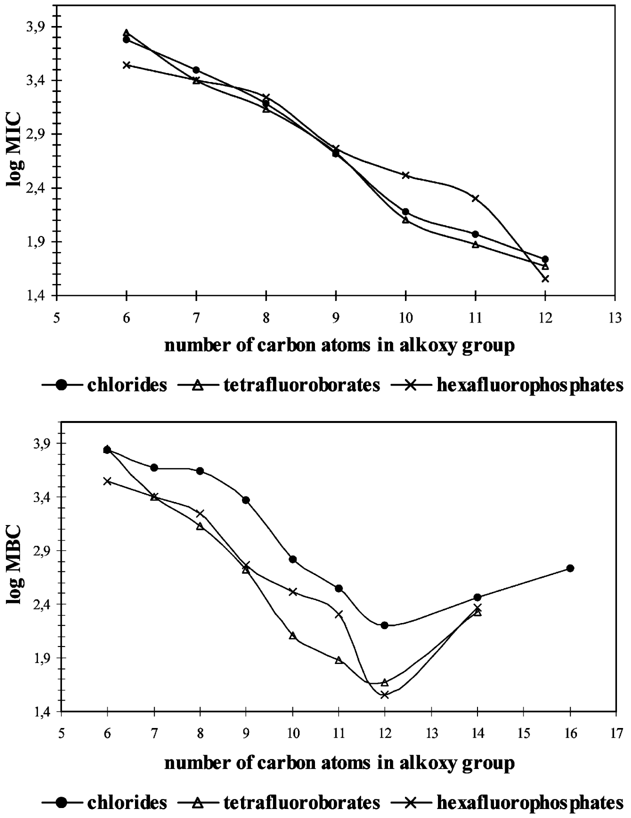

Fig. 1 Mean MIC and MBC values for cocci.

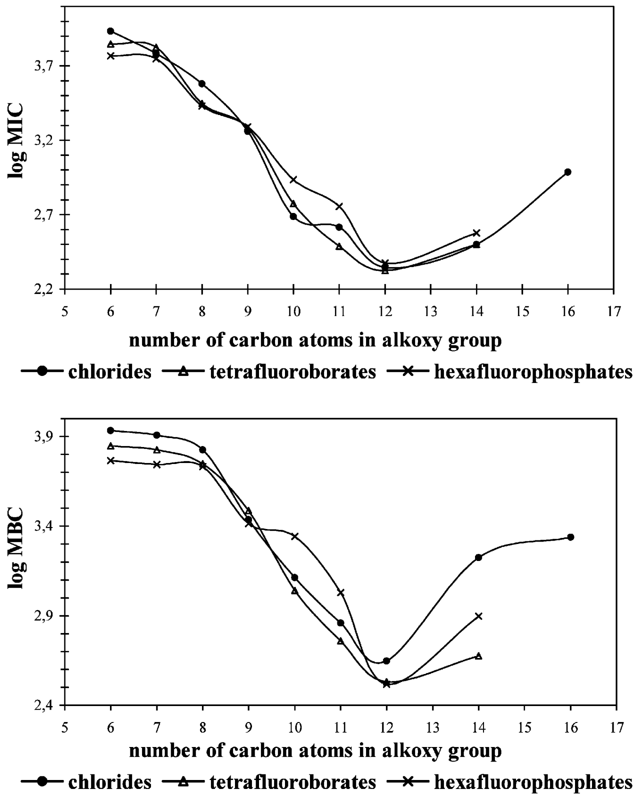

Fig. 2 Mean MIC and MBC values for rods.

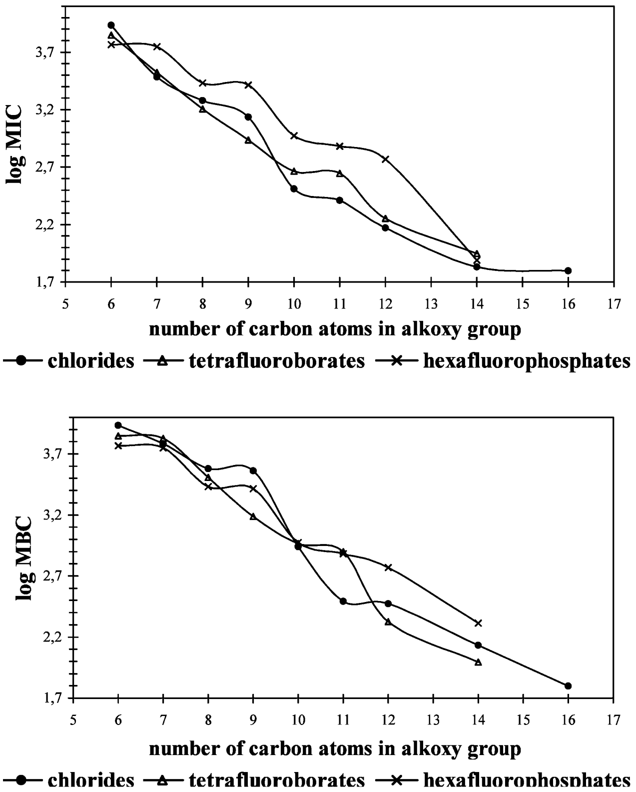

Fig. 3 Mean MIC and MBC values for fungi.

under study here. Though the observed increase of activity with number of carbon atoms in the alkoxy group will not be unlimited the hydrophobic chain has the important function of adsorbing onto the surface of the microbial cell.

The activity of salts **1j**, **2j**, and **3j** approach the activity of commercially available benzalkonium chloride (BAC in which R represents a mixture of alkyls from C_8H_{17} to $C_{18}H_{37}$). The ILs with short substituents (propoxymethyl, butoxymethyl and pentyloxymethyl) are not active against bacteria and fungi.

In summary we found that ILs showed anti-microbial activities. There is a relationship between the structure of the cation and the anti-microbial activities. These salts with short substituents are not active against bacteria and fungi. The results indicate that salts containing 10, 11, 12 and 14 carbon atoms in the alkoxy group show very high anti-microbial activities. The use of microorganisms in ILs requires consideration of their MIC values.

Experimental

3-Alkoxymethyl-1-methylimidazolium chlorides (**1**), tetrafluoroborates (**2**) and heksafluorophosphates (**3**) were prepared according to the published method.[36]

Anti-microbial actibity

Anti-microbial activity was determined by the tube dilution method. A series of imidazolium salt dilutions were prepared on Müller–Hinton broth medium (bacteria) or Sabouraud broth medium (fungi). A suspension of the microorganisms, prepared from 24 h cultures of bacteria in the Müller–Hinton broth medium and from 48 h cultures in the Sabouraud agar medium for fungi at a concentration of 106 cfu mL^{-1}, were added to each dilution in a 1 : 1 ratio. Growth (or lack thereof) of the microorganisms was determined visually after incubation for 24 h at 37 °C (bacteria) or 48 h at 28–30 °C (fungi). The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC. Then from each tube, one loopful was cultured on an agar medium with inactivates (0.3% lecithin, 3% polysorbate 80 and 0.1% cysteine L) and incubated for 48 h at 37 °C (bacteria) or for 5 days at 28–30 °C (fungi). The lowest concentration of the salt supporting no colony formation was defined as the MBC.

Microorganisms used: eleven standard strains representative of cocci; *Micrococcus luteus* ATCC 9341, *Straphylococcus epidermidis* ATCC 12228, *Staphylococcus aureus* ATCC 6538, *Staphylococcus aureus* MRSA, *Enterococcus hirae*, rods; *Escherichia coli* NCTC 8196, *Proteus vulgaris* NCTC 4635, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 15442, fungi; *Candida albicans* ATCC 10231, *Rhodotorula rubra* (Demml 1889, Lodder 1934). Standard strains were supplied by the National Collection of Type Cultures (NCTC) London and American Type Culture Collection (ATCC). The *R. rubra* was taken from the Department of Pharmaceutical Bacteriology, K. Marcinkowski University of Medical Sciences, Poznan.

Acknowledgments

This investigation received financial support from the Polish Committee of Scientific Research Grant KBN No 4 T09B 008 22.

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Preparation of optically active *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides by a combination of Diels–Alder reaction and complexation with optically active hosts and enantioselective Diels–Alder reaction in inclusion crystals in a water suspension medium

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Received 12th September 2002
First published as an Advance Article on the web 28th November 2002

Optically active Diels–Alder adducts were prepared using a one-pot preparative method and enantioselective Diels–Alder reaction with optically active hosts in a water suspension medium.

Introduction

Optically active enantiomers of the *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides, important as key starting materials for the synthesis of various bioactive compounds, have been prepared by biological synthesis. These, however, are neither always simple nor efficient. The Diels–Alder reaction is a simple and efficient tool to form the key step in the preparation of six-membered rings. Many procedures have been developed to increase the yields and selectivities of Diels–Alder reactions.[1] Recently, organic reactions in aqueous media, particularly in water, have received much attention, because water is economical and harmless to the environment.[2]

Optically active *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides were prepared by Diels–Alder reaction using optically active hosts and enantioselective Diels–Alder reactions in inclusion crystals in a water suspension medium.

Results and discussion

We report a one-pot preparative method[3] to prepare optically active compounds by a combination solid state Diels–Alder reaction in a water suspension medium and an enantioselective inclusion complexation of the product with an optically active host compound in the same aqueous medium. Heating *in vacuo* of the inclusion complex crystal isolated from the aqueous medium by filtration gave optically active product by distillation. Since no solvent is necessary throughout the reaction, inclusion complexation and isolation of the optically active product from the inclusion complex, this is genuinely sustainable and green chemistry. For example, when a mixture of *N*-ethylmaleimide **2b** (0.2 g, 1.60 mmol), 2-methyl-1,3-butadiene **1** (0.400 g, 5.87 mmol), and water (2 mL) was stirred at room temperature for 12 h, *rac*-**3b** was produced. To a water suspension medium of *rac*-**3b** was added the optically active compound **4c**[4] (0.405 g, 080 mmol) and the mixture was stirred for 12 h to give a 1:1 inclusion complex of **4c** with (+)-**3b**. Heating the filtered inclusion complex *in vacuo* gave (+)-**3b** with 94% ee (0.043 g, 31% yield). From the filtrate left after separation of the inclusion crystals, (−)-**3b** with 37% ee (0.043 g, 28% yield) was obtained by extraction with ethyl acetate. By the same procedure, optically active **3a** was prepared (Table 1). In the case of (+)-**3b**, the efficiency of enantiomeric resolution is very high. Optical resolution of **3a** using **4b** gave only the (−)-product. To clarify the results, we attempted to characterize the inclusion complex of **3a** with **4b** by X-ray analysis but unfortunately suitable single crystals could not be grown. Inclusion complexes of **3a** with **4c**, **3b** with **4a**, and **3c** with **4a–c** were not obtained (Table 1). Furthermore, optical resolution of *rac*-**3c** with **4c** by recrystallization was successful giving (+)-**3c** with 85% ee in 47% yield. Since the optically active host remained after separation of the optically active guest from its inclusion complex by distillation it can be used repeatedly. This one-pot method in water is thus both ecological and economical.

We also report enantioselective Diels–Alder reaction in inclusion crystals in a water suspension medium. A suspension of the powdered 2:1 inclusion compound of **4b** with **2c** (2.00 g, 3.1 mmol) and **1** (1.00 g, 14.70 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant to aid dispersion was stirred for 12 h. The solid reaction product was filtered off and the product dried. The filtered crystals included the product as shown by IR spectroscopy. The product in comparison with the starting material **2c** has a greater affinity towards the optically active host **4b**. Heating of the filtered crystals *in vacuo* gave (+)-**3c** with 11% ee in 81% yield. Since the optically active product was obtained the reaction occurred in the inclusion crystals. Optically active **3a** and **3b** were prepared by the same procedure (Table 2). **4b** did not form inclusion complexes with **3b** and **3c** after recrystallization.

Green Context

Diels–Alder reactions are perfectly atom economic. They also have the potential for being enantioselective and forming complex multifunctional products from relatively simple raw materials. This paper shows that such procedures can take place readily in aqueous environments with good enantiomeric purity. This is achieved through the formation of inclusion complexes in chiral hosts suspended in water. Heating the filtered solid allowed the Diels–Alder reaction to proceed to give the chiral product in good yield. No organic solvents are used in this sequence, although extraction was carried out with ethyl acetate. ***DJM***

DOI: 10.1039/b208921c

A suspension of the powdered 3 : 1 inclusion compound of **4b** with **1** (1.5 g, 5.5 mmol) and **2c** (0.168 g, 0.99 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant to aid dispersion was stirred for 12 h. The solid reaction product was filtered off and dried. The filtered crystals included the product as shown by IR spectroscopy. The product in comparison with the starting material **1** has a greater affinity towards the optically active host **4b**. Heating of the filtered crystals *in vacuo* gave (+)-**3c** with 77% ee in 13% yield. Since the optically active product was obtained the reaction occurred in the inclusion crystals. By the same procedure, optically active **3a** and **3b** were prepared (Table 3). In the case of (+)-**3c**, using the inclusion complex of **4b** with **1**, the efficiency of the enantiomeric resolution is high. We found enantioselective Diels–Alder reaction in inclusion crystals in a water suspension medium gave optically active *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides.

Conclusion

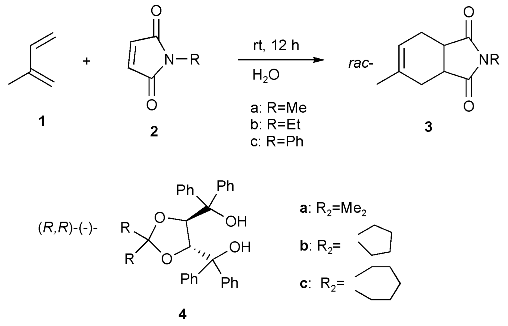
In conclusion, optically active Dies-Alder adducts were prepared by a one-pot preparative method and enantioselctive Diels–Alder reaction using optically active hosts in a water suspension medium.

Experimental

General procedure for one-pot preparation of optically active Diels–Alder adducts by a combination of synthesis and enantiomeric resolution with optically active hosts in a water suspension medium

To a suspension of 2-methyl-1,3-butadiene **1** (0.40 g, 5.87 mmol) in 2 mL water was added *N*-ethylmaleimide **2b** (0.20 g, 1.60 mmol), and the mixture was stirred at room temperature for 12 h to give *rac*-**3b** in 90% yield. To the water suspension medium of *rac*-**3b** was added powdered optically active host **4c** (0.405 g, 0.80 mmol), and the suspension stirred at room temperature for 12 h, the product filtered off, and dried to give the 1 : 1 inclusion complex of **4c** with (+)-**3b** as a colorless powder (0.51 g, 75% yield, mp 127–130 °C). IR (Nujol): ν_{max} 3409, 3305, 1684 cm^{-1}. Anal. Calc. for $C_{45}H_{49}NO_6$: C, 77.23; H, 7.06; N, 2.00. Found: C, 76.93; H, 7.12; N, 1.82%. Heating of the filtered inclusion crystals *in vacuo* (190 °C/22 mmHg)

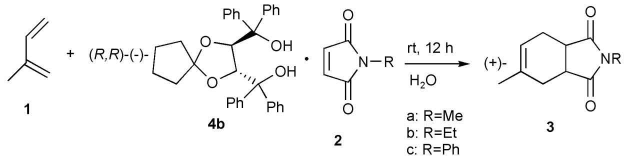
Table 1 Results of the one-pot preparative method of optically active cyclohex-4-ene-1,2-dicarboximides by a combination of Diels–Alder reaction and enantiomeric resolution in a water suspension medium



		Inclusion complex[a]		From complex			From filtrate		
Dienophile	Host (% ee)	Host : Guest	Mp/°C	Product	Yield (%)	Enantiomeric purity[b] (% ee)	Product	Yield (%)	Enantiomeric purity[b] (% ee)
2a	**4a** (100)	1 : 1	118–120	(+)-**3a**	35	29	(−)-**3a**	40	59
2a	**4b** (100)	2 : 1	132–135	(−)-**3a**	48	71	(+)-**3a**	40	63
2a	**4c** (100)						*rac*-**3a**	74	0
2b	**4a**						*rac*-**3b**	69	0
2b	**4b**	2 : 1	123–125	(+)-**3b**	76	78	(−)-**3b**	48	50
2b	**4c**	1 : 1	127–130	(+)-**3b**	31	94	(−)-**3b**	28	37
2c	**4a**						*rac*-**3c**	78	0
2c	**4b**						*rac*-**3c**	80	0
2c	**4c**						*rac*-**3c**	80	0

[a] All crystals are colorless powders. [b] Enantiomeric purities were determined by HPLC.

Table 2 Enantioselective Diels–Alder reactions using the 2 : 1 inclusion complex 2(**4b**)·**2** and **1** in a water suspension medium



	Inclusion complex[a]				
Dienophile	Host : Guest	Mp/°C	Product	Yield (%)	Enantiomeric purity[b] (% ee)
2a	2 : 1	146–150	(+)-**3a**	30	18
2b	2 : 1	125–130	(+)-**3b**	46	11
2c	2 : 1	120–123	(+)-**3c**	81	11

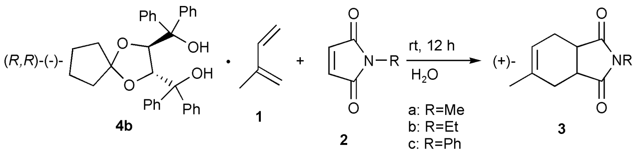
[a] All crystals are colorless powders. [b] Enantiomeric purities were determined by HPLC.

gave (+)-**3b** with 94% ee (0.047 g, 31% yield, $[\alpha]_D$ +48 (*c* 0.13, MeOH). The filtrate remaining after separation of the inclusion crystals was extracted twice with 10 mL ethyl acetate. The ethyl acetate solution was dried over $MgSO_4$, and evaporated to give (–)-**3b** with 37% ee (0.043 g, 28% yield, $[\alpha]_D$ −19 (*c* 0.11, MeOH)).

General procedure for enantioselective Diels–Alder reaction using the 2 : 1 inclusion compound 2(4b)·2 and 1 in a water suspension medium

When a solution of **4b** (2.10 g, 4.26 mmol) and **2c** (0.37 g, 2.14 mmol) in diethyl ether (10 mL) was allowed to stand at room temperature for 12 h, a 2 : 1 inclusion compound of **4b** and **2c** was obtained as a colorless powder (2.0 g, 81% yield, mp 120–123 °C), IR (Nujol): ν_{max} 3421, 3233 cm^{-1}. Anal. Calc. for $C_{76}H_{71}NO_{10}$: C, 78.80; H, 6.18; N, 1.21. Found: C, 78.86; H, 6.37; N, 1.25%. A suspension of powdered 2(**4b**)·**2c** (2.00 g, 3.1 mmol) and **1** (1.00 g, 14.70 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant was stirred for 12 h. The solid reaction product was filtered off and dried. Heating of the filtered crystals *in vacuo* gave (+)-**3c** with 11% ee (0.34 g, 81% yield, $[\alpha]_D$ +7 (*c* 0.30, MeOH)).

Table 3 Enantioselective Diels–Alder reactions using the 3 : 1 inclusion complex[a] 3(**4b**)·**1** and **2** in a water suspension medium



Dienophile	Product	Yield (%)	Enantiomeric purity[b] (% ee)
2a	(+)-**3a**	18	56
2b	(+)-**3b**	10	45
2c	(+)-**3c**	13	77

[a] All crystals are colorless powders. [b] Enantiomeric purities were determined by HPLC.

General procedure for enantioselective Diels–Alder reaction using the 3 : 1 inclusion compound 3(4b)·1 and 2 in a water suspension medium

When a solution of **4b** (2.60 g, 5.28 mmol) and **1** (0.68 g, 10 mmol) in diethyl ether (10 mL) was allowed to stand at room temperature for 20 h, a 3 : 1 inclusion compound of **4b** and **1** was obtained as a colorless powder (1.5 g, 55% yield, mp was not clear). IR (Nujol) ν_{max} 3435, 3228 cm^{-1}. A suspension of powdered 3(**4b**)·**1** (1.5 g, 5.5 mmol) and **2c** (0.168 g, 0.99 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant was stirred for 12 h. The solid reaction product was filtered off and dried. Heating of the filtered crystals *in vacuo* gave (+)-**3a** with 77% ee (0.30 mg, 13% yield, $[\alpha]_D$ +48 (*c* 0.13, MeOH)).

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Three-component coupling reactions in ionic liquids: an improved protocol for the synthesis of 1,4-dihydropyridines

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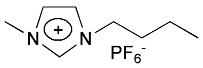
Received 11th October 2002
First published as an Advance Article on the web 3rd December 2002

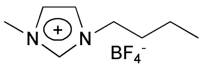
Three-component condensation of aldehyde, β-ketoester and methyl 3-aminocrotonate proceeds smoothly in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 or 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6 ionic liquids at room temperature under mild conditions to afford the corresponding 1,4-dihydropyridine derivatives in high yields. The recovered activated ionic liquids are recycled for four to five runs with no loss in activity.

Introduction

Hantzsh 1,4-dihydropyridines are a biologically, medicinally and synthetically important class of compounds in the field of drugs and pharmaceuticals.[1] They act as potent vasodilators, antihypertensives, branchodilators, antiatherosclerotics, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents.[2] DHPs are commercially used as calcium channel blockers (such as Nifedifine, Nitrendifine and Nimodifine) for the treatment of cardiovascular diseases.[3] A number of DHP calcium antagonists have been introduced, as potential drugs for the treatment of congestive heart failure.[4] They are also useful as cognition enhancers, neuroprotectants and platelet antiaggregatory agents.[5] Some of these 1,4-dihydropyridines acts as NADH mimics for the reduction of carbonyl compounds and their derivatives.[6] 1,4-Dihydropyridines are generally synthesized by the Hantzsh method,[7] which involves cyclocondensation of an aldehyde, β-ketoester and ammonia either in acetic acid or in refluxing ethanol.[8] 1,4-Dihydropyridines have also been synthesized on a solid phase for making combinatorial libraries.[9] The classical reactions are generally carried out in organic solvents such as methanol and acetic acid. Most of these methods often require tedious aqueous work-up to isolate the products and thus produce a large amount of waste. These organic solvents are often harmful to the environment and as a result are frequently subject to government restrictions and high waste disposal costs. Consequently, methods that successfully minimize their use are the focus of much attention. Thus use of solvents such as water, supercritical fluids and ionic liquids have received much attention in recent times in the area of green synthesis. In this respect, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible vapor pressure and recyclability.[10] Their high polarity and their ability to solubilise both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents. Accordingly, they are emerging as novel replacements for volatile organic solvents in organic synthesis. They are particularly promising as solvents for catalysis.[11] Ionic liquids however, have scarcely been used as both promoters and solvent although they provide advantages of easy recovery and reuse of the reaction media.[12] Moreover, ionic liquids are simple and inexpensive to prepare and easy to recycle and their properties can be fine-tuned by changing the anion or the alkyl group attached to the cation.



[Bmim]PF_6



[Bmim]BF_4

Because of distinct advantages of room-temperature ionic liquids as environmentally benign reaction media for catalytic processes, much attention has been currently focused on organic reactions promoted by ionic liquids.

Results and discussion

In view of the emerging importance of the imidazolium based ionic liquids as novel reaction media, we wished to explore the use of ionic liquids as environmentally friendly and recyclable solvent systems for the synthesis of 1,4-dihydropyridines under mild conditions (Scheme 1).

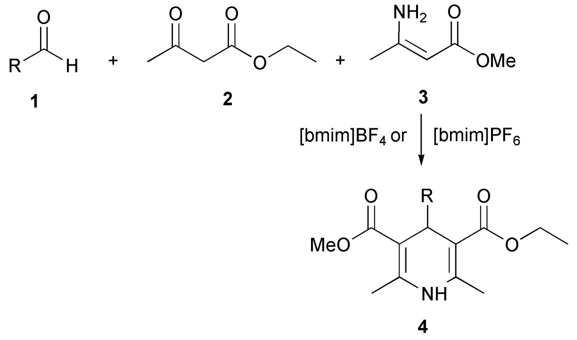
The condensation of benzaldehyde and ethyl acetoacetate with methyl-3-aminocrotonate in 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid afforded the corresponding 1,4-dihydropyridine in 90% yield. In a similar fashion, a variety of aldehydes reacted smoothly with ethyl acetoacetate and 3-aminocrotonate to give the corresponding 1,4-dihydropyridines in excellent yields. The reactions proceeded efficiently at ambient temperature with high selectivity. Enolizable and acid sensitive aldehydes such as cyclohexane carbaldehyde and furfural, worked well under these reaction conditions. This method is

Green Context

Dihydropyridines are extremely versatile intermediates in the synthesis of numerous pharmaceuticals including those for the treatment of cardiovascular diseases and congestive heart failure. Their synthesis normally involves the use of organic solvents and wasteful work-up procedures. In this article a new synthetic procedure for these important compounds is described. This is based on the use of ionic liquid solvents that are shown to be recyclable. Organic solvents are still used in the work-up of the reaction mixture offering future scope for improvement but the avoidance of a VOC reaction solvent and general process simplicity give the process green chemistry credentials. ***JHC***

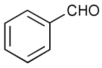
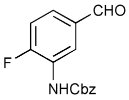
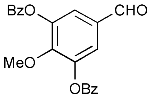
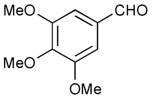
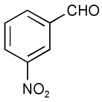
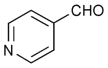
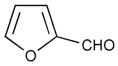
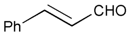
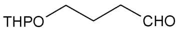
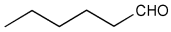
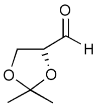
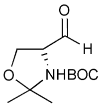
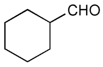
DOI: 10.1039/b210017g

compatible with highly acid sensitive protecting groups such as THP ethers, acetals, aminoacetals and carbamates present in the substrate. This method is equally effective for both electron rich as well as electron deficient aldehydes. All the products were characterized by ^{1}H NMR, IR and mass spectral analysis and also by comparison with authentic samples.[8] In this reaction, the efficiency of ionic liquid was strongly influenced by the nature of the anion. The reactions of various aldehydes, β-ketoesters and methyl 3-aminocrotonate were examined in hydrophilic 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids and the results are presented in Table 1. Among these ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) was found to be superior in terms of yields and reaction rates. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with diethyl ether. The remaining oily ionic liquid was thoroughly washed with diethyl ether and recycled in subsequent reactions. Second and third reactions using recovered ionic liquid afforded similar yields to those obtained in the first run. In the fourth and fifth runs, the yields were gradually decreased. For example, benzaldehyde, ethyl acetoacetate and methyl-3-aminocrotonate in [bmim]BF_4 afforded 90, 90, 89, 85 and 82% yields of the 1,4-dihydropyridine over five cycles. However, the activity of ionic liquid was consistent in runs and no decrease in yield was obtained when the recycled ionic liquid was activated at 80 °C under vacuum in each cycle. Furthermore, the products obtained were of the



Scheme 1

Table 1 Hantzsch synthesis of 1,4-dihydropyridines in ionic liquids

			[bmim]BF_4		[bmim]PF_6	
Entry	Aldehyde	Product	Time/h	Yield[a] (%)	Time/h	Yield[b] (%)
a	HCHO	**4a**	5.0	90	8.0	84
b		**4b**	6.5	85	9.0	81
c		**4c**	6.0	93	9.5	80
d		**4d**	5.0	91	8.0	83
e		**4e**	5.0	90	8.0	85
f		**4f**	7.0	88	11.0	81
g		**4g**	6.5	85	10.0	78
h		**4h**	5.0	91	8.0	87
i		**4i**	4.5	90	7.5	83
j		**4j**	7.0	87	12.0	79
k		**4k**	5.0	85	9.0	80
l		**4l**	8.0	80	10.0	72
m		**4m**	7.0	82	8.0	75
n		**4n**	5.0	89	7.0	84

[a] All products were characterized by ^{1}H NMR, IR and mass spectra. [b] Isolated and unoptimized yields after purification.

same purity as in the first run. However, the products were obtained in low to moderate yields (55–67%) after a long reaction period (15–24 h) when the reaction was carried out in refluxing ethanol. In further reactions the efficiency of various quaternary ammonium salts was studied. The three-component condensation was not successful when the reaction was carried out in other molten salts such as *n*-tetrabutylammonium chloride (*n*-Bu_4NCl) or 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl). The simple experimental and product isolation procedures combined with ease of recovery and reuse of these novel reaction media is expected to contribute to the development of a green strategy for the synthesis of 1,4-dihydropyridines. The scope and generality of this process is illustrated with respect to various aldehydes and ionic liquids and the results are presented in Table 1. The use of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) ionic liquid as reaction medium for this transformation allows avoiding the use of additives or acidic promoters and also eliminating aqueous work-up to isolate the products.

Conclusion

In summary, this paper describes a convenient and efficient process for the synthesis of 1,4-dihydropyridines through the three-component coupling of aldehydes, β-ketoester and 3-aminocrotonate using imidazolium based ionic liquids as novel reaction media. This method is very useful for the synthesis of 1,4-dihydropyridines especially from acid sensitive aldehydes. The notable features of this procedure are mild reaction conditions, simplicity in operation, improved yields and reaction rates, cleaner reaction profiles and recyclability of ionic liquids which make it a convenient, economic and user-friendly process for the synthesis of 1,4-dihydropyridines of biological and medicinal importance.

Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H, ^{13}C NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids were prepared according to the procedures reported in the literature.[13]

General procedure

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol) and methyl 3-aminocrotonate in 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate–*n*-hexane (1:9) to afford the pure 1,4-dihydropyridine. The remainder of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs. Solid products were purified by recrystallization in ethanol.

Recycling of ionic liquid

In the case of the hydrophilic ionic liquid, *i.e.* [bmim]BF_4, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* and the resulting product was purified either by column chromatography or by recrystallization to afford pure product. The ionic liquid can be recovered either by extracting the aqueous phase with ethyl acetate or by vaporating the aqueous layer *in vacuo*. The ionic liquid thus obtained was further dried at 80 °C under reduced pressure for use in subsequent runs.

Spectral data for selected products

4a: 3-Ethyl 5-methyl 2,6-dimethyl-1,4-dihydropyridine-3-5-dicarboxylate: liquid, IR (KBr) : ν 3328, 2925, 1743, 1542, 1233, 1041, 760 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, J = 6.9 Hz), 2.18 (s, 6H), 3.20 (s, 2H), 3.80 (s, 3H), 4.20 (q, 2H, J = 6.9 Hz), 5.20 (br s, 1H). EIMS: *m*/*z*: 239 (M^+), 225, 195, 167, 138, 109, 81.

4b: 3-Ethyl 5-methyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate: solid, mp 156–158 °C, IR (KBr): ν 3073, 2960, 1449, 1375, 1263, 1149, 1042, 974, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, J = 6.8 Hz), 2.50 (s, 6H), 3.80 (s, 3H), 4.20 (q, 2H, J = 6.8 Hz), 5.05 (s, 1H), 5.70 (br s, 1H), 7.25–7.35 (m, 5H). EIMS: *m*/*z*: 315 (M^+), 301, 271, 243, 213, 185, 157, 81, 77.

4h: 3-Ethyl 5-methyl 4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate: solid, mp 163–165 °C, ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, J = 6.8 Hz), 2.40 (s, 6H), 3.80 (s, 3H), 4.30 (q, 2H, J = 6.8 Hz), 5.30 (s, 1H), 5.80 (br s, 1H), 6.80–7.05 (m, 3H). EIMS: *m*/*z*: 305 (M^+), 246, 208, 174, 146, 99, 75, 43. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.5, 19.3, 19.4, 33.4, 51.0, 59.6, 96.2, 100.0, 104.4, 110.0, 140.8, 144.9, 145.3, 158.5, 167.1, 167.5.

4i: 3-Ethyl 5-methyl 4-(2-phenyl-1-ethenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate: solid, mp 149–150 °C, IR (KBr): ν 3027, 29298, 1679, 1449, 1263, 964, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, J = 7.0 Hz), 2.40 (s, 6H), 3.80 (s, 3H), 4.20 (q, 2H, J = 6.8 Hz), 5.10 (d, 1H, J = 5.5 Hz), 5.70 (br s, 1H), 6.10 (dd, 1H, J = 5.5, 16.8 Hz), 7.20 (d, 1H, J = 16.8 Hz), 7.25–7.35 (m, 5H). EIMS: *m*/*z*: 341 (M^+), 327, 297, 269, 211, 183, 104, 81, 77.

Acknowledgments

B. V. S. and A. K. B. thank CSIR, New Delhi for the award of fellowships.

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Gold catalysis in the reactions of 1,3-dicarbonyls with nucleophiles

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Received 15th October 2002
First published as an Advance Article on the web 28th November 2002

A new efficient gold(III) catalysed synthesis of β-enaminones from 1,3-dicarbonyl compounds and ammonia/amines providing an attractive and environmental friendly alternative to the more vigorous reagents and drastic conditions of the existing methodologies is described; the catalysis of gold(III) is also extended to reaction of cyclic 1,3-dicarbonyls with O-, P- and S-nucleophiles.

Introduction

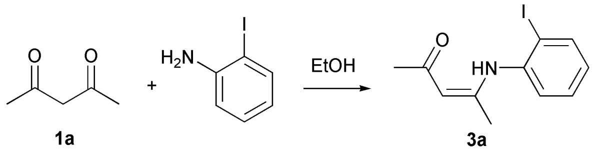
Currently, growing efforts of the scientific community of chemistry rely upon the development of economical processes based on the principles of green chemistry.[1] Our research interest towards the realisation of new green catalytic systems led us to provide resource-saving synthetic methodologies through transition-metal catalysed domino processes.[2] In particular, gold catalysts have been reported to allow sequential amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds with primary amines, aminoalcohols and α-aminoesters.[3] We described that $NaAuCl_4$ is an efficient catalyst not only in the activation of the acetylenic bond towards the nucleophilic attack of O- or N-groups, but also, in the cases we examined, this catalyst showed the specific quality of accelerating the condensation of 1,3-dicarbonyls with N-nucleophiles. Moreover, Kobayashi *et al.*[4] reported that $AuCl_3{\cdot}3H_2O$ exhibits higher catalytic activity compared to conventional Lewis acids in aza-Michael reactions of enones. Then, a further investigation of the gold-catalysed condensation of 1,3-dicarbonyl derivatives with amines to give β-enaminones promises to overcome some of the drawbacks caused by more vigorous reagents and drastic reaction conditions. The β-enaminones[5] are an important class of organic synthetic intermediates, particularly in heterocyclic chemistry. Enaminones were usually prepared by a condensation reaction of amines and 1,3-dicarbonils. For ammonia and a large variety of primary and secondary amines this reaction occurred in benzene, under reflux using a Dean Stark trap.[6] This procedure generally requires a large excess of amine: for instance the reaction with 1,3-dicarbonyls and ammonia requires a stream of gaseous ammonia. To avoid this problem the use of ammonium acetate[7] as a source of ammonia, in benzene at reflux and in the presence of acetic acid, was described. For a more efficient condensation of cyclohexane-1,3-dione derivatives with low boiling amines the use of stoichiometric boron trifluoride etherate[8] as an activator was reported. In recent years, environmentally benign synthetic methods have received considerable attention and new procedures for the synthesis of enaminones have been reported. On this subject, the use of montmorillonite K_{10} or SiO_2 as catalysts combined with microwave irradiation[9] and the condensation reaction of 1,3-dicarbonyls and amines in water[10] as solvent has been investigated. This last procedure is restricted to a limited range of hydrosoluble and more reactive amines. Consequently, the development of clean, mild and efficient protocols for condensation reactions of 1,3-dicarbonyl derivatives with ammonia/amines is still a synthetic challenge.

Herein we wish to report the results of the gold(III) catalysed synthesis of β-enaminones from 1,3-dicarbonyl compounds. The catalysis of gold(III) is also extended to reaction of cyclic 1,3-dicarbonyls with O-, P- and S-nucleophiles.

Results and discussion

The condensation reaction of *o*-iodoaniline and acetylacetone **1a** (Table 1) was selected as the model system and the

Table 1 Transition metal-catalysed synthesis of β-enaminone **3a** from **1a** and *o*-iodoaniline



[**1a**]: [*o*-iodoaniline]	Catalyst	Temperature/ °C	Time/h	**3a** Yield (%)
1 : 1	—	40	7	—[a]
1 : 1	$NaAuCl_4$	40	7	62
1 : 1	$NaAuCl_4$	r. t.	7	60
1 : 2	$NaAuCl_4$	r. t.	7	100
1 : 1	CuI	r. t.	7	10
1 : 1	$ZnCl_2$	r. t.	7	41
1 : 1	$AgNO_3$	r. t.	7	24
1 : 1	Na_2PdCl_4	r. t.	7	44

[a] 90% of *o*-iodoaniline recovered.

Green Context

Simplicity is an important feature of any truly green chemical process; reducing the auxiliaries present, the number of synthetic steps and the complexity of the process. β-Enaminones are normally synthesised in a process that involves a Dean–Stark reactor and hazardous solvents such as benzene. Here we have described a new catalytic route to these versatile synthetic intermediates. The method is based on a gold catalyst in ethanol as solvent and at room temperature. ***JHC***

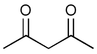
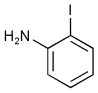
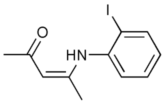
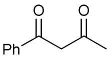
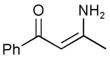
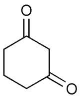
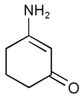
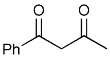
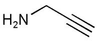
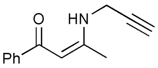
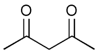
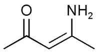
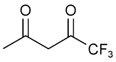
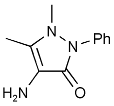
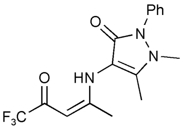
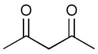
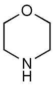
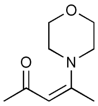
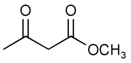
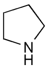
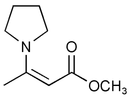
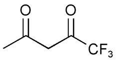
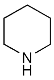
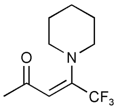
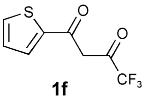
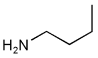
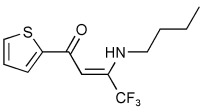
DOI: 10.1039/b210165c

preparation of the corresponding β-(2-halophenyl)amino-substituted α,β-unsaturated ketones **3a** was attempted under different reaction conditions. The β-(2-halophenyl)amino substituted α,β-unsaturated ketones have been proven to be very useful for construction of aza heterocycles *via* radical[11] or catalytic[12] cyclization.

The results reported in Table 1 show that without adding any catalyst the starting *o*-iodoaniline was recovered (90%) after reacting at 40 °C for 7 h in ethanol with **1a**. By contrast, in the presence of a catalytic amount of $NaAuCl_4 \cdot 2H_2O$ the β-enaminone **3a** has been isolated under the same reaction conditions with a 62% yield. Moreover, the gold(III)-catalysed amination reaction of 1,3-dicarbonyls can be carried out at room temperature. In these latter conditions **3a** has been isolated in 60% yield by using a molar ratio 1,3-dicarbonyl : amine of 1 : 1 and in quantitative yield with a molar ratio 1,3-dicarbonyl : amine = 1 : 2. In addition, a screening on the efficiency of other transition-metal salts revealed that gold(III) is more efficient than $AgNO_3$, Na_2PdCl_4, CuI and $ZnCl_2$ in the catalysis of condensation reactions of 1,3-dicarbonyls with amines. Although $ZnCl_2$, $AlCl_3$, $TiCl_4$ and other Lewis acid have been reported to be efficient catalysts and water scavengers in the condensation of ketones with amines,[13] to the best of our knowledge the gold-catalysed amination of ketones has not been investigated. On the other hand, the catalysis of organic reactions by gold-catalysts has received only little attention, this is especially true for homogeneous catalysis of organic reactions by gold catalysts.[14]

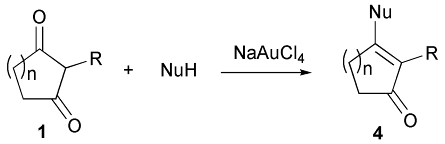
When the gold-catalysed amination was extended to other 1,3-dicarbonyl compounds the synthesis of β-enamino esters

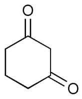
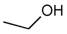
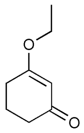
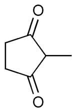
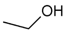
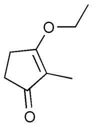
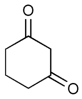
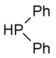
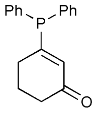
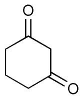
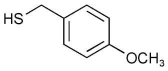
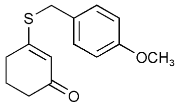
Table 2 Gold-catalysed synthesis of β-enaminones[a][b]

Entry	1,3-Dicarbonyl	Amine	Product	Previously reported results by existing methodologies
1	 **1a**		 **3a** (60%)	Benzene[12] under reflux, 4-methylbenzensulfonic acid (cat.) (72%)
2	 **1b**	NH_3	 **3b** (90%)[c]	$CH_3COO^-NH_4^+$, benzene[7] under reflux, AcOH (70%)
3	 **1c**	NH_3	 **3c** (86%)[d]	$CH_3COO^-NH_4^+$, benzene[7] under reflux, AcOH (85%)
4	 **1b**		 **3d** (68%)	
5	 **1a**	NH_3	 **3e** (84%)	$CH_3COO^-NH_4^+$, benzene[7] under reflux, AcOH (90%)
6	 **1d**		 **3f** (96%)	
7	 **1a**		 **3g** (62%)	Benzene at reflux,[15] *p*-toluenesulfonic acid (cat.) (61%)
8	 **1e**		 **3h** (96%)	Montmorillonite/microwave irradiation[9] (95%)
9	 **1d**		 **3i** (96%)	
10	 **1f**		 **3j** (95%)	

[a] Yields refer to single runs, are given for pure isolated products, and are based on **1**. [b] Unless otherwise stated, reactions were carried out at r.t. in ethanol under a nitrogen atmosphere using the following molar ratios: **1** : amine : $NaAuCl_4$ = 1 : 1 : 0.025. [c] Molar ratios: **1** : NH_3 : $NaAuCl_4$ = 1 : 3 : 0.025. [d] Molar ratios: **1** : NH_3 : $NaAuCl_4$ = 1 : 2 : 0.025.

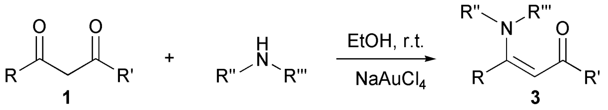
Table 3 Gold-catalysed synthesis of β-substituted cyclohexenones and cyclopentanones



Entry	Cyclic 1,3-dicarbonyls	Nucleophile	Solvent, temperature	Product[ab]
1	 **1c**		EtOH,[c] 40 °C	 **4a** (77%)
2	 **1g**		EtOH,[c] 40 °C	 **4b** (82%)
3	 **1c**		CH3CN, 60 °C	 **4c** (66%)
4	 **1c**		CH3CN, r.t.	 **4d** (98%)

[a] Yields refer to single runs, are given for pure isolated products, and are based on **1**. [b] Unless otherwise stated, reactions were carried using the following molar ratios: **1**:NuH:NaAuCl$_4$ = 1:1:0.025. [c] The reactions were carried out at 40 °C using the following conditions: **1**:NaAuCl$_4$ = 1:0.025 in ethanol (2 mL).

and enaminoketones **3** was accomplished with ammonia, primary and secondary amines according to Scheme 1.



Scheme 1

This procedure is quite general for a wide range of amines such as aliphatic, cyclic and aromatic amines. Our results are shown in Table 2 in comparison with the results reported in the literature by existing methodologies. It is clear from our results that the gold-catalysed condensation reaction of 1,3-dicarbonyls and amines to give **3** appears to provide a remarkably viable alternative route for the synthesis of enaminones and can be applied to a large variety of functionalized diketones or β-ketoesters. The catalysts NaAuCl$_4$·2H$_2$O is commercial available and has been used as purchased, without further purification. All the reactions were carried out at room temperature. It should be pointed out that in the reaction of arylalkyldicarbonyls with amines we observed the regioselective amination of the aliphatic carbonyl group (Table 2, entries 2, 4). In addition when the 1,1,1-trifluoroacetylacetone **1d** and 1-(2-thenoyl)-3,3,3,-trifluoroacetone **1f** were allowed to react with amines (Table 2 entries 9, 10) only the enaminones derived from the regioselective amination of the trifluoroacetyl group were observed. By contrast, **1d** led to **3f** through the exclusive amination of the acetyl group in the reaction with 4-aminophenazone.

Moreover we have developed an extremely simple approach to β-substituted cyclohexenones and cyclopentenones **4a–d** (Table 3) from the corresponding 1,3-diketones.

Indeed, the gold(III) catalysis have been extended to the reaction of cyclic 1,3-dicarbonyls with ethanol, diphenylphosphine and 4-methoxybenzyl mercaptan. The reported procedure for β-substituted cyclohexenones involved the formation of enone mesilates[16] which subsequently were transformed to the products **4** by reaction with nucleophiles.

In conclusion, we have developed by means of gold(III) catalysis a simple and green procedure for the synthesis of β-enaminones from 1,3-dicarbonyls and ammonia/amines that requires neither corrosive acid catalyst nor azeotropic conditions using a large excess of aromatic solvents such as benzene. Traditional stepwise formation of β-substituted cyclohexenones and cyclopentenones can be replaced by one-pot procedure.

Experimental

Typical procedure for the preparation of enaminones 3a–j

A 1:1 mol ratio mixture of 1,3-dicarbonyl **1** and amine was allowed to react in ethanol at room temperature under nitrogen. The reaction was monitored by TLC or GC–MS. After completion, the solvent was removed trough evaporation and the reaction mixture was purified by flash chromatography (silica gel, *n*-hexane–ethyl acetate) to give enaminones **3**.

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A convenient, rapid, highly selective and eco-friendly method for deprotection of aryl acetates using silica gel supported ammonium formate under microwave irradiation†

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Received 9th September 2002
First published as an Advance Article on the web 18th November 2002

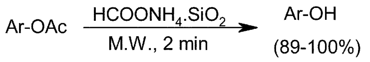
Several aryl acetates were rapidly and selectively deprotected to the corresponding phenols in excellent yields using silica gel supported ammonium formate under microwave irradiation. The process is environmentally benign.

Introduction

Phenolic hydroxyl groups occur widely in various bioactive natural products. The protection of these groups is generally required for modifications and synthesis of these phenol-containing products.[2] This protection is usually carried out by preparing the acetates of the compounds as the acetates can easily be formed and cleaved. Deprotection of aryl acetates can classically be carried out under acidic, basic or hydrogenatic conditions.[2] However, these deprotection methods may affect various sensitive functional groups present in the compounds. The methods for selective deprotection of aromatic acetates are limited. Some methods utilizing specific micelles,[3a] Zn–MeOH,[3b] cyclodextrin,[3c] metallo-enzymes,[3d] metal complexes[3e–g] and antibodies[3h] have been reported for selective deprotection of aryl acetates in the presence of alkyl acetates. However, most of these methods are associated with different drawbacks including the uses of non-available and costly reagents, harsh reaction conditions, tedious experimental procedures, long reaction times and low yields. Recently a selective deprotection procedure using natural kaolinitic clay has been discribed[4] but this clay is not commercially available and was collected from a specific geographical region. A microwave irradiation method using alumina has also been reported[5] but the selectivity of deprotection of aryl acetates was found to be lost on increasing the irradiation time beyond a certain value. Both phenyl and octyl acetates were reported to undergo deprotection under microwave irradiation in the presence of alumina within 2 min. Thus the discovery of efficient, selective and rapid methods for deprotection of aromatic acetates is necessary.

Results and discussion

During our recent work[6] on the development of novel synthetic methodologies we observed that silica gel supported ammonium formate ($HCOONH_4$) can catalyze efficiently and promptly the selective deprotection of aromatic acetates under microwave irradiation. $HCOONH_4$ is generally used as an *in situ* hydrogen source for catalytic hydrogen transfer reduction. The combination of this reagent with palladium and charcoal is very selective for reduction of a variety of important functional groups.[7] We discovered that aryl acetates, when irradiated with $HCOONH_4/SiO_2$ for 2 min under microwave irradiation, gave the corresponding phenols in excellent yields (Table 1).



$$\text{Ar-OAc} \xrightarrow[\text{M.W., 2 min}]{HCOONH_4.SiO_2} \underset{(89\text{-}100\%)}{\text{Ar-OH}}$$

The method showed excellent selectivity for deprotection of aryl acetates as alkyl acetates remained totally unaffected. Even when the irradiation time was increased to 6 min no change of alkyl acetates was observed but irradiating for longer led to docomposition of the compounds. Double bonds, carbonyl groups, ether linkages, lactone rings and benzoate were also unchanged. The conversion can be conducted in the presence of other protecting groups such as N-acetyl, N-Boc and OTs groups. The presence of electron donating or withdrawing groups in the aryl acetates did not influence the yields of the phenols. The structures of the products were established from their spectral (^{1}H NMR and MS) data and by comparison with authentic samples.

$HCOONH_4$ is easily available, inexpensive and non-toxic. Although hygroscopic, in the presence of silica gel as solid support the reagent can conveniently be used for microwave irradiation. We have observed when silica gel alone was applied the yields of the generated phenols were low (42–47% after irradiation for 3 min) under our experimental conditions. $HCOONH_4$ can also be used conventionally for deprotection of aryl acetates by treating the compounds with the reagent in MeOH at room temperature for 12 h to produce the corresponding phenols (yield 67–74%). The microwave irradiation method using silica gel supported $HCOONH_4$ is better since it rapidly (2 min) generates the phenols with higher yields (89–100%) from the aromatic acetates. The experimental procedure is also simple.

Green Context

Rapid efficient deprotection methods are of use in synthetic chemistry. Phenols are sensitive substrates which often require protection by acetate functions to avoid oxidative decomposition. The combination of ammonium formate, silica and microwave irradiation is a very fast, energy efficient route to their liberation with little effect on other functional groups. ***DJM***

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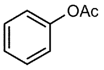
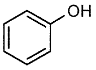
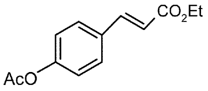
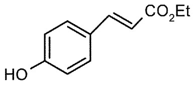
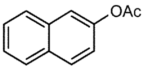
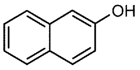
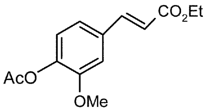
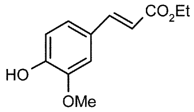
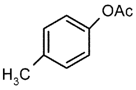
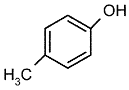
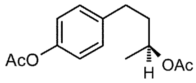
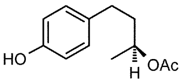
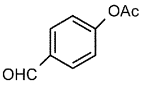
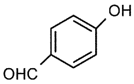
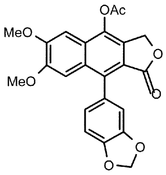
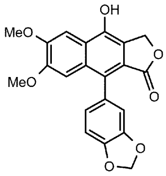
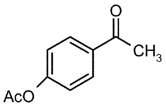
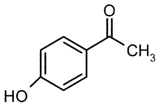
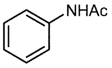
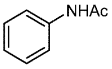
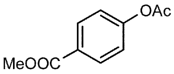
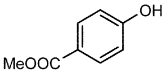
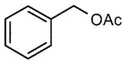
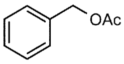
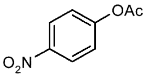
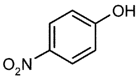
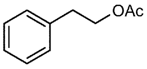
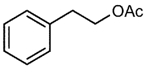
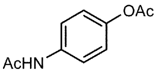
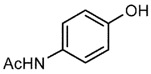
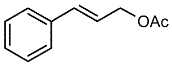
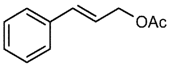
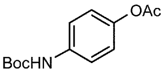
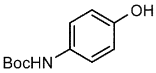
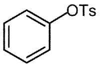
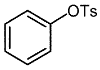
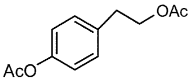
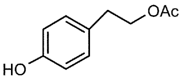
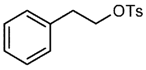
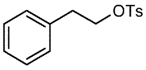
† Part 20 in the series 'Studies on Novel Synthetic Methodologies', for part 19, see ref. 1

DOI: 10.1039/b208811h

Table 1 Deprotection of aryl acetates under microwave irradiation

Entry	Substrate	Product	Isolated yield of phenol (%)	Entry	Substrate	Product	Isolated yield of phenol (%)
1			92	11			100
2			94	12			99
3			96	13			93
4			99	14			98
5			96	15			0
6			100	16			0
7			100	17			0
8			89	18			0
9			94	19			0
10			98	20			0

In conclusion, a novel, simple and highly selective method has been developed for deprotection of aryl acetates using silica gel supported $HCOONH_4$ under microwave irradiation. The utilization of a commonly used reagent, operational simplicity, rapid conversion and the excellent yields of the products, constitute the present method a useful alternative to the available deacetylation procedures of aromatic acetates. The advantages of both the solid supported reagent and microwave irradiation have been utilized. The developed process is environmentally benign.

Experimental

Typical procedure for deprotection of aryl acetates

$HCOONH_4$ (63 mg, 5 mmol) was mixed thoroughly with silica gel (0.5 g, Merck, finer than 200 mesh) to form a powder. 4-Acetoxyphenylethyl acetate (222 mg, 1 mmol) was then added and mixed. The mixture was taken in a glass test tube (length: 15 cm, diameter: 1.5 cm) and placed at the centre of an alumina bath which was made by using a glass beaker (250 ml; length: 9.5 cm, diameter: 7.5 cm) three-quarters filled with alumina. The alumina bath was placed inside a microwave oven (BPL, BMO, 700T, 450 W) and the reaction mixture was irradiated for 2 min. The mixture was cooled, shaken with EtOAc (10 ml) and filtered. The filtrate was concentrated to afford the deprotected product, 4-hydroxyphenylethylacetate (176 mg, 98%).

Spectral properties of some representative phenols are given below

4-Hydroxyacetanilide (entry 8). ^1H NMR (DMSO-d_6, 200 MHz): δ 9.34 (1H, br s, –NH–), 8.56 (1H, br s, –OH), 7.28 (2H, d, J = 8.0 Hz, Ar–H), 6.66 (2H, d, J = 8.0 Hz, Ar-H), 2.02 (3H, s, –Ac); MS: m/z 151 ($M^{+\cdot}$).

4-Hydroxyphenylethyl acetate (entry 10). ^1H NMR ($CDCl_3$, 200 MHz): δ 6.98 (2H, d, J = 8.0 Hz, Ar–H), 6.72 (2H, d, J = 8.0 Hz, Ar–H), 5.64 (1H, br s, –OH), 4.22 (2H, t, J = 7.0 Hz, $-CH_2O-$), 2.82 (2H, t, J = 7.0 Hz, $ArCH_2-$), 2.02 (3H, s, –OAc); MS: m/z 180 ($M^{+\cdot}$).

Rhododendrol monoacetate (entry 13). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.00 (2H, d, J = 8.0Hz, Ar–H), 6.70 (2H, d, J = 8.0 Hz, Ar–H), 4.86 (1H, m, $>$CHO–), 2.61 (2H, t, J = 7.0 Hz, $ArCH_2-$), 2.08 (3H, s, –OAc), 1.98–1.85 (2H, m, $-CH_2-$), 1.25 (3H, d, J = 7.0 Hz, Me); MS: m/z = 208 ($M^{+\cdot}$).

Acknowledgements

The authors thank UGC and CSIR, New Delhi for financial assistance.

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Synthesis of dimethyl carbonate and glycols from carbon dioxide, epoxides and methanol using heterogeneous Mg containing smectite catalysts: effect of reaction variables on activity and selectivity performance

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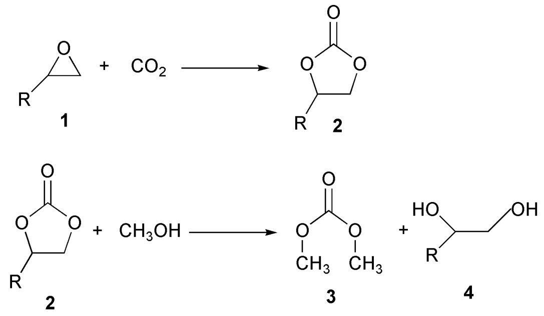
Received 7th August 2002
First published as an Advance Article on the web 18th November 2002

This paper reports the effect of various reaction variables on the activity and selectivity performance on a two-step synthesis of dimethyl carbonate (DMC) and glycol from propylene oxide, carbon dioxide and methanol using a heterogeneous Mg containing smectite catalyst. The first step, the reaction of propylene oxide with CO_2 to form propylene carbonate, and the second step, the transesterification reaction of the cyclic carbonate such as ethylene carbonate with methanol to DMC and ethylene glycol, have been studied. The catalyst was found to be effective for one-pot synthesis of DMC, *i.e.* the sequential reaction of the epoxide, CO_2 and methanol.

1 Introduction

Dimethyl carbonate (DMC) synthesis using carbon dioxide is considered as one of the promising reactions in the development of environmentally benign processes based on the utilization of naturally abundant carbon resources such as carbon dioxide.[1,2] DMC finds extensive applications as a solvent, an octane booster in gasoline to meet oxygenate specifications, and a starting material for organic synthesis *via* carbonylation and methylation, replacing poisonous phosgene and dimethyl sulfate.[3,4] It is also used as a precursor for polycarbonate resins. DMC is synthesized by oxidative carbonylation of methanol (non-phosgene route) or by phosgenation of methanol. Both routes involve the use of poisonous and/or corrosive gases of chlorine, phosgene and carbon monoxide and there is a possibility of explosion hazards in the case of methanol carbonylation.[5–7] There are several reports on direct synthesis of DMC from carbon dioxide and methanol in the presence of organometallic complexes,[8-11] inorganic bases[12–14] or zirconium oxide.[15] However, most of these systems suffer from several drawbacks such as low yields and/or high cost of the starting materials and problems associated with catalyst–product separation due to the homogeneous nature of the catalysts. Recently, we have reported that DMC can be synthesized from epoxide compounds of ethylene oxide or propylene oxide by a two-step reaction in which the formation of cyclic carbonates is involved (Scheme 1) using basic metal oxide catalysts.[16] In the first step, the epoxide reacts with CO_2 producing a corresponding cyclic carbonate. In the second step, the carbonate is transesterified with methanol to DMC and a corresponding glycol.

Smectite is a layered clay minerals, in which one layer consists of one octahedral sheet sandwiched by two tetrahedral sheets. The octahedral sheet contains divalent or trivalent cations such as Mg^{2+} and Al^{3+} surrounded by six oxygen atoms and the tetrahedral sheet contains Si^{4+} cations surrounded by four oxygen atoms. The trilayers are negatively charged and are held together by electrostatic interaction with exchangeable cations in the interlayer region. It is possible to introduce various transition metal cations in the octahedral sheet and alkali metal cations in the interlayer. We have earlier reported the synthesis of various smectites containing Ni and Mg that



Scheme 1

Green Context

The utilisation of dimethyl carbonate (DMC) in a variety of applications is growing, and clean routes to its synthesis are of great value. The work presented here is aimed at developing a viable route from carbon dioxide and methanol, and is based on the addition reaction of an epoxide with CO_2 catalysed by various metal based catalysts. The cyclic carbonate (useful in its own right) can then be transformed into DMC either in a separate step, or in a one-step process. This concept eliminates the requirement for toxic and wasteful intermediates such as phosgene. ***DJM***

DOI: 10.1039/b207750g

have both acidic and basic sites.[17] The acidic and basic properties of the smectites are tunable,[17] this being a great advantage for them to be used as catalysts. Recently, we have reported that Mg and/or Ni containing smectites catalysts are effective catalysts for both steps in Scheme 1 and the catalytic activity strongly depends on the amounts of alkali-metal atoms incorporated in the smectite catalysts[18]

In this work using a selected smectite catalyst, effects of reaction parameters have been studied in detail for the reaction of propylene oxide with CO_2 to the corresponding cyclic carbonates and for the transesterification reaction of the ethylene carbonate with methanol to DMC and ethylene glycol. For the latter reaction, propylene oxide and other alcohols have been used as well. A combination of the two reactions, one-pot synthesis of DMC from propylene oxide, methanol and CO_2, has also been examined.

Results and discussion

In our previous works,[18] it has been reported that the catalytic activities for both the first and second steps of DMC synthesis are higher for a smectite catalyst containing a larger amount of alkali-metal atoms. Hence, most of the reaction experiments were carried out with the S-Mg-1 sample (see Experimental section).

CO_2 addition to propylene oxide

When the reaction of propylene oxide (PO) and CO_2 was carried out with S-Mg-1, propylene carbonate (PC) was produced as a main product. Byproducts consisted of propylene glycol (PG) and oligomers of PO and/or PC. Fig. 1 illustrates the changes of the PO conversion and the selectivity for PC (mol of PC formed/mol of PO reacted) with time at 150 °C. The reaction progresses gradually and the PO conversion reaches 84% after 15 h, at which the PC yield is 57%. The selectivity for PC obtained at 3 h is lower than those obtained at the longer reaction times. It was found that the amount of PC increased with reaction time while that of PG little changed. Thus, the selectivity for PC obtained at 3 h is low but it increases to more than 60% at longer reaction times.

Fig. 2 demonstrates the influence of CO_2 pressure on the PO conversion and the selectivity for PC. The CO_2 pressure does not significantly affect the conversion and the selectivity in the region between 3 and 10 MPa; however, both the conversion and the selectivity decrease sharply at 15 MPa. It is highly probable that the reaction system consists of three phases: CO_2–liquid–solid at the lower pressures, while it should be in a homogeneous phase at 15 MPa. Such a phase change would cause an increase in the volume at the location where the reaction proceeds.[14] Hence, the concentration of the catalyst and/or PO would be low at 15 MPa, resulting in low PO conversion at this pressure. As Fig. 2 shows, the lowest selectivity is obtained at 15 MPa. Such a high pressure might promote oligomer formation.

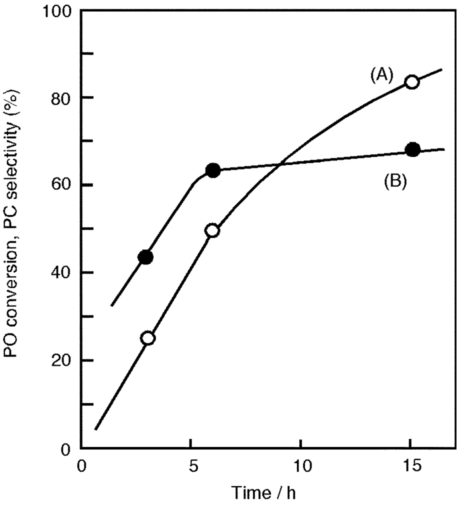


Fig. 1 Variations of (A) PO conversion and (B) selectivity for PC with reaction time. PO, 57 mmol; catalyst, 0.5 g; CO_2, 8 MPa; temperature, 150 °C.

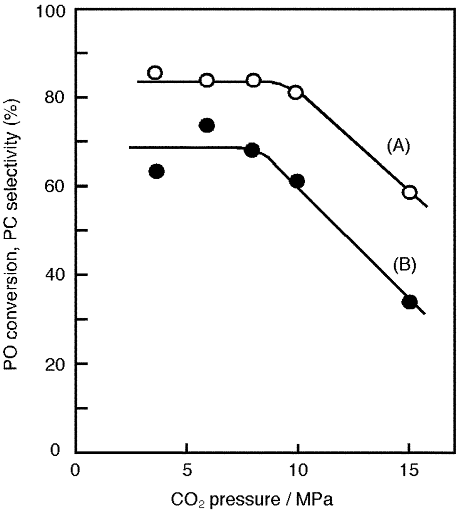


Fig. 2 Effect of CO_2 pressure on (A) PO conversion and (B) selectivity for PC. PO, 57 mmol; catalyst, 0.5 g; temperature, 150°C; time, 15 h..

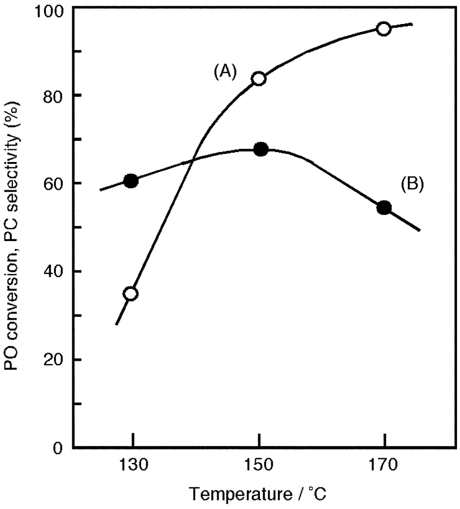


Fig. 3 Effect of temperature on (A) PO conversion and (B) selectivity for PC. PO, 57 mmol; catalyst, 0.5 g; CO_2, 8 MPa; time, 15 h.

The effect of the reaction temperature on the reaction of PO and CO_2 was investigated (Fig. 3) and the PO conversion was found to increase with temperature. However, the selectivity decreases at 170 °C and thus the optimum reaction temperature is 150 °C.

Transesterification of ethylene carbonate with methanol

Transesterification of ethylene carbonate (EC), *i.e.* the second step reaction in Scheme 1, was carried out under various conditions. Fig. 4 shows the yields of DMC and ethylene glycol (EG) *vs.* time. The yields of DMC and EG are almost the same as expected from Scheme 1 and reach constant values after about 2 h. The selectivities for DMC and EG (mol of DMC or EG formed/mol of EC reacted) were 100% for the initial 2 h.

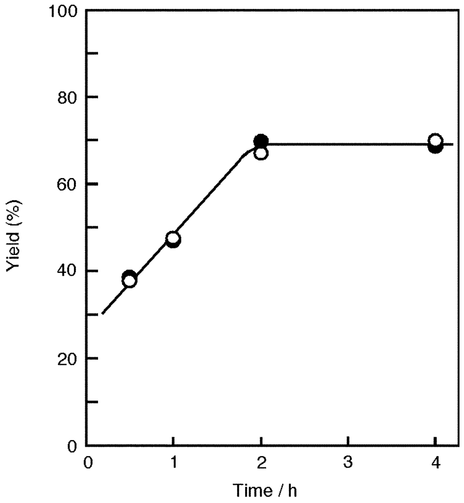


Fig. 4 Variations of (○) DMC and (●) EG yields with reaction time. EC, 25 mmol; methanol, 200 mmol; catalyst, 0.25 g; temperature, 150 °C.

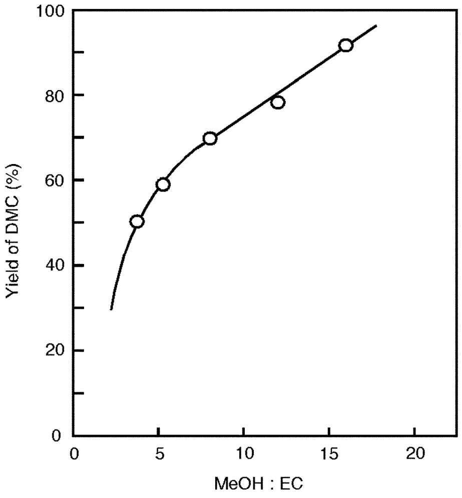


Fig. 5 Change of DMC yield with the molar ratio of methanol to EC. Catalyst, 0.25 g; temperature, 150 °C; time 4 h.

Table 1 Influence of temperature on the reaction of EC and methanol

		Yield (%)	
Temperature/°C	EC conversion (%)	DMC	EG
100	15	15	14
125	44	44	44
150	73	66	67
175	77	60	64

EC, 25 mmol; methanol, 200 mmol; S-Mg-1, 0.25 g; 4 h.

Table 2 Recycle use of the smectite catalyst for the reactionof EC and methanol

	Yield (%)	
Run	DMC	EG
1	66	70
2	67	70
3	65	70

EC, 25 mmol; methanol, 200 mmol; S-Mg-1, 0.25 g; 150 °C; 2 h.

However, these selectivity values were found to decrease to 90% after 4 h, probably due to the decomposition of EC to EO.[16,19] Table 1 shows the effect of reaction temperature on the EC conversion and the DMC and EG yields. As the reaction temperature is increased, the conversion increases and the selectivities do not change much below 150 °C; however, the selectivity decreases from 90% at 150 °C to 80% at 175 °C. Thus, again, the optimum reaction temperature is 150 °C with respect to the DMC yield.

When the reaction was conducted with various amounts of EC at 150 °C for 4 h using a constant amount of methanol, the EC conversion decreased with increasing amount of EC. In a reverse manner, when the reaction was conducted with various amounts of methanol while keeping the amount of EC unchanged, the EC conversion increased with increasing the amount of methanol. Fig. 5 shows the relationship between the molar ratio of methanol to EC and the DMC yield. The selectivities to DMC and EG did not change with the molar ratio. Thus, both DMC and EG yields increase with the molar ratio. To obtain higher EC conversion, the reaction should be conducted with a high methanol to EC ratio.

After a reaction run, the catalyst was separated by filtration, rinsed with acetone a few times and dried. Then the catalyst was reused for a subsequent run. Table 2 shows the reaction results with the same sample for the repeated runs. The activity of the smectite catalyst is seen to be stable upon recycling with no loss of activity being observed.

The effect of various alcohols was also investigated for the transesterification of ethylene carbonate (EC) and of propylene carbonate (PC). Fig. 6 gives conversion data obtained for methanol, ethanol and propanol. DMC, diethyl carbonate and dipropyl carbonate were obtained along with ethylene glycol and propylene glycol for the reaction of EC and PC, respectively. It is shown that the yield of dialkyl carbonate from EC as the starting material is always higher than that from PC, and that the reactivity decreases with increase in the number of carbon atoms of the alcohol for both EC and PC. The difference between EC and PC could be attributed to the steric hindrance effect caused by replacement of –H by the bulkier $-CH_3$ group.

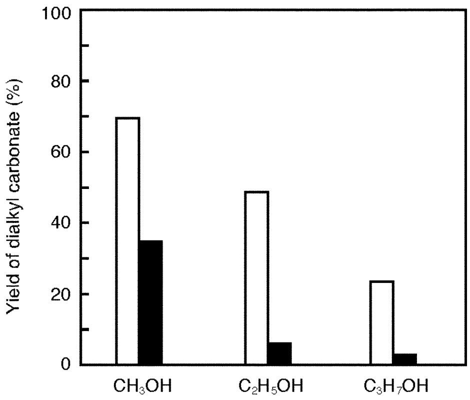
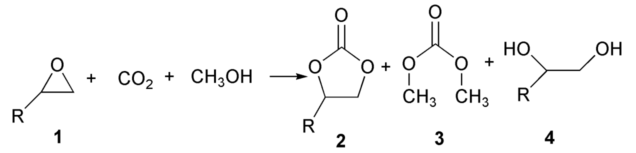


Fig. 6 Transesterification of EC (white bars) and PC (black bars) with various alcohols. EC, 25 mmol; PC, 25 mmol; catalyst, 0.25 g; temperature, 150°C; time, 4 h.

One-pot synthesis of DMC

It is interesting to integrate these two reactions into a one-pot reaction (Scheme 2). Table 3 shows the results of this integration for propylene oxide. For comparison, our previous result obtained with MgO catalyst[16] is also listed in Table 3. DMC, propylene glycol and propylene carbonate are formed with the side-products 1-methoxy-2-propanol and 2-methoxy-1-propanol. These by-products are formed from propylene oxide by methanolysis (Scheme 3). The selectivity for DMC depends on the catalyst used. The highest selectivity of 33.6%

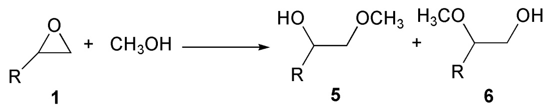


Scheme 2

Table 3 One-pot synthesis of DMC from PO, CO_2 and methanol

Catalyst	PO conversion (%)	Selectivity[a] (%) 2	3	4	5	6
S-Mg-1	95	24	34	36	15	6
S-Mg-2	95	20	4	5	43	28
MgO	99	14	14	15	22	30

PO, 21 mmol; methanol, 200 mmol; catalyst, 0.5 g; CO_2, 8 MPa; 150 °C; 15 h.[a] Mol of the product formed/mol of PO reacted..



Scheme 3

is obtained with S-Mg-1. This selectivity value is 2.5 times that obtained with MgO, which was considered to be the best catalyst among the metal oxide catalysts tested in the previous work.[16] The difference between the catalysts would result from the difference in the amount and strength of basic sites existing on the catalysts. Although the best catalyst S-Mg-1 still gives the side products 1-methoxy-2-propanol and 2-methoxy-1-propanol, the results in Table 3 suggest that further controlling the basic properties of the catalyst could give more active and selective catalysts, contributing towards the development of one-step method for DMC, EG, EC synthesis from epoxide and carbon dioxide.

Conclusion

In conclusion, the effect of various reaction variables on the activity and selectivity performance on a two-step synthesis of dimethyl carbonate (DMC) and glycol from epoxide, carbon dioxide and methanol using a heterogeneous Mg containing smectite catalyst has been optimized. For the first step, the reaction of PO with CO_2 to form PC, the optimum reaction temperature is 150 °C. The CO_2 pressure does not have a significant influence on the yield of PC formation. For the second step, the transesterification reaction of the cyclic carbonate such as ethylene carbonate with methanol to give DMC and ethylene glycol, the optimum temperature and time are 150 °C and 2 h, respectively. The smectite catalyst was also found to be effective for the one-pot synthesis of DMC, *i.e.* the sequential reaction of the epoxide, CO_2 and methanol. As compared with MgO, the smectite catalyst shows improved selectivity for DMC by avoiding the undesirable methonolysis reaction between PO and methanol.

Experimental

Two Mg containing smectite catalysts (designated S-Mg-1 and S-Mg-2) were synthesized according to a hydrothermal method developed by Torri and Iwasaki.[20] In brief, an alkali-metal solution was added to an acidic aqueous solution of sodium silicate and magnesium or nickel chloride. The precipitated hydrous oxide obtained, after being filtered off, was autoclaved at temperatures between 110 and 300 °C. The material obtained was dried in an oven at 110 °C for 15 h. The composition of the smectite catalysts prepared was determined by X-ray fluorescence. Numbers of constituent cations in the unit cell (Si : Mg- : Na : K) were 8 : 6.44 : 2.81 : 0.13 for S-Mg-1 and 8 : 6.17 : 0.63 : 0.02 for S-Mg-2. BET surface areas of S-Mg-1 and S-Mg-2 were 110 $m^2 g^{-1}$ and 339 $m^2 g^{-1}$, respectively.

All recation experiments were carried out in a 50 mL autoclave reactor. The details of experimental setup have been reported earlier.[16] Typical conditions and procedures are as follows: propylene oxide (57 mmol) and the catalyst (0.5 g) were charged into the reactor. Then CO_2 was injected up to around 1 MPa. The reactor was heated to 150 °C and then liquid CO_2 was further injected up to 8 MPa under stirring. The mixture was stirred for 15 h. After the reaction, the reactor was cooled to 0°C with ice-water and depressurized by a back pressure regulator. The liquid reaction mixture was analyzed by a gas chromatograph with a flame ionization detector and a mass spectrometer. The transesterification reactions were also conducted in a similar fashion. Ethylene carbonate (25 mmol), methanol (200 mmol), and the catalyst (0.25 g) were charged into the reactor. Then CO_2 was injected up to around 1 MPa and the reactor was heated to 150 °C. Although CO_2 is not required for the transesterification, the presence of CO_2 prevents the decomposition of EC, as reported in our previous work.[16] The reaction mixture was analyzed in similar procedures as described above.

Acknowledgement

We wish to thank for financial support obtained from Japan Science and Technology (JST) under the CREST program.

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An effective and recyclable catalyst for hydrogenation of α,β-unsaturated aldehydes into saturated aldehydes in supercritical carbon dioxide

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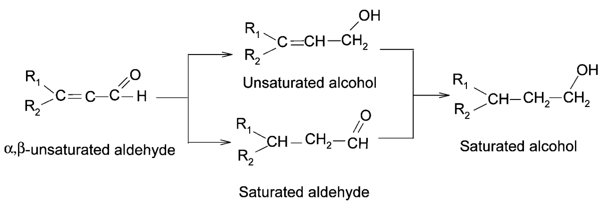
Received 20th September 2002
First published as an Advance Article on the web 11th December 2002

A carbon supported palladium catalyst (Pd/C) is successfully used in selective hydrogenation of α,β-unsaturated aldehydes in $scCO_2$ and under solventless reaction conditions. The reactions take place very rapidly in $scCO_2$ and the average turnover frequency values for cinnamaldehyde and crotonaldehyde at 100% conversion maximally reached 3.1 and 11.6 s^{-1}, respectively. The catalyst can be recycled several times without loss of activity and selectivity. The products (liquid), solvent ($scCO_2$) and catalyst (solid) can be easily separated by a simple phase separation process. The present reaction is an ideal green chemical process in the view of industrial applications.

Introduction

Much attention has been paid for selective hydrogenation of α,β-unsaturated aldehydes into the corresponding unsaturated alcohols owing to their applications in the synthesis of fine chemicals such as perfumes and pharmaceuticals.[1,2] The production of saturated aldehydes from unsaturated ones has also industrial and biological applications. For example, hydrocinnamaldehyde derived from cinnamaldehyde hydrogenation can be used in the synthesis of an intermediate reagent of anti-viral pharmaceuticals, particularly HIV protease inhibitors.[3] Hydrogenation of α,β-unsaturated aldehydes to specific products (Scheme 1) such as saturated aldehydes and alcohols, as well as unsaturated alcohols, can be achieved by choosing suitable metal catalysts. Palladium is one of the most active and selective catalysts for the hydrogenation of unsaturated aldehydes to produce saturated aldehydes in conventional organic solvents.[4–7] However, the rate of catalytic hydrogenation in a gas–liquid system is not as high as wished due to the low solubility of gaseous H_2 in conventional organic solvents. In contrast, H_2 is completely miscible with supercritical carbon dioxide ($scCO_2$), and the proper use of $scCO_2$ in heterogeneous catalysis can eliminate gas–liquid phase transfer resistance, enhance reaction rate and mass- and heat-transfer, control selectivity, and/or improve catalyst lifetime and regeneration.[8–10] It has been reported that $scCO_2$ medium can improve the reaction rate and selectivity of cinnamaldehyde hydrogenation over supported platinum catalysts.[11,12] In the present work, a palladium supported on carbon catalyst (10% Pd/C) has been used for the selective hydrogenation of α,β-unsaturated aldehydes such as cinnamaldehyde and crotonaldehyde in $scCO_2$. The influence of some parameters such as H_2 pressure, CO_2 pressure, temperature, and reaction time has been investigated, and the effectiveness of $scCO_2$ reaction medium has been compared with organic solvents and solventless conditions. The catalyst recycling has also been examined in $scCO_2$. We report that a 10% Pd/C catalyst in $scCO_2$ is a highly efficient catalytic system for α,β-unsaturated aldehyde hydrogenation into saturated aldehydes.



Scheme 1 Hydrogenation of α,β-unsaturated aldehydes.

Results and discussion

Table 1 shows the results of hydrogenation of cinnamaldehyde and crotonaldehyde with Pd/C catalyst in different solvents. It is evident that only C=C double bond was hydrogenated in the hydrogenation of crotonaldehyde in $scCO_2$, producing butanal with 100% selectivity. However, the diacetal was formed as a byproduct in 1-propanol, which is a more active organic solvent compared with toluene. When the reaction was conducted in an

Green Context

The conversion of unsaturated aldehydes into saturated ones has industrial and biological relevance. The hydrogenation reaction requires a catalyst but even with very active palladium-based catalysts, reaction rates can be slow due to the poor solubility of the H_2 in organic solvents. By substituting supercritical carbon dioxide as solvent, this problem is overcome and we relieve the environmental problems associated with the use of VOCs. Here a novel methodology for the hydrogenation of unsaturated aldehydes based on the use of Pd/C catalyst and $scCO_2$ solvent is described. ***JHC***

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DOI: 10.1039/b209252m

Table 1 Results of hydrogenation of α,β-unsaturated aldehydes with 10% Pd/C catalyst

Reactant	Solvent	Time/min	Conversion (%)	TOF[a]/s^{-1}	Selectivity (%)		
					HCAL	HCOL	COL
Cinnamaldehyde	CO_2 (8.0 MPa)	60	100	3.1	87	13	0
	Toluene	60	18	0.6	88	12	0
	1-Propanol[b]	60	75	2.3	71	22	0
	1-Propanol + CO_2 (8 MPa)[b]	60	90	2.8	80	17	0
	Solventless	60	64	1.9	87	13	0
					Butanal	Butanol	Butenol
Crotonaldehyde	CO_2 (8.0 MPa)	10	78	27.1	100	0	0
	CO_2 (8.0 MPa)	30	100	11.6	100	0	0
	Toluene	30	48	5.6	100	0	0
	1-Propanol[b]	10	65	22.6	73	0	0
	Solventless	10	45	15.7	100	0	0

Reaction conditions: catalyst 10% Pd/C 0.01 g (including Pd 0.0094 mmol) cinnamaldehyde 2.5 g (18.8 mmol), crotonaldehyde 2.5 g (35.6 mmol), temperature 323 K, H_2 pressure 4.0 MPa, organic solvent toluene, 1-propanol 15 ml. HCAL hydrocinnamaldehyde, HCOL hydrocinnamyl alcohol, COL cinnamyl alcohol.[a] TOF: moles of substrate reacted per mole of exposed surface Pd atoms per second. [b] In the presence of 1-propanol, acetals were formed.

apolar solvent such as toluene or under solventless conditions, similar selectivity to butanal was obtained as that obtained in $scCO_2$, but the reaction rate is lower. In the case of cinnamaldehyde, both C=C and C=O bonds were hydrogenated and hydrocinnamaldehyde was formed predominantly over hydrocinnamyl alcohol, but no cinnamyl alcohol was formed under the reaction conditions used. The reaction rate and selectivity to hydrocinnamaldehyde were improved in $scCO_2$ compared with 1-propanol, in which the diacetal was also produced as a byproduct, but the selectivity to hydrocinnamaldehyde was lower compared with that in $scCO_2$. When 1-propanol and $scCO_2$ were used at the same time, both the reaction rate and selectivity were improved compared with that obtained in 1-propanol alone. When the reaction was conducted in toluene and under solventless conditions, the selectivity to hydrocinnamaldehyde was almost the same as that obtained in $scCO_2$, but the conversion is lower. Similar product distributions were previously found for Pd catalyzed coupling reactions of iodoarenes in $scCO_2$ and solventless conditions.[13] It can be seen from the results in Table 1 that the TOF was remarkably enhanced in $scCO_2$ under identical reaction conditions. Extremely high TOF values of 3.1 and 11.6 s^{-1} were obtained for cinnamaldehyde and crotonaldehyde at 100% conversion, respectively. The amount of cinnamaldehyde dissolved in $scCO_2$ is estimated to be less than 3% by visual inspection under the reaction conditions, which suggests that the reactions proceeded mainly in the liquid phase even though $scCO_2$ was used as the reaction medium. Therefore, the same reaction mechanism can be proposed in solventless and $scCO_2$ conditions. The improvement of the reaction rate in $scCO_2$ can be explained by the fact that H_2 is completely miscible in $scCO_2$ and the liquid substrate dissolves a high quantity of CO_2, resulting in an 'expanded liquid', and thus significantly increasing the H_2 concentration in the vicinity of the solid catalyst.[14] The reaction rate was shown to increase with increasing H_2 pressure.[6,11,15] This is in agreement with the results given in Table 2, showing the results of cinnamaldehyde hydrogenation under different reaction conditions. The conversion increases with increasing H_2 pressure, while the changes in the selectivity are negligible. It was reported that the liquid phase hydrogenation of cinnamaldehyde over Pd/C catalyst in propanol[6] and Pt/SiO_2 catalyst in ethanol[15] was first order to H_2 pressure. The same result was also reported in $scCO_2$ with Pt/Al_2O_3 catalyst.[11] These results are consistent with the present results at H_2 pressure up to 2 MPa.

As shown in Table 2, the conversion of cinnamaldehyde increases with increasing CO_2 pressure, while the selectivity changes very slightly. It is proposed that much more H_2 can be dissolved in the liquid phase with increasing CO_2 pressure, so that the rate of reaction is enhanced. It was found that the optical absorption spectrum of small gold particles measured in $scCO_2$ depended significantly on the pressure, suggesting a direct interaction between the gold particles and the $scCO_2$ medium.[16] It was also speculated that the interaction between $scCO_2$ and metal particles on the support could vary the product selectivity. We have reported that the selectivity to cinnamyl alcohol increases with increasing CO_2 pressure when hydrogenation of cinnamaldehyde was conducted with Pt/Al_2O_3[11] and Pt/SiO_2[12] catalysts. However, the present work shows a different result in that the product distribution does not depend on CO_2 pressure and similar selectivity values are also obtained under the solventless conditions.

The conversion increased with reaction time and reached 100% after 60 min with the selectivity remaining unchanged. No further hydrogenation of C=O bonds was found even upon extending the reaction time after 100% conversion. This means that the C=O bond of hydrocinnamaldehyde is difficult to be hydrogenated and the hydrocinnamyl alcohol arises completely from cinnamyl alcohol. Otherwise, one would predict the selectivity to hydrocinnamaldehyde to decrease with time due to the decrease in the concentration of hydrocinnamaldehyde as a result of its hydrogenation to hydrocinnamyl alcohol. To verify this, the hydrogenation of hydrocinnamaldehyde was carried out under identical reaction conditions (hydrocinnamaldehyde 18.8 mmol, 10% Pd/C catalyst 0.01 g (including Pd 0.0094 mmol), H_2 4.0 MPa, CO_2 8.0 MPa, temperature 323 K, reaction

Table 2 Results for cinnamaldehyde hydrogenation under different reaction conditions in CO_2 with 10% Pd/C catalyst

Pressure (MPa)		Time/ min	Conversion (%)	Selectivity (%)		
H_2	CO_2			HCAL	HCOL	COL
1.0	8.0	60	46	89	11	0
2.0	8.0	60	79	88	12	0
4.0	8.0	60	100	87	13	0
6.0	8.0	60	100	87	13	0
4.0	0	40	54	87	13	0
4.0	7.0	40	72	88	12	0
4.0	8.0	40	74	88	12	0
4.0	14.0	40	83	88	12	0
4.0	8.0	20	46	88	12	0
4.0	8.0	40	74	88	12	0
4.0	8.0	60	100	87	13	0
4.0	8.0	180	100	87	13	0

Reaction conditions: cinnamaldehyde 2.5 g (18.8 mmol), 10% Pd/C catalyst 0.01 g (including Pd 0.0094 mmol), temperature 323 K, HCAL hydrocinnamaldehyde, HCOL hydrocinnamyl alcohol, COL cinnamyl alcohol.

time 1 hour) but no detectable amount of hydrocinnamyl alcohol was found. This indicates that all the hydrocinnamyl alcohol obtained in the reduction of cinnamaldehyde is completely produced through the formation of cinnamyl alcohol as an initial step in this reaction. This result is in contrast to previous studies of cinnamaldehyde hydrogenation with Pt/SiO_2 catalyst in ethanol,[15] in which the hydrocinnamyl alcohol was confirmed to be produced from the hydrogenation of hydrocinnamaldehyde first and then from cinnamyl alcohol after the former was consumed completely. However, Mahmoud *et al.*[17] reported that the reaction rate of the reduction of cinnamyl alcohol to hydrocinnamyl alcohol is about 30 times higher than that of the hydrogenation of cinnamaldehyde to cinnamyl alcohol with Pd/SiO_2 in toluene, and no cinnamyl alcohol can be detected in the products. This may also be the case for the present hydrogenation in $scCO_2$. Thus, we can assume different adsorption modes of CAL on the surface of Pt and Pd particles. The strength of adsorption is CAL > HCAL > COL on Pt, while the order is CAL > COL > HCAL on Pd.

The effect of additives on the reaction rate and selectivity has also been examined in the present work. An additive such as potassium acetate was reported to significantly enhance the formation of hydrocinnamaldehyde in the hydrogenation of cinnamaldehyde with Pd/C catalyst in propanol.[6] In contrast, the addition of potassium acetate and potassium carbonate not only decreases hydrocinnamaldehyde formation but also lowers the reaction rate significantly in $scCO_2$ as shown in Table 3. The results obtained indicate that the reaction medium plays a very important role in α,β-unsaturated aldehyde hydrogenation.

Table 3 Effects of additives on the hydrogenation of cinnamaldehyde in $scCO_2$ at 323 K

Additive	Conversion (%)	Selectivity (%) HCAL	HCOL	COL
KOAC	17	77	23	0
K_2CO_3	37	80	20	0
—	74	88	12	0

Reaction conditions: 10% Pd/C catalyst 0.01 g, cinnamaldehyde 2.5 g, H_2 4.0 MPa, CO_2 8.0 MPa, reaction time 40 min, KOAC, K_2CO_3 0.1 mmol, HCAL hydrocinnamaldehyde, HCOL hydrocinnamyl alcohol, COL cinnamyl alcohol.

Catalyst recycling has been examined in $scCO_2$. 10% Pd/C catalyst (0.01 g) was used several times under the following conditions: cinnamaldehyde 1.0 g, H_2 4.0 MPa, CO_2 8.0 MPa, temperature 323 K, reaction time 60 min. After the catalyst was used three times, it still showed the same activity and selectivity, as shown in Table 4. From TEM observation we did not find any difference in the state of the Pd particles between fresh and recycled catalysts.

Table 4 Results of Pd/C catalyst recycling in the hydrogenation of cinnamaldehyde in $scCO_2$ at 323 K

Run	Conversion (%)	Selectivity (%) HCAL	HCOL	COL
1	100	85	15	0
2	95	86	14	0
3	96	87	13	0

Reaction conditions: 10% Pd/C catalyst 0.01 g, cinnamaldehyde 1.0 g, H_2 4.0 MPa, CO_2 8.0 MPa, temperature 323 K, reaction time 60 min, HCAL hydrocinnamaldehyde, HCOL hydrocinnamyl alcohol, COL cinnamyl alcohol.

Conclusions

Palladium supported on carbon catalyst (Pd/C) is a very effective, selective and recyclable catalyst for the hydrogenation of α,β-unsaturated aldehydes in $scCO_2$. The reaction rate increases with increasing H_2 and CO_2 pressures, but the selectivity does not change with the reaction conditions. Higher selectivity to saturated aldehydes can be achieved in $scCO_2$ and under solventless conditions, compared with that in 1-propanol. Enhanced TOF values of 3.1 and 11.6 s^{-1} were obtained for cinnamaldehyde and crotonaldehyde, respectively, at 100% conversion in $scCO_2$. The separation of product, catalyst and solvent is very easy *via* simple phase separation and the catalyst can be reused for several times without loss in the activity and selectivity.

Experimental

A commercial 10% Pd on activated carbon (Pd/C) catalyst was purchased from Wako Pure Chem. Ind. The Pd/C catalyst was reduced by flowing H_2 at 473 K for 3 h and then stored in a desiccator before reaction. The total surface area (893 $m^2\ g^{-1}$) was determined by the BET nitrogen adsorption method and the degree of palladium dispersion (0.18) was measured by hydrogen adsorption at room temperature. The size of palladium metal particles (~5–10 nm) was measured on a JEM-2000EX electron microscope operated in the black field mode.

Hydrogenation reactions were carried out in a 50 ml high-pressure stainless steel reactor. Reactants and a set amount of catalyst were charged into the reactor, and the reactor was then sealed, flushed with 2.0 MPa carbon dioxide three times and heated to 323 K. After the introduction of hydrogen, liquid carbon dioxide was introduced into the reactor with a high-pressure liquid pump to the desired pressure. The reaction was conducted by stirring the mixture for a desired time. It was then cooled with an ice-water bath for about 10 min, carbon dioxide and hydrogen were then carefully vented, and the liquid reaction mixture was separated from the catalyst by filtration. The reaction mixture was analyzed with a gas chromatograph (HP 6890, HP 5 capillary column: 15 m, 0.32 mm, 0.2 μm) with flame ionization detector. We define the selectivity towards reaction products and the turnover frequency (TOF) as

$$\text{Selectivity } i = \frac{\text{moles of a certain product } i}{\text{total moles of all products}} \times 100\%$$

$$\text{Average TOF} = \frac{\text{moles of substrate reacted}}{\text{(moles of exposed surface Pd atoms) (time)}}$$

where *i* is saturated aldehyde, unsaturated alcohol, or saturated alcohol.

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Direct formation of 2,4-disubstituted tetrahydropyranols in water mediated by an acidic solid resin

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Received 24th October 2002
First published as an Advance Article on the web 20th December 2002

Amberlite® IR-120 Plus resin, a readily regenerated acidic solid resin, mediates the formation of tetrahydropyranol derivatives in water. Various aldehydes were reacted with homoallyl alcohol under the reaction conditions to yield the desired tetrahydropyranol derivatives in moderate to good yields.

Tetrahydropyrans are a prevalent subunit encountered in many natural products such as carbohydrates, polyether antibiotics and marine toxins.[1] The Prins cyclization,[2] which entails the formation of a C–C bond, is an important method in the formation of tetrahydropyran derivatives. Initially discovered in 1899, it consisted of the condensation of olefins with aldehydes under strongly acidic conditions and high reaction temperatures which limited its potential as an effectual synthetic methodology. Currently there has been an actualization of the potentiality in the utilization of the Prins cyclization for the formation of tetrahydropyran derivatives in a stereocontrolled manner.[3] However, in keeping with our interest in green chemistry[4] methodology, we were interested in exploring the possibility of running the reaction in water at a lower temperature while utilizing a commercially available solid acid[5] source which could be easily filtered from the reaction media.

Previously, we reported our investigation[6] into the efficacy of the Prins cyclization utilizing $InCl_3$, which is a mild Lewis acid, relative to the stronger Lewis acid catalysts (*e.g.* $TiCl_4$, $SnCl_4$) previously developed. However, the usage of a Lewis acid with a nucleophilic anion resulted in the formation of 4-halotetrahydropyran derivatives (Taddei–Chan method),[7] which is not as synthetically useful as 4-tetrahydropyranol derivatives. Recently, we have found that the usage of a catalytic amount of scandium triflate,[8] a Lewis acid with a non-nucleophilic anion, allowed for the formation of oxygenated tetrahydropyran derivatives in refluxing chloroform.[9]

However, one of the primary and fundamental objectives in our methodology development, has always been to incorporate effective methodology with the principles of green chemistry. The direct formation of the desired and synthetically valuable derivative is in accordance with our green chemistry objective in two ways: (1) usage of an environmentally benign solvent and (2) elimination of an additional step required to convert from the halogenated to the oxygenated derivative. To this end, we recently reported the direct formation of tetrahydropyranol derivatives using ionic liquid as the reaction media in the presence of a catalytic amount of Lewis acid.[10]

Herein, we wish to report the direct formation of tetrahydropyranol derivatives in water using the Amberlite® IR-120 Plus resin—an acidic resin with a sulfonic acid moiety. A mixture of an aldehyde and homoallyl alcohol in water, in the presence of the resin and under sonication, yielded the desired tetrahydropyranol derivatives (Fig. 1).† However, without sonication, the reaction does not proceed.[11] This is the first example we are aware of that allows for the direct selective formation of tetrahydropyranol derivatives in water. The merits of this methodology are threefold: (1) the resin can be easily removed from the reaction mixture by filtration and reused;[12] (2) water, the solvent of choice, is relatively economical and most environmentally friendly; and (3) the overall reaction is a cross-molecular isomerization that is atom-economical.[13]

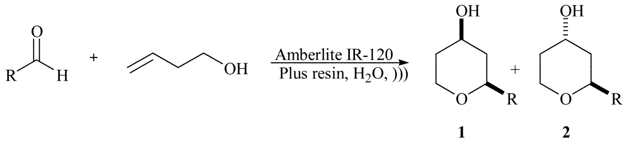


Fig. 1 Formation of tetrahydropyranol derivatives.

As shown in Table 1, the overall yields of the various aldehydes are good. Due to a solubility factor, when the aldehyde used is a solid (*i.e.*, entries 3, 6, 7, 8, 9), the conversion rates[14] are lower relative to the liquid aldehydes (*i.e.*, entries 1, 2, 4, 5, 10, 11).

A tentative mechanism for the direct tetrahydropyranol formation is shown in Scheme 1. Initially, the acidic resin activates the aldehyde *via* protonation, followed by a nucleophilic attack of the activated carbonyl by the homoallyl alcohol to generate the hemiacetal. A Prins-type cyclization accompanied by the quenching of the resultant carbocation by water furnishes the desired tetrahydropyranol. The surface of the resin may provide an environment that prevents competing by-product formation. Selective formation of the *cis* isomer is mostly due to thermodynamic control.

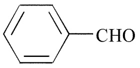
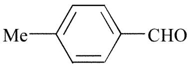
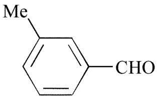
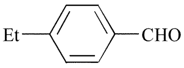
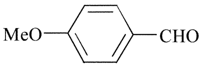
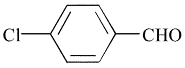
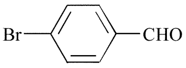
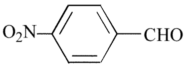
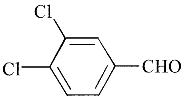
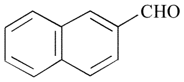
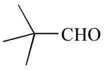
In summary, we have developed a method for the direct formation of synthetically useful tetrahydropyranol derivatives in water. We believe that there are many additional applications of this resin and further investigation into its utilization will result in its expanded and increased usage as an alternative acid source in aqueous media.

Green Context

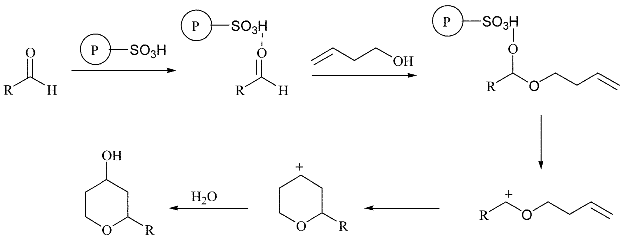
Achieving the cleaner synthesis of organic compounds can be done in several ways including VOC solvent avoidance, the use of heterogeneous catalysts and atom economical reactions. By combining these greener methods we can move towards the 'ideal synthesis' whereby auxiliaries, energy, resources and waste are minimised. Here we see a nice example of a cleaner synthesis involving multiple improvements. Thus an atom economical synthesis of tetrahydropyranols is carried out in water, using a recoverable heterogeneous catalyst. ***JHC***

DOI: 10.1039/b210486e

Table 1 Tetrahydropyranol derivatives *via* acidic resin mediated cyclization

Entry	Aldehyde	Conversion^a (%)	Yield (%)		
			cis-**1**^{b}	*trans*-**2**^{b}	Overall
1		94	87	< 2	87
2		90	72	4	76
3		67	59	4	63
4		92	79	5	84
5		64	50	10	60
6		67	58	7	65
7		80	62	4	66
8		79	67	3	70
9		67	57	4	61
10		88	61	4	65
11		94	54	< 2	54

^{a} ^{1}H NMR conversion. ^{b} Isolated yield.



Scheme 1

This work was supported by the NSF CAREER Award, NSF-EPA Joint Program for a Sustainable Enviroment, and a Louisiana Board of Regents Graduate Fellowship (C. C. K. K.).

Notes and references

† *General procedure* for the reaction: to a solution of resin (3 g) in 2.5 mL H_2O, was added benzaldehyde (147 mg, 1.39 mmol) and the reaction mixture allowed to sonicate (commercial Branson sonicator, 100 W) at room temperature for 20 min. The homoallyl alcohol (50 mg, 0.693 mmol) was then added and the reaction was monitored by TLC. Upon completion (2 days), the resin was filtered off, washed with water (5 mL) and the aqueous layer was extracted with diethyl ether (5 mL × 5). The crude mixture was concentrated *in vacuo* and purified using column chromatography on silica gel with eluent (2:1 hexanes–ethyl acetate) to yield the major product (97 mg, 87%).

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11 The energy usage of sonication was not calculated.
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14 During our optimization of the reaction, we found that longer reaction times did not result in a higher conversion.

A novel and simple method for the silylation of alcohols in DMSO–hexane without a catalyst

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Received 27th September 2002
First published as an Advance Article on the web 16th January 2003

Reaction of alcohols with *tert*-butyldimethylsilyl chloride in DMSO–hexane provides the corresponding *tert*-butyldimethylsilyl ethers in high yields under mild reaction conditions. This convenient reaction proceeds very smoothly at room temperature without a catalyst. Additionally, alcohols having an allylic alcohol, cyclopropane, and tetrahydrofuran moiety underwent chemoselective silylation to give the TBS ethers in good yields with no undesired reactions.

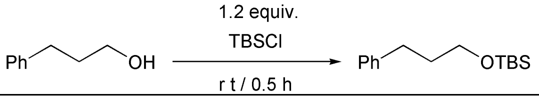
Introduction

Silyl ethers are a most popular and promising protecting group of hydroxy functions in synthetic organic chemistry, and various types of silyl ethers have been developed so far.[1] Silyl ethers are very easy to introduce and to remove, and have general stability for most non-acidic reagents and high solubility in non-polar solvents. Silyl ethers are commonly obtained by the reaction of the parent alcohols with the corresponding trialkylsilyl halide in the presence of stoichiometric amounts of a base, such as imidazole,[2] 4-dimethylaminopyridine,[3] *N*,*N*-diisopropylethylamine,[4] and so on.[5] However, these base-catalyzed silylation methods have a serious disadvantage, since careful extraction and filtration processes are required to remove annoying ammonium salts.[6] Very recently, we have reported novel catalyst-less reactions: direct conversion of alcohol tetrahydropyranyl ethers or alcohol triphenylmethyl ethers into the corresponding acetates by the reaction with acetyl bromide.[7] These transformations have some outstanding green-chemical features. From the viewpoint of green chemistry, a catalyst-less reaction is very significant and attractive in synthetic organic chemistry. However, efficient silylation of alcohols without a catalyst has been scarcely reported.

On the other hand, it has been recently reported that spontaneous aldol and Michael reactions of enoxytrimethylsilanes proceed smoothly in dipolar aprotic solvents, such as dimethyl sulfoxide (DMSO).[8] This reaction presumably proceeds *via* an activation of the enoxysilane by coordination of the DMSO oxygen atom to the silicon atom. Therefore, we envisioned that if a trialkylsilyl chloride was activated by DMSO, reaction of alcohols with the trialkylsilyl chloride would take place in DMSO to yield the corresponding trialkylsilyl ethers in high yields. In this communication, we report a simple and efficient method for the silylation of alcohols with trialkylsilyl chloride in DMSO with no catalyst.

Results and discussion

Table 1 The effect of solvents



Run	Solvent	Yield[a] (%)
1	DMF	37
2	DMSO	75
3	CH_2Cl_2	15
4	THF	15
5	Hexane	20
6	AcOEt	14
7	MeCN	6

[a] Isolated yields of purified product.

To begin with, we examined the solvent effects for the silylation of 3-phenyl-1-propanol (Table 1). The reaction of 3-phenyl-1-propanol with 1.2 equiv. of *tert*-butyldimethylsilyl chloride in *N*,*N*-dimethylformamide (DMF) for 0.5 h afforded the corresponding *tert*-butyldimethylsilyl (TBS) ether in 37% yield (run 1). On the other hand, when the reaction was carried out in DMSO, the reaction took place very smoothly and the corresponding TBS ether was obtained in 75% isolated yield (run 2). In the case of using other solvents such as CH_2Cl_2, THF, hexane, AcOEt, and MeCN, the corresponding TBS ethers were obtained in lower yields (runs 3–7). From these results, it could be presumed that DMSO strongly activated the silicon atom of trialkylsilyl chloride.

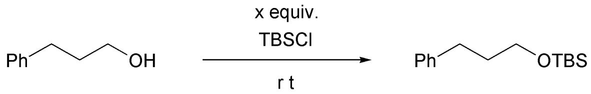
Next, we investigated the equiv. of the reagent and the loading of DMSO (Table 2). On increasing the equiv. of *tert*-butyldimethylsilyl chloride, the yields of TBS ethers were greatly improved (runs 1–3). However, treatment of alcohol with 2 equiv. of silyl chloride during 18 h gave the TBS ether in lower yield (run 4). This is owing to deprotection of the produced silyl ether with *in situ*-generated HCl. Therefore, to

Green Context

Silyl ethers are a very popular class of compounds in organic chemistry largely due to the versatility of the function as a protecting group. They are normally prepared by the reaction of an alcohol with a trialkylsilyl halide using at least a stoichiometric quantity of base. The desired product is then accompanied by a salt, which has to be separated. Thus the standard procedure employs an auxiliary, involves a separation stage and produces a waste product. In this paper this conventional thinking is challenged—do we need a base? By screening various solvents the authors find that reaction will occur without base and that with DMSO hexane in particular, quantitative formation of the silyl ether could be achieved. ***JHC***

DOI: 10.1039/b209506h

Table 2 The effect of reaction conditions



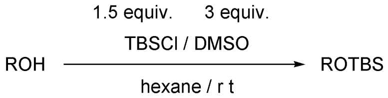
Run	Solvent	*x*/equiv.	Time/h	Yield[a] (%)
1	DMSO	1.2	0.5	75
2	DMSO	1.5	0.5	86
3	DMSO	2.0	0.5	90
4	DMSO	2.0	18	69
5[b]	Hexane	1.5	1	94
6[b]	Hexane	1.5	18	93

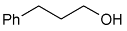
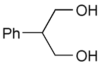
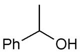
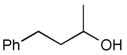
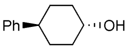
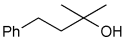
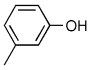
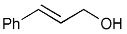
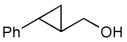
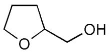
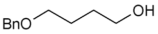
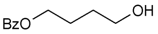
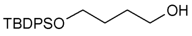
[a] Isolated yields of purified product. [b] 3 equiv. of DMSO were added (DMSO–hexane = 1 : 8).

prevent the deprotection, the reaction was performed with 3 equiv. of DMSO in hexane. After completion of the reaction, the corresponding TBS ether was obtained in 94% yield (run 5). In spite of the extension of reaction time for 18 h, no deprotection of once formed TBS ether was observed under the reaction conditions (run 6).

Representative and successful examples for the synthesis of various alcohol TBS ethers are collected in Table 3. As well as primary alcohols, secondary alcohols were readily transformed into the corresponding TBS ethers in high yields (runs 3–5). In the case of tertiary alcohol and phenol, the yields of TBS ethers were rather lower (runs 6 and 7).

Table 3 Silylation of various alcohols with TBSCl

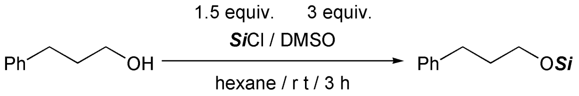


Run	ROH	Time/h	Yield[a] (%)
1		3	94
2[b]		3	79
3		5	90
4		5	93
5		5	93
6		24	13
7		24	23
8		7	76
9		3	89
10		3	80
11		3	91
12		3	89
13		3	89

[a] Isolated yields of purified product. [b] 3 equiv. of TBSCl and 6 equiv. of DMSO were used.

Additionally, alcohols having an allylic alcohol, cyclopropane, and tetrahydrofuran moiety underwent chemoselective silylation to give the TBS ethers in good yields with no undesired reactions (runs 8–10). In the presence of other protecting groups of the hydroxy function, silylation of alcohols also proceeded chemoselectively with these protecting groups unaffected (runs 11–13).

Table 4 Silylation of alcohol with various trialkylsilyl chlorides



Run	*Si*	Yield[a] (%)
1	*tert*-BuMe$_2$Si	95
2	*tert*-BuPh$_2$Si	90
3	Ph$_3$Si	87
4	*i*-Pr$_3$Si	23

[a] Isolated yields of purified product.

Finally, in order to establish the generality of the benign reaction, we attempted the silylation of 3-phenyl-1-propanol with various trialkylsilyl chlorides (Table 4). By using *tert*-butyldiphenylsilyl or triphenylsilyl chloride, which are a sterically hindered silyl moiety, the corresponding *tert*-butyldiphenylsilyl (TBDPS) or triphenylsilyl (TPS) ethers were similarly formed in high yields (runs 2 and 3). In contrast, the reaction of alcohol with triisopropylsilyl chloride gave the corresponding triisopropylsilyl (TIPS) ether in only 23% yield (run 4).

In conclusion, we have accomplished a new method for the synthesis of silyl ethers from alcohols in DMSO–hexane. This reaction proceeds very smoothly at room temperature and the desired silylated products were obtained in high yields under mild reaction conditions. By this method, neither a base nor an acid catalyst is necessary to complete the reaction. Therefore, this catalyst-less method is broadly applicable to the silylation of alcohols having base- or acid- sensitive functional groups. In addition to its significance as a green-chemical method, this method serves also potential utility in the syntheses of complex natural products. Further research addressing the scope and elucidation of the reaction mechanism is under way in our laboratory.

Experimental

Typical procedure for the silylation of alcohol in DMSO–hexane

To a solution of 3-phenyl-1-propanol (40.9 mg, 0.3 mmol) in hexane (0.5 ml) was added dimethyl sulfoxide (64 μl, 0.9 mmol) and *tert*-butyldimethylsilyl chloride (67.8 mg, 0.45 mmol) at room temperature under an argon atmosphere. The resultant mixture was stirred for 3 h at room temperature and quenched with water. The organic materials were extracted with Et$_2$O and dried over anhydrous magnesium sulfate. The solvent was evaporated and *tert*-butyldimethyl(3-phenylpropoxy)silane (70.7 mg, 94%) was isolated by thin-layer chromatography on silica gel (ether : hexane = 1 : 20). The product gave satisfactory NMR and IR spectra.

Spectroscopic data

***tert*-Butyldimethyl(3-phenylpropoxy)silane**. IR (neat, cm^{-1}) 2930, 2850, 1460, 1250, 1100, 830, 770, 690; δ_H (400 MHz, CDCl$_3$) 7.29–7.27 (m, 2H), 7.20–7.15 (m, 3H), 3.63 (t, *J* 6.2 Hz, 2H), 2.67 (t, *J* 7.8 Hz, 2H), 1.87–1.80 (m, 2H), 0.91 (s, 9H), 0.05 (s, 6H); δ_C (75 MHz, CDCl$_3$) 142.29, 128.45, 128.26, 125.65, 62.37, 34.45, 32.10, 25.95, 18.32, −5.28.

1,3-Bis(*tert*-butyldimethylsilyloxy)-2-phenylpropane. IR (neat, cm^{-1}) 2930, 2858, 1468, 1254, 1107, 1022, 838, 776, 698; δ_H (400 MHz, CDCl$_3$) 7.29–7.27 (m, 5H), 3.92–3.88 (dd, *J* 6.4, 9.7 Hz, 2H), 3.84-3.80 (dd, *J* 5.5, 9.9 Hz, 2H), 2.90–2.84 (m, 1H), 0.87 (s, 18H), −0.03 (s,12H); δ_C (75 MHz, $CDCl_3$) 141.4, 128.5, 127.9, 126.3, 63.7, 50.6, 26.0, 18.4, −5.4.

***tert*-Butyldimethyl(3-phenylallyloxy)silane**. IR (neat, cm^{-1}) 2931, 2860, 1472, 1252, 1127, 1080, 964, 776, 698; δ_H (400 MHz, $CDCl_3$) 7.40–7.37 (m, 2H), 7.32–7.27 (m, 2H), 7.24–7.20 (m, 1H), 6.59 (d, *J* 15.6 Hz, 1H), 6.31–6.24 (m, 1H), 4.35 (d, *J* 6.8 Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H); δ_C (75 MHz, $CDCl_3$) 137.3, 129.5, 129.2, 128.5, 127.3, 126.4, 63.9, 26.0,18.5, −5.1.

***tert*-Butyl(1,1-dimethyl-3-phenylpropoxy)dimethylsilane**. IR (neat, cm^{-1}) 2955, 2856, 2363, 1363, 1253, 1210, 1045, 835, 772, 698; δ_H (400 MHz, $CDCl_3$) 7.29–7.25 (m, 2H), 7.19–7.14 (m, 3H), 2.72–2.67 (m, 2H), 1.74–1.70 (m, 2H), 1.26 (s, 6H), 0.89 (s, 9H), 0.10 (s, 6H); δ_C (75 MHz, $CDCl_3$) 143.4, 128.4, 128.3, 125.5, 73.3, 47.2, 30.8, 29.8, 25.9, 18.2, −2.0.

***tert*-Butyldimethyl-*m*-tolyloxysilane**. IR (neat, cm^{-1}) 2930, 2850, 1604, 1488, 1281, 1160, 957, 841, 781; δ_H (400 MHz, $CDCl_3$) 7.13–7.08 (m, 1H), 6.80–6.76 (m, 1H), 6.65–6.35 (m, 2H), 2.30 (s, 3H), 0.98 (s, 9H) 0.18 (s, 6H); δ_C (75 MHz, $CDCl_3$) 155.6, 139.4, 129.0, 122.1, 120.9, 117.0, 25.7, 21.4, 18.2, −4.4.

***tert*-Butyldimethyl(2-phenylcyclopropylmethoxy)silane**. IR (neat, cm^{-1}) 2954, 2857, 1604, 1466, 1254, 1097, 838, 776, 695; δ_H (400 MHz, $CDCl_3$) 7.26–7.22 (m, 2H), 7.15–7.11 (m,1H), 7.07–7.05 (m, 2H), 3.74–3.70 (dd, *J* 5.7, 10.8 Hz, 1H), 3.63–3.59 (dd *J* 6.0, 10.8 Hz, 1H), 1.82-1.78 (m, 1H), 1.38–1.33 (m, 1H), 0.96–0.91 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); δ_C (75 MHz, $CDCl_3$) 143.0, 127.3, 125.1, 65.8, 25.4, 21.6, 20.0, 13.7, −4.5.

Acknowledgements

T. W. thanks the Sasakawa Scientific Research Grant from The Japan Science Society for generous financial support.

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Heptadecafluorooctanesulfonic acid catalyzed ring opening reactions of methylenecyclopropanes with aromatic amines, sulfonamides and alcohols in supercritical carbon dioxide

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Received 7th November 2002
First published as an Advance Article on the web 13th January 2003

The ring opening reactions of methylenecyclopropanes (MCPs) with $ArNH_2$, RSO_2NH_2 and alcohols can be carried out in $scCO_2$ in the presence of heptadecafluorooctanesulfonic acid which offer a way to synthesize homoallylic amines, sulfonamides and ethers in environmentally benign conditions.

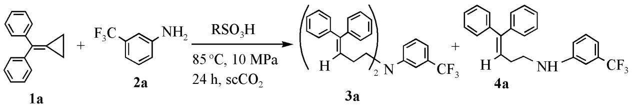
Introduction

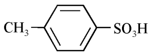
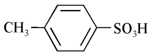
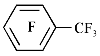
Chemistry has made a great contribution to the development of human society. The pollution and waste from chemical industries and laboratories, however, have deteriorated our environment. In order to achieve mutual societal, economic and environmental benefits, scientists have developed 'green chemistry' which is providing challenges and opportunities to those who practice chemistry in industry, education and research.[1–5] Presently the area of employing 'novel' solvent alternatives is receiving increasing attention. Among suitable alternatives such as ionic liquids,[6] perfluorinated hydrocarbons[7]and water,[8] supercritical carbon dioxide has been widely investigated and has been most attractive in green chemistry. Several of the advantages include that CO_2 is inexpensive, nonflammable, environmentally benign and readily separated from products.[9–11] Above the critical temperature and pressure, (T_c = 31 °C, P_c = 7.4 MPa) CO_2 has a gas-like viscosity and a liquid-like density. These moderate critical conditions allow for safe commercial and laboratory operating conditions. For example, in 1994 Noyori and coworkers,[12] reported one of the first synthetically useful homogeneous catalytic hydrogenetions catalyzed by an Ru(II) catalyst involving $scCO_2$ as both solvent and substrate. Tanko and coworkers,[10,11]Wells and DeSimone,[12] Jessop *et al.*,[13] and Beckman and coworkers[14] reported radical reactions in $scCO_2$. In addition, many applications such as oxidation,[15] hydroformylation,[16] Diels–Alder cycloaddition,[17] Mukaiyama aldol condensation[18] and various metal-catalyzed[19] reactions have been carried out in the presence of $scCO_2$.

Recently, we have reported that metal Lewis acid such as $Sn(OTf)_2$ or $Yb(OTf)_3$ catalyzed reactions of MCPs with $ArNH_2$ and alcohols in 1,2-dichloroethane (DCE).[20] However, is well known that halogenated solvents are environmentally hazardous materials. In addition, many metal catalysts are also pollution sources for the environment. In order to explore an environmentally benign condition for this process, we attempted to carry out this reaction in $scCO_2$ in the absence of metal catalyst. Herein, we wish to report the ring opening reactions of MCPs with aromatic amines, sulfonamides or alcohols catalyzed by the Brønsted acid R_fSO_3H in $scCO_2$ under mild conditions.

First of all, we chose various RSO_3H as Brønsted acid catalysts (10 mol%) to promote the reaction of diphenylmethylenecyclopropane **1a** (0.45 mmol) with 3-(trifluoromethyl)aniline **2a** (0.15 mmol) at 85 °C and 10 MPa in $scCO_2$. The results are listed in Table 1 (entry 1). The reaction proceeded smoothly to give two adducts: dialkylated product **3a** (39%) and monoalkylated **4a** (11%) in moderate yields in the presence of CF_3SO_3H (Table 1, entry 1). Using $C_8F_{17}SO_3H$ as the catalyst under the same conditions the two adducts were obtained in very high yields (Table 1, entry 2).[21] It should be noted that no reaction occurred when using *p*-toluenesulfonic acid as the

Table 1 The effects of various RSO_3H on the reactions of MCP **1a** with **2a** in $scCO_2$



			Yield[a] (%)	
Entry	RSO_2H	Additive	**3a**	**4a**
1	CF_3SO_3H	—	39	11
2	$C_8F_{17}SO_3H$	—	52	47
3		—	—	—
4			—	—

[a] Isolated yields.

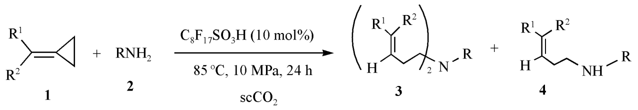
Green Context

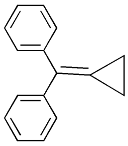
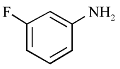
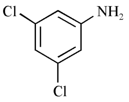
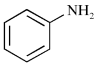
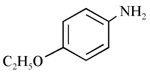
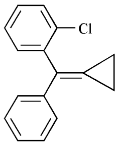
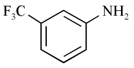
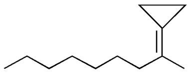
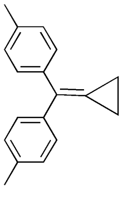
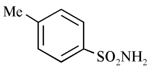
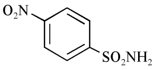
Supercritical carbon dixide is now widely recognised as an environmentally benign solvent for chemical transformations and has now been proven in this context on an industrial scale. Many organic reactions require catalysis to enable the reaction to be carried out under moderate conditions or to give good product selectivity. Here a new catalyst–$scCO_2$ combination is described. Perfluorooctylsulfonic acid in $scCO_2$ is shown to be a good catalyst for the ring opening reactions of methyl cyclopropanes with various nucleophites. ***JHC***

Brønsted acid catalyst even with the addition of perfluorotoluene as a CO_2-philic additive (Table 1, entries 3 and 4). A long chain perfluorinated sulfonic acid should be used as a promoter for this novel ring opening reaction. This is because a long perfluorinated alkyl chain can allow the $scCO_2$ reaction system to become an effective homogenous phase. Viewing through the high pressure glass window placed in the $scCO_2$ reaction vessel, we confirmed that the $C_8F_{17}SO_3H$, **1a**, and aniline are completely dissolved in $scCO_2$ to form a homogeneous system.

Further investigations were performed using various MCPs and $ArNH_2$ or RSO_2NH_2 to examine this reaction (Table 2). We chose different MCPs and RNH_2 or RSO_2NH_2 as substrates. As can be seen from Table 2, many of the reactions take place to give two adducts **3** and **4** in moderate to high yields catalyzed by $C_8F_{17}SO_3H$ (10 mol%) in $scCO_2$. The ring opened products are obtained in higher yields when using aromatic amines which bear an electron-withdrawing group on the benzene ring.[20] For example, the reaction of **1a** with **2b** or **2c** affords the corresponding adducts in high yields, respectively (Table 2, entries 1 and 2). For aniline **2d** and aromatic amine **2e** having an electron-donating group, the reactions also proceeded smoothly to give the two products in good yields (Table 2, entries 3 and 4). For MCP **1b** having an electron-withdrawing group on the benzene ring and aliphatic MCP **1c**, the reactions can take place as well. However, the ring opened products were obtained in lower yields (Table 2, entries 5 and 6). On the other hand, the yields can be improved dramatically using MCP **1d** having an electron-donating group on the phenyl ring instead of aliphatic MCP **1c** (Table 2, entry 7). Apart from aromatic amines, the reaction of **1a** with various sulfonamides also can proceed smoothly to give **3** and **4** in the presence of $C_8F_{17}SO_3H$ (10 mol%) in $scCO_2$. For example, the reactions of **1a** with **2f** and **2g** give the two corresponding adducts **3i** or **3j** and **4i** or **4j** in high yields, respectively (Table 2, entries 8 and 9). However, using *p*-nitrobenzenesulfonamide **2h** as a substrate to react with **1a** under the same conditions led to no reaction owing to the insolubility of *p*-nitrobenzenesulfonamide **2h** in $scCO_2$. Based on these results, we can conclude that $C_8F_{17}SO_3H$ is an excellent Brønsted acid catalyst in $scCO_2$ and it is applicable to extensive ring opening reactions of MCPs with $ArNH_2$ or RSO_2NH_2.

Table 2 The reactions of MCPs with $ArNH_2$ or RSO_2NH_2 catalyzed by $C_8F_{17}SO_3H$ (10 mol%) in $scCO_2$

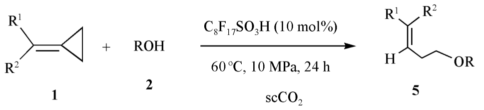


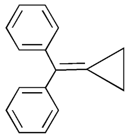
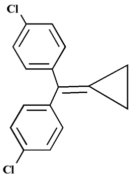
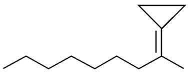
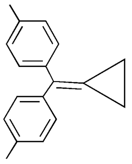
					Yield[a] (%)	
Entry	MCP		$ArNH_2$		3	4
1		1a		2b	**3b** (65)	**4b** (21)
2		1a		2c	**3c** (95)	
3		1a		2d	**3d** (42)	**4d** (18)
4		1a		2e	**3e** (37)	**4e** (20
5		1b		2a	**3f** (7)	**4f** (10)
6		1c		2a	**3f** (18)	**4g** (19)
7		1d		2a	**3b** (72)	**4g** (19)
8		1a		2f	**3i** (48)	**4i** (41)
9		1a	$CH_3SO_2NH_2$	1g	**3j** (30)	**4j** (42)
10		1a		2h	—	—

[a] Isolated yield.

The ring opening reaction of MCPs (0.5 mmol) with ethanol (200 µL, 3.4 mmol) was also carried out in scCO$_2$ in the presence of C$_8$H$_{17}$SO$_3$H (15 mg, 10 mol%) to give the ring opened product **5a** in very high yield (Table 3, entry 1). In general, it was found that the reactions proceed very well and the corresponding ring opened products **5** were obtained in excellent yields with complete conversions for various MCPs under the same conditions (Table 3). We believe that this is because the alcohols themselves can modify the physical properties of scCO$_2$ and subsequently enhance the solubilities of the reactants in scCO$_2$ and improve the reaction efficiency.

Table 3 The reactions of MCPs with alcohols catalyzed by C$_8$F$_{17}$SO$_3$H (10 mol%) in scCO$_2$



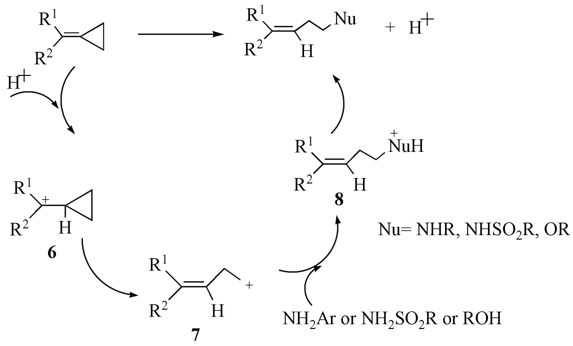
Entry	MCP		ROH	Conv.[a] (%) MCP	Yield[a] (%) 5
1		**1a**	EtOH	100	**5a** (95)
2		**1a**	^{i}PrOH	100	**5b** (93)
3		**1a**	^{i}BuOH	100	**5c** (92)
4		**1b**	EtOH	100	**5d** (97)
5		**1c**	EtOH	100	**5c** (97)
6		**1d**	EtOH	100	**5f** (98)

[a] Isolated yield.

It should be emphasized here that the CO$_2$-philic catalyst C$_8$F$_{17}$SO$_3$H can be recovered from the reaction mixture by extraction with toluene. The catalyst C$_8$F$_{17}$SO$_3$H is insoluble in toluene whereas the products are soluble in toluene. The extracts can be subjected to column chromatography and the catalyst residue can be reused for the next reaction as a catalyst.

A plausible mechanism for the ring-opening reactions of MCPs with ArNH$_2$, NH$_2$SO$_2$R and ROH is shown in Scheme 1. The MCPs first give cation **6** which immediately rearranges to the ring-opened cation **7**[21] in the presence of Brønsted acid C$_8$F$_{17}$SO$_3$H. The subsequent nucleophilic attack of RNH$_2$, NH$_2$SO$_2$R or ROH to **7** affords the adduct **8**. The final product is formed after proton elimination.

In conclusion, serious environmental problems necessitate our rethinking of strategies toward organic synthesis. The ideal reaction would incorporate all of the atoms of the reactions. Major benefits that derive from atom-economic processes include more effective use of limited raw materials and decreased emissions and waste disposal. In this article, we have disclosed an atom-economical reaction of MCPs applied to scCO$_2$ catalyzed by the Brønsted acid C$_8$F$_{17}$SO$_3$H.[22] This reaction offers an access to the formation of homoallylic amines, sulfonamides and ethers in environmentally benign conditions. By comparison of the reaction procedure in scCO$_2$ reported in this paper with those reported in previous papers,[20a] it is very clear that when the reaction is carried out in scCO$_2$ by means of a CO$_2$-philic catalyst C$_8$F$_{17}$SO$_3$H, the use of the hazardous solvent 1,2-dichloroethane can be avoided and the very similar yields can be achieved. Especially, for the reactions of MCPs with alcohols in scCO$_2$, the reactions proceed completely and no chromatography is required. We also hope that this type of reaction is conducive to the development of green chemistry as well as new organic syntheses.



Scheme 1

Experimental

Typical reaction procedure: **1a** (93 mg, 0.45 mmol), **2a** (24 mg, 0.15 mmol) and C$_8$F$_{17}$SO$_3$H (7.5 mg, 10 mol%)[22] were placed in the scCO$_2$ reactor. The reaction proceeded at 85 °C at 10 MPa for 24 h. The residue was purified by flash chromatography (SiO$_2$) using EtOAc–hexane (1:100) or CH$_2$Cl$_2$–hexane (1:8) as the eluent to yield **3a** (45 mg, 52%) as a colorless solid and **4a** (26 mg, 47%) as an oil.

3a: mp 118–120 °C, IR (neat): ν 3052, 3028, 2925, 1609, 1495, 1454, 1322 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, TMS), δ 2.30–2.38 (m, 4H, CH$_2$), 3.29 (t, 4H, J = 7.6 Hz, CH$_2$), 6.05 (t, 2H, J = 7.5 Hz, =CH), 6.40–6.43 (m, 1H, Ar), 6.69 (s, 1H, Ar), 6.81 (d, 1H, J = 8.0 Hz, Ar), 7.07–7.39 (m, 21H, Ar); MS (EI): m/z 573 (M$^+$, 0.3), 380 (54), 167 (100), 129 (61), 91 (53%); Anal. Calc. for C$_{39}$H$_{34}$F$_3$N (%): C, 81.68; H, 5.93; N, 2.44. Found: C, 81.72; H, 6.09; N, 2.41.

4a: IR (neat): ν 3421, 3054, 2986, 1614, 1495, 1449, 1421, 1265 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, TMS), δ 2.43–2.50 (m, 2H, CH$_2$), 3.24 (t, 2H, J = 6.8 Hz, CH$_2$), 3.81 (s, 1H, NH), 6.12 (t, 1H, J = 7.5 Hz, =CH), 6.64–6.67 (m, 1H, Ar), 6.74 (s, 1H, Ar), 6.90–6.92 (d, 1H, J = 7.5 Hz, Ar), 7.10–7.41 (m, 11H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$, TMS), δ 29.81, 43.89, 109.79, 111.49, 113.88, 123.75 (q, J = 271.4 Hz), 125.80, 127.27, 127.39, 127.45, 128.37, 128.58, 129.80, 129.94, 130.060 (q, J = 31.6 Hz), 139.87, 143.54, 145.98, 149.83; MS (EI): m/z 367 (M$^+$, 1.8), 174 (100), 145 (9), 91 (6), 77 (3%); HRMS (EI): Calc. for C$_{23}$H$_{20}$F$_3$N 367.1548 (M$^+$), Found: 367.1526.

The products **3i** and **4i** were isolated by column chromatography as colorless oily compounds (eluent: EtOAc–hexane (1:10)).

3i: IR (neat): ν 3055, 2986, 1653, 1598, 1494, 1266 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, TMS), δ 2.16–2.24 (m, 4H, CH$_2$), 2.35 (s, 3H, CH$_3$), 3.13 (t, 4H, J = 7.5 Hz, CH$_2$), 5.92 (t, 2H, J = 7.3 Hz, =CH), 7.03–7.59 (m, 24H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$, TMS), δ 21.78, 28.75, 47.38, 125.15, 127.18, 127.59, 128.36, 128.42, 128.58, 128.72, 129.87, 129.97, 137.38, 139.89, 142.33, 143.21, 144.18; MS (EI): m/z 583 (M$^+$, 2.0), 390 (47), 193 (17), 155 (8), 167 (100), 91 (41%); HRMS (EI): Calc. for C$_{24}$H$_{24}$NSO$_2$ 391.1606 (M$^+$ − C$_{15}$H$_{13}^+$) (M$^+$ = C$_{39}$H$_{57}$NSO$_2$). Found: 391.1570.

4i: IR (neat): ν 3283, 3056, 2928, 1638, 1598, 1494 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS), δ 2.24–2.31 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 3.02–3.08 (m, 2H, CH_2), 4.40 (t, 1H, J = 6.0 Hz, NH), 5.90 (t, 1H, J = 7.5 Hz, =CH), 7.08–7.71 (m, 14H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS), δ 21.79, 30.07, 43.29, 124.81, 127.25, 127.31, 127.32, 127.46, 127.52, 128.37, 128.62, 129.95, 137.02, 139.65, 142.21, 143.61, 144.82; MS (EI): m/z 193 ($M^+ - C_8H_{10}NSO_2$, 44.0), 184 (16), 155 (18), 91 (28), 84 (100%); HRMS (EI): Calc. for $C_{23}H_{23}NSO_2$ 377.1449 (M^+), Found: 377.1432.

The products **3j** and **4j** were isolated by column chromatography as colorless oily compounds (eluent: EtOAc–hexane (1 : 4)).

3j: IR (neat): ν 3038, 2928, 1654, 1599, 1494, 1445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS), δ 2.27–2.34 (m, 4H, CH_2), 2.69 (s, 3H, CH_3), 3.18 (t, 4H, J = 7.5 Hz, CH_2), 5.99 (t, 2H, J = 7.6 Hz, =CH), 7.11–7.39 (m, 20H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS), δ 28.97, 39.16, 47.05, 124.91, 127.44, 127.52, 127.55, 128.44, 128.61, 129.90, 139.81, 142.20, 144.42; MS (EI): m/z 507 (M^+, 1.3), 314 (6), 193 (24), 167 (38), 105 (100), 91 (21), 84 (86), 77 (61%); HRMS (EI): Calc. for $C_{33}H_{33}NSO_2$ 507.2232 (M^+), Found: 507.2214.

4j: IR (neat): ν 3291, 3028, 2939, 1653, 1599, 1494, 1444 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS), δ 2.35–2.42 (m, 2H, CH_2), 2.83 (s, 3H, CH_3), 3.17–3.24 (m, 2H, CH_2), 4.64 (t, 1H, J = 5.8 Hz, NH), 6.04 (t, 1H, J = 7.3 Hz, =CH), 7.14–7.41 (m, 10H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS), δ 30.65, 40.47, 43.34, 124.78, 127.50, 127.55, 127.62, 128.56, 128.67, 130.32, 139.74, 142.19, 145.0; MS (EI): m/z 301 (M^+, 13.9), 206 (57), 193 (100), 165 (17), 115 (56), 91 (19%); HRMS (EI): Calc. for $C_{17}H_{19}NSO_2$ 301.1136 (M^+), Found: 301.1143.

Acknowledgements

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China (20025206 and 20272069) for financial support.

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Solid base catalysts for the synthesis of phytosterol esters

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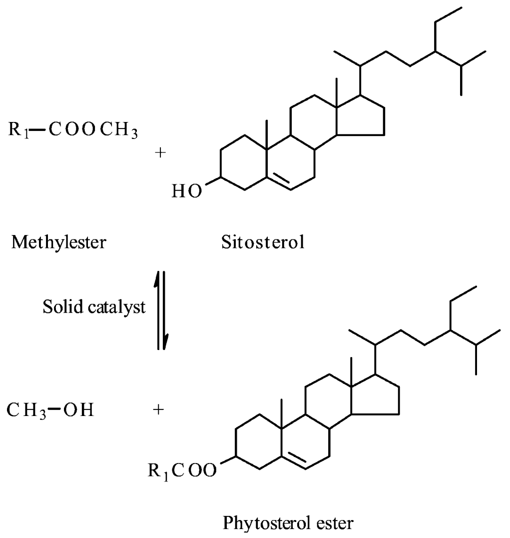
Received 24th September 2002
First published as an Advance Article on the web 20th January 2003

The main objective of this study is the synthesis of phytosterol esters from natural sterols and methyl esters in the presence of basic solid catalysts which are less corrosive and more selective than homogeneous catalysts such as alkaline hydroxides and carbonates. Phytosterol esters are effective in reducing both blood cholesterol levels and triglycerides and can be used as biological compounds in pharmaceutics and cosmetics. The highest yields of phytosterol esters are obtained in the presence of magnesium oxide or zinc oxide. However, magnesium oxide which is more basic basic favored the side reaction of sitosterol dehydration. The phytosterol ester yields can reach 80% and the formation of dienes is strongly inhibited when the reaction is carried out under a nitrogen flow.

Introduction

The aim of this work consists in the synthesis of phytosterol esters from sterols and fatty acids or fatty methyl esters in an esterification or transesterification reaction performed in the presence of solid catalysts (Scheme 1). In our laboratory, a general program on the selective transformation of fatty acids or esters and polyols originating from vegetable oils was performed to replace homogeneous catalysts by new solid catalysts which are more easily recycled and environmentally friendly.[1–4] Besides triglycerides, plant sterols (sitosterol, stigmasterol, campesterol,…) are present in the unsaponifiable fraction of vegetable oils. In food applications phytosterol esters are effective in reducing levels of both serum cholesterol and triglycerides. As the free sterols (unesterified) are poorly soluble in fats and oils, improvement of solubility for incorporation in foods could result from sterol esterification with fatty acids. On the other hand, phytosterol esters can be used in cosmetics as emulsifiers (significant solubility in water) or as anti-inflammatory and antioxidant compounds.[5,6]



Scheme 1 Synthesis of phytosterol esters.

Phytosterol esters can be prepared by esterification or transesterification reactions but the usual esterification reaction requires acid catalysts (H_2SO_4, H_3PO_4 or *p*-TSA) which may also favor the dehydration of sterols to stigmastadienes. Sodium alkoxides (NaOMe, NaOEt,…) are mainly used in transesterification reactions[7–9] as well as hydroxides (NaOH, KOH, $Ca(OH)_2$…)[10] or alkaline sulfates or carbonates.[11,12] Unfortunately, these bases are well known to favor the formation of soaps. Moreover, homogeneous catalysts are corrosive, difficult to separate from the products and lead to excessive waste.

The ability of oxide catalysts such as magnesium or zinc oxide to prepare phytosterol esters from fatty methyl esters and sitosterols without solvent[13] are investigated and presented in this paper.

Experimental

Catalytic test

The transesterification of β-sitosterol with methyl dodecanoate was chosen in this study as a model reaction. This reaction was carried out at atmospheric pressure under a nitrogen flow in a Pyrex reactor equipped with a mechanical stirrer. 0.07 mol of sterol (15 g) and 0.07 mol of methyl dodecanoate (29 g) were heated to 240 °C. Then 2 g of catalyst (5 wt%) was added to the mixture (starting time of the reaction). Samples of the reaction medium were analyzed with a GPC equipped with a FID detector and an on-column injector. The percentage of each compound was determined by using standardization methods with hexadecane as an internal standard. The conversion was

Green Context

Phytosterol esters are useful in food applications and in other areas such as cosmetics. Their synthesis is based on classic esterification methodology involving strong acids or transesterification methods based on strong bases. Here a greener chemical method based on solid reusable catalysts is described. Basic solid catalysts such as magnesium or zinc oxide are shown to be effective for the transesterification of β-sitosterol with methyl dodecanoate. Reuse characteristics of the solid catalysts are excellent. ***JHC***

estimated with respect to the initial and the final content of fatty methyl ester and free sterol in the solution.

Catalysts

The usual catalyst Na_2CO_3 was dried at 100 °C for 24 h before use. Zinc oxide and magnesium oxide were supplied by Union Minière and by Prolabo, respectively. The oxide catalysts were used after a pretreatment with nitrogen at 450 °C for 4 h.

Results and discussion

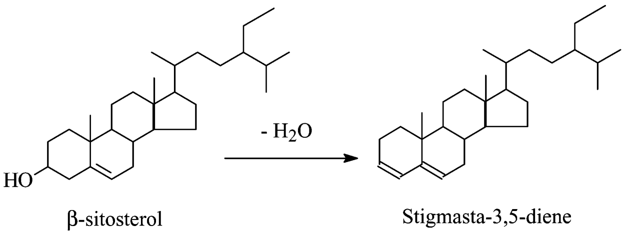
Transesterification of methyl dodecanoate with β-sitosterol in the presence of usual basic catalysts

First, the transesterification of the methyl dodecanoate with β-sitosterol was carried out in the presence of Na_2CO_3. Table 1 shows that the conversion of the sterol is three times higher than the conversion of methyl dodecanoate when the reaction is performed without catalyst but the yield of the phytosterol ester is low (12%). The main products of the reaction are the phytosterol ester and stigmasta-3,5-diene which is the side-product of the dehydration of the β-sitosterol (Scheme 2). Due to the high temperature and the free residual acidity, there is a competition between the transesterification reaction and the dehydration of the sterol since the selectivity to the phytosterol ester and diene are close to 50% (Fig. 1).

Table 1 Preparation of phytosterol ester from methyl dodecanoate and β-sitosterol in the presence of basic oxide catalysts

Catalyst	Conversion (%)		Selectivity (%)			Yield (%)	Activity/ mmol g^{-1} h^{-1}
	Ester	Sterol	Sterol ester	Diene	Other		
None	25	74	49	46	5	12	—
Na_2CO_3	69	62	92	4	4	63[a]	—
MgO	98	95.1	80	10	10	78	21
LiMgO	100	98	38	40	22	38	40
ZnO	82	97	93	3	4	76	9

Temperature = 240 °C, reaction time = 7 h, D_{N_2} = 5 L h^{-1}, ester/sterol ratio = 1, catalyst = 5 wt%.[a] Soap formation.



Scheme 2 Dehydration of β-sitosterol to stigmasta-3,5-diene.

When sodium hydroxide was used at 240 °C, the main reaction was the saponification of the methyl ester leading to the formation of soaps. However, with sodium carbonate, the side reaction of dehydration of β-sitosterol was lowered and the yield of the phytosterol ester increased from 12 to 63%. Similarly to NaOH, sodium carbonate totally solubilized in the reagents, and reacted with methyl dodecanoate with formation of soaps (30%).

Transesterification of methyl dodecanoate with β-sitosterol in the presence of basic oxide catalysts

In order to replace homogeneous catalysts with solid and more easily recycle catalysts, some basic solids were studied in the reaction of the sterol with methyl dodecanoate. As reported in Table 1, the activity of catalysts varied with the acido-basicity of the oxides. The most active oxide was magnesium oxide whereas zinc oxide was less active. The strong basicity of MgO influenced the selectivity to the phytosterol ester. Owing to strong basic sites, the dehydration of the sterol was favored over MgO.

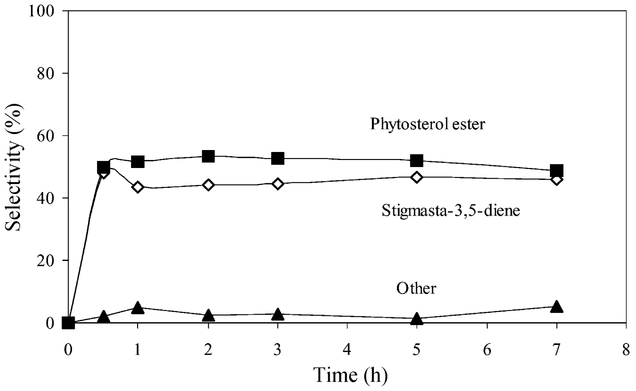


Fig. 1 Preparation of phytosterol ester from methyl dodecanoate and β-sitosterol in the absence of catalyst. Temperature = 240 °C, reaction time = 7 h, D_{N_2} = 5 L h^{-1}, ester/sterol ratio = 1, catalyst = 5 wt%.

Influence of experimental conditions.

Nitrogen flow. As the transesterification reaction was a reversible reaction, the effect of nitrogen flow (to remove methanol) was studied under standard conditions in the presence of oxides (not calcined). The phytosterol ester yield reached a maximum for a nitrogen flow between 5 and 12 L h^{-1} (Fig. 2). At high nitrogen flow, a fraction of methyl dodecanoate was also removed so that all experiments were carried out with a nitrogen flow of 5 L h^{-1}.

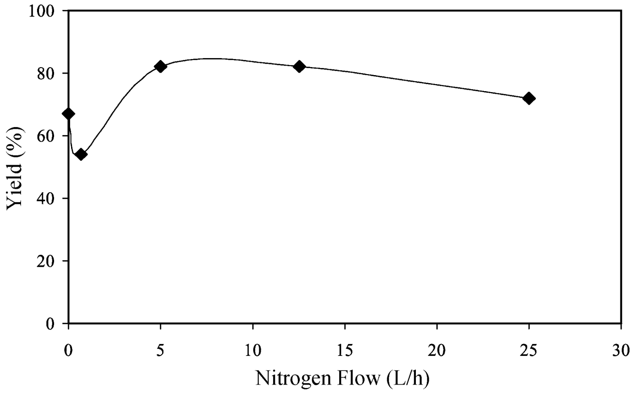


Fig. 2 Preparation of phytosterol ester from methyl dodecanoate and β-sitosterol in the presence of zinc oxide. Influence of the nitrogen flow. Temperature = 240 °C, reaction time = 7 h, ester/sterol ratio = 1, catalyst = 5 wt%.

Reaction temperature. In order to evaluate the influence of the temperature, a series of experiments was performed at 230, 240 and 250 °C in the presence of oxide catalysts. As expected, the conversion of ester and sterol increased with the temperature (Table 2). However, increasing temperature favored the side reaction of degradation of reactants with the diene selectivity increasing from 3.5 to 6.8%. The activation energy calculated from experimental data was 128 kJ mol^{-1}, a value similar to that obtained in the reaction of fatty acid methyl esters and glycerol.[14]

Catalyst recycling. After the reaction, the catalyst can be filtered and reused. It is thus possible (i) to reduce the cost of the

Table 2 Preparation of phytosterol ester from methyl dodecanoate and β-sitosterol in the presence of zinc oxide. Influence of reaction temperature

Temperature/ °C	Conversion (%)		Selectivity (%)			Yield (%)
	Ester	Sterol	Sterol ester	Diene	Other	
230	72.9	75.1	88	3.5	8.5	64
240	85.1	89.6	92.6	3.8	3.6	79
250	88.4	99	89.1	6.3	4.6	79

Reaction time = 7 h, D_{N_2} = 5 L h^{-1}, ester/sterol ratio = 1, catalyst = 5 wt%.

process and (ii) to improve industrial processes in avoiding wax formation. To prove the efficiency of the catalyst, a series of four tests was performed. At the end of the reaction, the hot reaction mixture was filtered and the removed solid was reintroduced inside the reactor without washing. The results reported in Table 3 showed that, after four cycles of reaction, the catalytic properties were essentially unchanged since the conversion of the reactant was above 95% and the selectivity to the phytosterol esters was above 90%.

Table 3 Preparation of phytosterol ester from methyl dodecanoate and β-sitosterol in the presence of zinc oxide catalyst. Recycle of catalyst

Run	Conversion (%)		Selectivity (%)			Yield (%)
	Ester	Sterol	Sterol ester	Diene	Other	
1	82	97	93	3	4	76
2	81	99	93	4	3	75
3	81	98	94	2	4	75
4	80	96	91	3	6	72

Temperature = 240 °C, reaction time = 7 h, D_{N_2} = 5 L h^{-1}, ester/sterol ratio = 1, catalyst = 5 wt%.

Conclusion

The synthesis of phytosterol ester from the transesterification of methyl dodecanoate with β-sitosterol generally performed in the presence of homogeneous catalysts can be carried out in the presence of basic solid catalysts. Indeed, the best yield of phytosterol ester (above 75%) is obtained over magnesium oxide or zinc oxide. However, the strong basic sites of magnesium oxide favored the side-reaction of dehydration of sitosterol to stigmasta-3,5-diene. The reaction must be carried out under nitrogen flow to remove the methanol formed at 240 °C. A series of four experiments showed that the catalytic performances were not affected when the catalyst was reused (without washing).

In conclusion, basic oxides represent a new class of solid catalysts, effective for phytosterol ester synthesis, and appear attractive to replace homogeneous and corrosive catalysts such as strong mineral acids or bases in transesterification processes.

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New procedure for recycling homogeneous catalyst: propylene carbonate synthesis under supercritical CO_2 conditions

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Received 11th October 2002
First published as an Advance Article on the web 24th January 2003

Polyfluoroalkyl phosphonium iodides, Rf_3RPI (Rf = $C_4F_9C_2H_4$, $C_6F_{13}C_2H_4$, $C_8F_{17}C_2H_4$; R = Me, Rf), catalyzed propylene carbonate synthesis from propylene oxide and carbon dioxide under supercritical CO_2 conditions, where propylene carbonate was spontaneously separated out of the supercritical CO_2 phase. The Rf_3RPI catalyst could be recycled with maintaining a high CO_2 pressure and temperature by separating the propylene carbonate from the bottom of the reactor followed by supplying propylene oxide and CO_2 to the upper supercritical CO_2 phase in which the Rf_3RPI remained.

Due to its environmentally friendly nature, supercritical carbon dioxide has attracted much interest as a substitute for organic solvents in various fields including homogeneous catalysis.[1] Supercritical CO_2 is also very effective for accelerating the transformation of CO_2 which is usually very inert.[2] In addition, by utilizing supercritical CO_2 as a new dense phase that separates organics and water, we can simplify the separation process. Especially, if the product spontaneously comes out of the supercritical CO_2 phase, an efficient separation without losing high pressure and temperature can be realized.

Five-membered cyclic carbonates such as ethylene carbonate and propylene carbonate are synthesized by the cycloaddition of CO_2 to epoxides in the presence of homogeneous or heterogeneous catalysts.[3] In our recent studies on propylene carbonate synthesis using supercritical CO_2, we found that propylene oxide and supercritical CO_2 initially formed a uniform phase while the produced propylene carbonate spontaneously separated out of the supercritical CO_2 phase by forming a lower phase in the reactor, as illustrated in Fig. 1.[4] This finding suggested to us that the product could be recovered from the bottom of the reactor, while maintaining a high CO_2 pressure and temperature inside the reactor. In addition, if one can obtain a catalyst which is selectively soluble in supercritical CO_2, the reaction can be repeated without catalyst separation.[5]

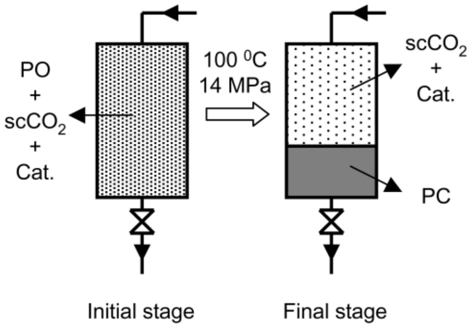

Fig. 1 Schematic diagram of the reaction behavior for the propylene carbonate synthesis from propylene oxide and supercritical CO_2 at 100 °C and 14 MPa. PO; propylene oxide, $scCO_2$; supercritical CO_2, PC; propylene carbonate.

We synthesized novel polyfluoroalkyl phosphonium iodides, Rf_3RPI (Rf = $C_6F_{13}C_2H_4$, R = Me (**1**); Rf = $C_8F_{17}C_2H_4$, R = Me (**2**); Rf = R = $C_4F_9C_2H_4$ (**3**); Rf = R = $C_6F_{13}C_2H_4$ (**4**)), by reacting tri(polyfluoroalkyl)phosphines with either methyl iodide or the corresponding polyfluoroalkyl iodides.[6] The catalytic performances of Rf_3RPI for the cycloaddition reaction of CO_2 to propylene oxide were first evaluated using a conventional batch reactor (20 cm^3 inner volume) in the same manner as previously described.[4a,7] Table 1 summarizes the yield and selectivity of propylene carbonate at 100 °C and 14 MPa. All the phosphonium catalysts (**1**–**4**) exhibited high yields and selectivities comparable to those of a conventional catalyst, Bu_4PI,[8] although the yield obtained by the catalyst with the shortest fluoroalkyl chain (**3**) was slightly lower than those obtained by the others. The CO_2 pressure dependence of the reaction using **1** clearly demonstrated the preferential effect of the supercritical conditions for promoting the reactivity of CO_2

Table 1 Propylene carbonate synthesis from propylene oxide and carbon dioxide catalyzed by polyfluoroalkyl phosphonium iodides[a]

Entry	Catalyst	Yield (%)	Selectivity (%)
1	$(C_6F_{13}C_2H_4)_3MePI$ (**1**)	93	99
2	$(C_8F_{17}C_2H_4)_3MePI$ (**2**)	92	97
3	$(C_4F_9C_2H_4)_4PI$ (**3**)	83	97
4	$(C_6F_{13}C_2H_4)_4PI$ (**4**)	89	99
5	Bu_4PI	90	99

[a] Reactions were carried out using a conventional batch reactor (20 cm^3 inner volume). *Reaction conditions*: catalyst (0.572 mmol, 1 mol%), propylene oxide (57.2 mmol), CO_2 (14 MPa), 100 °C, 24 h.

Green Context

Cyclic carbonates are useful synthetic intermediates which can be advantageously synthesised in supercritical CO_2. Here, it is shown that a fluorous phosphonium catalyst can be used in $scCO_2$ as a homogeneous catalyst. This has the advantage of allowing the synthesis of *e.g.* propylene carbonate to take place under supercritical conditions, with the direct and spontaneous separation of the carbonate. The supercritical phase retains the catalyst allowing for continuous reaction.
DJM

DOI: 10.1039/b210007j

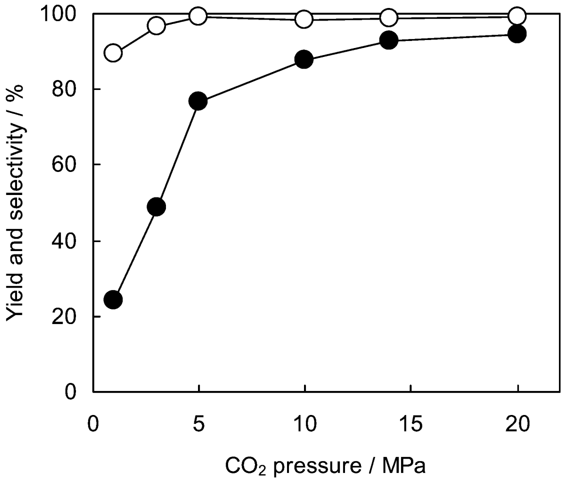

Fig. 2 CO_2 pressure dependence of the yield (●) and selectivity (○) of propylene carbonate for **1**. *Reaction conditions*: **1** (0.572 mmol, 1 mol%), propylene oxide (57.2 mmol), 100 °C, 24 h.

as seen in Fig. 2. The yield and selectivity increased with the increasing CO_2 pressure, and a high CO_2 pressure of 10 MPa or above was notably effective for achieving high yields.

We next investigated the product separation and catalyst recycling employing a reactor (20 cm^3 inner volume) equipped with a mechanical stirrer, sapphire windows, and a valve at the bottom of the reactor for recovering the product. A typical procedure is as follows. The reaction of propylene oxide (57.2 mmol) and CO_2 was first run at 100 °C and 14 MPa in the presence of Rf_3RPI (0.572 mmol, 1 mol%) and biphenyl (200 mg, internal standard for GC analysis). Visual observation through sapphire windows revealed that all the components were miscible and formed a uniform phase at the beginning of the reaction, confirming the homogeneous catalysis of Rf_3RPI. As the reaction proceeded, the product solution separated from the uniform phase gradually accumulated to form a lower phase in the reactor as previously observed,[4a] and finally the volume ratio of the upper supercritical phase to the lower phase became approximately three. After 24 h, the lower phase was taken out of the reactor by slowly opening the valve. During this process the pressure decreased from 14 to 11 MPa. The reaction was then repeated by supplying propylene oxide (57.2 mmol) containing biphenyl (200 mg, internal standard for GC analysis) to the reactor at 11 MPa followed by readjusting the pressure to 14 MPa upon the introduction of CO_2. These results are summarized in Fig. 3, where the yield was calculated based on the amount of propylene carbonate in the separated lower phase and the amount of supplied propylene oxide. When using polyfluorinated phosphonium salts (**1** and **3**), propylene carbonate was produced in the second run with almost the same yield as the first run showing that Rf_3RPI remains in the upper supercritical phase as we expected. In a separate experiment, deposition of the catalyst was observed inside the reactor as a white solid when CO_2 was released after the separation of the lower phase, indicating that the catalyst had been dissolved in the supercritical phase.

In contrast, Bu_4PI is preferentially dissolved in the lower-phase carbonate solution. Hence, once the lower phase was removed, no carbonate phase appeared in the second run. Note that the yield in the second run determined by releasing CO_2 was only 3% (Fig. 3). On the other hand, the Rf_3RPI catalysts gave a high yield even in the third run. Thus, the fundamental idea of the new catalyst recycling during homogeneous catalysis has been demonstrated by using supercritical CO_2 and a CO_2-philic catalyst. The merit of the present procedure is easy separation of the product, catalyst, and supercritical CO_2 without losing the high pressure and temperature of the supercritical phase.

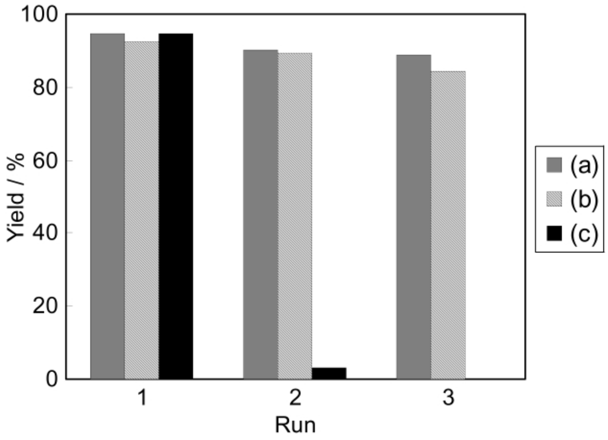

Fig. 3 Yield of propylene carbonate during the repeated reaction using (a) **1**, (b) **3**, and (c) Bu_4PI catalysts. *Reaction conditions*: catalyst (0.572 mmol, 1 mol%), propylene oxide (57.2 mmol), CO_2 (14 MPa), 100 °C, 24 h. The reaction was repeated by removing the product solution at 100 °C and 14 MPa followed by supplying propylene oxide (57.2 mmol) and CO_2 (14 MPa). The yield of Bu_4PI in the second run was determined by releasing CO_2; see text.

In conclusion, we have demonstrated that propylene carbonate can be repeatedly synthesized from propylene oxide and CO_2 by using supercritical CO_2- and CO_2-philic polyfluoroalkyl phosphonium iodides with maintaining a high CO_2 pressure and temperature. The utilization of supercritical CO_2 is also advantageous in terms of the reactivity enhancement and solvent-free processes. In order to improve the efficiency of the catalyst recycling, modification of the catalyst structure, optimization of the separation conditions, and addition of a third component will be future subjects.

Acknowledgement

L.-N. H. acknowledges the New Energy and Industry Technology Development Organization (NEDO) of Japan for a postdoctoral fellowship.

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7 After the reaction at 100 °C and 14 MPa for 24 h, the autoclave was cooled to room temperature and CO_2 was slowly released by bubbling into DMF at −20 °C for trapping any unreacted propylene oxide. The liquid products and the DMF solution were mixed and analyzed by means of GC and GC-MS.

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Conversion of the hydroxyl group in 1-hexyl alcohol to an amide group in supercritical water without catalyst

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Received 22nd November 2002
First published as an Advance Article on the web 27th January 2003

The main reaction pathway in the reaction between 1-hexyl alcohol and acetamide in subcritical and supercritical water without catalyst is proposed and the optimum conditions where amidation of 1-hexyl alcohol can selectively occur are explored.

Water can be considered as a promising solvent that is benign to the environment.[1] If water can be utilized under its supercritical condition (T_c = 374.2 °C, P_c = 22.1 MPa, ρ_c = 0.32 g cm^{-3}), it can act like most organic solvents by manipulating the reaction temperature and pressure. Recently, a large number of researches regarding not only hydrolysis of polymers (*e.g.* polyethylene terephthalate[2] and cellulose[3]) and hazardous organic chemicals,[4] but also synthesis of organic materials[5] in subcritical and supercritical water have been reported. Katritzky *et al.*[6] and Chandler *et al.*[7] found that Friedel–Crafts alkylation of phenol and *p*-cresol occurred at 275 °C under a catalyst free condition by adding *tert*-butyl alcohol and isopropyl alcohol. Sato *et al.*[8] found that reaction of phenol and isopropyl alcohol could successfully form isopropyl phenol under non-catalytic conditions in supercritical water. Akiya *et al.*[9] reported that dehydration of cyclohexanol to cyclohexene took place in near-critical water in a selective manner. Experimental results for Diels–Alder reactions,[10] aldol condensation,[11] Claisen rearrangement,[11] and the Rupe rearrangement[11] in supercritical water have also been reported.

Notably, Ikushima *et al.*[12] reported that ε-caprolactam could be quantitatively synthesized by the Beckmann rearrangement of cyclohexanone oxime in supercritical water in the absence of catalyst. This finding is of great importance to solve the problem of emission of ammonium sulfate, which is a by-product of the conventional synthetic processes, and to develop an efficient method of ε-caprolactam production. Another production method for ε-caprolactam is a UCC (Union Carbide Co.) method,[13] in which cyclohexanone is oxidized by Baeyer–Villiger oxidation to form ε-caprolactone, followed by the formation of ε-caprolactam *via* the reaction between ε-caprolactone and ammonia under hydrothermal conditions. This method seemed to be promising from the viewpoint of green chemistry,[14] but the yield and purity of ε-caprolactam obtained were low. Ito *et al.*[15] carried out this reaction in supercritical water and proposed that in the main reaction pathway ε-caprolactone hydrolyzed to 6-hydroxyhexanoic acid and subsequently reacted with ammonia to form 6-hydroxyhexanamide. They also found that a high yield of ε-caprolactam (87%) could be achieved at temperatures of 400–450 °C, over 10–60 min using water densities of 0.3–0.5 g cm^{-3}.

In the above study, an interesting point is that an amide bond can form by intramolecular dehydration between a hydroxyl group and an amide group in 6-hexylhexanamide. In general, this reaction does not occur in water under catalyst free conditions. This finding suggests that hydroxyl groups in primary alcohols can be converted to amide groups in supercritical water without catalyst. In this communication, we report results of the reactions between 1-hexyl alcohol and acetamide in subcritical and supercritical water without catalyst for determining the optimum conditions where amidation can occur in a selective manner in the absence of catalyst.

Reactions were conducted using a 6.0 cm^3 stainless steel 316 tube bomb reactor. 1-Hexyl alcohol (99.0% purity, Wako Pure Chem. Ind., Ltd.) and acetamide (99.0% purity, Wako Pure Chem. Ind., Ltd.) were loaded into the reactor and a given amount of distilled water, which corresponds to a density of water of 0–0.5 g cm^{-3}, was introduced. The air in the reactor was substituted to argon gas by repeated purging and then the reactor was sealed. The molar ratio of acetamide to 1-hexyl alcohol was 5–50, corresponding to concentrations of 0.33 mol L^{-1} for 1-hexyl alcohol (**1**) and 1.66–16.6 mol L^{-1} for acetamide (**7**). The reactor was submerged into a sand-bath heated to 300–450 °C. After 5–60 min, the reactor was quickly quenched. Products were identified by GC-MS and by comparing their GC and HPLC retention times with those of standards. Quantitative analysis of the products was performed using HPLC. The conversion of **1** (X) and the yield of product $\boldsymbol{i}$ (Y_i) are defined as $X = ([\mathbf{1}]_0 - [\mathbf{1}])/[\mathbf{1}]_0)$ and $Y_i = [i]/[\mathbf{1}]_0$. The selectivity of the product $\boldsymbol{i}$ was also calculated using $S_i = Y_i/X$.

Fig. 1 shows the yield of the main products derived from **1** at 400 °C, 0.5 g cm^{-3} and $[\mathbf{7}]_0$ = 1.66 mol L^{-1}. Products

Green Context

Supercritical water is a fascinating material, which has been used for several organic transformations recently (see *e.g.* Hamley *et al.*, *Green Chem.*, 2002, 4, 235). Here, it is shown that it is possible to alkylate amides at the N atom using alcohols in supercritical water without catalyst. Selectivity was very good, especially considering the potential number of side-reactions which could occur. *DJM*

DOI: 10.1039/b211451h

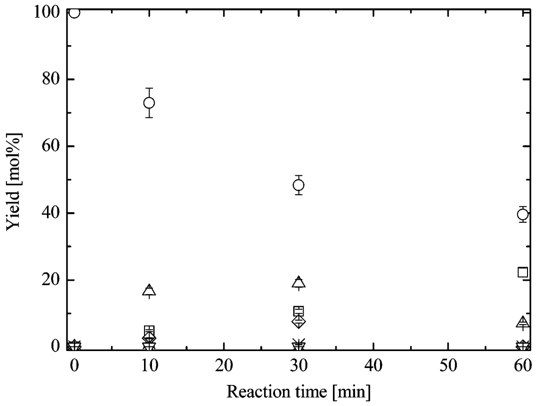
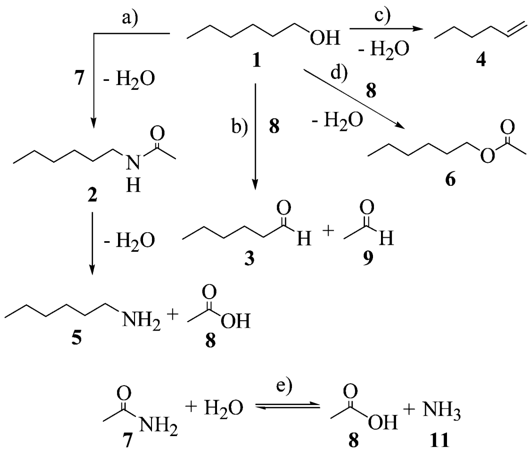


Fig. 1 Yields of the main products at 400 °C, 0.5 g cm^{-3}, 1-hexyl alcohol $[\mathbf{1}]_0$ = 0.33 mol L^{-1} and acetamide $[\mathbf{7}]_0$ = 1.66 mol L^{-1}: (○) 1-hexyl alcohol (**1**); (□) *N*-hexylacetamide (**2**); (△) hexanal (**3**); (◇) hexene (**4**); (×) hexylamine (**5**); (▽) hexanoic acid (**10**); (+) hexyl acetate (**6**).

identified in this study were *N*-hexylacetamide (**2**), hexanal (**3**), hexene (**4**), hexylamine (**5**), hexylacetate (**6**), acetic acid (**8**) and hexanoic acid (**10**). Conversion X increased with time and reached about 60% at 60 min. The yield Y_2 was 21.9% at 60 min while the yields Y_3 and Y_4 reached about 20% and 8% at 30 min and then decreased with time. Yield Y_6 was 4.4% at 10 min and then decreased to 0.8% at 60 min. The yield of **5**, a hydrolysis product of **2**, was low (1.5%), although it was expected that **2** should easily hydrolyze to **5** in supercritical water. The reason for the low level of **5** may be that **2** is stablized over **5** due to solvation in supercritical water, or that **2** is converted to **1** and **7** by the reverse reaction of amidation. Under the used reaction conditions, about 70% of **7** hydrolyzed to form **8** at 10 min and the yield Y_8 scarcely changed even for extended reaction times. In summary, amidation between **1** and **7** took place in supercritical water. Moreover, we evaluated any possibility of the formation of **2** and/or **5** from the reaction between **4** and **7** in subcritical and supercritical water and found that they did not form.

Based on these results, we propose the main reaction pathway in the 1-hexyl alcohol–acetamide–water system in subcritical and supercritical water as shown in Scheme 1. The main reaction paths are (a) intermolecular dehydration between **1** and **7**, (b) a reverse Cannizzaro reaction between **1** and **8** formed by the dissociation of **7**, (c) intramolecular dehydration to **4**, (d) intermolecular dehydration (esterification) between **1** and **8**, and (e) hydrolysis of **7** to **8** and ammonia (**11**). It has already been reported that the Cannizzaro reaction takes place in supercritical water under catalyst free conditions.[16] From a preliminary experiment, we also confirmed that the reverse Cannizzaro reaction can take place in supercritical water.[13]



Scheme 1 Main reaction pathway in the 1-hexyl alcohol (**1**)–acetamide (**7**)–water system in subcritical and supercritical water.

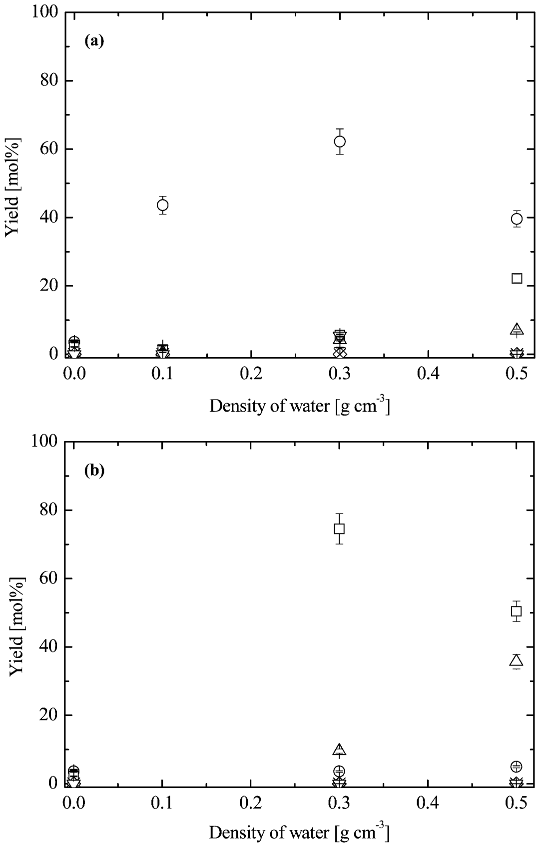


Fig. 2 Water density dependence of the product distributions at 400 °C, 60 min, $[\mathbf{1}]_0$ = 0.33 mol L^{-1} and water densities ranging 0 to 0.5 g cm^{-3}: (a) $[\mathbf{7}]_0$ = 1.66 mol L^{-1}; (b) $[\mathbf{7}]_0$ = 16.6 mol L^{-1}: (○) 1-hexyl alcohol (**1**); (□) *N*-hexylacetamide (**2**); (△) hexanal (**3**); (◇) hexene (**4**); (×) hexylamine (**5**); (▽) hexanoic acid (**10**); (+) hexyl acetate (**6**).

The effect of the density of water on amidation was examined under the conditions: 400 °C, 60 min and $[\mathbf{1}]_0$ = 0.33 mol L^{-1}. Fig. 2(a) and (b) shows the results at $[\mathbf{7}]_0$ = 1.66 and 16.6 mol L^{-1}, respectively. At low $[\mathbf{7}]_0$, as shown in Fig. 2(a), gaseous products were mainly formed by pyrolysis of **1** in argon atmosphere and low water densities of 0.1 and 0.3 g cm^{-3}. By contrast, at a higher water density (0.5 g cm^{-3}), gaseous products were scarcely detected and liquid products, especially **2**, mainly formed. With increasing $[\mathbf{7}]_0$ (see Fig. 2(b)), the yield Y_2 became higher at 0.3 and 0.5 g cm^{-3}. This experimental finding demonstrates that amidation of **1** can be promoted at high water densities in supercritical water.

Next, the effect of the reaction temperature on amidation was examined under the condition of $[\mathbf{1}]_0$ = 0.33 mol L^{-1}, $[\mathbf{7}]_0$ = 1.66 mol L^{-1} and 0.3 g cm^{-3}. Table 1shows the experimental results conducted at temperatures of 300, 400 and 450 °C. At 300 °C, X was 31% and S_2 was low (29%). **3** was formed at a similar level to **2** by a reverse Cannizzaro reaction between **1** and **8**. In this case, the yield Y_5 was 4.0%. At 400 °C, X was over 96% and Y_2 reached 74.5% (selectivity: 77%) at 60 min with **5** not forming at all. At 450 °C and 10 min, X became even higher while Y_2 was comparatively high (57.2%). In this case,

Table 1 The effect of the reaction temperature on the main products with $[\mathbf{1}]_0$ = 0.33 mol L^{-1} and $[\mathbf{7}]_0$ = 16.6 mol L^{-1}; at 400 °C; at water density 0.3 g cm^{-3} and 60 min (300 and 400 °C), or at water density 0.35 g cm^{-3} and 10 min (450 °C)

		Y (mol%)				
T/°C	$100 - X$ (mol%)	2	3	4	5	6
300	60.8	11.3	14.2	n.d.	4.0	7.1
400	3.6	74.5	9.6	n.d.	n.d.	2.0
450	3.8	57.2	10.1	n.d.	n.d.	n.d.

however, the carbon recovery of liquid products was low. This is probably because gaseous products form by the thermal degradation of **1** and its primary products. From these experimental results, it was confirmed that the amidation of 1-hexyl alcohol in supercritical water was more suitable than that in subcritical water from the view point of a rapid and selective process. Also, it was suggested that subcritical water might be applicable as a reaction medium for hydrolyzing amides to amines.

Further, reactions of **1** with other amidation reagents (benzamide and hexanamide) were conducted and results are shown in Table 2. With both reagents, the amide compounds (*N*-hexylbenzamide and *N*-hexylhexanamide, respectively) could be synthesized, but the selectivity of these products were low compared with the case of acetamide. This is probably because the thermal stabilities of the amide compounds are not high under the used conditions.

Table 2 Experimental results of reactions of **1** with other amidation agents in supercritical water. *Conditions*: 400 °C, 0.3 g cm^{-3}, initial concentration of each amidation agent $[R]_0 = 0.33$ mol L^{-1} and 60 min

R	$[R]_0/[\mathbf{1}]_0$	$100 - X$ (mol%)	Y_{Amide} (mol%)	S_{Amide} (mol%)
Benzamide	10	25.3	18.6	24.9
Hexanamide	20	4.1	16.7	17.4

In summary, we have demonstrated the conversion of the hydroxyl group in 1-hexyl alcohol to an amide group in supercritical water without catalyst. This experimental finding leads to the development of a new method for efficient production of amide compounds from primary alcohols. Future efforts will be directed to elucidate the reaction mechanism further and to explore optimum conditions for rapid and selective amidation in supercritical water.

Acknowledgement

The authors gratefully acknowledge support for a Grand-in-Aid for Scientific Research on Priority Area (Grant 11450295) from the Ministry of Education, Culture, Sports, Science and Technology.

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