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Cutting-edge research for a greener sustainable future

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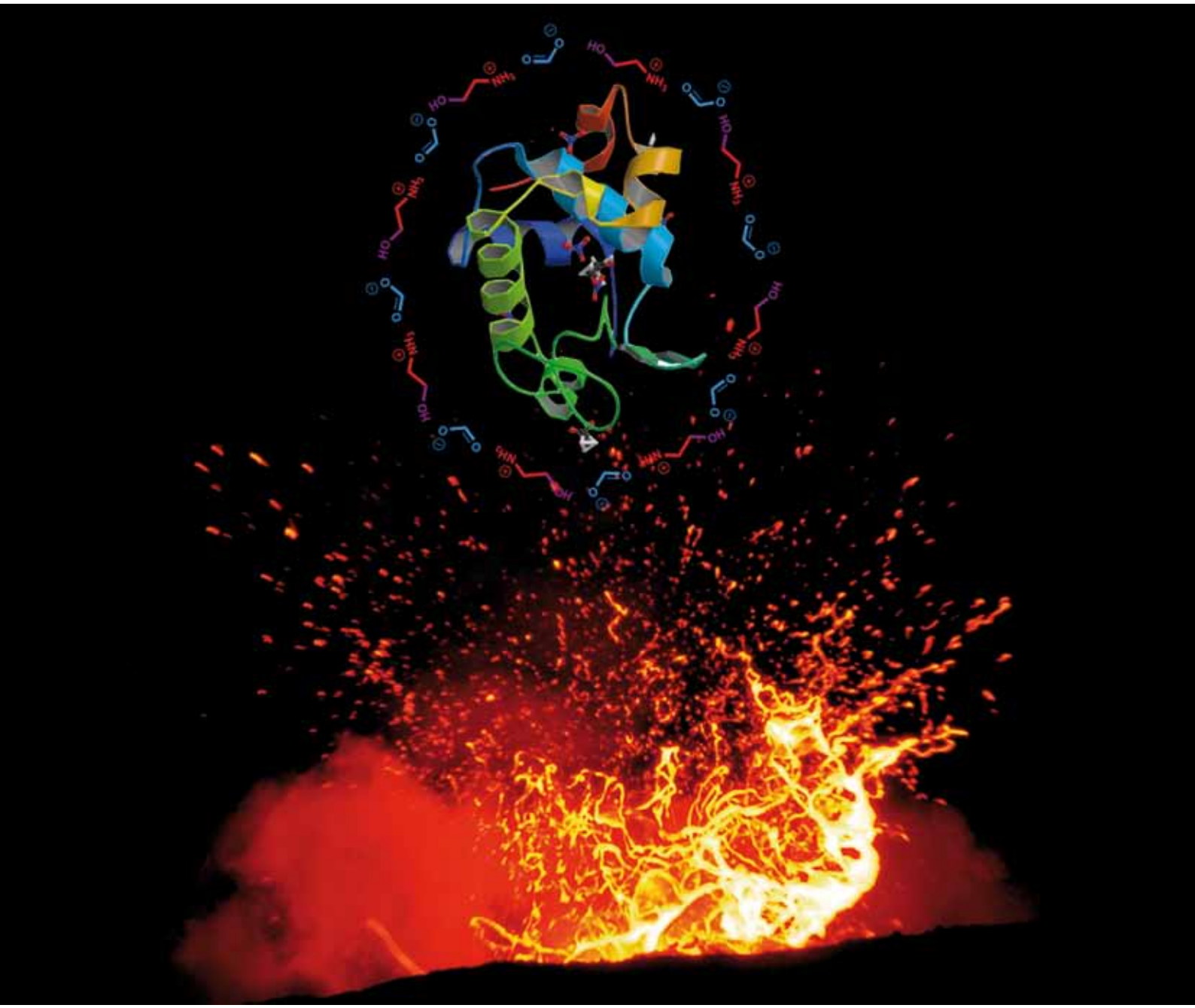
Volume 11 | Number 6 | June 2009 | Pages 741–896



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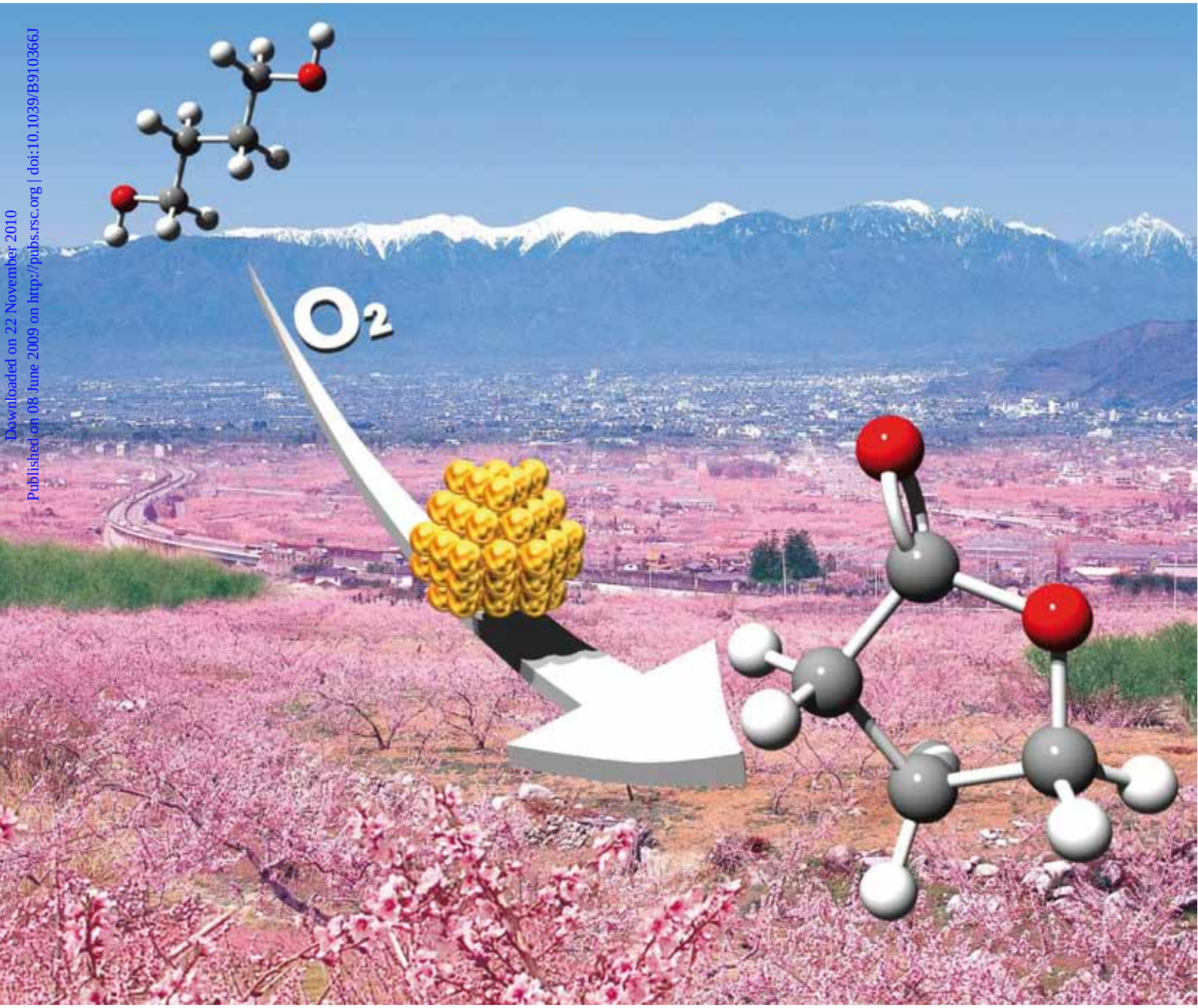

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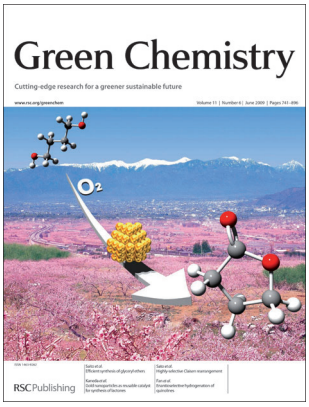
ISSN 1463-9262 CODEN GRCHFJ 11(6) 741–896 (2009)

Cover
See Atkin *et al.*, pp. 785–792. Variation in the molecular structure of protic room temperature ionic liquids produces remarkable differences in the thermal stability and activity of lysozyme. Background image is the 'Kilauea lava vent at night', October 2008. Image reproduced with permission from Siobhann Niamh McCluskey, from *Green Chem.*, 2009, **11**, 785.



Inside cover
See Kaneda *et al.*, pp. 793–797. The background is the full blossom of Japanese peach trees. Synthetic lactones are commonly used as perfumes with the fragrance of peach. The pink colour represents the gold nanoparticles, the blue sky is the symbol of air (oxygen). The scheme shows the lactonization from diols by the gold nanoparticle catalyst. Image reproduced with permission from Kiyotomi Kaneda from *Green Chem.*, 2009, **11**, 793.

CHEMICAL TECHNOLOGY

T41

Drawing together research highlights and news from all RSC publications, *Chemical Technology* provides a 'snapshot' of the latest applications and technological aspects of research across the chemical sciences, showcasing newsworthy articles and significant scientific advances.

Chemical Technology

June 2009/Volume 6/Issue 6

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COMMUNICATIONS

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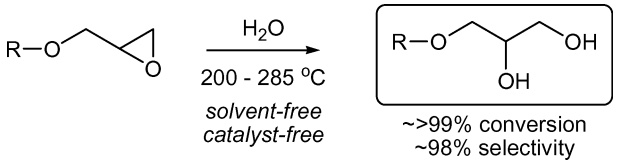
An efficient synthesis of glyceryl ethers: catalyst-free hydrolysis of glycidyl ethers in water media

Akira Saito,* Takeshi Shirasawa, Shinichiro Tanahashi, Mitsuru Uno, Nobuhiro Tatsumi and Tomohito Kitsuki

Hydrolysis of hydrophobic glycidyl ethers in pressurized water media afforded the corresponding glycidyl ethers in good to excellent selectivity within several minutes without catalyst.



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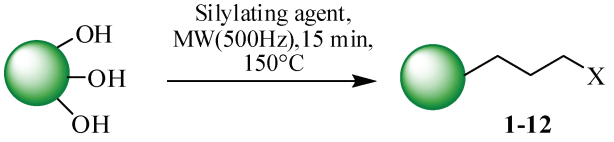

X= SH, NH_2; Cl, $(CH_3)_2$; CN; NCO; $(CH_2)_4CH_3$; 
$NH(CH_2)_2NH_2$; Ph; $[NH(CH_2)_2]_2NH_2$; $NHC(O)NH_2$.

General MW-assisted grafting of MCM-41: Study of the dependence on time dielectric heating and solvent

Antonio Procopio,* Giuseppina De Luca, Monica Nardi, Manuela Oliverio and Rosina Paonessa

A fast and versatile MW-assisted method for the post-calcination functionalization of MCM-41 is proposed. The efficiency of the grafting is improved in the absence of solvent and depends on the MW-heating time.

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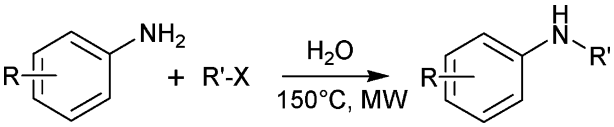

Microwave-promoted mono-*N*-alkylation of aromatic amines in water: a new efficient and green method for an old and problematic reaction

Giovanni Marzaro, Adriano Guiotto and Adriana Chilin*

A greener improvement to direct mono-*N*-alkylation of aromatic amines by alkyl halides was achieved using microwave irradiation in water without any catalyst.

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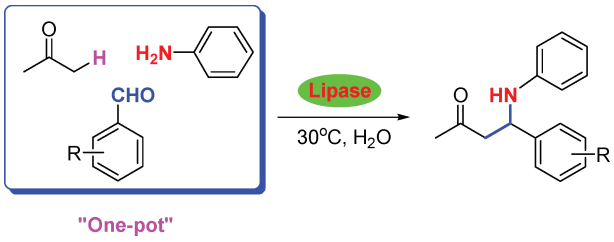

Lipase-catalysed direct Mannich reaction in water: utilization of biocatalytic promiscuity for C–C bond formation in a "one-pot" synthesis

Kun Li, Ting He, Chao Li, Xing-Wen Feng, Na Wang* and Xiao-Qi Yu*

Lipase-catalysed direct Mannich reaction, which is the first example of three-component biocatalytic promiscuity for C–C bond formation. Aromatic aldehyde, aniline and acetone reacted in "one-pot" to form β-amino-ketone compounds in water with high yield.

PAPERS

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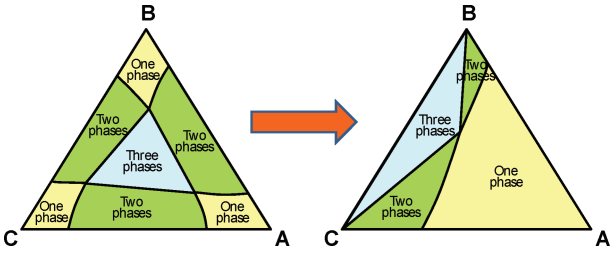

Phase behaviour of trihexyl(tetradecyl)phosphonium chloride, nonane and water

Kris Anderson,* Héctor Rodríguez and Kenneth R. Seddon

The mixture of trihexyl(tetradecyl)phosphonium chloride, water and nonane can form a stable three-phase system in equilibrium, in which the upper phase is virtually pure nonane, and the lower phase is virtually pure water.

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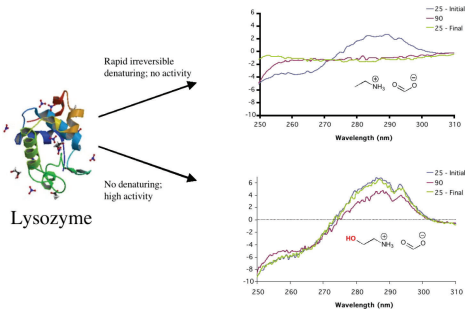

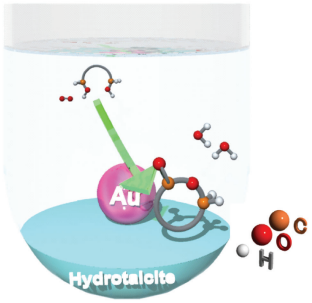

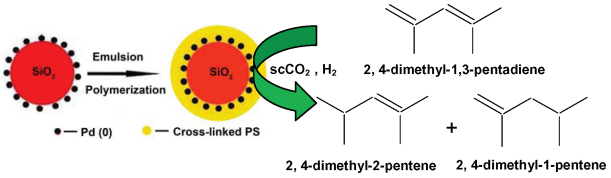

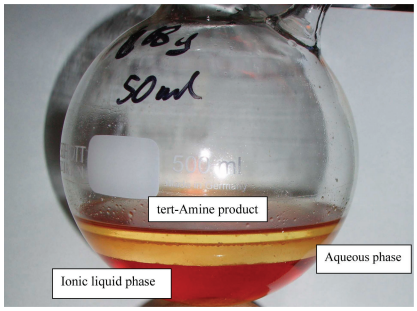

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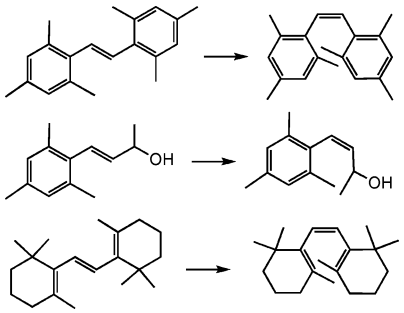

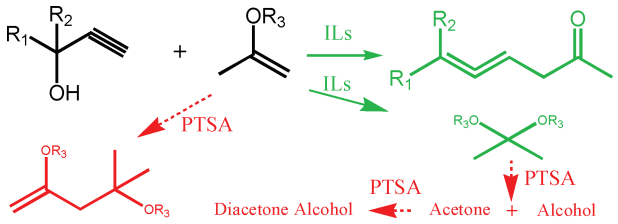

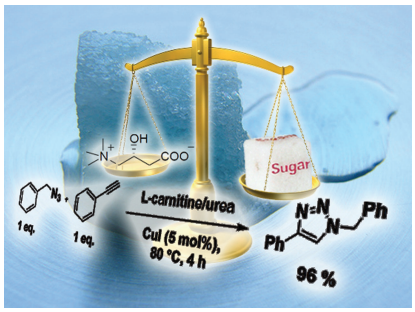

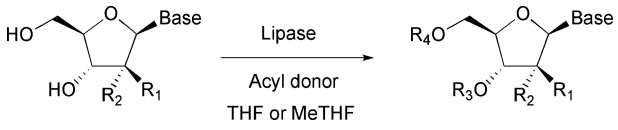

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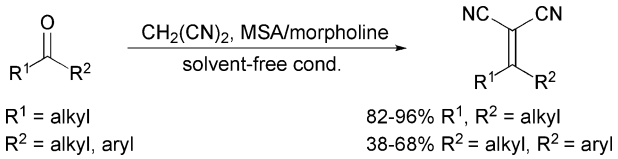

Solvent-free condensations of ketones with malononitrile catalysed by methanesulfonic acid/morpholine system

M. Góra,* B. Kozik, K. Jamroży, M. K. Łuczyński, P. Brzuzan and M. Woźny

The new, alternative and greener route for Knoevenagel condensations of ketones with malononitrile without the need for organic solvents is described.

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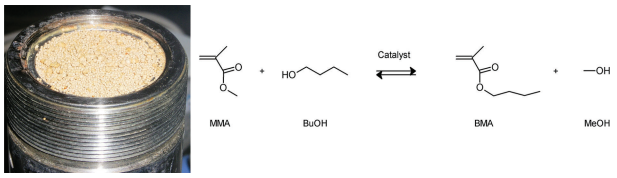

An efficient, practical and cost-effective polymer-supported catalyst for the transesterification of methyl methacrylate by 1-butanol

Gaëlle Baquey, Marie-Hélène Alvès, Magalie Graullier, Alain Riondel, Jean-Michel Paul, Marc Birot and Hervé Deleuze*

Cheap and efficient polymer-supported titanium alkoxide catalyst with a very low metal leaching under continuous use as alternative of a homogeneous industrial transesterification process.

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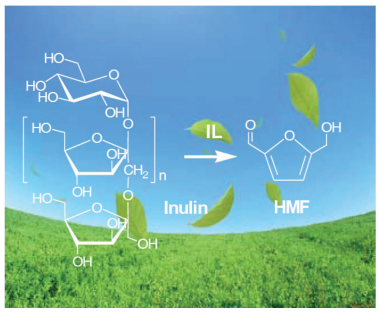

Direct conversion of inulin to 5-hydroxymethylfurfural in biorenewable ionic liquids

Suqin Hu, Zhaofu Zhang, Yinxi Zhou, Jinliang Song, Honglei Fan and Buxing Han*

The non digestible inulin stored in many plants can be directly converted to 5-hydroxymethylfurfural (HMF) in acidic biorenewable ionic liquids (ILs) with a good yield. The IL can be recycled easily with high activity.

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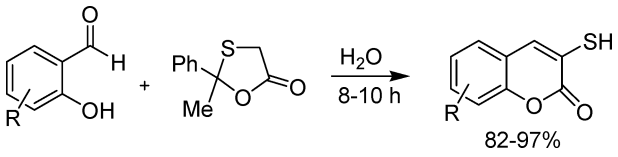

Catalyst-free, step and pot economic, efficient mercaptoacetylative cyclisation in H_2O: synthesis of 3-mercaptocoumarins

Lal Dhar S. Yadav,* Santosh Singh and Vijai K. Rai

An environmentally friendly, tandem Knoevenagel condensation and mercaptoacetylative cyclisation procedure is reported. The reaction between 2-methyl-2-phenyl-1,3-oxathiolan-5-one and a variety of salicylaldehydes was carried out in water to afford 3-mercaptocoumarins in excellent yields (82–97%).

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Invitation

On behalf of the conference organizing committee, we would like to invite you to participate in the Joint Conference of the 4th International Conference on Green and Sustainable Chemistry (GSC-4) and the 2nd Asian-Oceanian Conference on Green and Sustainable Chemistry (AOC-2), which will be held in Beijing, August 20-24, 2009. The purpose of the conference is to stimulate the interaction and exchange of ideas of practitioners in green and sustainable chemistry and to promote the cleaner chemistry across the world. This conference will consist of plenary lectures, keynotes, oral and poster presentations. We sincerely hope that the scope of the conference will serve the interest of the participants. We warmly welcome all participants and sponsors of the event.

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Green catalysis
Alternative solvents
Renewable and green raw materials
Green chemistry for energy
Clean processes

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Chemical Technology

Portable screening device detects pollutants in drinking water

Biosensor in a briefcase tests toxicity

Safe drinking water is a priority for soldiers on field duty but water testing can be impractical. Now US scientists have developed an easy-to-use, portable water-screening device powered by a battery pack.

Mark Widder, at the US Army Center for Environmental Health Research, Fort Detrick, and colleagues, grew a monolayer of mammalian cells on a fluidic chip's electrodes. They injected water samples into the chip and electrically monitored the cells' response. They showed that the cells' impedance (resistance to current) changed when the water contained toxins.

Cellular impedance is a proven monitor of chemically induced toxicity, explains Widder. For example, toxins may affect cell membrane porosity, which leads to a change in a cell's resistance. But until now, the difficulty in keeping cells healthy for extended periods has limited their use in portable sensors.

Widder's sensor integrates the impedance-measuring chip with automated cell maintenance – a computer-controlled pump delivers cell-culture media to the cells from a bag attached to the lid of the device's case. Using this simple system, which is powered by a rechargeable battery, the group kept the cells healthy and responsive for up to four months and showed they could detect five different pollutants.

The toxicity sensor and automated cell maintenance system are stored in an easy-to-transport case

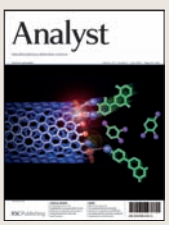
'The system does not require trained technicians and a cell-culture facility,' comments Widder. 'All that is required of the operator is to reconstitute the pre-packaged cell media in 20 millilitres of water sample, temperature equilibrate the sample with a control sample then inject the two samples.' He adds that the pump-controlling computer also analyses the impedance measurements.

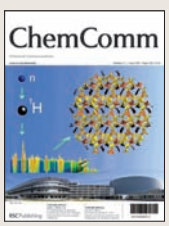
Eugen Gheorghiu, an expert in impedance-based analysis at the International Centre of Biodynamics, Bucharest, Romania, says that although the samples' concentrations were high and he wonders about the sensor's sensitivity, the method 'is a promising development that could pave the way to wider applicability and relevance of cell-based lab-on-a-chip platforms'.

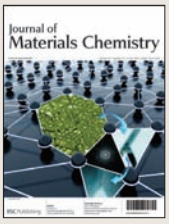
Widder acknowledges that the sensitivity may not be good enough for drinking water standards but it meets military exposure guidelines. The team are continuing to work on the sensitivity, he adds. They have also developed an enhanced version of the device that incorporates multiple biochips, enabling analysis of multiple samples. They will perform field testing after they complete laboratory validation, says Widder. *Frances Galvin*

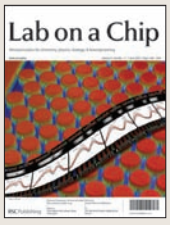
Reference
T M Curtis *et al*, *Lab Chip*, 2009, DOI:10.1039/b901314h

In this issue









The latest applications and technological aspects of research across the chemical sciences

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Application highlights

Cell damage minimised by three-pronged channel

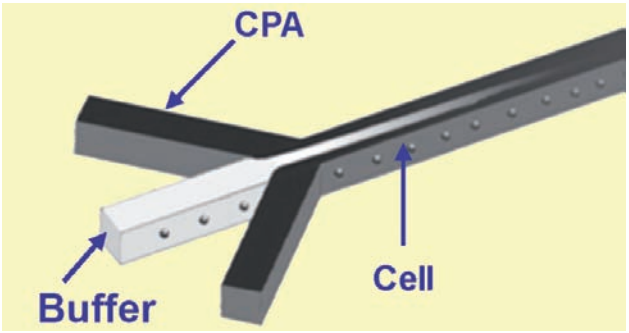
Microfluidics doesn't shock cells

Scientists have used microfluidic technology to improve the survival rates of frozen cells.

Cryopreservation is a process in which cells are cooled down to subzero temperatures, which stops their biological activity. Unfortunately, this freezing process can damage the cells. Scientists add chemicals called cryoprotectants (CPAs) to lower the cells' freezing temperatures and reduce ice crystal formation, which can crush the cells. When they want to use the cells, they warm them up to body temperature and remove the CPAs. But even these chemicals designed to protect the cells can cause damage.

Now, Utkan Demirci, at Harvard Medical School, Cambridge, US, and colleagues have increased the chance of cell survival by 25 per cent over standard cryopreservation methods.

Demirci explains that osmotic shock is one of the major causes of cell damage during cryopreservation. It is caused by water moving into and out of the cell. When CPA is added to the cell mixture, the CPA concentration outside of the cell is high, which draws water out of and CPA into the cell. The reverse occurs during CPA unloading and the water flow into the cell can cause the cell to swell and burst.



The microfluidic device has a long microfluidic channel with three inputs

Demirci used a microfluidic channel with three input channels – one in the middle for the cells and one at each side for the CPAs. Cells travelling along the channel experienced a gradual increase in CPA concentration. After thawing, Demirci removed the CPAs using a buffer solution injected into the side channels. By controlling the flow rates, and so the CPA concentration, he was able to greatly reduce the incidence of osmotic shock.

'[The microfluidic chip] can be built as a prototype automated device for general lab use in the future,' says Demirci.

Palaniappan Sethu, an expert in microfluidic systems at the University of Louisville, US, is impressed by the technology. 'The device ensures uniform processing conditions throughout the sample. This minimises inter- and intra-sample variability that is common with conventional macroscale techniques,' he says. *Sylvia Pegg*

Reference
Y S Song *et al*, *Lab Chip*, 2009, DOI: 10.1039/b823062e

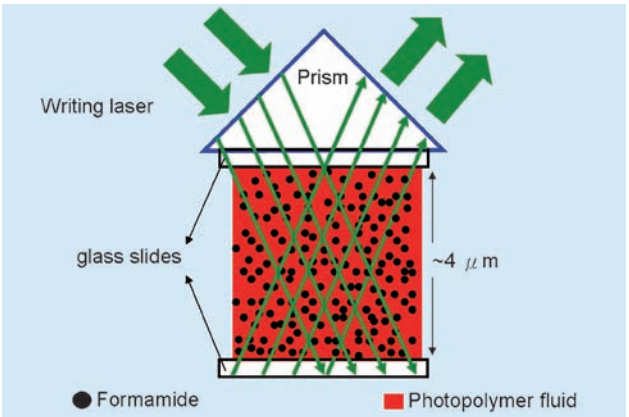
Photopatterning leaves formamide in the dark

Holography generates porous crystals

A polar solvent is the key to making polymeric photonic crystals (PCs) that could be used as biological sensors, say scientists from Taiwan and the US.

Alexander Cartwright, at the State University of New York, Buffalo, US, Vincent Hsiao, at the National Chi Nan University, Puli, Taiwan, and colleagues used a method known as holographic photopatterning to make their PCs.

The team mixed formamide, a highly polar solvent, with a non-polar solution of monomers and surfactant. The formamide formed emulsion droplets within the solution and the mixture was sandwiched between two glass slides. They shone a laser through a prism on to the slides, which created a pattern of incident and reflected beams. In the pattern's bright regions, the monomers polymerised, driving the formamide droplets into the dark regions. After switching off the laser, the team opened the sandwich to evaporate the formamide, leaving behind a polymeric film with a periodic structure.



Polymerisation in the interference pattern's bright regions drives the formamide to the dark regions

Scientists have previously reported holographic patterning using liquid crystal additives but Cartwright says using formamide is simpler. 'We wanted to develop a more direct route to the production of these porous structures,' he explains.

Cefe López, an expert in PCs at the Institute of Materials Science of Madrid, Spain, says the use of the formamide additive is significant but adds, 'What is more interesting is the smart way of preparing a multilayer by herding the [formamide] micelles into dark regions while, at the same time, the light regions are crosslinked.'

A PC's periodic structure disrupts the passage of light through it. By altering the periodicity, scientists have made a range of PCs that reflect different colours. Cartwright says he hopes to optically tune his polymeric PCs so they can be used as biosensors.

'The ability to produce large areas of the films will be a challenge,' predicts Cartwright. 'More importantly, we would like to include additional functionality within the film but this will require a change in the way we fabricate the structures.' *Mary Badcock*

Reference
V K S Hsiao, *J. Mater. Chem.*, 2009, DOI: 10.1039/b823247d

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Encapsulated manganese improves safety of magnetic resonance imaging

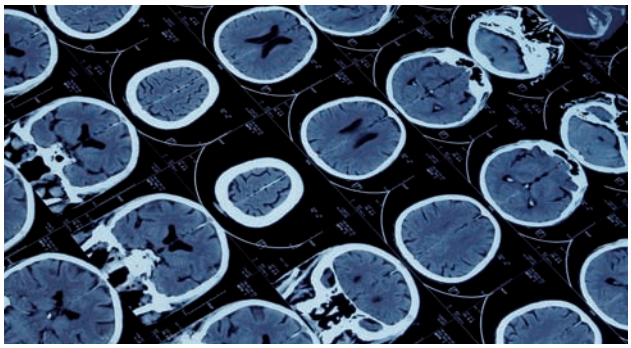
Nanocolloids identify blood clots

JUPITER IMAGES

US and UK scientists have discovered a safer contrast agent for magnetic resonance imaging (MRI). The agent is an alternative to commonly used, but potentially harmful, gadolinium-based agents.

MRI uses paramagnetic metals (contrast agents) to produce high resolution, non-invasive images of the body's internal structure. It is particularly useful in cardiovascular research for visualising blood clots in arteries, which can cause heart attacks and strokes. Although scientists normally use gadolinium as the contrast agent, its recent association with a serious tissue disorder in patients with kidney failure has prompted the development of imaging agents based on non-lanthanide metals, such as manganese .

Dipanjan Pan, at Washington University School of Medicine, St Louis, US, and colleagues stirred manganese oxide nanoparticles in a vegetable oil and surfactant mixture to form manganese oxide nanocolloids with phospholipid shells. They showed that the nanocolloids are highly sensitive to fibrin, a major component of blood clots, and so are effective contrast agents.



Magnetic resonance imaging can identify blood clots in the brain

The colloids can be easily metabolised and excreted by the human body, explains Pan, unlike other manganese-based contrast agents, which are difficult to eliminate and create a hazardous tissue residue. 'Bigger metal crystals are not metabolised and they are typically too large to be excreted through the kidney or bile, presenting an issue for long-term safety. We incorporate tiny manganese oxides or organically soluble chelated manganese into a stable nanoparticle, which is constrained within the vasculature [blood vessels]. This inherent difference over non-excretable nanocrystals should greatly improve the prospects of safety and clinical translation.'

Taeghwan Hyeon, an expert in nanocrystalline materials at Seoul National University, Korea, agrees. '[These colloidal nanoparticles] can overcome the biosafety issues of other nanoparticle-based MRI contrast agents. Future in vivo applications of these colloidal nanoparticle-based MRI contrast agents are highly anticipated.'

Pan's group is working to prove the efficiency and safety of the imaging agents in vivo, in collaboration with Gregory Lanza at the Consortium for Translational Research in Advanced Imaging and Nanomedicine, St Louis. *Sandra Fanjul*

Reference
D Pan *et al*, *Chem. Commun.*, 2009, DOI:10.1039/b902875g

Partial dark field lights up malarial pigment in red blood cells

Raman catches a killer

CDC

Raman microscopy could improve and simplify malaria diagnosis in remote locations, claim a team of scientists from Australia and Germany.

Malaria is one of the world's most devastating diseases. It kills more than a million people each year, mostly in Africa. Easy-to-use dipstick tests can rapidly detect malaria in blood but they do not reveal the number of malarial parasites, which scientists use to decide upon a treatment. Although some diagnostic tools can both identify and quantify the parasites, they are difficult to use.

Don McNaughton, at Monash University, Clayton, Australia, and colleagues have combined bright-field and dark-field microscopy with Raman spectroscopy to detect malarial parasites in blood. The method is as easy to use as a normal microscope, they say, and can be automated so the operator does not have to make the diagnosis.

Malaria parasites are spread through mosquito bites

Bright-field microscopy illuminates a sample and its surroundings from below. The surroundings appear bright while the sample appears dark. In dark-field microscopy, only the light scattered by the sample is seen through the lens, so the sample appears bright and the surroundings dark.

By combining these techniques, the team created a partial dark-field effect that lights up a malarial pigment called haemozoin, which they then detected by Raman spectroscopy. Malarial parasites are difficult to see by bright-field microscopy alone because cells may be overlaid and so obscured from the light, McNaughton explains.

'This combinatorial approach opens the way towards a new powerful malaria diagnostic tool in routine clinical practice,' says Juergen Popp, an expert in microscopy and biophotonics at Friedrich Schiller University of Jena, Germany.

The next step is to see if this new technique can differentiate between different stages of the parasite life cycle, remarks NcNaughton. 'We hope to achieve this by correlating the Raman spectral images with stained sections [from conventional diagnostic techniques] and determining spectral markers for each stage of the life cycle.' *Rebecca Brodie*

Reference
D McNaughton *et al*, *Analyst*, DOI:10.1039/b822603b

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Electrochemical determination of Tamiflu starting material

Shikimic acid detection hots up

A hot copper wire can detect important biochemical intermediates, say Chinese scientists.

Jian-Jun Sun and colleagues at Fuzhou University used thin copper wire to make an oxide-covered copper electrode, which they heated using an electric current. They found that the high temperature accelerated redox reaction rates at the electrode, enabling sensitive detection of polyhydroxylated compounds, such as shikimic acid (SA).

SA is a biochemical intermediate found in plants and microorganisms. It is also an effective anti-thrombosis drug and is used to make Tamiflu, the antiviral drug currently being used to treat swine flu. SA cannot be synthesised cheaply and so most of it is extracted from star anise. As the demand for Tamiflu increases and scientists look for new ways to produce SA, its determination and extraction are of great interest, says Sun.

Until now, scientists have detected SA using a UV detector coupled to liquid chromatography or capillary electrophoresis (CE) separation techniques. No electrochemical methods for detection have been reported before, comments Sun, because SA's functional groups cannot be easily oxidised or reduced using traditional bare electrodes made from glassy carbon, gold or platinum.

Shikimic acid is Tamiflu's starting material

The heated oxide-covered electrode electrochemically detects SA by electrocatalytically oxidising its hydroxy groups. It can detect SA levels as low as 0.01 parts per million, much lower than the UV detection limit of 0.3 parts per million, Sun explains. He adds that it also shows good responses for other analytes, including glucose, amino acids, purine bases and ribonucleosides.

'The idea of using thin metal wires and passing a current through them to heat them in solution is both simple and elegant,' remarks Phil Bartlett, an expert in electrochemistry at the University of Southampton, UK. 'Extending this to metals such as copper, where a catalytic oxide can be formed, has great promise, since it does not require significant capital investment or complex equipment to apply.'

Many analytes exhibit similar electrocatalytic responses to SA, meaning that their voltammetric peaks overlap. To overcome this problem, the electrochemical detector must be coupled with separation techniques such as high performance liquid chromatography or CE, says Sun. 'The design of a heated electrode adapted to the interface of the [separation] instrument is the primary challenge,' he adds.

Philippa Ross

Reference
H Wei *et al*, *Chem. Commun.*, 2009, 2842 (DOI:10.1039/b904673a)

Air bubble protects blood from electrolytic reaction

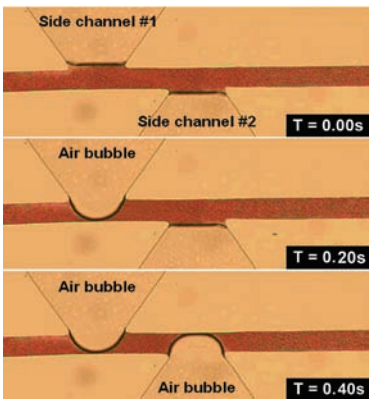
Microfluidics pumps it up

Chemists in Taiwan have developed a bubble-activated micropump that can transport blood on a microchip. The pump could improve point-of-care disease diagnosis, they claim.

Sheng-Hung Chiu and Cheng-Hsien Liu from the National Tsing Hua University, Hsinchu, electrolytically generated hydrogen and oxygen bubbles from water and used them to control a micropump.

Micropumps provide the pressure that drives fluids through channels in lab-on-a-chip microsystems. Although many micropumps have been developed, most require high temperatures or voltages, which can damage blood cells. Electrochemically activated pumps are known but they alter the pH of blood, harming the cells.

The new design overcomes these limitations by confining the pump's electrolysis reaction to an electrolyte-filled side channel on the chip, explains Liu. Its separation from the main, blood-containing channel stops it altering the main channel's pH.



The micropump uses air bubbles to drive blood through the channel

When Liu and Chiu applied a voltage to the pump's platinum electrodes, the electrolytically generated bubbles increased the pressure in the side channel. This pushed forward an air bubble between the electrolyte and the blood, moving the blood in the main channel. When Liu turned off the voltage, the electrolytic bubbles escaped through vents in the side channel and the air bubble retreated. Using two side channels in sequence produced a flow of liquid through the channel.

'Separating the electrolytic solution from the working solution by a trapped air bubble is a clever design,' comments Abraham Lee, an expert in microfluidic chips at the University of California, Irvine, US.

Liu says he hopes that the pump will be 'integrated with other multiple components to form microfluidic systems for lab-on-a-chip systems, biochips and drug delivery'. *Nicola Wise*

Reference
S-H Chiu, *Lab Chip*, 2009, DOI: 10.1039/b900139e

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Interview

Catching counterfeits

Facundo Fernández talks to Jennifer Newton about the fight against counterfeit drugs and whitewater kayaking

Facundo Fernández

Facundo Fernández is an assistant professor in the school of chemistry and biochemistry at the Georgia Institute of Technology, US. He is on the *Analyst* advisory editorial board and his research focuses on the instrumentation and applications of bioanalytical mass spectrometry.

What inspired you to become a scientist?
I've always been very curious, even as a child. What really drove me to be a scientist is that it allows me to constantly answer new questions, push new boundaries and play with new instruments and techniques. In other words, the amount of freedom that one has is enormous, and it is pretty much impossible to get bored!

Some of your work involves detecting fake drugs, How big a problem is pharmaceutical counterfeiting?
Everybody agrees it is a very large problem, but it is difficult to come up with hard numbers as it requires sampling multiple products all over the world in a statistically significant way. This is not a trivial task to pursue. We are trying to address part of the technical challenges associated with this issue by developing faster methods for determining their chemical composition using mass spectrometry.

You are researching direct analysis in real time (DART). Can you explain what this is?
DART is a technique invented by Robert Cody and co-workers which was first reported in the scientific literature in 2005. It is a direct ionisation method that operates in the open air and under atmospheric pressure conditions. In other words, a sample such as a pharmaceutical tablet can be directly analysed by simply placing it in front of the DART ion source, which is facing the mass spectrometer inlet. We have used it extensively to examine the quality of antimalarial drugs collected in southeast Asia. DART revealed the presence of a large number of wrong active ingredients in fake drugs. The concern is that some of these wrong ingredients may mask the symptoms of malaria without really curing it. Another concern is that some of these ingredients may stimulate parasite resistance.

What other projects are you working on?
Too many! Some that I particularly enjoy involve imaging using ambient ionisation techniques. We have recently published an article where we imaged the surface of algae for identifying the regions in space where metabolites are excreted.[1] These metabolites have shown promise as new drugs to treat malaria.

What is the next big thing that you would like to tackle in your lab?
We are trying to find a rapid mass spectrometry diagnostic test for ovarian cancer. This promises to be another of those tricky projects.

What do you do in your spare time?
I enjoy many things, including watching movies (any kind), dancing salsa with my wife (she wants me to also learn ballroom dancing) and rock climbing. I recently took four days off and climbed, with a friend and fellow scientist, some beautiful limestone walls in Mexico. I also enjoy mountain biking with a colleague from the school of civil and environmental engineering, although he is much better than I am. More recently I started whitewater kayaking with my neighbour, as well as my own photoblog.

What achievement are you most proud of so far in your career?
I can think of two projects, very different from each other. The first one was at Stanford University, when we finally obtained good and stable signals with a newly developed Hadamard-transform time-of-flight mass spectrometer. The second achievement is when we used some of the analytical techniques developed in my lab to help in identifying a source where a large number of fake antimalarials were being produced.

If you had one piece of advice to pass on to young scientists, what would it be?
Do your best at balancing work and personal life. If you have to work a full weekend, make sure you take a rest day later on.

Reference

1 Amy L Lane *et al*, *Proc. Nat. Acad. Sci. USA*, 2009, DOI: 10.1073/pnas.0812020106

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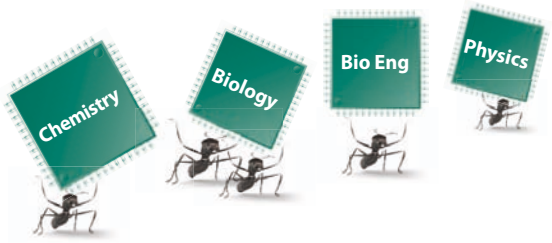

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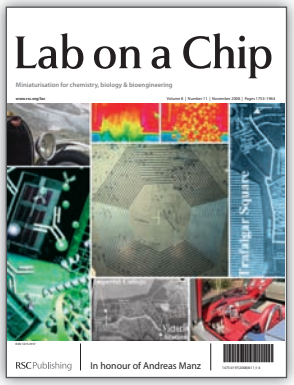

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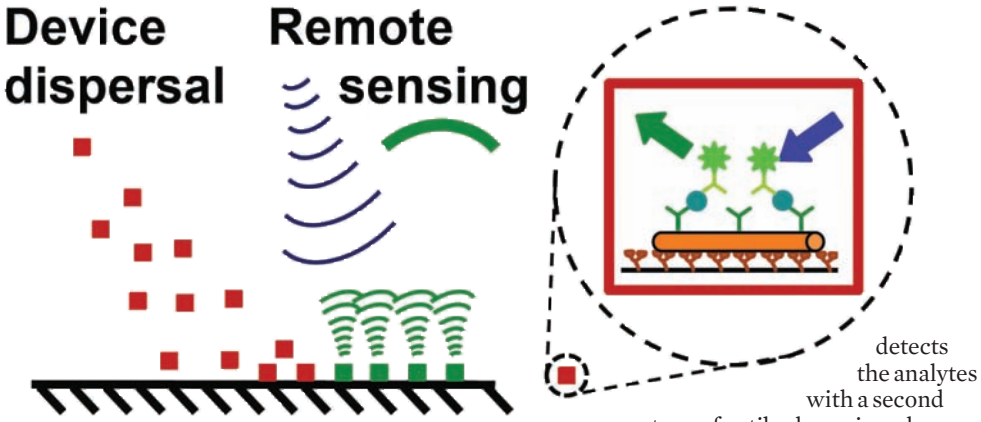
Instant insight

Molecular shuttle power

Smart dust biosensors may be smaller than a grain of sand but they have big potential, say Henry Hess, at the University of Florida, Gainesville, US, and colleagues



With a built-in power source and driven by molecular motors, smart dust biosensors are remotely activated to detect toxins

A beehive is a very interesting biosensor: bees disperse from the hive, sample a large area and report their findings back to the hive. The concept of smart dust devices mimics this remote environmental monitoring process. A large number of devices dispersed over an area would be left to interact with a sample and then communicate their findings to scientists from a distance. To be economically feasible, such single-use devices have to be cheap, even cheaper than the radio-frequency identification tags currently used to track the inventory of warehouses, for example. Consequently, the devices cannot be much larger than a grain of sand, thus the name 'smart dust'.

The design of smart dust sensors is a new frontier in the miniaturisation of lab-on-a-chip devices, since the traditional model of a passive cartridge inserted into a hand-held or desktop device has to be abandoned. The smart dust concept originated in the 1990s, but the size of the assembled microelectronic devices exceeded a cubic millimetre. In 2005, scientists suggested a bottom-up, particle-based strategy, where the spectral properties of engineered porous silicon microparticles changed as they were exposed to hydrocarbon fumes.

A third conceptual approach uses hybrid devices, combining synthetic components with active nanostructures of biological origin. This approach is promising because cells have evolved many sub-systems that are also critical in a lab-on-a-chip context. Active nanoscale transport is one such subsystem. Biomolecular motors, such as the motor protein kinesin, use energy provided by adenosine triphosphate (ATP) hydrolysis to move along the cytoskeleton and distribute a variety of cargo. Reconstituting this active transport mechanism in a smart dust device would overcome one of the bottlenecks to designing an autonomous microdevice: the pump or battery required for transport by pressure-driven fluid flow and electro-osmotic flow could be replaced by ATP-powered nanotransporters assembled from proteins.

Research efforts into the design of such nanotransporters, also called molecular shuttles, have laid the foundation for designing a complex smart dust biosensor. Scientists have developed approaches to guide molecular shuttles along predetermined paths, load them with a variety of cargo and control their activation.

At the heart of this biosensor is the double-antibody-sandwich (DAS) assay, a workhorse in biotechnology. A traditional DAS assay captures analytes with surface-adsorbed antibodies. It detects the analytes with a second type of antibody equipped with an optical tag or an enzyme catalysing a colour-changing reaction. While the traditional assay involves multiple exchanges of solution, the smart dust sensor exploits antibody-functionalised shuttles to capture the analytes, transport them to a tagging station and then move tagged analytes to a detection zone.

Designing such a biosensor not only requires some advanced molecular engineering but also consideration of the real world challenges that the device will encounter. These challenges include storing molecular shuttles long-term and creating fluorescence signals of sufficient brightness for remote read-out.

The design, fabrication and testing of complex devices provides a focal point for the technological concepts and a proving ground for the specific solutions. Smart dust biosensors integrate the advances of the last decade in the field of nanoscale transport systems.

Read more in 'Smart dust biosensors powered by biomolecular motors' in issue 12 of Lab on a Chip.

Reference
G D Bachand *et al*, *Lab Chip*, 2009, DOI: 10.1039/b821055a

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Essential elements

Celebrating bioscience

Experimental Biology 2009, New Orleans, US, 18–22 April, saw the perfect opportunity for RSC Publishing to display its impressive bioscience journals portfolio. Visitors to the RSC picked up free copies of recently launched journals *Integrative Biology* and *Metallomics*, as well as the established *Molecular BioSystems*, *Organic & Biomolecular Chemistry*, *Photochemical & Photobiological Sciences* and *Natural Product Reports*. RSC staff were also available to provide online demonstrations of enhanced HTML articles via *RSC Prospect*. Many visitors also entered the competition to win an iPod Touch, and the lucky winner, drawn at random from the entries, is Abu-Bakr Al-Mehdi, University of South Alabama, Mobile, US.

Also at this event, *Integrative Biology* celebrated its 2009 launch in style on 19 April with an evening reception. Guests were welcomed with refreshments and the editor, Harp Minhas, was on hand to provide details and answer questions regarding this exciting new journal. *Integrative Biology* focuses on quantitative multi-scale biology using enabling technologies and tools to exploit the convergence of biology with physics, chemistry, engineering, imaging and informatics.

'*Integrative Biology is looking great – just hits the mark and all the articles are innovative, highly of interest and thought provoking.*' Philip Day, University of Manchester, UK

Visit our booth at the 34th FEBS conference in Prague, the Czech Republic, this July. We will be holding another reception, this time to celebrate *Molecular BioSystems*' 5th year of publication.

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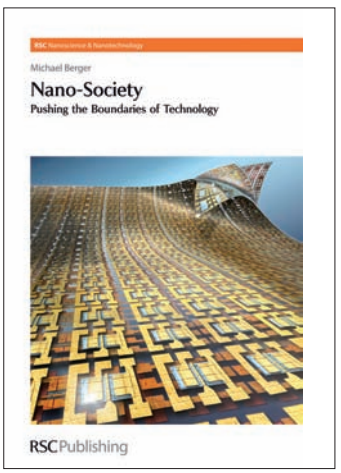

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An efficient synthesis of glyceryl ethers: catalyst-free hydrolysis of glycidyl ethers in water media

Akira Saito,*[a] Takeshi Shirasawa,[b] Shinichiro Tanahashi,[b] Mitsuru Uno,[a] Nobuhiro Tatsumi[b] and Tomohito Kitsuki[a]

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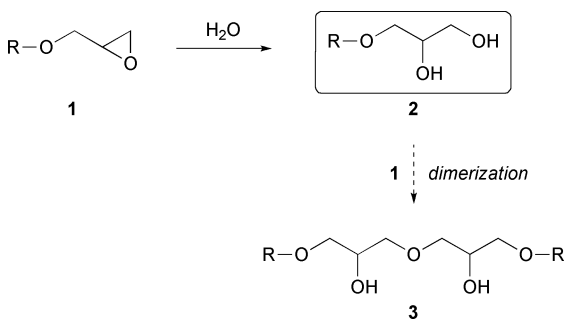
Hydrolysis of hydrophobic glycidyl ethers in pressurized water media afforded the corresponding glyceryl ethers in good to excellent selectivity within several minutes without catalyst.

Glyceryl ether and its derivatives are well known as a group of ether lipids and are of great interest due to their pharmaceutical and physical properties.[1] In particular, alkyl glyceryl ethers are utilized as nonionic surfactants and have been widely applied to cosmetics, personal care and household products.[2] In general, alkyl glyceryl ethers are obtained from corresponding alkyl glycidyl ethers, and various synthetic methods have been proposed.[3] For example, Urata *et al.* reported that alkyl glycidyl ethers were converted into corresponding dioxolanes or 1-*O*-alkyl-2,3-di-*O*-acetylglycerols and subsequent hydrolysis was carried out to provide alkyl glyceryl ethers in high yield and high selectivity.[4] Although these methods were useful, it was necessary to make great efforts for purification and a lot of waste materials were generated for industrial production. To solve such problems, direct hydrolysis of glycidyl ethers with water molecules has been suggested (Scheme 1).[5] However, a dimerization reaction occurred preferentially because of the low solubility of glycidyl ethers in water. Therefore, a decrease in yield and selectivity of glyceryl ethers often resulted without appropriate organic solvents.



Scheme 1

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Table 1 Hydrolysis of glycidyl ethers under hydrothermal conditions [a]

Entry	Substrate	Water/**1** (mol/mol)	Reaction time/min	Conversion (% of **1**[b])	Selectivity (% of **2**[b])
1	**1a**	2	120	>99	66
2		8	10	>99	89
3		20	5	>99	95
4	**1b**	2	540	>99	70
5		6	140	>99	82
6		20	120	>99	91

[a] All reactions were carried out at 200 °C, 1.5 MPa. [b] Determined by GC analysis.

Recently, Jamison's group revealed that the cascade epoxide-opening reaction was promoted by hot water to obtain polyether marine natural products selectively.[6] Furthermore, Qu *et al.* reported that hydrolysis of epoxides and aziridines proceeded in hot water, and they proposed hot water acted as a moderate acid catalyst, reactant and solvent.[7] These results suggested that epoxy compounds were able to be hydrolyzed in several hours by the use of a large excess of water. In this paper, we report our experiments on the direct hydrolysis of glycidyl ethers in pressurized water media at high temperature. By adopting this method, hydrophobic glycidyl ethers were able to be converted selectively into corresponding glyceryl ethers without catalyst within several minutes.

Our initial examination was focused on the possibility of selective hydrolysis of glycidyl ethers **1** under hydrothermal conditions. Different equivalents of water were added to an autoclave reactor with butyl glycidyl ether **1a** (R = butyl) as a representative substrate. Although **1a** was completely consumed in 120 min with 2 molar equivalents of water (200 °C, 1.5 MPa), butyl glyceryl ether **2a** was obtained in only 66% selectivity (entry 1 in Table 1) and the dimerization product **3a** was formed as the main by-product. The excessive amount of water played an important role in hydrolysis of glycidyl ethers both in reactivity and selectivity. With 8 and 20 molar equivalents of water, the reaction proceeded immediately within 10 min to give **2a** in 89 and 95% selectivity, respectively (entries 2 and 3). Subsequently, we carried out the reactions with the more hydrophobic substrate **1b** (R = 2-ethylhexyl). In contrast to previous examinations, the consumption of **1b** was sluggish and **2b** was obtained in 91% selectivity after 120 min at 200 °C, even if 20 molar equivalents of water were applied to the reaction (entry 6).

To accomplish further improvement of reactivity and selectivity, we next examined the influence of reaction temperature against hydrolysis of **1b**. For this purpose, we designed a

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Table 2 Hydrolysis of glycidyl ethers with tubular reactor [a]

Entry	Substrate	R	Water/**1** (mol/mol)	Temp/ °C	Pressure/MPa	Residence time/min	Conversion (% of **1**[b])	Selectivity (% of **2**[b])
7	**1b**	2-ethylhexyl	10	250	5.0	7.2	88	92
8			40	250	5.0	5.2	>99	96
9			80	250	5.0	3.9	>99	98
10[c]	**1c**	isodecyl (isomer mixture)	100	250	5.0	1.3	41	>99
11[c]			100	270	6.5	1.3	83	>99
12[c]			100	270	6.5	2.5	>99	>99
13	**1d**	hexyl	80	250	5.0	4.0	>99	98
14	**1e**	3,5,5-trimethylhexyl	80	250	5.0	4.0	98	90
15	**1f**	phenyl	80	250	5.0	4.0	>99	99

[a] Reaction tube: 1 mm i.d., 1700 mm. [b] Determined by GC analysis. [c] These reactions were carried out with 1 mm i.d., 10 000 mm tube.

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tubular reactor system equipped with plunger pumps and a back pressure regulating valve (Fig. 1).† The substrate and water were injected to the reaction coil respectively and heated at a certain temperature. The molar ratio of water and **1b** was set to 10/1 by adjusting the flowing quantity of each pump. The pressure was set, using the back-pressure regulating valve, to be higher than the saturated aqueous vapor pressure at that temperature. Fig. 2 illustrates the rate of consumption of glycidyl ether **1b** at various reaction temperatures. At 230 °C, the consumption of **1b** was still sluggish. However, the reaction

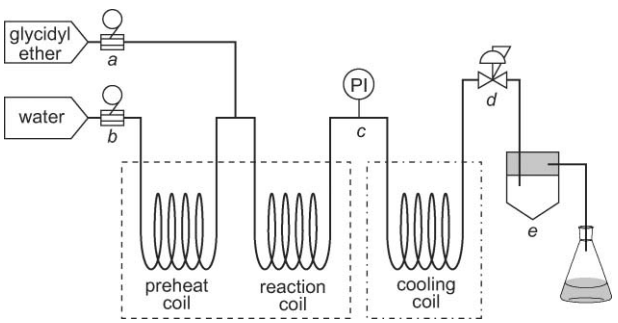

Fig. 1 Schematic diagram of flow reaction system for hydrolysis of glycidyl ethers. (*a*, *b*: plunger pumps, *c*: pressure indicator, *d*: back pressure regulating valve, *e*: water/oil separator).

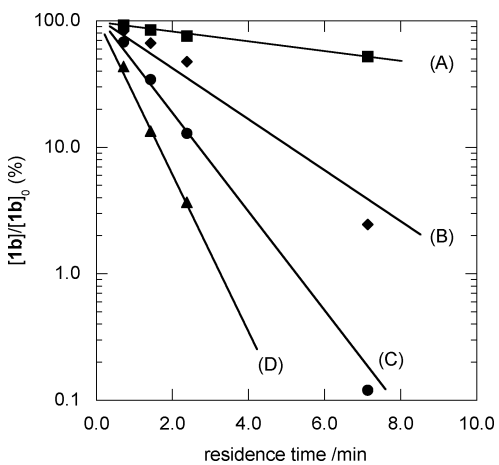

Fig. 2 Consumption rate of **1b** at various temperatures. All reactions were carried out with 10 molar equivalents of water. (A) 230 °C, (B) 250 °C, (C) 270 °C, (D) 285 °C.

was accelerated tremendously with an increase in temperature and the conversion of **1b** was up to 99% within 10 min at 250 °C or more. And we have found that the selectivity of **2b** could be improved by increasing the amount of water (entries 7–9, in Table 2). The more hydrophobic substrate **1c** (R = isodecyl, isomer mixture) was hydrolyzed selectively within 3 minutes, although a high reaction temperature was required (entries 10–12). In addition, we attempted hydrolysis of other aliphatic and aromatic glycidyl ethers, and corresponding glyceryl ethers were obtained efficiently and selectively (entries 13–15).

According to our experimental results, the hydrolysis reaction of glycidyl ethers did not require any catalysts and the selective addition of water molecule was observed in pressurized water media at high temperature within several minutes. Water under these conditions is called subcritical water and has been widely used for extraction of valuable materials from biomass,[8] for oxidative degradation of hazardous materials[9] and for hydrolysis of triglycerides.[10] However, applications of subcritical water for selective organic synthesis seems to be limited.[11]

Since the critical point of water is 374 °C and 22.1 MPa, there is a wide range of temperatures and pressures between ambient and supercritical water conditions. Water in the subcritical region has unique characteristics, such as dramatically decreased dielectric constant (permittivity) and surface tension with increasing temperature under moderate pressures.[12] For instance, the dielectric constant of water at 250 °C is equal to that of methanol at ambient temperature. Therefore, the solubility of nonpolar organic compounds in water is greatly enhanced with increasing temperature. In the hydrolysis of glycidyl ethers, it is conceivable that the improvement of selectivity and reactivity was able to be achieved owing to the enhancement of the solubility of glycidyl ethers by tuning of temperature and water ratio.

Thus, we have found that glyceryl ethers can be prepared selectively by the direct hydrolysis of corresponding glycidyl ethers in pressurized water media at high temperature. In the case of using glycidyl ethers having middle-to-long alkyl chain as substrates, the products and water were easily separated after cooling to ambient temperature at atmospheric pressure. Since this reaction requires no catalysts and solvents, no impurities (except for those originating from the raw materials) are present in the separated water. Therefore, it is possible to reuse the collected excessive water by a simple separation process. By adopting a water recycling system, we achieved 90% water

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recovery and confirmed the hydrolysis reaction was continuously executable.

Acknowledgements

We are grateful to Dr A. Kawamata and Mr N. Katada of Kao Corporation for permission to publish this paper. And we also acknowledge for Mr M. Okutsu, Mr S. Tamaki and Mr O. Tabata for useful comments and suggestions.

Notes and references

† The flow reaction system (Fig. 1); deionized water was introduced into the preheated coil from a plunger pump and heated with oil bath. The preheated water from the coil went through a T-connector and the glycidyl ether was introduced at this connector from another plunger pump. The water–glycidyl ether mixture then passed through the reaction coil (1 mm i.d., 1700 mm). At the end of the reaction tube, the overall reaction pressure was checked with an indicator. After passing the cooling coil, the reaction mixture was introduced into a water–oil separator through a back pressure regulating valve. For a typical reaction (Table 2, entry 9), the oil bath was set to a temperature at 250 °C, the water pump was then set to a constant flow of 300 μL min^{-1}, and then water flow was commenced as the oil bath was heated. The back pressure regulator was set for an overall system pressure of 5.0 MPa and the cooling bath was operated at 80 °C. The pump for 2-ethylhexyl glycidyl ether **1b** was set to a constant flow of 43.1 μL min^{-1} (the molar ratio of water/**1b** became 80/1) and introduced into the system. After hydrolysis, the water/oil stream was cooled and depressurized, and collected in a water–oil separator. 2-Ethylhexyl glyceryl ether **2b** was obtained from oil phase.

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A green and efficient oxidation of alcohols by supported gold catalysts using aqueous H_2O_2 under organic solvent-free conditions†

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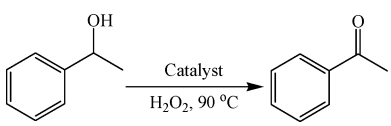
The use of supported gold nanoparticles as an efficient, green and reusable catalyst for the oxidation of various alcohols to the corresponding carbonyl compounds using aqueous hydrogen peroxide as an environmentally benign oxidant is presented. The reaction proceeds with good to excellent yields in particular for nonactivated alcohols under base-free conditions.

Oxidation of alcohols to their corresponding carbonyl compounds is one of the most important processes for production of fine and specialty chemicals.[1] Traditional methods involve use of toxic and expensive stoichiometric metal oxidants, such as chromate and permanganate,[2] or harmful organic solvents,[3] or require vigorous reaction conditions.[4] From both the environmental and economic points of view, there is a strong incentive to develop a green, economic and efficient alcohol oxidation process.[5] In this context, much recent attention has been directed toward the aerobic oxidation of alcohols with reusable heterogeneous solid catalysts in aqueous media under mild conditions,[6] which is particularly suitable for industrial practices. However, very few catalysts are sufficiently active for nonactivated alcohols, like aliphatic and alicyclic alcohols.[7] In particular, bases such as KOH or K_2CO_3 are frequently needed for oxidation of primary aliphatic alcohols (*e.g.* 1-octanol) in water,[8] which is clearly not green and presents notorious problems such as corrosion and waste base treatment. In this respect, the development of a novel catalytic system that exhibits a wide range of substrate tolerance under mild and base-free aqueous conditions still remains a major challenge.

Supported gold catalysts have attracted tremendous recent attention owing to their unique catalytic properties for a broad array of organic transformations,[9] especially for aerobic oxidation of alcohols under mild conditions.[6c,d,9a,10–12] Over the last few years, our group,[11] Kobayashi *et al.*[6c] and Corma *et al.*[12] reported that Au nanoclusters deposited on metal oxides or polymers are highly effective for aerobic oxidation of various alcohols. In general, organic solvents and/or bases are necessary to achieve high yield and selectivity.[11] The oxidation of alcohols under solvent- and base-free conditions was reported,[12,13] the yield of target product was, however, much lower than that obtained with organic solvent and/or base conditions. Herein, we report the development of a new efficient H_2O_2–Au system exhibiting significantly enhanced activity for the oxidation of alcohols under base-free aqueous conditions. Hydrogen peroxide (H_2O_2), previously established to be an ideal oxidant for the green oxidation of alcohols with homogeneous metal peroxo complexes,[14] has shown to be particularly effective for gold catalyzed selective oxidation of nonactivated alcohols. To the best of our knowledge, this study also forms the first hectogram-scale clean synthesis of aliphatic acids using gold catalysts.

First of all, 1-phenylethanol was used as a model substrate to study the catalytic activity of the different supported gold catalysts. The results of these studies (Table 1) show that gold supported on carbon leads to very low conversion (*ca.* 12%). The Au/Fe_2O_3 and Au/Al_2O_3 catalysts show moderate activity (*ca.* 34–37%), while Au/TiO_2 supplied by the World Gold Council and Au/CeO_2 give a higher conversion value (*ca.* 58–62%), gold supported on TiO_2 supplied by Mintek afford the highest conversion (*ca.* 99%), with yields of isolated product of between 98 and 100%.‡ No conversion was found in the absence of catalyst or the use of Au-free TiO_2 catalysts under similar reaction conditions. Additional examination of the relationship between the alcohol oxidation activities and a series of Mintek Au/TiO_2 catalysts calcined at elevated temperatures (Fig. S1–4 in ESI)† revealed that use of smaller Au nanoparticles gave higher activity, as shown in Fig. 1. This result, together with the fact that the small Au NPs can substantially facilitate the crucial H_2O_2 decomposition,[15] strongly suggests that the high dispersion of Au NPs in combination with a beneficial synergetic interaction with the TiO_2 support is the key factor

Table 1 Oxidation of 1-phenylethanol by aqueous H_2O_2 [a]



Entry	Catalyst	Conversion (%)
1[b]	0.8% Au-C (WGC)	12
2	4.5% Au-Fe_2O_3 (WGC)	34
3	1.5% Au-TiO_2 (WGC)	62
4	0.9% Au-Al_2O_3 (Mintek)	37
5	1% Au-TiO_2 (Mintek)	99
6	1% Au-CeO_2	58

[a] Reaction conditions: 10 mmol 1-phenylethanol, 10 mL H_2O, 90 °C, 5% H_2O_2 added dropwise, substrate:H_2O_2:Au = 100:150:1. [b] This sample catalyst was used as-received. According to the characterizations of the Au/C sample provided by the World Gold Council, the water content of the Au/C reference catalyst was equal to 40%.

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† Electronic supplementary information (ESI) available: Experimental section, TEM and XPS data. See DOI: 10.1039/b820197h

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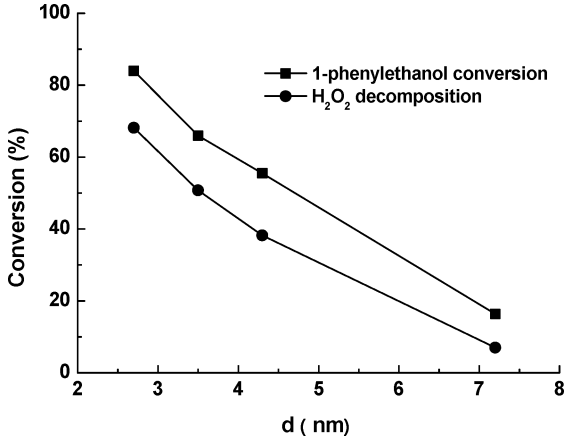


Fig. 1 1-Phenylethanol conversion and H_2O_2 decomposition *versus* gold particle dimension; oxidation of 1-phenylethanol: 10 mmol 1-phenylethanol, Au/TiO_2 (Mintek), 10 mL H_2O, 90 °C, 5% H_2O_2 added dropwise, substrate:H_2O_2:Au = 100:110:1; H_2O_2 decomposition: 1.5 wt% H_2O_2 aqueous solution 10 mL, Au/TiO_2 (Mintek) 80 mg, 25 °C for 80 min in open air. The rate of decomposition was calculated based on the amount of H_2O_2 remaining, which was measured by the titration of 0.1 M $Ce(SO_4)_2$ with 1.5 w/v% ferroin solution as an indicator.

for achieving high activity in the H_2O_2-mediated oxidation of alcohols.

The Mintek Au/TiO_2 catalyst was stable and can be easily reused in the oxidation of 1-phenylethanol. After the first alcohol oxidation, the catalyst was separated from the reaction mixture by filtration, thoroughly washed with water, and then reused as catalyst for the next run under the same conditions. As shown in Fig. 2, the acetophenone yields remained essentially constant for the five successive cycles, reflecting the high stability and reusability of the catalyst. This was consistent with the characterization results for this catalyst. TEM and XPS results (Fig. S5 and S7 in ESI)† showed essentially no changes in the mean diameters of the Au nanoparticles and in the metallic state of Au, respectively, after the five successive runs. Moreover, it was confirmed by induced coupled plasma (ICP) techniques that the Au content of the used Au/TiO_2 catalyst was the same as that of the fresh catalyst and that no Au was in the filtrate.

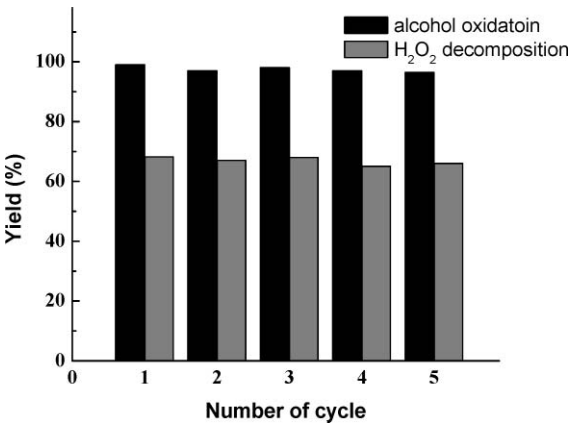
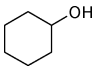
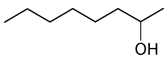
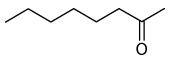
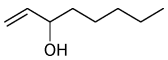
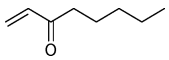
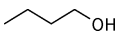
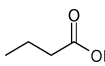
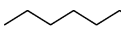
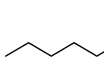
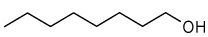
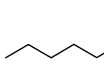


Fig. 2 Recycling of the Mintek Au/TiO_2 catalyst for the oxidation of 1-phenylethanol: 10 mmol substrate, 10 mL H_2O, 90 °C, 5% H_2O_2 added dropwise. Substrate:H_2O_2:Au = 100:150:1. For comparison, the corresponding H_2O_2 decomposition rates are also included.

Table 2 Oxidation of non-activated alcohols by aqueous H_2O_2[a]

Entry	Substrate	Product	Conv. (%)	Sel. (%)
1			87	100
2			98	100
3			>99	100
4[b]			>99	100
5[b]			>99	>99
6[b]			>99	90[c]

[a] Reaction conditions: 10 mmol Substrate, 10 mL H_2O, 90 °C, 5% H_2O_2 added dropwise, substrate:H_2O_2:Au = 100:150:1. [b] Substrate:H_2O_2:Au = 100:250:1. [c] Octyl octanate was found as by-product.

To examine the scope of the alcohol reaction with the H_2O_2–Au/TiO_2 system, we extended our studies to various structurally different alcohols. The results are summarized in Table 2. It was found that primary and secondary alcohols were oxidized to the corresponding carboxylic acids and ketones, respectively. Notably, H_2O_2–Au/TiO_2 was capable of catalyzing the oxidation of various nonactivated alcohols. For alicyclic alcohols and secondary aliphatic alcohols, *i.e.* 2-octanol, they gave ketones in excellent yields of 87–98% (Table 2, entries 1–2). Moreover, it was found that the chemoselective oxidation of allylic alcohols having a terminal double bond, such as 1-hexene-3-ol, also proceeded efficiently (Table 2, entry 3). Contrastingly, a previously reported H_2O_2–Pt black system is found to be totally inactive for this substrate, owing to a strong coordination of the –C=CH_2 group to the Pt^0 complex.[16] It is especially noteworthy that H_2O_2–Au/TiO_2 was highly active for the oxidation of primary aliphatic alcohols, the most inactive alcohols, in the absence of any bases (Table 2, entries 4–6). For example, the yield of 1-hexanoic acid in 1-hexanol oxidation was as high as 99% at a 100% conversion.

Furthermore, it was found that the H_2O_2-mediated oxidations also proceeded smoothly in a hectogram-scale synthesis to give a high yield of formation of the corresponding carboxylic acids. As shown in Scheme 1, by stirring a mixture of 1-hexanol (100 g) in the presence of a 0.01 molar amount of Au catalyst and 3.0 molar amount of aqueous H_2O_2 (5%) for 2.5 h, 1-hexanoic acid could be obtained in a 93% yield (105.6 g). Notably, this is the first example of a hectogram-scale clean oxidation of alcohols under base-free conditions in neat water using a heterogeneous gold catalysts.

Activated alcohols, such as benzylic alcohols, were also oxidized at 90 °C with H_2O_2 in the presence of Au/TiO_2 to give the corresponding carbonyl compounds in good to excellent yields (Table 3). Like most of the catalysts reported

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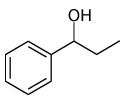
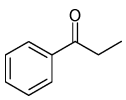
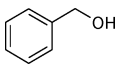
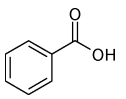
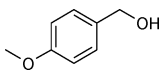
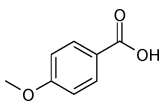
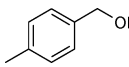
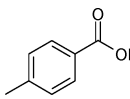
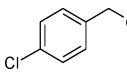
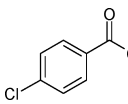
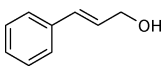
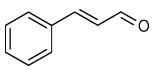
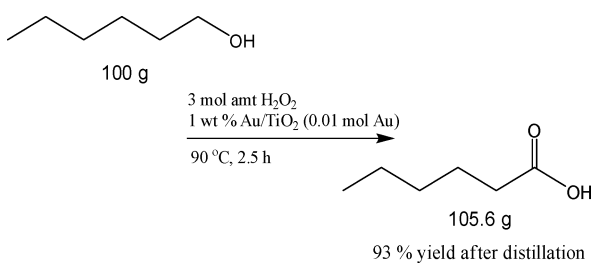
Table 3 Oxidation of activated alcohols by aqueous H_2O_2[a]

Entry	Substrate	Product	Conv. (%)	Sel. (%)
1[b]			>99	100
2			>99	85[c]
3			>99	44[c]
4			>99	61[c]
5			>99	37.5[c]
6[b]			>99	100

[a] Reaction conditions: 10 mmol substrate, 10 ml H_2O, 90 °C, 5% H_2O_2 added dropwise, substrate:H_2O_2:Au = 100:250:1. [b] Substrate:H_2O_2:Au = 100:150:1. [c] Aldehyde was found as by-product.



Scheme 1 Hectogram-scale oxidation of 1-hexanol.

previously,[6–12] Au/TiO_2 efficiently catalyzed the oxidation of secondary aromatic alcohol, such as 1-phenylpropanol (Table 3, entry 1), almost quantitatively to their target products (~99% yields). Benzyl alcohol was oxidized to benzoic acid at a 100% conversion, although with a selectivity of only 85% (Table 3, entry 2; the other product was mainly benzaldehyde). Benzyl alcohols with electron-donating groups were also successfully oxidized, in which a shift in selectivity from acids to benzaldehydes was observed (Table 3, entries 3–5). It is worth noting that chemoselective oxidation of cinnamyl alcohol with the sole formation of cinnamaldehyde could be accomplished (Table 3, entry 6). Interestingly, an epoxidized compound of cinnamyl alcohol was not observed. All these results clearly showed the efficiency of the H_2O_2–Au/TiO_2 system in the oxidation of both activated and nonactivated alcohols in water.

Attempting to gain insight into the origin of the enhanced activity achieved by using aqueous H_2O_2 as oxidant is important. Although an extensive mechanistic study has not yet been conducted, it is known that the α-hydrogen abstraction of an alcohol may be involved in the rate determining step based on the isotope kinetic study (k_H/k_D = 1.7–2.0).[17] In addition, H_2O_2 was found to be indispensable for the reaction progress as inferred by the data in Fig. 1, which prompted us to propose a possible mechanism of the present H_2O_2–Au-mediated alcohol oxidation, as illustrated in Fig. S8 (ESI).† The key aspect of H_2O_2 is to facilitate the abstraction of the α-hydrogen as a hydrogen scavenger, leading to the formation of a metal-alcoholate species during the initial step of the reaction. The Au-alcoholate complex may be further attacked by H_2O_2 or the Au-hydridoperoxide complex generated from the reaction of Au^0 with H_2O_2, to form the final carbonyl compound *via* a β-elimination pathway. The overall effect is that a dramatically boosted activity for alcohol oxidation is achieved in contrast to the normal aerobic process in which dioxygen or air was used as the oxidant.

In summary, we have demonstrated that the Au/TiO_2 catalyst has great potential for the environmentally benign oxidation of alcohols with aqueous hydrogen peroxide under mild and organic solvent-free conditions. The H_2O_2–Au/TiO_2 protocol has been proven to be particularly efficient in the oxidative transformation of nonactivated alcohols in aqueous media. The stability of the catalyst has also been demonstrated convincingly by conducting five successive runs without a significant drop in the reaction rate. Further extension of the present H_2O_2–Au catalytic system to many other key oxidative transformations is currently being explored.

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Notes and references

‡ Without the use of H_2O_2 (under an air atmosphere), acetophenone was obtained in only <10% yield over the Mintek Au/TiO_2 catalyst.

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15 The higher H_2O_2 decomposition rate achieved for catalysts with smaller Au particle size can be attributed to the higher abundance of low-coordinated Au atoms, which are also believed to be the key sites for low temperature CO oxidation.

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Synthesis of novel 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides under microwave irradiation in neat water†

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Novel 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides were prepared in one step by nucleophilic substitution reaction of 6-choloropurine nucleosides with diethanolamine. Shorter reaction times and higher yields were achieved under microwave irradiation conditions in neat water.

Nucleosides play important roles in many biological processes. Many nucleoside analogues with modifications on the heterocyclic bases have been investigated for their antiviral and anticancer activities.[1] There are extensive interests in the study of purine derivatives with various substituents at C6 due to their broad spectrum of biological activities.[2] N6-(2-hydroxyethyl)adenosine (HEA) (**1**), which behaves as a Ca^{2+} antagonist and an inotropic agent, was isolated from cordyceps and isaria species.[3] 6-[*N*,*N*-Bis (2-hydroxyethyl)amino]-9-(2-β-*C*-methyl-β-D-ribofuranosyl)-purine (**2**)[4] and 6-[*N*,*N*-bis-(2-hydroxyethyl)aminomethyl]-9-(β-D-ribofuranosyl)purine (**3**)[5] showed potency in inhibiting HCV RNA replication (Fig. 1).

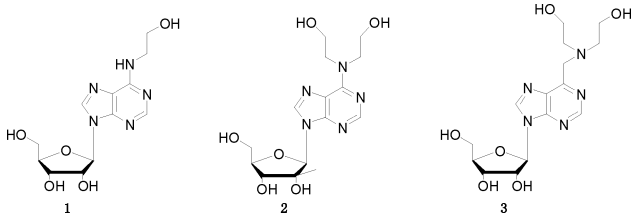
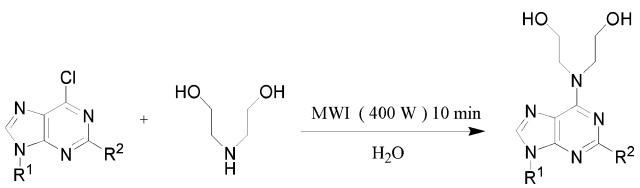


Fig. 1 Structures of some 6-hydroxyethylpurine nucleosides.

However, there are few reports on the synthesis of such 6-hydroxyethylpurine nucleosides[6a,6b] and no detailed study on such compounds. Recently, we have reported the synthesis of C6-modified purine nucleosides such as C6-cyclo secondary amine substituted purine analogues, C6-phosphonated purine nucleosides and 6-*N*-(2-hydroxyethyl)aminopurine nucleosides under microwave irradiation.[7] The results showed that the microwave-promoted method was very successful for various modifications of nucleoside analogues. Based on our preliminary study, we carried out a rapid and convenient method for the preparation of novel 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides in good to excellent isolated yields under microwave irradiation in neat water, aiming at providing an efficient route to the synthesis of new nucleoside analogues which are important candidates for biologically active compounds.

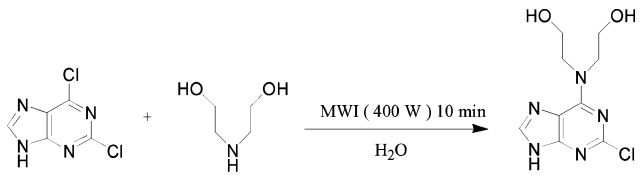
6-[*N*,*N*-Bis(2-hydroxyethyl)amino]purine nucleosides were prepared from commercially available 6-chloropurine nucleosides and various N9-substituted 6-chloropurine nucleosides that can be synthesized by alkylation of 6-chloropurine with nonsugar carbon chain, and then reacted with diethanolamine under microwave irradiation (Scheme 1). The procedures for synthesis of nucleosides analogues under microwave irradiation were well developed in our laboratories. Products (**3a–3m**) were purified by column chromatography in yields of 57–91%. Their structures were confirmed by NMR spectra and high-resolution mass spectrometry.



Scheme 1 Microwave-promoted synthesis of 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides.

To initiate our study, the influence of reaction conditions was examined. As shown in Table 1, when CH_2Cl_2 was used as the solvent, no reaction was observed (entry 1), when CH_3CH_2OH

Table 1 Effect of solvent and the optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Solvent	*T*/°C	Time/min	Yield[b] (%)
1	CH_2Cl_2	40	10	No reaction
2	CH_3CH_2OH	80	10	40
3	DMF	60	10	89
4	H_2O	80	15	88
5	H_2O	100	10	91
6	H_2O	120	8	90

[a] Reaction conditions: 2,6-dichloropurine (1 mmol), diethanolamine (1.5 mmol), H_2O (5 mL), MWI 400 W (100 °C). [b] Isolated yields based on nucleobases.

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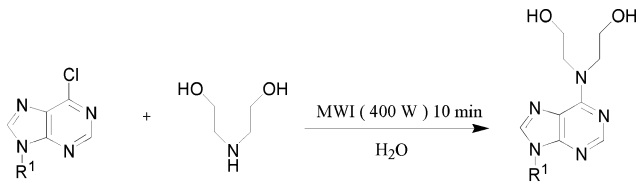
was used as the solvent, low yield was obtained (entry 2) (40%). With increasing solvent polarity, the yields were improved. When DMF was used as the solvent, the yields could reach to 89% (entry 3), but many side products were produced in this reaction medium. To overcome the disadvantages of these organic solvent, we used neat water as the solvent, and product **3a** was still formed in good yield (entry 5) (91%). It is noteworthy that no side products were obtained in water and the product **3a** could crystallize from the reaction system and could be separated easily by direct filtration. At room temperature, the yield was low. By increasing the temperature to 80 °C, the reaction completed within 15 min with a yield of 88% (entry 4). By increasing the temperature to 100 °C, the reaction completed within 10 min with a yield of 91% (entry 5). By increasing the temperature to 120 °C, no significant change in yield was observed (entry 6) (90%). Therefore, 100 °C and 10 min were the optimized reaction conditions. Further screening of irradiation power confirmed that 400 W was the best condition.

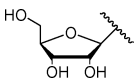
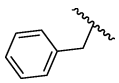
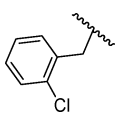
The substrate scope of 6-chloropurine nucleosides is summarized in Table 2, a group of different substituents at N9 were subjected to the optimized reaction conditions, including ribofuranosyl, *n*-butyl, allyl, benzyl, *etc.* The kinds of substituents had some impact on the yields. When R^1 was H, the yield was much higher (entry 1) (90%), ribofuranosyl-substituted substrates also give high yield (entry 2) (82%), and allyl-substituted substrates gave product **3f** with 78% (entry 3). With all these substrates, the products were prepared in good to excellent yields by using this one-step reaction.

Intrigued by the above-described results, more electron-rich 2-amino-6-chloropurine nucleosides were chosen as the substrates to probe whether the nucleophilic substitution could be easily accessed. As shown in Table 3, under microwave irradiation, 2-amino-6-chloropurine **1k** reacted with diethanolamine to afford **3k** with 83% yield (entry 3) and 2-amino-6-chloropurine nucleoside **1l** gave the corresponding product **3l** with 80% yield (entry 6), which indicated that 2-amino-6-chloropurine nucleosides can also react with this nucleophile smoothly in good yields. Our synthetic method using microwave irradiation is definitely valuable for the rapid access of these bioactive heterocyclic bases. The results in Table 3 also show that the relative activity of heterocyclic substrates for the nucleophilic substitution is in the order: 2,6-dichloropurine > 6-chloropurine > 2-amino-6-chloropurine, which indicated that

Table 2 Reaction of diethanolamine with various 6-chloropurines[a]

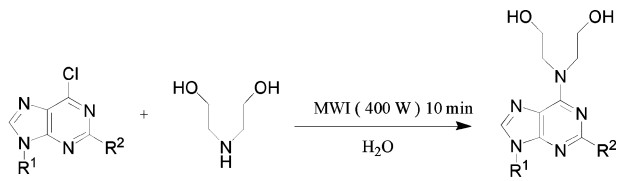


1e-1j **2a** **3e-3j**

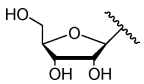
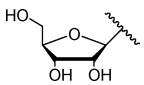
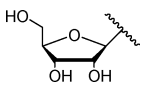
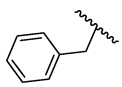
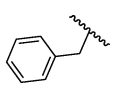
Entry	Product	R^1	Yield[b] (%)
1	**3e**	H	90
2	**3f**		82
3	**3g**		78
4	**3h**		75
5	**3i**		68
6	**3j**		61

[a] Reaction conditions: 6-chloropurine nucleosides (1 mmol), diethanolamine (1.5 mmol), H_2O (5 mL), MWI 400 W (100 °C). [b] Isolated yields based on nucleobases.

Table 3 Reaction of diethanolamine with various 6-chloropurines, 2,6-dichloropurines and 2-amino-6-choloropurines[a]



R^2=Cl, R^2=H, R^2=NH_2 **1a-1d, 1e-1h, 1k-1l** **2a** R^2=Cl, R^2=H, R^2=NH_2 **3a-3d, 3e-3h, 3k-3l**

Entry	Product	R^1	R^2	Yield[b] (%)
1	**3e**	H	H	90
2	**3a**	H	Cl	91
3	**3k**	H	NH_2	83
4	**3f**		H	82
5	**3b**		Cl	85
6	**3l**		NH_2	80
7	**3g**		H	78
8	**3c**		Cl	79
9	**3h**		H	68
10	**3d**		Cl	72

[a] Reaction conditions: 6-chloropurines (2,6-dichloropurines or 2-amino-6-chloropurines) nucleosides (1 mmol), diethanolamine (1.5 mmol), H_2O (5 mL), MWI 400 W (100 °C). [b] Isolated yields based on nucleobases.

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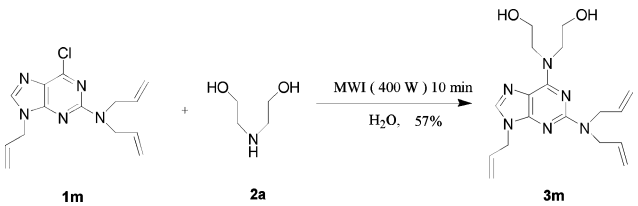
the electron-donating effects on C2 could lead to decrease of the yields.

In order to compare the efficiency of microwave irradiation with conventional heating, 2-amino-6-chloropurine was heated with 1.5 equiv of diethanolamine at 100 °C in an oil bath for 10 min to give 30% of 2-amino-6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine, far less than the 85% under microwave irradiation. This clearly indicated that the microwave-assisted reaction exhibited significant advantages over the conventional heating by not only reducing the reaction time but also improving the reaction time.

The use of microwave irradiation to generate 6-hydroxyethylpurine nucleosides was also tested on other 6-chloropurine derivatives. For example, 9-allyl-2-(*N*,*N*-diallyl)-6-[*N*,*N*-bis-(2-hydroxyethyl)amino]purine could also be synthesized from the corresponding 9-allyl-2-(*N*,*N*-diallyl)-6-chloropurine with an isolated yield of 57% using the same reaction conditions (Scheme 2).



Scheme 2 Reaction of diethanolamine with 9-allyl-2-(*N*,*N*-diallyl)-6-chloropurine.

It was found that the reaction of 6-chloropurine nucleoside and its analogues with diethanolamine could occur efficiently under microwave irradiation within 10 min. It is very easy to handle because most of the products can crystallize from the solution and the pure samples can be obtained in excellent yields after simple filtration and washing. And using water as solvent makes this method environmentally benign. This will be a highly useful method for the synthesis of 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides.

In conclusion, we have developed a rapid and operationally simple method for the preparation of various 6-[*N*,*N*-bis(2-hydroxyethyl)amino]purine nucleosides which are important candidates for biologically active compounds. The synthetic method using microwave irradiation is definitely valuable for the rapid access of these bioactive heterocyclic bases, and the pharmacological evaluation of these compounds is underway in our laboratories.

Acknowledgements

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Highly-selective and high-speed Claisen rearrangement induced with subcritical water microreaction in the absence of catalyst†‡

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Highly-selective, high-speed aromatic and aliphatic Claisen rearrangement was shown to give the corresponding product in an excellent yield induced by subcritical water microreaction in the absence of catalyst.

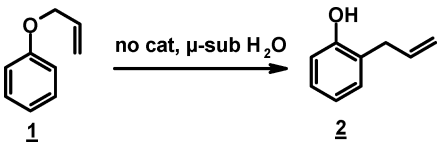
Introduction

The Claisen rearrangement is a fundamental organic reaction for the production of a large variety of important intermediates and fine chemical products.[1] Continuous efforts have been devoted to the development of a catalytic Claisen rearrangement with Lewis acids, such as BCl_3,[1a,2a] R_2AlCl[2b] and $PdCl_2(MeCN)_2$,[2c] to replace environmentally damaging processes which consume energy due to long reaction times and generate a large amount of solvent waste.[1b]

The Claisen rearrangement of allyl phenyl ether (**1**) to *o*-allylphenol (**2**) has been tested as a non-catalytic reaction model in a batchwise process to provide essential knowledge of [3,3] sigmatropic reactions (Table 1, entries1–4).[3] For example, in a solvent-free conventional heating method, **2** was produced with an 85% yield at 220 °C, ambient pressure and in long reaction time of 6 h.[3a] While in a similar batchwise process, but using subcritical water ($subH_2O$), the yield of **2** was 84% in a shorter reaction time of 10 min, at 240 °C and 3.4 MPa.[3b] In the same process, as the temperature increases to 245 °C and the reaction time to 60 min, the yield of **2** decreased to 45% due to the formation of by-products like 2-hydroxypropylphenol and 2-methylcoumaran. Furthermore, at 250 °C, 4.0 MPa and 60 min, 2-methylcoumaran was exclusively formed in a 72% yield.[3c]

Considering the solvent-free microwave heating process, **2** was obtained in a poor yield of 21% at 325–361 °C, 0.1 MPa and 10 min. However, the yield of **2** was drastically improved to 92% using DMF as solvent at 300–315 °C, 0.1 MPa and in a shorter reaction time of 6 min.[1b]

Herein, we report a new highly efficient non-catalytic Claisen rearrangement using a microreaction system in $subH_2O$, as shown in Scheme 1.



Scheme 1

The prefix "micro", applied to chemical micro processing, is generally defined as a continuous flow through regular domains with characteristic fluid channels of the "sub-millimetre" range,[4] hence the term "micro" will be used hereafter (see the ESI).‡

The concept of this methodology is based on the assumption that $subH_2O$ itself could work as a Lewis acid,[5a] but also that the dielectric constant (ε) could be controlled in the $subH_2O$ region[6,5b,c] through the adjustment of the pressure and temperature.[7] The $subH_2O$ microreaction system can provide a continuous operation characterized by an instantaneous heating and a subsequent quenching of the substrates with vigorous mixing, which leads to a high-speed Claisen rearrangement as well as preventing the consecutive hydrolysis and pyrolysis of the substrate and product. The obtained results confirm the feasibility of this approach and provide an insight for the function of water as a Lewis acid in the $subH_2O$ water region. They also demonstrate that the selectivity and separation procedure is effective compared to other methods, such as conventional organic solvents or solvent-free conditions.

Results and discussion

In an exploratory study, the Claisen rearrangement of **1** (0.77 mol kg^{-1}) to **2** was carried out in a $subH_2O$ microreaction system (see ESI)‡ as a test reaction.

At first, to determine the appropriate reaction conditions, the yield of **2** was plotted against the temperature, at a fixed pressure of 5 MPa and residence time of 81 s (see ESI, Fig. S1).‡ At around 265 °C, **2** was produced in the maximal yield of 73% with a 74% selectivity and without any sequential by-products, such as 2-hydroxypropylphenol and 2-methylcoumaran. When the pressure was changed to 10 MPa, under the same temperature of 265 °C and residence time of 81 s, the change in the product yield was minimal (76%) and within the experimental error limit

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‡ Electronic supplementary information (ESI) available: General experimental procedures and additional results. See DOI: 10.1039/b819106a

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Table 1 Claisen rearrangement from **1** to **2** by various methods

Entry	Method	Reactor type	Cat.	Solvent	Conc./mol kg^{-1}	T/°C	P/MPa	Reaction time	Sel. (%)	**2** yield (%)	Reference
1	CH[a]	B[c]	—	—	7.5	220	0.1	6 h	—	85	1b and 3a
2	subH_2O	B	—	H_2O	0.29	240	3.4	10 min	—	84	3b
3	MW[b]	B	—	—	—	325–361	0.1	10 min	—	21	1b and 3c
4	MW	B	—	DMF	—	300–315	0.1	6 min	—	92	1b and 3c
5	μ-SF[d]	F[f]	—	—	6.9	265	5	360 s	68	37	This work
6	μ-subH_2O[e]	F	—	H_2O	0.77	265	5	81 s	74	73	This work
7	μ-subH_2O	F	—	H_2O	0.27	265	5	149 s	98	98	This work

[a] Conventional heating. [b] Microwave heating. [c] Batchwise reactor. [d] Microreaction-solvent-free. [e] Microreaction with subH_2O. [f] Flow reactor.

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(see ESI, Fig. S2).‡ Therefore, 5 MPa was adopted as the optimal pressure at 265 °C and residence time of 81 s.

The residence time can be changed by the substrate flow rate and/or the water flow rate in a microreaction system. Fig. 1 exhibits the variation of residence time with conversion, selectivity and yield, at 265 °C and 5 MPa. The variation of the substrate flow rate from 0.25 to 0.75 g min^{-1} at a fixed water flow of 4.97 g min^{-1} results in an increase in the yield of **2** that follows an S-shaped trend with respect to the residence time (Fig. 1; line O–A–C–E). For example, the yield of **2** was 73% at a residence time of 81 s and a substrate flow rate of 0.49 g min^{-1} (Fig. 1; point C). The yield was increased to 88% as the residence time and the substrate flow rate was changed to 152 s and 0.25 g min^{-1}, respectively (Fig. 1; point E). Interestingly, increasing the water flow rate from 4.97 to 6.96 g min^{-1} at a fixed substrate flow rate of 0.49 g min^{-1} increased the yield of **2** to 95% with a 92% selectivity at 78 s (Fig. 1 and Fig. 2; point D); and, amazingly, when the substrate flow rate was changed to 0.25 g min^{-1}, **2** was exclusively produced with 98% yield and selectivity at 149 s (Fig. 1; point F). Hence, it is possible to obtain **2** with very high yields without any acid catalyst nor even any organic solvent.

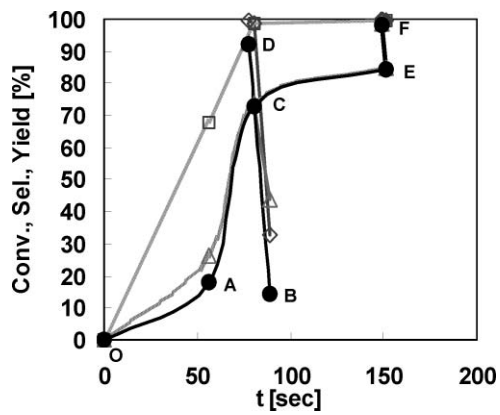

Fig. 1 Residence time *vs.* conversion (square), selectivity (triangle) and yield (filled circle) for the Claisen rearrangement of allyl phenyl ether (**1**) with subH_2O at 265 °C and 5MPa. Each point corresponds to the following water flow rates (g min^{-1}) and substrate flow rates (g min^{-1}); O (0.00, 0.00), A (4.9, 0.75), B (2.49, 0.49), C (4.97, 0.49), D (6.96, 0.49), E (4.97, 0.25) and F (6.96, 0.25). See also Fig. 2 for an enlargement of the region near points B, C and D.

In a typical procedure, a stream of **1** is placed across a high-speed flow of subH_2O and the resulting mixture is introduced into a microreactor, where the Claisen rearrangement proceeds rapidly as a result of the vigorous mixing caused by a turbulent

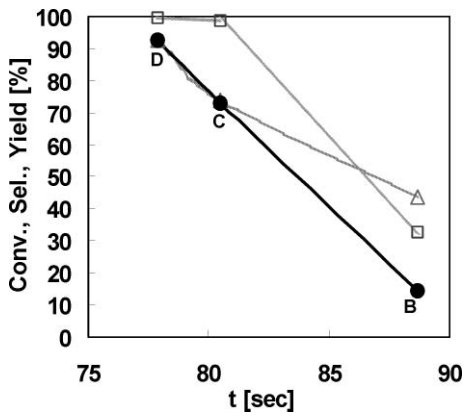

Fig. 2 Residence time (78 to 89 s) *vs.* conversion (square), selectivity (triangle) and yield (filled circle) for the Claisen rearrangement of allyl phenyl ether (**1**) with H_2O with a substrate flow rate of 0.49 g min^{-1}, at 265 °C and 5MPa. Each point corresponds to the following water flow rates (g min^{-1}) and substrate flow rate (g min^{-1}); B (2.49, 0.49), C (4.97, 0.49) and D (6.96, 0.49).

flow with a Reynolds number of around 1.7×10^4. The Claisen rearrangement occurs exclusively by the 'on-water' mechanism.[8] No significant side reactions, such as hydrolysis, hydration, or pyrolysis occurred, which leads to a conversion, selectivity and yield for **2** of above 98%. After the conversion is completed, at around 265 °C and 5 MPa with a reaction time of 149 s (Fig. 1), the product **2** accumulates at the bottom of the aqueous solution and can be obtained in a nearly pure state by being easily, and almost quantitatively, isolated by phase separation.

Table 1 summarizes the results obtained under various reaction conditions. Solvent-free microreaction without H_2O was also conducted using the same microreaction system to reveal the effect of subH_2O. **2** was obtained in a poor yield of 37% at 265 °C, 5 MPa and 360 s (Table 1, entry 5); therefore, subH_2O was proved to be an important factor to accelerate the reaction with an excellent yield of 98% (Table 1, entry 7). Furthermore, these yields could be grouped according to specific densities, which is a ratio of the estimated density against the critical density of water ($\rho_C = 0.314$ g cm^{-3}), into two groups: liquid or gas phase subH_2O.[7b] The most effective reaction took place in gas phase subH_2O which gave **2** in an excellent yield (Fig. 3). This finding is related to the change in dielectric constant, as the reaction seems to prefer the region of low dielectric constants (see ESI, Fig. S3).‡ Obviously, this enhancement in the low polarity region of subH_2O should be distinguished from the

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Table 2 Johnson–Claisen rearrangement from **3** and **4** to **5** with the subH$_2$O system

Entry	Method	Reactor type	Cat. (eq.)	Solvent	Conc./ mol kg^{-1}	T/°C	P/MPa	Reaction time	Sel. (%)	**5** Yield (%)	Reference
1	CH[a]	B[b]	$C_5H_{11}CO_2H$ (0.13eq)	—	3.13	100–166	0.1	6 h	—	86–88	3d
2	μ-SF[c]	F[e]	—	—	6.90	265	5	18 min	40	40	This work
3	μ-subH$_2$O[d]	F	—	H_2O	0.10	265	5	284 s	95	95	This work

[a] Conventional heating, molar ratio **3** : **4** = 1.0 : 1.13. [b] Batchwise reactor. [c] Microreaction-solvent-free, molar ratio **3** : **4** = 1.0 : 1.0. [d] Microreaction with subH$_2$O, molar ratio **3** : **4** = 1.0 : 1.0. [e] Flow reactor.

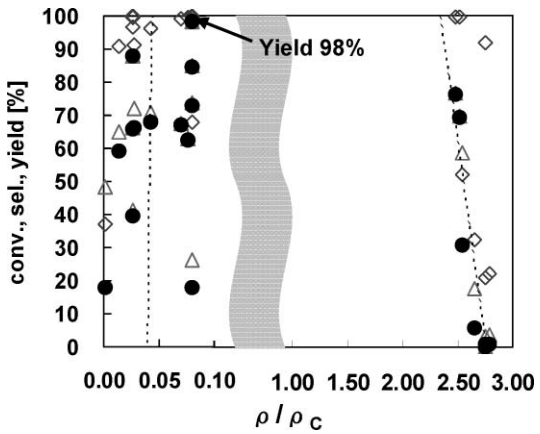
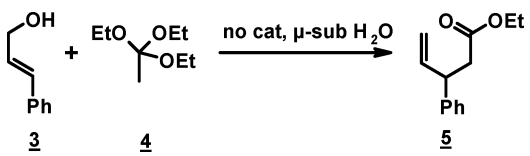


Fig. 3 Specific density *vs.* conversion (square), selectivity (triangle) and yield (filled circle) of the Claisen rearrangement of allyl phenyl ether (**1**) with subH$_2$O at various temperatures and pressures.

rate acceleration using high polarity solvents in a conventional heating process.[1d]

In order to extend the application of the present reaction system, the method was also applied to the aliphatic Claisen rearrangement, Johnson–Claisen rearrangement,[1c] for the preparation of ethyl 3-phenyl-4-pentenate (**5**) from cinnamyl alcohol (**3**) and triethyl *ortho*-acetate (**4**)[3d] (Scheme 2), which is a multi-step process including the formation of diethyl ether from **3** and **4** and the elimination of ethanol, followed by a Claisen rearrangement of vinyl allyl ether. An excellent yield of 95% for **5** was obtained using subH$_2$O under similar conditions as described before and in the absence of any catalyst, which was superior to the solvent-free microreaction and conventional methods (Table 2).



Scheme 2

It has to be mentioned that the water molecules in the subH$_2$O would play a catalyst-like role by transferring a proton along locally formed hydrogen bonds with the substrate,[9a] which leads to a lowering of the energy for the bond cleavage and bond formation.[9b] The role of water in the intermolecular hydrogen transfer has also been supported by quantum chemical calculations.[9c]

E-factor[10b] and energy consumption, as well as yield and selectivity, are important parameters in green chemistry[10] and were inspected for this reaction as represented in Scheme 1 (see ESI, Fig. S4–S6).‡ Conventional heating showed a low E-factor, even at longer reaction times, and a large energy consumption, but the product **2** was obtained with a good yield of 85%. While microwave heating in DMF attained a high yield of 92% in a shorter reaction time and with lower energy consumption, it resulted in a high E-factor due to the non-reusable DMF in the reaction mixture. In contrast, the subH$_2$O microreaction is superior to the other processes with an excellent yield of 98% at a shorter reaction time (149 s), with a low E-factor of 0.02 due to the reusable water, and a low energy consumption of 414 kJ kg^{-1}. Therefore, the Claisen rearrangement with the subH$_2$O microreaction was confirmed as a green process. The Claisen rearrangement with the subH$_2$O microreaction system can easily be extended to various substrates and work in this direction is underway.

Conclusion

We have developed a high-speed, highly-selective aromatic and aliphatic Claisen rearrangement in the absence of catalyst with the use of a flow-type subH$_2$O microreaction system, with an excellent selectivity, over 90%, at a temperature of 265 °C, pressure of 5 MPa and residence time between 149–284 s. This system nicely demonstrates the potential benefits resulting from the combination of the subH$_2$O properties and microprocess for the Claisen rearrangement. Finally, it seems worth noting that this approach induced by a subH$_2$O microreaction system is environmentally benign, and therefore, it draws general attention for "green" organic synthesis.

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Highly enantioselective hydrogenation of quinolines under solvent-free or highly concentrated conditions†

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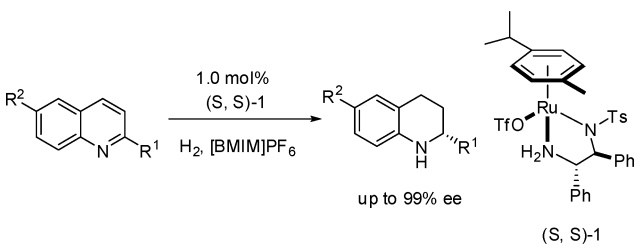
The phosphine-free chiral cationic Ru(OTf)(TsDPEN)(η⁶-cymene) complex was found to be an efficient catalyst for the enantioselective hydrogenation of quinolines under more environmentally friendly solvent-free or highly concentrated conditions. Excellent yields and enantioselectivities (up to 97% ee) were obtained at only 0.02–0.10 mol% catalyst loading.

The principles of green chemistry and green engineering dictate that avoiding the use of solvents is an important way to prevent the generation of waste.[1] For practical synthesis, reactions under solvent-free or highly concentrated conditions may have other advantages, including reduced energy consumption, decreased reaction times and considerable batch size reduction. Therefore, much research effort has been devoted to the development of solvent-free or highly concentrated reactions.[2] Among them, however, relatively few examples concerning solvent-free and concentrated catalytic asymmetric reactions have been reported so far.[2c,3,4] This is not surprising because asymmetric catalytic processes are usually highly sensitive to solvent and concentration of substrates. For solvent-free catalytic reactions, the reaction medium changes significantly as reagents and substrates are converted to products. Therefore, it is still a big challenge to develop highly enantioselective solvent-free and concentrated catalytic reactions. In particular, asymmetric hydrogenation of heteroaromatic compounds under solvent-free conditions is expected to be more difficult due to the potential poisoning of the catalysts by the substrates and/or the reduced products.

Transition metal-catalyzed asymmetric hydrogenations have been extensively studied, and are considered a versatile method for the preparation of optically active compounds.[5] Although a variety of chiral Rh, Ru, and Ir complexes have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones, and imines, most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of heteroaromatic compounds.[6] A few successful examples of the asymmetric hydrogenation of quinolines have recently been reported.[7] Iridium complexes containing chiral diphosphine[7a–c] or diphosphinite ligands,[7d] and P, N ligands[7e,f] have been found to be effective in the hydrogenation of 2-substituted quinolines. In most cases, however, good to excellent enantioselectivity and activity could only be obtained by using iodine as additive, and often at a low substrate-to-catalyst ratio (S/C) of 100. From a practical application viewpoint, it is highly desirable to develop air-stable phosphine-free catalysts for such reactions.

In comparison with chiral diphosphines, chiral diamine ligands are more readily available and air-stable.[8] Their Ru, Rh and Ir complexes have been widely used in the asymmetric transfer hydrogenation of ketones.[9] However, only a few of them were found to be capable of activating molecular hydrogen.[10,11] Recently, Noyori and Ohkuma reported that chiral Ru(OTf)(TsDPEN)(η⁶-cymene) and Cp*Ir(OTf)(MsDPEN) [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine; TfO^- = trifluoromethanesulfonate; Cp* = pentamethylcyclopentadienyl; MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine] complexes could be used for the asymmetric hydrogenation of prochiral ketones under slightly acidic conditions.[11] Later on, we found that ruthenium complex **1** is also an efficient catalyst for asymmetric hydrogenation of quinolines in pure ionic liquid with high enantioselectivity (Scheme 1).[12] Herein, we report our continuing effort on developing a more efficient process for this difficult transformation. Unlike the reported asymmetric hydrogenation of quinolines employing organic solvents, it was found that reactions under solvent-free or highly concentrated conditions provided the tetrahydroquinoline derivatives with much higher reactivity and excellent enantioselectivity at only 0.10–0.02 mol% catalyst loading.



Scheme 1 Asymmetric hydrogenation of quinolines catalyzed by Ru-catalyst (*S*,*S*)-**1** in [BMIM]PF_6 (BMIM=1-*n*-butyl-3-methylimidazolium).

We initially focused on the evaluation of the substrate concentration effects in the asymmetric hydrogenation by using 2-methylquinoline (**2a**) as a model substrate and methanol as the solvent.[8a] As shown in Table 1, when the reaction was run at 0.2 mol L^{-1} substrate concentration in methanol, decreasing the

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Table 1 Comparison of the asymmetric hydrogenation of 2-methylquinoline **2a** catalyzed by (*S*,*S*)-**1** in MeOH and under solvent-free conditions[a]

Entry	S/C	Solvent	Time/h	Conv. (%)[b]	ee (%)[c]
1	200	MeOH (0.2 M)	4	29	95
2	500	MeOH (0.2 M)	12	12	94
3	1000	MeOH (0.2 M)	24	<5	N. D.
4	1000	MeOH (2.0 M)	24	38	95
5	1000	MeOH (2.0 M)	48	76	95
6	200	Solvent free	4	>95	97
7	500	Solvent free	12	>95	96
8	1000	Solvent free	24	95	96
9[d]	5000	Solvent free	24	57	93
10[e]	100	Solvent free	20	50	77

[a] Reaction conditions: 0.2–2.0 mmol **2a** in 1 ml MeOH or under solvent-free conditions, 50 atm H_2, rt. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis with Chiralpak OJ-H Column, the product was in the *S*-configuration. [d] 0.1 mol% TfOH was used as an additive. [e] Ir-catalyst generated *in situ* from [Ir(COD)Cl]$_2$ and P-Phos in combination with 5 mol% I_2 used as additive.

Table 2 Temperature and hydrogen pressure effect on the asymmetric hydrogenation of **2a** under solvent-free conditions[a]

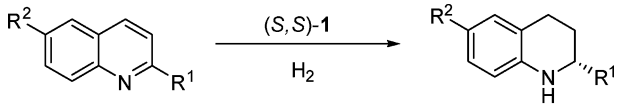
Entry	Temp./°C	H_2/atm	Time/h	Conv. (%)[b]	ee (%)[c]
1	0	50	24	23	97
2	25	50	24	>95	96
3	50	50	8	>95	94
4	80	50	4	60	90
5	25	80	12	100	96
6	25	50	12	86	96
7	25	20	12	46	96
8	25	1	24	6	96

[a] Reaction conditions: 2.0 mmol **2a**, 0.1 mol% (*S*,*S*)-**1**. [b] Determination by ^{1}H NMR. [c] Determined by chiral HPLC analysis.

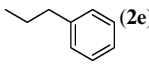
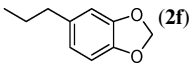
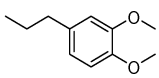
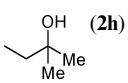
catalyst loading resulted in a significant decrease in reactivity (entries 1–3). It was noted that a higher conversion was obtained when increasing the substrate concentration from 0.2 to 2.0 mol L^{-1} at 0.1 mol% catalyst loading (entries 4 and 5). Thus, we speculated that the employment of solvent-free conditions would further increase the reactivity and allow a reduction in catalyst loading. To our delight, the reaction proceeded efficiently under solvent-free conditions in quantitative conversion with a slightly higher enantioselectivity as compared to those obtained in methanol under otherwise the same conditions (entries 6–8). *Remarkably, even when the catalyst loading was further reduced to 0.02 mol%, the reaction still gave the product in 57% conversion with 93% ee in the presence of 0.1 mol% TfOH.* To the best of our knowledge, this is the first example of highly enantioselective hydrogenation of heteroaromatic compounds under solvent-free conditions. In contrast, the same reaction catalyzed by the reported Ir(P-Phos)/I_2 catalytic system[7b] under solvent-free conditions at high catalyst loading (1.0 mol%) gave only 50% yield with 77% ee (entry 10).

We then examined the effects of the reaction temperature and hydrogen pressure on the solvent-free asymmetric hydrogenation of **2a**, and the results are listed in Table 2. It was found that increasing the temperature led to a high conversion rate but at a cost of slightly lower enantioselectivity (entries 1–4). Notably, a similar high enantioselectivity was achieved at various hydrogen pressures although a low conversion was observed by decreasing the hydrogen pressure (entries 5–8).

Table 3 Asymmetric hydrogenation of quinolines catalyzed by (*S*,*S*)-**1** under solvent-free or highly concentrated conditions[a]



2a~2k **3a~3k**

Entry	R^1/R^2	H_2/atm; Temp./°C	Yield (%)[b]	ee (%)[c]
1	H/Me (**2a**)	50; 25	99	97
2	H/Et (**2b**)	50; 25	98	95
3	H/n-Pr (**2c**)	50; 25	97	94
4	H/n-Pentyl (**2d**)	80; 25	99	94
5[d]	H/  (**2e**)	50; 50	95	92
6[d]	H/  (**2f**)	80; 80	99	87
7[d]	H/  (**2g**)	80; 80	98	85
8[d]	H/  (**2h**)	80; 50	92	97
9[d]	H/  (**2i**)	80; 80	98	97
10[d]	MeO/Me (**2j**)	80; 80	99	93
11[d]	F/Me (**2k**)	80; 80	96	90

[a] Reaction conditions: 1.0–2.0 mmol substrate, 0.1 mol% (*S*,*S*)-**1**, 24–60 h. [b] Isolated yield. [c] Determined by HPLC analysis with Chiralpak OJ-H (or OD-H and AS-H) Column. [d] 0.1 mL 2-propanol and 0.1 mol% TfOH were added.

Next, a variety of 2-substituted quinoline derivatives (**2a–2k**) were hydrogenated in the presence of 0.1 mol% of catalyst (*S*,*S*)-**1** under solvent-free or highly concentrated conditions. Nearly quantitative yields and high enantioselectivities (up to 97% ee) were obtained in all cases (Table 3). In the case of liquid substrates, 2-alkyl substituted quinolines, the reactions proceeded smoothly under solvent-free conditions. It was found that the length of side chain slightly influenced the enantioselectivity and reactivity (entries 1–4). For the solid substrates, hydrogenation was carried out under highly concentrated conditions (10 mol L^{-1}) in the presence of 0.1 mol% of TfOH. As compared with 2-alkyl substituted quinolines, 2-phenethyl substituted quinolines also gave high yield, albeit with slightly lower enantioselectivities (entries 5–7). It was noted that quinolines with a free hydroxyl group on the side chain could be hydrogenated smoothly in high yield with excellent enantioselectivities (entries 8–9). However, the presence of substituted groups at C-6 led to slightly lower enantioselectivities (entries 10 and 11).

Finally, we applied this attractive new protocol to the synthesis of a biologically active tetrahydroquinoline alkaloid, angustureine.[13] Asymmetric hydrogenation of 2-pentyl

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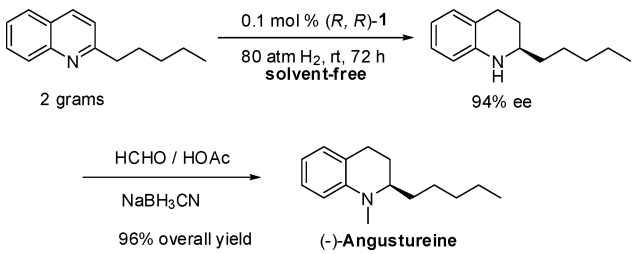
substituted quinoline was carried out on a gram scale at a catalyst loading of 0.1 mol%, giving the tetrahydroquinoline derivative in quantitative conversion with 94% ee. Subsequent *N*-methylation of the hydrogenated product afforded the desired natural product in 96% overall yield (Scheme 2).



Scheme 2 Synthesis of naturally occurring tetrahydroquinoline alkaloid, (−)-angustureine.

In conclusion, the first highly enantioselective hydrogenation of quinolines catalyzed by phosphine-free chiral cationic Ru-TsDPEN catalyst has been achieved under more environmentally friendly solvent-free or highly concentrated conditions at low catalyst loading (low to 0.02 mol%). This new method provides a practical synthetic approach to optically active tetrahydroquinoline derivatives.

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General MW-assisted grafting of MCM-41: Study of the dependence on time dielectric heating and solvent†

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A fast and versatile microwave- (MW)-assisted method for the post-calcination functionalization of MCM-41 is proposed. The efficiency of the grafting is improved in the absence of solvent and depends on the MW-heating time. Moreover, working under the same reaction conditions, the organic loadings strictly depend on the silylating agent.

Surfactant-templated mesostructures have played a prominent role in materials chemistry during the last decade since the exciting discovery of the novel family of hexagonally ordered mesoporous silicate structures reported by the researchers at Mobil Research and Development Corporation.[1] The extremely high specific surface areas and the large pore size (relative to that of microporous zeolites) have made these materials highly desirable for numerous applications, and, in spite of the one-dimensionality of its pore channels, MCM-41 has been the main focus of applicative studies because of its ease of preparation. However, the original mesoporous silicates exhibit a number of limitations, including lower hydrothermal stability and lower reactivity than zeolites with comparable compositions. One important way of modifying the physical and chemical properties of mesoporous silicates has been the incorporation of organic components, either on the silicate surface, as part of the silicate walls, or trapped within the channels.[2]

Finding ways to introduce organic or inorganic functional groups onto the surface of these silica particles has been an important target of research since the surface properties of silica materials are influenced by the nature of the surface functional groups. Thus, surface functionalized silica particles have found application in catalysis,[3,4] remediation,[5a–c] or biological applications involving the encapsulation of large biomolecules, such as enzymes and other proteins,[6a,b] and drug delivery.[7] The incorporation of functionalities can be achieved in three ways: simultaneous reaction of condensable inorganic silica species and silylated organic compounds (co-condensation or one-pot synthesis), the use of periodic mesoporous organosilicates (PMOs) or the post synthetic attachment of organic components onto the surface of the silica matrix (grafting),[8–10] and in any case, the original structure of the mesoporous support is generally maintained after grafting. If a high surface functional groups coverage is desired, it is important to maintain a large number of surface silanol groups after the mesoporous material preparation. When the surfactant removal is carried out by calcination at typical temperatures (400–550 °C), many surface unreacted silanol groups are lost, thus, the surface of calcined MCM-41 must be rehydroxylated.[11] Reported methodologies for synthesis and functionalization of MCM-41 often are time-consuming, labor-intensive and involve the use of toxic solvents. Microwave heating has recently been applied to the synthesis[2,12–13] or to the co-condensation of mesoporous silica[14–17] and in some cases the reaction times have been reduced to less than an hour and the temperature lowered to room temperature. However, at the best of our knowledge, there are no reports of application of microwave-assisted procedures to the grafting of organic molecules on the surface of MCM-41 silica. The only examples of a MW-assisted functionalization reported are the amination of a controlled-pore glass (CPG) as support for the solid phase synthesis of nucleic acids and our very recent publication on a new mesoporous silica-supported Er(III) catalyst.[18]

The present work is an exploration of the potential of the MW-heating for the grafting on the surface of mesoporous silica. The use of microwaves make it possible to perform an ultra-fast and clean protocol for the functionalization of MCM-41. The method is versatile since it can be applied to a wide series of organic grafting, depending on the time exposition to MW and the functionalization can be optimized working in solvent-free conditions.

In order to make a direct comparison between a classical grafting and a MW-assisted grafting, MCM-41 was functionalized both under the reaction conditions reported in literature[19–23] (Path A, Scheme 1) and under MW-heating (Path B, Scheme 1). We used dry toluene as solvent and (3-mercaptopropyl)-trimethoxysilane (MPTMS), (3-aminopropyl)triethoxysilane (APTES), (3-cyanopropyl) triethoxysilane (CNPTES) and (3-aminoethylaminopropyl) trimethoxysilane (AEAPTMS) as silylating agents.

In both cases MCM-41 silica needed an activation process that in the first case was a thermal activation at 120 °C for 2 h as reported in the literature, while in the second case was a pre-treatment of mesoporous silica with an HCl solution (25%) at room temperature for 3 h. The acid treatment increased the –OH functionalities on the silica surface The Raman spectra comparison (Fig. 1) shows that, in the treated sample, the

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† Electronic supplementary information (ESI) available: Experimental procedures and Raman spectra, FT-IR spectra and ^{13}C-NMR spectra of samples 1–12. See DOI: 10.1039/b820417a

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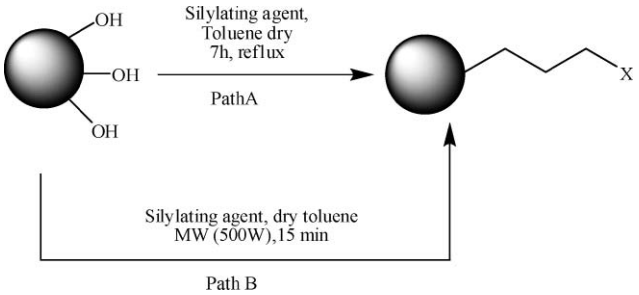


Scheme 1 General pathway of MCM-41 functionalization by classical method (Path A) and by MW-assisted method (Path B).

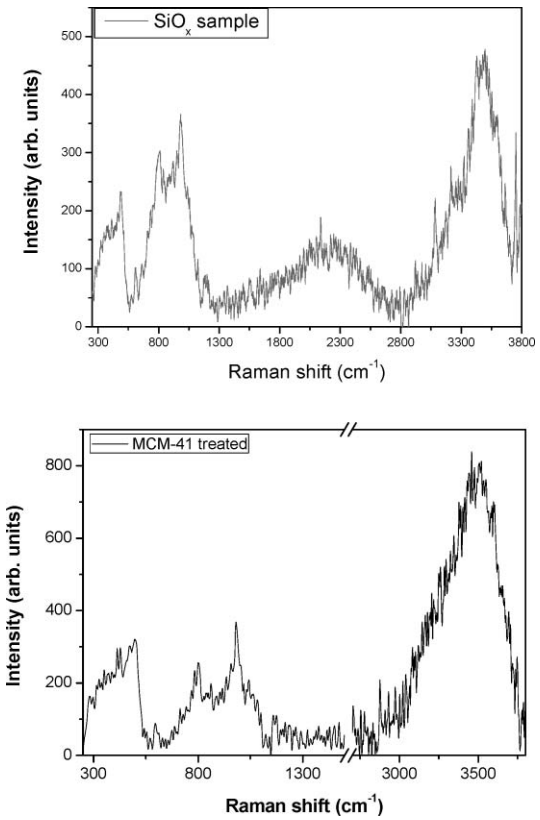


Fig. 1 Raman spectra of commercial MCM-41 (top spectrum) and pre-treated MCM-41 (bottom spectrum).

intensity of the vibrational band around 3500 cm^{-1} related to –OH and the broadness of the peak was increased.

The covalent grafting of the organic moiety on the MCM-41 surface was checked by FT-IR and ^{13}C-NMR and the loading was determined by TOC (total organic carbon) measurements and by elemental analysis (see ESI†).

The classical functionalization was time and energy consuming (7 h in refluxing toluene) and the loading was lower or comparable with the one achieved after only 15 min of microwaves exposition (Table 1).

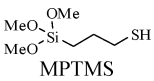
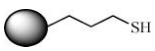
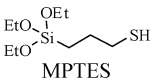
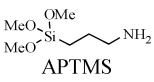
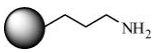
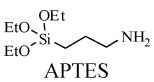
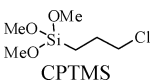
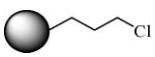
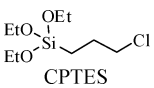
As it is shown in Table 2, there is not a direct dependence between the yield of the grafting and the nature of the leaving group.

Encouraged by these results, we decided to optimize the MW-assisted grafting looking for the dependence on the MW-exposition time and the reaction solvent. For this reason we studied the grafting of the acid pre-treated MCM-41 silica with

Table 1 TOC values (mmol C g^{-1} of catalyst) of mesoporous silica functionalized by a classical method (A) and a MW-assisted method (B)

Entry	Method	MPTMS	APTMS	CNPTMS	AEAPTMS
1	A	1.04	2.27	2.35	2.27
2	B	1.74	2.92	2.4	2.3

Table 2 Effect of leaving group on MW-assisted fuctionalization of mesoporous silica with silylating agents

Entry	Prod.	Siylylat. agent	mmol func./g silica
		 MPTMS	1.74
1			
		 MPTES	2.34
		 APTMS	4.11
2			
		 APTES	3.59
		 CPTMS	2.14
3			
		 CPTES	2.59

MPTMS after 5, 10 and 15 min of MW-irradiation both in the presence of dry toluene as solvent and in solvent-free conditions (Fig. 2).

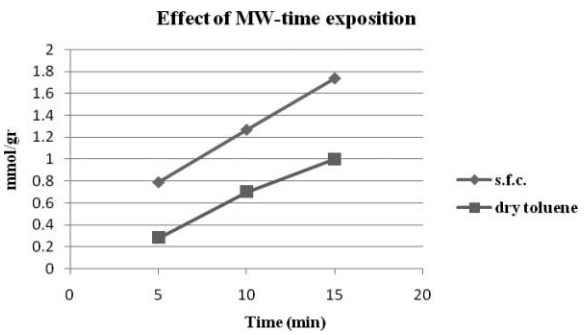


Fig. 2 Effect of MW-exposition time on fuctionalization of mesoporous silica with MPTMS (s.f.c. = solvent free conditions).

In both cases, the loading was strongly dependent on the time of microwave irradiation with an almost linear trend. When the reaction was performed in toluene, the loading ranged from

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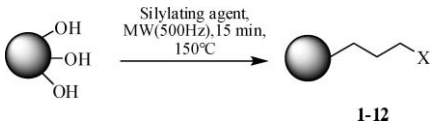
Table 3 Solvent free-MW assisted fuctionalization of mesoporous silica with different silylating agents

Entry	Reactant	Product	%C %N %H	TOC/g Kg^{-1}	mmol g^{-1}
1	APTES	≡Si–$(CH_2)_3NH_2$	10.54 3.71	148.3	4.11
2	MPTES	≡Si–$(CH_3)_3SH$	3.42 8.48 —	84.58	2.34
3	CPTES	≡Si–$(CH_3)_3Cl$	1.86 9.06 —	93.49	2.59
4	*i*-BTES	≡Si–$CH_2CH(CH_3)_2$	2.0 6.77 —	90.25	1.87
5	CNPTES[a]	≡Si–$(CH)_3CH_2CN$	2.22 11.56 2.13	128.5	3.67
6	*i*-CNPTES	≡Si–$(CH_2)_3NCO$	2.12 15.91 3.05	177.9	2.68
7	OTES	≡Si–$(CH_2)_7CH_3$	3.16 11.48 —	129.1	1.34
8	DAPTMS	≡Si–$(CH)_3NH(CH_2)_2NH_2$	2.77 13.86 5.20	172.2	2.85
9	PTMS	≡Si–Ph	4.19 14.73 —	160.3	2.22
10	GPTMS	≡Si–$(CH_3)_3$–(epoxide)	1.87 19.67–3.97	208.3	3.46
11	DETAPTMS	≡Si–$(CH)_3[NH(CH_2)_2]_2NH_2$	17.15 6.50	213.2	2.54
12	UPTMS	≡Si–$(CH_2)_3NHC(O)NH_2$	4.76 15.41 4.88 3.59	188.8	3.92

[a] A peak at 1640 cm^{-1} in the FT-IR spectrum shows a probably partial hydrolysis of nitrile to amide.

0.28 mmol g^{-1} to 1 mmol g^{-1}, while in the solvent free conditions an increase up to 1.74 mmol g^{-1} was registered. Thus, the functionalization is much more efficient in neat conditions, and it is possible to tune the loading on the MCM-41 surface by choosing the time of MW irradiation; so, all the next reactions were performed in solvent free conditions (Scheme 2 and Table 2 and 3).



1-12

Scheme 2 General procedure of the MW-assisted functionalization of MCM-41 in solvent free conditions.

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In order to study how the grafting depends on the leaving group of the silylating agent, we compared the MW-assisted grafting of MCM-41 silica with the trimethoxysilyl derivatives (MPTMS, APTMS, CPTMS) to the triethoxysilyl ones (MPTES, APTES, CPTES), in solvent free conditions for 15 min.

Finally, as it is summarized in Table 3, we tested the versatility of the method performing the same reaction using several trialcoxysilylpropyl derivatives as silylating agents.

The yields of the grafting were, in all cases, much higher than the values reported in the literature[19–23] for a classical grafting, ranging from 1.34 to 4.11 mmol g^{-1} of silica.

As shown in Table 3, the best results were obtained with the 3-propylamino (entry 1), 3-isocyanate (entry 5), the 3-glycidyloxy (entry 10) and the 3-urea (entry 12) propyl derivatives and, in general, the loading with the polar silylating agents was more significant. In fact, the use of some hydrocarbons-derivatives such as the isobutyl (entry 4), the octadecyl (entry 7), and the phenyl (entry 9) trialcoxysilanes gave the lowest loading values.

An interesting trend is shown by the mono-, di- and tri-amino derivatives (entries 1, 8 and 11), that is in agreement with the results reported earlier in the literature.[18] In fact, it seems that the yield of the grafting depends on the number of the amino groups, so that the worst functionalization was reported for structurally more complicated derivatives (entries 8 and 11).

A microwave assisted protocol for a rapid and efficient solvent-free functionalization of MCM-41 has been reported. The methodology described here can be applied to several different functional groups, and can be potentially employed for different applications since the loading can be easily tuned simply by choosing the appropriate time of MW-dielectric heating. The protocol fits some of the most important principles of "Green chemistry and technology" such as minimization of time and energy, avoidance of solvents and maximization of efficiency.

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Microwave-promoted mono-*N*-alkylation of aromatic amines in water: a new efficient and green method for an old and problematic reaction†

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A greener improvement to direct mono-*N*-alkylation of aromatic amines by alkyl halides was achieved using microwave irradiation in water without any catalyst.

Selective synthesis of *N*-alkylanilines plays a crucial role in organic chemistry due to the relevance of this type of amines as raw materials, intermediates or final products in nearly every field of the chemical industry.[1] Even though many synthetic methods were researched and reported in order to obtain mono- or dialkylarylamines, the preparation of *N*-monoalkylated derivatives *via* direct *N*-alkylation by alkyl halides is one of the most frequently used procedures.[2]

Many recent efforts were made to make this synthesis eco-friendlier: in this way, usual but hazardous volatile organic solvents were replaced with water, using mild basic conditions to reduce the amount of catalysts,[3] and/or conventional heating was substituted by microwave irradiation.[4,5] All the aqueous-mediated methods were efficient and successful but they all needed catalysts and also long reaction times, if MAOS (microwave-assisted organic synthesis) was not used. Moreover the troublesome problem of polyalkylation was only partially solved, working with a near equimolar ratio between arylamine and alkyl halide.[3]

To make the direct *N*-alkylation of aromatic amines fully green, possibly obtaining monoalkylation, we studied the possibility of carrying out the reaction with alkyl halide not only using water as solvent, but moreover avoiding the use of any catalyst, taking advantage of the MAOS technique.

As a basis of this study, a standard reaction between *p*-toluidine[6] and benzyl chloride was carried out in water under microwave irradiation at various times and temperatures (Table 1), using a monomode microwave reactor.

The alkylating reagent was initially added in a 1 : 1 ratio of substrate/halide. The best yield of *N*-benzyl-*p*-toluidine (75%) was achieved at 150 °C in 20 min (Table 1; entry 4): this temperature lies in the lower part of the so-called near-critical region of water[7] and performing the reaction under "superheated conditions" takes advantage of the favorable changes of chemical and physical properties of water at high temperatures and pressures.[8]

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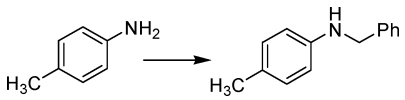
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds. See DOI: 10.1039/b900750d

Table 1 Effects of time and temperature on *N*-benzylation of *p*-toluidine[a]



Entry	Time/min	Temp/°C	Yield (%)[b]
1	10	110	0
2	10	130	5
3	10	150	60
4	20	150	75
5	30	150	75
6	20	150	82[c]

[a] Reaction conditions: *p*-toluidine (3 mmol) and benzyl chloride (3 mmol) in water (1 ml) were irradiated in a monomode microwave reactor. [b] Yield of isolated product. [c] Benzyl chloride: 6 mmol.

Different molar ratios of substrate/halide were also tested, finding that doubling the halide concentration increased the yield of monoalkylated toluidine up to 82% (Table 1; entry 6). It is interesting to note that even with a three-fold excess of the halide, only mono-*N*-alkylation occurred, without trace of the dibenzylated product. In fact, the reaction mixture contained only monoalkyltoluidine and unreacted starting compound.

On the contrary, the recently reported method of aqueous-mediated alkylation with mild base needed a 1 : 1.1 molar ratio to achieve mono-*N*-alkylation, but with a long reaction time and with 10% of dialkylated product.[4]

Parallel experiments were also performed under thermal heating. The reaction between *p*-toluidine and benzyl chloride (1 : 2 molar ratio) in water was carried out in autoclave at 150 °C for 40 min,[9] affording a complex reaction mixture containing starting toluidine as the major product, mono- and dialkyltoluidine as minor products, together with many unidentified products. This finding indicated that microwave irradiation provided higher conversion and selectivity compared to conventional heating conditions.

We experimented with the same reaction also in the presence of bases (Table 2; entries 1–4), with the catalysts frequently used in similar procedures[5,10] (Table 2; entries 5–6), and with organic solvents (Table 2; entries 7–11).

In all the aqueous mediated conditions the yields were lower than that of the standard procedure, thus proving that the presence of bases and/or catalysts negatively affected the course and the yield of the reaction. Moreover, if organic solvents were used instead of water, the reaction didn't occur in the absence of

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Table 2 Effects of bases, catalysts and solvents on the *N*-benzylation of *p*-toluidine[a]

Entry	Base	Catalyst	Solvent	Yield (%)[b]
1	KOH	—	H_2O	40
2	TEA	—	H_2O	35
3	K_2CO_3	—	H_2O	45
4	$NaHCO_3$	—	H_2O	48
5	—	KI	H_2O	40
6	—	CuI	H_2O	0
7	—	—	DMF	0
8	—	—	DMSO	0
9	—	—	Dioxane	0
10	—	—	MeCN	0
11	—	KI	MeCN	10[c]

[a] Reaction conditions: *p*-toluidine (3 mmol) and benzyl chloride (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product. [c] Dialkylated compound was the major product.

bases and/or catalysts, and anyway the yields are very poor and dialkylation occurred preferentially.

Now that optimised conditions had been established, the reaction was attempted with a range of different alkyl halides. With all halides, the alkylation was achieved with high yield and selectivity (Table 3; entries 1–6), without trace of dialkylated product[11] and with no difference between bromo or iodoalkane (Table 3; entries 1–2).

Only with α,ω-dibromoalkanes selective mono-alkylation did not occur. As already reported, although in slightly different reaction conditions,[12] with 1,4-dibromobutane a cyclocondensation took place *via* double *N*-alkylation of starting aniline to obtain *N*-arylpyrrolidine (Table 3; entry 7).

With 1,2-dibromoethane intramolecular cyclization didn't occur, but two different alkylation products were obtained (Table 3; entry 8): *N*,*N*′-di-*p*-tolylethylenediamine, corresponding to mono-alkylation for each bromine of the halide, and *N*,*N*′-di-*p*-tolylpiperazine, corresponding to a particular dialkylation involving a second molecule of the halide. Even increasing the excess of halide up to ten fold, the final yields and the ratio between the two products remained practically the same, together with the formation of by-products (detected by HRMS).

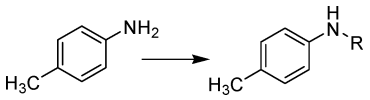
Then the reaction was tested with different starting arylamines and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride as alkylating agent.

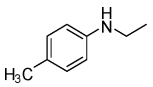
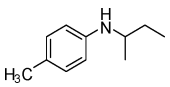
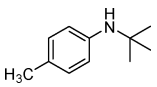
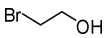
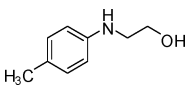
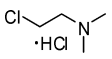
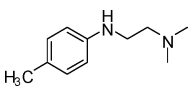
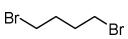
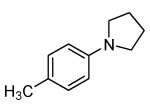
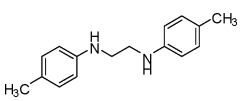
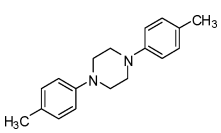
We chose this alkyl halide among the tested ones for its interesting features. It allows easy functionalization of aromatic amines with a dialkylaminoalkyl chain, which is one of the most common substituents in many pharmaceutical products,[13] and is usually obtained by substitution of aryl halides and not by direct alkylation of arylamines.[14] Moreover, it must be used as the hydrochloride to avoid aziridinium formation and the hydrochloride is water soluble, so optimal for our reaction conditions, but, on the contrary, not useful with conventional organic solvents, as commonly required.

The results are summarised in Tables 4 and 5.

Aniline and toluidines were easily alkylated in good yields (Table 4, entries 1–3).

Table 3 *N*-Alkylation of *p*-toluidine with different alkyl halides[a]



Entry	Alkyl halide	Product	Yield (%)[b]
1			85
2			88
3			73
4			68
5			66
6			90
7			85
8			20
			20

[a] Reaction conditions: *p*-toluidine (3 mmol) and alkyl halide (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product.

Activated anilines were well derivatized, as in the case of *o*-anisidine (Table 4, entry 4), but if a strong deactivating group was also present, as in the case of 2-methoxy-4-nitroaniline, the yield was considerably reduced (Table 4, entry 5).

The *N*-alkylation of electron-poor anilines took place with variable yields, from a low yield for 4-nitroaniline to a moderate yield for 4-aminobenzoic acid (Table 4, entries 6–7), up to a satisfactory yield for *p*-chloroaniline (Table 4, entry 8). Anyway the reaction mixture contained only monoalkylarylamine and unreacted starting product.

Naphthylamines were also monoalkylated with very good yields (Table 4, entries 9–10).

Heteroaryl amines, such as 2-aminopyridine and 1-aminoisoquinoline, didn't react in this condition, probably owing to their deactivation properties (Table 4, entries 11–12).

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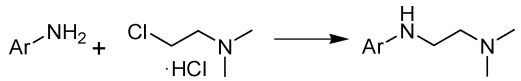
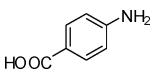
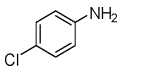
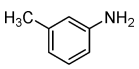
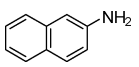
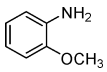
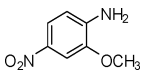
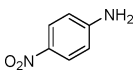
Table 4 *N*-Alkylation of different arylamines[a]



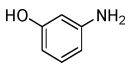
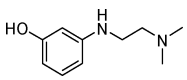
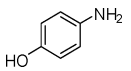
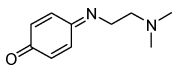
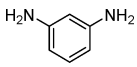
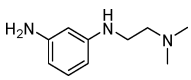
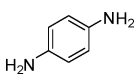
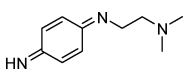
Entry	Arylamine	Yield (%)[b]	Entry	Arylamine	Yield (%)[b]
1		89	7		35
2		74	8		67
3		82	9		78
4		72	10		75
5		20	11		—
6		10	12		—

[a] Reaction conditions: arylamine (3 mmol) and 2-chloro-*N,N*-dimethylethylamine hydrochloride (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product.

The reaction with hydroxyanilines was chemoselective achieving only the mono-*N*-alkyl derivatives (Table 5, entry 1–2), but in the case of *p*-hydroxyaniline the product was easily oxidized to the corresponding quinone (Table 5, entry 2). In a similar way, with phenylenediamines only one amino group preferentially reacted, although with moderate yield (Table 5, entry 3), and with *p*-phenylenediamines only the corresponding quinoneimine was formed (Table 5, entry 4).

In conclusion, we have set up a green way to mono-*N*-alkylated aromatic amines under microwave irradiation. The reaction was carried out in water at 150 °C with twice the amount of the appropriate alkyl halide and without any catalyst. This synthetic procedure works very well with a variety of arylamines and in a satisfactory way also with deactivated amines; it allows only mono-*N*-alkylated products to be obtained and it is chemoselective in the presence of more than one functional group. The reaction is efficient, rapid and clean. Indeed, the described method could be a useful synthetic way to achieve alkylarylamines avoiding the use of organic solvents and catalysts or additives.

Table 5 *N*-Alkylation of hydroxyanilines and phenylenediamines[a]

Entry	Alkyl halide	Product	Yield (%)[b]
1			45
2			n.d.[c]
3			32
4			n.d.[c]

[a] Reaction conditions: arylamine (3 mmol) and 2-chloro-*N,N*-dimethylethylamine hydrochloride (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product. [c] Yield not determined: structures identified by HRMS analysis.

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Lipase-catalysed direct Mannich reaction in water: utilization of biocatalytic promiscuity for C–C bond formation in a "one-pot" synthesis†

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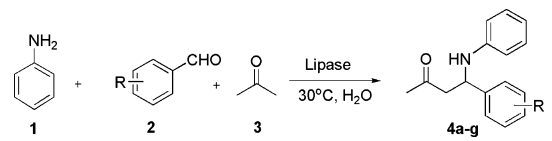
A novel lipase-catalysed direct Mannich reaction has been developed under aqueous conditions in a "one-pot" strategy. Interestingly, these promiscuous reactions can be greatly promoted by water and generally require aromatic aldehydes.

Enzymes have been widely used in modern organic synthesis due to their simple processing requirements, high selectivity and mild reaction conditions.[1] In recent years, a new frontier, known as biocatalytic promiscuity, has emerged and largely extended the application of enzymes. Namely, it is the ability of a enzyme to catalyse synthetic reactions which may vary from its natural role.[2] As one of the most rapidly growing areas in enzymology, biocatalytic promiscuity not only highlights the existing catalysts, but may provide novel and practical synthetic pathways which are not currently available. Some elegant reports address the importance and wide application of biocatalytic promiscuity in organic synthesis.[3] For example, lipase from *Candida antarctica* (CAL-B), which possesses lipid hydrolysis as its native activity, can also promiscuously catalyse various C–C, C–N and C–S bond formations.[4] Similarly, lipase from porcine pancreas (PPL) was shown to catalyze an aldol reaction in our previous study.[5] Although a variety of two-component reactions have been developed in the study of biocatalytic promiscuity, three-component reactions, which can form multi-functional compounds, have never been reported. This is possibly due to the problem of side reactions caused by multi-reagents and the strict range of substrates in enzymatic reactions.

In our efforts to explore the application of this new area, we became interested in the Mannich reaction, which is atom-economic and a powerful synthetic method for generating carbon–carbon bonds and nitrogenous compounds.[6] Traditional chemical methods (referred to as the indirect Mannich reaction), however, usually adopted imines or iminium salts and preformed enolate equivalents to carry out the reaction. Due to the disadvantages of the pretreatments and the drawbacks caused by the isolation and purification, recent efforts have been devoted to performing the direct Mannich reaction *via* the metal catalyst systems and organocatalysts.[7,8] Yet, to the best of our knowledge, a hydrolase-catalysed Mannich reaction, which could be performed under facile and eco-friendly reaction conditions, has never been reported. Herein, we described the first lipase-catalysed direct, three-component Mannich reaction with ketone, aldehyde and amine (under aqueous conditions) to form β-amino-ketone compounds (Scheme 1). A series of substrates have been explored, resulting in moderate to good yields.



Scheme 1 Lipase-catalysed direct Mannich reaction in water.

Water is the most abundant, inexpensive, and environmentally friendly solvent, thus the development of organic reactions in aqueous media is one of the practical trends in current chemistry.[9] Although some methods had realised the indirect Mannich reaction in the presence of water, few examples of direct three-component Mannich reactions in water have been reported.[10] Initially, we chose an acetone/water 1 : 1 (v/v) system as the reaction medium, based on our previous research. The substrates acetone, aniline and 4-nitrobenzadehyde were catalysed by lipase in a one-pot synthesis to yield the Mannich product. A wide variety of lipases had been investigated in order to study the potential range of this enzyme's promiscuous catalytic activity (Table 1). To our surprise, some lipases did, in fact, exhibit detectable catalytic activity in the experiments.

Table 1 The catalytic activities of Mannich reaction by different lipases[a]

Entry	Catalyst	Yield (%)[b]
1	No Enzyme	3.2
2	Lipase from *Penicillium camemberti*	3.7
3	Lipase from *Candida rugosa*	8.2
4	Lipase from *Pseudomonas fluorescens*	16.1
5	Lipase from *Penicillium roqueforti*	3.5
6	Lipase from porcine pancreas, type II	14.9
7	Lipase from *Mucor javanicus*	4.5
8	Lipase from *Burkholderia cepacia*	16.7
9	Lipase from *Rhizopus oryzae*	12.0
10	Lipase from *Candida cylindracea*	10.1
11	Lipase from *Candida antarctica*	48.3
12	Lipase from *Mucor miehei* (MML)	72.2
13	Denatured MML[c]	8.2

[a] Reaction conditions: a solution of 4-nitrobenzaldehyde (**2**, 0.1 mmol), aniline (**1**, 0.11 mmol), acetone (**3**, 1 ml), water (1 ml) and 10 mg lipase was shaken at 200 rpm at 30 °C for 24 h. [b] Yield was calculated based on **2**. [c] Pre-treated with urea at 60 °C for 12 h.

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† Electronic supplementary information (ESI) available: Further experimental information. See DOI: 10.1039/b817524a

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Lipase from *Mucor miehei* (MML) was identified to be the most effective catalyst for the direct Mannich reaction (Table 1, Entry 12). CAL-B also showed moderate catalytic activity, while other tested lipases presented very low activity in this reaction. Additional experiments were also performed to confirm the notable catalytic activities of MML in the Mannich reaction. As expected, the control experiments and those using denatured MML showed poor activity. All the results suggested that the promiscuous catalytic activities of enzymes in the direct Mannich reaction largely depend on the special spatial conformation of the natural lipases.

Solvents play an important role in the reaction process. Therefore, we investigated the effect of different solvents on the Mannich reaction (Fig. 1). In pure organic solvents such as toluene, dichloromethane, DMF, THF, acetone, the reaction most commonly observed was the formation of a Schiff base (>90% yield), as opposed to the Mannich reaction. Interestingly, substantial yields can be obtained in the mixture of water and organic solvents in the same conditions, indicating that water can obviously accelerate the MML-catalysed Mannich reaction.

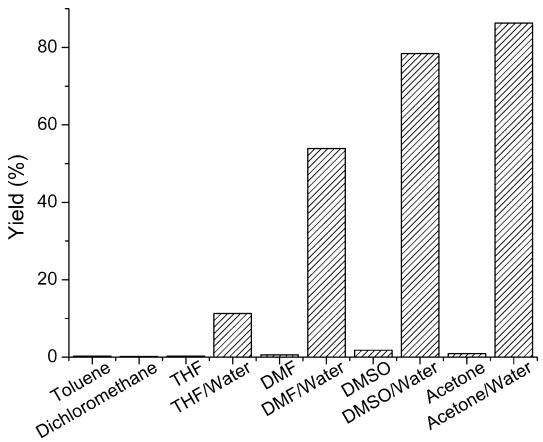

Fig. 1 The influence of solvents on the Mannich reaction. (Reaction conditions: a solution of 4-nitrobenzaldehyde (**2**, 0.1 mmol), aniline (**1**, 0.11 mmol), acetone (**3**, 1 ml), 2 ml solvent (the ratio of the mixture solvent is 1 : 1 in volume) and 10 mg MML was shaken at 200 rpm at 30 °C for 48 h.)

Notably, it is important to confirm the optimal percentage of water in order to enhance the biocatalytic promiscuity of the direct Mannich reaction. Therefore, experiments had been performed to ascertain the catalytic activity of MML with different amounts of water in the reaction system. The results are shown in Fig. 2. In general, the effect of the water concentration on the catalytic activity could be described using a hill-shaped curve. It is hard to observe any Mannich product if no water is present in the reaction system. The rate of the enzymatic reaction can be accelerated by increasing the concentration of water used, and reaches the highest rate between 40–50% water content. However, once the water content surpasses 60%, the yield of Mannich product drops down, due to the insolubility of the substrates. All the results indicated that water is obviously essential in the promiscuous biocatalysis of the Mannich reaction. Further experiments were performed to investigate the yield of the Mannich adduct during the time course (Fig. S1†).

Table 2 Direct Mannich reaction of other aromatic aldehydes and amines[a]

Entry	Time/h	R	Yield (%)[b]
1	48	4-NO_2	83.5
2	48	3-NO_2	82.4
3	24	H	87.3
4	24	4-OCH_3	89.1
5	48	4-OH	43.6
6	48	4-CN	65.3
7	48	4-Cl	83.1

[a] Reaction conditions: a solution of aldehyde (**2**, 1 mmol), aniline (**1**, 1.1 mmol), acetone (**3**, 8 ml), 8 ml water and 50 mg MML was shaken at 200 rpm at 30 °C for 24 or 48 h. [b] Isolated yield.

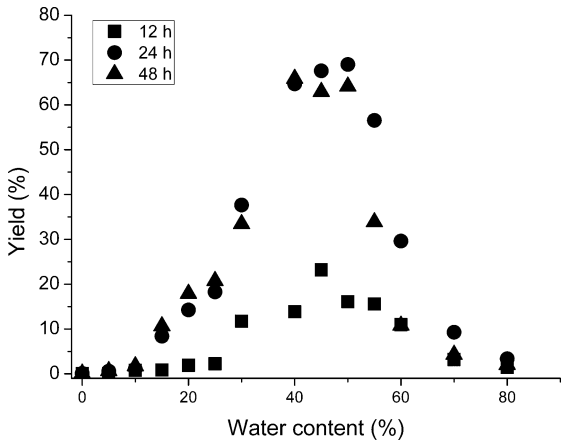

Fig. 2 The influence of water concentration on the MML-catalysed Mannich reaction under these conditions: MML 10 mg, 4-nitrobenzaldehyde (**2**) 0.1 mmol, aniline (**1**, 0.11 mmol) and 2 ml solvent were shaken at 200 rpm at 30 °C, deionized water from 0% to 80% [water/(water + acetone), v/v].

Based on the remarkable results obtained using the above reaction conditions, some other aldehydes were used to expand upon this MML-catalysed direct Mannich reaction to show the generality and scope of this new biocatalytic promiscuity (Table 2). It was found that a wide range of aromatic aldehydes can effectively participate in the MML-catalysed Mannich reaction. In addition, several aliphatic aldehydes (such as acetaldehyde and propaldehyde) were also investigated, but no products were detected using these reactants.

It is widely accepted that the hydrolysis active site in hydrolase is also responsible for the promiscuous catalysis.[11] Combining that viewpoint with our observations, as described above, we theorized the mechanism of the lipase-catalysed Mannich reaction, summarized in Scheme 2. First, the aldehyde and an amine can react to form the Schiff base quickly, and the ketone is pre-activated by the lipase to form the enolate anion at the same time. Second, the Schiff base can form complex **5**, with the assistance of the His residue possessed by lipase. Third, a proton is transferred from the Schiff base to the enolate anion to form a new carbon–carbon bond, and then the Mannich adduct is released from the oxyanion hole. This proposed catalytic mechanism is based on the results reported by the Berglund *et al.*[4] Formation of the enolate anion and complex **5** are expected to be the key steps in this enzymatic

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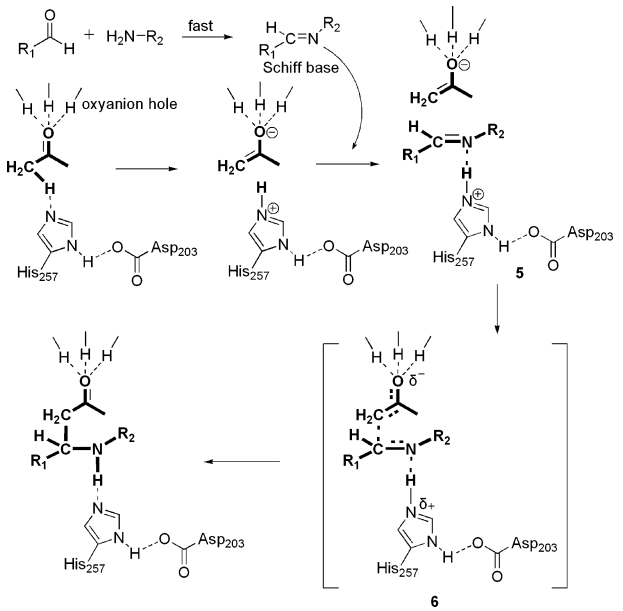

Scheme 2 Proposed mechanism of lipase-catalysed Mannich reaction.

process. In the pure organic solvents, the enolate was difficult to form and the Mannich reaction could not happen. Once water (an accelerating agent of the enolate formation) is added into the reaction system, the reaction could proceed. However, further experiments are necessary to prove this hypothesis.

On the other hand, although three-component, direct Mannich reactions can be catalysed by metal complexes and organocatalyst systems, almost all the systems need to first mix the aldehyde and amine to form the Schiff base and avoid side reactions, such as the aldol reaction. Interestingly, in our biocatalytic system, the order of the reagent addition did not affect the yield of the product, and the Mannich reaction can be easily carried out in one vessel. Moreover, the recovery of metal complexes and organocatalysts is difficult, while lipase MML can be reused at least six times without a significant loss of activity (Fig. S2†). Although various conditions were tested to improve the enantioselectivity, no clear progress has been made at this time. Thus, other methods such as directed evolution, site-directed mutagenesis, and enzymatic resolution are being investigated as potential solutions to this problem.

In conclusion, we describe here the first lipase-catalysed, three-component direct Mannich reactions. Lipase MML efficiently catalysed the Mannich reaction, while lipase CAL-B showed moderate catalytic activity. Notably, these promiscuous reactions can be greatly promoted by water. The "one-pot" lipase-catalysed, direct Mannich reaction provides a novel case of catalytic promiscuity and might be a useful synthetic method for bioorganic synthesis.

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Phase behaviour of trihexyl(tetradecyl)phosphonium chloride, nonane and water

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This research details our investigations into the potential for separating the ionic liquid trihexyl(tetradecyl)phosphonium chloride ([P_{66614}]Cl) from nonane using water. A miscible two component mixture of [P_{66614}]Cl and straight chain hydrocarbon separates upon addition of water into a three-phase mixture. The phase behaviour for [P_{66614}]Cl/water/nonane is presented, showing a stable three-component phase, whereby any additional water or nonane separates into its own immiscible layer. Although this limits the potential use of this system for entirely separating hydrocarbons from this ionic liquid, it has potential for other uses, such as triphasic catalysis.

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Introduction

Over recent years there has been a greater than exponential increase in research concerning ionic liquids, much of which has the ultimate aim of large scale industrial application.[1] A fundamental aspect to the application of ionic liquids for industrial processes is their use with hydrocarbons. Some of their most common applications will involve their use as a reaction medium for organic synthesis or as an extraction solvent for separation. The most obvious method for separating organics from ionic liquids is through distillation, taking advantage of their negligible vapour pressure under atmospheric conditions.[2] Distillation is, however, not always a suitable option and can be limited by factors such as distillate stability and intensive energy demands, which are particularly relevant for large scale applications.[3] It has been previously reported that phosphonium ionic liquids can be separated from organics through addition of water.[4] This method is, in principle, far less energy intensive than distillation and therefore has great potential in terms of green chemistry. This paper aims to assess the potential of this method for the separation of hydrocarbons from [P_{66614}]Cl.

[P_{66614}]Cl is an ionic compound with several important uses. Up until the late 1990 s, this material was most commonly used as a phase transfer catalyst,[5] but has recently gained increasing use as a solvent/component in the field of ionic liquid research.[6] It is especially important in this field, as it can undergo metathesis to form a broad range of ionic liquids. It can also be derived from industrial processes involving trialkylphosphines, which coupled with the aforementioned applications has led to it becoming one of the few ionic liquids to be manufactured in bulk to date.[7] This is especially relevant as low cost, large scale manufacture has been highlighted as an important precursor to the successful implementation of ionic liquids in industrial processes.[8] Many potential industrial applications also require the use of either hydrocarbons or water and often both, which could lead to their release to the environment. As [P_{66614}]Cl is the most readily available of the phosphonium-based ionic liquids, it serves as a good starting point for developing this understanding. [P_{66614}]Cl has also previously shown interesting phase behaviour with other ionic liquids and this research adds to the understanding of its fluid phase behaviour.[9] This study also forms part of our broader research relating to the area of liquid–liquid equilibria (LLE) involving ionic liquids, and its relation to green chemistry.[10]

Nonane was chosen for this study to provide a general representation of a hydrocarbon phase. It was preferential to other hydrocarbons, as it is liquid over a fairly wide temperature range (from 220 K to 424 K), which minimises error relating to evaporation of the solvent when using the experimental technique explained in the following section.

We report the LLE of [P_{66614}]Cl, nonane and water at both 298 K and 323 K. We also examine the binary interactions between each pair of components as a function of temperature and propose an explanation for the observed phase behaviour in terms of solution enthalpy.

Experimental

Materials

[P_{66614}]Cl was obtained from Cytec Industries Inc. and had a typical purity of 96–97%, a water content of 0.097 wt%, density of 0.8914 g cm^{-3} at 293.15 K and viscosity of 2152 mPa s at 298.15 K. To increase purity and to remove as much water as possible, [P_{66614}]Cl was heated to 363.15 K under a vacuum of 4×10^{-4} bar for 36 h. This resulted in a final water content of 0.0036 mol fraction. Anhydrous nonane (>99.9%) was purchased from Sigma-Aldrich. Ultrapure water (resistivity >18 MΩ cm at 298.15 K) was obtained using an Elga Maxima Ultra Pure Water system.

Determination of binary data

Binary data were determined using a slight variation on the cloud point method.[12] As the quantities being measured are often of

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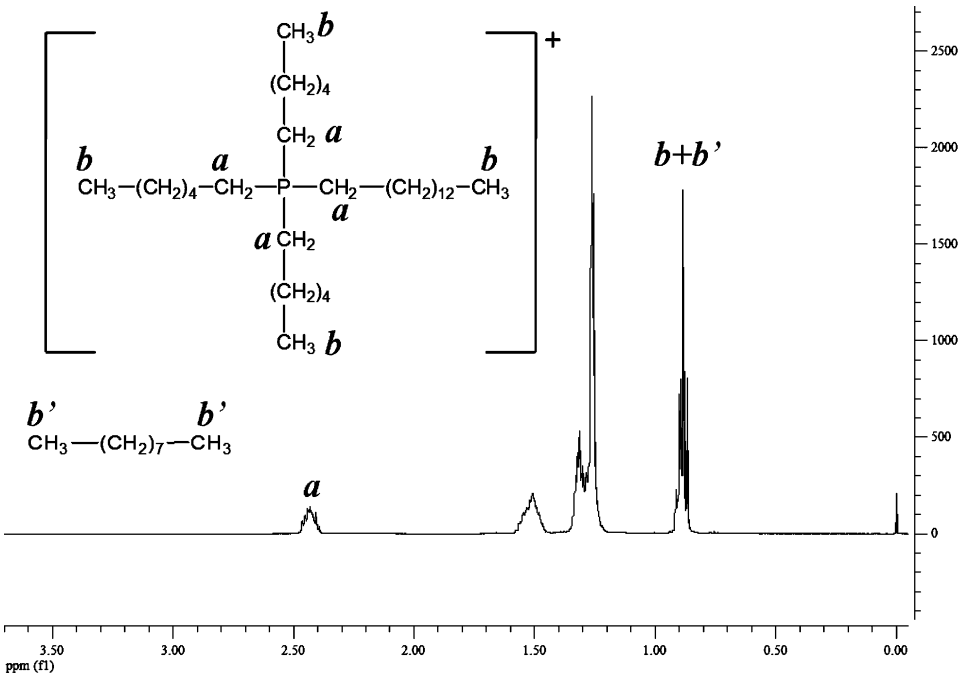

Fig. 1 Example ^{1}H NMR spectrum of a mixture containing $[P_{66614}]Cl$, nonane and water.

relatively small mass, the scale of the experiment was increased. For example, as the maximum solubility of $[P_{66614}]Cl$ in nonane is a small mol fraction, the scale of the experiment had to be increased to get an accurate measurement of the mass added. As the scale of the experiment varies, it is therefore necessary to state the associated error for each mutual solubility determination. As $[P_{66614}]Cl$ is hygroscopic, all binary experiments with nonane were performed under a dry nitrogen atmosphere.

The solubility of $[P_{66614}]Cl$ in water was too small to be measured using the cloud point method, so was determined by measuring the chloride ion content using ion chromatography.[11] This involved mixing an excess amount of $[P_{66614}]Cl$ with water and allowing the sample to equilibrate for 24 h.

Determination of phase boundaries

The determination of the phase regions for $[P_{66614}]Cl$, nonane and water is not straightforward. The monophasic/biphasic boundary curve was determined using the standard cloud point method.[12] The biphasic/triphasic boundary curve was determined using a step-wise procedure. For example, a small measured quantity of one component was added to a triphasic mixture, and the mixture agitated for 1 min. The mixture was then left unagitated until distinct clear layers had formed (typically 1–5 min), enabling visual determination of the number of phases present. This step-wise process was repeated until the component being added made up greater than 98 mol% of the overall mixture. The phase boundary data were obtained by adding $[P_{66614}]Cl$ to set mixtures of nonane and water. This was mainly due to ease of mixing, as $[P_{66614}]Cl$ is the most viscous component of the three. The temperature of all the samples was maintained using a RCT Kika Labortechnik Basic Heater/Stirrer, with temperature control accuracy of ±0.2 K.

Determination of tie line data

The LLE tie line data were obtained using the following procedure. A glass cell was charged with a three component composition known to be in either the biphasic or triphasic region. The three components were then thoroughly agitated for 1 h with a magnetic stirrer, ensuring that the mixture was well homogenised. The agitation was ceased and the mixture was left to equilibrate for 12 h. After equilibration, each layer was sampled using a glass syringe fitted with a metal needle. The organic content of each layer was analysed by ^{1}H NMR at 298.15 K, using a Bruker Avance DRX-500 spectrometer. All NMR samples were dissolved in $CDCl_3$ solvent purchased from Apollo Scientific Ltd. (99.8%, containing 0.03% tetramethylsilane). The water content of each layer was analysed by Karl Fischer titration using a GR Scientific Cou-Lo Compact coulometer. All sample weight measurements were achieved using a Sartorius Basic BA61 analytical balance precise to within $\pm 1 \times 10^{-4}$ g.

An example ^{1}H NMR spectrum for a mixture containing $[P_{66614}]Cl$, nonane and water is shown in Fig. 1. The spectrum for nonane consists of one peak for the two terminal methyl groups (b' in Fig. 1) and a group of overlapping peaks for all the methylene groups. As both sets of peaks overlapped with peaks from $[P_{66614}]Cl$, the area of the terminal methyl groups of nonane had to be calculated by subtracting the area due to the terminal methyl groups of $[P_{66614}]Cl$ (peak denoted as $b + b'$ in Fig. 1). The $[P_{66614}]Cl$ terminal methyl group area contribution was calculated from the $[P_{66614}]Cl$ peaks denoted by a in Fig. 1. This method is quantitative as peak areas on a ^{1}H NMR spectrum are proportional to the molar quantity of hydrogen atoms present in the sample. The accuracy of the ^{1}H NMR method of analysis was found to be ±2 mol% and was determined by analysing a broad range of homogeneous samples of known concentrations with global compositions near the immiscibility regions. The

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accuracy achieved is sufficient to gain considerable insight into the phase behaviour of this system. Further detail of the use of ^{1}H NMR spectroscopy for the determination of LLE systems involving ionic liquids and hydrocarbons has been published previously.[13]

Results and discussion

Binary data

Nonane was found to have a maximum mol fraction solubility of 0.854 ± 0.001 in [P_{66614}]Cl at 298.15 K, whereas [P_{66614}]Cl has a maximum mol fraction solubility of $(2.9 \pm 0.6) \times 10^{-3}$ in nonane at 298.15 K. Water was found to display similar phase behaviour. The maximum mol fraction solubility of water in [P_{66614}]Cl was found to be 0.818 ± 0.001 at 298.15 K, whereas [P_{66614}]Cl has a mol fraction solubility in water of $(1.7 \pm 0.2) \times 10^{-5}$ at 298.15 K. The high miscibility between [P_{66614}]Cl and both nonane and water, is a common feature of many similar materials to [P_{66614}]Cl, often collectively referred to as surfactants or phase transfer catalysts. The hydrocarbon miscibility derives from the van der Waals interactions between the long and straight alkyl chains, whereas the water miscibility derives from the polar water molecules hydrogen bonding to the chloride.[14]

The very low mutual solubility between water and hydrocarbons is common knowledge and has been studied extensively over the years. The maximum mol fraction of nonane that dissolves in water at 298.15 K is 2×10^{-8} and the mol fraction of water that dissolves in nonane at 298.15 K is 5.6×10^{-4}.[15]

The influence of temperature on each of the binary pairs can be explored using the van't Hoff equation. The van't Hoff equation[16] relates the equilibrium constant to the change in temperature. A plot of the logarithm of the equilibrium constant *versus* the reciprocal of temperature yields a straight line, of which the change in enthalpy can be calculated from the slope, and the change in entropy from the intercept. For the dissolution of nonane in [P_{66614}]Cl, the change in enthalpy was found to be (3.2859 ± 0.0001) kJ mol^{-1} and the change in entropy (10.09 ± 0.01) J K^{-1} mol^{-1}. Such a large increase in enthalpy is consistent with many other examples of solubility where the heat of dissolution dominates, resulting in greater solubility at higher temperature.[17] The relative facility with which solubility can be altered by temperature implies many potentially useful applications such as in inorganic biphasic catalysis[18] or enzyme based catalysis.[19]

At least 4×10^{-3} mol fraction of [P_{66614}]Cl was required to achieve immiscibility with nonane at 298.15 K. However, as the temperature increases so does the quantity of [P_{66614}]Cl required to achieve immiscibility. This is illustrated in Fig. 2, which also shows that the binary mixture exhibits an upper critical solution temperature at ~314 K. This is slightly different from the value of ~306 K reported by Saracsan *et al.*[20] Possible explanations for this discrepancy may come from purity differences between the two sources of [P_{66614}]Cl and from water content differences, which they did not state.

The solubility data for water in [P_{66614}]Cl as a function of temperature were taken from those published by Freire *et al.*[21] As the solubility of [P_{66614}]Cl in water is so close to zero, we could assume a zero value for the purpose of calculating the

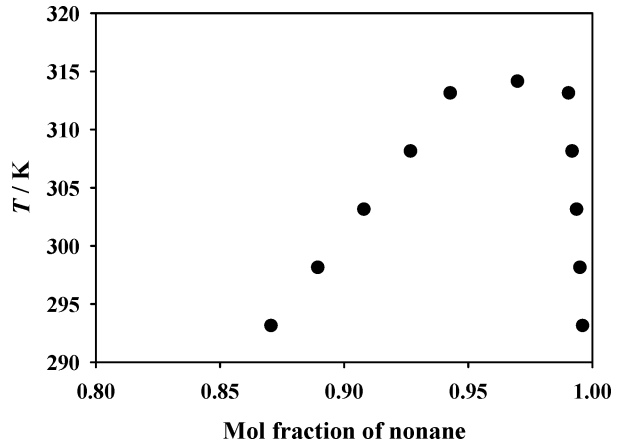

Fig. 2 Temperature-composition diagram for the binary system ([P_{66614}]Cl + nonane). Please note that the *x*-axis ranges only from 0.80 to 1.00 in mol fraction.

equilibrium values. Based on this assumption, the enthalpy of mixing was calculated to be (0.5688 ± 0.0001) kJ mol^{-1} and the entropy of mixing to be –(0.22 ± 0.01) J K^{-1} mol^{-1}. These values are far smaller than those calculated for nonane in [P_{66614}]Cl, indicating that the miscibility between water and [P_{66614}]Cl is relatively uninfluenced by moderate variations in temperature.

Ternary data

Cloud point determinations of the boundary lines at 298.15 K revealed that this three component system forms monophasic, biphasic and triphasic regions. Any composition that would lie within the triphasic region (shaded area in Figs. 3 and 4), will split into three phases, where the central phase forms the composition at the vertex of the shaded triangle (point B in Figs. 3 and 5). Of the remaining two layers, the upper layer consists of >0.99 mol fraction nonane and the lower layer consists of >0.99 mol fraction water (points A and C respectively, in Figs. 3 and 5).

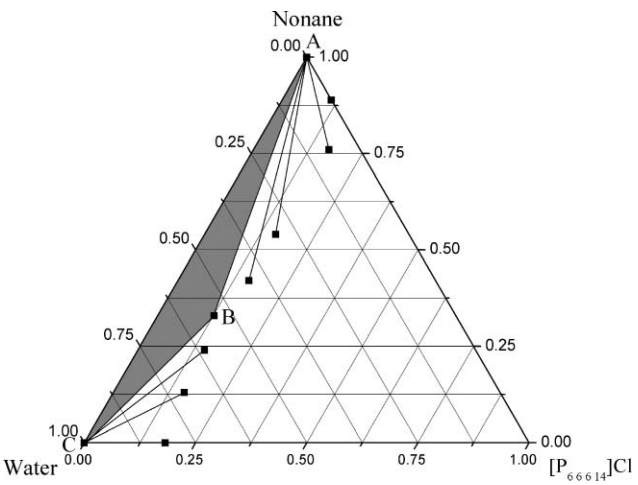

Fig. 3 Triangular diagram with the LLE at 298.15 K for the ternary system ([P_{66614}]Cl + nonane + water). The shaded area indicates the triphasic region.

A three component phase diagram of this sort can be best classified as a type III, according to the classification system

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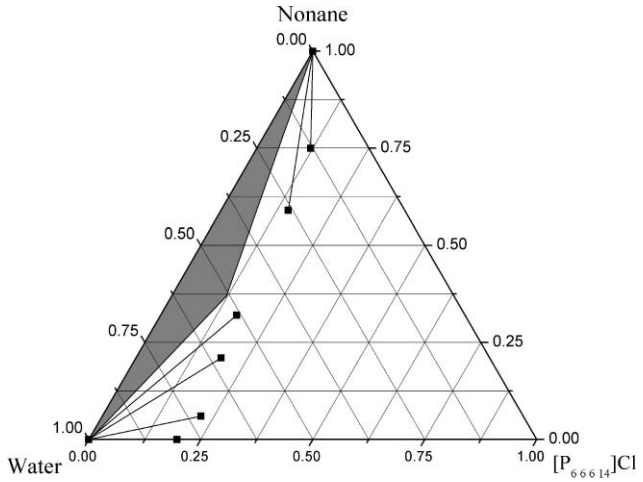

Fig. 4 Triangular diagram with the LLE at 323.15 K for the ternary system ([$P_{6\,6\,6\,14}$]Cl + nonane + water). The shaded area indicates the triphasic region.

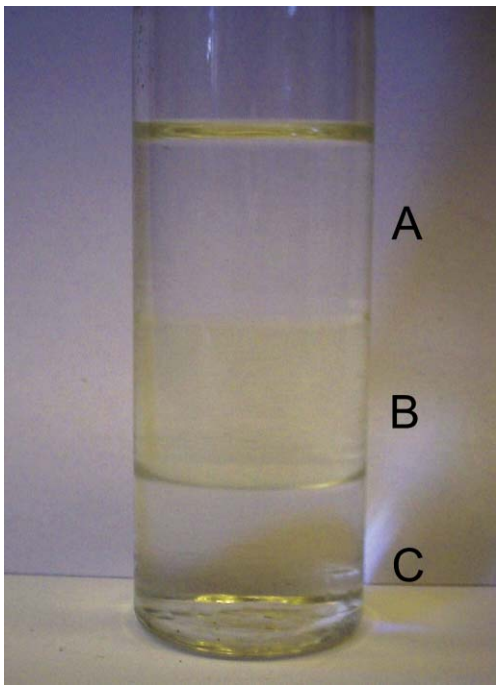

Fig. 5 Photograph of an equilibrated sample from the triphasic miscibility region, where layer A is virtually pure nonane, layer B is [$P_{6\,6\,6\,14}$]Cl saturated with nonane and water, and layer C is virtually pure water.

proposed by Treybal.[22] Type III phase diagrams consist of three partially miscible binary pairs, whose associated biphasic areas in the ternary system converge to create a region in which three phases co-exist in thermodynamic equilibrium (Fig. 6).

The binary data showed that an increase in temperature from 298.15 K to 323.15 K results in total miscibility between [$P_{6\,6\,6\,14}$]Cl and nonane. This manifests itself in the ternary diagram at 323.15 K (see Fig. 4) which shows that for ternary mixtures near 100% nonane, the biphasic miscibility region is far smaller than at 298.15 K.

Tables 1 and 2 show the tie-line data for the biphasic region at 298.15 K and 323.15 K respectively. These data have also been

Table 1 Experimental tie lines within the biphasic region for the system ([$P_{6\,6\,6\,14}$]Cl (1) + nonane (2) + water (3)) at 298.15 K

Upper Phase			Lower Phase		
x_1	x_2	x_3	x_1	x_2	x_3
Biphasic region No. 1					
0.01	0.99	0.00	0.17	0.76	0.07
0.01	0.99	0.00	0.16	0.54	0.30
0.01	0.99	0.00	0.16	0.42	0.42
Biphasic region No. 2					
0.15	0.24	0.61	0.00	0.00	1.00
0.16	0.13	0.71	0.00	0.00	1.00

Table 2 Experimental tie lines within the biphasic region for the system ([$P_{6\,6\,6\,14}$]Cl (1) + nonane (2) + water (3)) at 323.15 K

Upper Phase			Lower Phase		
x_1	x_2	x_3	x_1	x_2	x_3
Biphasic region No. 1					
0.01	0.99	0.00	0.12	0.75	0.13
0.01	0.99	0.00	0.15	0.59	0.26
Biphasic region No. 2					
0.17	0.32	0.51	0.00	0.00	1.00
0.19	0.21	0.60	0.00	0.00	1.00
0.22	0.06	0.72	0.00	0.00	1.00

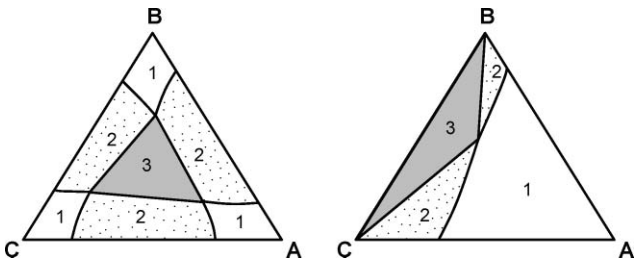

Fig. 6 Schemes of Type III ternary LLE systems, according to Treybal's classification.[22] The diagram on the left exemplifies a conventional system of this type, with relatively equivalent biphasic regions and a centred triphasic region; whereas the diagram on the right corresponds to a 'distorted' system in which the triphasic region is practically tangent to one of the sides of the diagram. The cardinals indicate the number of phases in equilibrium: three phases (shaded regions), two phases (dotted regions) and one phase (blank regions).

plotted on the triangular diagrams in Figs. 3 and 4. For water contents greater than ~0.50 mol fraction, some of the water separates out as a virtually pure layer (>0.99 mol fraction). For water contents of less than ~0.50 mol fraction, some of the nonane separates out to form an effectively pure layer (>0.99 mol fraction).

Potential applications

This research initially attempted to ascertain if it was possible to cleanly separate a mid – range molecular weight hydrocarbon (nonane) from [$P_{6\,6\,6\,14}$]Cl, through the simple addition of water. The phase equilibrium data reveal that it is not possible to completely separate nonane from [$P_{6\,6\,6\,14}$]Cl by the addition of water. This is because a stable three component mixture is formed, whereby any further addition of either nonane or water separates into its own immiscible layer. However as the upper critical solution temperature for the system ([$P_{6\,6\,6\,14}$]Cl + nonane)

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is strongly influenced by the presence of water, a dry mixture of $[P_{66614}]Cl$ and nonane can be made to separate through addition of <0.1 mol fraction of water without adjustment of temperature. Alternatively, since the upper critical solution temperature is near ambient conditions (314 K under near anhydrous conditions), only moderate adjustment of temperature is required to induce phase separation. A similar method has been proposed by Scurto *et al.*[23] using gaseous carbon dioxide to induce separation of ionic liquids from water. It may be possible to use this approach in combination with, or in series, to further separate the central ionic liquid layer into individual components.

There is potential to apply these data for triphasic catalytic reactions requiring a phase transfer catalyst. The ability to mix immiscible reagents, whilst also being able to subsequently separate products and by-products into pure water and hydrocarbon phases, has been shown by Carmichael *et al.*[24] to be viable. By using a triphasic system for the Heck reaction, they were able to separate the reaction products into the hydrocarbon phase and the reaction by-products into the aqueous phase, whilst simultaneously immobilising the catalyst in the central ionic phase. This concept has since been further developed by Perosa *et al.*[25] with solid nanoparticles. They found that the central ionic layer is able to immobilise catalytically active metal particles, allowing the clean separation of the products without leaching of the nanoparticles. The research presented in this paper shall hopefully add to the understanding and development of this emerging area of catalysis.

Another potential interesting application is in liquid–liquid extraction. As the triphasic region contains three phases of greatly varying polarity, it may serve as a platform to separate compounds where currently no suitable solvent extraction system exists.

Conclusions

The binary data show that the miscibility between $[P_{66614}]Cl$ and nonane is strongly influenced by temperature, resulting in large changes in entropy and enthalpy. This is in contrast to $[P_{66614}]Cl$ and water, which is relatively uninfluenced by temperature. The ternary phase diagram for water, $[P_{66614}]Cl$ and nonane, shows triphasic and biphasic regions. Although the separation is insufficient for cleanly separating hydrocarbons from $[P_{66614}]Cl$, the ability to easily change from one phase to two or even three phases, offers potential for many interesting catalytic applications or complex separation problems. The data reveal that it is possible to change from monophasic to biphasic or from biphasic to triphasic (and *vice versa*) by either moderate adjustment of temperature or by moderate adjustment of composition.

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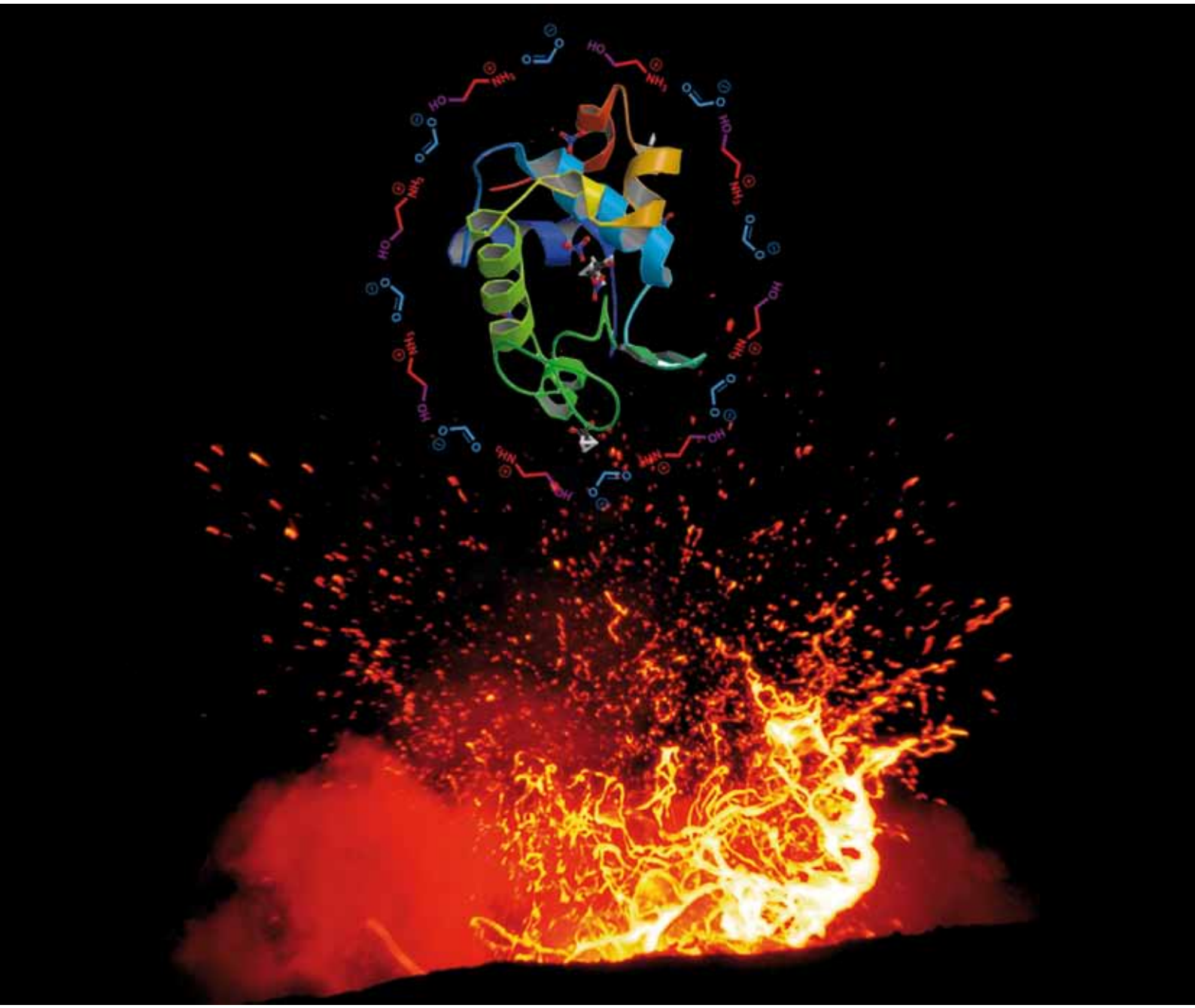

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Activity and thermal stability of lysozyme in alkylammonium formate ionic liquids—influence of cation modification†

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The stability and activity of hen's egg white lysozyme in the presence of four protic room temperature ionic liquids (ethylammonium formate (EAF), propylammonium formate (PAF), 2-methoxyethylammonium formate (MOEAF) and ethanolammonium formate (EtAF)) have been investigated. Near UV CD experiments have been used to determine protein structure in aqueous solutions of 25 wt%, 50 wt% and 75 wt% ionic liquid, and to assess the proteins ability to refold after heating to 90 °C. It was determined that EAF and MOEAF are similarly effective refolding additives, while PAF is more effective at promoting refolding at concentrations up to ~62.5 wt%, but at higher PAF concentrations the protein spontaneously denatures. Both of these effects are attributed to the increased hydrophobicity of the cation. EtAF is shown to stabilise lysozyme against unfolding at high temperature, and renaturing appears to be near complete upon cooling. Studies of enzyme kinetics reveal increased protein activity in the presence of all ionic liquids examined, but the most significant increase is noted for EtAF, where rates are six times higher than those determined for lysozyme in buffered water.

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Introduction

Enzymes are proteins that accelerate chemical reactions. They are highly substrate specific and have extraordinary catalytic power; a typical enzyme catalysed reaction proceeds millions of times faster than that of comparable uncatalysed reactions.[1] Enzymes are synthesised in cells through DNA transcription and translation,[2] then fold into the functional conformation, either spontaneously or with the assistance of chaperone proteins. Folding is driven and reinforced by the formation of a variety of bonds (hydrogen bonding, disulfide bridging, ionic attractions and hydrophobic attraction), by localised conditions, and the requirement to minimise unfavourable hydrophobic and hydrophilic interactions between parts of the protein chain.[2] These bonds are influenced by solvent temperature, pH, ionic strength and polarity. Enzyme structure is described on four levels: primary (ordering of amino acid residues in the peptide chain), secondary (the formation of structures such as alpha helixes and beta sheets *via* inter-residue hydrogen bonds), tertiary (folding into the active three dimensional morphology), and quaternary (combination of two or more protein chains).

For many years the use of enzymes was restricted to dilute aqueous solution. The use of organic solvents as enzyme reaction media was pioneered by Klibanov.[3] Surprisingly, enzymes often retained their active conformation and in many cases enzymes demonstrated increased stability and activity. Water insoluble reaction precursors could now be dissolved in enzymatic solution, vastly increasing the range of enzyme catalysed reactions, and product recovery was simpler. Today both aqueous and organic solvents are considered typical enzyme reaction media.

In 1994 it was found that enzymatic activity in organic solvents was dependent upon the presence of trace water.[4] Many enzymes (lipases, hydrolases and proteases) work well in organic solvents, but for optimal performance require a certain degree of hydration that is dependent on water activity. This biological water is associated with the enzyme's surface and helps maintain crucial three-dimensional structure. Hydrophobic solvents do not strip this water from the enzyme surface,[5] but hydrophilic organic solvents do and this leads to protein denaturing.[6] As a result, enzymes are active in water and in non-polar organic solvents, but generally inactive in protic and polar solvents. This creates a miscibility gap for enzyme catalysed reactions, as substrates strictly soluble in protic or polar solvents cannot be dissolved in solution with the active form of the enzyme.

Over the last decade, a considerable amount of attention has been focused on the development of novel solvents to help bridge this miscibility gap. Room temperature ionic liquids (ILs) are at the forefront of this research.[7–9] ILs are organic salts that are liquid at temperatures below 100 °C. They often have negligible vapour pressure and high thermal stability, but their key feature is their 'tuneable' nature, whereby important physical parameters (polarity, viscosity, Lewis acidity, *etc*) can be controlled by selection of appropriate cation and anion types in the first instance, with fine control facilitated by subtle variation in molecular structure of the individual IL components. These 'designer' characteristics, combined with their ability to

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† Electronic supplementary information (ESI) available: Supplementary Fig. A. Near UV CD spectrum of aqueous lysozyme. See DOI: 10.1039/b900021f

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solubilise unusual combinations of chemical species, has led to a vast number of research articles in which ILs are employed as solvents for chemical synthesis.[10–12] Notwithstanding this, comparatively little is known about the relationship between cation and anion molecular structure and physical properties (especially for protic ILs),[13,14] and even less concerning the nature of interactions with dissolved proteins.

In aqueous solutions, the influence of inorganic electrolytes on enzyme stability was first systematised by Hofmeister.[15] The Hofmeister series has since found widespread applications in other areas including colloid, polymer, and surface chemistry.[16] While in some cases there seems to be specific interactions between enzymes and ions, the similarity of results obtained in a wide variety of systems suggests a more universal mechanism.[16] One possibility is that ion-induced changes in water structure either promotes or hinders the binding of ions to the protein interface, leading to changes in stability. The Hofmeister series potentially provides a starting point for our understanding of the interactions between ILs with proteins, and an article has recently appeared to this end.[7] However, the complexity of IL ions, and particularly their hydrophobicity,[14] means that specific interactions with the protein are much more likely than for inorganic salts. Indeed, Constantinescu *et al.* state 'some biocatalysed reactions are conducted in "neat" ILs as solvents (little or no water).[7] In these cases the effect of ions on the stability/activity of enzymes seems to be much more complicated and does not follow the Hofmeister series'.

In hydrophobic ILs (for example, those including a PF_6^- or $(CF_3SO_2)_2N^-$ anion), enzymes often have high stability,[8,17] attributed to the presence of biological water as per hydrophobic organic solvents. In these systems the protein is not actually dissolved, but present as a finely divided dispersion acting as a heterogeneous catalyst.[17] Increased stability in hydrophilic ILs (either the pure IL or as a water co-solvent) is more difficult to explain.

Summers and Flowers first demonstrated that the use of hydrophilic ILs ($R_4N^+NO_3^-$) as aqueous co-solvents suppressed enzyme aggregation in addition to increasing reaction yields.[18] It was suspect that adsorption of the IL cation to hydrophobic regions of the protein exposed upon heating created electrostatic repulsions that prevented protein aggregation, while coulumbic attractions between the ions and the charged portions of the enzyme stabilise secondary structure. Byrne *et al.* obtained similar results a few years later,[19] and also reported previously unheard-of multi-year stabilisation of lysozyme in the presence of ethylammonium nitrate (EAN). Differential scanning calorimetry (DSC) experiments revealed that while the temperature of the endotherm maximum was the same as for aqueous buffered samples, the protein was able to unfold and refold over repeated heating–cooling cycles. In pure aqueous solutions of lysozyme at equivalent concentrations 70% protein is lost after one heating cycle. In subsequent experiments the IL structure was varied and it was concluded that the availability of the N–H proton was the critical factor.[20] A measure of the N–H availability was obtained using nuclear magnetic resonance spectroscopy and it was found that maximal refolding occurred for N–H chemical shifts between 7 and 9 ppm. Outside this region, enzyme unfolding was irreversible.

The precise reason for increased enzyme re-naturing and thermostability in the presence of some ILs is unclear,[21] with changes in hydration levels, structure compaction, free volume contributions, salt bridges, confinement effects and the bulk structure of the IL[22] all mooted as potential contributors. Similarly, there are several possible reasons for protein deactivation in other ILs including stripping of biological water,[21] interactions between the proteins charged groups and the IL[8] and the breaking of intra-protein hydrogen bonds,[8] all of which could lead to loss of tertiary structure. In this article we present results demonstrating that IL concentration, and subtle variation in the cation structure, can dramatically influence lysozyme stability and activity.

Results and discussion

CD experiments

CD measures the absorption difference between left-handed and right-handed polarised light arising from structural asymmetry.[23] The absence of regular structure produces zero CD single, while ordered structures produce a spectrum containing both positive and negative outputs. The near UV CD spectral region (250–350 nm) is sensitive to certain aspects of an enzymes tertiary structure.[23] The signals in this region are associated with phenylalanine (254, 256, 262 and 267 nm), tyrosine, (276 and 283 nm) tryptophan (280–300 nm) and disulfide chromophores, which give rise to broad, but weak signals. The signals in this region are sensitive to the chromophores' local environment and, consequently, the enzymes' tertiary structure. As such, near UV CD spectra provide a 'fingerprint' of protein morphology, but little quantitative structural information can be derived from this region.[23] Secondary structural content can be calculated from the far UV CD spectrum, but some IL absorption bands interfere with the far UV, particularly those based on the nitrate anion. For this reason, formate based ILs, that do not interfere with this region of the spectrum, are the focus of this study. CD measurements are primarily used to ascertain whether the protein is in its folded or unfolded state as temperature is increased, and its ability to refold upon cooling.

The aromatic amino acid residues of lysozyme (phenylalanine, tyrosine and tryptophan) and disulfide chromophores produce the protein's near UV CD spectrum.[24,25] The positive triplet-like signal in the 280 to 300 nm range dominates the spectrum, and is indicative of lysozyme's active conformation (Fig. 1a).[26] In particular, the weak negative band at 295 nm has been attributed to tryptophan 108, which is associated with the active site (boxed region Fig. 1a).[24] This provides direct insight into the immediate environment of the active zone.

As the cell temperature is increased, lysozyme begins to denature with the increased thermal energy breaking the bonds that maintain lysozyme's active conformation. Lysozyme unfolds, exposing the internalised hydrophobic core[27,28] to the surrounding medium. Attraction between exposed hydrophobic cores, or electrostatic interactions between oppositely charged residues (or a combination of both), potentially leads to aggregation or misfolding, whereupon the enzyme is irreversibly denaturated. While renaturating of lysozyme is possible at low concentrations in pure water, refolding is known to be

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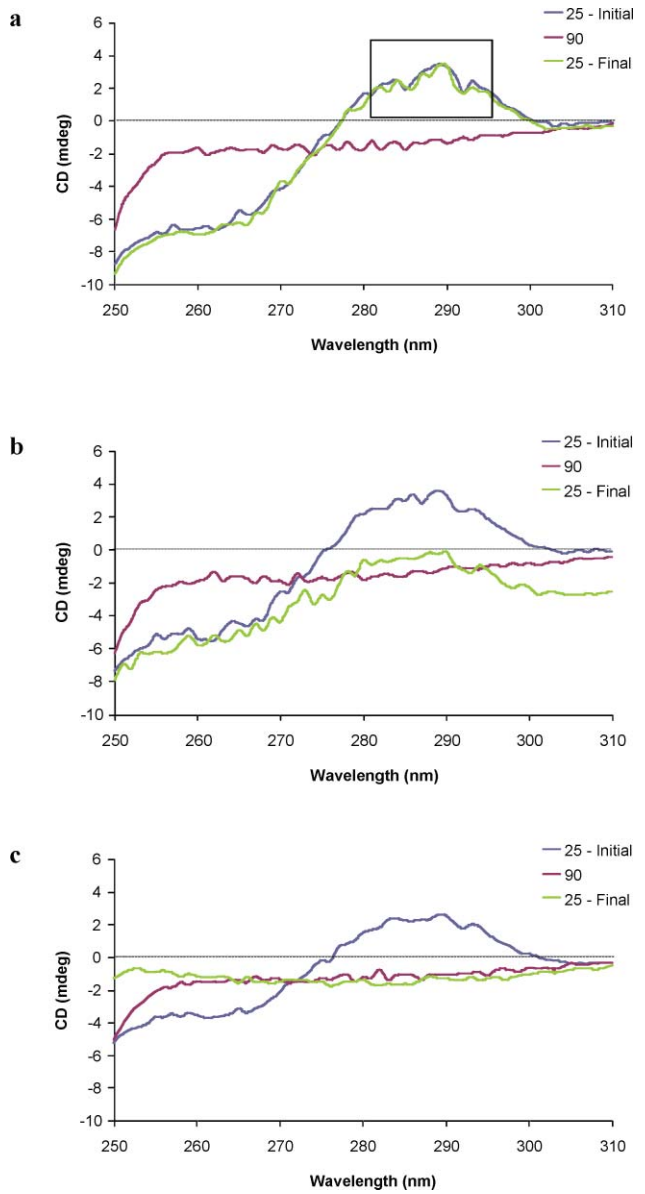

Fig. 1 Near UV CD spectrum of aqueous lysozyme (3.4×10^{-4} mol dm^{-3}) in water with EAF loadings of (a) 25 wt%, (b) 50 wt% and (c) 75 wt%.

problematic at concentrations greater than ~1 mg ml^{-1} due to aggregation.[18] Our CD based evaluations of lysozyme stability in ILs uses concentrations of 5 mg ml^{-1}. Irreversible denaturing is the baseline result in water.

The near UV CD spectra of 3.4×10^{-4} mol dm^{-3} (5 mg ml^{-1}) lysozyme in water with EAF loadings of 25 wt%, 50 wt% and 75 wt% for the 25–90–25 °C heating and cooling cycle are presented in Fig. 1. These relatively high IL loadings have been selected to elucidate the effect of IL concentration on temperature stability and protein activity for formate based ILs. It is worth noting that similar pure ILs can possess nanoscale order,[29] and experiments monitoring conductivity as pure IL is added to water suggest non-ideal behaviour.[30] It is possible that short alkyl group cations form self-assembled aggregates at these concentrations in water in the absence of lysozyme.

The CD signal for the lysozyme/75 wt% water/25 wt% EAF system increases from –8 mdeg at 250 nm to –6.5 mdeg at 255 nm. The signal plateaus at this value up to 265 nm, after which it increases to 0 at 277 nm. In this region (up to 276 nm) the spectral features are primarily due to phenylalanine residues. At wavelengths greater than 276 nm the CD signal, produced by asymmetric tyrosine and tryptophan groups, continues to increase reaching a maximum of 3.7 mdeg at the apex of the primary peak of the triplet feature (289 nm). These data are essentially consistent with results obtained for lysozyme in buffered water (see ESI Fig. A†), the primary difference being that the peak at ~290 nm is slightly weaker and broader due the presence of IL ions in the vicinity of trytophan residues, which alters the local environment (*cf*. Fig. 1a and 1b). Examination of lysosyme activity (below) confirms maintenance of a constitutively active protein.

Upon heating to 90 °C the CD spectrum changes dramatically. The signal now increases rapidly from –6 mdeg at 250 nm to –2 mdeg at 255 nm. This value is essentially constant up to 295 nm, after which it gently increases to ~0 mdeg at 310 nm. This comparatively featureless spectrum indicates that the protein has unfolded. The non-zero CD signal is due to disulfide bonds which are known to remain intact at elevated temperatures.[27,28] This high temperature spectrum is essentially the same as that obtained for reduced lysozyme concentrations at 90 °C in the absence of IL (see ESI Fig. A†). Upon cooling to 25 °C the CD spectrum is broadly consistent with that recorded prior to heating, suggesting that most of the lysozyme has refolded correctly.

When the EAF concentration is increased to 50 wt% the fine structure of the triplet feature is not as well resolved; it more closely resembles the triplet observed with 25% EAF after cooling from 90 to 25 °C (Fig. 1a and 1b) and the ability of lysozyme to refold after heating is reduced. The diminution of this characteristic triplet signal is more pronounced at 75 wt% EAF with a reduction in intensity also noted, 2.4 mdeg (75 wt% EAF) at 288 nm *versus* 3.6 mdeg (25 and 50 wt% EAF). At this high concentration the triplet feature has almost disappeared and cycling to lower temperatures does not initiate protein refolding, indicating that lysozyme has irreversibly denatured.

Summers and Flowers postulated that when unfolded, lysozyme's exposed hydrophobic core favourably interacts with the hydrophobic alkyl side chain of the ethylamonium cation (EA^+). Cation adsorption results in acquisition of a net positive charge preventing aggregation *via* electrostatic repulsion. It was also suggested that the protein's secondary structure was stabilized by co-ordination of cations and anions to charged residues. Combined, these interactions prevent aggregation and other denaturation mechanisms. Upon cooling, EA^+ must desorb from the hydrophobic surface of the core and from lysozyme's charged residues if the protein is to properly refold (re-nature). For this to occur the energy of refolding must be sufficient to overcome the cation adsorption energy.

Our data clearly suggest that the protein refolding energy is greater than that of the adsorbed cations and refolding occurs at 25 wt% EAF. This is consistent with previous reports.[18,19] However, with increasing IL concentration, the cation chemical potential also increases, favouring adsorption to the protein. At these higher concentrations (and especially at 75 wt%) the energy

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associated with refolding is insufficient to drive the cation from favourable (hydrophobic and/or electrostatic) interactions such that desorption does not occur. As a result the protein does not refold, but aggregation is prevented due to the presence of adsorbed IL, consistent with the absence of any cloudy appearance in post-analysed samples.

The effect of increasing cation hydrophobicity was examined using PAF, which has a C_3 alkyl group. CD spectra recorded at PAF loadings of 25 wt%, 50 wt%, and 75 wt% are presented in Fig. 2. An additional 62.5 wt% sample was also prepared for this IL due to the marked change in behaviour that occurs between 50 wt% and 75 wt%. For all IL concentrations, the spectra at 25 °C show clear deviation form that obtained in pure water (and EAF), particularly between 285 nm and 295 nm where the triplet feature is no longer apparent. This demonstrates that the environment of the tryptophan residues (at least) is markedly different in the presence of PAF compared to EAF and buffered aqueous samples. As the only difference between EAF and PAF is the size of the alkyl group, the increased hydrophobic interactions are responsible for this difference.

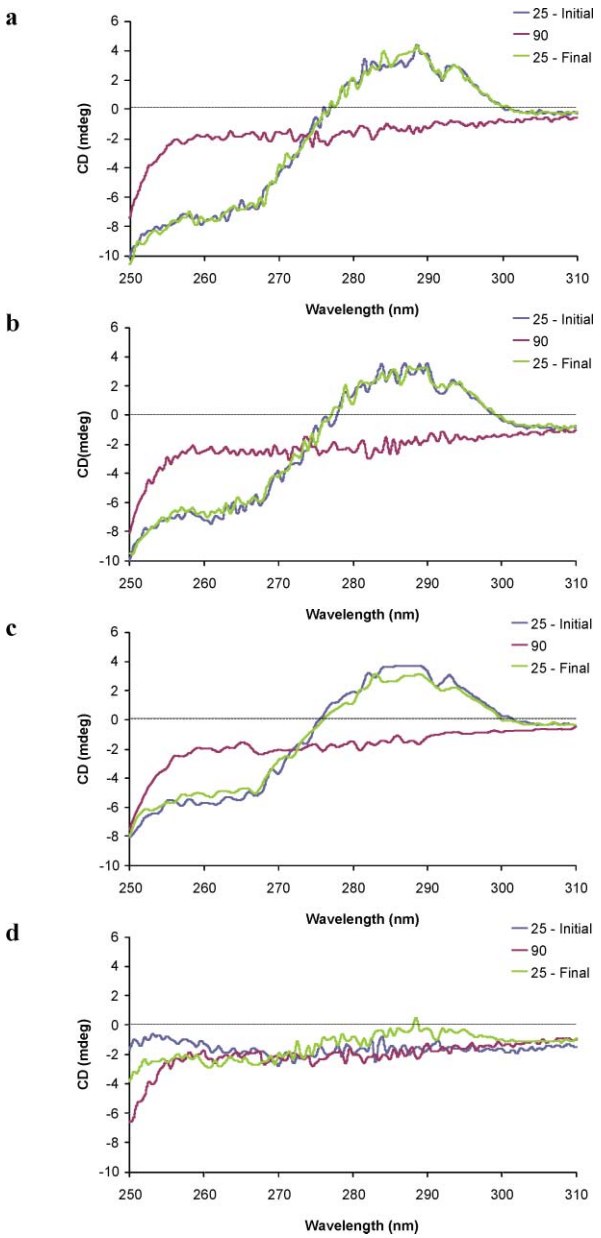

Fig. 2 Near UV CD spectrum of aqueous lysozyme (3.4×10^{-4} mol dm^{-3}) at PAF loadings of (a) 25 wt%, (b) 50 wt%, (c) 62.5 wt% and (d) 75 wt%.

The CD data indicate that lysozyme is able to refold into a structure similar to its original conformation for PAF loadings up to 50 wt% (Fig. 2b), and remains constitutively active (data presented below). At a PAF loading of 62.5 wt% the lysozyme partially refolds (Fig. 2c), but the differences between the both the initial and final CD spectrum and that of lysozyme in pure water are marked, indicating non-native structure. At 75 wt% PAF the protein is denatured even before heating (Fig. 2d). This is likely due to the hydrophobicity of PAF creating a liquid environment agreeable for the hydrophobic core, and the protein unfolds. This suggests that increasingly hydrophobic ILs destabilise lysozyme, so lowering the hydrophobic nature of the IL should increase stability, demonstrated below using EtAF and MOEAF.

The ability of the protein to refold at concentrations up to 62.5 wt% PAF compared to between 25 wt% to 50 wt% for EAF is surprising given that the refolding mechanism proposed above requires desorption of IL cations. Intuitively, one would expect that the strength of electrostatic interactions between the cation and the protein would be the same for both EA^+ and PA^+, but that hydrophobic interactions would be significantly enhanced for PA^+ due to its longer alkyl group. This means that the PA^+ would be more strongly bound to lysozymes hydrophobic core, which should prevent refolding, but in fact the opposite situation occurs. Most likely, self-aggregation of PAF in water is greater than for EAF due to the cation's increased hydrophobicity which lowers the energetic cost of desorbing PA^+ compared to EA^+. As a result, the protein is able to refold at higher PAF concentrations.

The effect of increasing the length of the cation alkyl chain without substantially changing hydrophobicity (relative to EAF) was investigated using MOEAF. MOEAF has a slightly longer aliphatic backbone than PAF due to the ether group two carbons from the amine, but this ether group also disrupts hydrophobic interactions, and MOEAF is slightly more polar than EAF. The CD spectra obtained for 25 wt%, 50 wt% and 75 wt% MOEAF are presented in Fig. 3. The results obtained are similar those for EAF at equivalent concentrations, the key differences being that the characteristic triplet feature disappears at lower IL loadings, and that re-naturing is more efficient for MOEAF than for EAF at 50 wt% IL. The first observation suggests that the immediate environment of tryptophan differs for the two ILs. The second observation is consistent with decreased strength of hydrophobic interactions between $MOEA^+$ and lysozyme's hydrophobic core, permitting refolding at higher IL concentrations according to the stated mechanism.

Given the enhanced stability noted for MOEAF, subsequent experiments examined the effect of demethylation to the free alcohol moiety affording EtAF, which is more hydrophilic than the ether group cation, and thus more disruptive to hydrophobic interactions. Alcohol substituted cations will interact less strongly with the hydrophobic core of lysozyme, but more

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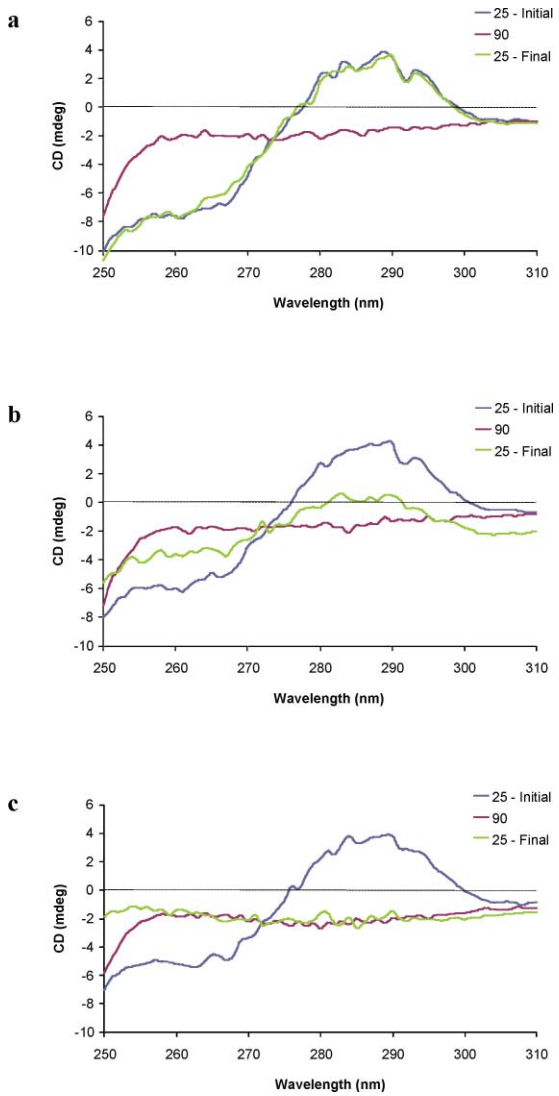

Fig. 3 Near UV CD spectrum of aqueous lysozyme (3.4×10^{-4} mol dm^{-3}) at MOEAF loadings of (a) 25 wt%, (b) 50 wt%, (c) 75 wt%.

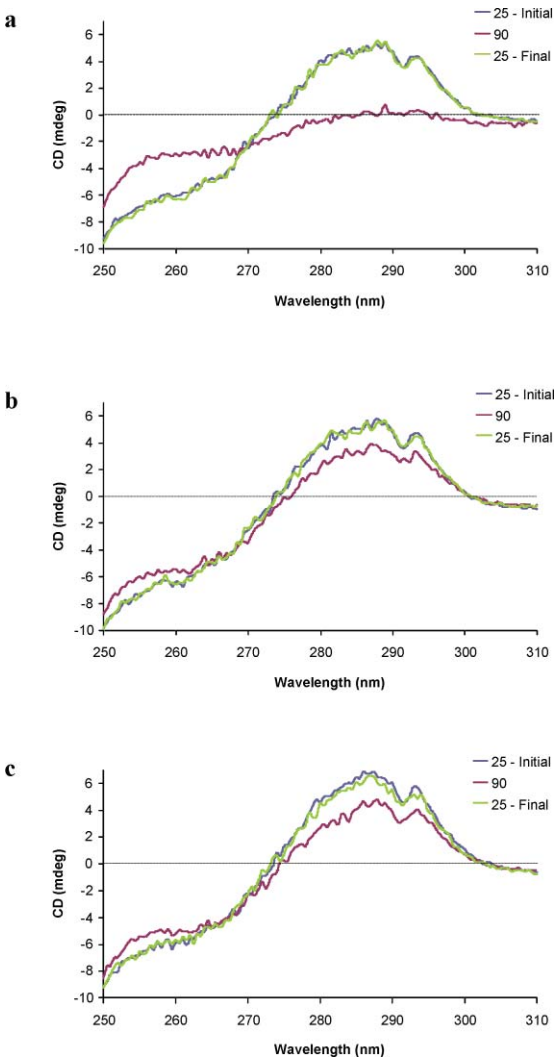

Fig. 4 Near UV CD spectrum of aqueous lysozyme (3.4×10^{-4} mol dm^{-3}) at EtAF loadings of (a) 25 wt%, (b) 50 wt%, (c) 75 wt%.

favourably with the hydrophilic regions which are normally exposed in aqueous environments even when the protein is folded. Alcohol groups have a significantly stronger electron withdrawing effect compared to unsubstituted aliphatic chains, which significantly decreases the N–H proton availability.[19]

CD spectra for EtAF for 25 wt%, 50 wt% and 75 wt% are shown in Fig. 4. The characteristic triplet feature is of reduced intensity but activity data (below) clearly show that the protein is active. The striking feature is increased temperature stability. On the timescale of the experiment, protein unfolding is clearly reduced for 25 wt% EtAF as the temperature is cycled from 25 °C to 90 °C and back to 25 °C, and refolding into the initial state appears to be complete, although this will undoubtedly be partially due to the fact that the protein does not completely denature. Increased temperature stability is even more pronounced at 50 wt% EtAF, then decreases slightly for 75 wt% EtAF. It should be noted that the viscosity of EtAF is approximately 8 times greater than that of EAF[31] but viscosity decreases rapidly as water is added and the temperature increases, such that for the different ILs investigated here the viscosity difference is less pronounced.[32] The fact that stability is only slightly reduced for the highest EtAF loading shows that temperature stability is not purely due to viscosity.

The CD signal at 288 nm (the primary peak) for lysozyme immersed in 75 wt% EtAF and 25 wt% water at 90 °C (15 °C higher than lysozyme's reported melting temperature[18]) as a function of time is presented in Fig. 5. For comparison lysozyme in buffer solution is also shown. In the absence of IL the protein is unfolded by the time the first CD measurement is completed, but with added EtAF approximately 1 hour passes before lysozyme unfolding is complete.

The reason for enhanced temperature stability in the presence of EtAF compared to ILs that do not contain an alcohol group is not immediately obvious. We believe EA^+ interacts with negatively charged residues electrostatically, hydrogen bonds to the protein *via* amine protons, and interacts with hydrophobic regions *via* its alkyl tail. While electrostatic interactions between EtA^+ and lysozyme are expected to be about the same as for

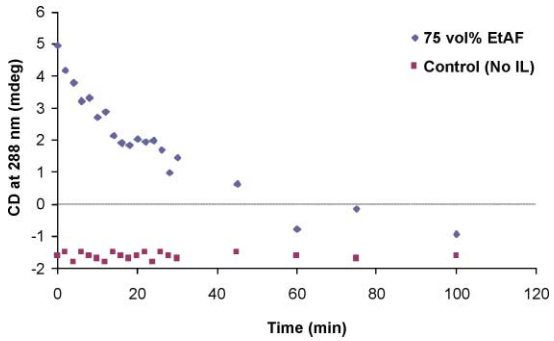

Fig. 5 CD signal at 288 nm for lysozyme immersed in 75 wt% EtAF and 25 wt% water at 90 °C as a function of time. A control experiment of lysozyme in water is shown for comparison.

EA^+, the alcohol group of EtA^+ provides and extra hydrogen bonding donor/acceptor site and will markedly reduce the strength of hydrophobic interactions with the protein. The fact that enhanced temperature stability is not observed for MEOAF, where the ether oxygen can act as a hydrogen bond acceptor, suggests an additional hydrogen bond donor group is pivotal to the observed increase in stability. Therefore, our results suggest that cations with multiple hydrogen bond donor sites co-ordinate to the protein more effectively than cations with a single hydrogen bond donor/acceptor group and non-alcohol containing alkyl chain, and thereby stabilise structure more effectively.

Activity Measurements

The rate at which lysozyme hydrolyses 1,4-β-linkages in gram-positive cells (between *N*-acetylmuramic acid (NAM) and *N*-acetyl-D-glucosamine (NAG) residues in peptidoglycans and between *N*-acetyl-D-glucosamine residues in chitodextrins) is strongly influenced by preparative methods and the cell substrate conditions (whether freeze dried or fresh). As a result there is no accepted 'rate' of lysozyme action, and kinetics are examined by comparison with a control sample.[18,26] The cell suspension is initially opaque, but as lysozyme hydrolyses the cell turbidity decreases, eventually yielding a transparent solution. Lysozyme activity measurements were performed on suspended *Micrococcus lysodeikticusce* cells for each of the four protic ILs at 25 wt%, 50 wt% and 75 wt%, *cf*. Fig. 6, except for 75 wt% PAF as the protein is immediately denatured in this solution. Solution turbidity was monitored using UV-Vis spectroscopy

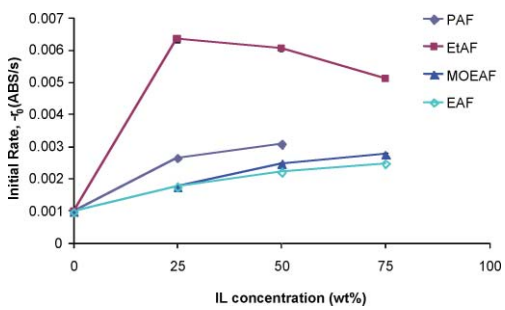

Fig. 6 Rate of hydrolysis from lysozyme (2.6×10^{-8} mol dm^{-3}) in 0.0014% (w/v) *Micrococcus lysodeikticusce* at varying IL concentrations.

and the initial rate determined from a tangent drawn to the first few data points. The turbidity of blank solutions containing suspended cells and IL but no lysozyme was invariant over the timescale of the experiment, approximately 1 hour.

The first and perhaps most important result is that lysozyme is active in the presence of all four protic ILs at 25 °C. This shows that the structural changes that produce differences in CD spectra as a function of IL species and concentration have not deactivated the protein. It should be noted that activity measurements were also completed on lysozyme in the presence of 25 wt% IL following a temperature denaturing cycle. The activity was essentially equal to that determined for the lysozyme which had not been subjected to a temperature denaturing cycle.

The activity as a function of concentration for EAF, PAF, and MOEAF (ILs that do not possess alcohol moieties) follow similar trends; activity increases with IL concentration. The results for EAF and MOEAF are indistinguishable within error, with rates about twice that measured for lysozyme in buffered water obtained at 50 wt% and 75 wt% IL. Lysozyme is considerably more active in PAF at all concentrations, with rates about three times greater than that measured in buffered water obtained at higher IL loadings.

Lysozyme is even more active in the presence of EtAF, with rates six times faster than those determined for buffered water determined for 25 wt% IL. This activity decreases slightly at higher IL loadings to about five times faster than for buffered water at 75 wt% EtAF. As the viscosity of pure EtAF is several times higher than the viscosity of the other ILs investigated, the EtAF solutions will be the most viscous at equivalent concentrations, so increased activity for this IL will not be a mass transport phenomenon.

In general terms, the activity measurements follow trends observed in the protein denaturing–renaturing CD experiments. The greatest activity and most complete refolding was determined for EtAF, followed by PAF, while EAF and MOEAF were about equally effective in terms of activity enhancement and refolding. At the moment it is unclear how these two sets of results are related, but it may be that the ILs re-enforce protein structure such that it is able to perform its lysing function more vigorously. Further experiments are required to test this hypothesis, but it would explain the correlations between protein activity, stability and IL species.

Conclusions

CD experiments have been used to probe lysozyme structure in aqueous solutions of 25 wt%, 50 wt% and 75 wt% IL (EAF, PAF, MOEAF, EtAF), and to assess the protein's ability to refold after heating to 90 °C. EAF and MOEAF are similarly effective refolding additives, while PAF is more effective at concentrations up to ~62.5 wt%. At higher PAF concentrations lysozyme denatures spontaneously, as adsorption of PA^+ to the protein's hydrophobic core effectively protects it from the bulk hydrophilic solvent. EtAF is stabilises lysozyme against unfolding at high temperature, and renaturing appears to be near complete upon cooling. This could be a consequence of differences in the way this alcohol-containing IL interacts with lysozyme compared to ILs that do not contain alcohols. Electrostatic interactions

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between EtA^+ and lysozyme are expected to be about the same as for the other ILs, but the alcohol group of EtA^+ provides an extra hydrogen bonding donor/acceptor site which also reduces the strength of hydrophobic interactions with the protein. As enhanced temperature stability is not noted for MEOAF, where the ether oxygen can act only as a hydrogen bond acceptor, our results suggest that an additional hydrogen bond donor group is key. The temperature stability trends correlate well with activity data. Both EAF and MEOAF moderately increase lysozyme activity, with increased activity noted in the presence of PAF, and activity several times greater noted in the presence of EtAF. It is possible that the ILs re-enforce protein structure such that it is able to perform its lysing function more readily, which would account for activity being highest for EtAF, the IL which is the most effective stabilising agent.

Materials and methods

Lysozyme from chicken egg white (lyophilized powder, Protein ≥90%, ≥40,000 units mg^{-1} protein) and *Micrococcus lysodeikticusce* cells (ATCC No. 4698) were purchased from Sigma and used without further purification. Ethylamine (70%), propylamine (70%), 2-methoxyethylamine (99%), ethanolamine (>99%), propanolamine (>99%), and formic acid (>98%) were also obtained from Sigma-Aldrich and used without further purification.

The protic room temperature ILs ethylammonium formate (EAF), propylammonium formate (PAF), ethanolammonium formate (EtOAF), and 2-methoxyethylammonium formate (MOEAF) were prepared by reacting equimolar amounts of the amine and concentrated formic acid to produce an aqueous solution.[33–35] Water was then removed by rotary evaporation at 25 °C, the last vestiges of water was removed by lyophilization affording ILs with water contents less than 0.5% (Karl Fischer titration). IL purity and identity was verified using ^{1}H-NMR spectroscopy. Formate based ILs are known to form amides *via* condensation reactions, *e.g.* after 50 months at room temperature 25% of EAF has been converted to amide.[36] In light of this, all experiments performed here used freshly prepared ILs. NMR revealed that during a heating–cooling cycle not more than 1% of IL reacted to form amide, and frequently conversion was much less.

CD measurements were performed on an Applied Photophysics Chirascan Spectrometer. Lysozyme concentrations of 3.4×10^{-4} mol dm^{-3} were examined in the near UV region (310 to 250 nm) in a 0.1 cm path length quartz cell at a bandwidth and step size of 1 and 0.5 nm respectively. Solutions containing 25, 50 and 75 wt% IL were prepared approximately one hour prior to measurements. Each sample was subject to a heating cycle of 25–90–25 °C at a rate of 20 °C min^{-1} (total analysis time = 6.5 min). Data was obtained in the form of CD (mdeg) *versus* wavelength (nm) and used without further modification.

Lysozyme assays were performed on a Shimadzu UV-1700 UV/Vis Spectrometer. Cell suspensions containing 0.0014% (w/v) *Micrococcus lysodeikticusce* cells were prepared to give an initial absorbance of 1.4 at 450 nm and 25 °C. Stock solutions of 6.8×10^{-6} mol dm^{-3} lysozyme in water–IL mixtures (25, 50 and 75 wt% IL, along with 62.5 wt% for PAF) were prepared and chilled to 4 °C prior to measurement. 2.9 cm^3 of the cell suspension was placed into a 1 cm path length quartz cell and allowed to equilibrate to instrument's operating conditions (25 °C and 1 atm). 0.1 cm^3 of the lysozyme solution was then added to the cell suspension and quickly inverted five times prior to measurement. The absorbance was then measured at 450 nm and 25 °C.[18,26] Control solutions of the cell suspension and IL but no lysozyme produced a constant absorption signal for several hours.

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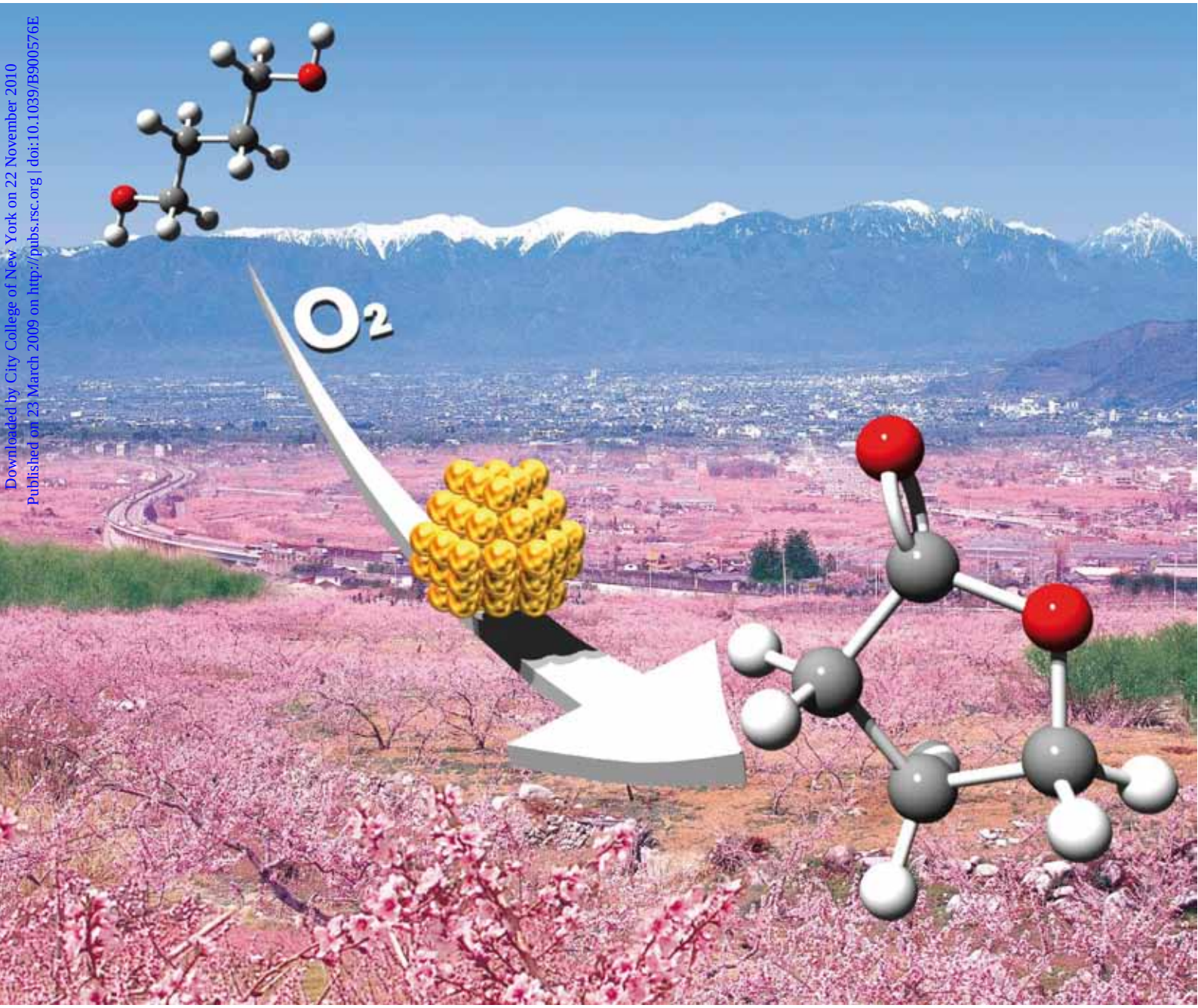

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Supported gold nanoparticles as a reusable catalyst for synthesis of lactones from diols using molecular oxygen as an oxidant under mild conditions†

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The oxidative lactonization of various diols using molecular oxygen as a primary oxidant can be efficiently catalyzed by hydrotalcite-supported Au nanoparticles (Au/HT). For instance, lactonization of 1,4-butanediol gave γ-butyrolactone with an excellent turnover number of 1400. After lactonization, the Au/HT can be recovered by simple filtration and reused without any loss of its activity and selectivity.

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Introduction

The selective synthesis of lactones is of considerable interest to both academic and industrial chemists because lactones are ubiquitous among natural and synthetic organic compounds.[1] Among the various methods of synthesizing lactones, oxidative lactonization of α,ω-diols is one of the most promising methodologies for industrially acceptable process.

Traditionally, stoichiometric lactonization of α,ω-diols has been carried out using large amounts of metal reagents such as silver carbonate[2] and chromium compounds.[3] However, these reagents are expensive and/or toxic. To date, several homogeneous catalytic lactonizations have appeared utilizing Ru,[4] Rh,[5] Pd,[6] and Ir[7] as catalysts combined with organic co-oxidants such as ketones and alkenes. In light of ever-increasing environmental concerns, much interest has been directed toward the development of promising catalytic protocols employing molecular oxygen (O_2) as a primary oxidant, which is readily available, and producing water as the sole byproduct. A more environmentally benign and practical method of oxidative lactonization would utilize O_2 as an oxidant in combination with highly active and reusable catalysts under mild reaction conditions.[8]

Hydrotalcite (HT, $Mg_6Al_2(OH)_{16}CO_3{\cdot}nH_2O$) is a layered anionic clay consisting of a positively charged two-dimensional brucite layer with anionic species such as hydroxide and carbonate located in the interlayer.[9] HT has attracted attention not only for adsorption[10] and drug delivery[11] applications, but also for catalysis[12] due to the following characteristics: (i) the cation-exchange ability of the brucite layer; (ii) the anion-exchange ability of the interlayer; (iii) the tunable basicity of the surface; and (iv) the adsorption capacity. We have previously reported on the benefit of utilizing HT as an inorganic support for various organic syntheses involving the oxidation of various alcohols, where the synergistic effect between the metal and the base sites of the HT can lead to high-performance heterogeneous catalysts.[13] Recently, the use of gold nanoparticles on organic and inorganic supports for the aerobic oxidation of alcohols has attracted considerable interest because of the high catalytic activities.[14] In these systems, the choice of supports is one of the most important factors for achieving high catalytic activities.[15]

Herein, we report on the formation of small Au nanoparticles on the surface of HT to give HT-supported Au nanoparticles (Au/HT), which operated as a highly efficient solid catalyst for lactonization of α,ω-diols under mild reaction conditions. The Au/HT catalyst can overcome the problems such as the requirements for high temperatures, additives, and high catalyst loading that have plagued the previously reported lactonization catalyst systems. Moreover, Au/HT shows wide applicability for various substrates and good reusability without any loss of its activity and selectivity.

Results and discussion

The synthesis of the Au/HT catalyst was as follows. First, hydrotalcite (HT) was prepared according to a procedure in the literature.[9] The obtained HT (1.0 g) was then added to 50 mL of an aqueous solution of $HAuCl_4$ (2 mM). After stirring for 2 min, 0.09 mL of aqueous NH_3 (10%) was added and the resulting mixture was stirred at room temperature for 12 h. The obtained slurry was filtered, washed with deionized water, and dried at room temperature in vacuo. Subsequent treatment with KBH_4 at room temperature for 1 h yielded Au/HT as a purplish red powder. The XRD peak positions of Au/HT were similar to those of the parent HT, and the Au loading on Au/HT was estimated to be 0.89 wt% by elemental analysis. k^3-Weighted Au L-edge extended X-ray absorption fine structure (EXAFS) of Au/HT revealed a peak at around 2.6 Å in the Fourier transform, which was assignable to the Au–Au shell. From transmission electron microscopy, Au nanoparticles were identified on the surface of the HT support with a mean diameter of 2.7 nm and a narrow size distribution with a standard deviation of 0.7 nm.[16]

For the catalysis, a mixture of 1,4-butanediol (**1**) and Au/HT in toluene was heated at 80 °C under atmospheric O_2 pressure. The substrate **1** was smoothly oxidized to afford the

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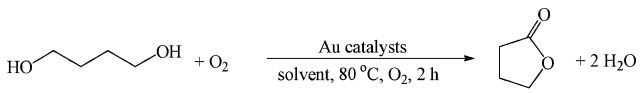
[b]*Research Center for Solar Energy Chemistry, Osaka University, 1-3Machikaneyama, Toyonaka, Osaka 560-8531, Japan*
† Electronic supplementary information (ESI) available: EXAFS and TEM of Au/HT. See DOI: 10.1039/b900576e

Table 1 Oxidation of 1,4-butanediol using supported gold catalysts[a]



1 2

Entry	Catalyst	Solvent	Conv. (%)[b]	Yield (%)[b]	Particle size (nm)
1	Au/HT	Toluene	99	99	2.7
2	Au/HT[c]	Toluene	99	99	2.7
3	Au/HT[d]	Toluene	83	82	4.6
4[e]	Au/HT	Toluene	99	99	
5[f]	Au/HT	Toluene	96	96	
6[g]	Au/HT	Toluene	99	96	
7[h]	Au/HT	Toluene	99	99	
8	Au/HT	TFT	93	93	
9	Au/HT	Ethyl acetate	91	91	
10	Au/HT	Heptane	80	76	
11	Au/HT	*tert*-Butanol	70	66	
12	Au/HT	DMA	63	63	
13	Au/HT	Acetonitrile	45	36	
14	Au/MgO	Toluene	72	70	3.1
15	Au/MgO[c]	Toluene	28	24	3.4
16	Au/Al_2O_3	Toluene	51	51	3.6
17	Au/Al_2O_3[c]	Toluene	24	20	4.2
18	Au/TiO_2	Toluene	18	16	3.7
19[i]	Au/TiO_2	Toluene	64	64	
20	Au/SiO_2	Toluene	1<	1<	14
21[j]	Pd/HT	Toluene	42	19	
22[j]	Ru/HT	Toluene	1	1<	
23[j]	Ag/HT	Toluene	1<	1<	

[a] Reaction conditions: Supported Au catalysts (Au: 0.45 mol%), 1,4-butanediol (1 mmol), solvent (5 mL). [b] Determined by GC using internal standard technique. [c] H_2 was used as a reductant in place of KBH_4. [d] Hydrazine was used as a reductant in place of KBH_4. [e] Reuse 1. [f] Reuse 2. [g] Substrate (0.5 mmol), 40 °C, 2 h. [h] Under air atmosphere, 10 h. [i] Na_2CO_3 (3 mmol) was added. [j] M/HT (M: 0.45 mol%) was employed in place of the use of Au catalyst.

corresponding lactone γ-butyrolactone (**2**) in 99% yield after 2 h (Table 1, entry 1). Among the solvents examined, less polar solvents such as toluene, TFT, and ethyl acetate were superior to polar solvents (entries 1, and 8–10 *vs*. entries 11–13). The choice of solid supports was found to influence the catalytic efficiency; using the other basic supports, Au/MgO and Au/Al_2O_3 also functioned as catalysts (entries 14, and 16), while Au/TiO_2 and Au/SiO_2 gave low yields of **2** (entries 18 and 20). Interestingly, adding Na_2CO_3 as a base to the reaction mixture for the Au/TiO_2 system significantly improved the yield of **2** (entry 18 *vs*. 19). Among the basic supports of HT (entries 1–3), MgO (entries 14 and 15), and Al_2O_3 (entries 16 and 17), the yield of **2** increased with decreasing the particle size, respectively. From these results, it can be said that the basicity of the supports and the size of the Au particles are key factors in promoting the above oxidative lactonization. In addition, we also attached other metal particles with catalytic potential such as Pd, Ru, and Ag to the HT support and employed them in lactonization under similar reaction conditions. The use of Pd/HT gave a moderate yield of **2** (entry 21), while only trace amounts of **2** were obtained using Ru/HT and Ag/HT (entries 22 and 23). The Au/HT catalyst clearly gave the best activity for lactonization of **1**.

Au/HT was filtered from the reaction mixture at 50% conversion of **1**. Continued stirring of the filtrate under similar conditions did not give any products. Inductively coupled plasma (ICP) analysis of the filtrate showed that no Au was present (detection limit: 0.10 ppm). These results indicate that lactonization occurred on the Au nanoparticles immobilized on HT. Notably, using Au/HT promoted lactonization successfully even at 40 °C (entry 6). Moreover, the Au/HT catalyst was effective when pure O_2 was replaced with ambient air; a quantitative yield of **2** was obtained within 10 h (entry 7).

The scope of this Au/HT catalyst system was investigated for the lactonizations of other diols (Table 2). A wide range of α,ω-diols was oxidized to afford the corresponding lactones in high yields. The diol bearing an olefinic group, *cis*-2-butene-1,4-diol, was chemoselectively converted to an unsaturated lactone 2(5*H*)-furanone with suppression of hydrogenation of the olefinic group (entries 8 and 9). The catalyst system was also applicable to the syntheses of heterocyclic lactones that included oxygen and nitrogen atoms. For example, diethyleneglycol and *N*-methyldiethanolamine gave the corresponding lactones in high yields (entries 14 and 15).

In scale-up conditions, **1** (70 mmol; 6.3 g) successfully gave **2** (91% isolated yield; 5.5 g) with a TON of up to 1400 (entry 3). This value is considerably greater than those reported for the aerobic lactonization of **1** by other catalysts: (PVP-stabilized Au:Pd nanoparticles with K_2CO_3 (TON: 428),[8a] Au/FeOx (TON: 322),[8b] Au/TiO_2 (TON: 102),[8c] Pd/AlO(OH) (TON: 50),[8d] and Ru-$Co(OH)_2$-CeO_2 (TON: 4)[8e]). Although some catalytic lactonizations required the addition of a base such as *t*-BuOK,[4a] NEt_3,[4d,4e] or K_2CO_3,[6a,8a] our Au/HT catalyst did not require any additives to facilitate the catalytic cycle even under an air atmosphere. Furthermore, Au/HT was durable and recyclable for the lactonization. After the Au/HT catalyzed reaction of **1**, Au/HT was recovered by a simple filtration and

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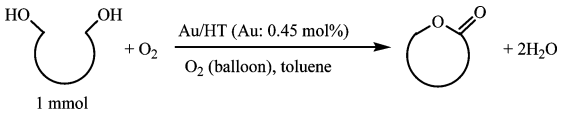
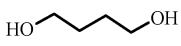
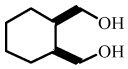
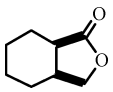
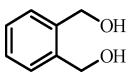
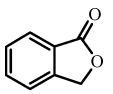
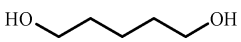
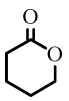
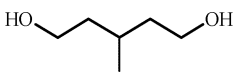
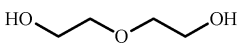
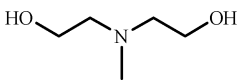
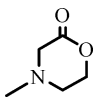
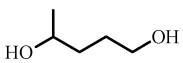
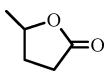
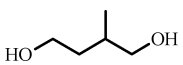
Table 2 Oxidation of various α,ω-diols using Au/HT[a]

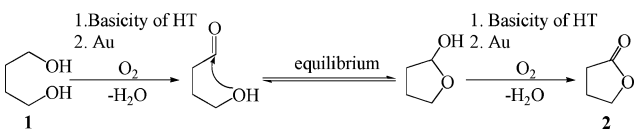


Entry	Diol	Product	Temp. (°C)	Time (h)	Conv. (%)[b]	Yield (%)[b]
1			80	2	99	99 (96)
2[c]			40	2	99	96
3[d]			100	48	92	92 (91)
4			80	1	99	99 (96)
5[c]			40	2	99	97
6			80	1	99	99 (95)
7[c]			40	2	99	98
8			80	2.5	96	96 (91)
9[c]			40	2	98	98
10			110	1	98	96 (96)
11[e]			40	8	99	98
12			110	1	98	98 (96)
13[c]			40	14	99	98
14			110	1	93	92 (87)
15			110	2	90	89 (86)
16[f]			80	4	88	44 (44)
17			80	2	99	95 (89)
						β:α = 1:1

[a] Reaction conditions: Au/HT (0.1 g, Au: 0.45 mol%), diol (1 mmol), toluene (5 mL). [b] Determined by GC and LC using an internal standard technique; values in parentheses are the yield of the isolated products. [c] Substrate (0.5 mmol). [d] Substrate (70 mmol), Au/HT (1.0 g, Au: 0.06 mol%), toluene (180 mL), DMA (5 mL). [e] Substrate (0.3 mmol). [f] 5-Hydroxy-2-pentanone and 4-oxo-pentanal were formed as byproducts.

showed good reusability without any loss of its activity and selectivity in several reuse experiments (Table 1, entries 4 and 5).

A possible reaction mechanism of the lactonization is proposed based on cooperative action between Au and HT. We have found that basic supports and an additive base have a strongly positive effect on the oxidative lactonization (Table 1, entries 1, 14, 16, and 19) (*vide supra*). In this mechanism, a basic site on the HT could promote the formation of an Au–alcoholate species, allowing smooth oxidation of one of the hydroxyl groups of the diol to hydroxyaldehyde, which is equilibrium with a lactol.[17] Subsequent further oxidation of the lactol would furnish the corresponding lactone (Scheme 1).



Scheme 1 Reaction path of lactonization.

Conclusions

We have prepared a Au/HT catalyst which can facilitate aerobic lactonization of various diols without additives under mild reaction conditions. Unlike previous catalyst systems, this Au/HT catalyst is able to achieve lactonization without the need

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for high temperatures, additives, and high catalytic loading. In addition, Au/HT could be reused without any loss of its activity and selectivity.

Experimental

General

All organic reagents were purified before use. $HAuCl_4 \cdot xH_2O$ was obtained from N. E. Chemcat. Co. Ltd. MgO (GR for analysis) was purchased from Merck Chemical Industries Co. Ltd. Al_2O_3 (JRC-ALO-3), SiO_2 (JRC-SIO-6) and TiO_2 (JRC-TIO-4) were obtained from the Catalysis Society of Japan as reference catalysts. Powder X-ray diffraction (XRD) was measured using an X'pert diffractometer (Philips Co. Ltd.). Inductively coupled plasma (ICP) spectroscopy was performed using a Nippon Jarrell-Ash ICAP-575 Mark II. ^1H and ^{13}C Nuclear magnetic resonance (NMR) spectra were recorded on Jeol JNM-AL400 and 270 MHz. Gas chromatography (GC-FID) was performed on a Shimadzu GC-2014 equipped with a KOCL-3000T column (2 m). High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-10ADvp: STR ODS-II (150 × 4 mm). Au L-edge X-ray absorption spectra were recorded at room temperature using a fluorescence-yield collection technique at the beam line 01B1 station attached with a Si(111) monochromator at SPring-8, Japan Atomic Energy Research Institute (JASRI), Harima, Japan. Data analysis was performed using the REX 2000 program, ver. 2.0.4 (Rigaku). Fourier transformation (FT) of k^3-weighted extended X-ray absorption fine structure (EXAFS) data was performed to obtain the radial structural function.

Characterization of Au/HT

Elemental analysis showed that the Au loading was 0.89 wt% Au L-edge X-ray absorption spectra and transmission electron microscopy (TEM) showed that Au nanoparticles were formed on the surface of the HT support with a mean diameter of 2.7 nm and a narrow size distribution with a standard deviation of 0.7 nm. The mean diameters, d, and standard deviations (σ) of the Au particles for the Au/MgO, Au/Al_2O_3, Au/TiO_2, and Au/SiO_2 systems were d = 31 Å (σ = 10.8 Å), 36 Å (σ = 7.7 Å), 37 Å (σ = 7.9 Å), and 140 Å (σ = 66.5 Å), respectively.

General reaction procedures

A typical procedure for the lactonization of **1** using the Au/HT catalyst was as follows. Au/HT (0.10 g, 0.0045 mmol Au) was placed in a reaction vessel, followed by the addition of toluene (5 mL) and **1** (1 mmol), and the reaction mixture was vigorously stirred at 80 °C for 2 h under O_2 balloon (500 mL). After the lactonization reaction, the Au/HT was removed by filtration, and the resulting solution was evaporated. The resulting residue was purified by column chromatography using silica gel (Wakogel C-200, 75–150 μm) to give γ-butyrolactone **2** (82.7 mg, 96% as a colorless oil).

Product identification

γ-Butyrolactone, phthalide, 2(5*H*)-furanone, δ-valerolactone, γ-valerolactone were commercially available. The yields of products were determined by GC and HPLC [STR ODS-II (150 × 4 mm); detection at 254 nm, flow rate 1.0 mL/min, eluent: a mixture of acetonitrile and water (3 : 7)]. Gas chromatography (GC) and/or LC retention times and ^1H and ^{13}C NMR chemical shifts of products were in agreement with those of authentic samples and also with the reported data.

NMR data

***γ*-Butyrolactone.** ^1H NMR (400 MHz, $CDCl_3$) δ 2.23–2.31 (m, 2H), 2.49 (t, J = 8.3 Hz, 2H), 4.35 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.10, 27.69, 68.40, 177.45. See ref. 18, SDBS No. 1325.

***cis*-Hexahydrophthalide.** ^1H NMR (270 MHz, $CDCl_3$) δ 1.16–1.31 (m, 3H), 1.56–1.69 (m, 3H), 1.74–1.87 (m, 1H), 2.08–2.13 (m, 1H), 2.43–2.53 (m, 1H), 2.62–2.68 (m, 1H), 3.93 (dd, J = 8.8, 1.4 Hz, 1H), 4.19 (dd, J = 8.8, 5.0 Hz, 1H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 20.79, 22.44, 22.85, 23.34, 35.29, 39.33, 71.55, 178.08. See ref. 7.

Phthalide. ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.55 (dd, J = 7.6, 7.4 Hz, 1H) 7.70 (dd, J = 7.6, 7.4 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.60, 121.99, 125.62, 125.75, 128.96, 133.89, 146.42, 171.06.

See ref. 18, SDBS No. 1158.

2(5*H*)-Furanone. ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (dd, J = 2.2, 1.7 Hz, 2H), 6.15 (dt, J = 5.8, 2.2 Hz, 1H), 7.60 (dt, J = 5.8, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.08, 121.51, 152.62, 173.49. See ref. 19.

***δ*-Valerolactone.** ^1H NMR (400 MHz, $CDCl_3$) δ 1.83–1.95 (m, 4H), 2.55 (t, J = 7.0 Hz, 2H), 4.34 (t, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.02, 22.25, 29.74, 69.28, 171.07. See ref. 7.

4-Methyltetrahydropyran-2-one. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 7.0 Hz, 3H), 1.48–1.57 (m, 1H), 1.90–1.96 (m, 1H), 2.04–2.17 (m, 2H), 2.63–2.71 (m, 1H), 4.23–4.30 (m, 1H), 4.39–4.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.40, 26.50, 30.60, 38.17, 68.39, 170.93. See ref. 4(*h*).

4-Methylmorpholine-2-one. ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.64 (t, J = 5.5 Hz, 2H), 3.26 (s, 2H), 4.40 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.89, 51.00, 57.41, 68.64, 167.08. See ref. 4(*f*).

***γ*-Valerolactone.** ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J = 6.3 Hz, 3H), 1.78–1.88 (m, 1H), 2.32–2.56 (m, 1H), 2.52–2.59 (m, 2H), 4.60–4.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.00, 29.00, 29.63, 77.09, 176.90. See ref. 7.

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using a facility in the Research Center for Ultrahigh Voltage Electron Microscopy, Osaka University.

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16 See ESI†.

17 The Au/HT also showed high catalytic activity for the oxidation of various mono-alcohols to carbonyl compounds. For example, the Au/HT catalyst could oxidize 1-phenylethanol and benzyl alcohol efficiently, affording acetophenone and benzaldehyde in 99% yields after 20 min and 4 h, respectively, under similar reaction conditions to Table 1 entry 1.

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Cross-linked polymer coated Pd nanocatalysts on SiO_2 support: very selective and stable catalysts for hydrogenation in supercritical CO_2

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Using greener solvents, enhancing the selectivity and stability of catalysts is an important aspect of green chemistry. In this work, we developed a route to immobilize Pd nanoparticles on the surface of silica particles with cross-linked polystyrene coating by one-step copolymerization, and Pd(0) nanocatalysts supported on the silica particle supports with cross-linked polystyrene coating were successfully prepared. The catalysts were characterized by Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), plasma optical emission spectroscopy, and thermogravimetric analysis (TGA), and were used for hydrogenation of 2,4-dimethyl-1,3-pentadiene to produce 2,4-dimethyl-2-pentene and allyl alcohol to produce 1-propanol. It was found that the selectivity of the reaction was enhanced significantly by the polymer coating, and the catalysts were very stable due to the insoluble nature of the cross-linked polymers. Supercritical (sc)CO_2 can accelerate the reaction rates of the reactions catalyzed by the specially designed catalysts significantly. The excellent combination of polymer coating and $scCO_2$ has wide potential applications in catalysis.

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Introduction

It is known that metal nanoparticles are highly active and selective catalysts for many reactions. However, the naked nanoparticles aggregate easily, resulting in a decrease in catalytic activity and selectivity. To solve this problem, metal nanocatalysts have been immobilized using different supports such as carbon, metal oxides, molecular sieves,[1] and polymers.[2] Some functional polymers have also been used to stabilize metal nanocatalysts. For example, Jiang and Gao prepared heterogeneous Pd(0) nanoparticle catalysts by encapsulating the nanocatalysts in polyamidoamine dendrimers on SBA-15.[3] The organic-inorganic hybrid composites showed highly catalytic activity and selectivity for the hydrogenation of allyl alcohol. Bruening and coworkers embedded Pd nanoparticles in multilayer polyelectrolyte films around alumina particles, which were prepared by the layer-by-layer deposition method.[4] The supported catalysts were used to catalyze hydrogenation of allyl alcohol, 1-penten-3-ol and 3-methyl-1-penten-3-ol, which differ only in the substituents at the α-carbon of the double bond, and it was demonstrated that the polyelectrolytes limited aggregation of the metal nanoparticles, and reaction rates of the alcohols were very different due to restricting access to active sites of the branched alcohols.

Hydrogenation is among the most important processes in the chemical industry. In many cases it is very important to control the selectivity of hydrogenation reactions.[3,4] The design and preparation of special catalytic materials with steric effects is an effective way to do this.[5] It is known that cross-linked polymers are not soluble in ordinary solvents or reaction substrates. Therefore, the nanocatalysts on the particle supports with a cross-linked polymer coating should be very stable, and the polymer coating may restrict access of some active bonds to the active sites of the catalysts, and improve the selectivity of the reactions with multiple active bonds. However, how to coat nanocatalysts on particle supports with cross-linked polymer films is challenging. Besides, the coating should reduce the reaction rate of reactions. Therefore, acceleration of the reaction rate for the reactions catalyzed by this kind of specially designed catalyst is also important.

It is known that supercritical (sc)CO_2 is a cleaner solvent and a promising alternative to organic solvents. The interfacial tension of $scCO_2$ is zero and its diffusivity is much larger than liquids, which can enhance the rates of many reactions.[6] Therefore, it is possible to increase the reaction rate of the polymer-coated metal nanoparticles using $scCO_2$.

In this work, we developed a route to immobilize Pd nanoparticles on the surface of silica particles with cross-linked polystyrene coating by one-step copolymerization. The supported Pd catalysts were used to catalyze the hydrogenation of 2,4-dimethyl-1,3-pentadiene and allyl alcohol (Scheme 1). It was found that the selectivity of the reaction was enhanced

Scheme 1 Illustration of Pd(0) nanocatalysts on SiO_2 particles with a cross-linked polystyrene coating and hydrogenation of 2,4-dimethyl-1,3-pentadiene and allyl alcohol.

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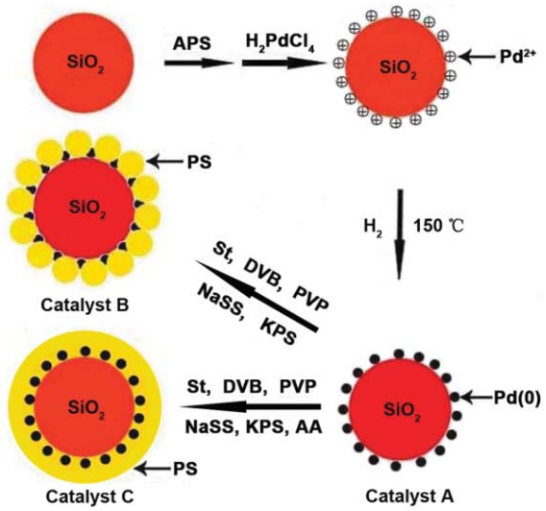
significantly by the polymer coating, and the catalysts were very stable due to the insoluble nature of the cross-linked polymers. As far as we know, this is the first work to coat the nanocatalysts on particle supports with cross-linked polymers. This method can be potentially used to prepare the cross-linked polymer-coated nanocatalysts of some other metals. Our work demonstrated that supercritical (sc)CO_2 can accelerate the reaction rates significantly. We believe that the idea to combine cross-linked polymer-coated nanocatalysts on supports and $scCO_2$ can be applied to enhance the selectivity of many reactions with two or more active bonds effectively.

Results and discussion

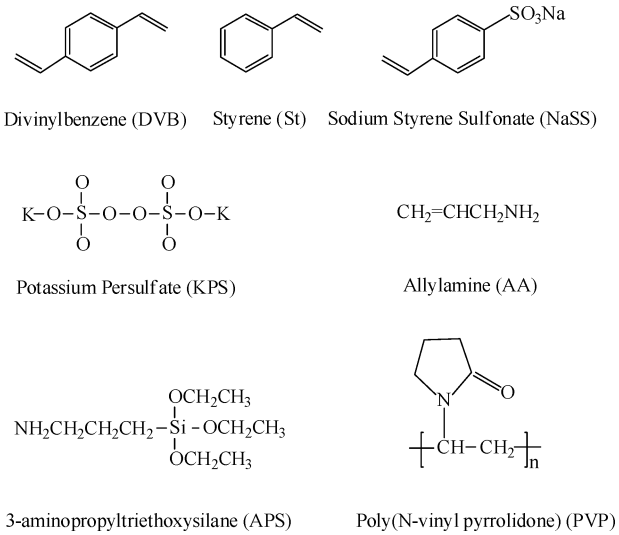
Synthesis of the polymer-coated catalyst

Scheme 2 shows the route to fabricate the cross-linked polystyrene-coated catalysts. The detailed procedures to prepare the catalysts are described in the Experimental section, and the chemical structures of styrene (St), divinylbenzene (DVB), potassium persulfate (KPS), 3-aminopropyltriethoxysilane (APS), poly(*N*-vinyl pyrrolidone) (PVP), sodium styrene sulfonate (NaSS) and allylamine (AA) are given in Scheme 3. The monodispersed SiO_2 particles with the average size of about 230 nm were prepared by the method in the literature.[7]



Scheme 2 General scheme of synthesis of polystyrene-coated Pd(0) nanoparticles on the surface of SiO_2.

Fig. 1 shows FTIR spectra of pure SiO_2 and amino-functionalized SiO_2 particles. The bands at 3425 and 1630 cm^{-1} are attributed to the stretching and bending vibrations of water molecules adsorbed on the surface of SiO_2. After the functionalization of SiO_2 with APS, the intensity of the band at 967 cm^{-1} (Si-OH bending vibration peak) obviously decreases and a new band appears at 2980 cm^{-1} due to C-H stretching vibration, suggesting that SiO_2 particles were functionalized by APS.[8] Pd^{2+} ions were then anchored onto the surface of amino-functionalized SiO_2 particles. The Pd^{2+} on the functionalized-SiO_2 particles was reduced by H_2 at 150 °C for 5 hours to obtain dark brown Pd(0)-SiO_2 particles (catalyst A), as shown in the TEM image in Fig. 2a. It can be seen that Pd(0) nanoparticles with the size of 2–5 nm were uniformly decorated on the surface



Scheme 3 The chemical structures of some chemicals used.

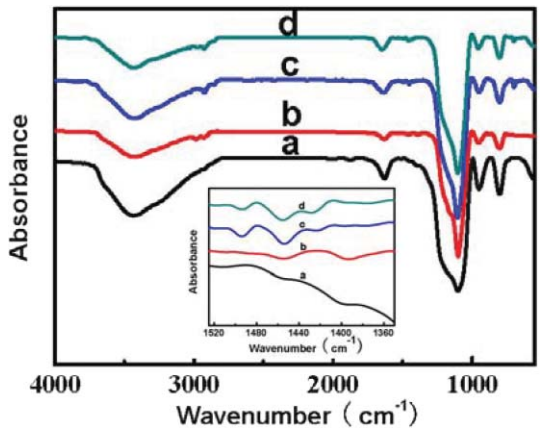


Fig. 1 FTIR spectra of (a) original SiO_2, (b) amino-functionalized SiO_2, (c) catalyst B and (d) catalyst C. The inset shows magnified FTIR spectra.

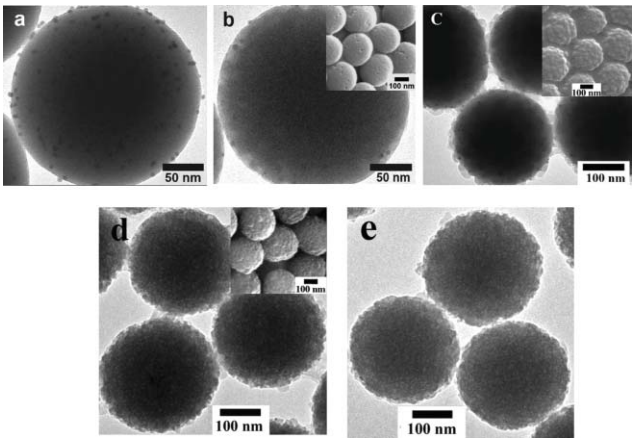


Fig. 2 TEM images of (a) catalyst A without the polymer coating, (b) catalyst A after used 4 times, (c) catalyst B with incomplete polystyrene coating, (d) catalyst C with complete polystyrene coating, (e) catalyst C after used 4 times. The inserts of (b), (c), and (d) are corresponding SEM images.

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of SiO_2 particles. Coating of the cross-linked polystyrene on the catalyst A was achieved by emulsion polymerization using St as the monomer, DVB as a crosslinker, PVP as a stabilizer, KPS as an initiator, NaSS as an emulsifier and AA as a copolymeric monomer. It can be observed that incomplete polystyrene coating was formed without the addition of AA (Fig. 2c), while complete coating was formed with the addition of AA (Fig. 2d). The reason may be that the surface of SiO_2 was functionalized by APS containing richly cationic amines.[9] On the other hand, polystyrene particles prepared by emulsion polymerization using KPS as an initiator and NaSS as an emulsifier exhibited a negatively charged surface.[10] Without addition of AA, incomplete polystyrene coating on Pd(0) nanoparticles (catalyst B) was therefore formed by electrostatic adsorption of polystyrene particles on the surface of SiO_2 particles. In the presence of AA, however, AA firstly interacted with Pd nanoparticles on the surface of SiO_2 particles by means of terminal amines of AA, and then copolymerized with monomer St *via* a C=C double bond of AA, resulting in the formation of complete polystyrene coating on Pd(0) nanoparticles (catalyst C) with the average thickness of polystyrene coating about 25 nm, which was estimated from the diameters of the coated and uncoated particles. This indicates that the existence of AA can greatly affect the morphology of polystyrene coating. FTIR spectra of catalysts B and C (Fig. 1, Spectra c and d) further confirm the presence of the cross-linked polystyrene on the surface of SiO_2 particles according to the typical absorption bands of polystyrene at 1452, 1492, 2928 and 3028 cm^{-1}.[11] The contents of Pd(0) in catalyst A, B and C were 0.47%, 0.35% and 0.28%, respectively, which was determined by inductively coupled plasma optical emission spectroscopy (ICP-AES, Vista-MPX).

Fig. 3 shows the TGA results of catalyst B and catalyst C. The major weight losses occurred in the temperature range from 250 to 500 °C because of the thermal decomposition of polystyrene. The final weights (assumed to be Pd(0)-SiO_2) were 81.4 and 69.5% for catalysts B and C, respectively. This indicates that the content of polystyrene in catalyst C was higher than that in catalyst B. The two-step decomposition of catalyst C may result from the existence of AA in the polymer films. The thickness of catalyst C calculated from the densities and mass percents of the silica and polystyrene in the catalyst was about 24 nm, which agrees with that estimated from the diameters of the coated and uncoated catalyst particles.

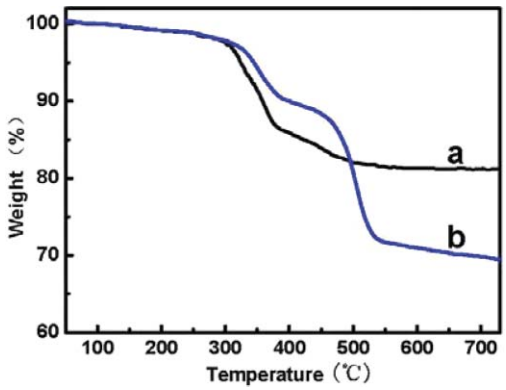

Fig. 3 Thermogravimetric curves for catalyst B (a) and catalyst C (b).

Hydrogenation reactions

We studied the hydrogenation of 2,4-dimethyl-1,3-pentadiene and allyl alcohol (Scheme 1) using the three catalysts, and the results are listed in Tables 1 and 2, respectively. The naked Pd(0) nanoparticles in catalyst A were much more active than the polymer-coated Pd(0) nanoparticles in catalyst B and catalyst C. This is easy to understand because the polymer coating

Table 1 The conversion, selectivity and turnover frequency (TOF) of hydrogenation of 2,4-dimethyl-1,3-pentadiene using different catalysts at 40 °C [a]

						Selectivity [%]		
Entry	Catalyst	P_{CO2} [MPa]	Time [h]	Conversion [%]	TOF[b]	2,4-dimethyl-2-pentene	2,4-dimethyl-1-pentene	2,4-dimethyl-pentane
1	A	0	0.2	>99.7	28000	51.2	48.4	0.4
1-1[c]	A	0	0.3	>99.7	18667	51.5	48.2	0.3
1-2[c]	A	0	0.5	>99.7	14000	51.1	48.3	0.6
1-3[c]	A	0	0.7	>99.7	8000	51.2	48.5	0.3
1-4[c]	A	0	1.0	>99.7	5600	51.3	48.2	0.5
2	B	0	2.5	>99.7	2604	65.0	34.5	0.5
3	C	0	99.0	>99.7	57	75.2	24.5	0.2
4	C	2	16.0	27.5	96	75.5	24.4	0.1
5	C	5	16.0	54.8	192	77.2	22.7	0.1
6	C	8	16.0	>99.7	350	80.1	19.8	0.1
6-1[d]	C	8	16.0	>99.7	350	80.2	19.6	0.2
6-2[d]	C	8	16.0	>99.7	350	79.9	20.0	0.1
6-3[d]	C	8	16.0	>99.7	350	80.0	19.9	0.1
6-4[d]	C	8	16.0	>99.7	350	79.5	20.4	0.1
7	C	11	16.0	86.2	302	77.1	22.8	0.1
8	C	14	16.0	79.1	277	77.0	22.9	0.1
9	Pd/C[e]	0	0.25	>99.7	22400	50.5	48.9	0.6

[a] Reaction conditions: H_2, 3.0 MPa; the molar ratio of 2,4-dimethyl-1,3-pentadiene to Pd(0) is 5600. [b] The turnover frequencies (TOFs) are moles of reacted substrate per mole of Pd(0) per hour. [c] Hydrogenation reaction over catalyst A after being used 4 times. [d] Hydrogenation reaction over catalyst C after being used 4 times. [e] Commercial Pd/C with 5% Pd on carbon powder from Baoji Rock Co. Ltd, China.

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Table 2 The conversion, selectivity, and turnover frequency (TOF) of hydrogenation of allyl alcohol using different catalysts at 40 °C [a]

Entry	Catalyst	P_{CO2} [MPa]	Time [h]	Conversion [%]	TOF[b]	Selectivity [%][c]
1	A	0	1.0	>99.7	7500	75.3
1-1[d]	A	0	1.1	>99.7	6818	75.6
1-2[d]	A	0	1.2	>99.7	6250	75.4
1-3[d]	A	0	1.3	>99.7	5769	75.3
1-4[d]	A	0	1.5	>99.7	5000	75.7
2	B	0	5.0	>99.7	1500	83.1
3	B	8	3.5	>99.7	2140	86.4
4	C	0	9.0	>99.7	833	92.4
5	C	8	5.0	>99.7	1500	93.1
5–1[e]	C	8	5.0	>99.7	1500	92.9
5–2[e]	C	8	5.0	>99.7	1500	93.0
5–3[e]	C	8	5.0	>99.7	1500	92.6
5–4[e]	C	8	5.0	>99.7	1500	92.4
6	Pd/C[f]	0	1.5	>99.7	5000	74.0

[a] Reaction conditions: H_2, 2.0 MPa, the molar ratio of allyl alcohol to Pd(0) is 7500. [b] The turnover frequencies (TOFs) are moles of reacted substrate per mol of Pd(0) per hour. [c] The selectivity to 1-propanol (product). [d] Hydrogenation reaction over catalyst A after being used 4 times. [e] Hydrogenation over Catalyst C after being used 4 times. [f] Commercial Pd/C, 5% Pd on carbon powder from Baoji Rock Co. Ltd, China.

restricts the access of the reactants to the active sites of the catalysts. At the same time, this provides further evidence that Pd nanocatalysts were coated by the polymer.

Table 1 shows that the selectivity of the reaction to the two products, 2,4-dimethyl-1-pentene and 2,4-dimethyl-2-pentene, was nearly the same when catalyst A was used (entry 1), while the selectivity to 2,4-dimethyl-2-pentene was much higher than that to 2,4-dimethyl-1-pentene when catalyst C was used (entry 3). For catalyst A, the two double bonds of the pentadiene with similar activity have similar opportunity to contact the naked Pd(0) nanoparticles on SiO_2 particles, leading to approximately the same selectivity for the two pentenes. For catalyst C, however, the selectivity to 2,4-dimethyl-2-pentene was 75.2%, which is much higher than that catalyzed by silica-supported PAMAM-Pd complexes with 2,4-dimethyl-2-pentene selectivity of 59.0%.[5c] In other words, more terminal double bonds were hydrogenated. This is understandable because the reactant is a linear molecule, it prefers to approach the Pd particles perpendicularly through the coating surface. Therefore, the terminal double bond has more opportunity for access to Pd(0) nanoparticles than the internal double bond. As catalyst B was used, the selectivities to 2,4-dimethyl-2-pentene and 2,4-dimethyl-1-pentene lie between those of catalyst A and catalyst C because of the incomplete coating (entry 2).

In this work, we also studied the reaction in $scCO_2$ catalyzed by catalyst C because it was the most selective. The results at different pressures are also listed in Table 1 (from entry 3 to entry 8). Obviously, $scCO_2$ can enhance the reaction rate significantly. Moreover, under $scCO_2$ conditions, the selectivity to 2,4-dimethyl-2-pentene can reach 80.1% using catalyst C (entry 6), which is higher than that under solvent-free conditions (entry 3). This may result from the higher diffusivity of the molecules in $scCO_2$. After the hydrogenation of the terminal double bond, the product diffuses out more quickly than the case without $scCO_2$.

The selectivity at different conversions using catalysts A and C are shown in Fig. 4. It can be seen that for the two catalysts used the selectivities to 2,4-dimethyl-2-pentene and 2,4-dimethyl-1-pentene are almost constant with increasing conversion. It is also worth noticing that the formation of pentane is almost negligible prior to complete consumption of the pentadiene for both catalyst A and catalyst C.

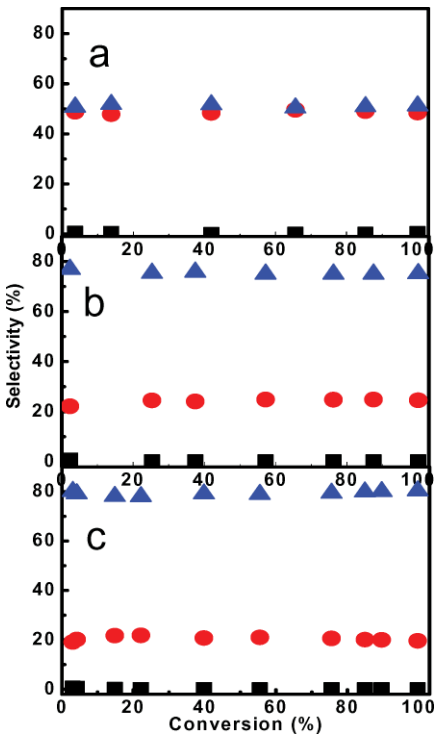

Fig. 4 The selectivity of products *versus* conversion of 2,4-dimethyl-1,3-pentadiene over catalyst A under solvent-free conditions (a), catalyst C under solvent-free conditions (b), and catalyst C under $scCO_2$ (8.5 MPa) condition (c). (■) 2,4-dimethylpentane; (●) 2,4-dimethyl-1-pentene; (▲) 2,4-dimethyl-2-pentene. Reaction conditions: H_2 3.0 MPa, temperature 40 °C, the molar ratio of substrate and Pd(0) was 5600.

For the hydrogenation of allyl alcohol to produce 1-propanol in Table 2, the selectivity was also greatly improved by the polymer coating on Pd(0) nanoparticles. Especially, the selectivity to 1-propanol approached 92.4% when catalyst C was used (entry 4), which was much higher than that of catalyst

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A (75.3%, entry 1) and commercial Pd/C (74.0%, entry 6), suggesting that the selectivity to 1-propanol was enhanced by the polystyrene coating. The mechanism to enhance the selectivity of this reaction is different from that of the hydrogenation of 2,4-dimethyl-1,3-pentadiene. During hydrogenation of allyl alcohol performed with Pd(0) nanoparticles, allyl alcohol also easily isomerizes into byproduct propanal or acetone.[3,4,12] As catalyst C was used, the polymer coating in the catalysts suppressed isomerization of allyl alcohol during hydrogenation because it modified both the environment of active sites and access to these active sites, similar to the function of dendrimers[3] and polyelectrolyte multilayers[4] The reaction catalyzed by catalyst C was also conducted in $scCO_2$. As can be seen in Table 2, the activity of catalyst C under $scCO_2$ condition (entry 5) is much higher than in the absence of CO_2 (entry 4), which further demonstrated that $scCO_2$ can accelerate the reaction rates significantly. The main reason for this is that $scCO_2$ has high diffusion and low viscosity, which is favourable to the mass transfer of the reactant and the product.

Reusability of the catalysts

The recyclability of catalysts A and C was tested in this work. After each cycle, the catalyst was reused after washing with ethanol and drying. The results are also presented in Table 1 (entries 1-1, 1-2, 1-3 and 1-4 for catalyst A and entries 6-1, 6-2, 6-3 and 6-4 for catalyst C) and Table 2 (entries 1-1, 1-2, 1-3 and 1-4 for catalyst A and entries 5–1, 5–2, 5–3 and 5–4 for catalyst C). Clearly, the reduction in activity and selectivity of catalyst C was negligible after being reused 4 times, while the activity of catalyst A reduced significantly. The reason is that the stable polymer coating can protect the Pd nanoparticles from aggregation and falling off the support. Figs. 2b and 2e show the TEM images of catalyst A and catalyst C after being used 4 times for hydrogenation of 2,4-dimethyl-1,3-pentadiene, respectively. Apparently, the number of Pd particles of the used catalyst A is much less than that of the original one, as can be seen from Figs. 1a and 1b. However, the morphology of catalyst C was not changed noticeably after being used 4 times (Fig. 2e, the Pd particles cannot be seen because of the coating), providing further evidence for the excellent stability.

Conclusions

In summary, Pd(0) nanocatalysts on a silica support with a cross-linked polystyrene coating were successfully prepared. Highly selective hydrogenation of 2,4-dimethyl-1,3-pentadiene to 2,4-dimethyl-2-pentene and allyl alcohol to 1-propanol can be achieved using the catalysts fabricated, and the catalysts are very stable. The polymer coating provides a steric effect for the high selectivity of the reactions and enhances the stability of the catalysts. $scCO_2$ can accelerate the reaction rates considerably. We believe that this method can also be used to prepare some other nanocatalysts on the particle supports with a very stable polymer coating, and this class of catalysts may also be used to enhance the selectivity of some other reactions with more than one active chemical bond of similar activity, where high selectivity is difficult to reach by other catalysts.

Experimental

Materials

Tetraethyl orthosilicate (TEOS) from Beijing Beihua Fine Chemical Company was distilled prior to use. Aqueous NH_3 solution with a NH_3 content of 25% was supplied by Beijing Yili Fine Chemical Company. 3-Aminopropyltriethoxysilane (APS, analytical grade) provided by Beijing Shenda Fine Chemical Company was used as received. Potassium persulfate (KPS), allylamine (AA), poly(*N*-vinyl pyrrolidone) (PVP), sodium styrene sulfonate (NaSS) and palladium chloride ($PdCl_2$) were all analytical grade and purchased from the Beijing Chemical Reagent Company. Styrene (St, analytical grade) from Beijing Chemical Reagent Company and divinylbenzene (DVB) from Tokyo Kasei Kogyo Company were distilled under reduced pressure before use. 2,4-Dimethyl-1,3-pentadiene and allyl alcohol were provided by Aldrich. Hydrogen (99.99%) and CO_2 (99.995%) were supplied by the Beijing Analytical Instrument Factory.

Preparation of SiO_2 particles

The monodisperse SiO_2 particles were synthesized according to the well-known Stöber method.[7] Typically, the ethanol solution of TEOS was quickly added into the other ethanol solution of NH_3 and H_2O in a 500 mL Erlenmeyer flask. The molar ratio of NH_3:H_2O:TEOS was 1:11:0.22 in the final gel mixture that was stirred at 30 °C for 4 hours. The resulting SiO_2 particles were centrifugally separated from the suspension, ultrasonically washed with ethanol three times, and finally dried at 100 °C.

Preparation of amino-functionalized SiO_2 particles

The monodisperse SiO_2 particles were functionalized with APS.[8] In a typical experiment, SiO_2 particles (1 g) and APS (1.2 g) were added into a round-bottomed flask containing 15 mL of toluene. After the mixture was stirred under refluxing at 110 °C for 24 hours, the obtained amino-functionalized SiO_2 particles were centrifuged, washed three times with toluene and twice with ethanol, respectively, and dried in air at 100 °C.

Preparation of Pd(0) nanoparticles on amino-functionalized SiO_2 particles

Amino-functionalized SiO_2 particles (1.2 g) were ultrasonically dispersed with 40 mL of water in a 100 mL round-bottomed flask, followed by the addition of 32 mL of $PdCl_2$ acidic solution (2 mmol L^{-1}, pH = 3). The mixture was stirred with a magnetic stirrer at room temperature for 30 min. Pd^{2+} ions formed a complex with the amine group on the surface of amino-functionalized SiO_2 particles. Separated centrifugally from the suspension and washed ultrasonically with deionized water, Pd^{2+}-adsorbed-amino-functionalized-SiO_2 particles were obtained and dried in air at 100 °C for 4 hours. The dried Pd^{2+}-adsorbed-amino-functionalized-SiO_2 particles were reduced using H_2 (3 MPa) at 150 °C for 5 hours in a 6 mL high-pressure stainless steel reactor, leading to the formation of dark brown Pd(0)-SiO_2 particles.

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Preparation of polymer-coated Pd nanoparticles on APS-functionalized SiO_2 particles

The dark brown Pd(0)-SiO_2 particles (0.3 g) were ultrasonically dispersed with 35 mL of water in a 250 mL round-bottomed flask equipped with a condenser. Allylamine (AA, 0.25 mL) and poly(*N*-vinyl pyrrolidone) (PVP, 0.5 g) were added into the flask and agitated with a magnetic stirrer at room temperature for 1 hour. Then, 0.25 g of sodium styrene sulfonate (NaSS), 0.15 g of potassium persulfate (KPS) and 40 mL of water were added into the flask and allowed to mix for 30 min. 2 mL of styrene (St) and 0.2 mL of divinylbenzene (DVB) were then added. Finally, the polymerization was carried out in a nitrogen atmosphere under stirring at 80 °C for 12 hours. The resulting polystyrene-coated Pd(0) nanoparticles on APS-functionalized SiO_2 particles were centrifugally separated from the suspension, ultrasonically washed three times with water and twice with ethanol, and dried under vacuum at 60 °C for 24 hours.

Hydrogenation reaction

Hydrogenation of 2,4-dimethyl-1,3-pentadiene and allyl alcohol was carried out in a 6 mL high-pressure stainless steel reactor with a magnetic stirrer with or without $scCO_2$. In the experiment, 2 mmol of substrate and the desired amount of catalyst were introduced into the reactor, and then the reactor was sealed. The air in the reactor was replaced by CO_2 and the reactor was then heated to 40 °C. After the introduction of H_2 to the desired pressure, CO_2 was charged into the reactor with a high-pressure pump (DB-80) to the desired pressure. The reaction was performed under stirring for a desired time. The reactor was then cooled in an ice bath and the gases were vented slowly. After the catalyst was centrifuged from the suspension, the liquid phase was analyzed by GC (Agilent 4890 D) equipped with a flame-ionized detector. The retention time of the products was compared with available authentic standards. The purity and structure of the products obtained at some typical experimental conditions were also checked by GC-MS methods. In the catalyst recycling experiments, the product and the catalyst were centrifuged at 16000 rpm for 5 min and the catalyst was reused after washing with ethanol and drying.

Characterization

Thermogravimetric analysis (TGA) was performed using a Perkin-Elmer 7 Series Thermal Analysis System. Dried samples were heated to 750 °C in air at a heating rate of 10 °C min^{-1}, and the observed mass loss was attributed to the quantitative degradation of the polystyrene. The morphologies of the samples were characterized using scanning electron microscopy (SEM) and transmission electron microscopy (TEM), which were performed on a JEOL JSM-6700F field emission microscope and on a JEOL 2010 transmission electron microscope operating at 200 kV, respectively. The Fourier transform infrared (FT-IR) spectra of the samples through compressing with KBr powder were obtained in the region of 400–4000 cm^{-1} by using a Bruker Tensor 27 spectrometer. The contents of Pd(0) in catalyst A, B and C were 0.47%, 0.35% and 0.28%, respectively, which was determined by inductively coupled plasma optical emission spectroscopy (ICP-AES, Vista-MPX).

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N-alkylation of N-heterocyclic ionic liquid precursors in ionic liquids†

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The room temperature ionic liquids [BMIM][PF_6] and [P14][Tf_2N] in conjunction with KOH are superior reaction media for the alkylation of the secondary amine 3-azabicyclo[3.2.2]nonane under mild conditions. The factors examined were alkyl halide chain length (C1 to C4) and halide identity (Cl, Br, I). The tertiary amine products are released from the reaction medium as a separate layer and can be isolated in good yields by simple decantation.

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Introduction

Amines are important intermediates and end-products for a large range of applications such as pharmaceuticals, agrochemicals, fine chemicals and more recently the key-components of ionic liquids.[1,2] Hence the C–N bond formation is a key operation in organic synthesis which continues to receive considerable attention in order to provide new and improved synthetic routes.[1]

Although a variety of sophisticated methods, including catalytic reactions,[3–7] reductive amination,[8–14] and the amination of alkenes and alkynes[15] have been developed, the most straightforward method to produce tertiary amines is the direct alkylation of a secondary amine with an alkyl halide.[15–20] However, this approach can have shortcomings such as: (i) low yields due to formation of quaternary ammonium salts (the resulting mixtures with tertiary amines and starting material are difficult to separate), (ii) the use of expensive bases.

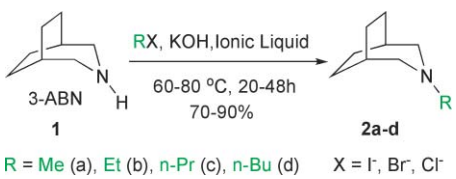
A limited number of reports have advised new methods in order to alleviate the problems associated with the alkylation of secondary amines. Ju and Varma[21] described a microwave assisted synthesis in water and in the presence of an inexpensive inorganic base which is generally very useful and proceeds with 60–92% yield depending on the substrates. Unfortunately, a controlled microwave synthesizer is usually not standard laboratory or custom synthesis equipment. Soloshonok *et al.*[22] reported a convenient and high yielding method employing Hünig's base in acetonitrile which tolerates otherwise sensitive functional groups. Typically the examples in these reports comprise sterically simple primary and secondary amines and the majority of alkylating reagents are benzyl halides.

In this paper we wish to contribute to the topic of C–N bond formation by showing how the alkylation of the tropane alkaloid 3-azabicyclo[3.2.2]nonane (3-ABN) can be carried out under relatively mild conditions in an ionic liquid/KOH medium. Although ionic liquids have proven their merits as "green" reaction media or catalysts in many synthetic applications,[2] only very few reports relate to the direct alkylation of amines. Chiappe and Pierazzini reported the high yielding and selective alkylation of benzylic primary amines with primary and secondary alkyl halides in imidazolium and pyridinium based ionic liquid/CsOH media.[23] Seddon *et al.* described the selective N-alkylation of indoles in 1-butyl-3-methylimidazolium hexafluorophosphate using reaction mediums of [BMIM][PF_6]/KOH and [BMIM][PF_6]/K_2CO_3,[24] whereas Chi *et al.*[25] reported the regioselective alkylation of pyrroles and indoles in [BMIM][X]/K_2CO_3 (X = SbF_6^-, PF_6^-, BF_4^-, OTf^-, NTf_2^-) media. Importantly, these accounts contain very little detail relating to the issue of recycling the ionic liquid reaction medium. In our current work, we address this important aspect as it is a significant component in the development of a green synthetic process.

Results and discussion

Synthesis and reaction conditions

As part of our research project in the area of electrolyte materials we synthesised new ionic liquids based on the *N*-heterocycle 3-azabicyclo[3.2.2]nonane (3-ABN).[26] This required, in the first step, the preparation of the tertiary amines **2a–d** shown in Scheme 1. Initially the application of conventional methods, involving alkylation in KOH/ethanol, KOH/acetonitrile, NaH/Et_3N/DME, Hünig's base/acetonitrile at moderate temperatures (60–80 °C), gave only unsatisfactory yields along with quaternary ammonium salts.



Scheme 1 Alkylation of 3-ABN.

As Nucleophilic substitution reactions are strongly dependent on the polarity of the reaction medium,[27] we therefore decided to attempt the alkylation of 3-ABN in an ionic liquid as an alternative to polar molecular solvents.[2] The results of the reactions which were conducted on small and large scales

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Table 1 Alkylation of 3-ABN with 1-iodoethane in [BMIM][PF_6] and [P14][Tf_2N]

Entry	Temp./°C	Time/h	Scale/g	IL : 3-ABN/ vol : weight	Yield (%)
1	60	48	0.5	3.4	66
2	60	48	1	3	71
3[a]	60	48	0.5	3.4	70
4[b]	60	48	6	3.7	75
5	80	24	3	3.3	74
6[b]	80	24	1	4	77
7	80	24	0.5	7	64
8	80	48	1	7	>90
9	60	48	25	3.4	>90
10[c]	60	48	1	3.3	17
11[d]	60	48	1	3.3	73

[a] Used [BMIM][PF_6] which was regenerated by filtration of a CH_2Cl_2 solution. [b] Used [BMIM][PF_6] which was regenerated by water washing. [c] Used [BMIM][PF_6] which was regenerated by simple filtration from inorganic salts. [d] [P14][Tf_2N] used as reaction medium.

Table 2 Alkylation of 3-ABN with different alkyl halides in [BMIM][PF_6][a]

Entry	R-X	Temp/°C	Time/h	Yield (%)
1	^{n}Pr-I	80	20.5	82
2	^{n}Pr-I	RT	20.5	63
3	^{n}Pr-Br	80	20.5	70
4	^{n}Pr-Br	80	67	82
5	^{n}Pr-Cl	80	20.5	37
6	^{n}Bu-Br[b]	60	48	78

[a] [BMIM][PF_6] : 3-ABN = 1.5 ml : 0.5 g. [b] 3-ABN: 14 g.

(0.5–30 g) are summarised in Tables 1 and 2. The respective alkyl halides were added slowly to mixtures of 3-ABN/2 equiv. KOH/ionic liquid and the reaction mixture was subsequently heated at 60–80 °C. The result was an opaque orange/yellow solution from which the product separated as an individual phase as the reaction progressed. During small scale operations, the tertiary amine was isolated *via* extraction into diethylether, whereas work-up and isolation procedures were modified in larger scale operations (see regeneration and work-up section). Under these conditions **2a–d** were obtained in good to very good yields and good purity according to NMR (see experimental section) and GC analysis (Fig. 1). A final purification step was performed by flash chromatography on neutral alumina.

We investigated aspects such as reaction temperature, reaction time, substrate concentration and the influence of the halide leaving group for the reaction. Yields of 70–77% were obtained with high substrate concentrations in 1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF_6], after 48 h at 60 °C (Table 1, entries 1–4) and after 24 h at 80 °C respectively (Table 1, entries 5–6). Two reactions were also conducted at low substrate concentration (Table 1, entries 7–8). A yield comparable to the previous reactions was obtained after 24 h at 80 °C, whereas doubling the reaction time leads to almost quantitative product formation. A 90% yield was, however, also achieved with high substrate concentrations under the 48 h at 60 °C conditions in the large scale run 9. From these results it becomes evident that: (i) the economic use of relatively small solvent amounts is feasible; (ii) alkylation can proceed to completion with extended reaction times at mild temperatures. Clearly, adjustment of reaction time and temperature leaves further room for optimisation but this was outside the scope of the research project.

The success of nucleophilic substitution reactions depends on the nature of the leaving group of the alkylating reagent. For alkyl halides the reactivity typically follows the order $I^- > Br^- > Cl^-$, but invariably the economics (price per mol alkylating reagent) also follows the same order. With the aim to provide an economically more feasible option for the alkylation of 3-ABN and, more generally, other secondary amines we trialled the three propyl derivatives under the previous conditions in [BMIM][PF_6] (Table 2). As expected, the highest yield was obtained with the iodo derivative. However, the same yield was achieved with the less expensive propyl bromide upon extending the reaction time to 67 h. The chloro derivative reacted poorly resulting in a mixture of product and starting material according to ^{1}H NMR analysis.

Solvent regeneration and product isolation

For processes to be truly environmental and economically benign, it is important that solvents can be efficiently recovered and recycled and that products can be conveniently isolated from the reaction mixture. At all points, procedures that require excessive energy, material and time intensive steps must be

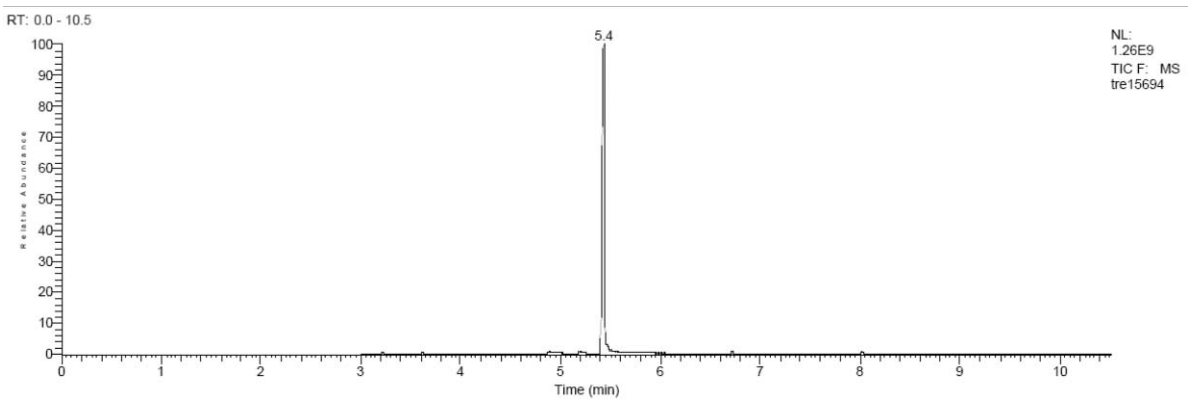

Fig. 1 Typical GC of a reaction product from the alkylation of 3-ABN obtained after separation from the ionic liquid reaction medium.

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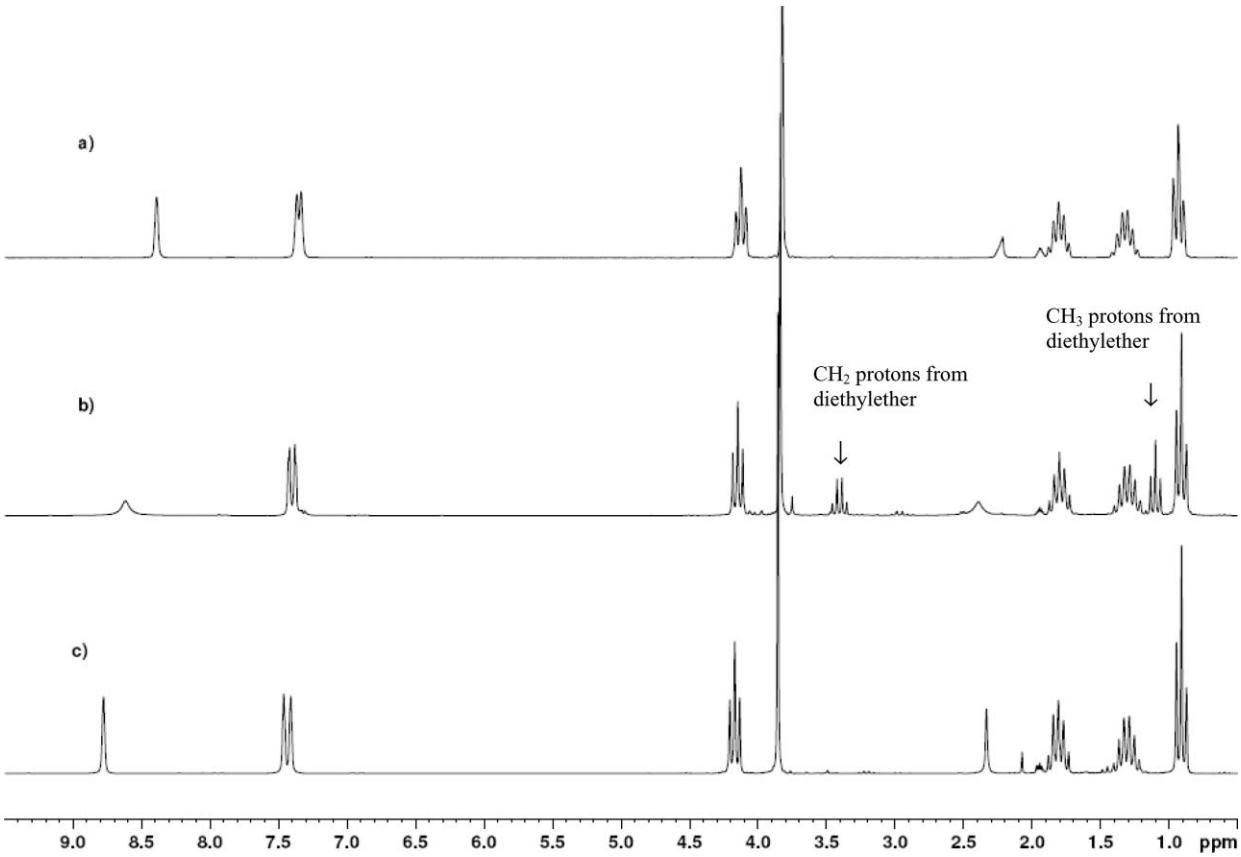

Fig. 2 ^{1}H NMR of [BMIM][PF_6] (a) fresh commercial material (b) material after use in the alkylation reaction and prior to regeneration (signals at 1.1 and 3.4 ppm are from residual ether) (c) material after regeneration.

avoided. In view of this benchmark, we have investigated the extent to which the present reaction follows these principles.

Initial recovery of [BMIM][PF_6] was attempted by simple filtration of insoluble materials (KOH, KX). The identity was confirmed by ^{1}H, ^{13}C and ^{19}F NMR (Fig. 2). At this stage the NMR purity of the reaction medium was quite remarkable, showing only minor signals for 3-ABN related compounds. ^{1}H NMR signals of small intensity at 3.7 and 7.3 ppm may be assigned to the presence of a second [BMIM] species. Use testing this material, however, gave only poor yields (Table 1, entry 10). By contrast when the recovered IL was freed from insoluble inorganic salts by either filtration of a dichloromethane solution or by water washing no considerable reduction in product yield was encountered in subsequent use-tests (Table 1, entries 3, 4, 6). The recovery of [BMIM]PF_6 was excellent after filtration of CH_2Cl_2 solutions, which indicated the stability of the reaction medium under the applied conditions. The low boiling CH_2Cl_2 can be separated and recovered from the IL under mild distillative conditions. When water washing (3 × 1–2 volumes per volume of IL) was applied in the purification of the IL, the recovery was reduced by an average of 15–20 wt%. The reason for this loss is not quite clear, however there are several possibilities:

Firstly, under the strongly basic conditions (excess KOH) the reactivity of the ionic liquid could be difficult to control through the labile proton at the C-2 position of the imidazolium cation[28] and/or the PF_6^- anion.[29] The latter has been reported to undergo slow hydrolysis. We therefore conducted the same alkylation reaction in 1-butyl-1-methylpyrrolidinum bis(trifluoromethylsulfonylimide) [P14][Tf_2N] as the reaction medium, where the saturated heterocycle is devoid of a labile proton and the anion is not sensitive. After isolation of the tertiary amine in 73% yield and filtration of the ionic liquid medium, the recovery of [P14][Tf_2N] by mass was approximately 93%. Analysis by ^{19}F and ^{13}C NMR spectra revealed, however, the presence of two distinct [P14] compounds. According to NMR and MS (ESI), the recovered liquid also contains a small amount of a quarternary *N*,*N*-diethyl-3-ABN cation. Washing of the liquid with water, which is accompanied by a 12% reduction in mass, gave the expected [P14][Tf_2N]. Two other very likely causes for losses of the ionic liquid reaction medium are inefficient phase separation and partial ion exchange with excess hydroxide and iodide ions in the aqueous phase. After concentration of the water phase obtained from the work-up of the larger scale butylation of 3-ABN (Table 2, entry 6), a yellow oil precipitated which represented approximately 12 wt% of the initial mass of [BMIM]PF_6. According to NMR and MS (ESI) analysis, the recovered material consisted of the imidazole cation and a mixture of the anions PF_6^- and I^-.

In the initial small scale experiments, product isolation was conducted by extraction into ether or ethyl acetate and subsequent phase separation (see experimental section).

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During larger scale operations, however, it became clear that upon resting, the reaction mixture separated into a biphasic system with the tertiary amine forming the upper oily layer. Encouraged by this observation, we developed a benign work-up/isolation procedure for this system using 1-bromobutane as the alkylating reagent (Table 2, entry 6). After completion of the reaction water (approx. 1 volume per volume IL) was added and stirring of the emulsion was stopped shortly afterwards. Within a few minutes a liquid three phase system was established where initially the product separated from the IL/water emulsion followed by the IL separating out of the water phase as larger droplets forming the bottom layer (Fig. 3).‡ The product layer was decanted and the light yellow oil washed with water and dried under vacuum. A good purity was established by GC analysis (98%) and NMR. The mass yield was 76%. The purity of the IL after separation and drying was similar to previously recovered IL reaction media and no product signals were detected (Fig. 2). The aqueous phase was extracted with ether to yield, after separation, a small amount of product representing 1.5% of the total mass. As an alternative to the gravity phase separation, product isolation can also be achieved by distillation (**2d**: bp 56–57 °C at 0.1–0.2 mmHg) since ionic liquids have a very low vapour pressure. Which technique is preferred in terms of engineering in large scale operations will depend on individual energy requirements, material losses, capital expenses, suitability for a broad product range, *etc.*

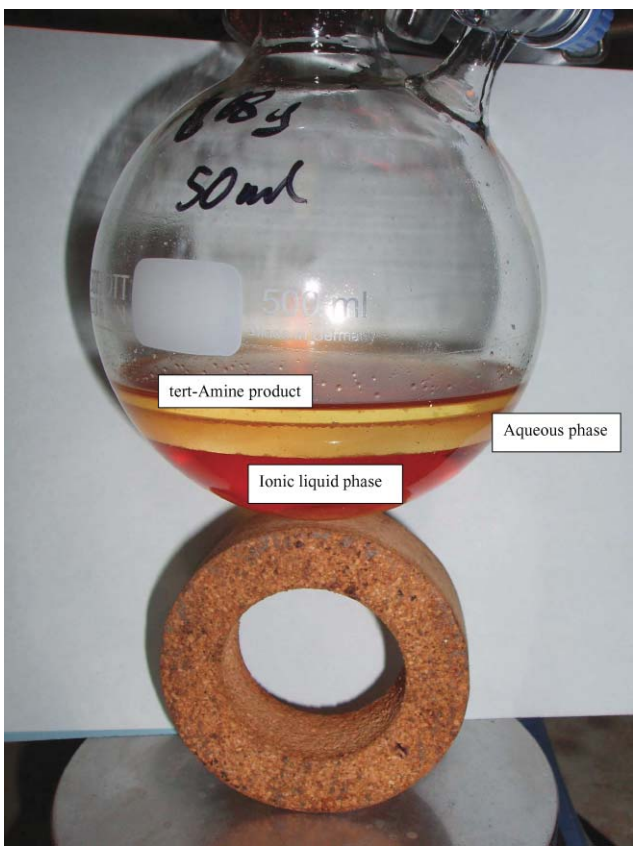

Fig. 3 Triphasic system after completion of reaction.

‡ A video presentation of this process can be obtained from the author.

Conclusions

We have described an efficient green method for the alkylation of sterically hindered secondary amines. This methodology has several benign features:

- improved yields (typically 70 to >90%) without significant quarternary amine by-product formation
- use of less expensive alkyl bromides affords products in ≥80% yield
- convenient product isolation from the reaction mixture due to formation of a three-phase system after quenching with water
- use of the inexpensive inorganic base (KOH)
- facile recycling of the ionic liquid reaction medium

Experimental

General

Commercially available reagents were purchased from Aldrich and Merck. 3-Azabicyclo[3.2.2]nonane (City Chemicals, USA) was sublimed prior to use.

All solvents used in the synthetic procedures were commercial high purity (HPLC or analytical [p.a.] grade) products. All glassware was pre-rinsed with the solvent used in individual synthetic procedures prior to reactions which were carried out on a vacuum Schlenk line under dry nitrogen.

Measurements

^{1}H and ^{13}C NMR spectra were recorded on a Bruker BioSpin Av200 spectrometer operating at 200.13 MHz. Chemical shift values are reported relative to $CDCl_3$ solutions of TMS (^{1}H, ^{13}C) as the external references. Mass spectra were acquired on a VG Platform mass spectrometer using a cone voltage of 50 or 30 V and the source was maintained at 80 °C. The solvent used was CH_3OH with a flow rate of 0.04 ml min^{-1}. Elemental analysis (C, H, and N) was carried out by the Microanalytical Unit of the Research School of Chemistry at the Australian National University in Canberra.

Synthetic procedures

Sublimation of 3-azabicyclo[3.2.2]nonane 1 (3-ABN). The as received, sticky brownish material was placed into a round bottom Schlenk flask equipped with a tube which had an outer mantel fitted in the middle part and a hose adapter at the top part. The mantel was filled with dry ice, the flask immersed into an oil bath and the sublimation apparatus connected to a high-vacuum Schlenk line. Sublimation was carried out at 55–65 °C and 1–5 × 10^{-2} mbar when a crystalline white material condensed in the lower part of the glass tube. Under these conditions 10–20 g lots of crude 3-ABN could be sublimed within one day. Most of the material was removed from the apparatus mechanically by means of a long spatula and difficult to remove remaining material was rinsed off with methanol which was subsequently allowed to evaporate in a fume cupboard (rotary evaporation is more difficult because the water bath temperature must be kept below the sublimation temperature at a given vacuum, *e.g.* 30 °C/~20 mbar). Typical recoveries from the commercial material after exhaustive sublimation were in the order of

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70–80 wt%. The pure compound is best stored under an inert atmosphere at 4 °C (refrigerator) to prevent the development of a yellow brown colour over time.

General small scale procedure for the synthesis of 3-alkyl-3-azabicyclo[3.2.2]nonanes 2a–d. To a mixture of 1-butyl-3-methylimidazolium hexafluorophosphate, 3-ABN and KOH (2 equiv.) was slowly added the appropriate alkyl iodide or alkyl bromide (1.1 equiv.). The Schlenk flask was sealed and the reaction mixture stirred at 60–80 °C for 24–48 h. The tertiary amine product was removed from the reaction mixture by extraction into diethyl ether or ethyl acetate. After washing with water and removal of the solvent under reduced pressure the obtained products are usually of acceptable purity. Further purification can be achieved by flash chromatography through a plug of activated alumina giving faint yellow oils in 66–>90% yield. The 3-alkyl-3-azabicyclo[3.2.2]nonanes appeared to be of limited stability and are best stored under an inert atmosphere at 4 °C (refrigerator) to slow the development of a yellow brown colour over time.

General large scale procedure for the synthesis of 3-alkyl-3-azabicyclo[3.2.2]nonanes 2a–d. To a biphasic mixture of 1-butyl-3-methylimidazolium hexafluorophosphate (3.4 v/w 3-ABN) and KOH (2 equiv.) in a Schlenk flask was added 3-ABN which dissolved upon heating to 60 °C. The appropriate alkyl iodide or alkyl bromide (1.1 equiv.) was slowly added *via* an addition funnel at close to ambient temperature under good stirring. The Schlenk flask was then sealed (in case of longer carbon chain alkyl halides, a reflux condenser can also be used) and the reaction mixture stirred at 60 °C for 24–48 h.

After the set reaction time, the orange brown reaction mixture was cooled to ambient temperature and water (approx. the same volume as the ionic liquid) was added slowly under rapid stirring. The emulsion was allowed to settle into a three phase system: initially the amine layer separated from a water/IL emulsion, then the IL separated in large droplets from its emulsion with water.

The tertiary amine layer was decanted, washed two times with water (in some cases the amine was diluted with a small amount of ether to push out excess dispersed water and to achieve faster phase separation), dried over $MgSO_4$, and filtered.

3-Methyl-3-azabicyclo[3.2.2]nonane 2a. ^{1}H NMR δ_H (200 MHz; d_3-$CDCl_3$): 1.58 (4H, m, ring-CH_2), 1.75 (4H, m, ring-CH_2), 1.85 (2H, m, bridgehead-CH), 2.29 (3H, s, N-CH_3), 2.55 (4H, dd, ring-(CH_2)$_2$N); ^{13}C NMR δ_C (200 MHz; d_3-$CDCl_3$): 25.78 (ring CH_2), 30.27 (bridgehead CH), 46.65 (N-CH_3) and 65.67 (N-CH_2-ring).

3-Ethyl-3-azabicyclo[3.2.2]nonane 2b. ^{1}H NMR δ_H (200 MHz; d_3-$CDCl_3$): 1.03 (3H, t, J = 7 Hz, -CH_2CH_3), 1.4–1.9 (10 H, m, ring-CH_2 and CH), 2.43 (2H, q, J = 7 Hz, N-CH_2CH$_3$), 2.54 (4H, dd, J = 4.4 Hz, ring-(CH_2)$_2$N); ^{13}C NMR δ_C (200 MHz; d_3-$CDCl_3$): 12.44 (-CH_2CH_3), 25.74 (ring CH_2), 30.33 (bridgehead CH), 52.11 (N-CH_2CH_3) and 62.29 (N-CH_2-ring); elemental analysis found: C, 77.85 H, 11.83 N, 8.89%. calcd. for $C_{10}H_{19}N$: C,78.37; H, 12.50; N, 9.14%.

3-Propyl-3-azabicyclo[3.2.2]nonane 2c. δ_H (200 MHz; d_3-$CDCl_3$): 0.88 (3H, t, J = 7.2 Hz, -$CH_2CH_2CH_3$), 1.3–1.9 (12 H, m, ring-CH_2, CH and side chain -$CH_2CH_2CH_3$), 2.30 (2H, t/d, J = 7 Hz, N-C$H_2CH_2CH_3$), 2.53 (4H, dd, J = 4.2 Hz, ring-(CH_2)$_2$N); ^{13}C NMR δ_C (200 MHz; d_3-$CDCl_3$): 14.02 (-$CH_2CH_2CH_2CH_3$), 20.63 (-$CH_2CH_2CH_2CH_3$), 25.71 (-$CH_2CH_2CH_2CH_3$), 29.44 (ring CH_2), 30.38 (bridgehead CH), 58.03 (N-$CH_2CH_2CH_3$) and 62.80 (N-CH_2-ring); elemental analysis found: C, 79.06 H, 12.49 N, 8.55%. calcd. for $C_{10}H_{19}N$: C, 78.97; H, 12.65; N, 8.37%.

3-Butyl-3-azabicyclo[3.2.2]nonane 2d. ^{1}H NMR δ_H (200 MHz; d_3-$CDCl_3$): 0.91 (3H, t, J = 7 Hz, -CH_2CH_2-CH_2CH_3), 1.60–2.0 (14 H, m, ring-CH_2, CH and side chain -$CH_2CH_2CH_2CH_3$), 2.36 (2H, t/d, J = 7 Hz, N-C$H_2CH_2CH_2CH_3$), 2.54 (4H, dd, J = 4.2 Hz, N-CH_2-ring); ^{13}C NMR δ_C (200 MHz; d_3-$CDCl_3$): 14.02 (-$CH_2CH_2CH_2CH_3$), 20.63 (-$CH_2CH_2CH_2CH_3$), 25.71 (-$CH_2CH_2CH_2CH_3$), 29.44 (ring CH_2), 30.38 (bridgehead CH), 58.03 (N-$CH_2CH_2CH_3$) and 62.80 (N-CH_2-ring).

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Deep oxidative desulfurization of fuels in redox ionic liquids based on iron chloride

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Three redox ionic liquids based on iron chloride were synthesized and employed in extraction and catalytic oxidation desulfurization systems for removal of benzothiophene (BT), dibenzothiophene (DBT) and 4,6-dimethyldibenzothiophene (4,6-DMDBT) in model oil. Sulfur removal selectivity for S-compounds followed the order of DBT > 4,6-DMDBT > BT. Due to the redox properties of 1-butyl-3-methylimidazolium chloride iron chloride ([bmim]Cl/$FeCl_3$) with addition of hydrogen peroxide, DBT removal can reach 99.2% under mild reaction conditions, which is not only higher than mere extraction with ionic liquid (IL), but also superior to two other ILs based on iron chloride under the same reaction conditions. Herein, [bmim]Cl/$FeCl_3$ played a dual role in the process of desulfurization, not only acting as catalyst but also acting as an extractant. [bmim]Cl/$FeCl_3$ is insoluble in *n*-octane, and the solubility in the model oil is also negligible. The used ionic liquid could be recycled for six times with a slight decrease in activity.

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Introduction

New processes for deep desulfurization of transportation fuels are needed urgently, as sulfur compounds in fuels have greatly contributed to the pollution of the environment. SO_x emission from automobile exhausts not only pollutes air heavily, but also irreversibly poisons the metal catalysts in automobiles. To keep pace with the increasingly strict regulatory constraints, it is greatly desired to develop new approaches to get little-to-no sulfur fuels (S-content < 10 ppm).[1] In the petroleum refining industry, hydrodesulfurization (HDS) is a conventional method for the removal of sulfur compounds. However, some refractory sulfur compounds, such as benzothiophene (BT), dibenzothiophene (DBT), and their derivatives, are difficult to remove due to their steric hindrance. To achieve the desired low level of sulfur in fuels requires both high temperature and high hydrogen pressure, which inevitably lead to high capital expenditure.

In the past several years, alternative deep desulfurization techniques have been extensively investigated, for example, extraction,[1–11] oxidation,[12–22] adsorption,[23–25] ultrasound[26] and bioprocesses.[27] Among these, oxidative desulfurization (ODS) is regarded as a promising strategy to achieve low sulfur content fuel. Various studies on the ODS process have employed different oxidizing agents such as molecular oxygen,[28,29] hydrogen peroxide,[15–22] nitric acid/NO_2,[30] and *tert*-butyl hydroperoxide (*t*-BuOOH),[31] Among these, hydrogen peroxide has been widely used, because it is cheap, nonpolluting, not strongly corrosive and commercially available. In the ODS process, sulfur compounds are oxidized into their corresponding sulfones, which can be removed by the later selective extraction with organic solvents.[17] Then low-sulfur fuels can be obtained. However, a large number of flammable and volatile organic compounds (VOCs) are used as extractants, which would cause further environmental and safety concerns.

Considered as "green solvents", room temperature ionic liquids (RTILs)[32] have been extensively employed in green chemistry instead of organic solvents because of their low melting point, wide liquid range, negligible vapor pressure and good solubility characteristics *etc.*,[33] which can effectively avoid further environmental concerns. There have already been many investigations on the new approach for sulfur removal of diesel fuels by extraction desulfurization (EDS) with ILs.[1–11,34] More recently, combining chemical oxidation with ILs extraction has increased desulfurization efficiency significantly, and has proved to be a promising desulfurization method.[20–22]

Ionic liquids containing metal halide anions, such as iron (III) ion, showed positive results in EDS at room temperature. However, the molar ratio of 1-butyl-3-methylimidazolium chloride-$FeCl_3$ ([bmim]Cl/$FeCl_3$) was too high.[11] Up to now, much attention has been paid to the Lewis acidic character of [bmim]Cl/$FeCl_3$ when applied to organic synthesis.[35,36] However, there was rare study on its oxidation–reduction character, especially when used as a catalyst in oxidative reactions.

The aim of this work is to develop a more efficient extraction coupled with oxidative desulfurization (EODS) system for sulfur compounds in a model oil. We found that redox [bmim]Cl/$FeCl_3$ exhibited high activity in the oxidization of DBT with hydrogen peroxide as oxidant, which not only served as extractant and reaction media but also acted as catalyst. Then deep desulfurization can be achieved. The performance of the recycled IL was also examined.

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Table 1 Comparison of different desulfurization systems of model oil

Entry	Desulfurization system	Sulfur removal (%)
1	[bmim]Cl/$FeCl_3$	66.0
2	Anhydrous $FeCl_3$+ H_2O_2	57.4
3	[bmim]Cl/$FeCl_3$+ H_2O_2	99.2

Experiment conditions: m(model oil)/m(IL) = 3 : 1, m(model oil) = 2.6 g, n(S)/n(H_2O_2) = 1 : 3, T = 30 °C, t = 10 min, m(anhydrous $FeCl_3$) = 0.403 g.

Results and discussion

Effect of different catalytic systems containing $FeCl_3$ species on DBT removal

Different desulfurization systems were conducted: extraction, chemical oxidation and extraction coupled with oxidative desulfurization (EODS). The results are listed in Table 1. When [bmim]Cl/$FeCl_3$ was used as extractant for DBT-containing model oil, the S-removal reached 66.0%. With addition of H_2O_2, the removal of DBT increased sharply and the desulfurization efficiency of 99.2% was acheived with the EODS system. This result indicated that hydrogen peroxide played a significant role in the desulfurization with [bmim]Cl/$FeCl_3$. The redox [bmim]Cl/$FeCl_3$ not only served as extractant and reaction media but also acted as catalyst. However, in the case of the system comprising anhydrous $FeCl_3$ and H_2O_2, S-removal was only 57.4%.

It is clearly demonstrated that a combination of extraction and catalytic oxidation in [bmim]Cl/$FeCl_3$ could deeply remove the sulfur from model oil. The remarkable advantage of this process in the desulfurization of model oil by mere solvent extraction with IL can also be seen. The possible explanation is discussed below as a mechanism of a Fenton-like reagent.

Effect of different ionic liquids on DBT removal

Three ILs were used in two different desulfurization systems of extraction (EDS) and extraction coupled with oxidative desulfurization (EODS). The ILs were immiscible with the model oil, and formed bi-phasic systems. As shown in Table 2, sulfur removal was in the range of 35.4% to 68.3% with the three ionic liquids by a single extraction. [bmim]Cl/$FeCl_3$ and [omim]Cl/$FeCl_3$ ionic liquids showed higher extractive ability than $Et_3NHCl/FeCl_3$, which could be attributed to the principle of similitude-compatibility for aromatic cycle-containing ILs. Sulfur removal can only reach 66.0% in the extractive desulfurization system with [bmim]Cl/$FeCl_3$. With addition of H_2O_2, the activity increased sharply, reaching 99.2%. [omim]Cl/$FeCl_3$ also had an increase in DBT removal with 87.0% compared to the sulfur removal of 68.3% in the EDS. [omim]Cl/$FeCl_3$, with the long alkyl chain of the imidazole cation, exhibited higher desulfurization activity than [bmim]Cl/$FeCl_3$ in the EDS. However, the activity of the long alkyl chain imidazole cation IL decreased in EODS.

Table 2 Comparison of different ionic liquids in desulfurization systems

		Sulfur removal of different desulfurization system (%)	
Entry	IL	EDS	EODS
1	[bmim]Cl/$FeCl_3$	66.0	99.2
2	[omim]Cl/$FeCl_3$	68.3	87.0
3	$Et_3NHCl/FeCl_3$	35.4	37.2

Experiment conditions: m(model oil)/m(IL) = 3 : 1, m(model oil) = 2.6 g, n(S)/n(H_2O_2) = 1 : 3, T = 30 °C, t = 10 min.

Effect of time and temperature on DBT removal with [bmim]Cl/$FeCl_3$

To optimise the performance of [bmim]Cl/$FeCl_3$ in EODS, the sulfur removal ability was tested under different reaction conditions in the presence of H_2O_2. Fig. 1 displays the effect of the reaction temperature and time on the content of DBT in the model oil. An increase in the reaction temperature from 30 °C to 50 °C led to a remarkable decrease in DBT removal. More hydrogen peroxide decomposed as the temperature increased, so H_2O_2 is not good for use at higher temperatures. There was a remarkable drop in sulfur removal when the reaction temperature reached 50 °C, only 79.0% removal of DBT was obtained even when prolonging the reaction time to 12 min. The reaction time could be shortened to 10 min if the reaction temperature was retained at 30 °C. Therefore, room temperature was chosen as the suitable temperature in the present study.

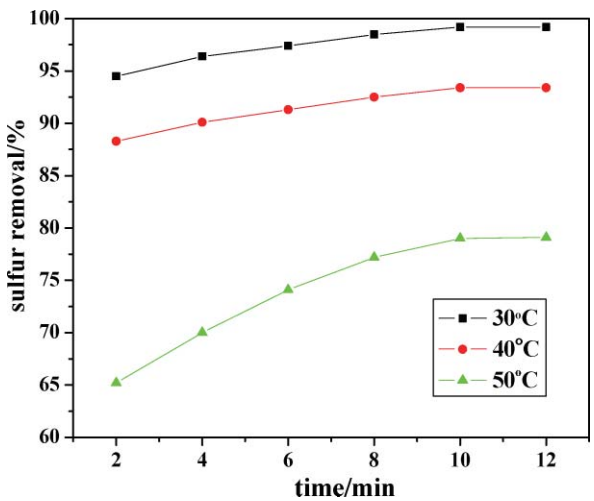

Fig. 1 Sulfur removal with different times and temperatures in EODS using [bmim]Cl/$FeCl_3$.

Effect of the amount of [bmim]Cl/$FeCl_3$ on DBT removal

The amount of [bmim]Cl/$FeCl_3$ was an important factor in EODS. The data in Fig. 2 show the dependence of the extraction desulfurizations of DBT as the mass ratio of IL and model oil varied from 1 : 6 to 1 : 3. As seen in Fig. 2, the sulfur removal increased linearly with an increase in the mass ratio of IL and model oil. This result implied that more IL was good for the combination between [bmim]Cl/$FeCl_3$ and H_2O_2 existing in EODS. So an extremely low sulfur level might be attained by changing the mass ratio of IL and model oil. When the mass ratio of ionic liquid and model oil was fixed at 1 : 6, 94.8% desulfurization was obtained at 30 °C, and when the mass ratio

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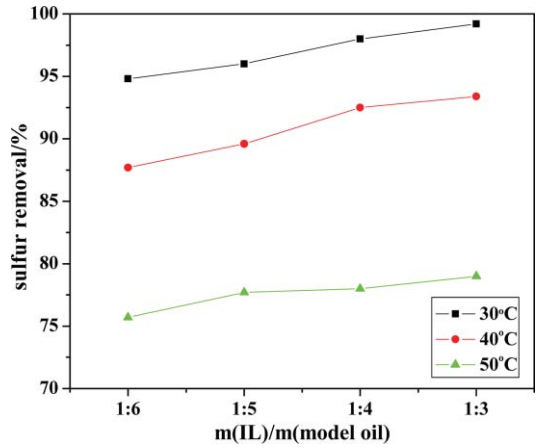

Fig. 2 Sulfur removal with different mass ratio between IL and model oil using [bmim]Cl/$FeCl_3$.

was set at 1 : 3, the efficiency can reach 99.2%. Fig. 2 also shows that the high reaction temperature was not favorable to the oxidation desulfurization.

Effect of molar ratio of sulfur and H_2O_2 (S/O) with [bmim]Cl/$FeCl_3$ on DBT removal

To investigate the effect of the amount of oxidizing agent on the desulfurization system, reactions under various S/O ratios were carried out at 30 °C. According to the stoichiometric reaction, to oxidize the sulfur-containing compounds to their corresponding sulfones using hydrogen peroxide, 2 mol of hydrogen peroxide is consumed per 1 mol of sulfur-containing compound. However, as shown in Fig. 3, [bmim]Cl/$FeCl_3$ gave an attractive sulfur removal of 99.2% in 10 minutes with $n(S)/n(H_2O_2) = 1 : 3$. From the data in Fig. 3, we know that the molar ratio of H_2O_2 and DBT has a strong influence on the reaction rate.

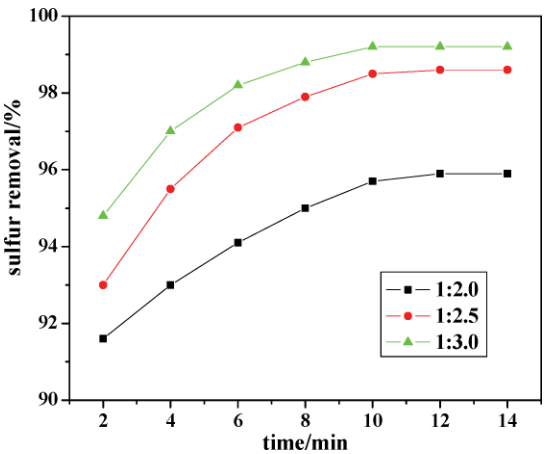

Fig. 3 Sulfur removal with different S/H_2O_2 (S/O) molar ratio using [bmim]Cl/$FeCl_3$.

Two desulfurization systems with different substrates

In the previous section, it was shown that DBT in *n*-octane can be effectively removed by EODS. In order to facilitate the comparison, three model sulfur compounds, DBT, benzothiophene (BT) and 4,6-dimethyldibenzothiophene (4,6-DMDBT),

Table 3 Different substrates in the process of EDS and EODS with [bmim]Cl/$FeCl_3$

		Sulfur removal (%)	
Entry	Substrates	EDS[a]	EODS[a]
1	DBT	67.6	99.2
2	4,6-DMDBT	60.3	90.3
3	BT	46.3	75.9
4[b]	Actual diesel	46.3	71.3

[a] Experimental conditions: m(model oil)/m(IL) = 3 : 1, m(model oil) = 2.6 g, $[n(S)/n(H_2O_2)] = 1 : 3$, $T = 30$ °C, $t_{EDS} = 30$ min, $t_{EODS} = 10$ min. [b] m (actual diesel) =2.66 g, m(actual diesel)/m(IL) = 1.5 : 1, $[n(S)/n(H_2O_2)] = 1 : 20$, $T = 30$ °C, $t = 30$ min.

were investigated by EDS and EODS, respectively. As shown in Table 3, the removal of DBT, 4,6-DMDBT and BT was 67.6%, 60.3% and 46.3% in EDS, respectively. With addition of H_2O_2, the removal of three sulfur compounds all increased, reaching 99.2%, 90.3% and 75.9%, respectively. The S-removal through the EODS process decreased in the order DBT > 4,6-DMDBT > BT, which agreed well with the system of polyoxometalates/H_2O_2.[21] The electron density on the sulfur atom of BT is significantly lower, leading to the lowest reactivity to BT. For DBT and 4,6-DMDBT, the difference in the electron density on the sulfur was very small (5.756 for DBT, 5.760 for 4,6-DMDBT).[21] Therefore, reactivity was mainly affected by the steric hindrance of the methyl groups, which became an obstacle for the approach of the sulfur atom to the catalytically active species.[20]

The investigation of desulfurization in actual diesel was also carried out. Actual diesel contains a wide range of aromatic sulfur-containing compounds, including thiophene, BT, DBT and their alkyl-substituted derivatives. The reaction conditions were optimized for the complicated components of actual diesel. However, compared with the model compound system, the sulfur removal of actual diesel was lower than that of the model oil.

Effect of recycling of used [bmim]Cl/$FeCl_3$

The effect of recycling used [bmim]Cl/$FeCl_3$ was studied in the EODS of DBT-containing model oil. The data shown in Fig. 4 indicate that the desulfurization system could be recycled

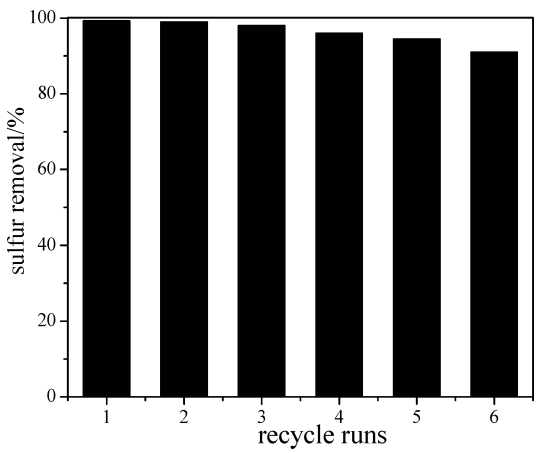

Fig. 4 Effect of recycling of used ionic liquid.

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six times with a slight decrease in activity. The sulfur removal dropped from 99.2% to 90.9% under the same experimental conditions. However, at the end of each cycle of six reactions, the ionic liquid phase (underlayer) was re-extracted with tetrachloromethane in a water bath at 45 °C twice. The regenerated IL was then recycled into the desulfurization. The results indicated that [bmim]Cl/$FeCl_3$ could be recycled nine times with an unnoticeable decrease in desulfurization activity, and sulfur removal only dropped from 99.2% to 98.6%.

The suggested process and mechanism of EODS

[bmim]Cl/$FeCl_3$ performs best among the three ionic liquids for desulfurization of the model oil in the presence of H_2O_2. It is challenging to discuss the mechanism of this phenomenon. Fenton-like reagent, a mixture of iron (III) ions and hydrogen peroxide, is widely applied to oxidize organic substrates.[37] As Fe^{3+} exists in the presence of H_2O_2, Fenton-like chemistry often occurs simultaneously. So, for the Fenton-like reagent, it is believed that initially no O–O bond of hydrogen peroxide breaking takes place, but instead an Fe^{3+} hydroperoxo intermediate is formed as in step (1) *via* hydrolysis.

$$Fe^{3+} + H_2O_2 \rightarrow [Fe^{III}OOH]^{2+} + H^+ \quad (1)$$

This intermediate might be able to react with organic substrates or break up into smaller active species as in step (2).

$$[Fe^{III}OOH]^{2+} \rightarrow Fe^{2+} + OOH^{\bullet} \quad (2)$$

The Fe^{3+} hydroperoxo may homolyze at the Fe–O bond,[37] generating Fe^{2+} and producing the reactive $OOH^{\bullet}$ radical, or at the O–O bond producing the ferryl ion and an $OH^{\bullet}$ radical (eqn (3)), which is a strong oxidizing agent.[37]

$$[Fe^{III}OOH]^{2+} \rightarrow [Fe^{IV}O]^{2+} + OH^{\bullet} \quad (3)$$

A possible EODS mechanism is given in Fig. 5. The extraction and catalytic oxidation desulfurization system of [bmim]Cl/$FeCl_3$ containing H_2O_2 was selected as the research model. The ionic liquid was immiscible with model oil, so the reactants formed a bi-phasic system. The sulfur-containing compounds, such as DBT, were extracted into the IL phase and then were selectively oxidized to $DBTO_2$ by the strong oxidant $OH^{\bullet}$ radical, thus a continuous decrease in the concentration of DBT in *n*-octane was observed during the process of oxidation. By this procedure, the $DBTO_2$ accumulated in the IL phase in successive runs. After the sixth cycle, the IL phase was re-extracted by tetrachloromethane at room temperature. Then, tetrachloromethane was seperated from IL and distilled at 80 °C until a white crystal solid was produced. The white crystal solid was characterized by IR. Two absorption bands at 1130 and 1288 cm^{-1} were attributable to sulfone groups.[38] The photos of [bmim]Cl/$FeCl_3$ and the reclaimed $DBTO_2$ are shown in Fig. 6.

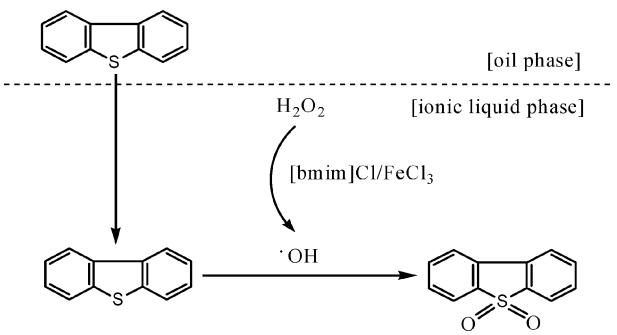
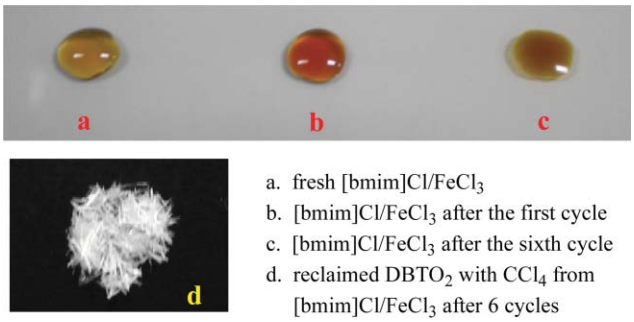


Fig. 5 The process of EODS of DBT in an oil–ionic liquid–H_2O_2 system.



a. fresh [bmim]Cl/$FeCl_3$
b. [bmim]Cl/$FeCl_3$ after the first cycle
c. [bmim]Cl/$FeCl_3$ after the sixth cycle
d. reclaimed $DBTO_2$ with CCl_4 from [bmim]Cl/$FeCl_3$ after 6 cycles

Fig. 6 The photos of [bmim]Cl/$FeCl_3$ and the reclaimed $DBTO_2$.

In EODS, although the desulfurization of three ILs containing Fe^{3+} ion was superior to the simple extraction with ILs, DBT removal by $Et_3NHCl/FeCl_3$ and [omim]Cl/$FeCl_3$ was less than that of [bmim]Cl/$FeCl_3$. A Fenton-like reaction occurred in these ILs in the presence of H_2O_2, due to the significant Brønsted acidic property of the 2-position-H in the imidazole-containing ILs.[39] Ferraz *et al.*[40] reported that the acidity of the media could enhance the oxidative power of the Fenton-like system. Accordingly, DBT removal by [omim]Cl/$FeCl_3$ and [bmim]Cl/$FeCl_3$ was higher when compared with that of the quaternary ammonium ionic liquid $Et_3NHCl/FeCl_3$. Interestingly, the ability of [omim]Cl/$FeCl_3$ to extract DBT from *n*-octane is better than that of [bmim]Cl/$FeCl_3$. However, the oxidation efficiency is lower. Steric hindrance of the long alkyl chain of the active species in Fe-containing ionic liquids became an obstacle for the approach of the sulfur atom to the catalytically active species in the IL. Therefore, in EODS, the catalyst with a short alkyl chain exhibited higher catalytic activity than that with a long alkyl chain. A large amount of polar sulfones accumulated in IL and could be easily separated from the IL by re-extraction with tetrachloromethane. In this way, ultra-deep desulfurization can be achieved.

Conclusion

In this paper, three redox ionic liquids based on iron chloride were synthesized and investigated in the removal of DBT, BT and 4,6-DMDBT from a model oil and actual diesel in EDS and EODS, respectively. The sulfur removal from the DBT-containing model oil in [bmim]Cl/$FeCl_3$ could reach 99.2% at 30 °C in 10 minutes, which was the remarkable advantage of this process over the desulfurization by simple extraction with IL. The IL could be recycled six times with a slight decrease in activity. Thus, the EODS method could be developed into a simple, mild, and environmentally benign method for deep desulfurization.

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Experimental

Preparation of ionic liquids

[bmim]Cl/$FeCl_3$ (1 : 1) and [omim]Cl/$FeCl_3$ (1 : 1) were prepared according to the published procedure.[41] $Et_3NHCl/FeCl_3$ (1 : 1) was synthesized using the method mentioned in the literature.[42]

Mutual solubility of ionic liquid and *n*-octane

The mutual solubility is considered as an important factor in choosing an IL as extractant because the noticeable solubility of imidazole-based ILs in the model oil may contaminate the fuel and would lead to possible NO_x pollution during the process to remove the SO_x pollution. Using high performance liquid chromatography (HPLC) (Agilent Technologies 1200 series equipped with a UV-Vis detector under 237 nm wavelength; column, C-18; mobile phase, methanol/water = 80/20; flow rate, 1.0 mL min^{-1}) to analyze the IL-saturated *n*-octane sample, no IL peak was found, which can be a proof that [bmim]Cl/$FeCl_3$ has negligible solubility in model oil. The solubility of the model oil in IL was measured using a gravimetric method by weighing the mass difference of a given amount of IL saturated with *n*-octane before and after solvent removal by vaporization at high temperature. The solubility of *n*-octane in [bmim]Cl/$FeCl_3$ was 0.636 wt%.

Preparation of model oil

Dibenzothiophene (1.466 g) was dissolved in *n*-octane (250 mL). The sulfur content of the model oil containing DBT was 1000 ppm. With the same method, the sulfur content of model oil containing benzothiophene (BT) and 4,6-dimethyldibenzothiophene (4,6-DMDBT) was 1000 ppm and 500 ppm, respectively. Commercial diesel (0#, with sulfur content 1078 ppm) was used as actual diesel.

EDS and EODS

The experiments of extractive desulfurization (EDS) were conducted in a home-made 40 mL two-necked flask. The mixture including 2.6 g of model oil and the required amount of IL [*m*(model oil)/*m*(IL) = 3] was stirred at 30 °C in a water bath. The experiments of extraction coupled with oxidative desulfurization (EODS) were also carried out in a home-made 40 mL two-necked flask. The mixture containing 2.6 g of model oil, 0.033 mL of 30 wt% H_2O_2 [$n(S)/n(H_2O_2) = 1 : 3$], and the required amount of IL [*m*(model oil)/*m*(IL) = 3 : 1] was stirred vigorously at 30 °C in a water bath for 10 minutes.

Recycling of used [bmim]Cl/$FeCl_3$

After the oxidation desulfurization reaction and removing the model oil phase (upperlayer), the ionic liquid phase (underlayer) was distilled in oil bath at 110 °C until H_2O_2 was removed entirely, and then fresh H_2O_2 and model oil were added in the ionic liquid phase for the next reaction.

Sulfur content analysis

The sulfur content in the model oil was tested by gas chromatography (GC). The conversion of DBT in the model oil was used to calculate the removal of sulfur compounds. After the reaction finished, the upper phase (model oil) was withdrawn at room temperature and analyzed by GC using an internal standard method (nitrobenzene) coupled with a flame ionization detector (GC-FID). A 15 m × 0.32 mm inner diameter × 1.0 μm film thickness SE-54 capillary column was used for separation. The total sulfur concentration of actual diesel was analyzed by microcoulometry (detection limit: 0.5 μg ml^{-1}).

Acknowledgements

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Catalytic aerobic oxidation of allylic alcohols to carbonyl compounds under mild conditions

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A new catalytic aerobic oxidation of alcohols to aldehydes under green conditions was developed (room temperature and pressure, water solution, open vials). The water-soluble platinum(II) tetrasulfophthalocyanine (PtPcS) catalyst showed the best selectivity for carbonyl derivatives, and in particular for α,β-unsaturated alcohols; the reactions are slow.

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Introduction

Metal catalyzed 'green' oxidation of organics has been proposed for the synthesis of several classes of chemicals.[1] Among these, the development of new air-based catalysts that can selectively oxidize alcohols to carbonyl compounds are of both considerable general interest and potential utility. For example, with primary alcohols, it is extremely important to selectively obtain aldehydes, whereas carboxylic acids are the usual dominant reaction products. The conventional industry/laboratory oxidants are often metal-based compounds, *e.g.* Cr(VI), RuO_4, $KMnO_4$, which are used in stoichiometric amounts, thus producing large amounts of toxic end-products.[2] Furthermore, the reactions are performed in environmentally unfriendly solvents, and typically in hydrocarbons, alcohols or chlorinated derivatives. Even the well described catalyst TEMPO requires transition metals,[3] hypochlorite[4] or nitrite salts that can be associated to both an organic (1,3-dibromo-5,5-dimethylhydantoin)[5] or an inorganic (hydrochloric acid)[6] co-catalyst. Apart from these TEMPO catalytic systems, only a few examples of transition-metal-free catalysts for alcohol oxidation can be found in the literature. Biocatalytic methods are promising for their green credentials and their high level of sustainability, although at present they are still too expensive for industrial applications.[7,8]

Bearing in mind these concepts, there is a definite need for catalytic oxidation systems that can use oxygen or hydrogen peroxide as oxidants and that have an acceptable selectivity for carbonyl derivatives also in the presence of other functional groups. In recent years, many catalytic methods for aerobic alcohol oxidation have been reported, with a large choice of transition metal catalysts (*e.g.* Fe, Co, Cu, Au, Ru, Pd, Os).[9] The palladium-based catalysts are of particular interest;[10] among these there is a very simple $Pd(OAc)_2$/pyridine catalytic system that was first reported by Uemura and colleagues.[11] Here, in the presence of molecular sieves, this system effectively catalyzes the aerobic oxidation of primary and secondary alcohols to carbonyl derivatives, in toluene. A few years later, Sigman and co-workers[12] reported on novel Pd-N-heterocyclic carbene catalysts for the oxidation of benzylic, aliphatic and allylic alcohols to carbonyl derivatives, again in toluene, and under both air and oxygen atmospheres. The catalytic system proposed by Sheldon,[13] which consists of water-soluble Pd(II)-phenanthroline or neocuproine derivatives, is also very effective for the oxidation of a wide range of alcohols at a very low catalyst/substrate ratio. In contrast to palladium, platinum has been poorly investigated in homogeneous catalysis, even though the literature is rich in examples of (supported) platinum as a heterogeneous catalyst for alcohol oxidation.[14]

We have used here the water-soluble platinum tetrasulfophthalocyanine (PtPcS) catalyst (Fig. 1), and also, for comparison purposes, the corresponding palladium derivative, whose characterization and catalytic properties towards shikimic acid have been described in preliminary studies.[15] Metal tetrasulfophthalocyanines (MPcS) have been successfully used both by us and by other groups to activate hydrogen peroxide: RuPcS and FePcS can promote deep oxidation of chlorophenols[16] and desulfurization of benzothiophene derivatives.[17]

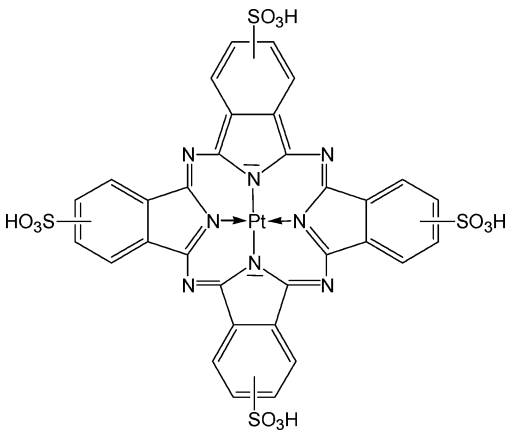

Fig. 1 Platinum tetrasulfophthalocyanine.

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Results

In the present study, we have investigated the aerobic oxidation of alcohols in water in the presence of catalytic amounts of the tetrasulfophthalocyanine derivatives MPcS (M = Pd, Pt). Although very slow (up to *ca.* 60% conversion within 14 days), the reactions were conducted under mild conditions (room temperature and pressure); in terms of conversion, neat oxygen led to a marked increase in the conversion, even if it was strongly dependent upon the substrate. Several aliphatic, allylic, benzylic and propargylic alcohols were tested.

For the palladium chemistry, contrary to the general high reactivities of palladium catalysts reported for alcohols for the production of carbonyl derivatives with PdPcS, both reactivity and selectivity were low; only in the presence of cyclohexanol and shikimic acid did we observed small amounts of oxidation products, which always remained <4%.

In the presence of PtPcS, the two propargylic alcohols and methallyl alcohol (Table 1) were totally insensitive to the catalytic system for the times investigated (14 days), whereas other primary allylic alcohols behaved differently. The most interesting results were obtained with *trans*-cinnamyl alcohol, where conversions after 14 days reached *ca.* 45%, with almost 100% selectivity in the corresponding aldehyde. In the case of substrates with smaller molecular weights (Table 1, entries 5–10), the mass balance was not completely satisfactory, probably because of evaporation (during the prolonged reaction times that were necessary) of both the carbonyl derivative and the starting material. Indeed, when present, aldehydes or ketones were also detected inside a charcoal trap placed at the top of the vial (keeping a fresh, very slow, air current inside the solution). Secondary alcohols, both allylic and non-allylic, showed similar reactivities (Table 1), leading to the corresponding ketones.

We carried out optimization of the effects of temperature on the rate of this oxidation reaction. However, both raising (60 °C) and lowering (5 °C) the temperature had no noticeable effects on the reaction rates. This can be reasonably attributed to the expected lower solubility of oxygen at higher temperatures, which negatively affects the observed rate; in contrast, at lower temperatures, the reaction becomes intrinsically slower. The only possibility to speed up the reaction rate was to conduct some experiments at higher pressures and temperatures. At 60 °C and 50 atm of air, both cinnamyl alcohol and 2-cyclohexen-1-ol oxidation showed higher conversion after 14 days, at up to 90%, but with lower selectivities (cinnamic acid was also produced).

Another important finding for consideration here is the oxygen concentration. In the present study, after 14 days there was an enhancement of conversion that ranged from 50% to 90% when the reactions were conducted in neat oxygen (at 1 atm) (see, for example, the data for 2-cyclohexen-1-ol in Fig. 2). The conversion data are not, however, in agreement with the direct implication of oxygen in the rate-determining step, as has been seen for aerobic oxidation with palladium complexes.[18] Indeed, experiments at high air pressure (20 atm and 50 atm) showed comparable conversions between the neat oxygen and high pressure experiments. With cinnamyl alcohol, there was an increase in the reaction rate between 0.2 atm and 1 atm, while

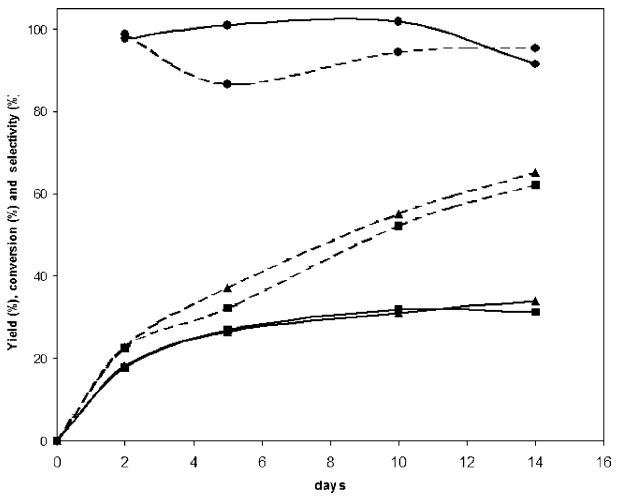

Fig. 2 Time course of catalyzed oxidation of 20 mM solution of 2-cyclohexen-1-ol by 1 mM PtPcS in the open air (continuous lines) and in 100% oxygen (hatched lines). Yield (squares), conversion (triangles) and 2-cyclohexen-1-one selectivity (circles). *N.B.* the values given are the sums of the mmol inside the water solution and the charcoal trap.

Table 1 Conversion and selectivity of 13 alcohols when treated in the open air and in a 100% oxygen atmosphere in the presence of PtPcS, for 14 days of reaction[a]

		Open air			100% oxygen		
Entry	Alcohol[b]	Conversion (%)	Carbonyl select. (%)	Acid select. (%)	Conversion (%)	Carbonyl select. (%)	Acid select. (%)
1	Methallylic alcohol	0	—	—	0	—	—
2	2-Cyclohexen-1-ol	35	92	—	65	95	—
3	Cinnamyl alcohol	25	100	0	45	95	0
4	Shikimic acid[c]	31	95[b]	—	55	95[b]	—
5	*cis*-2-Penten-1-ol	52	42	58	60	35	65
6	*trans*-2-Penten-1-ol	55	35	65	62	30	70
7	3-Methyl-2-buten-1-ol	55	33	67	65	28	72
8	4-Penten-1-ol	58	30	70	65	25	75
9	4-Penten-2-ol	18	85	—	25	72	—
10	Cyclohexanol	32	100	—	40	100	—
11	Benzylic alcohol	40	95	0	45	95	0
12	Propargylic alcohol	0	—	—	0	—	—
13	Phenylpropargilic alc.	0	—	—	0	—	—

[a] All substrates, in the absence of PtPcS, showed reactivities always <3%. [b] For concentrations, see Experimental section. [c] See ref. 15.

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at higher pressures the reaction became totally insensitive to the oxygen concentration (Fig. 3).

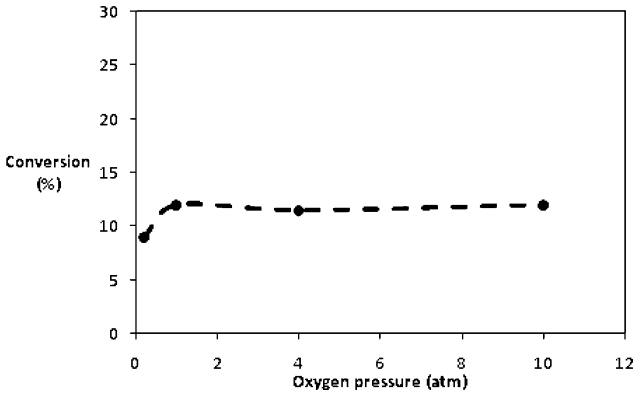


Fig. 3 Conversion of 20 mM cinnamyl alcohol in water solution in the presence of 1 mM PtPcS, *versus* the oxygen partial pressure: after 3 days at room temperature.

The reaction was carried out by default in non-buffered solutions (pH 6.5–7.0): under alkaline conditions (pH 12) no reaction took place, and also at a buffered pH 9 only negligible conversion was seen, although with the same product distribution.

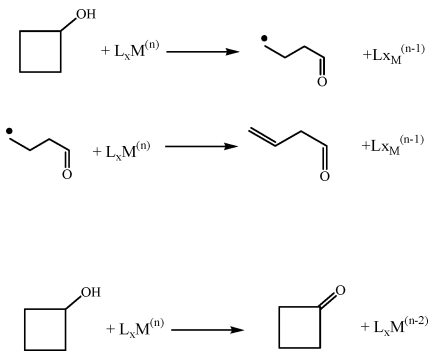
During the present aerobic reactions, the macrocyclic ring of the catalyst did not undergo degradation, as shown by the lack of change in the visible spectrum of PtPcS. The same conclusion was supported by electrospray ionisation mass spectrometry (ESI-MS). This observation is of particular importance, since in previously reported catalytic investigations that have used hydrogen peroxide or potassium monopersulfate as oxidants, sharp changes in the visible spectra of a number of the MPcS catalysts were seen, indicating a modification of the phthalocyanine ring. This was interpreted as ring opening, which was akin to the well-known verdoheme/biliverdin pathway of porphyrins.[19] Finally, whereas in quite a number of reactions that have used platinum complexes as catalyst, the formation of zero-valent metal was mentioned, which precipitated as black metal,[13a] in our case, we never saw the formation of black metal, again supporting the integrity of the macrocycle during the catalytic cycle.

To rationalize these data, we performed some additional studies that were aimed at providing an idea of the mechanisms involved. The relatively low conversion of some substrates posed the question whether the reaction is catalytic or not, also because we used a catalyst to substrate ratio of 5%. Table 2 provides some details of different concentrations of PtPcS for 2-cyclohexen-1-ol and cinnamyl alcohol. In the case of 2-cyclohexen-1-ol in the presence of 5 mM PtPcS, there was conversion of 100%, with a selectivity of close to 95% (considering the evaporated fraction inside the charcoal trap) after 16 days. Although the turn-over frequency (TOF) was lower at higher concentrations of the complex, our interpretation is that the anomalous behaviour of the TOF trend can be explained by extended stacking. It should be noted that higher concentrations of the complex led to a reduction in the relative concentrations of the monomeric form, and consequently of the active species, leading to a lowering of the TOF number. Therefore, we can conclude that the reaction is showing catalytic behaviour.

Table 2 TOF numbers at different concentrations of catalyst (PtPcS) and after 13 days of reaction

Substrate (20 mM)	Conc. PtPcS (mM)	% Conversion	TOF (d^{-1})
trans-Cinnamyl alcohol	1.0	25	0.38
	2.5	43	0.26
	5.0	65	0.20
2-Cyclohexen-1-ol	1.0	35	0.54
	2.5	63	0.39
	5.0	90	0.28

Another question that needed to be resolved was whether or not a radical mechanism was involved. No incorporation of deuterium inside the oxidation products was seen when the reactions were performed in D_2O. Further mechanistic proof was obtained by adding a common radical scavenger, 2-propanol (200 mM), to the reaction mixture: the result was a complete inertial participation, since with PdPcS the reaction did not proceed, while in the presence of PtPcS we saw the same reaction pattern. Finally, the radical clock experiment was carried out in the presence of cyclobutanol. Again, in the presence of PtPcS, only cyclobutanone was seen (see Scheme 1), providing strong evidence for the two-electron pathway (conversion of about 30%, after 3.5 days).[15,20]



Scheme 1 Oxidation of cyclobutanol leading to cyclobutanone or an open-chain unsaturated aldehyde, depending on the mechanism involved.

Discussion

The use of platinum catalysts in a homogeneous liquid phase has not been very common in the past, and probably only with the Baeyer Villiger reaction has this been investigated to any extent.[21] Also, for homogeneous alcohol oxidation, there are only reports of the closely-related, metal-like palladium.[12b,13c] The most accepted mechanisms with palladium in a homogeneous liquid phase can be assumed to be β-hydrogen abstraction, or alternatively β-hydride elimination. If the similarity we proposed between palladium and platinum is correct, the observed lack of reactivity at basic pH makes the β-hydrogen abstraction less probable in our catalytic system.

Kinetic isotope effects were evaluated for cinnamyl alcohol labelled with one (1.8, intramolecular) or two (2.1, intermolecular) deuterium atoms in allylic positions, and for 1-monodeuterated

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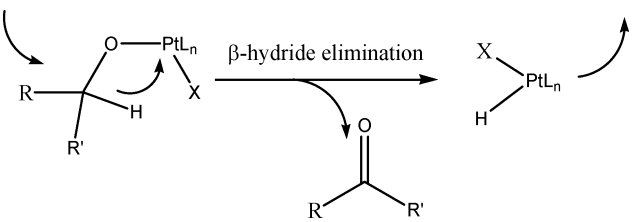
cyclohexanol (1.7, intramolecular), all at room temperature. These indicated a rate-determining step that involved the breaking of the C–H bond, with the occurrence of this concomitant transfer of a hydride unity (for analogous interpretations, see ref. 13a; to better interpret the intramolecular kinetic isotope effect, it would be necessary to carry out further studies at different temperatures, which, unfortunately, was not possible due to the above-mentioned weak dependence of the reaction upon the temperature). This mechanism was proposed by Szuromi *et al.*,[22] although in another typology of reaction (oxidation of an alkene), for which a platinum oxo-complex was isolated.

A zero valent metal in a colloidal form could explain the whole mechanism, as recently observed by Maayan and Neumann for secondary alcohols,[23] although in the presence of a stabilizing agent to obtain active nanoparticles. The alternative hypothesis points to a resting state of the catalyst compatible to the initial phthalocyanine molecule, and a platinum(IV) oxo derivative as the oxidizing form (see Scheme 2). It appears highly likely that, while several examples of M(IV) oxo complexes are reported in the literature for M=Pt, this is not the case for M=Pd,[24] with the latter, significantly, not being active in the present aerobic reactions.



Scheme 2 Part of the catalytic cycle showing the hypothesized β-hydride transfer.

Conclusions

Here, we have studied a new selective catalytic aerobic oxidation of alcohols to carbonyl derivatives. The reaction is worth noting since the experimental conditions are green: room pressure and temperature, water solution, and air as oxidant. Also, the problem of residual catalyst at the end of the reaction can be easily resolved by adding selective supports that act as sorbents for polar metal complex derivatives *i.e.* amberlite or other analogous inert materials.[25] The reaction times are, however, quite high and definitely need to be improved. For the reaction mechanism, our data are not sufficient to discriminate between the 0 valent metal species and a platinum oxo derivative. A rate-determining step involving a β-hydride transfer where oxygen is provided sequentially to re-oxidize the catalyst in a new active species is fully compatible with our experimental data.

Experimental

Chemicals were purchased from Aldrich, except shikimic acid, which was purchased from Dayang Chemicals Co. Ltd (China). Mono- and bis-deuterated cinnamyl alcohols (in allylic position) and 1-deutero-2-cyclohexen-1-ol were synthesized by reduction of *trans*-cinnamic acid, *trans*-cinnamaldehyde and 2-cyclohexen-1-one with $LiAlD_4$. PtPcS and PdPcS were prepared by template synthesis starting from K_2PtCl_4 (or $PdCl_2$), 4-sulfopthalic acid and urea, following earlier reported general procedures for the synthesis of metal-sulfophthalocyanines.[26] Water was used from a Milli Q apparatus.

In a 10 mL open tube containing 4 mL of 25 mM water solution of alcohol, 1 mL of water solution of 5 mM PtPcS (or PdPcS) was added, and left under stirring for the time necessary for the experiment. One mL aliquots were sampled for a direct NMR investigations. Experiments at different oxygen pressures were conducted in the presence of balloons containing neat oxygen and in an autoclave apparatus that supported an air pressure up to 100 atm.

The NMR measurements were performed with a Bruker Avance 300 MHz spectrometer equipped with a 5 mm BBO probe (30–300 MHz). Water suppression was determined by a presaturation sequence using a composite pulse (zgcppr; Bruker sequence). A co-axial capillary tube containing a 30 mM solution of 3-(trimethylsilyl)propionic-2,2,3,3-tetradeuterium acid, as the sodium salt (TSP) in water (D_2O), was used as the reference and for the lock procedure. The organic analyses were also performed on aliquots withdrawn with a microsyringe from the aqueous reaction mixtures, using an HP 6890 GLC instrument equipped with FID, and a 30 mHP-5 capillary column (0.32 mm i.d.; 0.25 mm film thickness), with the injection port kept at 250 °C (carrier gas: He). The identity of each product was confirmed by comparisons of the fragmentation patterns of the mass spectra obtained with a mass-selective detector (MD 800, Fisons) coupled to a gas chromatograph (GC 8000 series, Fisons) operating at 70 eV in electron ionization mode. The integrity of metal-sulfophthalocyanines at the end of the reactions was controlled by recording the visible spectra, 400–800 nm, 0.2 nm using a 6505 UV/Vis Jenway spectrophotometer and ESI-MS spectra.

The ESI-MS of Pd and PtPcS were performed using a Perkin Elmer Sciex API 150 MCA single-quadrupole mass spectrometer. Acquisitions were carried out in positive ion mode over the mass range of 500–1100 u.

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Further investigation of the biodegradability of imidazolium ionic liquids

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In continuation of our earlier investigations, this report presents a rationale behind the design of a series of imidazolium based ionic liquids and their biodegradation using the CO_2 headspace test (ISO 14593 method, OECD 310). The effect on biodegradability of these salts through variation of the *N*-substituted side chains of imidazolium ions was examined further through incorporation of various functional groups and increased alkyl chain lengths. A series of anions containing moieties known to be biodegradable were also incorporated into a number of imidazolium based salts and examined in a similar fashion.

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Introduction

Ionic liquids (ILs) initially attracted the attention of chemists because of the advantages they offer in electrochemistry, separation processes and heterogeneous catalysis.[1] The properties of ILs, such as good chemical and thermal stability, lack of vapor pressure and good solubility for a range of organic, inorganic, organometallic compounds and even gases, have presented several avenues of interest for chemists to explore.[2] Their architectural flexibility has broadened the scope of their applications to include their use in materials design,[3] immobilized phases,[4] catalyst anchoring,[5] functionalized phases,[6] supported synthesis,[7] to name only a few. ILs are now among chemists' first picks as unconventional reaction media, not only because of their blend of unique, tunable properties, but also because of their commercial availability and ease of synthesis and handling. Although the aforementioned solvent attributes have helped chemists to develop many green, operationally safer processes, their impact on the environment has been a topic of discussion.[8] In spite of the recent debates on their volatility,[9] it is thought that ILs would not pose any threat to air quality under operational conditions of typical chemical processes. Their impact on water and soil quality is certainly a concern to environmental chemists, mainly because these effects have not been evaluated to any great extent and nor are they predictable.[10] Several reviews and reports expressing the importance of conscientious design of chemicals have appeared over the last few years.[11] For new chemicals, such as ILs, it is important to evaluate their ecological impact while assessing them for other properties applicable for their end use.[12]

Many research groups, including ours, have considered the environmental effects of ILs by measuring their toxicity.[13] However, it is important to note that toxicity and biodegradability need not always be mutually exclusive.[11b] A toxic substance with good biodegradability is not necessarily as much of a concern as a non-toxic, recalcitrant substance. This is because the latter may persist and bio-accumulate exerting long term chronic effects. Biodegradation is a natural process involving a collective effort of different microorganisms breaking down the complex organic molecules into biomass and/or inorganic compounds, such as carbon dioxide and water. Hence, a biodegradable, but toxic, substance may exert an acute effect upon exposure to it but will be rendered non-toxic upon its biodegradation into biomass and/or inorganic compounds as mentioned above. Once released in water or soil, both the environmental and structural factors influence the mineralization of a substance. The biodegradation data obtained for any compound greatly depends on both the physiological and catabolic nature of the microbial population present in the medium.

The CO_2 headspace test (ISO 14593, OECD 310) was used to assess the biodegradability of ILs prepared in this investigation. The methods used for evaluating ready biodegradability are based on measuring non-specific parameters like dissolved organic carbon, biochemical oxygen demand and CO_2 production. The ready biodegradability tests are performed under stringent conditions of low microbial density and high concentrations of the test substance (as the only source of carbon for the microorganisms). A substance attaining the pass level in these tests at a certain rate after termination of the lag phase may be classified as "readily biodegradable". The pass level depends on the analytical parameter measured. A substance passes the CO_2 headspace test (OECD 310) when at least 60% of the theoretical carbon dioxide is liberated within the first 28 days. A positive result in a test for ready biodegradability can be considered as indicative of rapid and ultimate degradation in most environments including waste water treatment plants.

Our earlier work on biodegradable ILs was focused on investigating the environmental impact of imidazolium based ILs.[14] Although the conventional and most commonly used imidazolium based ILs are recalcitrant, higher biodegradability can be attained by suitably modifying the structure of the cation and anion. Integrating the ester side chain derived from C_5 alcohol and C_2 acid on the imidazolium cation helped to

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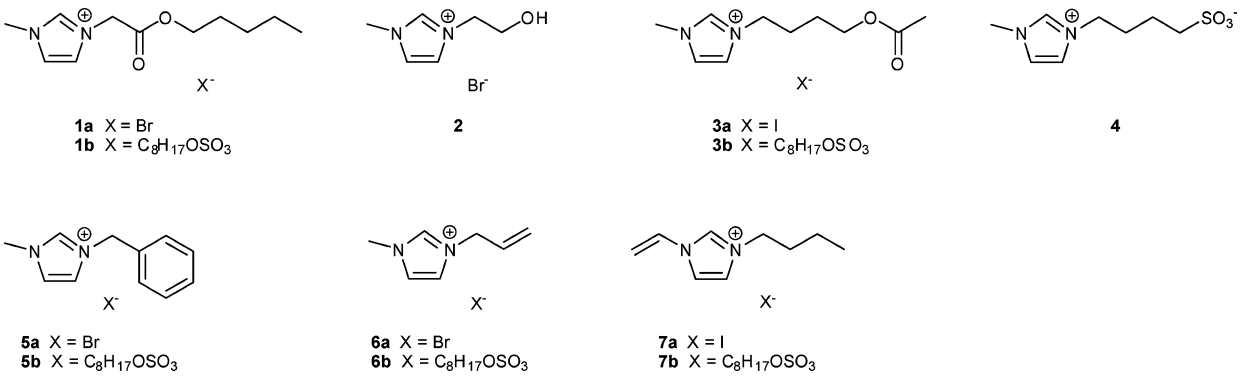

1a X = Br
1b X = $C_8H_{17}OSO_3$

2

3a X = I
3b X = $C_8H_{17}OSO_3$

4

5a X = Br
5b X = $C_8H_{17}OSO_3$

6a X = Br
6b X = $C_8H_{17}OSO_3$

7a X = I
7b X = $C_8H_{17}OSO_3$

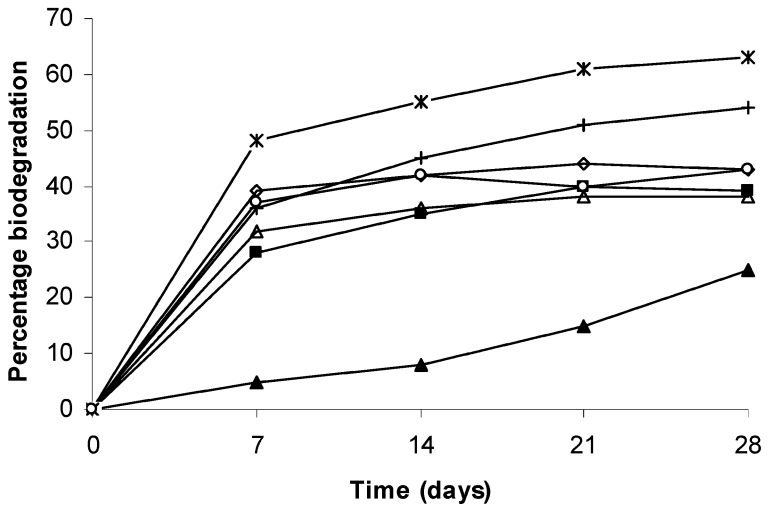

Fig. 1 Effect of cation modifications on percentage biodegradation, **1a** (■), **1b** (✳), **3a** (▲), **3b** (+), **5b** (△), **6b** (◇),**7b** (○). Compounds **2**, **4**, **5a**, **6a** and **7a** underwent <5% biodegradation (data not plotted).

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achieve higher biodegradation values.[14a,c] The ester group was chosen because esterases are not only the most common enzymes but are also known to offer broad substrate specificity. The studies carried out on the pyridinium based ILs have indicated that perhaps the presence of an ester group is necessary to obtain acceptable levels of biodegradability; however, unlike the imidazolium ring,[15] the pyridinium core is not refractory.[15,16] In the case of the imidazolium based salts/ILs, the C_8 based alkyl sulfate anion has been a preferred choice, since it has the optimal alkyl chain length to achieve high biodegradability while retaining good solvent properties.[14a,c]

Results and discussion

We noted that although imidazolium based ILs have been modified in various ways to enhance their biodegradability, many structural features that could potentially enhance the biodegradability of this class of ILs have yet to be explored, particularly with regards to modification of the anion. Hence, we aimed to synthesize and test a heretofore uninvestigated series of the imidazolium based ILs/salts for biodegradability. Some simple targets that are already known in the literature, or those that can be easily synthesized starting with commercially known starting materials, were of particular interest. In selecting the targets, we abided by the "rules of thumb" for biodegradability as described in a review article by Boethling *et al.*[11b] Some materials and anions derived from compounds with known toxicological profiles were also subjected to the biodegradation test. 3-Methyl-1-(pentoxycarbonylmethyl)imidazolium octylsulfate (**1b**), which was previously shown to meet the requirement for classification as 'readily biodegradable' as determined by the CO_2 headspace test,[14c] was included for comparative purposes in this study.

Although the biodegradability of the dialkylimidazolium ILs with ester containing side chains have been investigated, in all cases this side chain was derived from an α-halo ester which afforded the corresponding alkyloxycarbonylmethyl imidazolium salt.[14] The biodegradability of imidazolium ILs that bear either an alcohol functionality on the alkyl side chain or on the esters derived from them (*i.e.* with the ester functionality reversed) has yet to be examined. The presence of oxygen in the structure increases the tendency of a substance to metabolize. The quaternary salt **2** contains a primary alcohol group on the alkyl side chain. Both the quaternary iodide **3a** and the quaternary bromide **2** were conveniently derived from commercially available starting materials. Whereas **2** did not show significant biodegradation, **3a** showed reasonably good

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tendencies to biodegrade under the test conditions. Compound **3a** showed biodegradation at 25% after the standard 28 day incubation period (Fig. 1). Notably, the cation in both **3a** and **3b** can be regarded as a derivative of C_4 alcohol with a C_2 acid, and hence, possesses skeletal similarity to the cation of imidazolium based biodegradable ILs investigated earlier by our group.[14a] The replacement of the iodide in **3a** with the octyl sulfate anion, as in **3b**, increased the biodegradation to 54%. This is relatively close to the acceptable 60% level for a substance to be classified as readily biodegradable by this test.

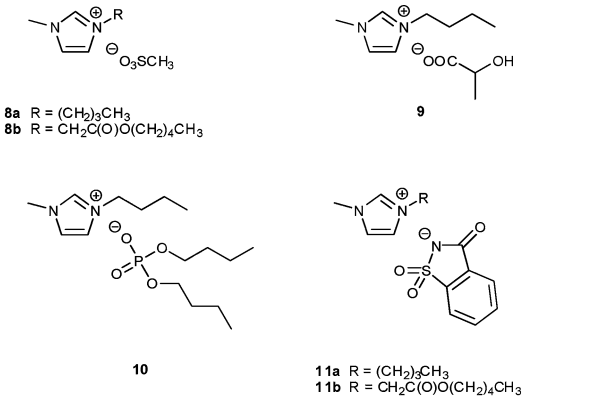
The zwitterionic imidazolium compound **4**, which was readily obtained by the *N*-alkylation of 1-methylimidazole with 1,4-butane sultone, did not show appreciable biodegradation. Compound **4** is a precursor for the synthesis of sulfonic acid containing imidazolium based task specific ILs. Whereas we have previously shown that the presence of alkyl sulfate anions paired with *N*,*N*-disubstituted imidazolium ions enhanced biodegradability,[14] it is evident that incorporation of the anionic sulfonate group on the alkyl side chain of the imidazolium cation does not help improve the biodegradation.

It is known that the incorporation of the phenyl ring in some molecules helps to improve their biodegradability,[11b] mainly because the phenyl ring is prone to attack by the oxygenases that oxidize the ring facilitating other metabolic processes that lead to mineralization. However, the quaternization of 1-methylimidazole with benzyl bromide yielded the quaternary bromide **5a** which showed <5% biodegradability after 28 days. The corresponding octyl sulfate salt **5b** showed biodegradation at 38%, which can be attributed to the anion alone. The poor biodegradability values obtained for **5a** does not necessarily mean that the phenyl group on the imidazolium salts cannot act as an oxygen handle, as the position of the phenyl group influences the ability of a compound to mineralize.[11b]

Other attempts to improve biodegradation involved the use of unsaturated groups that might increase the chances of metabolism of the imidazolium cation by redox enzymes. Unsaturated synthetic base fluids are known to undergo microbial biodegradation much faster than their corresponding saturated counterparts under anaerobic conditions.[11b,17] Thus, the allyl and vinyl group were incorporated onto the imidazolium cation (**6** and **7**, respectively). It was rationalized that side chains that are susceptible to oxidation at the carbon attached to the imidazolium nitrogen would afford intermediates which are unstable and not refractory in their nature. Both **6a** and **7a**, however, failed to show good biodegradability, whereas their octyl sulfate counterparts **6b** and **7b** showed biodegradation at 43% (Fig. 1).

We also endeavored to investigate the inclusion of potentially biodegradable anions such as alkylsulfites, lactates, dialkylphosphates, and the anion formed from saccharin, into imidazolium based ILs. ILs containing methylsulfite anions were prepared using a method reported in the literature.[18] Whereas **8a** containing the common dialkylimidazolium cation, 1-butyl-3-methylimidazolium [bmim], showed only 8% biodegradability, the replacement of this cation with one containing an ester side chain, **8b**, increased the percentage biodegradation to 35%.

Lactic acid, a fairly inexpensive, commercially available compound that is produced naturally in catabolic processes was an appealing synthon for an anion in these salts. The lactate ion has been previously incorporated as the anion in ILs that are considered to be greener, since they are produced from a material that is biocompatible and biorenewable.[19] Lactate was also of interest because polylactate is a commercial bioplastic that is also used for making biomaterials used for medical implants. Hence, [bmim][lactate] (**9**) was obtained from the reaction involving [bmim][Cl] with a silver salt of lactic acid and showed only 17% biodegradability after 28 days (Fig. 2). Therefore, **9** cannot be considered to be readily biodegradable.



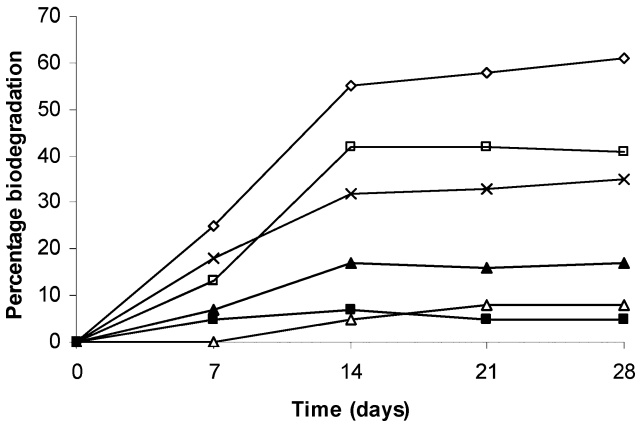


Fig. 2 Effect of anion modifications on percentage biodegradation **8a** (△), **8b** (×), **9** (▲), **10** (■), **11a** (□) and **11b** (◇).

Several natural products such as DNA, ADP, ATP, phospholipids, *etc.* and, perhaps more relevantly, some of the biodegradable detergents, are based on the phosphate group. The most commonly used phosphate containing IL, **10**, was synthesized according to a known protocol,[20] and tested. However, compound **10** also showed poor biodegradability at 5%.

ILs based on saccharin, a well known synthetic non-nutritive sweetener, have been reported in the literature.[21] Saccharin is a common ingredient in food products and therefore has a well established toxicological profile. Its structural features, such as the presence of a phenyl ring with the mixed *N*-acyl-*N*-sulfonyl imide group, makes it an interesting target for evaluation of biodegradability when incorporated into ILs. The [bmim] IL containing the anion produced from saccharin, **11a**, showed biodegradability at 41% (Fig. 2). It is notable that **11a** reached

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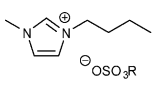
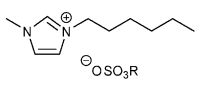
Table 1 Percentage biodegradation of alkyl sulfates based on [bmim] and [hmim] cations after 28 days as determined by the CO_2 headspace test (ISO 14593)



12a R = $(CH_2)_5CH_3$
12b R = $(CH_2)_6CH_3$
12c R = $(CH_2)_7CH_3$
12d R = $(CH_2)_8CH_3$
12e R = $(CH_2)_9CH_3$
12f R = $(CH_2)_{11}CH_3$



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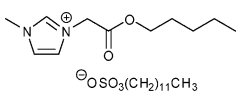
13e R = $(CH_2)_9CH_3$
13f R = $(CH_2)_{11}CH_3$



14

Entry	No.	Compound[a]	Biodegradation (%)
1	**12a**	[bmim] [$C_6H_{13}OSO_3$]	34
2	**12b**	[bmim] [$C_7H_{15}OSO_3$]	36
3	**12c**	[bmim] [$C_8H_{17}OSO_3$]	40
4	**12d**	[bmim] [$C_9H_{19}OSO_3$]	47
5	**12e**	[bmim] [$C_{10}H_{21}OSO_3$]	54
6	**12f**	[bmim] [$C_{12}H_{25}OSO_3$]	58
7	**13a**	[hmim] [$C_6H_{13}OSO_3$]	30
8	**13b**	[hmim] [$C_7H_{15}OSO_3$]	33
9	**13c**	[hmim] [$C_8H_{17}OSO_3$]	38
10	**13d**	[hmim] [$C_9H_{19}OSO_3$]	36
11	**13e**	[hmim] [$C_{10}H_{21}OSO_3$]	44
12	**13f**	[hmim] [$C_{12}H_{25}OSO_3$]	49
13	**14**	['ester'-mim] [$C_{12}H_{25}OSO_3$]	72

[a] IL concentration = 40 mg L^{-1}.

its highest level of biodegradability within 14 days of incubation, which has been associated with very high rates of biodegradation of the saccharin anion. The overall biodegradability of the saccharin based IL can be enhanced by incorporating the ester group on the alkyl side chain of the imidazolium ion as in **11b**, which showed biodegradability at 61%. Thus, **11b** containing both an ester linkage in the cation and the saccharin derived anion can be classified as 'readily biodegradable'. The cation modifications thus appear to be necessary to increase the overall biodegradability of saccharin containing ILs to the level where they can be deemed readily biodegradable.

Our previous attempts to search for a biodegradable IL disclosed that the alkyl sulfates are very good anion candidates.[14c,16] However, since the overall biodegradability of ILs appears to be a cumulative contribution from both the cation and the anion, higher biodegradability values are reached in the case of imidazolium based ILs by incorporating the ester group on the side chain in addition to the presence of an alkylsulfate ion.[14a,c] Unfortunately, the ester group on the cation introduces chemical instability, which greatly limits the range of applications for the imidazolium based biodegradable ILs. Therefore, we thought it would be worthwhile to do a thorough investigation on alkyl sulfates based on simple 1,3-dialkylimidazoliums, since they contain typically chemically inert cations, and also offer scope of varying alkyl chain lengths on both the cation as well as the anion.

To investigate how the length of alkyl chain on the alkyl sulfate anion influences the biodegradability of the IL, we first synthesized a series of ILs based on the common imidazolium cation [bmim]. The ILs based on [bmim] with hexyl **12a**, heptyl **12b**, octyl **12c**, nonyl **12d**, decyl **12e** and dodecyl **12f** sulfate were synthesized and tested for biodegradability (Table 1). These ILs were synthesized from [bmim][Cl] and alkyl sulfate ammonium salts obtained by reacting alcohols with sulfamic acid according to a reported procedure.[22] As expected, an increase in the alkyl chain length in the alkyl sulfate ion resulted in an increase in biodegradability. Thus, going from hexyl sulfate **12a** to dodecyl sulfate **12f** the biodegradability increased from 34% to 58%, (Table 1, entries 1 and 6). These findings indicate that the biodegradability of the alkyl sulfate based ILs can be significantly enhanced by increasing the chain length of the alkyl sulfate anion. The recalcitrant nature of the simple 1,3-dialkylimidazolium cation, however, seems to limit the biodegradability values for this series of salts.

We anticipated that an increase in the alkyl chain length on the cation of the 1,3-dialkylimidazolium sulfates would enhance their biodegradability due to increased lipophilicity, which would, in turn, lead to faster absorption of compounds through the cell membranes of the microorganisms present in the test. Thus, the alkyl sulfates based on the 1-hexyl-3-methylimidazolium, [hmim], cation and hexyl **13a**, heptyl **13b**, octyl **13c**, nonyl **13d**, decyl **13e** and dodecyl **13f** sulfates were synthesized and tested for biodegradability. When compared with the corresponding [bmim] based counterparts, the [hmim] based alkyl sulfates showed slightly lower values of biodegradability. With an increase in the alkyl chain length from C_6 to C_{12} on the alkyl sulfate anion, the biodegradability increased from 30% to 49% (Table 1, entries 7–12).

We initially thought that the slightly lower biodegradability observed for the [hmim] series (relative to [bmim]) may have been a result of the longer alkyl chain imparting a biocidal effect. Previous studies have found that the antimicrobial activity of dialkylimidazolium ILs is associated with the cation, and that potency increases with alkyl chain length.[23] In order to assess the potential toxicity of the 1,3-dialkylimidazolium cations to the aerobic microorganisms responsible for biodegradation, solutions containing a mixture of the test substance and a reference compound (sodium *n*-dodecyl sulfate, SDS) were tested (Table 2, entries 1–3). Biodegradation percentages for the mixtures of dialkylimidazolium octylsulfates and SDS were calculated based on the theoretical inorganic carbon (IC) yield from the anion and SDS only, as the imidazolium cation was found to undergo negligible mineralisation in this test.[14c] In both cases, similar rates were observed for the mixtures (IL + SDS) and the reference substance SDS alone. This suggests that neither the [bmim] or [hmim] cations are inhibitory to the inoculum at the concentration used in the biodegradation tests. Furthermore,

Table 2 Percentage biodegradation of **12c** and **13c** at different concentrations and in combination with the reference substance SDS

Entry	Compound[a]	Concentration/ mgC L^{-1}	Biodegradation (%)[a]
1	SDS	20	82
2	[bmim][$C_8H_{17}OSO_3$] + SDS	20 + 20	85
3	[hmim][$C_8H_{17}OSO_3$] + SDS	20 + 20	81
4	[bmim][$C_8H_{17}OSO_3$]	6	40
5	[bmim][$C_8H_{17}OSO_3$]	11	45
6	[bmim][$C_8H_{17}OSO_3$]	20	42
7	[hmim][$C_8H_{17}OSO_3$]	6	38
8	[hmim][$C_8H_{17}OSO_3$]	11	40
9	[hmim][$C_8H_{17}OSO_3$]	20	40

[a] Percent biodegradation after 28 days as determined by the CO_2 headspace test (ISO 14593).

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the dialkylimidazolium octylsulfates **12c** and **13c** were each tested at different concentrations (6, 11 and 20 mgC L^{-1}) and were found to undergo similar levels of biodegradation in each case (Table 2, entries 4–6 and 7–9). This result also supports the conclusion that these dialkylimidazolium cations are not inhibiting the inoculum. Alternatively, the slightly higher values of biodegradation for the [bmim] based alkyl sulfates, when compared to the corresponding [hmim] alkyl sulfates, may be attributed to the larger ratio of mineralized organic carbon (alkylsulfate anion) to total organic carbon content (alkylsulfate anion + 1,3-dialkylimidazolium cation).

Conclusion

In conclusion, functionalization of the *N*-substituent of imidazolium based ILs appears to impart a degree of biodegradability. When paired with alkylsulfate ions, biodegradability of these salts increases appreciably. This is consistent with earlier studies performed by our group.[14] Amongst the anions tested, lactate and that derived from saccharin seem to possess good mineralization abilities. The saccharin based ILs offer good biodegradability values with very high initial biodegradation. Their biodegradability values are as high as their octyl sulfate based counterparts, making them a good anion alternative. The biodegradability of the 1,3-disubstituted imidazolium alkyl sulfates increases with an increase in the alkyl chain length on the alkyl sulfate, but decreases slightly with an increase in the alkyl chain length on the imidazolium cation. Accordingly, the percent biodegradation found after 21 days reflects the proportions of the refractory imidazolium cation and the biodegradable alkylsulfate anion in the IL, when expressed as a percentage of the theoretical amount of inorganic carbon (ThIC).

Experimental

^{1}H and ^{13}C NMR spectra of the purified products were recorded in $CDCl_3$ (Cambridge Isotope Laboratories Inc., 99.8% D) or DMSO-d_6 (Cambridge Isotope Laboratories Inc., 99.9% D) on a Bruker Avance DPX 300 spectrometer at 300 and 75.4 MHz, respectively. Low resolution mass spectra using electrospray ionisation (MS-ESI) were obtained using a Micromass Platform II instrument.

Synthesis of ammonium octylsulfate[22]

1-Octanol (3.00 g, 15.7 mL, 100 mmol) and sulfamic acid (9.70 g, 100 mmol) were heated at 110 °C for 24 h in a moisture guarded assembly. The reaction mixture was allowed to cool down to room temperature, when it solidified. The fused waxy mass was treated with hexane (500 mL) and stirred vigorously for 1 h after mechanically crushing the lumpy solid. The filtration of hexanes yielded the crude product which was washed with hexane (3 × 50 mL) and dried under reduced pressure. The crude product was stirred with dichloromethane (200 mL) for 1 h, followed by precipitation with hexane (800 mL) to yield the pure product. The product was filtered, washed with hexane (3 × 50 mL) and dried under reduced pressure. Yield 69%. ^{1}H NMR (DMSO-d_6): δ 0.83–0.87 (t, J = 6.6 Hz, 3H), 1.24 (br s, 10H), 1.44–1.51 (m, 2H), 3.67–3.71 (t, J = 6.6 Hz, 2H), 6.93–7.26 (t, J = 49.2 Hz, 4H). ^{13}C NMR (DMSO-d_6): δ 14.0, 22.2, 25.6, 28.8, 28.9, 29.2, 31.4, 66.0. MS (ESI, 20 eV): m/z 209.3 $[C_8H_{17}OSO_3]^-$.

General method for the synthesis of the dialkylimidazolium halides 1a, 5a and 6a

Alkyl halide (40.0 mmol) was added to the solution of 1-alkylimidazole (33.3 mmol) in toluene (20 mL) at 0 °C. The reaction mixture was maintained under a nitrogen atmosphere. The stirring was continued at room temperature for 1 h under nitrogen and then heated at 70 °C for 24 h. The work-up and isolation procedures were the same as with method 1 above. These quaternary salts/ILs, being hygroscopic, were handled under nitrogen at each stage of synthesis and purification.

1-Methyl-3-(pentoxycarbonylmethyl)imidazolium bromide (1a)[14c]. Yield 97%. ^{1}H NMR (DMSO-d_6): δ 0.86–0.90 (t, J = 6.9 Hz, 3H), 1.26–1.34 (m, 4H), 1.57–1.66 (m, 2H), 3.92 (s, 3H), 4.13–4.18 (t, J = 6.6 Hz, 2H), 5.26 (s, 2H), 7.73–7.74 (m, 2H), 9.11 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.7, 21.6, 27.3, 27.5, 35.9, 49.4, 65.6, 123.3, 123.6, 137.6, 166.8. MS (ESI, 20 eV): m/z 211.1 $[M–Br^-]^+$; MS (ESI, 20 eV): m/z 78.9 and 80.9 $[Br]^-$.

3-Benzyl-1-methylimidazolium bromide (5a). Yield 97%. ^{1}H NMR (DMSO-d_6): δ 3.89 (s, 3H), 5.58 (s, 2H), 7.30–7.34 (m, 3H), 7.51–7.54 (m, 2H), 7.86–7.87 (m, 1H), 7.98–7.99 (m, 1H), 9.66 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 35.9, 51.4, 122.0, 123.7, 128.3, 128.5, 128.7, 134.8, 136.4. MS (ESI, 20 eV): m/z 173.1 $[M–Br^-]^+$; MS (ESI, 20 eV): m/z 78.9 and 80.8 $[Br]^-$.

3-Allyl-1-methylimidazolium bromide (6a). Yield 95%. ^{1}H NMR (DMSO-d_6): δ 3.90 (s, 3H), 4.93–4.95 (d, J = 6.0 Hz, 2H), 5.26–5.27 (m, 1H), 5.30–5.32 (m, 1H), 5.95–6.08 (m, 1H), 7.87 (s, 2H) 9.45–9.46 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 35.8, 50.4, 120.1, 122.1, 123.5, 131.6, 136.4. MS (ESI, 20 eV): m/z 123.1 $[M–Br^-]^+$; MS (ESI, 20 eV): m/z 78.9 and 80.8 $[Br]^-$.

General method for the synthesis of the dialkylimidazolium halides 2, 3a and 7a

A mixture of 1-alkylimidazole (33.3 mmol) and alkyl halide (40.0 mmol) in toluene (20 mL) was heated at 110 °C for 24 h under a nitrogen atmosphere. The completion of reaction was marked by the separation of either dense IL or salt. The product was isolated by decanting toluene to remove any unreacted starting materials and solvent. Subsequently, the IL was washed with diethyl ether (4 × 20 mL) and the ether layer was separated from the IL/salt by decantation. In some cases, the ether washings resulted in the formation of a solid. The solid was purified by dissolving in acetonitrile (10–20 mL) and precipitation with diethyl ether (60–70 mL). In each case, the IL or salt was finally dried under reduced pressure to get rid of the volatile organic compounds.

3-(2-Hydroxyethyl)-1-methylimidazolium bromide (2). Yield 98%. ^{1}H NMR (DMSO-d_6): δ 3.68–3.73 (m, 2H), 3.88 (s, 3H), 4.23–4.26 (t, J = 5.1 Hz, 2H), 5.11–5.14 (t, J = 5.25 Hz, 1H), 7.76–7.79 (m, 2H), 9.24 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 35.8, 51.4, 59.1, 122.5, 123.1, 136.6. MS (ESI, 20 eV): m/z 127.0 $[M–Br^-]^+$; MS (ESI, 100 eV): m/z 78.8 and 80.8 $[Br]^-$.

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3-(4-Acetoxybutyl)-1-methylimidazolium iodide (3a). Yield 96%. ^{1}H NMR (DMSO-d_6): δ 1.48–1.58 (m, 2H), 1.78–1.88 (m, 2H), 1.97 (s, 3H), 3.86 (s, 3H), 3.95–3.99 (t, J = 6.5 Hz, 2H), 4.20–4.25 (t, J = 7.2 Hz, 2H), 7.75 (s, 1H), 7.83–7.84 (m, 1H), 9.22 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 20.8, 24.7, 26.1, 36.0, 48.3, 63.0, 122.1, 123.4, 136.4, 170.3. MS (ESI, 20 eV): m/z 197.1 [M-I$^-$]$^+$; MS (ESI, 70 eV): m/z 127.0 [I]$^-$.

1-Butyl-3-vinylimidazolium iodide (7a). Yield 100%. ^{1}H NMR (DMSO-d_6): δ 0.85–0.90 (t, J = 7.4 Hz, 3H), 1.21–1.33 (m, 2H), 1.76–1.86 (m, 2H), 4.20–4.25 (t, J = 7.4 Hz, 2H), 5.40–5.44 (dd, J = 2.4, 8.7 Hz, 1H), 5.94–6.00 (dd, J = 2.4, 15.6 Hz, 1H), 7.26–7.34 (dd, J = 8.7, 15.6 Hz, 1H), 7.97–7.98 (m, 1H), 8.21–8.23 (m, 1H), 9.60–9.61 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 13.2, 18.6, 30.9, 48.9, 108.7, 119.1, 123.1, 128.6, 135.0. MS (ESI, 20 eV): m/z 151.2 [M–I$^-$]$^+$; MS (ESI, 70 eV): m/z 127.0 [I]$^-$.

General method for the synthesis of the dialkylimidazolium octylsulfates 1b, 3b, 5b, 6b, 7b and 14

The quaternary 1,3-dialkylimidazolium halide (2 mmol) was dissolved in water to obtain a clear solution. The aqueous solution of quaternary halide was treated with the aqueous solution of ammonium octyl sulfate (2 mmol in 10 mL of water) and the resulting mixture was stirred for 10 min. The product was isolated by solvent extraction using dichloromethane (3 × 10 mL). The extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield the required product.

1-Methyl-3-(pentoxycarbonylmethyl)imidazolium octylsulfate (1b).[14c] Yield 98%. ^{1}H NMR (DMSO-d_6): δ 0.84–0.90 (m, 6H), 1.25–1.34 (m, 14H), 1.45–1.50 (m, 2H), 1.60–1.64 (m, 2H), 3.64–3.69 (t, J = 7.4 Hz, 2H), 3.91 (s, 3H), 4.13–4.18 (t, J = 6.6 Hz, 2H), 5.24 (s, 2H), 7.72 (s, 2H), 9.07 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.7, 13.8, 21.6, 22.0, 25.5, 27.3, 27.6, 28.6, 28.7, 29.0, 31.2, 35.9, 49.4, 65.4, 65.7, 123.3, 123.7, 137.7, 166.8. MS (ESI, 20 eV): m/z 211.2 [M–$C_8H_{17}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 209.1 [$C_8H_{17}OSO_3$]$^-$.

3-(4-Acetoxybutyl)-1-methylimidazolium octylsulfate (3b). Yield 94%. ^{1}H NMR (DMSO-d_6): δ 0.84–0.88 (t, J = 6.6 Hz, 3H), 1.25 (br s, 10H), 1.45–1.61 (m, 4H), 1.79–1.89 (m, 2H), 2.00 (s, 3H), 3.64–3.69 (t, J = 6.8 Hz, 2H), 3.85 (s, 3H), 4.00–4.04 (t, J = 6.6 Hz, 2H), 4.17–4.21 (t, J = 7.2 Hz, 2H), 7.70 (s, 1H), 7.76 (s, 1H), 9.09 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.8, 20.6, 22.0, 24.7, 25.5, 26.1, 28.6, 28.7, 29.0, 31.2, 35.7, 48.3, 63.0, 65.4, 122.2, 123.6, 136.6, 170.3. MS (ESI, 20 eV): m/z 197.1 [M-$C_8H_{17}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 209.0 [$C_8H_{17}OSO_3$]$^-$.

3-Benzyl-1-methylimidazolium octylsulfate (5b). Yield 88%. ^{1}H NMR (DMSO-d_6): δ 0.84–0.88 (t, J = 6.2 Hz, 3H), 1.25 (br s, 10H), 1.45–1.50 (m, 2H), 3.65–3.69 (t, J = 6.6 Hz, 2H), 3.86 (s, 3H), 5.42 (s, 2H), 7.39–7.43 (m, 5H), 7.70–7.71 (m, 1H), 7.77–7.78 (m, 1H) 9.20 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.9, 22.0, 25.5, 28.6, 28.7, 29.0, 31.2, 35.8, 51.8, 65.4, 122.3, 124.0, 128.3, 128.7, 128.9, 134.8, 136.7. MS (ESI, 20 eV): m/z 173.2 [M–$C_8H_{17}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 209.1 [$C_8H_{17}OSO_3$]$^-$.

3-Allyl-1-methylimidazolium octylsulfate (6b). Yield 91%. ^{1}H NMR (DMSO-d_6): δ 0.84–0.88 (t, J = 6.3 Hz, 3H), 1.25 (br s, 10H), 1.45–1.50 (m, 2H), 3.64–3.69 (t, J = 6.6 Hz, 2H), 3.86 (s, 3H), 4.83–4.85 (d, J = 6.0 Hz, 2H), 5.27–5.39 (m, 2H), 5.98–6.11 (m, 1H), 7.70–7.72 (m, 2H) 9.09 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.8, 22.0, 25.5, 28.6, 28.7, 29.0, 31.2, 35.7, 50.7, 65.5, 120.1, 122.3, 123.7, 131.7, 136.6. MS (ESI, 20 eV): m/z 123.0 [M–$C_8H_{17}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 209.2 [$C_8H_{17}OSO_3$]$^-$.

1-Butyl-3-vinylimidazolium octylsulfate (7b). Yield 87%. ^{1}H NMR (DMSO-d_6): δ 0.83–0.94 (m, 6H), 1.24–1.36 (m, 12H), 1.43–1.50 (m, 2H), 1.76–1.86 (m, 2H), 3.66–3.70 (t, J = 6.9 Hz, 2H), 4.18–4.23 (t, J = 7.2 Hz, 2H), 5.40–5.44 (dd, J = 2.4, 9.0 Hz, 1H), 5.92–5.98 (dd, J = 2.1, 15.6 Hz, 1H), 7.24–7.32 (dd, J = 8.7, 15.6 Hz, 1H), 7.92–7.93 (m, 1H), 8.18–8.19 (m, 1H), 9.48 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.2, 13.8, 18.7, 22.0, 25.5, 28.6, 28.7, 29.0, 31.0, 31.2, 48.9, 65.5, 108.6, 119.1, 123.2, 128.8, 135.3. MS (ESI, 20 eV): m/z 151.2 [M–$C_8H_{17}OSO_3^-$]$^+$; MS (ESI, 70 eV): m/z 209.1 [$C_8H_{17}OSO_3$]$^-$.

1-Methyl-3-(pentoxycarbonylmethyl)imidazolium dodecylsulfate (14). Yield 95%. ^{1}H NMR (DMSO-d_6): δ 0.83–0.91 (m, 6H), 1.25–1.33 (m, 22H), 1.45–1.49 (m, 2H), 1.60–1.64 (m, 2H), 3.64–3.69 (t, J = 6.8 Hz, 2H), 3.91 (s, 3H), 4.13–4.18 (t, J = 6.6 Hz, 2H), 5.24 (s, 2H), 7.72 (s, 2H), 9.07 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.7, 13.8, 21.6, 22.0, 25.5, 27.3, 27.6, 28.6, 28.7, 28.9, 29.0, 29.0, 31.2, 35.9, 49.4, 65.4, 65.6, 123.3, 123.7, 137.7, 166.8. MS (ESI, 20 eV): m/z 211.1 [M–$C_{12}H_{25}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 265.2 [$C_{12}H_{25}OSO_3$]$^-$.

4-(1-Methylimidazolium-3-yl)butane-1-sulfonate (4). Compound **4** was prepared using literature methodology;[24] yield 100%. ^{1}H NMR (D_2O): 1.80–1.90 (m, 2H), 2.08–2.18 (m, 2H), 3.02–3.07 (t, J = 7.7 Hz, 2H), 4.00 (s, 3H), 4.33–4.38 (t, J = 7.1 Hz, 2H), 7.54–7.55 (m, 1H), 7.60–7.61 (m, 1H), 8.83 (s, 1H). ^{13}C NMR (D_2O): δ 21.1, 28.2, 35.8, 49.0, 50.2, 122.3, 123.8, 136.1. MS (ESI): m/z 219.1 (100%, [$C_8H_{14}N_2O_3S$ + 1]$^+$).

General method for the synthesis of the dialkylimidazolium methanesulfonates 8a–b[18]

The mixture of 1-alkylimidazole (33.3 mmol) and butylmethanesulfonate (36.6 equiv.) was refluxed for 24 h in toluene (20 mL) maintaining an inert atmosphere. The IL separates from the reaction mixture. The toluene layer was separated from the IL by decantation. The separated IL was washed with diethyl ether (3 × 20 mL) followed by drying/removal of volatile components by evaporation under reduced pressure.

3-Butyl-1-methylimidazolium methanesulfonate (8a). Yield 97%. ^{1}H NMR (DMSO-d_6): δ 0.87–0.92 (t, J = 7.4 Hz, 3H), 1.22–1.30 (m, 2H), 1.71–1.81 (m, 2H), 2.31–2.32 (m, 3H), 3.85 (s, 3H), 4.14–4.19 (t, J = 7.1 Hz, 2H), 7.69–7.70 (m, 1H), 7.76–7.77 (m, 1H), 9.14 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.2, 18.7, 31.3, 35.6, 39.7, 48.4, 122.3, 123.6, 136.7. MS (ESI, 20 eV): m/z 139.2 [M–$CH_3SO_3^-$]$^+$; MS (ESI, 20 eV): m/z 95.0 [CH_3SO_3]$^-$.

1-Methyl-3-(2-oxo-2-(pentyloxy)ethyl)imidazolium methanesulfonate (8b). Yield 88%. ^{1}H NMR (DMSO-d_6): δ 0.85–0.93 (m, 6H), 1.22–1.31 (m, 6H), 1.58–1.63 (m, 2H), 1.75–1.80 (m, 2H), 2.30–2.31 (m, 3H), 4.13–4.17 (t, J = 6.6 Hz, 2H), 4.22–4.26 (t, J = 7.1 Hz, 2H), 5.24 (s, 2H), 7.74–7.75 (m, 1H), 7.82–7.83 (s, 1H), 9.16–9.17 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.2, 13.7, 18.7, 21.6, 27.3, 27.6, 31.3, 39.7, 48.7, 49.5, 65.7, 122.1, 123.9,

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137.3, 166.8. MS (ESI, 20 eV): m/z 253.4 $[M–CH_3SO_3^-]^+$; MS (ESI, 20 eV): m/z 95.0 $[CH_3SO_3]^-$.

3-Butyl-1-methylimidazolium lactate (9). To the solution of [bmim][Cl] (2.44 mmol) in water (10 mL) was added the solution of silver lactate (2.93 mmol) in water (10 mL). The reaction mixture was stirred for 10 min at room temperature in the dark. The reaction mixture was freeze dried to yield the IL containing silver chloride. The IL was extracted in chloroform. The extract was filtered to remove the insoluble silver chloride, dried over anhydrous magnesium sulfate and finally evaporated at reduced pressure to yield **9**: yield 91%. ^{1}H NMR (DMSO-d_6): δ 0.87–0.91 (t, J = 7.4 Hz, 3H), 1.04–1.08 (d, J = 5.6 Hz, 3H), 1.22–1.29 (m, 2H), 1.71–1.81 (m, 2H), 3.45–3.52 (q, J = 7.1 Hz, 1H), 3.86 (s, 3H), 4.15–4.20 (t, J = 7.2 Hz, 2H), 7.73–7.74 (m, 1H), 7.80–7.81 (m, 1H), 9.42 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.2, 18.7, 21.5, 31.3, 35.6, 48.4, 67.00, 122.2, 123.6, 136.9, 176.9. MS (ESI, 20 eV): m/z 139.1 $[M–C_3H_5O_3^-]^+$; MS (ESI, 20 eV): m/z 89.1 $[C_3H_5O_3]^-$.

3-Butyl-1-methylimidazolium dibutylphosphate (10)[20]

The mixture of 1-methylimidazole (33.3 mmol) and tributyl phosphate (33.3 mmol) were heated in a moisture guarded assembly at 150 °C for 24 h. The resulting brown viscous liquid was washed with diethyl ether (3 × 20 mL). The resultant IL was first heated at reduced pressure by rotary evaporation followed by removal of all volatile residues under reduced pressure over 24 h under vacuum; yield 92%. ^{1}H NMR ($CDCl_3$): δ 0.84–0.96 (m, 9H), 1.29–1.43 (m, 6H), 1.54–1.63 (m, 4H), 1.79–1.89 (m, 2H), 3.82–3.89 (m, 4H), 4.04 (s, 3H), 4.25–4.30 (t, J = 7.4 Hz, 2H), 7.20–7.21 (m, 1H), 7.31–7.32 (m, 1H), 10.48 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.4, 13.8, 19.1, 19.5, 32.2, 33.0, 33.1, 36.4, 49.6, 64.9, 65.0, 121.7, 123.6, 139.2. MS (ESI, 20 eV): m/z 139.2 $[M–C_8H_{18}O_4P^-]^+$; MS (ESI, 20 eV): m/z 209.2 $[C_8H_{18}O_4P]^-$.

General method for the synthesis of the dialkylimidazolium saccharinates 11a–b

The syntheses of **11a** and **11b** was achieved by slightly modifying the procedure reported earlier, in that a two fold excess of sodium saccharin was used which bypassed the purification step that involves column chromatography.[21] Acetone (100 mL) was added to the mixture of 1,3-dialkylimidazolium chloride (33.3 mmol) and finely crushed saccharin sodium salt (66.6 equiv.). The resultant biphasic mixture was stirred vigorously at room temperature for 24 h. After completion of the metathesis, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure to yield the saccharin based ILs.

3-Butyl-1-methylimidazolium saccharinate (11a). Yield 88%. ^{1}H NMR ($CDCl_3$): δ 0.88–0.93 (t, J = 7.4 Hz, 3H), 1.25–1.40 (m, 2H), 1.79–1.89 (m, 2H), 4.07 (s, 3H), 4.26–4.31 (t, J = 7.4 Hz, 2H), 7.25–7.27 (m, 1H), 7.32–7.33 (m, 1H), 7.55–7.59 (m, 2H), 7.74–7.81 (m, 2H), 10.00 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.3, 19.3, 32.0, 36.4, 49.6, 119.5, 122.1, 123.1, 123.6, 131.3, 132.0, 134.8, 137.2, 144.7, 170.1. MS (ESI, 20 eV): m/z 139.1 $[M–C_7H_4NO_3S^-]^+$; MS (ESI, 20 eV): m/z 182.1 $[C_7H_4NO_3S]^-$.

1-Methyl-3-(pentoxycarbonylmethyl)imidazolium saccharinate (11b). Yield 91%. ^{1}H NMR ($CDCl_3$): δ 0.85–0.91 (t, J = 8.6 Hz, 3H), 1.26–1.33 (m, 4H), 1.58–1.67 (m, 2H), 4.05 (s, 3H), 4.14–4.18 (t, J = 6.9 Hz, 2H), 5.34 (s, 2H), 7.33–7.34 (m, 1H), 7.43–7.45 (m, 1H), 7.55–7.59 (m, 2H), 7.71–7.79 (m, 2H), 9.94 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 14.0, 22.3, 27.9, 28.1, 36.7, 50.2, 67.0, 119.9, 123.2, 123.4, 123.8, 131.7, 132.2, 134.7, 139.2 144.6, 166.6, 170.2. MS (ESI, 20 eV): m/z 211.4 $[M–C_7H_4NO_3S^-]^+$; MS (ESI, 20 eV): m/z 182.3 $[C_7H_4NO_3S]^-$.

General method for the synthesis of dialkylimidazolium alkylsufates (12a–f and 13a–f)[25]

The primary alcohol (26.4 mmol) and sulfamic acid (26.4 mmol) were heated at 85 °C for 24 h in a moisture guarded assembly. The reaction mixture was allowed to cool down to room temperature, during which it might solidify. The reaction mass was extracted into water (100 mL) and [bmim][Cl] or [hmim][Cl] (20.24 mmol) was added to the solution and the mixture stirred for 10 min. The resultant aqueous solution was washed with diethyl ether (3 × 50 mL), and the product was finally extracted into dichloromethane (3 × 50 mL). The dichloromethane extracts were dried over anhydrous $MgSO_4$, and concentrated by evaporation of the solvent under reduced pressure. The resulting oil was stirred at reduced pressure at 60 °C for 4 h.

3-Butyl-1-methylimidazolium hexylsulfate (12a). Yield 37%. ^{1}H NMR ($CDCl_3$): δ 0.64–0.77 (m, 6H), 1.07–1.30 (m, 8H), 1.39–1.50 (m, 2H), 1.62–1.74 (m, 2H), 3.68–3.83 (m, 5H), 4.04–4.10 (t, J = 7.2 Hz, 2H), 7.36–7.38 (m, 1H), 7.44–7.46 (m, 1H), 9.27 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.0, 13.6, 19.0, 22.1, 25.1, 29.1, 31.1, 31.7, 35.9, 49.2, 67.2, 122.1, 123.6, 136.9. MS (ESI, 20 eV): m/z 139.6 $[M–C_6H_{13}OSO_3^-]^+$; MS (ESI, 20 eV): m/z 181.1 $[C_6H_{13}OSO_3]^-$.

3-Butyl-1-methylimidazolium heptylsulfate (12b). Yield 36%. ^{1}H NMR ($CDCl_3$): δ 0.61–0.73 (m, 6H), 0.95–1.23 (m, 10H), 1.32–1.50 (m, 2H), 1.60–1.73 (m, 2H), 3.73–3.81 (m, 5H), 4.00–4.06 (t, J = 7.2 Hz, 2H), 7.34–7.36 (m, 1H), 7.41–7.42 (m, 1H), 9.21 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.9, 13.5, 18.9, 22.0, 25.3, 28.5, 29.1, 31.3, 31.6, 35.7, 49.1, 67.0, 122.0, 123.5, 136.7. MS (ESI, 20 eV): m/z 139.2 $[M–C_7H_{15}OSO_3^-]^+$; MS (ESI, 20 eV): m/z 195.4 $[C_7H_{15}OSO_3]^-$.

3-Butyl-1-methylimidazolium octylsulfate (12c). Yield 83%. ^{1}H NMR (DMSO-d_6): δ 0.84–0.93 (m, 6H), 1.23–1.30 (m, 12H), 1.45–1.50 (m, 2H), 1.74–1.79 (m, 2H), 3.65–3.70 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 4.14–4.19 (t, J = 7.2 Hz, 2H), 7.69–7.70 (m, 1H), 7.76–7.77 (m, 1H), 9.10 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.2, 13.8, 18.7, 22.0, 25.5, 28.6, 28.7, 29.0, 31.2, 31.3, 35.7, 48.4, 65.4, 122.2, 123.6, 136.5. MS (ESI, 20 eV): m/z 139.1 $[M–C_8H_{17}OSO_3^-]^+$; MS (ESI, 20 eV): m/z 209.3 $[C_8H_{17}OSO_3]^-$.

3-Butyl-1-methylimidazolium nonylsulfate (12d). Yield 83%. ^{1}H NMR ($CDCl_3$): δ 0.82–0.96 (m, 6H), 1.27–1.41 (m, 14H), 1.58–1.69 (m, 2H), 1.78–1.90 (m, 2H), 3.97–4.03 (m, 5H), 4.18–4.24 (t, J = 7.2 Hz, 2H), 7.37–7.39 (m, 1H), 7.47–7.49 (m, 1H), 9.42 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.4, 14.1, 19.5, 22.7, 26.0, 29.3, 29.4, 29.6, 29.7, 31.9, 32.1, 36.4, 49.8, 67.9, 122.2, 123.9, 137.5. MS (ESI, 20 eV): m/z 139.2 $[M–C_9H_{19}OSO_3^-]^+$; MS (ESI, 20 eV): m/z 223.4 $[C_9H_{19}OSO_3]^-$.

3-Butyl-1-methylimidazolium decylsulfate (12e). Yield 19%. ^{1}H NMR ($CDCl_3$): δ 0.81–0.95 (m, 6H), 1.21–1.40 (m, 16H),

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1.57–1.65 (m, 2H), 1.81–1.89 (m, 2H), 3.96–4.01 (m, 5H), 4.18–4.24 (t, $J = 7.2$ Hz, 2H), 7.39–7.40 (m, 1H), 7.49–7.50 (m, 1H), 9.47 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.3, 14.0, 19.4, 22.6, 25.8, 29.2, 29.3, 29.5, 29.5, 29.6, 31.8, 32.0, 36.3, 49.7, 67.6, 122.3, 123.9, 137.4. MS (ESI, 20 eV): m/z 139.2 [M–$C_9H_{19}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 237.4 [$C_{10}H_{21}OSO_3$]$^-$.

3-Butyl-1-methylimidazolium dodecylsulfate (12f). Yield 95%. ^{1}H NMR (DMSO-d_6): δ 0.83–0.93 (m, 6H), 1.21–1.30 (m, 20H), 1.45–1.49 (m, 2H), 1.74–1.79 (m, 2H), 3.65–3.69 (t, $J = 6.6$ Hz, 2H), 3.85 (s, 3H), 4.14–4.18 (t, $J = 7.2$ Hz, 2H), 7.69 (s, 1H), 7.76 (s, 1H), 9.10 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.3, 14.0, 19.3, 22.6, 25.8, 29.3, 29.3, 29.5, 29.5, 29.6, 29.6, 29.6, 31.8, 32.0, 36.2, 49.6, 67.6, 122.2, 123.9, 137.3. MS (ESI, 20 eV): m/z 139.1 [M–$C_{12}H_{25}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 265.2 [$C_{12}H_{25}OSO_3$]$^-$.

3-Hexyl-1-methylimidazolium hexylsulfate (13a). Yield 46%. ^{1}H NMR ($CDCl_3$): δ 0.84–0.90 (m, 6H), 1.27–1.39 (m, 12H), 1.59–1.69 (m, 2H), 1.83–1.92 (m, 2H), 3.98–4.06 (m, 5H), 4.22–4.28 (t, $J = 7.5$ Hz, 2H), 7.52–7.55 (m, 1H), 7.65–7.67 (m, 1H), 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 14.0, 22.4, 22.6, 25.6, 25.9, 29.5, 30.2, 31.1, 31.5, 36.3, 49.9, 67.5, 122.5, 124.1, 137.1. MS (ESI, 20 eV): m/z 167.1 [M–$C_6H_{13}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 180.8 [$C_6H_{13}OSO_3$]$^-$.

3-Hexyl-1-methylimidazolium heptylsulfate (13b). Yield 74%. ^{1}H NMR ($CDCl_3$): δ 0.84–0.90 (m, 6H), 1.26–1.41 (m, 14H), 1.62–1.69 (m, 2H), 1.85–1.91 (m, 2H), 3.98–4.05 (m, 5H), 4.21–4.28 (t, $J = 7.3$ Hz, 2H), 7.51–7.53 (m, 1H), 7.64–7.66 (m, 1H), 9.46 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 14.0, 22.4, 22.6, 25.9, 29.0, 29.2, 29.6, 30.2, 31.1, 31.7, 36.3, 49.9, 67.6, 122.4, 124.1, 137.2. MS (ESI, 20 eV): m/z 167.1 [M–$C_7H_{15}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 194.8 [$C_7H_{15}OSO_3$]$^-$.

3-Hexyl-1-methylimidazolium octylsulfate (13c). Yield 93%. ^{1}H NMR ($CDCl_3$): δ 0.83–0.90 (m, 6H), 1.21–1.41 (m, 16H), 1.62–1.69 (m, 2H), 1.83–1.90 (m, 2H), 3.99–4.06 (m, 5H), 4.20–4.26 (t, $J = 7.4$ Hz, 2H), 7.39–7.41 (m, 1H), 7.53–7.55 (m, 1H), 9.47 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 14.1, 22.4, 22.6, 25.9, 29.3, 29.4, 29.5, 29.6, 30.2, 31.1, 31.8, 36.3, 49.9, 67.6, 122.3, 124.0, 137.3. MS (ESI, 20 eV): m/z 167.1 [M–$C_8H_{17}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 208.8 [$C_8H_{17}OSO_3$]$^-$.

3-Hexyl-1-methylimidazolium nonylsulfate (13d). Yield 80%. ^{1}H NMR ($CDCl_3$): δ 0.84–0.90 (m, 6H), 1.14–1.40 (m, 18H), 1.59–1.69 (m, 2H), 1.82–1.90 (m, 2H), 3.98–4.06 (m, 5H), 4.20–4.27 (t, $J = 7.3$ Hz, 2H), 7.47–7.49 (m, 1H), 7.61–7.62 (m, 1H), 9.46 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.0, 14.1, 22.4, 22.7, 25.9, 29.1, 29.3, 29.4, 29.5, 29.6, 30.2, 31.1, 31.9, 36.3, 49.9, 67.7, 122.3, 124.0, 137.3. MS (ESI, 20 eV): m/z 167.1 [M–$C_9H_{19}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 222.8 [$C_9H_{19}OSO_3$]$^-$.

3-Hexyl-1-methylimidazolium decyl sulfate (13e). Yield 93%. ^{1}H NMR ($CDCl_3$): δ 0.84–0.90 (m, 6H), 1.21–1.45 (m, 20H), 1.62–1.69 (m, 2H), 1.83–1.91 (m, 2H), 3.93–4.06 (m, 5H), 4.20–4.26 (t, $J = 7.5$ Hz, 2H), 7.44–7.46 (m, 1H), 7.57–7.60 (m, 1H), 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 14.1, 22.4, 22.7, 25.90, 25.93, 29.3, 29.4, 29.5, 29.6, 29.7, 30.2, 31.1, 31.9, 36.4, 50.0, 67.7, 122.2, 124.0, 137.4. MS (ESI, 20 eV): m/z 167.1 [M–$C_{10}H_{21}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 236.9 [$C_{10}H_{21}OSO_3$]$^-$.

3-Hexyl-1-methylimidazolium dodecylsulfate (13f). Yield 81%. ^{1}H NMR ($CDCl_3$): δ 0.76–0.82 (m, 6H), 1.04–1.35 (m, 24H), 1.54–1.60 (m, 2H), 1.76–1.82 (m, 2H), 3.90–3.98 (m, 5H), 4.11–4.18 (t, $J = 7.4$ Hz, 2H), 7.37–7.40 (m, 1H), 7.51–7.53 (m, 1H), 9.43 (s, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 14.1, 22.3, 22.6, 25.8, 25.9, 29.3, 29.4, 29.51, 29.54, 29.5, 29.6, 29.6, 30.1, 31.0, 31.8, 36.3, 49.9, 67.6, 122.2, 123.9, 137.3. MS (ESI, 20 eV): m/z 167.1 [M–$C_{12}H_{25}OSO_3^-$]$^+$; MS (ESI, 20 eV): m/z 265.0 [$C_{12}H_{25}OSO_3$]$^-$.

ISO 14593-carbon dioxide head space test

To evaluate the biodegradability of the test ILs, the "CO_2 headspace" test (ISO 14593) was applied. This method allows the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganisms by analysis of inorganic carbon. The test IL, as the sole source of carbon and energy, was added at a concentration of 40 mg L^{-1} to a mineral salt medium. These solutions were inoculated with activated sludge collected from an activated sludge treatment plant, washed and aerated prior to use and incubated in sealed vessels with a headspace of air. Biodegradation (mineralization to carbon dioxide) was determined by measuring the net increase in the total organic carbon (TOC) levels over time compared with unamended blanks. Sodium *n*-dodecyl sulfate (SDS) was used as a reference substance. The tests ran for 28 days. The extent of biodegradation was expressed as a percentage of the theoretical amount of inorganic carbon (ThIC) based on the amount of test compound.

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An efficient copper-catalytic system for performing intramolecular *O*-arylation reactions in aqueous media. New synthesis of xanthones†‡

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A safe, efficient protocol for the copper-catalysed intramolecular *O*-arylation of 2-halobenzophenones on water to afford the valuable xanthone framework is reported. The recovery and the successful reutilization of the aqueous solution containing the copper catalyst are also presented. Moreover, the scalability and the easy setup and purification tasks of this sustainable method make it appealing for bulk industry applications.

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Introduction

The xanthone skeleton constitutes the core of an important natural and biologically active family of compounds present in higher plants and microorganisms. These secondary metabolites have interesting pharmaceutical properties such as anticancer,[1] antithrombotic,[2] antihypertensive,[2] antibacterial,[3] antitumoral,[4] opiaceous,[5] cytotoxic,[6] antiviral[7] and anti-inflammatory activity,[7] among others. Moreover, they are also effective against pathogenic fungi[8] and in the inhibition of both gastric secretion[9] and biosynthesis of prostaglandin E2.[10] According to several authors, the biological role of xanthones can be modulated by introducing specific substituents in their structure (Fig. 1).[11,12]

Typically employed methods for the synthesis of the xanthone scaffold imply the previous formation of benzophenones or diarylethers by means of harsh experimental conditions or harmful reactants.[15,16] In recent years, alternative routes to access this appealing family of compounds have been developed. Some of them involve photooxidative cyclisation[17] or cycloaddition[18] of 2-styrylchromones. More recently, another synthesis of the xanthone core was carried out *via* the Diels–Alder reaction of chromone-3-carboxaldehydes with *o*-benzoquinodimethane, followed by the *in situ* oxidation of the cycloadducts.[19] Furthermore, Larock and co-workers[20] have designed a novel strategy to prepare xanthones starting from salicylates and commercially available silylaryl triflates, which act as aryne precursors in the presence of four equivalents of CsF. Under these mild reaction conditions an annulation step takes place to afford the target products in a one-pot synthesis. They have also prepared xanthones by palladium-catalysed arene C–H addition to nitriles through the formation of ketones from substituted phenols and 2-fluorobenzonitriles, followed by an intramolecular cyclisation in the presence of K_2CO_3.[21] Another approach to the xanthone framework accomplished by the same group implied an aryl to imidoyl palladium migration process involving intramolecular C–H activation.[22]

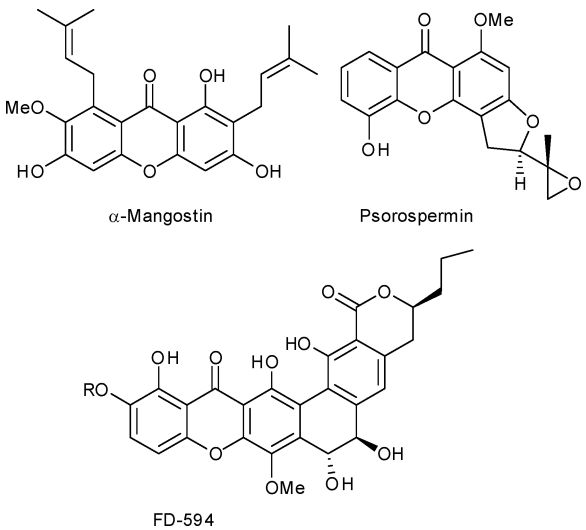

Fig. 1 Some relevant natural xanthones,[13] and the antibiotic FD-594.[14]

Although the latter methods are elegant and efficient for the synthesis of the xanthone core, the drawbacks of palladium catalytic systems, such as the high cost of the metal, its relative toxicity, its air/moisture sensitivity and the difficulties found on its removal at purification steps, have limited their use in bulk industry.

An emerging alternative to most palladium-catalysed cross-coupling processes is the use of copper in this context.[23,24] Indeed, the copper-catalysed Ullmann-type coupling of phenols with aryl halides has been steadily studied.[25–28] These classical Ullmann conditions were strongly limited by the large amounts of copper catalysts and the high reaction temperatures required (~200 °C), the poor substrate scope and the low to moderate yields reached.[29] As a representative example, Watson reported the synthesis of a pyrroloxanthone by a sequence of Ullmann

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† Dedicated to Professor Luis Castedo on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Typical experimental procedures, including spectroscopic and analytical data for all the new intermediates along with NMR spectra of the new compounds. See DOI: 10.1039/b900931k

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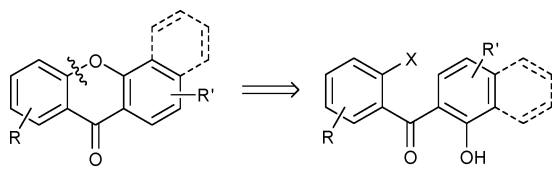
coupling/F–C acylation.[29] Stoichiometric amounts of copper (Cu bronze and CuI), anhydrous conditions and temperatures around 200 °C were required for the Ullmann coupling step. All the aforementioned factors made these strategies unappealing for the industry and difficult to scale-up. Research on the use of bidentate ligands, such as aliphatic diamines,[30] 1,10-phenantroline,[31] ethylene glycol,[32] β-keto esters[33] and PPAPM,[34] and additives (8-hydroxyquinoline,[35] 1-naphthoic acid,[25] amino acids,[36] Schiff bases,[37] *inter alia*) has attracted much attention, since they overcome some of these inconvenient drawbacks. Moreover, the use of soluble copper-complexes,[38] ligand free conditions,[39] Cu nanoparticles[40] or microwave[41,42] and ultrasonic[43] irradiation has also contributed positively to the efficient development of copper-catalysed *O*-arylation of substituted phenols.[44] Therefore, these modifications not only shorten the reaction time but also allow the performance of the reactions under milder conditions.

The pursuit of inexpensive and more benign and environmentally friendly methodologies for the synthesis of xanthones still remains a challenge. In this context, and considering the experience of our group in the preparation of heterocycles through copper-assisted arylation processes in aqueous media,[45] we envisaged an approach based on the latter strategy to access a new family of xanthones (Scheme 1). The advantages derived from the use of water as solvent are numerous, such as safety, non-toxicity, low cost, easy-handling, availability and greater chemoselectivity, compared with organic solvents.[46,47]



Scheme 1 Retrosynthetic pathway to access the xanthone framework.

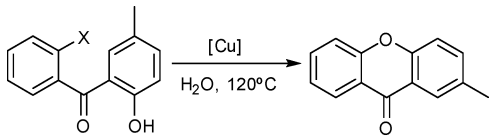
Herein, we report an active catalytic system for the straightforward synthesis of the xanthone scaffold from *o*-halobenzophenones through a copper-catalysed intramolecular *O*-arylation reaction in water as the only solvent. Taking into account the easy setup, recyclability and the sustainability of this procedure, it could be transferred to industrial purposes.

Results and discussion

Initially, in order to optimise the copper-catalysed *O*-arylation reaction to furnish target xanthone **1a**, 2-bromo- and 2-iodobenzophenones **2a** and **2a′** were selected as model substrates (Table 1). These key intermediates were easily prepared in a one-step Friedel–Crafts acylation with graphite and methanesulfonic acid in relatively short times (3–4 hours), following the procedure described in the literature.[48] The main reason to choose this modern protocol was the recyclability of the employed cheap graphite, which would make our whole synthetic sequence even more environmentally friendly.

Accordingly, a range of assays employing a survey of copper sources and commercially available ligands in an aqueous solution were performed. The main results of the optimisation

Table 1 Selected *O*-arylation assays for the synthesis of xanthone **1a**



2a X = I
2a' X = Br
1a

Entry	X	Copper salt, base, ligand[a,b]	Yield (%)[c]
1	I	CuI, TMEDA	83
2	Br	CuI, TMEDA	90
3	I	CuI, CHDA	69
4[d]	I	CuI, NMP, K_2CO_3	95
5[d,e]	Br	CuI, NMP, K_2CO_3	59
6[d]	Br	CuI, NDMP, K_2CO_3	75
7[d]	I	CuI, D, L-proline, K_2CO_3	66
8	I	CuI, PMDTA	57
9[d]	I	CuI, BPDA, K_2CO_3	32
10[d,f,g]	I	CuI, dba, K_3PO_4	tr
11	Br	CuI, TMEDA, K_2CO_3	79
12[g]	Cl	CuI, TMEDA	tr
13	Br	$Cu(OTf)_2$, TMEDA	62
14	Br	$Cu(OAc)_2{\cdot}H_2O$, TMEDA	89
15	Br	CuBr, TMEDA	86
16	Br	Cu_2O, TMEDA	64
17	Br	TMEDA	10
18	Br	CuI	—
19	Br	—	—

[a] 10 mol% of the Cu salt and 3.5 equiv. of ligand when no additional base was used. All reactions were run in water (12 mL per mmol of **2**) at 120 °C. [b] CHDA: *trans*-1,2-diaminocyclohexane; NDMP: *N*,*N*′-dimethylpiperazine; dba: *trans*,*trans*-dibenzylidene acetone; PMDTA: *N*,*N*,*N*′,*N*′,*N*′-pentamethyldiethylenetriamine; NMP: *N*-methylpiperazine; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; BPDA: *rac*-2,2′-biphenyldiamine. [c] Yield of isolated products. [d] 20 mol% of ligand and 2.0 equiv. of base. [e] A similar yield was obtained when Cs_2CO_3 was used. [f] Complex mixture of inseparable products. [g] Only traces of the cyclised product were detected.

process are displayed in Table 1. Interestingly, when different copper salts were employed (Table 1, entries 2, 13–16), the yields obtained were quite similar. The possibility of using different copper sources, regardless of their oxidation state, to perform the target cyclisation makes this methodology advantageous and attractive from a synthetic point of view.

Although CuI, $Cu(OAc)_2{\cdot}H_2O$ and CuBr delivered the xanthone **1a** in fairly similar yields (86–90% yield), copper (I) iodide was selected due to its air and moisture stability. Then, we evaluated the combination of CuI with several commercially available aliphatic diamines, such as TMEDA, CHDA or PMDTA. As shown in Table 1, the more basic TMEDA provided considerably better yields (entry 1 *vs.* 3 and 8). Combining catalytic amounts of CuI along with other nitrogen containing ligands (NMP, NDMP, D,L-proline and BPDA) and additional bases gave in most cases poorer yields (entries 4–7 and 9). The combination of CuI and NMP in catalytic amounts with K_2CO_3 as base seemed to be a good choice, as it provided an excellent yield in the case of 2-iodobenzophenone **2a**. However, a considerably lower yield was obtained starting from the 2-bromo analogue **2a′** (entries 4–5).[49] An attempt to use the cheap dba as ligand for this intramolecular *O*-arylation reaction gave a complex mixture of inseparable products (entry 10). Unfortunately, the

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2-chlorobenzophenone derivative afforded negligible results and the product was hardly detected (entry 12).

Finally, we decided to run three blank experiments. The first one (Table 1, entry 17) was to verify that the copper was really necessary for the intramolecular *O*-arylation process, and to discard a classical aromatic substitution (S_NAr) in which the transition metal should not play any role. We recovered the unreacted starting material as the main product, just isolating a small amount (10%) of target xanthone **1a**, thus confirming the requirement of a copper complex to promote an effective *O*-arylation (Table 1, entry 2 *vs.* 17). The second assay (entry 18) proved that TMEDA (which probably acts both as base and ligand)[45] was clearly needed for the reaction, since otherwise no product was detected. Finally, no reaction was observed when we stirred 2-bromobenzophenone **2a′** in neat water (entry 19).

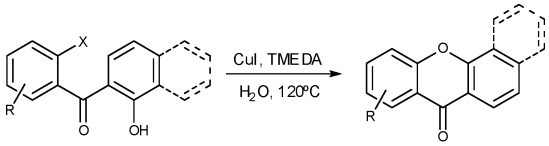
Taking into account all the experimental results it was decided that the best conditions involved stirring the starting material in the presence of 10 mol% of CuI and 3.5 equiv. of TMEDA in water at 120 °C. The ease of the reaction setup, the absence of side products and the lack of requirement for an inert atmosphere should be highlighted.

The Ullmann-type coupling process of substituted phenols with aryl halides has traditionally been accomplished using toxic and high-boiling organic solvents as reaction media.[25–28] A comparison of our procedure with the typically employed strategies to perform this kind of *O*-arylation reaction revealed that the target xanthone **1a** is obtained in much better yields when employing our simple protocol. When we carried out the reaction using the procedure reported by Buchwald and co-workers[25] in 1997 (which involved the use of catalytic amounts of unstable $(CuOTf)_2{\cdot}C_6H_6$ and EtOAc in the presence of Cs_2CO_3 and 1-naphthoic acid as additive in boiling toluene) and the method developed by Chang *et al.*[26] (catalytic amounts of CuI along with ^{n}BuNBr as phase transfer catalyst and K_3PO_4 in DMF at reflux) we only achieved yields of 45 and 63%, respectively. These two parallel experiments outlined the efficiency of our "on water" strategy.

Encouraged by these remarkable results, we decided to evaluate the scope and limitations of this strategy. Accordingly, the preparation of several differently substituted 2-iodo- and 2-bromobenzophenones **2** was carried out from commercially available 2-halobenzoic acids and substituted phenols by means of the aforementioned Friedel–Crafts acylation.[48] These precursors were subjected to the above described optimal conditions to undergo the intramolecular *O*-arylation reaction affording the cyclisation products with the results shown in Table 2.

Surprisingly, both 2-iodo- and 2-bromobenzophenones **2** delivered the cyclisation products with excellent results, regardless of the nature of the halogen substituent (83 *vs.* 90% and 84 *vs.* 73%, in entries 1 and 2, respectively). Only when the hydroxyarene moiety was 1-hydroxynaphthalene, was a remarkable difference in the yields found (62% from **2d** and 89% from **2d′**, Table 2, entry 4). In this case, the conversion of the reaction when **2d** was employed as substrate was incomplete, finding significant amounts of the unreacted starting material. Following with the hydroxyl group containing moiety, a relatively lower yield was obtained when electron-enriched derivative **2c** was employed (entry 3). With regard to the *o*-halide containing moiety, substrates bearing additional halogens such as fluoro or chloro

Table 2 Preparation of differently substituted xanthones **1**[a]



2 X=I, Br **1**

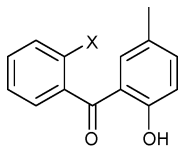
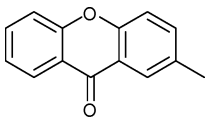
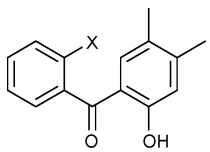
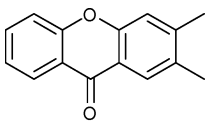
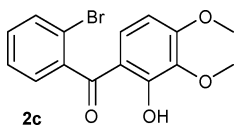
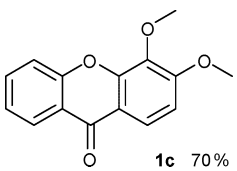
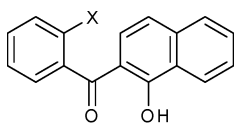
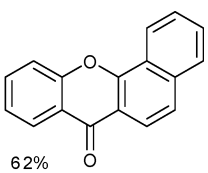
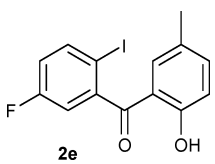
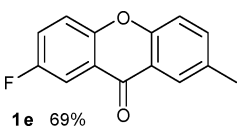
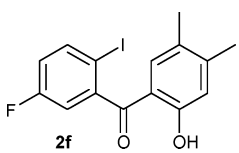
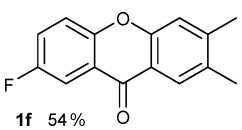
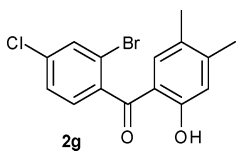
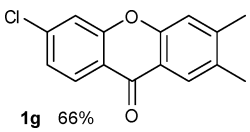
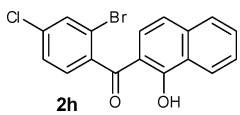
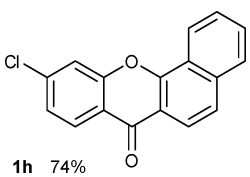
Entry	Substrate **2**	Xanthone **1**[b]
1	 **2a** X = I **2a'** X = Br	 **1a** 83%, 95%[c] 90%
2	 **2b** X = I **2b'** X = Br	 **1b** 84% 73%
3	 **2c**	 **1c** 70%
4	 **2d** X = I **2d'** X = Br	 **1d** 62% 89%
5	 **2e**	 **1e** 69%
6	 **2f**	 **1f** 54%
7	 **2g**	 **1g** 66%
8	 **2h**	 **1h** 74%

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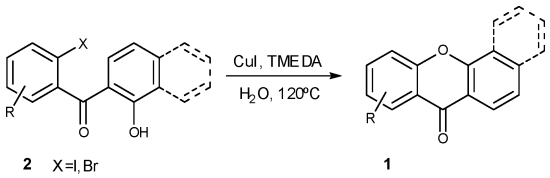
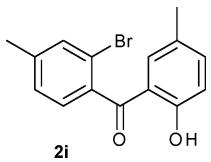
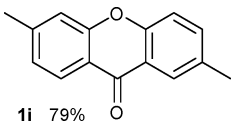
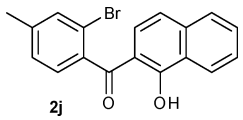
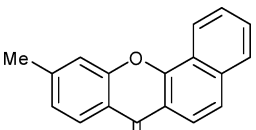
Table 2 *(Contd.)*



Entry	Substrate **2**	Xanthone **1**[b]
9	 **2i**	 **1i** 79%
10	 **2j**	 **1j** 96%

[a] 10 mol% of CuI, 3.5 equiv. of TMEDA and H_2O (12 mL per mmol of **2**) at 120 °C. [b] Yield of isolated products. [c] 10 mol% of CuI, 20 mol% of NMP, 2 equiv. of K_2CO_3 and H_2O (12 mL per mmol of **2a**) at 120 °C.

groups provided slightly lower yields (Table 2, entries 5–8). The presence of these halogens offer the possibility of carrying out a second aromatic substitution process or metal catalysed cross-couplings (Suzuki, Heck, *etc.*) to achieve a more substituted xanthone. In general, it could be affirmed that there is no clear trend related to the electronic nature of the substituents.

At this stage, we decided to evaluate the reutilization of the aqueous solution we used to prepare the xanthone **1a** starting from 2-bromobenzophenone **2a′**. This green solution presumably contained a water soluble copper-TMEDA complex formed during the process. Remarkably, when we reused this aqueous solution the target xanthone **1a** was obtained with an excellent yield of 97%, slightly better than the one obtained in the first run (90%). It should be pointed out that an additional extra amount of TMEDA had to be added to the reaction, due to its supposed double role in the process.[45] After the second run, a clear change of colour of the aqueous solution was observed, from green to brown. The third run with this brown water solution delivered the cyclised product **1a** in a still good yield of 58%, but observing in this case some unreacted starting material.

Finally, the scale-up of our method to 1 and 48 grams starting from the 2-bromobenzophenone **2a′** resulted in excellent results, obtaining xanthone **1a** in 93% and 91% yields, respectively, a bit higher ones than at small scale. This preliminary result opens the possibility of a multigram entry to biologically relevant xanthones.

Conclusions

In summary, a highly practical and sustainable methodology for the synthesis of the very valuable xanthone framework through a copper-catalysed intramolecular *O*-arylation process is presented. Considering that the appealing xanthone scaffold has normally been prepared by using harmful reagents and solvents, the reported protocol delivers the target tricyclic skeleton in good to excellent yields exclusively in a safe, harmless aqueous medium. The recyclability, scalability and the easy reaction setup combined with the low cost of the starting materials make this simple method transferable to pharmaceutical purposes. Finally, it can be outlined that several commercially available copper salts afforded the cyclisation products in fairly similar yields, not limiting the procedure to the use of only one copper source.

Experimental

Typical procedure

2-Methylxanthen-9-one (1a). [22] A screw-capped tube (approximate volume: 18 mL) was charged with 2-iodoarylbenzophenone **2a** (108.1 mg, 0.32 mmol), CuI (6.1 mg, 0.032 mmol), TMEDA (0.17 mL, 1.12 mmol) and water (3.8 mL) at room temperature. After closing, the tube was heated to 120 °C for 15 h, allowed to cool to room temperature and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a solid residue, which was redissolved and filtered through a short pad of silica gel. The filtrate was evaporated under reduced pressure to provide the target xanthone **1a** (55.9 mg, 83%) as a white powder.

The typical procedure was followed starting from 2-bromoarylbenzophenone **2a′** (92.2 mg, 0.31 mmol) and CuI (6.2 mg, 0.032 mmol) to afford xanthone **1a** (60.1 mg, 90%) as a white powder. In a scale-up experiment, the typical procedure (a round-bottom flask closed with a stopper was employed) was applied to 2-bromoarylbenzophenone **2a′** (48.0 g, 0.16 mol) and CuI (3.1 g, 0.016 mol) to provide xanthone **1a** (30.61 g, 91%) as a white powder.

2,3-Dimethylxanthen-9-one (1b). [20] The typical procedure was followed starting from 2-iodoarylbenzophenone **2b** (88.2 mg, 0.25 mmol) and CuI (4.8 mg, 0.025 mmol) to afford xanthone **1b** (47.1 mg, 84%) as a white powder.

The typical procedure was followed starting from 2-bromoarylbenzophenone **2b′** (84.5 mg, 0.28 mmol) and CuI (5.3 mg, 0.028 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1b** (42.3 mg, 73%) was obtained as a white powder.

3,4-Dimethoxyxanthen-9-one (1c). The typical procedure was followed starting from 2-bromoarylbenzophenone **2c** (99.9 mg, 0.30 mmol) and CuI (5.7 mg, 0.030 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1c** (53.7 mg, 70%) was obtained as a white powder. Mp 150–152 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1661, 1602, 1455, 1290 and 1091; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 4.01 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.01 (1H, d, *J* 9.0 Hz, H_2), 7.34–7.39 (1H, m, H_{arom}), 7.55–7.57 (1H, m, H_{arom}), 7.68–7.74 (1H, m, H_{arom}), 8.09 (1H, d, *J* 9.0 Hz, H_1) and 8.32 (1H, dd, *J* 7.9 and 1.7 Hz, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 56.4, 61.5 (OCH_3), 108.6 (C_2), 116.7 (C_{9a}), 118.0 (C_5),

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121.5 (C_{8a}), 122.4, 123.9, 126.6 (C_{arom}-H), 134.5 (C_6), 136.4 (C_4), 150.6 (C_{4a}), 156.1 (C_{4b}, C_3), 157.5 (C_3, C_{4b}) and 176.5 (CO); MS (CI) *m/z* 258 (M + 2, 13%), 257 (M + 1, 100) and 256 (M^+, 37). HRMS (CI) [M + 1]: calculated for $C_{15}H_{13}O_4$, 257.0814; found, 257.0813.

7*H*-Benzo[*c*]xanthen-7-one (1d). [20] The typical procedure was followed starting from 2-iodoarylbenzophenone **2d** (122.8 mg, 0.32 mmol) and CuI (6.2 mg, 0.033 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1d** (46.0 mg, 62%) was obtained as a white powder.

The typical procedure was followed starting from 2-bromoarylbenzophenone **2d′** (93.0 mg, 0.28 mmol) and CuI (5.4 mg, 0.028 mmol) to afford xanthone **1d** (63.1 mg, 89%) as a white powder.

2-Fluoro-7-methylxanthen-9-one (1e). The typical procedure was followed starting from 2-iodoarylbenzophenone **2e** (66.5 mg, 0.18 mmol) and CuI (3.5 mg, 0.018 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1e** (28.2 mg, 69%) was obtained as a white powder. Mp 152–154 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1661 and 1473; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.46 (3H, s, CH_3), 7.37 (1H, d, *J* 8.5 Hz, H_5), 7.41–7.49 (2H, m, H_8), 7.52–7.55 (1H, m, H_{arom}), 7.95 (1H, dd, *J* 8.3 and 2.9 Hz, H_6) and 8.07–8.08 (1H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 20.8 (CH_3), 111.1 (d, *J* 25.4 Hz, C_1), 117.7 (C_5), 119.9 (d, *J* 7.9 Hz, C_4), 120.6 (C_{8a}), 122.6 (C_{9a}), 122.7 (d, *J* 25.3 Hz, C_3), 125.9 (C_8), 133.9 (C_7), 136.6 (C_6), 152.3 (d, *J* 1.4 Hz, C_{4a}), 154.3 (C_{4b}), 158.6 (d, *J* 244.8 Hz, C_2) and 176.6 (d, *J* 2.2 Hz, CO); MS (CI) *m/z*: 229 (M + 1, 100%), 228 (M^+, 41) and 209 (12). HRMS (CI) [M + 1]: calculated for $C_{14}H_{10}FO_2$, 229.0665; found, 229.0659.

2-Fluoro-6,7-dimethylxanthen-9-one (1f). The typical procedure was followed starting from 2-iodoarylbenzophenone **2f** (106.9 mg, 0.29 mmol) and CuI (5.2 mg, 0.027 mmol). After a short flash chromatography (10 mol% EtOAc/hexane) xanthone **1f** (35.0 mg, 54%) was obtained as a white powder. Mp 168–169 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1661, 1625, 1467 and 1279; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.37 (3H, s, CH_3), 2.39 (3H, s, CH_3), 7.25–7.26 (1H, m, H_{arom}), 7.33–7.39 (2H, m, H_{arom}), 7.66–7.68 (1H, m, H_{arom}) and 7.72 (1H, s, H_8); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 19.2 (s, CH_3), 20.6 (s, CH_3), 111.3 (d, *J* 25.2 Hz, C_1), 118.0 (C_5), 118.8 (C_{8a}), 119.8 (d, *J* 7.8 Hz, C_4), 122.4 (d, *J* 25.3 Hz, C_3), 122.7 (d, *J* 7.1 Hz, C_{9a}), 126.2 (C_8), 133.3 (C_7), 145.8 (C_6), 152.3 (d, *J* 1.4 Hz, C_{4a}), 154.6 (C_{4b}), 158.5 (d, *J* 244.6 Hz, C_2) and 176.3 (d, *J* 2.1 Hz, CO); MS (CI) *m/z*: 243 (M + 1, 100%) and 242 (M^+, 45), 223 (15). HRMS (CI) [M + 1]: calculated for $C_{15}H_{12}FO_2$, 243.0821; found, 243.0816.

3-Chloro-6,7-dimethylxanthen-9-one (1g). The typical procedure was followed starting from 2-iodoarylbenzophenone **2g** (99.3 mg, 0.29 mmol) and CuI (5.6 mg, 0.029 mmol). After a short flash chromatography (20 mol% EtOAc, hexane) xanthone **1g** (50.1 mg, 66%) was obtained as a white powder. Mp 173–174 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1655, 1596 and 1420; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.35 (3H, s, CH_3), 2.38 (3H, s, CH_3), 7.21 (s, 1H, H_5), 7.30 (dd, *J* 8.5, 1.8 Hz, 1H, H_2), 7.44 (1H, d, *J* 1.8 Hz, H_4), 8.00 (1H, s, H_8) and 8.23 (1H, d, *J* 8.5 Hz, H_1); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 19.1 (CH_3), 20.5 (CH_3), 117.9 (C_4, C_5), 118.0 (C_5, C_4), 119.5 (C_{8a}, C_{8b}), 120.4 (C_{8b}, C_{8a}), 124.4, 126.2, 128.0 (C_{arom}-H), 133.5, 140.3, 145.7 (C_{arom}-C), 154.5 (C_{4b}), 156.2 (C_{4a}) and 176.1 (CO); MS (CI) *m/z*: 259 (M + 1, 100%) and 258 (M^+, 42). HRMS (CI) [M + 1]: calculated for $C_{15}H_{12}ClO_2$, 259.0526; found, 259.0526.

10-Chloro-7*H*-benzo[*c*]xanthen-7-one (1h). The typical procedure was followed starting from 2-bromoarylbenzophenone **2h** (91.9 mg, 0.25 mmol) and CuI (4.8 mg, 0.025 mmol). After a short flash chromatography (20 mol% EtOAc/hexane) xanthone **1h** (53.0 mg, 74%) was obtained as a white powder. Mp 204–205 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1655, 1602, 1431, 1379 and 1085; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 7.38 (1H, dd, *J* 8.5 and 1.9 Hz, H_{arom}), 7.64–7.63 (4H, m, H_{arom}), 7.88–7.91 (1H, m, H_{arom}), 8.20 (1H, d, *J* 8.2 Hz, H_{arom}), 8.29 (1H, d, *J* 8.5 Hz, H_{arom}) and 8.54–8.57 (1H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 117.5 (C_{6a}), 118.0 (C_{11}), 120.8 (C_{7a}), 121.2, 122.6 (C_{arom}-H), 123.7 (C_{11c}), 124.4, 125.2, 127.0, 127.9, 128.1, 129.7 (C_{arom}-H), 136.5 (C_{4a}), 140.3 (C_{10}), 153.4 (C_{11b}), 155.7 (C_{11a}) and 175.9 (CO); MS (CI) *m/z*: 283 (M + 3, 34%), 282 (M + 2, 31), 281 (M + 1, 100), 280 (M^+, 43) and 245 (10). HRMS (CI) [M + 1]: calculated for $C_{17}H_{10}ClO_2$, 281.0369; found, 281.0367.

2,6-Dimethylxanthen-9-one (1i). The typical procedure was followed starting from 2-bromoarylbenzophenone **2i** (98.3 mg, 0.32 mmol) and CuI (6.1 mg, 0.032 mmol) to afford xanthone **1i** (57.1 mg, 79%) as a white powder. Mp 118–119 °C (from hexane); IR ν_{max}(KBr)/cm^{-1} 1655, 1619, 1437, 1302 and 1226; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.45 (3H, s, CH_3), 2.48 (3H, s, CH_3), 7.14–7.17 (1H, m, H_{arom}), 7.24–7.25 (1H, m, H_{arom}), 7.35 (1H, d, *J* 8.5 Hz, H_4), 7.50 (1H, dd, *J* 8.5 and 2.2 Hz, H_3), 8.09–8.10 (1H, m, H_{arom}) and 8.20 (1H, d, *J* 8.1 Hz, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 20.8 (CH_3), 21.9 (CH_3), 117.6 (C_5), 119.5 (C_{8a}), 121.5 (C_{9a}), 125.2, 125.9, 126.5 (C_{arom}-H), 133.5 (C_2), 135.8 (C_3), 146.1 (C_6), 154.3 (C_{4a}), 156.3 (C_{4b}) and 177.0 (CO); MS (CI) *m/z*: 225 (M + 1, 100%) and 224 (M^+, 4%). HRMS (CI) [M + 1]: calculated for $C_{15}H_{13}O_2$, 225.0916; found, 225.0907.

10-Methyl-7*H*-benzo[*c*]xanthen-7-one (1j). The typical procedure was followed starting from 2-bromoarylbenzophenone **2j** (91.6 mg, 0.27 mmol) and CuI (5.1 mg, 0.026 mmol) to afford xanthone **1j** (67.1 mg, 96%) as a white powder. Mp 220 °C (decomposition); IR ν_{max}(KBr)/cm^{-1} 1643, 1437, 1379 and 1085; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.51 (3H, s, CH_3), 7.19–7.20 (1H, m, H_{arom}), 7.13–7.14 (1H, m, H_{arom}), 7.61–7.69 (3H, m, H_{arom}), 7.86–7.89 (1H, m, H_{arom}), 8.22–8.25 (2H, m, H_{arom}) and 8.56–8.59 (1H, m, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 117.5 (C_{6a}, C_{7a}), 117.7 (C_{arom}-H), 120.1 (C_{7a}, C_{6a}), 121.5, 122.7, 123.7 (C_{arom}-H), 124.0 (C_{11c}), 125.8, 126.2, 126.7, 128.0, 129.3 (C_{arom}-H), 136.4 (C_{4a}), 145.7 (C_9), 153.4 (C_{11b}), 155.7 (C_{11a}) and 176.6 (CO); MS (CI) *m/z*: 262 (M + 2, 19%), 261 (M + 1, 100) and 260 (M^+, 40). HRMS (CI) [M + 1]: calculated for $C_{18}H_{13}O_2$, 261.0916; found, 261.0918.

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Designing systems for one-way *trans* to *cis* photoisomerization for solar reactions

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We have examined triplet photosensitized isomerization of sterically crowded derivatives of stilbene, diene, triene and styrene. Under selective triplet sensitization, several such compounds proceeded in the synthetically desirable manner of complete one-way *trans* to *cis* conversion or in a highly stereoselective manner. In the process, we have identified several systems suitable for solar irradiation as a "green" procedure for preparation of hindered olefinic isomers. A simple procedure for determining the relative efficiency of a solar reaction has also been introduced.

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Introduction

Photoisomerization of olefinic compounds often produces mixtures of *cis*/*trans* isomers. But, there are known cases of apparently uni-directional (or one-way) photoisomerizations yielding a single isomer product mixture. The more common examples, not surprisingly, are those going from the high energy *cis* to the *trans*, examined in particular detail by the Tsukuba research group.[1] They cleverly took advantage of the shape of the distorted torsional potential curves (tilting toward the *trans*) of the excited state of sterically crowded aryl olefins to effect one-way isomerization. A key feature for these cases was high quantum yield of photoisomerization (frequently greater than unity).[1,2] Other photo-initiated radical or radical ion processes are also known to lead to exclusive *cis* to *trans* isomerization[3] but these, in reality, are catalyzed reactions on the ground state potential surfaces.

One-way photoisomerization in the opposite *trans* to *cis* direction, a counter thermodynamic process, is synthetically more useful, but one not commonly found in the literature. In fact, there appeared to be only one definitive example: the complete conversion of *trans*-β-ionol to its *cis* isomer *via* selective triplet sensitization[4] (see more below). In several other cases, complete disappearance of the *trans* isomer was achieved when the *cis* isomer formed was either removed by a secondary thermal reaction[5] or stabilized by H-bonding present in the *cis* isomer.[6] Following our recent demonstration that selective triplet photosensitization is a particularly clean solar reaction, we decided to make an effort to search for more examples of one-way *trans* to *cis* conversions. Additionally, we hope to be able to demonstrate that solar irradiation is a clean and green way of producing the hindered *cis* isomers of olefinic compounds.

Results and discussion

Enrichment of the *cis* isomer can often be achieved by either direct irradiation or by triplet sensitization, but the results can be quite different. We should first consider factors controlling one-way photoisomerization.

Direct irradiation

The photostationary state, pss, composition ([c]/[t]) of a pair of *cis* and *trans* isomers is determined by the product of the excitation and the decay ratios[7]

$$([cis]/[trans])_{pss} = (\text{excitation ratio})\,(\text{decay ratio})$$

For direct irradiation, the excitation ratio is that of the extinction coefficients at the wavelength of excitation ($\varepsilon_t/\varepsilon_c$) and the decay ratio is that of the decay rate constants from the excited species to the two isomers (k^d_c/k^d_t). With the exception of those systems used by the Tsukubo group, the decay ratios are usually close to unity. Thus, for pss to approach 100 (*i.e.*, completely *cis*), the ratio of extinction coefficients for the two isomers at the wavelength of excitation must be >100 (favoring the usually stronger absorbing planar *trans* isomer). This condition, however, is not easily achievable in preparative runs when the excitation light source is usually not mono-chromatic, although enrichment of the *cis* isomer is commonly attainable. Another complicating factor for reaction from the excited singlet state is competing side reactions in the form of symmetry-allowed concerted reactions (*e.g.*, electrocyclization or sigmatropic H-rearrangement).[8]

Two well-known examples of enrichment of the *cis* isomer by direct irradiation are the following. Irradiation at long wavelength (>310 nm) is a common way of enriching the *cis* isomer of stilbene and its derivatives. However, the reaction is accompanied by slow but irreversible formation of the colored dihydrophenanthrene.[9] Another example is enrichment of the visually important 11-*cis*-retinal through direct irradiation of the all-*trans* isomer in a polar solvent with long wavelength light.[10] The reaction is complicated by a slow rate of formation of 1,5-sigmatropic rearranged and 6e-electrocyclized products.[10b]

Triplet sensitization

A major advantage of reaction from the triplet state is the absence of symmetry-allowed reactions—energetically not possible while retaining spin-conservation. On the other hand, the

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cis/*trans* isomerization reaction does not have this problem because the perpendicular structure encountered in an isomerization process is an intermediate ideal for spin inversion. The possible use of a longer wavelength absorbing triplet photosensitizer is also an advantage, particularly for the purpose of tapping the stronger visible light for solar reactions.

For triplet sensitized irradiation, pss is also determined by a product of excitation and decay ratios:[7]

$$([cis]/[trans])_{pss} = (k^{tr}_{t}\,[trans]/k^{tr}_{c}\,[cis])\,(k^{d}_{c}/k^{d}_{t})$$

The excitation ratio is now that of rate constants of energy transfer from the triplet sensitizer to the two isomers (k^{tr}_{t} $[trans]/k^{tr}_{c}$ $[cis]$) and the decay ratio is that of the decay rate constants from the common perpendicular triplet species to each isomer (k^{d}_{c}/k^{d}_{t}).[7] The latter is again close to unity. Since the usually non-planar *cis* isomer is expected to have a higher triplet excitation energy than the *trans*, in principle, it should be possible to use a sensitizer with energy in between those of the two isomers to achieve a favorable rate of transfer to the *trans* isomers, thereby producing *cis* rich photostationary states.

However, exclusive formation of the *cis* isomer was rarely achieved under selective triplet sensitization. Hence, while it was well known that *cis*-stilbene can be enriched with sensitizers of triplet energy below that of the *cis* isomer (E_T = 62 kcal mol^{-1}),[11] the enrichment only reached a maximum of 92% *cis* with benzil as the triplet sensitizer (E_T = 52 kcal mol^{-1}). Further lowering of the sensitizer energy led to a gradual increase of the *trans* isomer (see Table 1 below). The same situation was encountered in other common olefinic substrates, such as 1,3-pentadiene (piperylene).[11]

The factor against one-way *trans* to *cis* isomerization for these cases is an unusual endothermic energy transfer process known as the "non-vertical" excitation favoring the non-planar *cis*[12] (even though later it became clear that there was not any "non-vertical" process as implied by the name).[4,13] The effect was clearly shown in the different pattern of endothermic energy transfer from the donor triplets to the two stilbene isomers reported by Herkstroeter and Hammond.[14] Their data are partially reproduced in Fig. 1.

The drop-off of endothermic energy transfer rates from sensitizer triplets to *trans*-stilbene was steep with a slope equivalent to a typical case of energy transfer to biacetyl (solid straight line). In contrast, the drop-off of energy transfer rates to *cis*-stilbene was less dramatic giving roughly a line less steep in slope (Fig. 1). The triplet energies of *cis*-stilbene and *trans*-stilbene are respectively

Table 1 Photostationary state compositions of stilbene and a hindered homolog **2** as function of triplet excitation energies of photosensitizers

Sensitizer (E_T/kcal mol^{-1})[a]	Compound	pss (% *cis*)	Compound	pss (% *cis*)[c]
Benzophenone (69)	Stilbene	59.6		
Michler's Ketone (62)	Stilbene		**2**	87[e]
Benzil (52)	Stilbene	90,[c] 92[b]	**2**	98.9[e]
9-Fluorenone (50)	Stilbene	85[c]	**2**	100[e]
Benzanthrone (46)	Stilbene	68[c]	**2**	98.6[d,e]

[a] From ref. 17. [b] From ref. 11. [c] This work, by NMR. [d] Maximum conversion from the *trans* and no reaction detected when starting from the *cis* isomer. [e] Corning 3–75 filter.

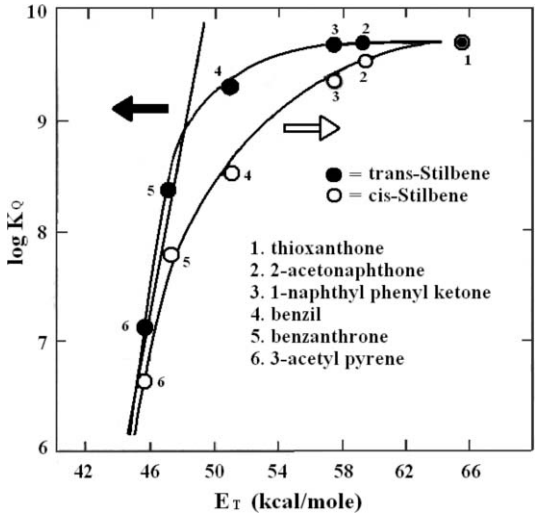

Fig. 1 A simplified figure showing rates of triplet–triplet energy transfer from common triplet sensitizers to *trans*- and *cis*-stilbene adapted from that of Herkstroeter and Hammond.[14] The solid straight line near the *trans* curve was that for endothermic T–T energy transfer to biacetyl. Notice the early decrease of transfer rates to *cis*-stilbene (E_T = 62 kcal mol^{-1}) relative to those of *trans*-stilbene (E_T = 55 kcal mol^{-1}) and the more gentle slope of the endothermic energy transfer line to *cis*-stilbene. We designate the shaded area the "*cis*-enrichment zone".

62 and 55 kcal mol^{-1}. Since exothermic energy transfer rates approach that of diffusion, the pss values are constant for sensitizers of high energy greater than 64 kcal mol^{-1}. For donors with energy below 62 kcal mol^{-1}, the rate to *cis* decreased while that to the *trans* remained close to diffusion rates. The gradual favorable excitation ratio ushers in the beginning of the "*cis*-enrichment zone" (enclosed area in Fig. 1). However, because of the drop-off of the rates of transfer to the *cis* relative to the *trans* in endothermic excitation, around 46 kcal mol^{-1} the rate of transfer to the *cis* approaches that of the *trans*, signaling the end of the "*cis*-enrichment zone". Eventually, the transfer to the *cis* became faster than to the *trans* even though both rates had become rather small for practical triplet sensitization on account of energy deficiency of the highly endothermic energy transfer processes.

It should be clear that if the "*cis*-enrichment zone" (the enclosed area) is, by some means, enlarged, the probability of effecting one-way *trans* to *cis* conversion will be enhanced. There are two possible ways to do so. First is to increase selectively the triplet energy of the *cis* isomer, *i.e.*, to displace the energy transfer curve of the *cis* to the right. Second is to decrease selectively the triplet excitation of the *trans* (a more difficult option), *i.e.* to displace the energy transfer curve of the *trans* to the left. We now wish to report results of several systems designed to meet the first strategy, *i.e.*, to increase selectively the excitation energy of the *cis*.

Stilbenes

Selected reported pss values of stilbene[11] as a function of sensitizer energies are reproduced in Table 1. Sensitizers with energy less than 62 kcal mol^{-1} produced mixtures containing progressively more of the *cis* isomer, reaching a maximum value for benzil.

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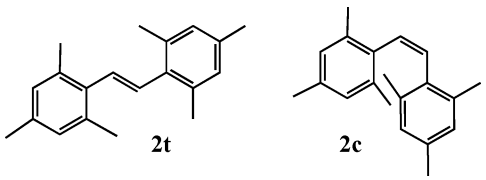
We now wish to report the corresponding values for 2,4,6,2′,4′,6′-hexamethylstilbene, **2**.[15] The *trans* isomer is likely to remain relatively planar, thus its triplet excitation energy should not be significantly perturbed (other than effects of methyl substitution) from that of *trans*-stilbene. The *cis* isomer, on the other hand, is severely congested, expected to exist in a highly twisted conformation about the two single bonds. Its triplet excitation energy should be proportionately raised associated with decreased conjugative interaction within the unsaturated chromophore. The net result is the likely displacement of the energy transfer curve of the *cis* isomer toward the right, thereby enlarging the "*cis*-enrichment zone". The pss values produced by low energy triplet sensitizers (Table 1) indeed reflect this expectation. Thus, with benzophenone or Michler's ketone, substantial amounts of *trans* remains in pss. But with the two lower energy sensitizers, the pss values are practically 100% *cis*. With an even lower triplet sensitizer (benzanthrone), conversion to *cis* became very slow to the extent complicating side reactions began to appear. Hence, pss was never reached from the *trans* side. But we note that when starting with a pure *cis* sample, benzanthrone failed to effect *trans* to *cis* isomerization.



Subsequently, we have also calculated[16] the preferred geometry of the two isomers of **2** and the energy change in twisting around the single bonds. The results (Fig. 2) showed that the above explanation of preferred excitation of the planar *trans* isomer over the twisted *cis* as the cause for 100% conversion to the *cis* is somewhat too simplified. The two curves show that the *trans* as well as the *cis* isomer exists in a highly twisted conformation (41.7 ° and 54.0°, respectively). However, the *trans* isomer is surrounded by a shallow potential well, making the relatively planar structures available at room temperature as acceptors in triplet sensitization. In contrast, the *cis* isomer is surrounded by steep potential wells making the relatively planar conformer not available as acceptors. Therefore, favorable endothermic energy transfer to the *trans* is more likely a reflection of its more accessible low-energy planar forms.

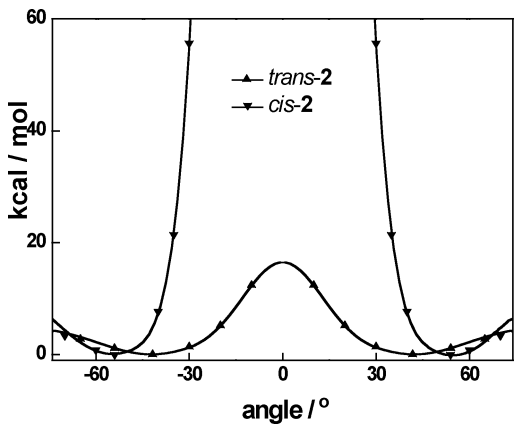
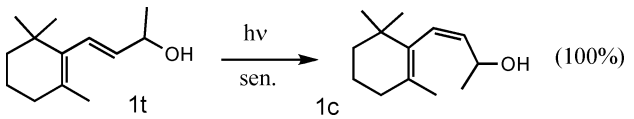


Fig. 2 Calculated energies of *trans*-**2** (lower line) and *cis*-**2** (upper off-scale line) upon twisting the single bonds between phenyl groups and the ethylenic linkage, demonstrating smaller twist for the equilibrated structure of the *trans* and that structures close to planarity are accessible at room temperature for the *trans* isomer but not the *cis*.

Dienes

Triplet excitation energies of conjugated dienes are usually between 55–60 kcal mol^{-1} with the cisoid dienes being slightly lower.[18] For 1,3-pentadiene, the energy difference between the *trans* and *cis* isomers is small (~59 *vs.* ~57 kcal mol^{-1} favoring the *cis*), and is further complicated by possible participation of cisoid diene with lower energy sensitizers.[19] Therefore, it was no surprise that selective triplet sensitization failed to produce high amounts of the *cis* isomer (a maximum amount of 45% when benzophenone was used as a sensitizer).[11]



The quantitative *trans* to *cis* conversion of β-ionol, a lower diene member of the retinoid series, deserves a closer examination. Because of the extra methyl groups surrounding the 7,8-double bond, the *cis* isomer is extremely congested forcing the diene chromophore to exist in a very twisted conformation.[20] For the *trans* isomer, the 6,7-dihedral angle is bound by a shallow potential well favoring slightly a twisted s-*cis* form.[21] The twist has apparently raised the triplet energy somewhat, making 9-fluorenone (E_T = 50 kcal mol^{-1}) (a common sensitizer to excite cisoid dienes[19]) not effective for sensitized isomerization of β-ionol to the *cis* isomer.[22] With 1-acetonaphthone (E_T = 57 kcal mol^{-1}), the conversion proceeded smoothly. Therefore, one may safely place the triplet excitation of the *trans*-ionol around 57–58 kcal mol^{-1}. The excitation energy of *cis*-ionol was estimated to be around 72 kcal mol^{-1}.[4] This value is unusually high for a diene and clearly substantially higher than that of *trans*-ionol (by ~15 kcal mol^{-1}), thus easily meeting the necessary criterion for selectively increasing the excitation of the *cis* isomer so as to enlarge the "*cis*-enrichment zone". The observed one-way isomerization to the *cis* isomer is therefore expected.[4,22]

Styryl derivatives

Compound **3** is a styrene analog of β-ionol and compound **4** a related tertiary alcohol. Since the triplet excitation energy of styrene (~70 kcal mol^{-1})[17] is higher than that of a diene, it was necessary to use sensitizers of higher triplet energy to effect efficient isomerization. For acetophenone (E_T = 74) as a triplet sensitizer (Table 2), a mixture of *trans* and *cis* isomers was obtained at pss (90% *cis*). However, with benzophenone (E_T = 69) as sensitizer the reaction yielded 100% of the *cis* isomer. Benzil was too low in energy to effect isomerization. Therefore, compound **3** followed the same pattern as β-ionol. Not surprisingly, the related tertiary alcohol **4** also gave the *cis* isomer in quantitative yield under selective triplet sensitization. On the other hand, the less congested compound **5** gave at best 80% of the *cis* isomer under favorable selective sensitization (Table 2).

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Table 2 Photostationary state compositions of other hindered compounds **1**, **3**, **4** and **5** and related compound **6** and enones **7** and **8** as a function of sensitizer triplet excitation energy

	Percent *cis* in photostationary states for compounds shown						
Sensitizer (E_T/kcal mol^{-1})[a]	**1**	**3**	**4**	**5**	**6**	**7**	**8**
Acetophenone (73)	71.8[b]	89.7[d]	95.7[d]				
4,4-Me_2-benzophenone (69)	86.5[b]	100[d]					
Benzophenone (69)	90.0[b]	100[d]	100[d]	67[e]			
Michler's Ketone (62)		>75[d,g]	100[d]	80[e]	60[f]	92.2[f]	38[f]
1-Acetonaphthone (57)	100[c]	91.8[d]					
Benzil (52)		no rx		no rx	56.2[f]	100[f]	35.4[f]
9-Fluorenone (50)	no rx[c]			no rx	77.8[f]	100[f]	30.6[f]
Benzanthrone (46)				no rx	93.7[f]		no rx
Direct irradiation, Pyrex			84	36			

[a] Ref 17. [b] Ref. 4. [c] Ref. 22. [d] Corning O-54 filter. [e] Corning O-52 filter. [f] Corning 3–75 filter. [g] Maximum conversion from *trans* with appearance of side products.

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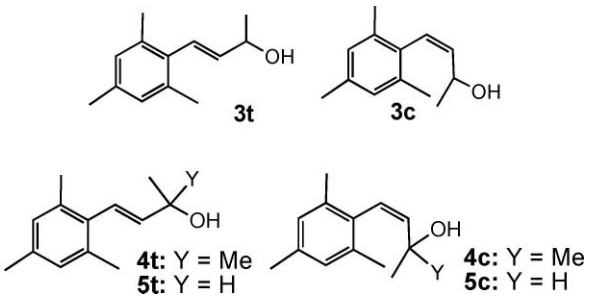
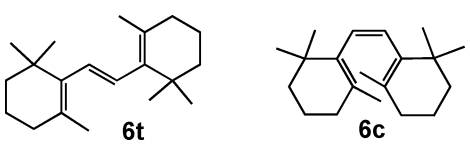


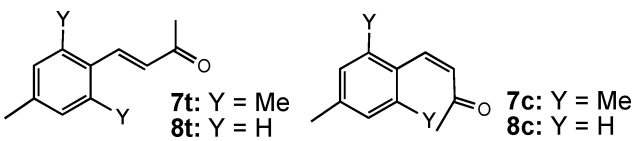
Triene (Mini-carotene-3), 6

Compound **6** is a non-aromatic analog of a crowded stilbene. It is also the smallest member of the β-carotene series (known as Mini-3).[23] Triplet excitation energies of the parent *trans*-hexatriene is around 48 kcal mol^{-1},[24] likely lower for the highly alkylated Mini-3. The energy of the crowded *cis*-Mini-3 should be higher but its exact value is unknown. Pss compositions of **6** with several low energy triplet sensitizers are also listed in Table 2. The amount of *cis* in fluorenone and benzanthrone sensitized pss mixtures show promising *cis*-enrichment. However, even in the best case of the benzanthrone sensitized reaction, the conversion to the *cis* isomer (93%) was short of being quantitative. Several other even lower energy triplet donors were tried but found to be ineffective. Thus, Rose Bengal (E_T = 40 kcal mol^{-1}) failed to produce any *cis* isomer even after prolonged irradiation, while 9,10-dichloroanthracene (42 kcal mol^{-1}) and benz[α]anthracene (47 kcal mol^{-1}) gave competing degradation products. We suspect that the known non-planarity of the trimethylcyclohexenyl rings in the retinoids[21] has caused twists in *trans*-Mini-3, thereby raising its triplet excitation energy and closing the "*cis*-enrichment zone" to an extent that makes it not possible to achieve one-way isomerization. Nevertheless, 93% still represents a good way of preparing *cis*-Mini-3.



Miscellaneous systems

We have also examined triplet sensitized reactions of enone **7** and the related but less crowded **8**. Because of the long-wavelength absorbing n–π band of these compounds, for sensitized reactions we had to use a larger amount of the sensitizer to achieve favorable triplet sensitization. The result turned out to be promising. For the hindered enone **7**, quantitative conversion to the *cis* isomer was achieved when benzil or fluorenone was used as selective triplet sensitizer. Without a triplet sensitizer (*i.e.*, direct irradiation), the *cis* isomer could also be prepared. But it required a much longer irradiation time on account of its weak absorption (n–π band) beyond 300 nm. Not surprisingly, for the less congested enone **8**, one-way *trans* to *cis* conversion was not possible (max. 38% *cis*, Table 2).



Solar reactions

Preparing *cis* isomers. One-way *trans* to *cis* photoisomerization is an ideal reaction for preparation of a group of hindered *cis* isomers. Since solar irradiation is a green way to carry out photochemical synthesis and colored photosensitizers (ideal for tapping a good portion of the visible light) had proven to be effective in most of the examples described above, we decided to explore possible use of the Hawaiian sunlight for preparation of several of the hindered *cis* isomers described above. For this part we borrowed the simple energy-saving solar reactors described recently.[22] The preferred reactor for this study was the "kick-board solar reactor" (the "boogie-board reactor" being more suitable for larger scale reactions). The results are quite promising. For compound **1**, (reported earlier)[22] the reaction required 7 h exposure to sunlight (a colorless photosensitizer) while compounds **2** and **3** (yellow photosensitizers) required less than 3 h exposure to sunlight in Honolulu in August. In all cases, the purified (after column chromatography) *cis* isomers were recovered in excess of 95% yield.

It should be mentioned that because of steric hindrance, these hindered *cis* isomers are not accessible through selective

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hydrogenation under common laboratory conditions of the corresponding alkynes. Therefore, the method described in this paper is not only a green way but also the only convenient way of preparing such crowded *cis* olefins.

Relative efficiency for solar reactions (RESR). Efficiency of a solar reaction[25] is dependent on its ability to tap the broad band of sunlight and the quantum yield of that reaction:

$$\text{Efficiency of solar reaction, ESR} = \text{Absorption efficiency} \times \text{quantum yield}$$

Efficiencies of several reactions were reported, ranging from the inefficient (~0.001) acetone triplet sensitized cycloaddition of ethylene to 5-alkoxy-[5*H*]-furan-2-one (utilization of the weak <330 nm light) to the efficient (0.54) Rose Bengal sensitized oxygenation of furfural.[25]

The different rates of triplet sensitized isomerization reactions of a given system reported in this paper are good reflections of the different absorption characteristics of sensitizers (quantum yields of reaction being the same). In Table 3, we have listed the different amounts of *cis*-stilbene obtained after exposure in parallel of a set of samples containing *trans*-stilbene and four different triplet photosensitizers. Benzil produced the largest amount of the photoproduct reflecting the light yellowish color of the triplet sensitizer. Its absorption through ~400 nm represents 45% efficiency in utilizing solar energy through 700 nm.[25] Since, the quantum yield of sensitized isomerization of *trans*-stilbene to *cis*-stilbene is known to be 0.55,[11] the solar efficiency of the benzil reaction is calculated to be 0.25. The corresponding values, *i.e.*, relative efficiencies of solar reaction, RESR, from the other three sensitizers were readily obtained when their conversions were compared to that of the benzil sample. The lower numbers of benzophenone and acetonaphthone are clearly due to the colorless nature of the sensitizers. And, the lower yield from the yellow 9-fluorenone is likely due to the lower efficiency of triplet–triplet energy transfer from this lower energy sensitizer.

Such easily obtainable RESR values are a quick indication of how facile a solar reaction proceeds. Using any one of the samples as standard (preferably the benzil sample because of the high amount of the *cis* isomer in the photostationary state, Table 1), a RESR value can be assigned to any new solar reaction. In Table 3, we have also listed efficiency values reported for the aforementioned acetone sensitized cycloaddition of ethylene to the furanone and Rose Bengal sensitized singlet oxygenation. We suggest that those reactions with RESR values greater than 0.05 be labeled as H (high efficiency), those less than 0.005 as L (low efficiency) and those in between as M (medium efficiency).[29]

Table 3 Relative efficiencies of solar reactions (RESR): triplet sensitized reaction of *trans*-stilbene and other reported triplet sensitized reactions[a]

Sensitizer	E_T[b] (tail absorp.)	Conv. to *cis*[c]	RESR[d]	Rx class[e]
Benzophenone	68 (~370 nm)	9.9%	0.08	H
1-Acetonaphthone	57 (~380 nm)	11.4%	0.10	H
Benzil	52 (~400 nm)	30.4%	0.25	H
9-Fluorenone	50 (~420 nm)	16.9%	0.20	H
Cycloadd. with acetone[f]	78 (~330 nm)		0.001	L
Oxygenation by RB[g]	40 (~580 nm)		0.55	H

[a] Initial concentration of *trans*-stilbene = 0.200 M, concentration of sensitizer = 0.05 M. [b] In kcal mol^{-1}. [c] After 45 min exposure to sunlight (>310 nm, Corning O-54 filter). [d] Calculated RESR values relative to extent of product formation of the benzil sample. [e] H for RESR > 0.05; L < 0.005; M for those in between. [f] Acetone sensitized addition of ethylene to furanone.[25] [g] Rose Bengal sensitized oxygenation of furfural.[25]

Experimental

Materials

All reagents were purchased from Aldrich. Compounds **2t**, **5t** and **6t** were prepared by standard McMurry coupling,[26] and compounds **3t** and **4t** were prepared by reaction of methyl Grignard with the corresponding aldehyde. Characterization data for isomers of these compounds are listed below. (For usage of ^{1}H NMR spectroscopy for assigning *cis*/*trans* isomers, see detailed analysis of spectra of isomers of vitamin A.[27])

Compound **2** ^{1}H NMR ($CDCl_3$), *trans* (signals used for evaluating pss compositions are italicised): *6.92* (s, 4H), 6.54 (s, 2H), 2.38 (s, 12H), 2.30 (s, 6H); *cis*: *6.74* (s, 4H), 6.63 (s, 2H), 2.21 (s, 6H), 1.95 ppm (s, 12H).

Compound **3** ^{1}H NMR ($CDCl_3$), *trans*: 6.86 (s, 2H), 6.50 (d, 1H, J = 16.5), *5.55* (dxd, 1H, J = 7.5, 16.5), 3.90 (m, 1H, J = 6.3, 7.5), 3.38 (s, 3H), 2.28 (s, 7H), 1.35 (d, 3H, J = 6.3); *cis*: 6.92 (s, 2H), 6.40 (d, 1H, J = 11.4), *5.62* (dxd, 1H, J = 9.0, 11.4, a typical small coupling constant for the *cis* isomer), 3.59 (m, 1H), 2.28 (s, 3H), 2.22 (s, 6H), 1.12 ppm (d, 3H, J = 8.7 ppm).

Compound **4** ^{1}H NMR ($CDCl_3$), *trans*: 6.86 (s, 2H), 6.50 (d, 1H, J = 16.5), *5.82* (d, 1H, J = 16.5), 2.26 (s, 3H), 2.25 (s, 6H), 1.62 (s, 1H), 1.44 (s, 6H); *cis*: 6.83 (s, 2H), 6.19 (d, 1H, J = 12.4, smaller J for *cis*), *5.74* (d, 1H, J = 12.4 Hz), 2.25 (s, 3H), 2.24 (s, 6H), 1.62 ppm (s, 1H), 1.57 (s, 6H).

Compound **5** ^{1}H NMR ($CDCl_3$), *trans*: 7.28 (d, 2H, J = 7.8), 7.12 (d, 2H, J = 7.8), 6.48 (d, 1H, J = 15.9), *6.02* (dxd, 1H, J = 7.8, 15.9), 3.87 (m, 1H, J = 6.3, 7.8), 2.32 (s, 3H), 1.56 (3, 1H), 1.31 (3H, J = 6.6); *cis*: 7.18 (d, 2H), 7.16 (d, 2H), 6.62 (d, 1H, J = 12.0), *5.57* (dxd, 1H, J = 9.0, 12.0, smaller J for *cis*), 4.33 (qxd, 1H, J = 6.0, 9.0), 2.39 (s, 3H), 1.66 (s, 1H), 1.38 ppm (d, 3H, J = 6.0 Hz).

Compound **6** ^{1}H NMR ($CDCl_3$), *trans*: *5.80* (s, 2H), 2.00 (m, 4H), 1.76 (s, 6H), 1.62 (m, 4H), 1.46 (m, 4H), 1.02 (s, 12H); *cis*, *5.92* (s, 2H), 2.00 (m, 4H), 1.62 (m, 4H), 1.46 (m, 4H), 1.38, higher-field 5-Me for 7-*cis* (s, 6H), 1.06 (s, 12H).

Compound **7** ^{1}H NMR ($CDCl_3$), *trans*: 7.67 (d, 1H, J = 16.8), 6.90 (s, 2H), *6.33* (d, 1H, J = 16.8), 2.39 (s, 3H), 2.33 (s, 6H), 2.29 (s, 3H); cis: 7.06 (d, 1H, J = 12.3), 6.89 (s, 2H), *6.28* (d, 1H, J = 12.3 Hz, smaller J for *cis*), 2.29 (s, 3H), 2.17 (s, 6H), 1.82 ppm (s, 3H).

Compound **8** ^{1}H NMR ($CDCl_3$), *trans*: 7.46 (d, 1H, J = 16.2), 7.43 (d, 2H, J = 8.4), 7.19 (d, 2H, J = 8.4), *6.70* (d, 1H, J = 16.2), 2.37 (s, 3H), 2.35 (s, 3H); *cis*: 7.40 (d, 2H, J = 8.1), 6.82 (d. 1H, J = 12.6, smaller J for *cis*), *6.11* (d, 1H, J = 12.6 Hz), 3.06 (s, 3H), 2.13 ppm (s, 3H).

Irradiation procedures

For determination of photostationary state (pss) compositions, all irradiations were carried out in a water-cooled bath with a

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200 W Hanovia medium pressure mercury lamp. NMR sample tubes, after being purged with nitrogen, were placed behind appropriate filter plates for irradiation. Reactions were followed by changes in ^{1}H NMR spectra (300 MHz spectrometer) until constant readings were reached. (NMR signals used to determine pss compositions are listed above.) For most cases, pss were approached from the *trans* isomer, with the exception of compound **2** of which the pss was also approached from the *cis* direction.

Preparative solar reactions

Sample tubes were placed in a "kick-board" reactor,[22] which was allowed to float on the surface of a small wading pool. No filter other than the Pyrex glass of the reaction vessel was used. The entire setup was placed on the roof of the Chemistry building. Solar reactions were carried out during late August in Honolulu, a period with strong sunlight intensity.[28]

cis-Hexamethylstilbene, *cis*-**2**. A $CDCl_3$ solution of 7 mg of *trans*-**2** and ~1 mg of fluorenone were placed in a 5 mm NMR sample tube. After purging with nitrogen the tube was capped. After 3 h exposure to the sunlight, the reaction was found to be complete. The sensitizer was readily removed after passing the irradiated mixture through a short silica gel column. A total amount of 6.8 mg of *cis*-**2** was collected (97% yield).

cis-**4**. A CH_2Cl_2 solution of 25 mg of *trans*-**4** and 4 mg of Michler Ketone were placed in a 3 ml test tube (purged with nitrogen and capped) which was placed in the "kick-board reactor" floating in a water bath. After about 3 h exposure to the sunlight, *trans*-**4** was found to have been totally converted to *cis*-**4**. The pure *cis* product was collected after passing the product mixture through a short silica gel column, with petroleum ether : ethyl ether = 4 : 1 as an eluent. A total amount of 23.5 mg of *cis*-**4** was collected (95% yield).[30]

RESR measurements

Into 5 mm NMR sample tubes 4.6 mg of benzophenone (0.05 M), 18 mg of *trans*-stilbene (0.2 M) and 0.5 ml of dicholoromethane-d_2 were introduced. After the solution was briefly purged with nitrogen, the sample tube was capped. In the same manner, sample tubes containing 1-acetonaphthone, benzil or 9-fluorenone with *trans*-stilbene were prepared. The sample tubes were placed in a water bath behind a Corning O-54 filter plate and were exposed simultaneously to sunlight. The reaction was interrupted after 45 min. The extent of conversion to *cis*-stilbene was determined by the ratio of integrated peak areas of singlets of the vinyl H's of the two isomers (7.31 for *trans* and 5.68 ppm for *cis*).

Acknowledgements

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Solvent-free synthesis of unsaturated ketones by the Saucy–Marbet reaction using simple ammonium ionic liquid as a catalyst

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Simple ammonium ionic liquids are efficient catalysts in promoting Saucy–Marbet reactions of unsaturated alcohols with unsaturated ethers to afford the corresponding unsaturated ketones, eliminating the need for volatile organic solvents. The effect of the anions and the cations of ionic liquids, quantity of ionic liquid, temperature, and chain-length of unsaturated alcohols on the reaction was investigated. The results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid and $[Et_3NH][HSO_4]$ had the best catalytic activity. The conversion and selectivity obtained with this method are significantly increased in comparison to those catalyzed by traditional acid. Furthermore, the ionic liquid could be easily separated and reused with a slight loss of its activity. It provided a good alternative way for the industrial synthesis of unsaturated ketones.

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Introduction

There is a growing need for greener and more sustainable processes in the chemical industry. Replacement or elimination of some toxic reagents or volatile organic solvents in chemical processes is one of the main goals of green chemistry. It is well known that unsaturated ketones such as 2-methyl-2-hepten-6-one, pseudoionone, and farnesylactone, are important substances and intermediates of flavors, fragrances, pharmaceuticals, and other fine chemicals.[1] The conventional method for the production of these unsaturated ketones is the Carroll reaction of unsaturated alcohols with alkyl acetoacetates in the presence of organic aluminium compounds.[2] The drawback of this method is a large amount of carbon dioxide—an atmospheric greenhouse gas that contributes to global warming—would be produced as a byproduct. An alternative method is the Saucy–Marbet reaction of unsaturated alcohols with unsaturated ethers.[3] For example, 6,10-dimethyl-4,5,9-undecatrien-2-one, a key intermediate of Vitamin E and Vitamin A, could be produced from 3,7-dimethyl-oct-6-en-1-yn-3-ol (dehydrolinalool) and 2-ethoxypropene by using the Saucy–Marbet reaction.[4] This reaction can be carried out in the presence of various acids used as catalysts, such as sulfuric acid, phosphoric acid, *p*-toluene sulfonic acid, trichloroacetic acid, and so on. The separation and recycling of catalysts are difficult. Furthermore, this reaction usually calls for volatile organic solvents such as halohydrocarbon, toluene, and petroleum ether,[5] otherwise the selectivity would obviously reduce. Despite numerous attempts to overcome these drawbacks, no benign methods with the advantages of easy separation, convenient recycling, and eliminating the need for volatile organic solvents have so far appeared for the synthesis of unsaturated ketones.

In recent years, ionic liquids have attracted more and more attention due to their special properties, such as an almost undetectable vapor pressure, high thermal stability, non-explosive properties, and strong solvent power for a wide range of organic, inorganic, and polymeric molecules.[6] Some ionic liquids have been successfully used as environmentally benign solvents or catalysts in a number of reactions,[7] such as the Diels–Alder reaction,[8] the Friedel–Crafts reaction,[9] esterification,[10] cracking reactions,[11] and so on. Among these ionic liquids reported in the past several years, a great deal of attention has been given to imidazolium ionic liquids. However, the industrial application of these imidazolium ionic liquids is limiting because of the difficult preparation, expensive cost and high toxicity.[12] Recently, some non-imidazolium ionic liquids such as phosphonium and ammonium ionic liquids have drawn much attention. For example, Bradaric *et al.* reported the industrial preparation of some representative phosphonium ionic liquids and discussed the comparisons with relevant imidazolium ionic liquids.[10] Han *et al.* presented the synthesis of guanidinium ionic liquids and an application for the desulfurization of flue gas.[14] Dai *et al.* reported a new family of cost-effective, highly proton conductive room temperature ionic liquids based on *N*,*N*-dimethylformamide and its potential application in the fuel cell industry.[15] Furthermore, we have succeeded in the industrial preparations of series of simple ammonium ionic liquids and the industrial application in the production of cinnamic acid using these ionic liquids as solvents and catalysts.[16] In special cases, these simple ammonium ionic liquids have attracted considerable interest in industry because of their advantages which include easy preparation, cheap cost, and low toxicity.

Being a part of our systematic research into ammonium ionic liquids and continuing our investigations into industrial applications, herein we reported a benign approach to

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Table 1 The effect of ionic liquids on the Saucy–Marbet reaction[a]

Entry	Catalyst	T/°C	Conv.(%)	Select.(%)
1	$[Et_2NH_2]HSO_4$	95	81	91
2	$[Et_3NH]HSO_4$	95	88	97
3	$[Pr_3NH]HSO_4$	95	85	95
4	$[Bu_3NH]HSO_4$	95	83	92
5	$[Et_3NH]H_2PO_4$	95	70	96
6	$[Hmim]HSO_4$	95	85	94
7	$[Bmim]H_2PO_4$	95	68	95
8	$[Bmim]PF_6$	Reflux	Trace	—
9	$[Bmim]BF_4$	Reflux	2	85
10	[Bmim]Cl	Reflux	Trace	—
11	[Bmim]Tfa	Reflux	8	97
12[b]	PTSA	95	89	72
13[c]	PTSA + Toluene	95	86	96

[a] Dehydrolinalool (0.05 mol), 2-ethoxypropene (0.15 mol), catalyst (0.25 mmol). [b] *p*-Toluene sulfonic acid was used. [c] *p*-Toluene sulfonic acid was used catalyst, and 20 ml toluene was used as solvent.

unsaturated ketones *via* Saucy–Marbet reactions catalyzed by simple ammonium ionic liquids under solvent-free conditions. High conversion and good selectivity could be obtained with these ammonium ionic liquids, eliminating the need for a volatile organic solvent and additional catalyst. In particular, these ionic liquids are very easy to be separate and reuse.

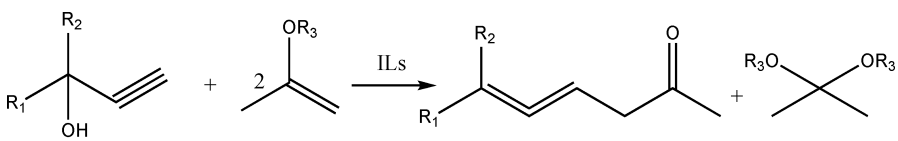
Results and discussion

The reaction of dehydrolinalool with 2-ethoxypropene was firstly used as an example to investigate the effect of ionic liquid on the Saucy–Marbet reaction (Scheme 1). Table 1 lists the effects of different ionic liquids on the reaction without any volatile solvent. It was clear that both conversion and selectivity of the reaction were heavily influenced by the anions of ionic liquids. The high conversion and good selectivity could be obtained when the strongly acidic HSO_4^- anion was used (Table 1, entries 1–5). For example, the conversion of 88% and selectivity of 97% were achieved when $[Et_3NH]HSO_4$ was used. However, the reaction was very slow, and therefore the conversion was lower than 10%, when neutral ionic liquids (Table 1, entries 9, 11) such as $[Bmim]BF_4$ were used. Furthermore, the reaction did not proceed at all in the presence of the $[Bmim]PF_6$ and [Bmim]Cl ionic liquids. When the $H_2PO_4^-$ anion was used (Table 1, entry 5), although the selectivity of the reaction was higher than 95%, the conversion of dehydrolinalool was clearly lower than those obtained with $[Et_3NH]HSO_4$ due to the weaker acidity of the dihydrogen phosphate ionic liquid. Above all, the results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid.

To obtain the higher conversion and selectivity, five different bisulfate ionic liquids were used in the reaction, also listed in Table 1. It was found that the conversion of dehydrolinalool would decrease when the chain-length of the ionic liquids increased due to its higher lipophilic character.[17] Compared with the effect of the anions, the effect of chain-length of the cations was weak. $[Et_3NH]HSO_4$ might be the best catalyst for the Saucy–Marbet reaction in all the ionic liquids, due to its cheap cost, low toxicity and convenient preparation.

An important feature of the reaction catalyzed by bisulfate ionic liquids is that there is no evidence for significant formation of a side reaction, which may be related to the mild acidity of the ionic liquid.[18] During the reaction, the intermediate 3-(1-ethoxy-1-methylethoxy)-3,7-dimethyl-6-octen-1-yne could transform gradually to the desired product 6,10-dimethyl-4,5,9-undecatrien-2-one, and diethoxypropane would be formed by reaction of 2-ethoxypropene and ethanol, which were identified by GC-MS. However, the volatile organic solvent such as toluene was necessary when this reaction was carried out using *p*-toluenesulfonic acid (PTSA) as a catalyst. Otherwise, the selectivity would decrease significantly to 72%. The side products such as 2,6,6-trimethyl-2-ethynyltetrahydro-2*H*-pyran and a 2-ethoxypropene dimer would form because of the strong acidity of *p*-toluentesulfonic acid (Table 1, entry 12). On the other hand, some other side products such as acetone and diacetone alcohol would also be produced due to the presence of water, which was formed by the reaction of *p*-toluene sulfonic acid and ethanol. Furthermore, the separation and recycling of *p*-toluene sulfonic acid are difficult because of the formation of *p*-toluenesulfonic acid ethyl ester. Based on previous reports[3–5] and the observed reaction products, the reaction pathways under solvent-free conditions could be postulated, which is shown in Scheme 2.

It should be noted that the influence of the concentration of the ionic liquid on the reaction was strong. As can be seen in Table 2, the conversion of the reaction was low when the concentration of the ionic liquid was lower than 0.2%. And the selectivity would decrease when the quantity of the ionic liquid was higher than 5.0% because of the formation of side products such as 2-ethoxypropene dimers, acetone, diacetone alcohol, 2,6,6-trimethyl-2-ethynyltetrahydro-2*H*-pyran, and so on. Therefore, the optimal concentration of the ionic liquid to use as a catalyst is about 0.5%. In addition, the reaction seemed to be heavily influenced by the temperature (Table 2, entries 2, 5, 6). The conversion would reduce from 88% to 52% when the temperature of the reaction decreased from 95 °C to 75 °C. At the same time, the selectivity would decrease remarkably from 98% to 45% due to the fact that the thermal cracking



R_1=CH_3
R_2=H or $(CH_3)_2CCH(CH_2)_2$ or $(CH_3)_2CCH(CH_2)_2(CH_3)CCH(CH_2)_2$
R_3=CH_3 or CH_2CH_3

Scheme 1 Saucy–Marbet reaction catalyzed by ionic liquids.

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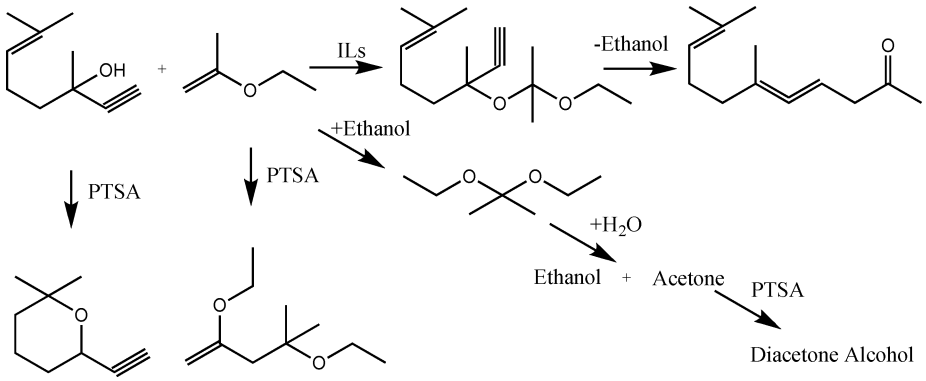

Scheme 2 Postulated reaction pathways under solvent-free conditions.

Table 2 The effect of temperature and concentration of ionic liquid on the Saucy–Marbet reaction[a]

Entry	Concentration	T (°C)	Conv. (%)	Select. (%)
1	0.2%	95	73	95
2	0.5%	95	88	97
3	1.0%	95	89	95
4	5.0%	95	92	84
5	0.5%	85	75	86
6	0.5%	75	52	45

[a] Dehydrolinalool (0.05 mol), 2-ethoxypropene (0.15 mol), $[Et_3NH]HSO_4$ (0.25 mmol).

Table 3 The effect of unsaturated alcohol and 2-alkoxypropene on the Saucy–Marbet reaction[a]

Entry	Unsaturated alcohol	2-alkoxypropene	Conv. (%)	Select. (%)
1	2-methyl-3-butyn-2-ol	2-ethoxypropene	91	98
2	Dehydronerolidol	2-ethoxypropene	80	93
3	Dehydrolinalool	2-methoxypropene	90	98
4	Dehydronerolidol	2-methoxypropene	84	95

[a] Unsaturated alcohol (0.05 mol), 2-alkoxypropene (0.15 mol), $[Et_3NH]HSO_4$ (0.25 mmol), 95 °C.

of the intermediate to the desired product is difficult at lower temperatures.

To test the influence of chain-length of unsaturated alcohols on the Saucy–Marbet reaction, 2-methyl-3-butyn-2-ol and dehydronerolidol were also investigated. It is shown in Table 3 that the conversion and selectivity of 2-methyl-3-butyn-2-ol would increase in comparison to dehydrolinalool. On the contrary, when the long chain unsaturated alcohol such as dehydronerolidol was used, the conversion in chain length of unsaturated alcohols. Furthermore, the effect of different 2-alkoxypropene on the reaction was investigated, which is also listed in Table 3. The results indicated that the conversion of 90% and selectivity of 98% were obtained owing to the higher activity of 2-methoxypropene (Table 3, entry 3), when 2-methoxypropene was used instead of 2-ethoxypropene.

The separation of products and ionic liquid is very easy because the raw materials and products are immiscible with water, while the ionic liquid is hydrophilic. When the reaction was completed, after distilling off the low boiling mixtures, such as 2-ethoxypropene and formed diethoxypropane, in high vacuum, water was added. Then the aqueous phase was separated from the organic phase by phase separation, and the ionic liquid could be recycled by separating out water under reduced pressure from the aqueous phase. It was necessary to remove traces of water because even a small amount of water in the ionic liquid would affect the Saucy–Marbet reaction. The product with a purity of 98.5% was isolated using vacuum distillation, which showed that ionic liquids did not contaminate it, although some of these ionic liquids were volatile.[19] It is shown in Table 4 that the ionic liquid could be recycled with a slight loss of its activity. It seemed that $[Et_3NH]HSO_4$ could have the potential to be used more than five times.

Table 4 The recycling of ionic liquid $[Et_3NH][HSO_4]$[a]

Entry	Cycle no.	Conv. (%)	Select. (%)
1	0	88	97
2	1	85	93
3	2	87	95
4	3	84	94
5	4	86	95

[a] All reactions were carried out at 95 °C.

Experimental

Materials

2-Methyl-3-butyn-2-ol (>99%), 3,7-dimethyl-oct-6-en-1-yn-3-ol (dehydrolinalool, >99%), and 3,7,11-trimethyl-dodec-10-en-1-yn-3-ol (dehydronerolidol, >98.5%) were provided by Zhejiang NHU Co., Ltd. 2-Methoxypropene (>99%) and 2-ethoxypropene (>99%) were provided by Zhejiang Jubang Hi-Tech Corporation. Sulfuric acid, phosphoric acid, trifluoroacetic acid, *p*-toluenesulfonic acid, diethylamine, triethylamine, *n*-tripropylamine, *n*-tributylamine, 1-methylimidazole, toluente, *n*-butyl bromide, *n*-butyl chloride, sodium bisulfate, sodium hexafluorophosphate, and sodium tetrafluoroborate were all used as received unless otherwise stated.

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Instruments

The NMR spectra of the ionic liquids and unsaturated ketones were recorded with a 500 MHz Bruker spectrometer in DMSO or $CDCl_3$ and calibrated with tetramethylsilane (TMS) as the internal reference. Samples of the reaction mixture were analyzed regularly to monitor the reaction by gas chromatography. The products and intermediates were identified by HP5973 GC-MS with a DP17 column (30 m × 0.25 mm × 0.25 μm) by comparing retention times and fragmentation patterns with authentic samples. The reaction conversion and selectivity were determined using GC112A equipped with an ATSE-30 column (30 m × 0.25 mm × 0.25 μm) and a flame ionization detector. Ethyl benzoate (99.9%) was applied as an internal standard for quantitative analysis.

Typical Saucy–Marbet reaction procedure

The simple ammonium ionic liquids of general type [amine][acid] were synthesized according to our former paper.[16] The NMR data and other physical properties of these simple ammonium ionic liquids in this paper are in good agreement with our early reports. Other ionic liquids used in this paper were synthesized according to standard literature methods.[20] A batch reactor, which composed of a four-neck flask connected with a reflux condenser, mechanical stirrer and an oil bath equipped with a thermostat, was used for this reaction. In a typical Saucy–Marbet procedure, the 2-ethoxypropene (12.9 g, 0.15 mol) was added slowly to the mixtures of dehydrolinalool (7.6 g, 0.05 mol) and triethylamine bisulfate ionic liquid (0.05 g, 0.25 mmol) at 90 °C and stirred for 2 h. Then the reaction mixture was stirred for an additional period of 24 h at 95 °C. After the reaction was completed, the low boiling mixtures were distilled off under reduced pressure, and water was added. The organic phase was separated and analysed by gas chromatography (typical data are listed in Table 1 and Table 2). The ionic liquids in the aqueous phase could be collected and reused by evaporating off water in high vacuum. The product of 8.0 g was obtained by using vacuum distillation with a purity of 98.5%. The main impurity was 2,6,6-trimethyl-2-ethynyltetrahydro-2*H*-pyran and dehydrolinalool. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.91 (s, 9H), 2.01–2.26 (m, 7H), 5.07 (m, 1H), 5.99 (d, 1H), 6.10 (d, 1H), 7.40 (m, 1H); IR (ν cm^{-1}): 2966.6, 2925.4, 2856.5, 1684.5, 1667.3, 1628.5, 1445.3, 1360.7, 1316.0, 1252.9, 973.8, 825.5; GC-MS, *m*/*z*: 41, 43, 69, 81, 109, 124, 149, 177, 192.

Conclusion

In summary, simple ammonium ionic liquids are highly efficient catalysts for Saucy–Marbet reactions of unsaturated alcohols with unsaturated ethers, eliminating the need for volatile organic solvents. The effect of ionic liquid on the Saucy–Marbet reaction was investigated and the results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid. The high selectivity of 97% and good conversion of 88% could be obtained using $[Et_3NH]HSO_4$ as the catalyst, which may be related to the mild acidity of ionic liquids. Furthermore, the separation and recycling of the ionic liquids were easy with only a slight loss of their activity. Considering the high conversion and good selectivity of this method, as well as the cheap cost, convenient preparation, and low toxicity of simple ammonium ionic liquid, it can provide a good alternative way for the industry synthesis of unsaturated ketones, which was also important to reduce carbon dioxide emissions from chemical industry.

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Organic reactions in low melting mixtures based on carbohydrates and L-carnitine—a comparison†

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A new L-carnitine/urea melt was developed and compared to previously reported sugar and sugar alcohol melts using several organic reactions for benchmarking. Physicochemical properties of the new L-carnitine melt, including the melting point and the polarity were determined by differential scanning calorimetry (DSC) and solvatochromatic measurements, respectively. The L-carnitine melt shows a very high polarity. Heck and Sonogashira cross-couplings, Diels–Alder reactions and Cu-catalysed 1,3-dipolar cycloadditions proceed cleanly in sugar and L-carnitine based melts, but the applicability of L-carnitine melts for standard organic reactions is limited by their lower thermal stability.

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Introduction

The use of appropriate alternative solvents for chemical transformations is becoming increasingly important for sustainable development in R & D and for the chemical industry. The use of alternative solvents is one of the 12 principles of Green Chemistry postulated by Anastas and Warner, and has gained growing interest as a response to legislative and social pressure and an increasing greener awareness of the industrial community.[1] Green solvents are meant to successively replace conventional solvents which continue to dominate processes and (to lesser extent) products.[2]

Classical organic solvents used for reactions in the laboratory or industrial processes may cause environmental problems, if they belong to the class of volatile organic compounds (VOC), such as chlorinated hydrocarbons derived from methane, ethane, and propane. Because of their persistence, they accumulate in the atmosphere, contribute to ozone depletion and smog in urban areas.[3] Conventional solvents show a high (eco)toxicity, are flammable and expensive. Despite the intrinsic drawbacks of solvents, most chemical transformations are performed in solution to efficiently control the heat flow, ensure rapid and safe conversion, to avoid undesired side products by dilution and to stabilize transition states, thus enhancing the reaction rate. Only a small number of organic reactions proceed in the solid state[4,5] and such approaches, like ball milling, are restricted by small reaction rates and difficult heat flow control.

To address the drawbacks of conventional solvents and still benefit from solvent effects, "green solvents" for synthetic organic chemistry have been developed, which are finding their way into laboratories and chemical production. These new "green" solvents include supercritical fluids,[6] ionic liquids,[7] water[8] and fluorous biphasic mixtures,[9] and have received growing interest over the last two decades.[10,11] Supercritical fluids like $scCO_2$ are beneficial because they are non-toxic, relatively inert, easily removable and recyclable. A widespread application in research and development, however, is hampered by the demand for advanced apparatus. Ionic liquids, usually based on 1,3-dialkyl imidazolium or pyridinium cations, which have a weakly coordination counter-ion, currently receive much attention, because of their thermal stability, a negligible vapour pressure, being inflammable and their catalytic effects on many types of reactions. Although industry has already started to incorporate IL-based applications like the BASIL or the Dimerosol process, the wider use of ILs has to be evaluated because they are still mainly based on non-renewable resources, the long term toxicity is unclear, while acute toxicity has already been tested positively.[12,13]

Water can be considered an ideal solvent, because it is non-toxic, cheap and easily available. However, limitations arise, especially when extraction with organic solvents becomes necessary or the water has to be removed, which is energy consuming.

We have recently introduced low melting mixtures consisting of carbohydrates, urea, and optionally inorganic salts as new alternative solvents for organic transformations.[14] The stable melts of the mixtures are environmentally benign, because they are easily biodegradable, relatively non-toxic and are available from bulk renewable resources without numerous energy consuming modification steps. Their simple production is advantageous for use as materials or replacement of organic solvents in developing countries with limited industrial infrastructure. In preliminary studies the physical and physicochemical properties were determined. Melting points were measured with differential scanning calorimetry (DSC) and found to be in the range of 65 to 85 °C. The solvent polarity, an important reaction parameter, especially when the transition state of a reaction is polar or ionic, was determined by UV measurements with Nile red and Reichardt's dye as solvatochromatic probes. The

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melts are very polar and exhibited polarities between DMSO and ethylene glycol.[15] Carbohydrate urea melts have very good solvent properties and were successfully used for chemical transformations such as Diels–Alder reactions, Stille and Suzuki cross-couplings and for hydrogenation reactions, illustrating the general use of the melts in organic synthesis.[16] A sustainability assessment of the melts, where solvent performances and ecological (dis)advantages of different solvent systems for the Diels–Alder reaction of cyclopentadiene and methyl acrylate were investigated, rated the new alternative media to be less toxic compared to other conventional and alternative solvents.[17]

Apart from sugar as a melt component, other renewable materials are suitable to form melts, which can be considered as alternative solvents. As a consequence, a broad spectrum of melts with different compounds is available with different solvent properties like polarity, melting point, dissolving ability and the price of the raw materials. Here, the right choice of solvent system for a specific chemical transformation becomes difficult and it is necessary to compare the performance of different melt systems based on renewable materials to reach high reaction rates and selectivities.

We report here a comparison of the performance of a new L-carnitine/urea melt to the established sugar and sugar alcohol melts using several important organic reactions for benchmarking. The Heck and Sonogashira cross-coupling, as well as the 1,3-dipolar copper catalysed cycloaddition reactions were performed in the alternative media to compare the systems. Apart from the chemical reactions, the polarity of the new L-carnitine/urea melt was determined with a solvatochromatic probe and found to be even higher than the typical sugar melt.

Results and discussion

Reactions in sugar and sugar alcohol melts

Mixtures based on carbohydrate, urea and salt were reported by us to form stable and clear melts with melting points between 65 and 85 °C and were successfully applied as solvents for Diels–Alder cycloadditions, catalytic hydrogenation and both Suzuki and Stille cross-coupling reactions. The workup of the melts is conducted simply by the addition of water leading to phase separation,[18] and allowing for the collection of the starting material and the crude product by pipetting off the supernatant.

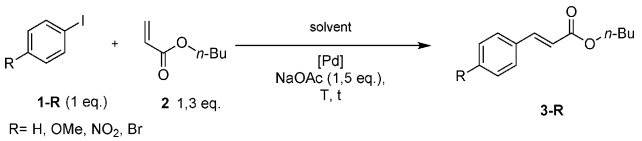
To prove the general applicability of sugar/urea/salt melts for chemical transformations, further typical reactions were tested using the melt as a solvent. Especially transition metal catalysed reactions were investigated, because of their good efficiency.

Heck cross-coupling

A widely used palladium-catalysed process in contemporary organic chemistry is the Heck-type coupling. In most cases a catalytic amount of a palladium complex, often with phosphine ligands, is used in a polar solvent at moderate temperatures.[19] Heterogeneous catalyst systems facilitate the catalyst recycling,[20] and avoid contamination of products by the palladium catalyst.[21]

To compare the difference in performance of homogeneous and heterogeneous palladium catalysts in this alternative media we used both types of catalysts and the results were compared between conventional and alternative solvents. Firstly, palladium on activated carbon (Pd/C) as a heterogeneous catalyst was used, because this catalyst is reported to have high activity and enjoys general use even for one-pot multi step reactions.[22]

The Heck cross-coupling of iodobenzene (**1-H**) and *n*-butyl acrylate (**2**) was studied using different catalysts and reaction conditions to afford *n*-butyl cinnamate (**3-H**) (Scheme 1). The use of a heterogeneous palladium catalyst was compared with homogeneous Pd-sources and with reactions in high boiling solvents like DMF and in [BMIM][PF_6] as a representative room temperature ionic liquid (RTIL).



Scheme 1 Palladium catalysed Heck cross-coupling with *n*-butyl acrylate and iodobenzenes in several solvent systems using different reaction conditions.

Table 1 shows the yields of the cross-couplings, indicating that the use of heterogeneous Pd/C catalysts is less suitable in melts, presumably due to their higher viscosity. To increase the reaction rate, ultrasound agitation was applied resulting in a significantly shorter reaction time with a slightly increased yield.[23] Using a homogeneous catalyst still gave a higher yield, which is comparable to isolated yields reported for conversions in classical organic solvents.

After the best source of metal catalyst for the Heck-reaction in the melt was identified, the addition of ligands to the homogeneous Pd salt was investigated, where $PdCl_2(PPh_3)_2$ seemed to be the catalyst of choice. The scope of the melt reaction conditions was investigated with a small series of substituted iodobenzenes (**1-R**), giving good to excellent isolated chemical yields of the reaction products. 1-Bromo-4-iodobenzene was found to be a good electrophile for the Heck reaction in this alternative medium. Reactions with this electrophile in melts are compared with different homogeneous catalysts in conventional ($AcNMe_2$, 87%)[24] and alternative solvents ([BMIM][PF_6], 33%)[25] to show the general applicability of sugar and L-carnitine melts. The comparison shows that good to excellent yields (62–91%) can be obtained using the carbohydrate melts at lower reaction temperatures compared to organic solvents or an ionic liquid.

Table 1 Isolated yields of the cross-coupling product under different reaction conditions

R	Pd-source	Reaction conditions[a]	Time/h	Isolated yield [%]
H	Pd/C	melt, 80 °C	12	63
H	Pd/C	melt, us, 73 °C	3	69
H	Pd/C	DMF, 80 °C	1	67
H	$PdCl_2$	[BMIM][PF_6], 120 °C	6	91
H	$Pd(OAc)_2$	melt, us, 73 °C	2	81
Br	$Pd(OAc)_2$	melt, 80 °C	4	85
H	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	77
OMe	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	86
NO_2	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	85
Br	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	91

[a] us = ultra sound, melt = D-mannose/DMU (3 : 7, wt/wt).

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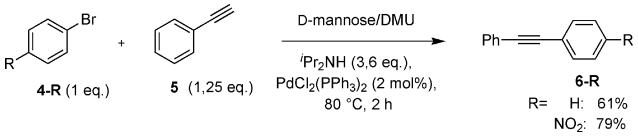
Sonogashira cross-coupling

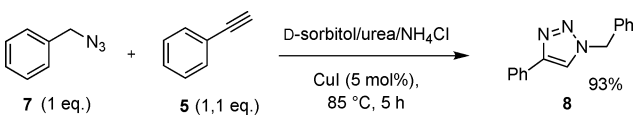
Another important palladium/copper-catalysed reaction for the synthesis of substituted alkynes from aryl halides and terminal acetylenes is the Sonogashira coupling.[26] The Sonogashira reaction is frequently used as a key step in natural product chemistry and for the synthesis of acetylene compounds for optoelectronic applications.[27] This well-established methodology has seen a huge variety of modifications during recent years. Remarkably is the elimination of the copper salt which was used to suppress the undesired homocoupling by the *in-situ* generated copper acetylides (the Glaser-coupling) to diynes by oxidative agents or air.[28] In our experiments a D-mannose/urea melt was used to couple aryl halides (**4-R**) and phenyl acetylene (**5**) without the use of a copper co-catalyst. Like in the Heck cross-coupling described above, the homogeneous catalyst $PdCl_2(PPh_3)_2$ was used due to the better performance compared to the heterogeneous Pd/C (Scheme 2). As expected, the nitro-substituted electrophile **4-NO$_2$** gave better yields (79%) after 2 h at 80 °C.



Scheme 2 Homogeneous Sonogashira cross-coupling with D-mannose/DMU as a solvent at 80 °C.

Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition

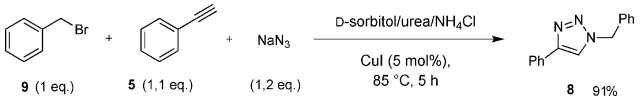
The Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC), a Cu^{I}-catalysed version of the Huisgen 1,3-dipolar cycloaddition,[29] has been established as a reliable method for the preparation of triazoles and is performed in conventional organic solvents,[30] ionic liquids[31] and water.[32] Here, a D-sorbitol/urea/NH_4Cl (7 : 2 : 1, wt/wt/wt) melt was used rather than a mannose melt due to its higher chemical stability avoiding potential side reactions induced by the strong nucleophile sodium azide. The sugar alcohol sorbitol is chemically less reactive than mannose and hence a good solvent for the reaction of benzyl azide (**7**) with phenyl acetylene (**5**) at 85 °C (Scheme 3) providing excellent isolated product yields.



Scheme 3 Cu(I) catalysed formation of 1,4-substituted 1,2,3-triazoles in the melt.

After isolation, the 1,4-regioisomer **8** was found to be formed exclusively.[33] Best yields were obtained using CuI as copper source; $CuSO_4$ with sodium ascorbate as reducing agent, used in many cases for the CuAAC, yielded only 84%. Upon ultrasound irradiation the conversion increased drastically, but the regioselectivity of the reaction decreased. After 30 min of reaction, a 4 : 1 mixture of the 1,4- and the 1,5-triazole was isolated, which indicates that under these conditions the non-catalysed reaction pathway is promoted.[34]

Reducing the number of individual synthetic steps to a product is economically and environmentally advantageous.[35] Therefore, a "one-pot" modification of the CuAAC was investigated. The azide formation and cycloaddition can be performed in one step (Scheme 4) in the D-sorbitol melt, still giving an excellent yield (91%). The conversions in the melt systems require no additional base, similar to the findings of CuAAC reactions in water.[36]



Scheme 4 One-pot fashion formation of 1,4-substituted 1,2,3-triazoles in the melt.

The discussed examples illustrate that many modern transition metal catalysed reactions can be performed in low melting mixtures of sugars, urea and salt.[37] Depending on the catalytic system used, the reaction benefits from the highly polar medium and simple and efficient work-up procedures. However, the higher viscosity of the melt compared to conventional organic solvents limits the use of heterogeneous catalyst systems, even if ultrasound was employed.

Properties and chemical reactions in L-carnitine based melts

Looking for new alternative melt systems consisting of renewable feedstock, L-carnitine (Fig. 1) was investigated. L-Carnitine, a natural betain, is biotechnologically accessible *via* both γ-butyrobetain and crotonbetaine and an interesting renewable bulk product.[38] This non-toxic (rat oral LD50 > 5000 mg kg^{-1}) and non-mutagenic (Ames-test negative) natural product shows almost no skin irritation and is reported to be a stable compound. L-Carnitine is used as renewable building block for biomaterials like polycarnitine, polycarnitine allylesters and polycrotonbetaines, retaining the initial properties of the monomers *e.g.* the "stiffening" effect.[39]

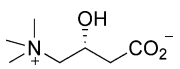


Fig. 1 L-Carnitine: 3-carboxy-2-hydroxy-*N*,*N*,*N*-trimethyl-hydroxide.

Screening the best combinations between L-carnitine and different substances like urea, DMU and NH_4Cl, which are known for potential melting point depression, DSC measurements gave the lowest melting point of 74 °C for a 2:3-mixture of L-carnitine/urea (wt:wt). For all further measurements and chemical reactions this ratio was used without further addition of melt components.

Solvatochromatic measurements were carried out to determine the polarity of the new L-carnitine/urea melt and compared with other melts (Fig. 2). Nile red was used as solvatochromatic probe in the melt and E_T values were calculated from UV-Vis measurements.

In comparison to other melts based on renewable feedstocks, the L-carnitine/urea mixture showed a rather high polarity with an E_T(NR) value of 49.89 kcal mol^{-1}. The E_T(NR) value is between the value of D-sorbitol/DMU and citric acid/DMU

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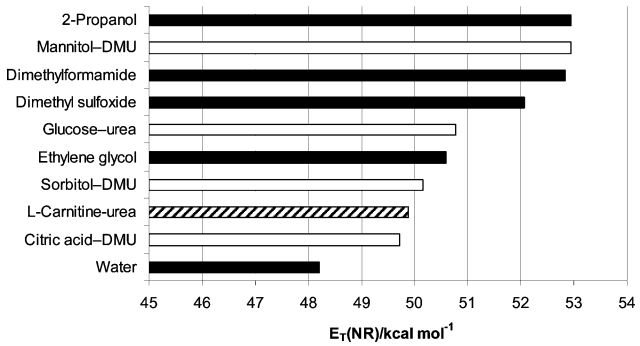


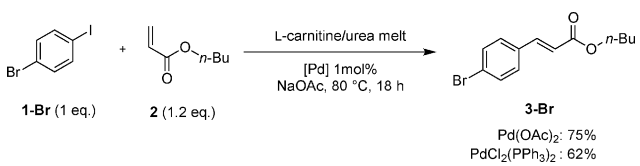
Fig. 2 Solvent polarity values E_T in L-carnitine/urea melt (dashed) and other solvents (black) and melts (white) for comparison at 80 °C; determined with Nile red as probe.

melts with 50.16 and 49.72 kcal mol^{-1}, respectively, and only slightly higher than the value for water.

Heck cross-coupling

Like the previously reported sugar based urea mixtures, the L-carnitine/urea mixtures show good solvent properties for chemical transformations. The viscosity, however, is slightly higher than in the case of the sugar melts.

First, the Heck cross-coupling reaction was investigated. Different palladium sources were tested and $Pd(OAc)_2$ worked best in this media for a reaction of *n*-butyl acrylate with 1-bromo-4-iodobenzene, which was found to be the best electrophile for the carbohydrate melts. Similar to in the sugar melts, palladium on charcoal as a catalyst exhibited lower conversions (Scheme 5).

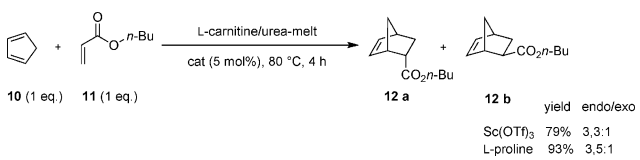


Scheme 5 Homogeneous Heck cross-coupling with *n*-butyl acrylate and 1-bromo-4-iodo benzene.

The work up of the reaction mixture is easy since both components of the melt have a high solubility in water, like the sugar melts. Activation by ultrasound was tested in the case of the Heck reaction, but gave very low conversions. We explain the low yields by the partial decomposition of L-carnitine under the reaction conditions poisoning the catalyst.

Diels–Alder cycloaddition

The Diels–Alder cycloaddition is widely used in organic synthesis.[40] The reaction proceeds in organic solvents and alternative solvents like ILs, $scCO_2$ and water. Scheme 6 shows the Diels–Alder reaction of cyclopentadiene and *n*-butyl acrylate with catalytical amounts of $Sc(OTf)_3$ or L-proline as catalysts.



Scheme 6 Diels–Alder cycloaddition of cyclopentadiene and *n*-butyl acrylate.

The reaction with 5 mol% L-proline as organocatalyst instead of $Sc(OTf)_3$ gave an excellent yield of 93% for **12a** and **12b**. The results obtained in the L-carnitine/urea melt are comparable to the previous findings in carbohydrate melts, where overall yields of **12a** and **12b** range from 72 to 95% for a D-fructose and lactose melt, respectively.[14]

Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition

Interestingly, the copper catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) proceeded slightly better in an L-carnitine based melt than in the sugar melt (Fig. 3). A possible coordination of the carnitine molecule to the Cu^I ion, resulting in a stabilizing effect during the cycloaddition, may promote the reaction. An analogue effect was demonstrated by the group of Ma, where L-proline functions as a ligand in Cu^I catalysed C–N bond formation reactions.[37] Fig. 4 shows the proposed coordination of the copper ion during amino acid promoted reactions. An analogous coordination of copper by L-carnitine is proposed to explain the better yields in the carnitine melts compared to the carbohydrate melts.[41]

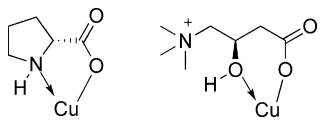


Fig. 3 Proposed coordination of copper(I) ions by L-proline and L-carnitine.

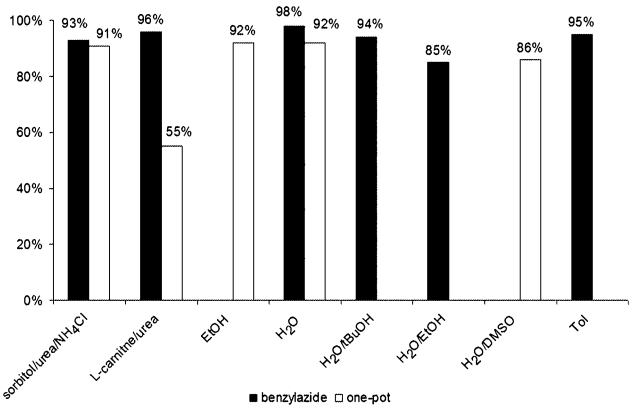


Fig. 4 Bar graph comparing click reactions yielding 1,4-substituted 1,2,3-triazoles in different solvent systems. Reactions starting from benzylazide and one-pot reactions using benzylbromide are shown separately. Reaction conditions for EtOH: 78 °C, 24 h; H_2O: 25 °C, 24 h (98%), 25 °C, 1 h (92%); H_2O/^{t}BuOH: 25 °C, 24 h; H_2O/EtOH: 25 °C, 3 h; H_2O/DMSO: 25 °C, 15 h; toluene: 60 °C, 24 h.[42]

The use of $CuSO_4$ instead of CuI was tried, but resulted in a reduced yield (81%) similar to the reaction performed in a carbohydrate melt. In all cases reported here no additional base was necessary, because of the reversible proton accepting property of the melt. This effect was observed for CuAAC reactions in water, as well.[32] The results obtained in carnitine and carbohydrate melt systems are compared with the outcome of the reaction in other commonly used organic solvents

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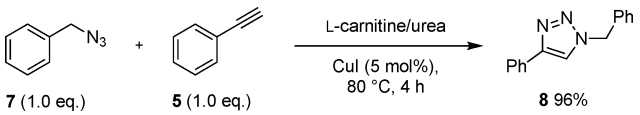
(Fig. 4). A comparison of CuAAC reactions starting from either benzylazide (benzylazide) or the benzylbromide (chloride) (one-pot) are given. The one-pot approach in L-carnitine melt resulted in a lower overall yield of 55%, which is attributed to the higher chemical reactivity of the melt. Both melts, however, showed very good applicability compared to aqueous and organic solvents (Scheme 7).



Scheme 7 Cu(I) catalysed formation of 1,4-substituted 1,2,3-triazole in the L-carnitine melt.

Experimental

General

All chemicals were used without further purification as received with the exception of $^{i}Pr_2NH$ which was distilled before use. Benzyl azide was prepared following the procedure of Alvarez and stored in the refrigerator.[43]

Preparation of melts

Unless otherwise stated, the constituents of the melts were ground with a mortar and pestle, filled into a resealable vial equipped with a stirring bar and placed into an oil bath. Upon formation of the melt, the reactants were loaded under nitrogen before the vial was sealed.

For the Sonogashira reaction, liquid reactants were deaerated with nitrogen prior to use. After formation of the melt the vial was evacuated and flushed with nitrogen to remove any oxygen from the melt. This procedure was repeated three times before the reactants were added.

For experimental accuracy, the work-up was carried out by extraction with organic solvents in commonly used amounts. For larger scale reactions, however, liquid extraction with organic solvents can be significantly reduced. Workup of small scale test reactions (1 mmol) required only very small amounts of organic solvents for phase separation. The addition of water (50 mL), brine (10 mL) and 3 mL of EtOAc to the reaction mixture will dissolve all melt components and separates the organic layer containing product and starting material after extraction. For analytical investigations, the remaining aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phase was analysed by gas chromatography (GC). For D-sorbitol/urea/NH_4Cl (7 : 2 : 1), D-mannose/DMU (3 : 7) and L-carnitine/urea (2 : 3) melt, no starting material or product could be detected by GC analysis confirming their complete extraction by 3 mL of EtOAc.

To test the recyclability of the Pd containing melt, a recycling experiment over three cycles was performed with *p*-iodo anisole and 1-bromo-4-iodobenzene as electrophiles in a sorbitol/urea melt (5 : 5). The catalyst remains active during the experiment, but its activity drops significantly with each reuse of the melt (see supporting information for experimental data).† The decreasing catalytic activity of the catalyst in reused melts is in agreement with earlier observations of Stille cross-coupling reactions in the melt.[16] After the last run of the recycling experiment the melts were dissolved in water (50 mL) and extracted with EtOAc (3 × 20 mL). GC analysis of the organic phase gave no detectable signals for starting material or product indicating its quantitative extraction during the recycling runs.

Typical procedure for homogeneous Heck reactions in D-mannose/DMU melt

In a 10 mL Schlenk tube containing deaerated D-mannose/urea-melt (2 g, D-mannose/DMU, 3:7, wt/wt) 4-iodoanisole (0.23 g, 1.0 mmol), *n*-butyl acrylate (0.19 mL, 1.3 mmol), sodium acetate (0.2 g, 1.5 mmol) and bis-(triphenylphosphin)-palladium(II) chloride (0.007 g, 0.01 mmol) were added at 80 °C under nitrogen. The reaction was stirred for 18 h at this temperature, water (3 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (EE : PE = 1 : 6, $R_f = 0.32$) to yield the desired product as colourless oil (0.2 g, 86%). The ^{1}H and ^{13}C NMR-spectroscopic data are in accordance with the literature.[44]

Typical procedure for Sonogashira cross-coupling in D-mannose/DMU melt

In a 10 mL Schlenk tube containing deaerated D-mannose/urea-melt (2 g, D-mannose/DMU, 3 : 7, wt/wt) 1-bromo-4-nitrobenzene (0.202 g, 1.0 mmol), phenylacetylene (0.128 g, 1.25 mmol), diisopropylamine (0.26 mL, 3.6 mmol) and dichloro-bis(triphenylphosphine)palladium(II) (0.014 g, 0.02 mmol) were added at 80 °C and under nitrogen. The reaction mixture was stirred for 2 h. After the reaction was stopped, water (3 mL) was added. After extraction with EtOAc (3 × 20 mL) the combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give the brown crude product. The crude solid was subjected to column chromatography (EE : PE = 1 : 19, R_f = 0.48) to obtain **6-NO$_2$** in 79% yield (0.176 g). The ^{1}H and ^{13}C NMR-spectroscopic data are in accordance with the literature.[45]

Cu-catalysed azide-alkyne cycloadditions in D-sorbitol/urea/NH_4Cl melt

To a capped vial equipped with a stirring bar containing D-sorbitol/urea/NH_4Cl melt (2 g, D-sorbitol/urea/NH_4Cl, 7 : 2 : 1, wt/wt/wt) benzyl bromide (0.12 mL, 1 mmol), phenyl acetylene (0.12 mL, 1.1 mmol), copper(I) iodide (9 mg, 0.05 mmol) and sodium azide (78 mg, 1.2 mmol) were added and the reaction was stirred for 5 h at 85 °C. At the end of the reaction water (3 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, evaporated and the crude product was subjected to column chromatography (EE : PE = 1 : 3, $R_f = 0.31$) to yield the 1,4-substituted 1,2,3-triazole as pale yellow solid (210 mg, 91%). The ^{1}H and ^{13}C NMR-spectroscopic data and the melting point are in accordance with the literature.[46]

The Heck and CuAAC reactions were performed in analogy to the carbohydrate melts using L-carnitine instead of the sugar component.

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Diels–Alder cycloaddition in L-carnitine/urea melt

To a capped vial equipped with a stirring bar containing L-carnitine/urea melt (2 g, 2:3, wt/wt) cyclopentadiene (0.16 mL, 2.0 mmol), *n*-butyl acrylate (0.29 mL, 2.0 mmol) and scandium-trifluoromethane sulfonate (0.01 g, 0.1 mmol) were added and the reaction was stirred for 4 h at 80 °C. At the end of the reaction water (3 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic phase was dried over anhydrous $MgSO_4$, evaporated and the crude product was subjected to column chromatography (PE, $R_f = 0.39$) to yield the product as colourless oil (0.306 g, 79%).

Determination of the polarity

Solvatochromatic measurement of the solvent polarity with Nile red (NR) as solvatochromatic probe: L-carnitine (10 g), urea (10 g) and Nile red (0.3 mg) were ground with a mortar and pestle. The mixture was filled into a reaction flask, stirred in an oil bath at 80 °C and equilibrated for 5 h until a transparent purple homogeneous melt was formed. A blank melt for comparison was prepared using L-carnitine (2 g) and urea (2 g) and stirred for 5 h. While still hot, the melts were consecutively transferred into preheated UV cuvettes and instantly measured with a UV-Vis spectrometer. The blank sample was used for background subtraction. λ_{max} was determined and used in the formula $E_T(NR)$ kcal mol^{-1} $= hc\lambda_{max}N_A = 28591/\lambda_{max}$ to obtain $E_T(NR)$. The measurement and determination of the polarity was repeated two times to confirm the reproducibility without significant variations.

Conclusions

Melts based on an L-carnitine/urea mixture show an overall lower efficiency as alternative solvents compared to established carbohydrate melts. The new medium was found to have a melting point of 74 °C for a 2 : 3 mixture of L-carnitine/urea (wt : wt) and a relatively high solvent polarity between the E_T values of ethylene glycol and water, as determined by solvatochromatic probes. For comparison, transition metal catalysed reactions were performed in the new melt and the previously reported carbohydrate melts. The Heck cross-coupling reaction with heterogeneous Pd/C showed low reaction rates, due to the high viscosity of the melts. Using a homogeneous Pd-source, the carbohydrate melts gave yields up to 91%, whereas the L-carnitine melt afforded only 75% yield for $Pd(OAc)_2$. Sonication increased the reaction rate in carbohydrate melts, but gave lower yields in L-carnitine/urea melts indicating a decomposition of the melt component. The Diels–Alder reaction gave comparable yields and selectivites in both melt systems when L-proline was used as an organocatalyst. The yields for Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) were slightly better (96%) in the L-carnitine/urea when compared to the carbohydrate melt reactions. The "one-pot" procedure of subsequent azide formation and conversion gave excellent results in the sugar based melts, while the yield for the L-carnitine melt was much lower (55%). A side reaction of the azide nucleophile with the carnitine melt component may account for the reduced yield. When $CuSO_4$ with Na-ascorbate as catalyst was used, the yields were found to be lower than for the CuI catalysis: 84% from carbohydrate melts and 81% from the L-carnitine melt of the desired product were isolated.

Comparing the performance in chemical transformations of the new L-carnitine melt to carbohydrate melts, L-carnitine was not as effective as a solvent for organic transformations. L-Carnitine contains a quaternary ammonium ion leading to chemical instability[47] in the presence of nucleophiles, like azides. Irradiation with ultrasound causes partial decomposition of the L-carnitine melt. Another aspect of evaluating alternative solvents is the price of the melt components. Considering the various parameters the carbohydrate melts have an advantage over L-carnitine melts. Fig. 5 summarizes the results from Heck-type and click reactions in carbohydrate and carnitine melts in terms of chemical yields. Carbohydrate melts, based on D-mannose or D-sorbitol, showed very good solvent properties for the Heck reaction with homogeneous Pd-sources, the Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition, performed well in "one-pot" CuAAC procedures and gave good results for the Sonogashira cross-coupling, while L-carnitine/urea is only suitable for some of these standard transformations in organic synthesis and therefore limited in general applicability.

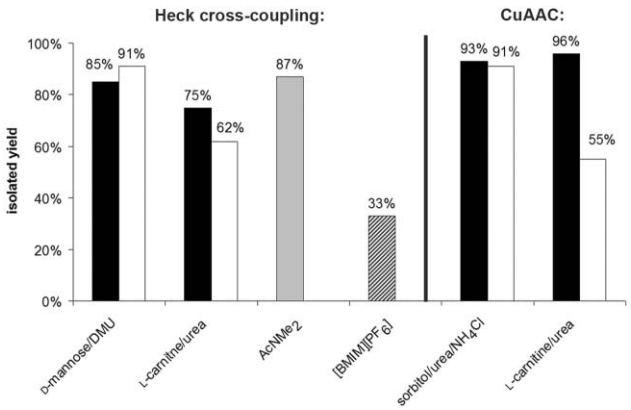

Fig. 5 Typical chemical yields of reactions in carbohydrate and carnitine melts. Heck cross-coupling (left): reactions of 1-bromo-4-iodobenze using $Pd(OAc)_2$ (black bar), $PdCl_2(PPh_3)_2$ (white bar), a furancarbothioamide derived palladacycle (grey),[24] or (bis-*N*-methylimidazole)$PdCl(CH_3)$[25] (dashed) as catalyst. CuAAC (right): 1,4-substituted 1,2,3-triazoles were obtained either from benzylazides (black bar) or in one-pot fashion (white bar).

List of abbreviations

Ac	Acetyl-
$AcNMe_2$	Dimthylacetamide
BASIL	Biphasic acid scavenging using ionic liquids
[BMIM][PF_6]	1- Butyl-3-methylimidazolium hexafluorophosphate
*t*BuOH	*tert*-Butanol
c	speed of the light
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMU	*N*,*N*′-Dimethyl urea
EE	Ethyl acetate
E_T	Transition energy
EtOAc	Ethyl acetate

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EtOH	Ethanol
h	Planck's constant
IL	Ionic liquid
λ_{max}	maximal absorption wavelength
N_A	Avogadro's constant
NMR	Nuclear magnetic resonance
OTf	Triflate
PE	Petrol ether
Ph	Phenyl
R & D	Research and development
$scCO_2$	Supercritical carbon dioxide
UV-Vis	Ultra violet/visible

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Regioselective enzymatic acylation of pharmacologically interesting nucleosides in 2-methyltetrahydrofuran, a greener substitute for THF

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1-β-Arabinofuranosyl uracil, 9-β-arabinofuranosyl adenosine, 2′-*O*-(2-methoxyethyl)-5-methyl uridine, adenosine and uridine were enzymatically acylated with hexanoic anhydride and vinyl esters by CALB lipase (lipase B from *Candida antarctica*) with excellent regioselectivity in many cases and analytical reaction yields above 90%. The influence of the stereochemistry of the hydroxyl group on C-2′ was studied. Some of these esterifications were carried out in 2-methyltetrahydrofuran (MeTHF), which is described as an excellent substitute for THF in biocatalysed processes in organic media. This application for this green solvent is a proof-of-concept opening the use of MeTHF in biotransformations.

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Introduction

Nucleosides and derivatives are relevant compounds in terms of pharmacological properties.[1] They have shown, among others, activity against some kinds of viruses (including the human immunodeficiency virus) and carcinogenic cells. For this reason, enormous efforts have been undertaken in the last 20 years to synthesize derivatives with potent antiviral and antitumor activities.[2] In this sense, the goal of the present research work was the regioselective synthesis of 1-β-arabinofuranosyl uracil (*ara*-U) and 9-β-arabinofuranosyl adenosine (*ara*-A) derivatives to be tested as prodrugs with antitumor activity.

Ara-U and *ara*-A are appealing compounds due to their cytotoxic activity. Nevertheless, they are extremely hydrophilic and, consequently, poorly absorbed enterically, so a different administration route would be desirable. For this reason, appropriate derivatives of the above-mentioned biologically active products should be developed. Different chemical structures can be proposed to produce nucleoside prodrugs, but ester formation is the most interesting reaction because of the high activity of human esterases, which can quickly liberate the drug. Besides, esters have higher lipophilicity, which facilitates the permeability through cell membranes. In fact, several esters from nucleoside analogues (such as acyclovir) have been prepared.[3] Among all possible derivatives, those with a small side chain in the OH-5′ position could give rise to products with enhanced pharmacokinetic properties. Indeed, the acylation on C-5′ would lead to a prodrug that could be administered transdermally or as a solid pharmaceutical preparation.

Although chemical acylations of nucleosides have been reported in few cases, this methodology usually implies the use of protecting groups and tedious separation processes, rendering low yields of the mono-*O*-acyl derivative.[4] In turn, regioselective enzymatic acylation of nucleosides[5] and hydrolysis[6] of the corresponding esters are being intensively investigated due to their feasibility and high efficiency. In general, biocatalysts used in these processes (lipases) are relatively cheap and environmentally friendly. Their use often avoids the need for protecting groups, the reaction conditions are mild, they can show high regioselectivity (reducing the appearance of side reactions) that can be modulated by modification of the reaction parameters and, in the case of immobilized enzymes, it is possible to reuse them,[7] so that the economical sustainability can be increased.

The benefits of using biotransformations can be further improved with a rational selection of the solvent. In this sense, we present an esterification study of the above-mentioned substrates with several vinyl esters as acylating agents and using different lipases and solvents. Remarkable results were obtained for the acylation of *ara*-U in 2-methyltetrahydrofuran (MeTHF), which is a versatile aprotic solvent that is being used more often in industrial synthetic processes because of its favorable properties.[8] In classical organic chemistry, MeTHF is increasingly being used as a THF substitute in the preparation of Grignard's reagents,[9a] for low-temperature lithiation,[9a,9b] for lithium aluminium hydride reductions,[9a] for the Reformatsky reaction,[9c] as well as for metal-catalyzed coupling reactions.[9d–9f] In fact, MeTHF has a higher log *P* value (0.99)[9g] compared to THF (0.49),[9g] and it is partially miscible with water (solubility of water in MeTHF ranges from 4% to 5% upon heating from 0 to 70.6 °C; solubility of MeTHF in water ranges from 21% to 6% in the same temperature range);[8] on the other hand, it has a boiling point of 89 °C, slightly higher than that of THF and, therefore, solvent evaporation during reaction is reduced. Besides, this solvent forms an azeotrope with 10.6% water, allowing the recycling of dry MeTHF; and gives clean water phase separations, useful for two phase reactions and product recovery. In many senses, MeTHF resembles toluene in terms of physical properties.[8] Most importantly, MeTHF

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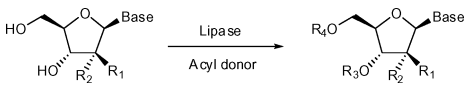
is the only aprotic solvent similar to THF that derives from renewable resources, *i.e.* it has low environmental impact, since it is produced from furfural, which is a chemical isolated from corn crops, sugar cane bagasse and oat hulls. Therefore, substitution of THF or other solvents like dichloromethane or dichloroethane for MeTHF will render greener processes, as the 3R desiderations—reduce, recycle and reuse—are all met by the introduction of MeTHF. As far as we know, and excluding a short statement in a old paper by Nakamura *et al.*[9g] (as one of many solvents and, of course, without emphasizing its green character at that time), this is the first description of MeTHF as a solvent in biotransformations.

Results and discussion

1-β-Arabinofuranosyl uracil (*ara*-U, **1**) and 9-β-arabinofuranosyl adenosine (*ara*-A, **15**), two cytotoxic compounds, were regioselectively acylated with vinyl esters by several lipases in different solvents with the aim of producing nucleoside derivatives with enhanced pharmacological properties (Scheme 1, Table 1). Most of the published research on enzymatic esterification of nucleosides is based on 2′-deoxy derivatives.[10] However, we show herein the broad applicability of lipase B from *Candida antarctica* (CALB) in such processes, since it is also capable of distinguishing among three hydroxyl groups.



Scheme 1

Acylation of 1-β-arabinofuranosyl uracil (*ara*-U)

Ara-U (**1**) was esterified at room temperature with hexanoic anhydride by Novozyme435, an immobilised CALB, using two solvents independently, THF and MeTHF. This process took place regioselectively at the hydroxyl group on C-5′, which is the preferred position for the lipase employed to react as demonstrated by 2′-deoxynucleosides.[11] These derivatives were characterized mainly by the ^{13}C NMR data, since the signal of the carbon supporting the acyl group (C-5′) moved downfield compared to the non-acylated. Thus, the neighboring carbon atom (C-4′) shifted upfield. The same regioselectivity has been obtained in the hydrolysis of nucleoside esters.[6]

Final conversion reached different values at the equilibrium with the different solvents, probably because of their different water miscibility and, therefore, also because of their different water activity. In fact, when using MeTHF, after 6 h, 90% of product 5′-*O*-hexanoyl-1-β-arabinofuranosyl uracil (**5**) was detected, but the yield decreased to 80% at 8 h, remaining stable after this time. The reaction in THF proceeded slightly slower but constantly increased up to a final value of 95% at 24 h. A similar behavior was observed for the esterification of uridine (**7**) under the same reaction conditions, in MeTHF the highest yield (95%) of 5′-*O*-hexanoyl uridine (**9**) was obtained after 4 h, decreasing then to 88% at 24 h; while in THF, the acylation proceeded slower but the product formation continuously increased up to 95% at 24 h. This fact may be caused by the different water miscibility of the solvents: thus, due to the liberation of hexanoic acid as the reaction is proceeding, the micropH in the enzyme surroundings may be altered, as described in ref. 12a, and causing a reversion in the equilibrium by promoting the acidolysis of the acylated product,[12b] this effect is more important when using MeTHF *vs.* THF.

With the aim of synthesizing derivatives of interesting cytotoxic agents *ara*-U and *ara*-A with short side chains in the molecule, the acylation of 1-β-arabinofuranosyl uracil with vinyl acetate (VA) by CALB in 2-methyltetrahydrofuran was performed. After 6 h, 93% of the corresponding derivative in the OH-5′ position was obtained (product **2**), along with 2% of starting material and 5% of 3′,5′-*O*-diacetyl-1-β-arabinofuranosyl uracil (**6**) (HPLC results, Table 2). This means that high regioselectivity was achieved with the above-mentioned lipase in only one step and short reaction time avoiding the use of a protection/deprotection strategy. Therefore, this procedure is atom economical and also environmentally friendly, since MeTHF was used. It is noteworthy that the reaction without enzyme did not work at all and only the initial substrate was detected.

Results with other vinyl esters such as vinyl propionate (VP) and butyrate (VB) largely paralleled those of vinyl acetate (Table 2). In the case of VP and VB, once the maximum reaction

Table 1 Structure of nucleosides and derivatives; U = uracil, 5-MU = 5-methyluracil, A = adenine

Base	R_1	R_2	R_3	R_4	Product
U	OH	H	H	H	**1**
U	OH	H	H	$COCH_3$	**2**
U	OH	H	H	$COCH_2CH_3$	**3**
U	OH	H	H	$CO(CH_2)_2CH_3$	**4**
U	OH	H	H	$CO(CH_2)_4CH_3$	**5**
U	OH	H	$COCH_3$	$COCH_3$	**6**
U	H	OH	H	H	**7**
U	H	OH	H	$COCH_3$	**8**
U	H	OH	H	$CO(CH_2)_4CH_3$	**9**
5-MU	H	$O(CH_2)_2OCH_3$	H	H	**10**
5-MU	H	$O(CH_2)_2OCH_3$	H	$COCH_3$	**11**
5-MU	H	$O(CH_2)_2OCH_3$	H	$COCH_2CH_3$	**12**
5-MU	H	$O(CH_2)_2OCH_3$	H	$CO(CH_2)_2CH_3$	**13**
5-MU	H	$O(CH_2)_2OCH_3$	H	$CO(CH_2)_4CH_3$	**14**
A	OH	H	H	H	**15**
A	OH	H	H	$COCH_3$	**16**
A	OH	H	H	$COCH_2CH_3$	**17**
A	OH	H	H	$CO(CH_2)_2CH_3$	**18**
A	OH	H	H	$CO(CH_2)_4CH_3$	**19**
A	H	OH	H	H	**20**
A	H	OH	H	$CO(CH_2)_4CH_3$	**21**

Table 2 Results obtained from the esterification of *ara*-U with CALB and several vinyl esters in MeTHF

	Ara-U (%)			5′-Ester (%)			3′,5′-Diester (%)		
Time/h	VA	VP	VB	VA	VP	VB	VA	VP	VB
4	13	6	4	83	88	91	4	6	5
6	2	—	1	93	93	94	5	7	5
8	3	—	1	91	93	94	6	7	5
24	—	—	—	90	93	94	10	7	6

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Table 3 Comparison of results obtained from the esterification of *ara*-U with vinyl esters in MeTHF by *Pseudomonas fluorescens* and CALB

		Ara-U (%)			5′-Ester (%)			3′,5′-Diester (%)		
Time/h	Enzyme	VA	VP	VB	VA	VP	VB	VA	VP	VB
4	CALB	13	6	4	83	88	91	4	6	5
4	PFL	56	37	50	40	60	49	4	3	1
6	CALB	2	—	1	93	93	94	5	7	5
6	PFL	30	33	45	64	62	51	6	5	4
8	CALB	3	—	1	91	93	94	6	7	5
8	PFL	20	29	34	74	63	60	6	8	6
24	CALB	—	—	—	90	93	94	10	7	6
24	PFL	2	2	1	85	72	70	13	26	19

yield was achieved (6 h) it did not decrease with time, while with VA it was slightly lower.

To check the viability of using some other biocatalysts, acylation of *ara*-U with vinyl esters was also tested with other lipases, such as those from native lyophilized *Mucor javanicus* (MJL), *Candida rugosa* (CRL), *Pseudomonas cepacea* (PCL) and *Pseudomonas fluorescens* (PFL), but the yields were lower than 10%, probably due to aggregation of these native preparations in the organic solvent and the concomitant diffusion problems. This problem is overcome by the use of a lipase supported on a carrier, such as in the CALB derivative used in this study, in which all lipase molecules are more accessible to the substrate.[13] The only exception was PFL, although enzymatic esterification with this lipase led to lower yields than CALB and higher proportion of the diacyl derivative in both 5′ and 3′ positions, as shown in Table 3.

Nevertheless, it is difficult to draw a direct comparison between the two catalysts, since they are used in a different state (native lyophilized preparation (PFL) or immobilised derivative (CALB)), and also because of their different intrinsic declared activity (see Experimental). We would like to emphasise that not many crude lipases are able to work efficiently in such a polar solvent as THF, it is well known that more hydrophobic solvents are generally preferred;[14] in fact, only very stable catalysts such as CALB (or the recently described use of crude lipase from *Pseudomonas stutzeri* in THF)[15] can be employed. Anyhow, when the reaction time was extended to several days the proportion of the diester (**6**) notably increased (Table 4). Remarkably, 2′,5′-*O*-diacetyl-1-β-arabinofuranosyl uracil was not detected at all.

In order to prove if the second acylation took place through an acyl transfer process or if it was indeed an esterification, 5′-*O*-acetyl-1-β-arabinofuranosyl uracil (**2**) was dissolved in MeTHF and maintained with stirring for 192 h at room temperature, but no transformation occurred. This result confirms that both acetyl groups came directly from the reagent (VA). The marked preference for the hydroxyl group on C-3′ as the second place to acylate was attributed to the higher steric hindrance of the 2′-OH, which is situated on the β-position like the nitrogenated base. In fact, uridine was treated with vinyl acetate under the same reaction conditions, giving rise after 192 h to 39% of the derivative esterified in the 5′-position (**8**) and 56% of a 70 : 30 mixture (ratio estimated from the NMR spectra) of the 2′,5′-*O*- and 3′,5′-*O*-diacetyl compounds, which were impossible to separate by traditional analytical methods. In this case, the OH at the C-2′ is not hindered by the base and, therefore, is also accessible for acylation.

High yields, but lower regioselectivity, was reported by Uemura *et al.* for the acylation of 2′-deoxyuridine with hexanoic anhydride by PFL in several organic solvents (DMA, DMSO and DMF) at room temperature after 24 h.[16]

Table 4 Esterification of *ara*-U with vinyl acetate by *Pseudomonas fluorescens* in MeTHF at longer reaction times

Time/h	*Ara*-U (%)	5′-Ester (%) (**2**)	3′,5′-Diester (%) (**6**)
24	3	82	14
48	—	76	24
72	—	72	28
96	—	69	31
192	—	59	41

Acylation of 9-β-arabinofuranosyl adenosine (*ara*-A)

Likewise, a comparative study of the *ara*-A (**15**) esterification with hexanoic anhydride by CALB in MeTHF and THF was performed. In this case, THF turned to be a better solvent for the substrate, giving rise to higher yields than MeTHF. In fact, 81% of 5′-*O*-hexanoyl-9-β-arabinofuranosyl adenosine (**19**) was rendered after 28 h.

A similar behavior was observed for the acylation of adenosine (**20**) under the same reaction conditions, achieving the highest yield after 30 h for the esterification in THF (**21**). In general, longer reaction times are needed for nucleosides with a purine-type base.[17]

Taking into account that for the esterification of *ara*-A with hexanoic anhydride by CALB much higher yields were rendered in THF, this was the solvent of choice for the reactions using vinyl esters as acylating agents. As mentioned before, nucleosides with a purine-type base reacted with a lower conversion rate than those with a pyrimidine-type, *i.e.* longer reaction times were needed for *ara*-A.

In Table 5, it can be noticed that the highest yield was achieved after 24 h for VP and VB, and 28 h for VA (88%). This way, esterification of *ara*-A with vinyl propionate by CALB in THF gave rise to 98% of the 5′ derivative (compound **17**) with total regioselectivity (2% of starting material remained unreacted). In the case of vinyl butyrate, regioselectivity was also excellent, since 97% of 5′-*O*-butanoyl-9-β-arabinofuranosyl adenosine (**18**) was detected together with 2% of substrate and 1% of the corresponding 3′,5′-dibutyrate derivative. The reaction with vinyl acetate underwent slightly slower and rendered a lower yield (product **16**), but the regioselectivity was

Table 5 Results obtained from the esterification of *ara*-A with CALB and several vinyl esters in THF

	Ara-A (%)			5′-Ester (%)			3′,5′-Diester (%)		
Time/h	VA	VP	VB	VA	VP	VB	VA	VP	VB
4	47	46	41	53	54	59	—	—	—
6	43	41	40	57	59	60	—	—	—
8	38	31	29	62	69	71	—	—	—
24	19	2	2	79	98	97	2	—	1
28	10	—	2	88	95	92	2	5	6

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Table 6 Results obtained from the esterification of 2′-*O*-methoxyethyl-5-methyluridine with CALB and several vinyl esters in MeTHF

	2′-*O*-methoxyethyl-5-methyluridine (%)			5′-Ester (%)		
Time/h	VA	VP	VB	VA	VP	VB
2	2	2	2	90	95	89
4	—	—	—	93	91	85
6	—	—	—	94	92	91
8	—	—	—	94	89	89
24	—	—	—	94	73	62

similar to the values measured for vinyl butyrate. Esterification of *ara*-A with the same vinyl esters but employing lipases from other microorganisms (MJL, CRL, PCL and PFL) was also tested. As occurred with the *ara*-U acylation, only PFL produced the 5′ ester derivative, but with rather irrelevant yields.

Acylation of 2′-*O*-(2-methoxyethyl)-5-methyl uridine

2′-*O*-Alkyl nucleosides are considered to be key building blocks of several second generation antisense oligonucleotides in clinical development. As promising therapeutic agents, much effort is being made towards the development of novel nuclease resistant oligonucleotides, which are capable of hybridizing with appropriate specificity and affinity to complementary sequences thus acting as effective inhibitors of gene expression.[18] However, these nucleotides should be modified to avoid rapid degradation by cellular nucleases. Therefore, we have esterified 2′-*O*-(2-methoxyethyl)-5-methyl uridine following the same strategy as for *ara*-A and *ara*-U.

Acylation of the latter with hexanoic anhydride in MeTHF gave rise directly to the diester in 3′ and 5′ position, achieving the highest yield after 6 h (89% of 2′-*O*-(2-methoxyethyl)-3′,5′-dihexanoyl-5-methyl uridine, **14**). However, the fact that the reaction was not regioselective and that 8% of compound **14** was formed in the sample without enzyme, prompted us to focus our attention again to vinyl esters. Reaction of this starting material with vinyl acetate rendered 94% of the 5′ acetyl derivative (compound **11**) after 6 h (Table 6). Slightly lower results were obtained with vinyl propionate (92%, product **12**) and vinyl butyrate (91%, compound **13**). This way, the regioselective synthesis of nucleoside derivatives with only the hydroxyl group at C-3′ free was accomplished.

Conclusion

The described enzymatic processes represent an excellent methodology to obtain valuable nucleoside derivatives. Reactions took place in many cases in short reaction times (6 h) and with total regioselectivity, which is arduous to achieve by pure chemical means due to the presence of various hydroxyl groups. A comparison between THF and environmentally friendly MeTHF was established, both solvents behaving in a similar way, while for the acylation of *ara*-U and uridine, MeTHF rendered better conversions. This green solvent can be really valuable in the biotransformations field.

Experimental

General

Ara-U and *ara*-A were kindly provided by Pro. Bio. Simt. S.p.A., 2′-*O*-methoxyethyl-5-methyl uridine by Ravi Chemicals and MeTHF by Penn Specialty Chemicals Inc. CALB (Novozyme435, immobilized lipase from *Candida Antarctica* B) was a gentle donation of Novozymes, Spain. Lipases from *Mucor javanicus* (MJL), *Candida rugosa* (CRL), *Pseudomonas cepacea* (PCL) and *Pseudomonas fluorescens* (Amano Lipase AK) were purchased from Sigma-Aldrich. All other chemicals were obtained from commercial sources. Reaction progress was followed by HPLC on an Agilent LC1200 using the C18 column Mediterranea Sea from Teknokroma, and by TLC on Kieselgel Plates 60 F254 (SDS). TLC plates were visualized under UV light or revealed with 10% H_2SO_4 in methanol and heating. Column chromatography was carried out, if necessary, on silica gel 60, AC, 40–63 μm (purchased from SDS). NMR spectra of samples in DMSO-d_6 were recorded on a Bruker Avance 250 (250 MHz) spectrometer. Compound assignments were based on ^{1}H, ^{13}C, HMQC and HMBC NMR experiments.

Experimental procedures

Esterification of *ara*-U with hexanoic anhydride

Ara-U (120 mg, 0.5 mmol) was dissolved in 50 mL of anhydrous MeTHF and 0.5 g of molecular sieves, 0.5 g of CALB (Novozyme435, 20% w/w loading,[19] 10 000 PLU g^{-1})[20] and 0.35 mL of hexanoic anhydride (1.5 mmol) were added, maintaining the reaction with orbital shaking for 24 h at room temperature. After that, MeOH was added, the reaction mixture was filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Then, silica gel was added, the solvent was evaporated at reduced pressure and the crude subsequently purified by column chromatography to give 75 mg (45%) of 5′-*O*-hexanoyl-1-β-arabinofuranosyl uracil (**5**): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.85 (3H, t, $J = 6.3$ Hz, $CH_3CH_2CH_2$), 1.26 (4H, m, $CH_3CH_2CH_2$), 1.54 (2H, t, $J =$ 6.7 Hz, CH_2CH_2CO), 2.33 (2H, t, $J = 7.2$ Hz, CH_2CH_2CO), 3.95 (2H, m, H-3′ and H-4′), 4.01 (1H, br s, H-2′), 4.21 (1H, dd, $J_1 = 3.4$ Hz, $J_2 = 11.8$ Hz, 1H-5′), 4.30 (1H, dd, $J_1 = 7.2$ Hz, $J_2 = 11.8$ Hz, 1H-5′), 5.58 (1H, d, $J = 8.1$ Hz, H-5), 5.67 (1H, br s, OH-3′), 5.76 (1H, d, $J = 3.9$ Hz, OH-2′), 6.04 (1H, d, $J = 3.4$ Hz, H-1′), 7.51 (1H, d, $J = 8.1$ Hz, H-6), 11.34 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 14.2 (CH_3), 22.2 ($CH_3CH_2CH_2$), 24.5 (CH_2CH_2CO), 31.0 ($CH_3CH_2CH_2$), 33.7 (CH_2CH_2CO), 63.8 (C-5′), 75.0 and 76.4 (C-2′ and C-3′), 82.1 (C-4′), 85.7 (C-1′), 100.5 (C-5), 142.6 (C-6), 150.8 (C-2), 163.6 (C-4), 173.2 (CO). Anal. Calcd. for $C_{15}H_{22}N_2O_7$: C, 52.63; H, 6.48; N, 8.18%. Found: C, 52.36; H, 6.44; N, 7.76%.

Acylation of uridine (7) with hexanoic anhydride

0.5 g of molecular sieves, 0.5 g of CALB and 0.35 mL of hexanoic anhydride were added to a solution of 120 mg uridine in 50 mL anhydrous MeTHF. After 24 h with orbital shaking at room temperature, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Silica gel was added, the

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solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 71 mg (42%) of 5′-*O*-hexanoyl uridine (**9**): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.87 (3H, m, CH_3), 1.27 (4H, m, $CH_3CH_2CH_2$), 1.52 (2H, m, CH_2CH_2CO), 2.34 (2H, t, J = 7.3, CH_2CH_2CO), 3.97 (2H, m, H-3′ and H-4′), 4.08 (1H, t, J = 5.0 Hz, H-2′), 4.18 (1H, dd, J_1 = 5.3 Hz, J_2 = 12.1 Hz, 1H-5′), 4.26 (1H, dd, J_1 = 3.6 Hz, J_2 = 12.1 Hz, 1H-5′), 5.33 (1H, br s, OH-3′), 5.52 (1H, br s, OH-2′), 5.67 (1H, d, J = 8.1 Hz, H-5), 5.76 (1H, d, J = 5.8 Hz, H-1′), 7.64 (1H, d, J = 8.1 Hz, H-6), 11.41 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 14.2 (CH_3), 22.2 ($CH_3CH_2CH_2$), 24.5 (CH_2CH_2CO), 31.0 ($CH_3CH_2CH_2$), 33.6 (CH_2CH_2CO), 64.0 (C-5′), 70.1 (C-3′), 73.0 (C-2′), 81.4 (C-4′), 89.0 (C-1′), 102.3 (C-5), 141.1 (C-6), 151.0 (C-2), 163.4 (C-4), 173.1 (CO). Anal. Calcd. for $C_{15}H_{22}N_2O_7$: C, 52.63; H, 6.48; N, 8.18%. Found: C, 52.83; H, 6.56; N, 7.62%.

Esterification of *ara*-U with vinyl esters

Ara-U (120 mg, 0.5 mmol) was dissolved in 50 mL of anhydrous MeTHF and 0.5 g of molecular sieves, 0.5 g of CALB and 1.5 mmol of vinyl ester (138 μL vinyl acetate, 163 μL vinyl propionate or 190 μL vinyl butyrate) were added, maintaining the reaction with orbital shaking for 7 h at room temperature. After that, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Then, silica gel was added and the solvent evaporated to dryness. Finally, the residue was purified by column chromatography over silica gel.

5′-*O*-acetyl-1-β-arabinofuranosyl uracil (2). 61 mg (43%): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.06 (3H, s, CH_3CO), 3.93 (2H, m, H-3′ and H-4′), 4.02 (1H, ddd, $J_1 = J_2$ = 4.5 Hz, J_3 = 7.0 Hz, H-2′), 4.21 (1H, dd, J_1 = 4.0 Hz, J_2 = 11.8 Hz, 1H-5′), 4.30 (1H, dd, J_1 = 7.1 Hz, J_2 = 11.8 Hz, 1H-5′), 5.60 (1H, d, J = 8.1 Hz, H-5), 5.71 (1H, d, J = 3.9 Hz, OH-3′), 5.78 (1H, d, J = 4.5 Hz, OH-2′), 6.05 (1H, d, J = 4.5 Hz, H-1′), 7.52 (1H, d, J = 8.1 Hz, H-6), 11.35 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 21.5 (CH_3), 64.5 (C-5′), 75.5 and 77.0 (C-2′ and C-3′), 82.5 (C-4′), 86.2 (C-1′), 101.0 (C-5), 143.1 (C-6), 151.3 (C-2), 164.1 (C-4), 171.1 (CO). Anal. Calcd. for $C_{11}H_{14}N_2O_7$: C, 46.16; H, 4.93; N, 9.79%. Found: C, 46.17; H, 5.00; N, 9.45%.

5′-*O*-propanoyl-1-β-arabinofuranosyl uracil (3). 87 mg (58%): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.03 (3H, t, J = 7.5 Hz, CH_3CH_2CO), 2.34 (2H, dd, J_1 = 7.5 Hz, J_2 = 15.6 Hz, CH_3CH_2CO), 3.92 (2H, m, H-3′ and H-4′), 4.01 (1H, m, H-2′), 4.23 (2H, m, 2H-5′), 5.58 (1H, d, J = 8.1 Hz, H-5), 5.67 (1H, d, J = 3.4 Hz, OH-3′), 5.74 (1H, d, J = 4.5 Hz, OH-2′), 6.02 (1H, d, J = 4.2 Hz, H-1′), 7.49 (1H, d, J = 8.1 Hz, H-6), 11.30 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 9.3 (CH_3CH_2CO), 27.1 (CH_3CH_2CO), 63.8 (C-5′), 75.0 and 76.4 (C-2′ and C-3′), 82.0 (C-4′), 85.7 (C-1′), 100.5 (C-5), 142.6 (C-6), 150.8 (C-2), 163.7 (C-4), 174.0 (CO). Anal. Calcd. for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.37; N, 9.33%. Found: C, 47.86; H, 5.38; N, 9.04%.

5′-*O*-butanoyl-1-β-arabinofuranosyl uracil (4). 84 mg (54%): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90 (3H, t, J = 7.4 Hz, $CH_3CH_2CH_2CO$), 1.57 (2H, m, $CH_3CH_2CH_2CO$), 2.33 (2H, t, J = 7.2 Hz, $CH_3CH_2CH_2CO$), 3.95 (2H, m, H-3′ and H-4′), 4.03 (1H, m, H-2′), 4.23 (1H, dd, J_1 = 3.8 Hz, J_2 = 11.8 Hz, 1H-5′), 4.32 (1H, dd, J_1 = 7.1 Hz, J_2 = 11.8 Hz, 1H-5′), 5.60 (1H, d, J = 8.1 Hz, H-5), 5.72 (1H, br s, OH-3′), 5.80 (1H, d, J = 4.2 Hz, OH-2′), 6.05 (1H, d, J = 4.2 Hz, H-1′), 7.52 (1H, d, J = 8.1 Hz, H-6), 11.36 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.7 ($CH_3CH_2CH_2CO$), 18.3 $CH_3CH_2CH_2CO$), 35.6 ($CH_3CH_2CH_2CO$), 63.7 (C-5′), 75.0 and 76.4 (C-2′ and C-3′), 82.1 (C-4′), 85.8 (C-1′), 100.5 (C-5), 142.6 (C-6), 150.8 (C-2), 163.7 (C-4), 173.1 (CO). Anal. Calcd. for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91%. Found: C, 49.67; H, 5.77; N, 8.70%.

Synthesis of 3′,5′-*O*-acetyl-1-β-arabinofuranosyl uracil (6). 1 g of molecular sieves, 1 g of *Pseudomonas fluorescens* (activity ≥20 000 U g^{-1}, pH 8.0, 55 °C using triolein as substrate)[21] and 276 μL of vinyl acetate were added to a solution of 240 mg of *ara*-U in 100 mL of anhydrous MeTHF. After 8 days with orbital shaking at room temperature, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Then, silica gel was added, the solvent evaporated at reduced pressure and the residue chromatographed on a silica gel column to give 158 mg (55%) of compound **2** and 139 mg (42%) of 3′,5′-*O*-acetyl-1-β-arabinofuranosyl uracil (**6**): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.06 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 4.15 (1H, ddd, $J_1 = J_2$ = 3.8 Hz, J_3 = 7.0 Hz, H-4′), 4.22 (1H, m, H-2′), 4.32 (2H, m, 2H-5′), 4.96 (1H, br s, H-3′), 5.63 (1H, d, J = 8.1 Hz, H-5), 6.02 (1H, d, J = 3.9 Hz, H-1′), 6.16 (1H, d, J = 4.3 Hz, OH-2′), 7.57 (1H, d, J = 8.1 Hz, H-6), 11.41 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 21.0 (CH_3CO), 21.1 (CH_3CO), 63.5 (C-5′), 72.5 (C-2′), 78.4 (C-3′), 79.8 (C-4′), 85.8 (C-1′), 100.7 (C-5), 142.4 (C-6), 150.7 (C-2), 163.6 (C-4), 170.1 (CO), 170.6 (CO). Anal. Calcd. for $C_{13}H_{16}N_2O_8$: C, 47.56; H, 4.91; N, 8.53%. Found: C, 47.83; H, 5.62; N, 7.09%.

Acylation of uridine with vinyl acetate by *Pseudomonas fluorescens*

Uridine (240 mg, 1 mmol) was dissolved in 100 mL of anhydrous MeTHF and 1 g of molecular sieves, 1 g of *Pseudomonas fluorescens* and 276 μL of vinyl acetate (3 mmol) were added, maintaining the reaction with orbital shaking for 8 days at room temperature. After that, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Then, silica gel was added and the solvent evaporated to dryness. Finally, the residue was purified by column chromatography over silica gel yielding 148 mg (53%) of a mixture consisting of 3′,5′-*O*-diacetyl uridine and 2′,5′-*O*-diacetyl uridine, and 106 mg (38%) of 5′-*O*-acetyl uridine (**8**): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.09 (3H, s, CH_3CO), 3.99 (2H, m, H-3′ and H-4′), 4.19 (3H, m, 2H-5′ and H-2′), 5.37 (1H, d, J = 4.5 Hz, OH-3′), 5.55 (1H, d, J = 4.9 Hz, OH-2′), 5.71 (1H, d, J = 8.0 Hz, H-5), 5.77 (1H, d, J = 4.7 Hz, H-1′), 7.67 (1H, d, J = 8.0 Hz, H-6), 11.42 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 21.0 (CH_3), 64.1 (C-5′), 70.1 (C-3′), 73.0 (C-2′), 81.4 (C-4′), 89.0 (C-1′), 102.4 (C-5), 141.2 (C-6), 151.0 (C-2), 163.5 (C-4), 170.6 (CO). Elemental analysis (Found: C, 46.53; H, 5.19; N, 8.89%. Calc. for $C_{11}H_{14}N_2O_7$: C, 46.16; H, 4.93; N, 9.79%).

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Esterification of *ara*-A with hexanoic anhydride

0.5 g of molecular sieves, 0.5 g of CALB and 0.35 mL of hexanoic anhydride were added to a solution of 135 mg of *ara*-A in 50 mL of anhydrous THF. After 24 h with orbital shaking at room temperature, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Silica gel was added, the solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 58 mg (31%) of 5′-*O*-hexanoyl-9-β-arabinofuranosyl adenosine (**19**): yellow solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.67 (3H, t, $J = 6.9$ Hz, CH_3), 1.05 (4H, m, $CH_3CH_2CH_2$), 1.31 (2H, m, CH_2CH_2CO), 2.12 (2H, t, $J = 7.2$ Hz, CH_2CH_2CO), 3.78 (1H, ddd, $J_1 = J_2 = 3.6$ Hz, $J_3 = 7.5$ Hz, H-4′), 3.97 (2H, d, $J = 3.6$ Hz, H-2′ and H-3′), 4.08 (1H, dd, $J_1 = 3.6$ Hz, $J_2 = 11.7$ Hz, 1H-5′), 4.19 (1H, dd, $J_1 = 7.5$ Hz, $J_2 = 11.7$ Hz, 1H-5′), 5.62 (2H, br s, OH-2′ and OH-3′), 6.11 (1H, d, $J = 4.2$ Hz, H-1′), 7.10 (2H, br s, NH_2), 7.93 and 7.95 (2H, s, H-2 and H-8); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 14.2 (CH_3), 22.2 ($CH_3CH_2CH_2$), 24.5 (CH_2CH_2CO), 31.0 ($CH_3CH_2CH_2$), 33.6 (CH_2CH_2CO), 64.1 (C-5′), 75.4 and 76.0 (C-2′ and C-3′), 81.3 (C-4′), 83.9 (C-1′), 118.5 (C-5), 140.7 (C-8), 149.7 (C-4), 152.9 (C-2), 156.3 (C-6), 173.2 (CO). Anal. Calcd. for $C_{16}H_{23}N_5O_5$: C, 52.59; H, 6.34; N, 19.17%. Found: C, 51.63; H, 6.01; N, 19.33%.

Acylation of adenosine with hexanoic anhydride

0.5 g of molecular sieves, 0.5 g of CALB and 0.35 mL of hexanoic anhydride were added to a solution of 135 mg of adenosine in 50 mL of anhydrous THF. After 24 h with orbital shaking at room temperature, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Silica gel was added, the solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 62 mg (33%) of 5′-*O*-hexanoyl adenosine (**21**): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.82 (3H, t, $J_1 = J_2 = 6.8$ Hz, CH_3), 1.21 and 1.48 (6H, m, CH_2), 2.28 (2H, t, $J_1 = J_2 = 7.3$ Hz, CH_2CO), 4.08 (1H, m, H-4′), 4.26 (3H, m, H-3′ and 2H-5′), 4.68 (1H, m, H-2′), 5.41 (1H, d, $J = 4.6$ Hz, OH-3′), 5.62 (1H, d, $J = 5.8$ Hz, OH-2′), 5.91 (1H, d, $J = 4.9$ Hz, H-1′), 7.32 (2H, br s, NH_2), 8.15 (1H, s, H-8), 8.31 (1H, s, H-2); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 14.1 (CH_3), 22.1 (CH_3CH_2), 24.4 (CH_2CH_2CO), 30.9 ($CH_3CH_2CH_2$), 33.6 (CH_2CO), 64.0 (C-5′), 70.6 (C-3′), 73.2 (C-2′), 81.8 (C-4′), 88.1 (C-1′), 119.5 (C-5), 140.1 (C-8), 149.7 (C-4), 153.0 (C-2), 156.4 (C-6), 173.1 (CO). Anal. Calcd. for $C_{16}H_{23}N_5O_5$: C, 52.59; H, 6.34; N, 19.17%. Found: C, 52.17; H, 6.20; N, 18.65%.

Esterification of *ara*-A with vinyl esters

Ara-A (135 mg, 0.5 mmol) was dissolved in 50 mL of anhydrous MeTHF and 0.5 g of molecular sieves, 0.5 g of CALB and 1.5 mmol of vinyl ester (138 μL vinyl acetate, 163 μL vinyl propionate or 190 μL vinyl butyrate) were added, maintaining the reaction with orbital shaking for 24 h at room temperature. After that, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Then, silica gel was added and the solvent evaporated to dryness. Finally, the residue was purified by column chromatography over silica gel.

5′-*O*-acetyl-9-β-Arabinofuranosyl adenosine (16). 102 mg (65%): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.04 (3H, s, CH_3CO), 3.98 (1H, m, H-4′), 4.20 (2H, br s, H-2′ and H-3′), 4.33 (2H, m, H-5′), 5.80 (1H, d, $J = 4.1$ Hz, OH-3′), 5.85 (1H, d, $J = 4.5$ Hz, OH-2′), 6.32 (1H, d, $J = 4.2$ Hz, H-1′), 7.32 (2H, br s, NH_2), 8.16 and 8.17 (2H, s, H-2 and H-8); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 21.0 (CH_3), 64.3 (C-5′), 75.4 and 76.0 (C-2′ and C-3′), 81.2 (C-4′), 83.9 (C-1′), 118.5 (C-5), 140.8 (C-8), 149.7 (C-4), 152.9 (C-2), 156.2 (C-6), 170.7 (CO). Anal. Calcd. for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.64%. Found: C, 45.96; H, 4.63; N, 22.51%.

5′-*O*-propanoyl-9-β-Arabinofuranosyl adenosine (17). 111 mg (68%): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.03 (3H, t, $J = 7.5$ Hz, CH_3), 2.35 (2H, dd, $J_1 = 7.5$ Hz, $J_2 = 14.9$ Hz, CH_3CH_2), 3.99 (1H, m, H-4′), 4.20 (2H, br s, H-2′ and H-3′), 4.34 (2H, m, H-5′), 5.79 (1H, d, $J = 3.7$ Hz, OH-3′), 5.85 (1H, d, $J = 4.1$ Hz, OH-2′), 6.31 (1H, d, $J = 4.0$ Hz, H-1′), 7.32 (2H, br s, NH_2), 8.15 and 8.16 (2H, s, H-2 and H-8); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 9.3 (CH_3), 27.1 (CH_3CH_2), 64.1 (C-5′), 75.4 and 75.9 (C-2′ and C-3′), 81.2 (C-4′), 83.8 (C-1′), 118.5 (C-5), 140.7 (C-8), 149.7 (C-4), 152.9 (C-2), 156.2 (C-6), 174.0 (CO). Anal. Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66%. Found: C, 47.97; H, 4.90; N, 21.68%.

5′-*O*-Butanoyl-9-β-arabinofuranosyl adenosine (18). 107 mg (63%): white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.88 (3H, t, $J = 7.3$ Hz, CH_3), 1.55 (2H, ddd, $J_1 = J_2 = 7.3$ Hz, $J_3 = 14.7$ Hz, CH_3CH_2), 2.32 (2H, t, $J_1 = J_2 = 7.1$ Hz, CH_2CO), 3.98 (1H, m, H-4′), 4.27 (2H, m, H-2′ and H-3′), 4.37 (2H, m, H-5′), 5.76 (1H, d, $J = 3.7$ Hz, OH-3′), 5.82 (1H, d, $J = 4.2$ Hz, OH-2′), 6.31 (1H, d, $J = 4.0$ Hz, H-1′), 7.31 (2H, br s, NH_2), 8.13 and 8.16 (2H, s, H-2 and H-8); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 13.8 (CH_3), 18.3 (CH_3CH_2), 35.6 (CH_2CO), 64.1 (C-5′), 75.4 and 76.0 (C-2′ and C-3′), 81.3 (C-4′), 83.9 (C-1′), 118.5 (C-5), 140.7 (C-8), 149.7 (C-4), 152.9 (C-2), 156.3 (C-6), 173.1 (CO). Anal. Calcd. for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.68; N, 20.76%. Found: C, 49.82; H, 5.57; N, 20.97%.

Acylation of 2′-*O*-(2-methoxyethyl)-5-methyl uridine with hexanoic anhydride

0.5 g of molecular sieves, 0.5 g of CALB and 0.35 mL of hexanoic anhydride were added to a solution of 160 mg 2′-*O*-(2-methoxyethyl)-5-methyl uridine in 50 mL of anhydrous MeTHF. After 24 h with orbital shaking at room temperature, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Silica gel was added, the solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 86 mg (43%) of 2′-*O*-(2-methoxyethyl)-3′,5′-dihexanoyl-5-methyl uridine (**14**): yellow solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.88 (6H, m, $2 \times CH_3$), 1.28 (8H, m, $2 \times CH_3CH_2CH_2$), 1.52 (4H, m, $2 \times CH_2CH_2CO$), 1.81 (3H, s, CH_3), 2.19 (2H, t, $J = 7.3$ Hz, CH_2CH_2CO), 2.35 (2H, t, $J = 7.3$ Hz, CH_2CH_2CO), 3.23 (3H, s, OCH_3), 3.45 (2H, *t*, $J = 4.6$ Hz, $OCH_2CH_2OCH_3$), 3.67 (2H, m, $OCH_2CH_2OCH_3$), 4.04 (3H, m, H-2′, H-3′ and H-4′), 4.24 (1H, m, 2H-5′), 5.85 (1H,

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d, $J = 4.9$ Hz, H-1′), 7.46 (1H, s, H-6), 11.43 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 12.5 (CH_3), 14.1 and 14.2 ($2 \times CH_3CH_2CH_2$), 22.1 and 22.2 ($2 \times CH_3CH_2CH_2$), 24.4 and 24.6 (CH_2CH_2CO), 31.0 and 31.1 ($2 \times CH_3CH_2CH_2$), 33.7 and 34.1 (CH_2CH_2CO), 58.4 (OCH_3), 63.8 (C-5′), 69.0 (C-3′), 69.4 ($OCH_2CH_2OCH_3$), 71.6 ($OCH_2CH_2OCH_3$), 80.6 and 81.6 (C-2′ and C-4′), 87.0 (C-1′), 110.1 (C-5), 136.4 (C-6), 150.9 (C-2), 164.0 (C-4), 173.1 and 175.0 ($2 \times$ CO). Anal. Calcd. for $C_{25}H_{40}N_2O_9$: C, 58.58; H, 7.87; N, 5.47%. Found: C, 56.40; H, 7.52; N, 5.87%.

Esterification of 2′-*O*-(2-methoxyethyl)-5-methyl uridine with vinyl esters

2′-*O*-(2-methoxyethyl)-5-methyl uridine (120 mg, 0.5 mmol) was dissolved in 50 mL of anhydrous MeTHF and 0.5 g of molecular sieves, 0.5 g of CALB and 1.5 mmol of vinyl ester (138 μL vinyl acetate, 163 μL vinyl propionate or 190 μL vinyl butyrate) were added, maintaining the reaction with orbital shaking for 5 h at room temperature. After that, MeOH was added, the reaction mixture filtered, neutralized with saturated $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. Then, silica gel was added and the solvent evaporated to dryness. Finally, the residue was purified by column chromatography over silica gel.

2′-*O*-(2-methoxyethyl)-5′-acetyl-5-methyl uridine (11). 128 mg, 70%: yellow solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.81 (3H, s, CH_3), 2.08 (3H, s, CH_3CO), 3.23 (3H, s, OCH_3), 3.48 (2H, m, $OCH_2CH_2OCH_3$), 3.68 (2H, m, $OCH_2CH_2OCH_3$), 4.05 (3H, m, H-2′, H-3′ and H-4′), 4.22 (2H, m, H-5′), 5.32 (1H, d, $J = 5.8$ Hz, OH-3′), 5.84 (1H, d, $J = 4.8$ Hz, H-1′), 7.47 (1H, s, H-6), 11.44 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 12.5 (CH_3), 21.0 (CH_3CO), 58.5 (OCH_3), 63.9 (C-5′), 69.0 (C-3′), 69.4 ($OCH_2CH_2OCH_3$), 71.6 ($OCH_2CH_2OCH_3$), 80.6 and 81.6 (C-2′ and C-4′), 87.1 (C-1′), 110.2 (C-5), 136.4 (C-6), 150.9 (C-2), 164.1 (C-4) and 170.6 (CO). Anal. Calcd. for $C_{15}H_{22}N_2O_8$: C, 50.28; H, 6.19; N, 7.82%. Found: C, 50.50; H, 6.26; N, 7.28%.

2′-*O*-(2-methoxyethyl)-5′-propanoyl-5-methyl uridine (12). 130 mg, 68%: white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.06 (3H, t, $J = 7.4$, CH_3CH_2CO), 1.81 (3H, s, CH_3), 2.37 (2H, dd, $J_1 = 7.5$ Hz, $J_2 = 14.9$ Hz, CH_3CH_2CO), 3.23 (3H, s, OCH_3), 3.48 (2H, m, $OCH_2CH_2OCH_3$), 3.68 (2H, m, $OCH_2CH_2OCH_3$), 4.05 and 4.11 (3H, m, H-2′, H-3′ and H-4′), 4.25 (2H, m, H-5′), 5.33 (1H, d, $J = 5.8$ Hz, OH-3′), 5.85 (1H, d, $J = 4.8$ Hz, H-1′), 7.46 (1H, s, H-6), 11.45 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 9.3 (CH_3CH_2CO), 12.5 (CH_3), 27.0 (CH_3CH_2CO), 58.5 (OCH_3), 63.8 (C-5′), 69.0 (C-3′), 69.4 ($OCH_2CH_2OCH_3$), 71.6 ($OCH_2CH_2OCH_3$), 80.6 and 81.6 (C-2′ and C-4′), 87.1 (C-1′), 110.2 (C-5), 136.4 (C-6), 150.9 (C-2), 164.1 (C-4) and 173.9 (CO). Anal. Calcd. for $C_{16}H_{24}N_2O_8$: C, 51.61; H, 6.50; N, 7.52%. Found: C, 51.56; H, 6.48; N, 7.28%.

2′-*O*-(2-methoxyethyl)-5′-butanoyl-5-methyl uridine (13). 128 mg, 65%: white solid; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.89 (3H, t, $J = 7.3$ Hz, $CH_3CH_2CH_2CO$), 1.57 (2H, ddd, $J_1 = J_2 = J_3 = 7.3$ Hz, $CH_3CH_2CH_2CO$), 1.81 (3H, s, CH_3), 2.35 (2H, t, $J = 7.2$ Hz, $CH_3CH_2CH_2CO$), 3.23 (3H, s, OCH_3), 3.48 (2H, m, $OCH_2CH_2OCH_3$), 3.67 (2H, m, $OCH_2CH_2OCH_3$), 4.05 (3H, m, H-2′, H-3′ and H-4′), 4.24 (1H, m, 2H-5′), 5.31 (1H, d, $J = 5.7$ Hz, OH-3′), 5.84 (1H, d, $J = 4.8$ Hz, H-1′), 7.46 (1H, s, H-6), 11.44 (1H, br s, NH); ^{13}C NMR (DMSO-d_6, 63 MHz): δ 13.0 and 14.2 (CH_3 and $CH_3CH_2CH_2CO$), 18.7 $CH_3CH_2CH_2CO$), 36.1 ($CH_3CH_2CH_2CO$), 59.0 (OCH_3), 64.2 (C-5′), 69.5 and 69.9 (C-3′ and $OCH_2CH_2OCH_3$), 72.1 ($OCH_2CH_2OCH_3$), 81.1 and 82.1 (C-2′ and C-4′), 87.6 (C-1′), 110.7 (C-5), 136.9 (C-6), 151.4 (C-2), 164.6 (C-4), 173.5 (CO). Anal. Calcd. for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25%. Found: C, 52.61; H, 6.80; N, 6.95%.

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Solvent-free condensations of ketones with malononitrile catalysed by methanesulfonic acid/morpholine system

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The preparation of ylidenemalononitriles *via* Knoevenagel condensations of ketones with malononitrile under solvent-free conditions is described. Good yields and short reaction time are the features observed with methanesulfonic acid (MSA)/morpholine used as the catalyst. The wide applicability of the protocol is shown by the fact that not only unconjugated, but also aryl-alkyl ketones gave satisfactory yields.

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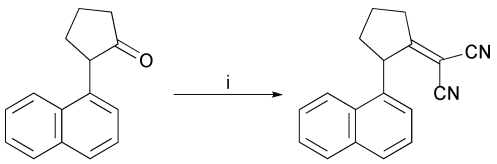
Introduction

Condensation of aldehydes and ketones with malononitrile is an important and routinely utilized transformation in organic synthesis. Over the past years a number of papers have been published in this area describing many new methods for condensation of aldehydes with malononitrile.[1] However, reports on analogous procedures of ketones are rare, probably due to the lower reactivity of these compounds. Although the conversion of ketones to ylidenemalononitriles may be effected by the classic Knoevenagel protocol,[2] this employs hazardous benzene and requires prolonged heating with continuous water removal. Recent variants have employed water and ionic liquids as solvents,[3] HMDS,[4] Ti(*i*-Pr)$_4$,[5] and various metalo-organic[6] and solid catalysts[7] with conventional or microwave heating. Nevertheless most of these methods involve hazardous materials or long reaction times.

Our continued interest in the exploration of acid-catalyzed cyclizations of ylidenemalononitriles to vicinal aromatic aminonitriles[8] as a PAH's source for biological studies[9] prompted us to investigate a new procedure for condensation of ketones with malononitrile. As there is increasing attention given to performing a wide variety of organic reactions under solvent-free conditions we decided to employ this approach for our purposes. Herein we describe a simple, rapid and efficient protocol for condensation of ketones with malononitrile under solvent-free conditions.

Results and discussion

We have previously reported the synthesis of 2-(1-naphthyl) cyclopentylidenemalononitrile **1b** (Scheme 1).[8a]



1a **1b** (93%)

Scheme 1 (i) $CH_2(CN)_2$, CH_3COONH_4, CH_3COOH, C_6H_6, 12 h, reflux.

Under classic conditions **1b** could be obtained with a yield of 93% after 12 h of heating in benzene solution followed by column chromatography. We chose this transformation for initial study on solvent-free Knoevenagel condensation. The results summarized in Table 1 reveal the influence of catalyst, temperature, time and reagents ratio on the yield of **1b**.

It should be noted that although piperidine and morpholine gave similar results, a reflux condenser was needed in the case of free amines due to strong evaporation of this amine at high temperature. However, on a small scale, morpholine-catalyzed condensations could be performed in a flask fitted only with a drying tube. We also observed that due to base-catalyzed polymerization, the addition of the second portion of malononitrile after 30 min was necessary to obtain complete conversion of the ketone **1a**. Postulating that buffering the reaction with an acid could improve the yield, Knoevenagel condensation was attempted with ammonium salt generated *in situ* from methanesulfonic acid and morpholine. In addition to the increase of the yield of the reaction, evaporation of amine was avoided. Our observation revealed that among the various reaction conditions used (Table 1) those indicated in Entry 6 were the most promising.

With, seemingly-optimal conditions in hand (see Experimental section), we checked the range of the procedure. The Knoevenagel reaction was carried out using a series of different unconjugated ketones. The results are summarized in Table 2.

Except for cycloalkanones (Entries 8–11), all reactions indicated in Table 2 were performed at 10 mmol scale

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Table 1 Influence of different catalysts and reaction conditions on the yield of **1b**

Entry	**1a**/$CH_2(CN)_2$ molar ratio	Catalyst	Temperature (°C)	Yield/time (%/h)
1	1 : 1.2	$CH_3COO\ NH_4$	100	46/1
2	1 : 1.2	Piperidine (morpholine)	80	72/2
3	1 : 1.2[a]	Piperidine (morpholine)	100	76/1
4	1 : 1.2[a]	Morpholine–MSA	80	82/2
5	1 : 1.2[a]	Morpholine–MSA	100	86/1
6	1 : 1.2[a]	Morpholine–MSA	120	92/1

[a] Second portion of malononitrile (1.2 mol equiv.) was added after 30 min.

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and monitored by means of TLC. The products were isolated by column chromatograpy or crystallization (Table 2, Entry 7). However, in most cases flash chromatography SiO_2/toluene led to compounds of a purity (above 93% on the basis on ^{1}H NMR spectra) suitable for most of our purposes.

Syntheses of cycloalkylidenemalononitriles were done on 50 mmol scale in order to make distillation of products more convenient. First, we tried to apply free morpholine as a catalyst but polymerisation of the products under solvent-free conditions resulted in a very low yield of the expected cycloalkylidenemalononitriles **9b** and **10b**. This process was most striking in the case of morpholine-catalyzed condensation of cyclopentanone at 100 °C, when after short period of time (5 min) only a small quantity of product **9b** could be isolated.

Moreover, cycloalkylidenemalononitriles required additional washing with water before distillation to avoid degradation. Although compounds **11b** and **12b** are much less prone to polymerization, attempted distillation of crude cyclopentylidenemalononitrile **9b** resulted in the formation of a polymer.

On the other hand, condensation of cyclooctanone with malononitrile after 15 minutes yielded 82% of the crude product contaminated with approximately 9% of unchanged ketone (on the basis on ^{1}H NMR spectrum). The addition of the second portion of malononitrile and prolonging the reaction time to 1 hour allowed the complete conversion of ketone **12a**, but the yield of **12b** was lower (69%).

Our attention turned to the study of the utility of this protocol in condensation of conjugated ketones with malononitrile. As was expected the reactions were more difficult with aromatic ketones. We attempted to optimize the reaction conditions but yields of the products were significantly lower than in the case of alkyl ketones (Table 3).

Applying a slightly modified procedure we noted that the yield of corresponding olefins is in the order of 40–70%. However, difficulties were still encountered in reactions of these ketones with malononitrile, especially at the purification stage. Apart from the dimerization[4] process leading to compounds which can be separated using flash chromatography (SiO_2/toluene) we found that column chromatography is not suitable for the isolation of products. Therefore all products outlined in Table 3 were, after flash chromatography, crystallized from the appropriate solvent[10] with the addition of a few drops of glacial acetic acid which prevented further dimerization.

It is also noteworthy that in the case of 4-aminoacetophenone (**17a**), the amine group works as a catalyst and only a small amount of MSA should be added to the reaction mixture. The less-reactive benzophenone **19a** failed to condense with malononitrile under these conditions.

Conclusions

In conclusion we have demonstrated that a major improvement is achieved when Knoevenagel condensation of ketones with malononitrile is performed under solvent-free conditions. Most available Knoevenagel condensation procedures published to date require long reaction time, addition of solvents, continuous removal of water or use of an expensive catalyst. The reported procedure is low-cost, simple and safe.

Experimental

All ketones were purchased from Aldrich and used without further purification or synthesized according to known methods. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance II spectrometer.

Typical procedure

In a 10 mL flask was placed 2-(1-naphthyl)cyclopentanone **1a** (2.10 g, 10.0 mmol), malononitrile (790 mg, 12.0 mmol), morpholine (50.0 mg, 0.57 mmol) and methanesulfonic acid (50.0 mg, 0.52 mmol). The flask was equipped with a drying tube (or small reflux condenser), placed into a preheated oil bath and stirred for 30 min. Then a second portion of malononitrile (790 mg, 12.0 mmol) was added and the reaction mixture was stirred for an additional 30 min. After allowing the mixture to cool to room temperature, the flask content was extracted with toluene (3 × 5 mL). Combined organic extracts were washed with water (2 × 20 mL) and concentrated *in vacuo*. Product was purified by column chromatography (SiO_2/toluene) to give 2-(1-naphthyl)cyclopentylidenemalononitrile **1b** (2.37 g, 9.2 mmol, 92%) as a yellowish, viscous oil which crystallized after 2 days yielding yellow needles mp 81–83 °C.

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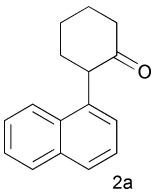
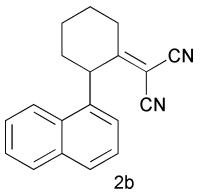
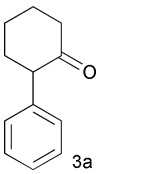
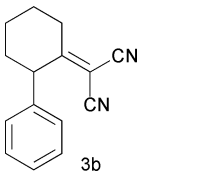
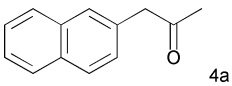
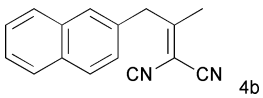
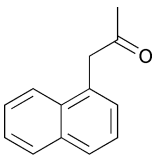
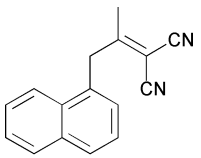
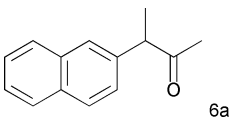
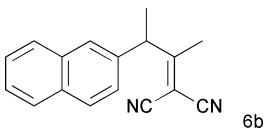
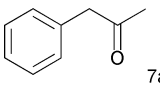
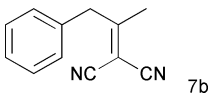
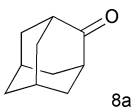
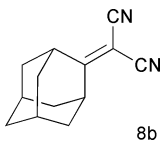
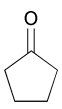
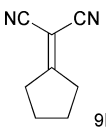
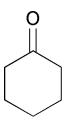
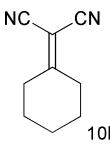
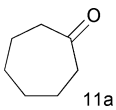
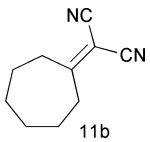
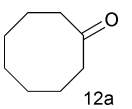
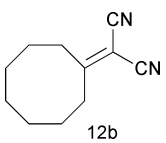
Table 2 Reactions of unconjugated ketones with malononitrile

Entry	Reactant	Product	Reaction time (h)/temp. (°C)	Yield (%)
1	 2a	 2b	1/120	92
2	 3a	 3b	1/120	96
3	 4a	 4b	1/120	93
4	 5a	 5b	1/120	88
5	 6a	 6b	1/120	75
6	 7a	 7b	1/120	95
7	 8a	 8b	0.25/120	84
8	 9a	 9b	0.25/120	87[a]
9	 10a	 10b	0.25/120	91[a]
10	 11a	 11b	0.25/120	86[a]
11	 12a	 12b	0.25/120	82[a,b]

[a] Only one portion of malononitrile (1.2 mol equiv) was added. [b] Crude product contains approximately 9% of unreacted ketone.

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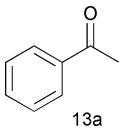
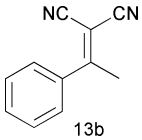
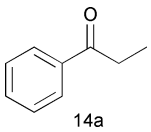
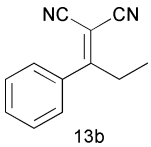
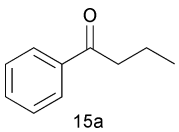
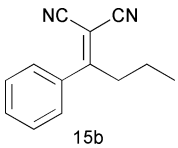
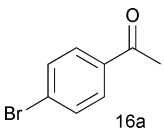
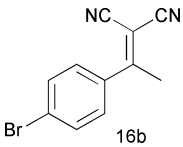
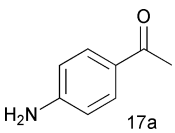
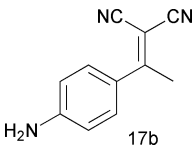
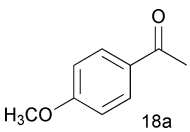
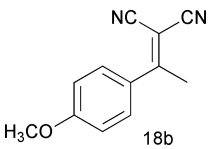
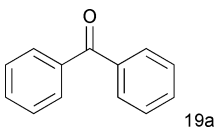
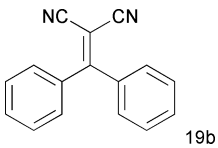
Table 3 Reactions of conjugated ketones with malononitrile

Entry	Reactant	Product	Reaction time (h)/temp. (°C)	Yield (%)
1	 13a	 13b	1/120	53
2	 14a	 13b	1/120	41
3	 15a	 15b	1/120	39
4	 16a	 16b	2/120	68
5	 17a	 17b	1/120	47
6	 18a	 18b	1/120	38
7	 19a	 19b	1/120	0

Acknowledgements

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10 For crystallization of compounds **13b–16b** 10–15 mL of ethanol with 2 drops of glacial acetic acid were used. **17b** was crystallized from toluene/heptane (10 mL/10 mL) mixture with 3 drops of glacial acetic acid. Crude **18b** was dissolved in a small volume of diethyl ether and after addition of 2 drops of glacial acetic acid, cooled to −20 °C in a refrigerator.

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An efficient, practical and cost-effective polymer-supported catalyst for the transesterification of methyl methacrylate by 1-butanol

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A straightforward and cost-effective synthesis of a polymer-supported titanium alkoxide catalyst is reported. The described synthesis involves cheap, readily available and relatively non toxic chemicals, solvents and workup procedures. Efficiency and stability of the catalyst were tested in a laboratory-scale continuous flow reactor under equilibrium conditions over a month period. The average daily titanium leaching was estimated to less than 1% of the total amount of titanium engaged. To our knowledge, this result is the best obtained, to date, concerning the use of heterogeneous titanate for the catalysis of transesterification reactions.

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Introduction

Transesterification is an important industrial reaction for the preparation of high boiling point methacrylic esters from methyl methacrylate, the low boiling by-product alcohol (*i.e.* methanol) being removed by continuous azeotropic distillation with the methacrylates.[1] This reaction requires a catalyst and, in the industrial processes currently in use, these catalysts are based on homogeneous tin or titanium derivatives.[2] Recently, bulky diarylammonium arenesulfonates have been proposed as alternative transesterification organocatalysts.[3] Although being very efficient, their high cost preclude, so far, their use in industrial process, especially in their polymer-supported version.[4] Due to cost and environmental concerns, titanium alkoxides tend to be preferred when possible.[5] The main drawback of such processes concerns the efficient removal of the catalyst from the final product. Low-boiling point methacrylic esters can be distilled off. However, in case of non-distillable compounds, titanium alkoxide has to be hydrolyzed *in situ* and separated, in some cases, a significant part of the waste remains in the commercial product. In these conditions, the catalyst recycling is difficult. Therefore, the development of a heterogeneous alternative would be a significant improvement. Several attempts have been made in this direction.[6,7] However, although the heterogeneous catalysts prepared by direct anchoring of Ti alkoxides on supports such as silica or zeolites have been claimed to be recyclable, a loss of activity with use has always been reported attributed to leaching of the metal in the homogeneous phase. This fact is mainly due to the usual high sensitivity of Ti–O bonds toward hydrolysis and alcoholysis, causing the leaching of the metal.[8] An early patent reported that titanium phenoxide catalysts were much more resistant toward hydrolysis and alcohol exchange than alkyl titanates.[9] Our previous studies on the synthesis of a polymer-supported titanium catalyst,[10] seemed to confirm this behaviour: the grafting of a trialkoxytitanium moiety onto a polymeric network through a titanium–phenoxy bond led to the synthesis of an active catalyst in transesterification and epoxidation reactions exhibiting a low metal leaching.[11] We present now an application of this observation to a reaction presenting an industrial interest: The continuous production of butyl methacrylate by transesterification of methyl methacrylate with butanol.

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Results and discussion

Synthesis of supported catalyst

The general route followed for the synthesis of the polymer-supported catalyst is represented in Scheme 1. The catalyst support was a *p*-acetoxystyrene-*co*-styrene-*co*-divinylbenzene (20/30/50 mol%) copolymer prepared in bead shape by suspension polymerisation.

The optimisation of the experimental parameters of the support synthesis was previously reported.[12] A good site isolation of the grafted catalytic moieties was insured by the preparation of highly crosslinked macroporous beads with a low loading level in order to avoid titanate condensation. A precipitant porogen (2-ethylhexanol, 40 wt%) was used to obtain a specific surface area value in the medium range.[13] The average characteristics of 16 successive 30 g-scale batches are reported in Table 1.

Grafting of the tributoxytitanium catalytic species on the support requires the conversion of acetoxyle functional groups into phenol groups. In our previous work, this step was performed by hydrazinolysis with hydrazine hydrate in dioxane at 80 °C.[10] This route was efficient, but the use of these toxic and potentially dangerous conditions is detrimental in the case of future industrial developments. In the present work, we preferred to access the polymer-supported phenol by using a based-catalysed hydrolysis reaction,[14] followed by a treatment with tetrabutyl titanate in chloroform at room temperature (Fig. 1).

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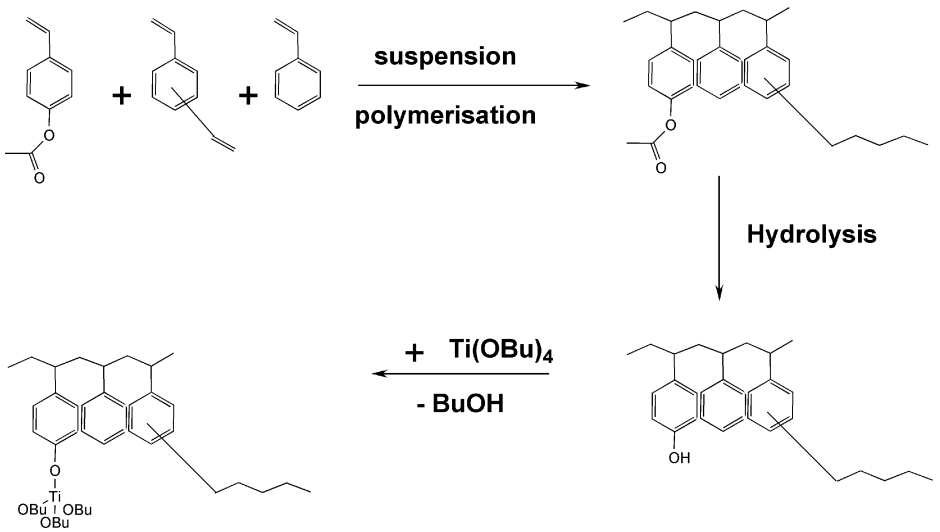
Table 1 Characteristics of the support beads

Specific surface area (BET)/m^2 g^{-1}	Standard deviation σ	Pores size (BJH)/nm	Standard deviation σ	Average particle diameter/μm	Standard deviation σ	Elemental analysis % C, H, O
208.0	35.0	11.1	0.7	380.0	12.0	86.80, 7.58, 5.42



Scheme 1 Synthesis of the supported catalyst.

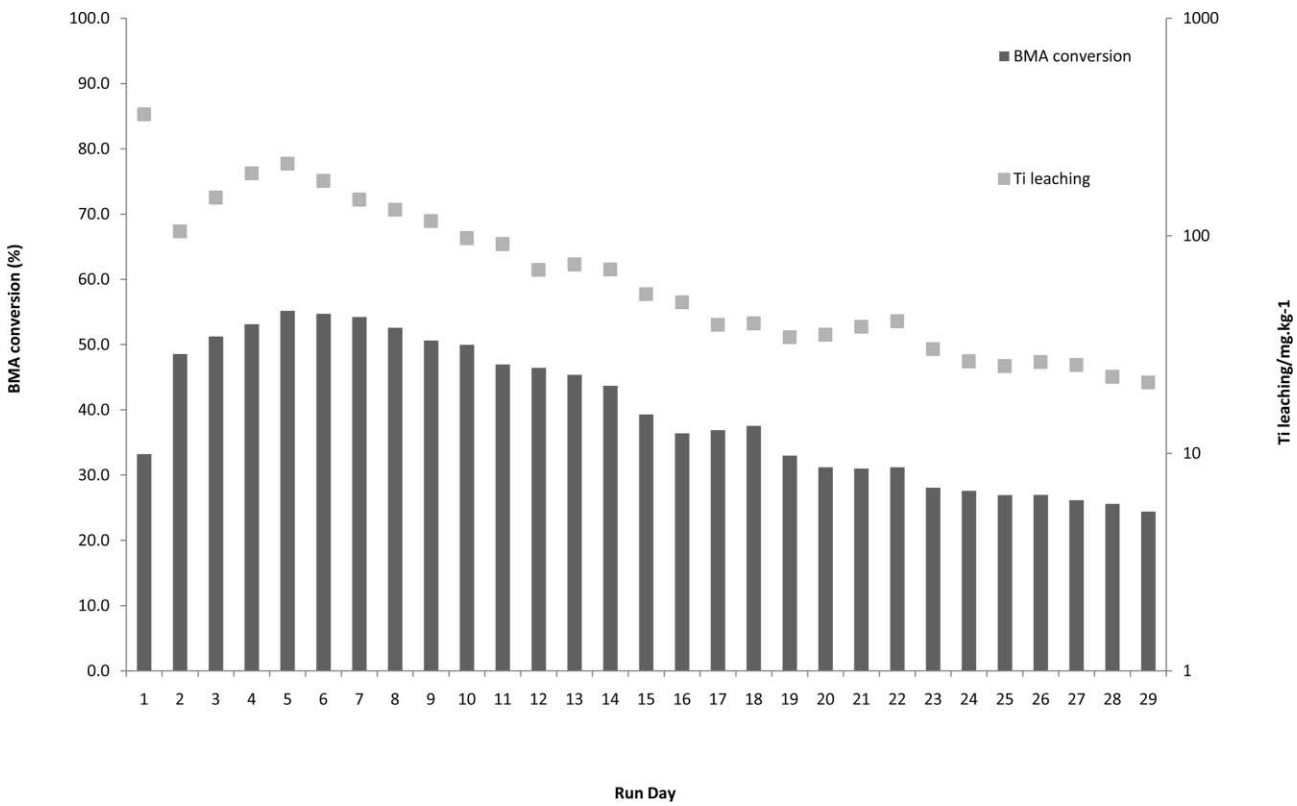


Fig. 1 Daily BMA conversion and Ti leaching.

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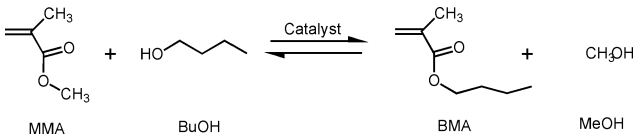
Catalytic experiments

The reaction studied was the transesterification of methyl methacrylate (MMA) with butanol (BuOH), giving butyl methacrylate (BMA) and methanol (MeOH) (Scheme 2) in the bulk (no solvent) with a molar ratio MMA : BuOH (2 : 1) at 115 °C. In these conditions, the experimental equilibrium constant value is about 0.8, giving a BuOH conversion at equilibrium around 60%.[15]



Scheme 2 Transesterification reaction.

In the industrial process, the equilibrium is displaced by continuous removal of the low boiling alcohol (methanol) using azeotropic distillation, thus leading to high BMA conversions. In this study, our main objective was to evaluate the lifetime of the heterogeneous catalyst. Therefore, we chose to work under equilibrium conditions (*i.e.* in a thermodynamically closed system) in order to obtain more reproducible results.

Some preliminary experiments were conducted in a 100 mL, mechanically stirred batch glass reactor (not shown). A BMA conversion of 50–55%, (85–90% of the equilibrium value) was obtained reproducibly by heating the mixture to 115 °C for 8 h, in the presence of *ca.* 0.4 mol% of supported catalyst. However, recycling catalyst beads using this apparatus appeared tedious and poorly reproducible mainly due to an almost unavoidable air intake during the manipulation. Therefore, we developed a continuous flow reactor with a fixed catalytic bed allowing a drastic reduction in manipulations. The diagram of the reactor system is depicted in Scheme 3. We are aware that the reaction conditions established for a batch stirred reactor are not directly transposable to a continuous tubular reactor, we chose initially to maintain the established values as much as possible. The reagent feedstocks were pumped through a tubular column containing 3 Å molecular sieves, followed by a similar column filled with the supported catalyst, both columns being placed in a furnace heated at 115 °C ± 0.5 °C. The entry flow was adjusted in order to allow an average resident time of the reagents of 8 h. The exit flow was cooled to −5 °C to avoid any loss of volatile compounds. Fractionation of the flow allows an average daily BMA conversion to be conducted by GC. The collected data over a 29 days period is reported on Fig. 1. We must highlight that this experiment can be seen as the equivalent of about 85 batches recycling!

An average BMA conversion value above 50% was reached after the second day of reaction (the first day was necessary to establish stable temperature and flow conditions in the column) and remained at this level for at least ten days. Afterwards, a slow decrease in conversion was observed with time, but even after two weeks, the yield in BMA was still around 40%. Later, the conversion continued to decrease steadily, when the reactor was stopped, after 29 days, the conversion was still around 25%.

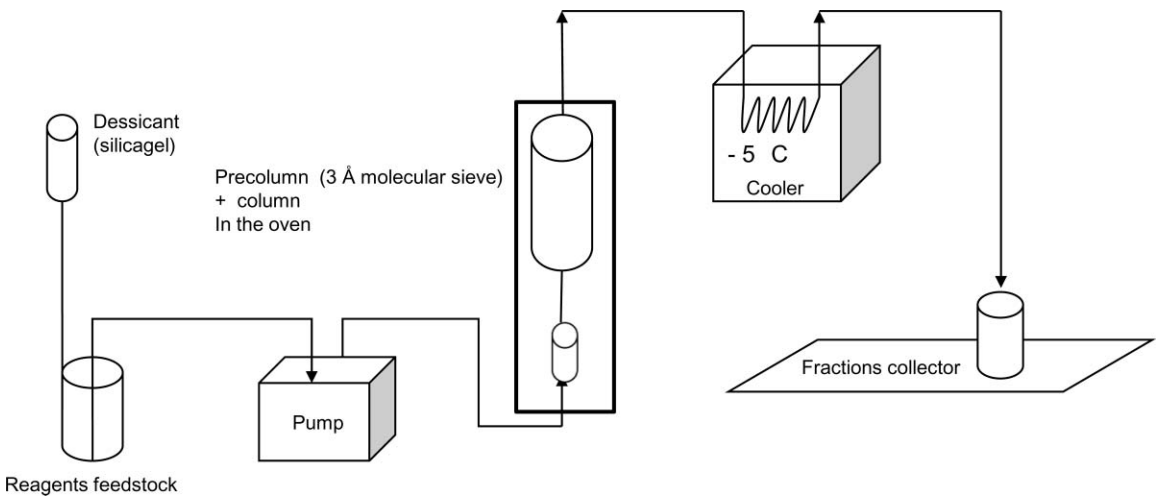
Analysis of titanium leaching

In order to evaluate the catalyst leaching during the reaction, daily reactor eluents were analyzed for titanium traces. The results are reported on Fig. 1.

Leaching during the first two days was important and can be attributed to non-grafted catalyst incompletely washed from the support. Afterward, the daily leaching gradually lowered from 150 to ~ 20 ppm. On average, the daily titanium leaching could be estimated around 2.5 mg, which corresponds to about 1% of the total amount of titanium grafted on the support engaged in the reaction.

Analysis of used catalyst

After washing with chloroform, the residual catalytic activity of some used beads was investigated in a batch experiment with a fresh mixture of reagents. In conditions similar to the preliminary experiments described previously, a BMA conversion of 40–45% was observed, which indicates that the supported



Scheme 3 Continuous flow reactor.

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catalyst was still active after almost a month of use in the continuous reactor.

Catalytic activity of the effluents

In order to control the possible catalytic activity of the leached species, the collected fraction presenting the highest conversion (n° 5, see Fig. 1) was reacted for 72 h with a fresh mixture of reagents in batch conditions. No increase in conversion could be detected. The level of titanium alkoxide needed to detect a catalytic activity in these conditions is well below the Ti amount leached on this fraction.[16] Therefore, it can reasonably be concluded that the titanium species leached into solution has little, or no, catalytic activity.

Analysis of water content of the reagents flow

Titanium alkoxides are sensitive toward hydrolysis giving inactive species. The water content of the reagents feedstock was estimated to about 700 ppm using the Karl-Fisher method. This rather high value led us to insert a tubular column containing 3 Å molecular sieve (8 g) into the reactor device before the reactor column, both columns being placed in the furnace heated at 115 °C ± 0.5 °C. With this improvement, the water content of the flow was reduced to 30 ppm, a value estimated acceptable for the catalyst stability.

Discussion

Loss of activity of the supported titanium catalyst with time can be attributed to three main causes: I) hydrolysis of the titanium alkoxide groups, leading to inactive species, ii) poisoning of the catalytic active sites and iii) leaching of the metal in solution due than an alcoholysis of the Ti grafting bond.

We estimate the hydrolytic contribution to catalyst deactivation as marginal considering the low water level observed in the reagents flow after addition of a molecular sieves column. Concerning the second point, it is well known in the industry that the reaction conditions used for the titanium alkoxide catalysed transesterification of methacrylic esters involves some polymerisation of those monomers.[17] In order to limit this very important problem, several radical inhibitors such as phenols derivatives, thiazines or nitroxyl compounds are added to the reagents mixture and, in addition, the reaction vessel is always aerated by a stream of oxygen.[18] Even with the added inhibitors, oxygen aeration was not technically possible in our device, which strongly limited their efficiency. However, we have not observed significant polymerisation of methacrylates in our device (which is usually evidenced by a rapid increase of the fluid pressure in the column). The total leaching of titanium over the total run length can be estimated at nearly 30% of the initial amount of titanium engaged in the reaction (*i.e.* grafted on the beads placed in the column). This loss can be correlated with the evolution of BMA conversion along the run: it reached 55% on day 4 and ended at 25% on day 29. Therefore, the most accurate explanation for the significant catalytic activity loss during a long continuous run seems to be the breaking of the phenoxy–titanium bond by alkoxy exchange with butanol. This reaction, even if slowed down with the use of a polystyrenic support (compared to what we observed previously with silica supports), seems unavoidable on the long term.

Conclusion

We have prepared a polymer-supported titanium catalyst for applications in a transesterification reaction of industrial interest with the idea to replace a homogeneous process.[19] We tried to develop a straightforward and cost-effective route for the catalyst synthesis using cheap, readily available and relatively non toxic chemicals, solvents and workup procedures. In order to assess the efficiency and stability of our catalyst we tested it in a laboratory-scale continuous flow reactor under equilibrium conditions. The results obtained indicate a good stability to metal leaching with deactivation being attributed to the slow alcoholysis of the phenoxy–titanium bond in the long term. To our knowledge, this result is the best obtained, to date, concerning the heterogenisation of a titanate for the catalysis in transesterification reactions.

Experimental

Instruments

The specific surface area was determined by N_2 adsorption measurements performed on a Micromeritics ASAP 2010. The resulting data were subjected to the Brunauer, Emmett and Teller (BET) and the Barrett, Joyner and Halenda (BJH) treatments.[20,21]

Chromatography experiments were performed using a VARIAN 3300 and the Star chromatography software. The capillary column was a DB5-like (5% phenyl groups). The BMA conversion was calculated from the peak area ratio of BMA relative to undecane as obtained from GC analysis using a calibration curve. Elemental analyses on solids were performed by the Service Central d'Analyses, Vernaison, France. Results are expressed in weight percent (wt%). Titanium content in effluents was estimated using ICP-MS technique by Antellis Company, Toulouse, France. Results are expressed in mg Ti kg^{-1} (ppm).

Chemicals

All the monomers (styrene (S, Aldrich), divinylbenzene (DVB, 80%, mixture of isomers, Aldrich), *p*-acetoxystyrene (AS, a gift from TOSH Corp, Japan) and other components involved in the polymerisation (azobisisobutyronitrile (AIBN, Acros), 2-ethylhexanol (Aldrich) and acacia gum (Aldrich) were used as received. Tetrabutoxy titanium (Aldrich) was also used without further purification. 1-Butanol and methyl methacrylate (Aldrich) were distilled under reduced pressure from CaH_2. All solvents were dried according to published procedures.

Synthesis of macroporous poly(4-acetoxystyrene-*co*-styrene-*co*-divinylbenzene) beads (ACP)

The suspension polymerisation was performed in a 500 mL parallel-sided glass reactor already described.[7] In a typical experiment, the organic phase was composed of acetoxystyrene (8.6 g, 53 mmol), styrene (8.33 g, 80 mmol), divinylbenzene

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(17.32 g, 133 mmol), AIBN (0.34 g) as the initiator and 2-ethylhexanol (22.6 g) as the porogen. The mixture was suspended in water (350 mL) containing a suspension stabiliser (acacia gum, 7 g) and stirred at 220 rpm. The polymerisation was performed at 80 °C for 15 h, after which time the resulting spherical particles were washed with water, then continuously extracted in a Soxhlet apparatus with ethanol (24 h), and finally dried under vacuum to give 33.5 g of white beads with a diameter between 200–500 μm. ($Y = 98\%$).

Conversion of ACP to poly(4-hydroxystyrene-*co*-styrene-*co*-divinylbenzene) beads (HP)

The resin beads (31 g) were suspended in methanol (100 mL), and a sodium hydroxide aqueous solution (200 mL, 1 mol L^{-1}) was then added and the reaction medium mechanically stirred for 2 days at RT. Next, the beads were filtered and copiously washed with successively water and methanol, then continuously extracted in a Soxhlet apparatus with water (24 h), followed by THF (24 h), and finally chloroform (24 h). Drying under vacuum at 50 °C gave 29 g of white beads, $Y = 100\%$.

Synthesis of catalyst TiP

The white opaque resin **HP** (200 μm < d < 500 μm, 29 g, 63 mmol of phenoxy groups) was suspended in anhydrous chloroform (300 mL) in a round-bottomed flask under argon. $Ti(OiPr)_4$ (21.6 g, 1.2 eq Ti/OH) was injected and the reaction mixture was mechanically stirred for 2 days at room temperature after which the resulting orange beads were continuously extracted for 2 days with chloroform using a Soxhlet apparatus. Finally resin **TiP** was dried under vacuum at 50 °C to give 33 g of orange-yellow beads, $Y = 80\%$, (titanium content: 0.95 mmol g^{-1}).

Transesterification of methyl methacrylate (MMA) with 1-butanol (BuOH) catalysed by TiP resin, batch reaction

In a typical procedure, a 100 mL, three-necked round-bottomed flask, connected with a condenser cooled at 0 °C, and equipped with a mechanical stirrer, was charged with **TiP** resin (0.5 g, ~0.5 mmol of Ti, ~0.4 mol%/BuOH) suspended in a mixture of 1-butanol (8.3 g, 112 mmol), methyl methacrylate (22.53 g, 225 mmol), phenothiazine (0.05 g, 0.1 mmol) as polymerisation inhibitor and undecane (5.23 g, 34 mmol) as internal standard for GC analysis. The mixture was heated at reflux (~115 °C) under a slow bubbling of dry air. Aliquots were periodically taken from the reaction mixture over an 8 h period and diluted with diethyl ether (20 mL) before GC analysis for BMA conversion determination.

Transesterification of methyl methacrylate (MMA) with 1-butanol (BuOH) TiP resin, continuous reaction

A stainless steel HPLC-type column (7 mm ID diameter, 300 mm useful length) was filled, in a glove box, with **TiP** resin beads (4.5 g, 215 mg Ti). The closed column was then connected to the device described in Scheme 3. The reagents feedstock consisted of a mixture of 1-butanol (74.12 g, 6.48 mol), methyl methacrylate (1292 g, 12.91 mol), 4-methoxyphenol (31 g, 0.249 mol) and phenothiazine (64 g, 0.310 mol) as polymerisation inhibitors, and undecane (100.8 g, 0.645 mol) as internal standard for GC analysis. This mixture (water content 700 ppm, KF determination) was pumped through a tubular column containing 3 Å molecular sieve (8 g) followed by the reactor column, both columns being placed in the furnace heated at 115 °C ± 0.5 °C. The entry flow (0.025 mL min^{-1}) was adjusted in order to allow an average residential time of the reagents of 8 h. After cooling at −5 °C in order to avoid any loss of volatile products, the exit flow was fractionated each 8 h and the BMA conversion estimated by GC using an internal standard.

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Direct conversion of inulin to 5-hydroxymethylfurfural in biorenewable ionic liquids

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In this work, we found that inulin is soluble in ionic liquids (ILs) choline chloride (ChoCl)/oxalic acid and ChoCl/citric acid, which are prepared entirely from cheap and renewable materials. On the basis of this discovery, we conducted the one pot reaction for the conversion of inulin into 5-hydroxymethylfurfural (HMF), which is a potential substitute for petroleum-based building blocks, using the two ILs as catalysts and solvents. The effects of reaction time, temperature and water added on the reaction were studied. It is demonstrated that the ILs are very efficient for the reaction at relatively lower temperature and could be reused after simple separation.

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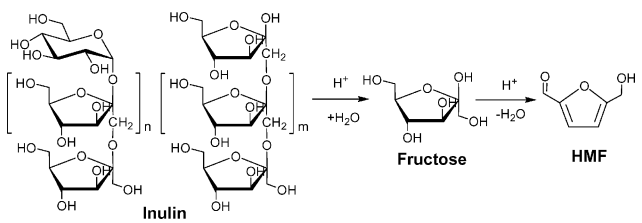
Introduction

The diminishing availability of petrochemical resources forces human beings to look for sustainable resources.[1] Biomass, as an abundant and widely-distributed sustainable resource, is a promising substitute for fossil-based resources to produce liquid fuels and intermediates for chemical industry.[2] Carbohydrates comprise the main class of biomass compounds.[1]

It is known that the direct production of useful organic compounds from five- and six-carbon carbohydrates is difficult.[3] 5-Hydroxymethylfurfural (HMF), which can be obtained from carbohydrates by dehydration, is an important "bridge" for the efficient use of carbohydrates.[1,4] As a versatile intermediate, HMF can be converted to many value-added compounds[5] and liquid fuels.[2a] Fructose can be converted to HMF more efficiently compared with other monosaccharides.[6] In recent years, many researchers have studied the conversion of fructose to HMF.[7–11] Unfortunately, most fructose is produced by isomerization of glucose in industry and glucose is produced by hydrolysis of starch, which would consume food supply.[12]

Inulin is a non digestible oligosaccharide consisting of glucose–$(fructose)_n$ or $(fructose)_m$ (Scheme 1) which is available in large quantities.[13] It exists in many plants, such as in the roots of chicory. The yield of inulin in the roots of chicory is approximately 8–12 t ha^{-1}, which can produce 5–7 t ha^{-1} of HMF.[14] The hydrolysis of inulin can produce fructose that can be further converted to HMF, and starting from inulin to produce fructose or HMF can reduce the expending of the food supply. This hydrolysis processed under enzymatic or acidic conditions with about an 80% fructose yield has been reported, but long reaction times, from 10 h to 10 days, were required.[15] The high cost resulting from complex processes or harsh conditions limits the industrial production of fructose from inulin.



Scheme 1 The pathways for acid-catalyzed hydrolysis and dehydration of inulin to produce HMF.

The combination of hydrolysis of inulin and dehydration of fructose in one pot is possible because both processes can be catalyzed by acids (Scheme 1), which avoids the production of fructose and the corresponding cost. Therefore, the one pot reaction is more advantageous for producing HMF. Up to now, the one pot reaction has been carried out in different solvents, such as in water at 80–110 °C with heterogeneous niobium, vanadium, titanium and zirconium based catalysts,[16] and in water–dimethylsulfoxide or water–acetone mixtures at 140–180 °C using mineral acids (*e.g.*, HCl, H_2SO_4) as catalysts.[4,10] When the reaction takes place in pure water, the yield of HMF is low; and when it takes place in an organic solvent–water mixture, the yield can be improved but the separation is more complex.

Room temperature ionic liquids (ILs), which are organic salts with a melting point lower than 100 °C, have attracted much attention in recent years.[17,18] ILs have some unusual properties, such as negligible vapor pressure, nonflammability, high thermal and chemical stability, and adjustable solvent power for organic and inorganic substances. Some ILs have been synthesized from biorenewable materials, such as choline chloride (ChoCl)-based ILs.[19] Some eutectic mixtures formed by heating ChoCl with urea, organic acids and metal chlorides, which also belong to the ILs group,[20] have been used not only as solvents and/or catalysts in chemical reactions,[19,21] but also as solvents and templates in the preparation of novel polymorphous materials.[22] Among them, ChoCl/oxalic acid dihydrate and ChoCl/citric acid monohydrate are prepared entirely from cheap and renewable materials.

In this work, we found that inulin is soluble in ChoCl/oxalic acid and ChoCl/citric acid ILs. On the basis of this discovery and the fact that these ILs are acidic, we carried out the one

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pot reaction for the conversion of inulin using the two ILs as catalysts and solvents. It was demonstrated that the ILs were very efficient for the reaction at relatively low temperature and could be reused after simple separation. As far as we known, this is the first example of converting inulin in ILs.

Experimental

Materials

Inulin was purchased from Alfa Aesar. The average degree of polymerization was about 29. HMF (99%) was purchased from Aldrich. The other starting materials (AR grade) were purchased from Beijing Chemical Reagents Company and used without further purification.

Analysis methods

The amount of HMF was calculated by using an external standard analyzed by HPLC with a Supelcosil LC-18 5 μm column at 25 °C, a Shimadzu LC-20AT pump, a Sama UV-Vis LC-830 detector at 282.0 nm, and methanol/water (50/50 v/v) as flowing phase at 0.8 mL min^{-1}. The amount of fructose was also calculated by using an external standard analyzed using HPLC with a Hypersil NH_2 5 μm column at 40 °C, a Shimadzu LC-20AT pump, a Shimadzu RID-10A detector at 40 °C, and acetonitrile/water (75/25 v/v) as flowing phase at 0.8 mL min^{-1}.

HMF identification

HMF was identified by ^{1}H NMR spectra which were recorded as solutions in $CDCl_3$ at room temperature in a 400 MHz Bruker spectrometer, and by GC-MS (GC: Agilent technologies 6890N; MS: Agilent technologies 5973 inert MS Detector) M.S.: m/z (% of max. intensity) 50 (8), 69 (32), 81 (7), 97 (100), 109 (11), 126 (75); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.75 (s, 2 H), 6.54 (d, $J = 3.4$ Hz, 1 H), 7.24 (d, $J = 3.4$ Hz, 1 H), 9.62 (s, 1 H).

Preparation of the choline chloride-based ILs

The ILs were synthesized following procedures reported in the literature.[22] In ChoCl/oxalic acid, the molar ratio of choline chloride to oxalic acid·$2H_2O$ was 1 : 1, and in ChoCl/citric acid, the molar ratio of choline chloride to citric acid·H_2O was 2 : 1.

General procedure for the reaction in ILs

Inulin (81.0 mg) and a known amount of IL were added into the reactor in a constant temperature oil bath, and the reaction system was stirred for the desired time. After reaction, the reactor was cooled to room temperature immediately. The yields were analyzed by HPLC.

Biphasic procedure and reusing of ChoCl/oxalic acid

Inulin (81.0 mg) and a known amount of IL were added into the reactor in a constant temperature oil bath at 80 °C. After stirring for 1 min, the desired amount of ethyl acetate was added into the reactor. After stirring for the desired time, the reaction system was cooled to room temperature immediately. Then, the ethyl acetate phase was poured out from the reactor and collected. The IL phase was extracted with fresh ethyl acetate (1 mL × 3). The ethyl acetate phases were combined and analyzed by HPLC. Then, the IL phase was used directly for the next run, where the procedure was the same as that described above.

Results and discussion

Effect of the reaction time on the yield

Our experiment in this work showed that the solubility of inulin in the two ILs is very high. For example, at 70 °C the solubilities of inulin in ChoCl/oxalic acid and ChoCl/citric acid are 150 mg g^{-1} and 28 mg g^{-1}, respectively. We studied the direct conversion of inulin to HMF in ChoCl/oxalic acid and ChoCl/citric acid. The functional parts of the ILs are the dicarboxylic or tricarboxylic acids. The ILs acted as both solvent and catalyst. Fig. 1 shows the results of the reaction at 80 °C. It is well known that in the acid-catalyzed hydrolysis, inulin is broken down to the fructofuranosyl cation in the first step,[23] and this cation is further dehydrated to produce HMF rapidly or reacts with water to form fructose. This is a complex reaction system and many by-products can be formed. For example, di-D-fructose dianhydrides can be produced from the fructofuranosyl cation,[24] and levulinic acid may be formed from HMF under aqueous acidic conditions.[1c] Fig. 1 shows that when the reaction carried out in ChoCl/citric acid, a large amount of fructose was produced within 10 min, then, the fructose was immediately converted to HMF, which resulted in a sharp decrease of the fructose yield and an increase of the HMF yield for 10 to 30 min. After 30 min, the HMF yield increased at a relatively slower rate and reached the maximum at a reaction time of about 120 min. When the reaction was in ChoCl/oxalic acid, 37% of HMF and only 4% of fructose were obtained within 10 min. This was very different from the reaction in ChoCl/citric acid and indicated that fructose was very unstable in ChoCl/oxalic acid and was quickly converted to HMF due to the higher acidity of the oxalic acid. Then, the HMF yield increased slowly and reached the maximum at a reaction time of about 120 min.

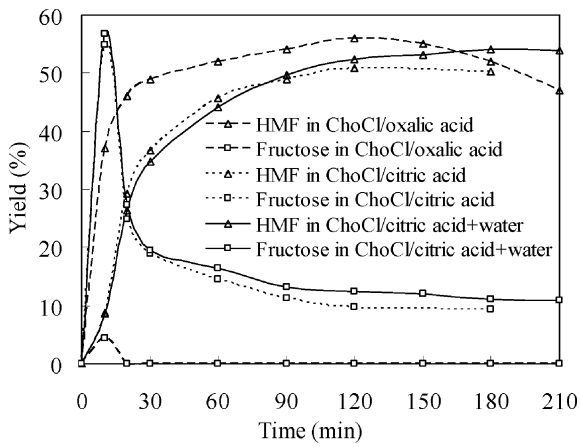

Fig. 1 Conversion of inulin to fructose and HMF in ILs at 80 °C: inulin (81.0 mg, 0.5 mmol fructose units), ILs (3 mmol based on acid moieties, 0.80 g for ChoCl/oxalic acid and 1.47 g for ChoCl/citric acid); water was 3 mmol in the ChoCl/citric acid–water mixture.

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Effect of additional water in ILs

It was mentioned above that inulin was converted to HMF, fructose and some di-D-fructose dianhydrides catalyzed by acids. The di-D-fructose dianhydrides that cannot be converted further to HMF were easily formed from inulin under anhydrous acidic conditions,[24] and the addition of water would reduce their yields. If we can suppress the formation of di-D-fructose dianhydrides by adding water, the HMF yield might be increased. To prove the above argument, we added different amounts of water to the ILs in the reaction.

Fig. 1 shows the yields of HMF and fructose in a mixture of ChoCl/citric acid and water at different reaction times. The molar ratio of the IL and water was 1 : 1. Similar to that in the neat IL, a large amount of fructose was produced within 10 min and, then, it quickly was converted to HMF; but the yield of fructose in the IL–water mixture was always higher than that in neat IL at the same reaction time. The maximum of the HMF yield in the mixture was reached at about 180 min, at which both the yields of HMF and fructose were higher than those in the neat IL, indicating that the addition of suitable amount of water into the IL indeed increased the HMF yield.

Fig. 2 shows the effect of the amount of water added on the yield of HMF. In ChoCl/citric acid, the yield increased with the increase of the amount of water added when R (R is the molar ratio of the additional water to fructose units in inulin) was less than 25, and then decreased when R exceeded 25. The main reason for this was that too much water would inhibit the dehydration of fructose to produce HMF. Similarly, in ChoCl/oxalic acid, the yield increased when R was in the range of 0–20, and then decreased with further increasing of the amount of water added. In short, the values of R at which the HMF yield began to decrease in ChoCl/oxalic acid and ChoCl/citric acid were 20 and 25, respectively. It is known that oxalic acid has two hydrated water molecules and citric acid contains one hydrated water molecule. The molar ratio of the acid moiety in the ILs and the fructose units in inulin was 3/0.5 in the reaction systems (Fig. 1 and 2). Therefore, in ChoCl/oxalic acid and ChoCl/citric acid the total molar ratios of water (hydrated and added) to fructose units in inulin at which the HMF yields began to decrease were 32 ($32 = 3/0.5 \times 2 + 20$) and 31 ($31 = 3/0.5 \times 1 + 25$), respectively. The two numbers are very close. These experiments further suggested that a suitable amount of water was favourable for promoting the yield of HMF.

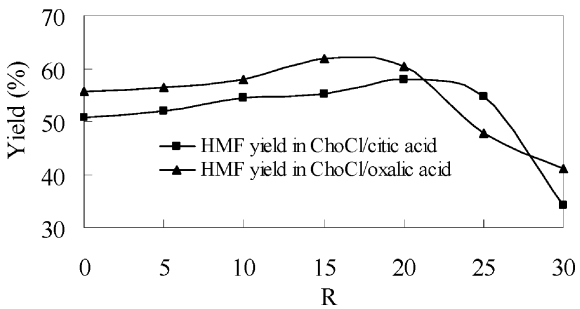

Fig. 2 The yields of HMF in the mixture of ILs and water: inulin (81.0 mg, 0.5 mmol fructose units), ILs (3 mmol based on acids moieties), 80 °C, 2 h.

Effect of reaction temperature

We also studied the effect of the temperature on the reaction. It was found that a higher temperature benefits the formation of HMF, and more fructose was produced at lower temperatures (Table 1, entries 2–6). Especially, 69% fructose yield was obtained in ChoCl/citric acid at 50 °C (Table 1, entry 7). On the basis of these results, we tested the two-temperature step reaction in a one pot reaction. Inulin was first converted at low temperature (50 °C) for 2 h, and then heated to 80 °C for 2 h. Indeed, the yield (57%) and selectivity (65%) were higher than when reacted only at 80 °C (Table 1, entries 2 and 8).

Reaction in an ethyl acetate (AcOEt)/IL biphasic system

Ethyl acetate (AcOEt) is a widely-used solvent in industry because it is cheap and displays low toxicity. It is known that HMF is soluble in AcOEt.[21a] The above results demonstrated that ChoCl/oxalic acid was the more efficient IL for the reaction. We studied the reaction in a biphasic system consisting of AcOEt and ChoCl/oxalic acid. Our experiments showed that at the reaction conditions of this work the product HMF is soluble in AcOEt while the solubility of the IL, the reactant inulin and fructose in AcOEt is negligible. Moreover, the reactant inulin and fructose are soluble in the IL, and AcOEt is only slightly soluble in the IL. This special phase behavior is favorable for conducting the reaction in the biphasic system. When the reaction was carried out in the biphasic system, the upper AcOEt phase would extract the product HMF from the IL-rich phase

Table 1 The conversion of inulin to HMF in ChoCl based ILs: inulin (81.0 mg, 0.5 mmol fructose units), ILs (3 mmol based on acid moieties)

Entry	Acid in IL	Temperature/°C	Time/h	HMF yield (%)	Fructose yield (%)	Selectivity (%)[a]
1	Oxalic acid	80	2	56	0	56
2	Citric acid	80	2	51	10	56
3	Oxalic acid	50	2	19	38	31
4	Oxalic acid	60	2	28	31	40
5	Oxalic acid	70	2	45	7	49
6	Oxalic acid	90	2	55	0	55
7	Citric acid	50	2	3	69	9
8[b]	Citric acid	50/80	2/2	57	12	65
9[c]	Oxalic acid	80	2	64	0	64

[a] Selectivity is equal to HMF yield/(100 – fructose yield). [b] Entry 8 was first stirred at 50 °C for 2 h, then at 80 °C for the next 2 h. [c] Entry 9 was the biphasic systems with IL and AcOEt (4.90 mL).

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continuously, which would produce more HMF and reduce the by-products. The separation of the product was also easy because the upper phase consisted only of the solvent and the product. A yield of 64% was achieved in the biphasic system with ChoCl/oxalic acid as the solvent and AcOEt as the extraction solvent, which is considerably higher than that in the neat IL (Table 1, entries 1 and 9).

Reusability of the IL

The recycling of ChoCl/oxalic acid in the biphasic system was investigated. The conditions were the same as those of entry 9 in Table 1. After reaction, there were two phases in the reactor. The upper phase consisted of AcOEt and HMF and the other phase was rich in IL. After separation of the two phases, the product in the IL was further extracted using fresh AcOEt and the IL was reused directly. The results of recycling the IL are presented in Fig. 3. It should be indicated that the activity of the recycled IL was still very high after being used six times.

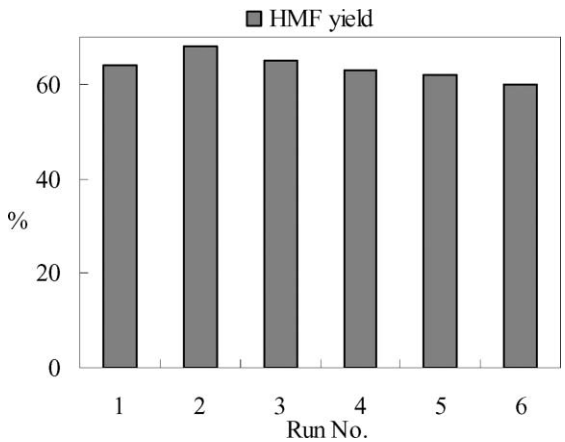

Fig. 3 Results of recycling ChoCl/oxalic acid in the ChoCl/oxalic acid/AcOEt biphasic reaction system. The conditions were the same as those of entry 9 in Table 1.

Our experiment showed that the accumulated residue (mainly di-D-fructose dianhydrides) and the IL in the IL phase could be separated by extraction using ethanol because the IL is soluble in ethanol, while the residue is not soluble in ethanol at room temperature. At room temperature, when 2 mL of ethanol were added into the IL phase which was recycled 6 times, the IL dissolved in the ethanol and the accumulated residue precipitated from the ethanol solution. Then, the precipitate was removed by filtration and the IL was refreshed after removing the ethanol from the filtrate by distillation.

Conclusion

In summary, inulin was efficiently converted to HMF in a one-pot reaction in ChoCl/oxalic acid or ChoCl/citric acid, which were prepared from cheap biorenewable materials. Moreover, the yield of HMF in the AcOEt/ChoCl/oxalic acid biphasic system was considerably higher. The IL phase could be recycled directly after removing the AcOEt phase that contained HMF, and the reduction in the yield was not considerable after the IL was recycled 6 times. We believe that this highly efficient and greener route has great potential for application.

Acknowledgements

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Catalyst-free, step and pot economic, efficient mercaptoacetylative cyclisation in H_2O: synthesis of 3-mercaptocoumarins

Lal Dhar S. Yadav,* Santosh Singh and Vijai K. Rai

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A novel, environmentally friendly, tandem Knoevenagel condensation and mercaptoacetylative cyclisation procedure is reported. The reaction between 2-methyl-2-phenyl-1,3-oxathiolan-5-one and a variety of salicylaldehydes was carried out in water to afford 3-mercaptocoumarins in excellent yields (82–97%). In this green synthetic protocol, water itself catalyses the reaction by hydrogen bonding and thus avoids the use of any other catalyst. Acetophenone obtained as a by-product was also recovered and recycled easily for further use.

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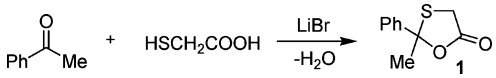
Introduction

One of the key areas of green chemistry is the elimination of catalysts and solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. In today's world, synthetic chemists in both academia and industry have a widespread current debate over the relative 'greenness' of different solvents such as ionic liquids, perfluorinated solvents, supercritical carbon dioxide and last but not least water. But water can undoubtedly be considered the best environmentally friendly, cleanest and cheapest solvent because its use not only eliminates the necessity of vigorous drying of solvents and substrates, but also because, owing to its highly polar character, unique reactivity and selectivity are often observed in aqueous reactions.[1]

Coumarins (2*H*-1-benzopyran-2-ones) are an elite class of compounds present in various natural products[2] which have found wide applications, *viz.*, as additives in food, perfumes, cosmetics and pharmaceuticals, in the preparation of optical brighteners, dispersed fluorescent, laser dyes and useful medicinal products.[3–5] Notable amongst these are the anti-coagulant dicoumarol, the antibiotics novobiocin and chlorobiocin, and the calanolides A and B, which have been shown to inhibit HIV-1 replication *in vitro*.[6–8] Moreover, it is well known that the presence of a thiol function in many enzymes (called SH enzymes) is essential for their enzyme activity. Likewise, incorporation of a thiol function in heterocycles, nucleosides, or nucleotides has led to a number of analogues possessing interesting biological and therapeutic properties.[9–15] Although mercaptocoumarins have been relatively less extensively studied, their chemistry and bioactivity appear to be quite interesting.[16]

Many classical routes to coumarins are well documented, such as Pechmann,[17] Knoevenagel,[18] Perkin,[19] Reformatsky,[20] and Wittig condensation reactions.[21] To expedite these classical approaches for coumarin synthesis, several variations in terms of catalyst and reaction conditions have also been developed, such as organopalladium,[22] sodium hydroxide in water,[23] zeolite,[24] clays,[25] Nafion-H,[26] Amberlyst 15,[27] W/ZrO_2 solid acid,[28] ionic liquids,[29] cation-exchange resins,[30] and solvent-free conditions along with solid-phase synthesis.[31] On the other hand, only limited reports are available on the synthesis of thiophenoxycoumarin.[16,32] However, all of these reactions suffer from one or more disadvantages, such as expensive reagents, long reaction times, low yields, tedious work-up, low selectivity, and large amounts of catalysts which would eventually result in the generation of large amounts of toxic waste.

Considering the above points and in continuation of our quest for developing green protocols for heterocyclic frameworks,[33,34] we planned an efficient synthesis of coumarins bearing a synthetically and pharmacologically readily manipulable thiol function on C-3. For this purpose, we utilized the mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**,[33] developed in our laboratory (Scheme 1), which leads to the desired mercaptoacetylative cyclisation and is the cornerstone of the present investigation. It is worth mentioning here that acetophenone, which was used to activate mercaptoacetic acid to act as a mercaptoacetyl transfer agent, was removed during the course of the reaction without requiring any protection-deprotection step and was recovered easily for further use.



Scheme 1 Formation of the mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**.

Herein, we report a conceptually new, practical, expedient and catalyst-free preparation of 3-mercaptocoumarins in water which may be utilized to exploit chemical diversity and generate drug-like screening libraries to identify lead candidates.

Results and discussion

For a model experiment, we first estimated the reactivity of salicylaldehyde (2 mmol) and 2-methyl-2-phenyl-1,3-oxathiolan-5-one (2 mmol) by refluxing these in water for 10 h and the corresponding 3-mercaptocoumarin **5a** was isolated in 91% yield (Table 1, entry 1). Then, we tried this reaction in solvent-free conditions using a microwave (Chemical Laboratory Microwave

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad, 211 002, India. E-mail: ldsyadav@hotmail.com

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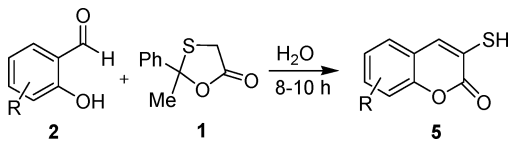
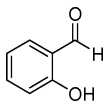
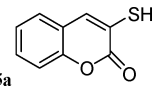
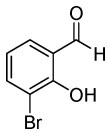
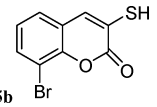
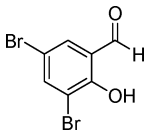
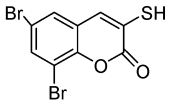
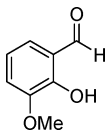
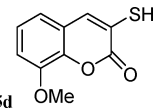
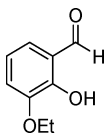
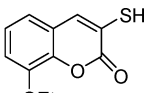
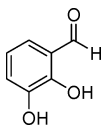
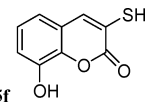
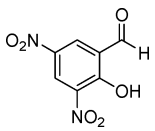
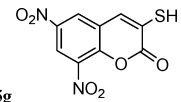
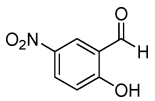
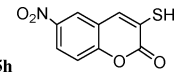
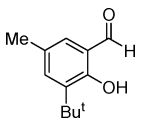
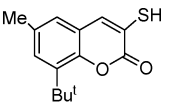
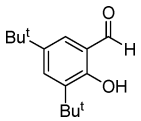
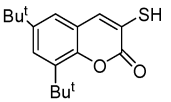
Table 1 Catalyst-free synthesis of 3-mercaptocoumarins **5** in water



2 **1** **5**

Entry	Salicylaldehyde **2**	Time/h[a]	3-Mercaptocoumarin **5**	Yield (%)[b,c]
1		10	 **5a**	91
2		10	 **5b**	85
3		10	 **5c**	82
4		9	 **5d**	96
5		10	 **5e**	92
6		8	 **5f**	97
7		9	 **5g**	89
8		8	 **5h**	90
9		10	 **5i**	—
10		10	 **5j**	—

[a] Refluxing time in water. [b] Yield of isolated and purified products. [c] All compounds gave C, H and N analyses within ±0.37%, and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

Oven, Model; BP-310/50, 230 volt, 50 Hz power input) but a relatively lower yield was obtained (79%), although the time required for the completion of the reaction was 10 min.

Thus, the present optimized synthesis is accomplished by refluxing an equimolar mixture of salicylaldehyde **2** and 2-methyl-2-phenyl-1,3-oxathiolan-5-ones **1** in water for 8–10 h (Table 1). The isolation and purification steps are very simple and done by filtration with a Büchner funnel followed by washing with water (2 × 10 mL) and recrystallization from EtOH. After isolation of the product, the aqueous layer was extracted with AcOEt (3 × 10 mL) and acetophenone was easily collected from the organic phase.

Next, in order to investigate the substrate scope for general validity of the present investigation, a variety of substituted salicylaldehydes **2** were used employing the present optimized reaction conditions, and different 3-mercaptocoumarins **5** were synthesised. The yields were consistently good (Table 1) and the highest yield was 97% (Table 1, entry 6). Salicylaldehydes **2** bearing lipophilic substituents (Table 1, entries 9 and 10) did not react at all and were recovered unchanged. This is probably due to complete immiscibility of these starting materials with water. Furthermore, relatively lower yields obtained in some other cases (Table 1, entries 2 and 3) also support the above point. In addition, it was observed that salicylaldehydes **2** bearing an electron-donating group, for example OMe and OAc, on the *para* position of the CHO group resulted in low yields (42% in the case of OMe and 37% in OAc) of coumarins.

The formation of **5** is rationalized by nucleophilic attack of the active methylene carbon (C-4) of **1** to the carbonyl group of salicylaldehyde **2** followed by dehydration leading to the isolable intermediate **4**. The driving force for the dehydration process is the presence of a high degree of conjugation of the C=C bond formed in intermediate **4**. The adduct **4** undergoes an intramolecular nucleophilic attack of the oxygen atom of the OH group at the carbonyl carbon (C-5) of the oxathiolan-5-one nucleus to yield target compounds **5** with elimination of acetophenone, which was easily recovered and reused for the preparation of the mercaptoacetyl transfer agent 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** by treatment with LiBr and mercaptoacetic acid, as depicted in Scheme 2. Thus, the formation of the products **5** occurs through the isolable intermediates **4**. This conclusion is based on the observation that the representative intermediate compounds **4a** (R = H), **4b** (R = 2-Br) and **4d** (R = 2-OMe) could be isolated in 47–58% yield, and that these could be converted into the corresponding coumarins **5a**, **5b** and **5d** in quantitative yields (*vide* Experimental), as well as that acetophenone was formed during the reaction (Scheme 2). It is noteworthy that in all these cases the intermediate **3** was never isolated.

Herein, water not only acts as solvent but it also catalyses the reaction through hydrogen bond formation with the carbonyl oxygen of the salicylaldehyde **2**, thereby increasing the electrophilic character of carbonyl carbon of **2**. Moreover, water also helps in enolization of **1** by making hydrogen bonds with the OH of **1′** and, thus, it increases the nucleophilic character of the methylene carbon (C-4) of **1**. Therefore, water activates both steps, *i.e.*, Knoevenagel condensation and mercaptoacetylative cyclisation in the envisaged synthetic strategy (Scheme 2). The reactions were clean and all the synthesised products were

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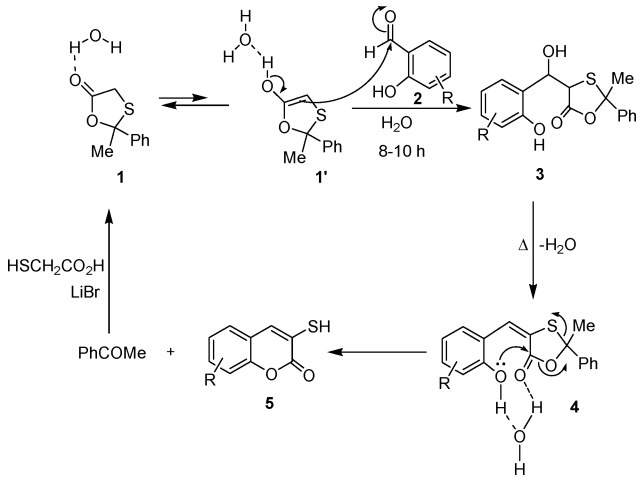

Scheme 2 Plausible mechanism for the mercaptoacetylative cyclisation leading to 3-mercaptocoumarins **5**.

characterized by their ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

Conclusions

In summary, we have documented a new, convenient, efficient and high yielding synthetic protocol for 3-mercaptocoumarins, adopting the stringent and growing environmental regulations of green chemistry. The envisaged, pot and step economic reaction was carried out in water using no catalyst, and acetophenone, the by-product formed, was also recovered and recycled successfully. Thus, this simple and green methodology would be a practical alternative to the existing procedures for the production of this kind of fine chemical to cater for the needs of academia as well as industry.

Experimental

General

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-d_6 and TMS was used as internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. A Chemical Laboratory Microwave Oven (Model; BP-310/50, 230 volt, 50 Hz power input) was used. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

2-Methyl-2-phenyl-1,3-oxathiolan-5-one (1). It was prepared employing a known method.[33] A mixture of acetophenone (3.5 mL, 30 mmol), mercaptoacetic acid (2.1 mL, 30 mmol) and a catalytic amount of lithium bromide (0.261 g, 3 mmol) was stirred for 2 h at 70 °C and kept overnight at room temperature. Water (50 mL) was added to the reaction mixture and the product thus obtained was recrystallized from water to give an analytically pure sample of **1** as white needles. After filtration of the product, the aqueous part of the reaction mixture was washed with AcOEt (2 × 30 mL) to remove any organic impurity, then it was evaporated to dryness under reduced pressure to afford LiBr, which was used in subsequent runs without any loss of the catalytic activity.

3-Mercaptocoumarins (5). 2-Methyl-2-phenyl-1,3-oxathiolan-5-one **1** (2 mmol) and salicylaldehyde **2** (2 mmol) were put in 20 mL water and refluxed for 8–10 h (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and filtered with a Büchner funnel and washed with water (2 × 10 mL). The crude product **5** thus obtained was recrystallized from EtOH to afford an analytically pure sample of **5**. The aqueous layer was extracted with EtOAc (3 × 10 mL) and acetophenone was easily recovered from the organic phase.

5a. Yellowish solid (Found: C, 60.83; H, 3.18. $C_9H_6O_2S$ requires C, 60.66; H, 3.39%); mp 136–138 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3051, 2551, 1771, 1605, 1579, and 1455; δ_H(400 MHz; DMSO-d_6; TMS) 1.58 (1 H, s, SH, exchanges with D_2O), 7.10–7.43 (4 H_{arom}, m) and 7.78 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6; TMS) 120.1, 125.8, 126.5, 127.8, 128.7, 130.5, 148.2, 153.2 and 172.5; (m/z) 178 (M^+).

5b. Yellowish solid (Found: C, 41.88; H, 2.13. $C_9H_5BrO_2S$ requires C, 42.04; H, 1.96%); mp 93–95 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3055, 2550, 1775, 1599, 1581, and 1451; δ_H(400 MHz; DMSO-d_6; TMS) 1.55 (1 H, s, SH, exchanges with D_2O), 7.08–7.31 (3 H_{arom}, m) and 7.81 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6; TMS) 118.9, 120.5, 126.7, 128.2, 129.1, 130.3, 147.9, 152.5 and 172.1; (m/z) 258 (M^+).

5c. Yellowish solid (Found: C, 32.41; H, 1.03. C_9H_4 Br_2O_2S requires C, 32.17; H, 1.20%); mp 113–115 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3048, 2555, 1770, 1601, 1585, and 1456; δ_H(400 MHz; DMSO-d_6; TMS) 1.56 (1 H, s, SH, exchanges with D_2O), 7.22 (1 H_{arom}, s), 7.51 (1 H_{arom}, s) and 7.89 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6; TMS) 120.8, 126.2, 127.9, 130.5, 132.7, 135.5, 147.5, 152.1 and 172.8; (m/z) 336 (M^+).

5d. Yellowish solid (Found: C, 57.91; H, 3.63. $C_{10}H_8O_3S$ requires C, 57.68; H, 3.87%); mp 142–144 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3058, 2549, 1781, 1593, 1580, and 1459; δ_H(400 MHz; DMSO-d_6; TMS) 1.59 (1 H, s, SH, exchanges with D_2O), 3.71 (3 H, s, OMe), 7.02–7.48 (3 H_{arom}, m) and 7.79 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6; TMS) 54.7, 115.7, 120.2, 126.2, 127.1, 129.9, 138.8, 147.5, 160.5 and 172.5; (m/z) 208 (M^+).

5e. Yellowish solid (Found: C, 59.18; H, 4.27. $C_{11}H_{10}O_3S$ requires C, 59.44; H, 4.53%); mp 161–163 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3050, 2553, 1773, 1602, 1578, and 1450; δ_H(400 MHz; DMSO-d_6; TMS) 1.39 (3 H, t, CH_3), 1.55 (1 H, s, SH, exchanges with D_2O), 3.89 (2 H, q, CH_2), 7.05–7.55 (3 H_{arom}, m) and 7.81 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6; TMS) 17.1, 66.5, 115.1, 120.6, 127.5, 128.9, 130.3, 138.3, 147.9, 158.8 and 172.1; (m/z) 222 (M^+).

5f. Yellowish solid (Found: C, 55.37; H, 3.29. $C_9H_6O_3S$ requires C, 55.66; H, 3.11%); mp 105–107 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3398, 3057, 2552, 1781, 1600, 1582, and 1453;

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δ_H(400 MHz; DMSO-d_6; TMS) 1.52 (1 H, s, SH, exchanges with D_2O), 6.33 (1 H, br s, OH, exchanges with D_2O), 7.12–7.69 (3 H_{arom}, m) and 7.85 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6; TMS) 115.4, 119.9, 126.2, 128.9, 130.5, 138.2, 148.2, 159.5 and 172.7; (m/z) 194 (M^+).

5g. Yellowish solid (Found: C, 40.07; H, 1.78; N, 10.59. $C_9H_4N_2O_6S$ requires C, 40.30; H, 1.50; N, 10.44%); mp 155–157 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3052, 2550, 1780, 1605, 1586, and 1448; δ_H(400 MHz; DMSO-d_6; TMS) 1.53 (1 H, s, SH, exchanges with D_2O), 7.09–7.31 (2 H_{arom}, m) and 7.80 (1 H, s, 4-H); δ_C(100 MHz; DMSO-d_6/TMS) 115.2, 120.2, 127.7, 129.5, 131.2, 148.5, 153.2, 158.5 and 172.3; (m/z) 268 (M^+).

5h. Yellowish solid (Found: C, 48.71; H, 2.49; N, 6.07. $C_9H_5NO_4S$ requires C, 48.43; H, 2.26; N, 6.28%); mp 178–180 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3046, 2548, 1779, 1599, 1581, and 1457; δ_H(400 MHz; DMSO-d_6; TMS) 1.61 (1 H, s, SH, exchanges with D_2O), 7.21–8.47 (4 H_{arom}, m); δ_C(100 MHz; DMSO-d_6; TMS) 120.5, 126.5, 128.8, 130.7, 132.8, 143.2, 147.9, 157.8 and 172.9; (m/z) 223 (M^+).

Isolation of 4a (R = H), 4b (R = 2-Br) and 4d (R = 2-OMe) and their cyclisation into coumarins 5a, 5b and 5d. The procedure followed was the same as described above for the synthesis of **5** except that the refluxing time in this case was 5 h instead of 8–10 h for **5**. The adducts **4** were recrystallised from ethanol to give an analytical sample of **4a**, **4b** and **4d**. Finally, these intermediates were refluxed in water for 5 h to give the corresponding cyclised products **5a**, **5b** and **5d**, quantitatively.

4a. Yellowish solid (Found: C, 68.59; H, 4.60. $C_{17}H_{14}O_3S$ requires C, 68.44; H, 4.73%); mp 118–120 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3390, 3047, 1778, 1601, 1583, and 1455; δ_H(400 MHz; DMSO-d_6; TMS) 2.33 (3 H, s, Me), 6.31 (1 H, br s, OH, exchanges with D_2O) and 6.71–7.29 (10 H_{arom}, m); δ_C(100 MHz; DMSO-d_6; TMS) 18.9, 85.8, 118.2, 124.5, 126.2, 127.1, 128.5, 129.8, 130.5, 131.1, 132.0, 132.9, 133.5, 156.5 and 172.5; (m/z) 298 (M^+).

4b. Yellowish solid (Found: C, 54.49; H, 3.62. $C_{17}H_{13}BrO_3S$ requires C, 54.12; H, 3.47%); mp 85 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3385, 3045, 1773, 1598, 1585, and 1451; δ_H(400 MHz; DMSO-d_6; TMS) 2.37 (3 H, s, Me), 6.30 (1 H, br s, OH, exchanges with D_2O) and 6.75–7.43 (9 H_{arom}, m); δ_C(100 MHz; DMSO-d_6; TMS) 19.2, 85.4, 117.7, 122.9, 125.9, 126.8, 128.2, 129.0, 130.7, 131.5, 132.4, 133.1, 134.5, 152.1 and 172.9; (m/z) 378 (M^+).

4d. Yellowish solid (Found: C, 65.65; H, 5.08. $C_{18}H_{16}O_4S$ requires C, 65.84; H, 4.91%); mp 128–130 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3388, 3051, 1776, 1605, 1580, and 1457; δ_H(400 MHz; DMSO-d_6; TMS) 2.31 (3 H, s, Me), 3.75 (3 H, s, OMe), 6.27 (1 H, br s, OH, exchanges with D_2O) and 6.85–7.51 (9 H_{arom}, m); δ_C(100 MHz; DMSO-d_6; TMS) 19.5, 54.8, 86.2, 115.5, 118.3, 123.2, 125.7, 126.4, 127.5, 128.9, 130.2, 131.1, 131.9, 132.8, 150.9 and 173.1; (m/z) 328 (M^+).

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Desulfurization of dibenzothiophene by chemical oxidation and solvent extraction with $Me_3NCH_2C_6H_5Cl{\cdot}2ZnCl_2$ ionic liquid

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Desulfurization of dibenzothiophene (DBT) by a combination of both chemical oxidation and solvent extraction was investigated. $Me_3NCH_2C_6H_5Cl{\cdot}2ZnCl_2$ ionic liquid was prepared from cheap starting materials and used as extractant for oxidative desulfurization of DBT in *n*-octane. DBT in oil phase was extracted into ionic liquid phase and then oxidized to its corresponding sulfone by H_2O_2 and equal volume of acetic acid. The desulfurization yield of DBT in *n*-octane was 94% at 30 min under the conditions of H_2O_2/DBT molar ratio at 6 and *V* (ionic liquid) : *V* (*n*-octane) = 1 : 5, which was remarkably higher than that by mere extraction with ionic liquid (28.9%). The $Me_3NCH_2C_6H_5Cl{\cdot}2ZnCl_2$ ionic liquid could be recycled six times without a significant decrease in activity. Kinetics of oxidative desulfurization of DBT by H_2O_2 and acetic acid was first-order with an apparent rate constant of 0.0842 min^{-1} and half-time of 8.23 min.

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Introduction

Air pollution, caused by diesel exhaust gas (SO*x*), is one of the most serious problems in the world, and much attention has been focused on deep desulfurization of light oils. To protect the environment against contamination, the S-limit will be reduced in USA to a maximum of 15 ppm by 2010 and to 10 ppm in Europe by 2009.[1] Many other countries also have tightened their sulfur content specifications.

The removal of sulfur-containing compounds is carried out industrially *via* hydrodesulfurization (HDS). However, the HDS is limited in treating benzothiophenes (BTs) and dibenzothiophenes (DBTs).[2] Therefore, approaches based on adsorption,[3] extraction,[4] oxidation[5] and biodesulfurization[6] have been explored. Among them, oxidative desulfurization (ODS) is more attractive because BTs and DBTs can be oxidized to their corresponding sulfoxides and sulfones easily, which can be removed by extraction with water[7] or water-soluble polar solvents, such as dimethyl sulfoxide (DMSO),[8] 1-methyl-2-pyrrolidinone (NMP) and dimethylformamide (DMF), *etc.*[9] Although the ODS processes are effective, one of the prime concerns is that the flammable and volatile organic compounds (VOCs) or water, employed as extractants, are leading to further environmental and safety concerns, such as wastewater emission and fire hazards.

Ionic liquids (ILs) have been extensively employed in gas separation,[10] liquid/liquid extraction,[11] chemical synthesis,[12] catalysis,[13] *etc.*,[14] because of their non-volatility, non-flammability, easy to handle, recyclable, good solubility characteristics, and high thermal stability.[15] Desulfurization of oils by extraction with ILs has been reported from 2001.[16–25] Compared with VOCs or water, ionic liquids have much higher extraction abilities which lead to shorter reaction time. Ionic liquids also have a much higher density, which makes it possible to readily recycle the ionic liquids for multiple extractions without additional environmental concern. Many types of ILs, such as [BMIm]$AlCl_4$,[16,17] [EMIm]$AlCl_4$,[16] [EMIm]BF_4,[18] [BMIm]BF_4,[18,19] [BMIm]PF_6,[18,19] [BMIm][$OcSO_4$],[20] [EMIm][$EtSO_4$],[20] [BMIm]Cu_2Cl_3,[21] [BMIm]DBP,[22] [C_8MIm]BF_4,[23] [C_4MPy]SCN,[24] [EMIm]$FeCl_4$,[25] have been employed in the extraction desulfurization of oils because of their high affinity to sulfur-containing compounds. The desulfurization yield of light oils, however, is relative low by only extraction with ILs. To improve efficiency of sulfur removal from light oils, a new effectual approach has been explored, which is chemical oxidation in conjunction with ILs extraction.[26–30] For instance, Gao and coworkers[26] used [HMIm]BF_4 as extractant and H_2O_2 as oxidant for sulfur removal of DBT-containing model oil, which could reach 60–93%. Li and coworkers[27,28] developed an extraction and catalytic oxidative desulfurization system composed of IL, H_2O_2 and catalyst. [BMIm]BF_4, [OMIm]BF_4, [BMIm]PF_6, [OMIm]PF_6, [BMIm]TA and [OMIm]TA doped with peroxotungsten and peroxomolybdenum complexes or molybdic compounds were selected for desulfurization as catalysts. The desulfurization yield of DBT-containing model oil could reach above 98%. Wei and coworkers[29] found [BMIm]PF_6 was a more effective solvent than [BMIm]BF_4 for providing an environment that results in a higher rate of chemical oxidation. Zhao *et al.*[30] studied the ODS of DBT by using [HNMP]BF_4 as extractant in the presence of H_2O_2 and pointed out that [HNMP]BF_4 was also a catalyst, which could decompose H_2O_2 to form hydroxyl radicals that were strong oxidizing agents for DBT.

However, the imidazolium- or pyrrolidonium-based ILs used as extractants previously are relatively expensive and it is impossible to use these ILs in industry. More recently, a series

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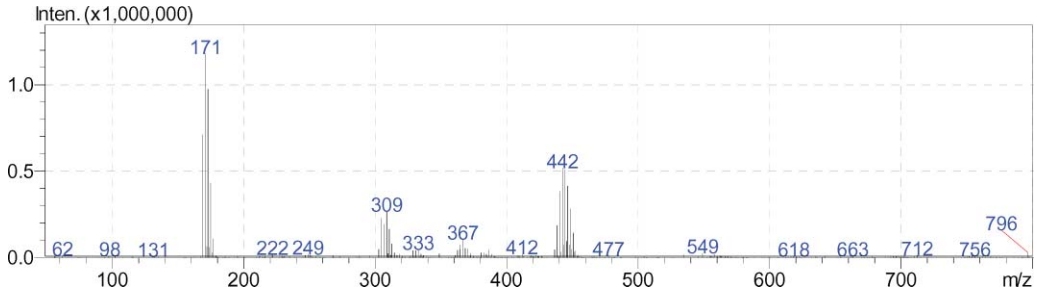

Fig. 1 Negative ion ESI-MS spectrum of BTMAC·2$ZnCl_2$.

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of inexpensive ILs have been prepared from cheap starting materials, such as choline chloride·$x$$ZnCl_2$ and trimethylammonium chloride·$x$$AlCl_3$, which have been used in Fischer indole reactions,[31] protection of carbonyls[32] and also desulfurization of fuels.[18] The Lewis acidic ILs containing metal halide anions, such as $AlCl_4^-$,[19] $FeCl_4^-$[25] and $CuCl_2^-$,[21] have showed promising results on the removal of sulfur-containing compounds because of their inherent low fluidity and the π-complexation of metal anions with thiophenes. In this paper, $Me_3NCH_2C_6H_5Cl$·$x$$ZnCl_2$ (BTMAC·$x$$ZnCl_2$, x = 1~3), has been prepared from cheap starting materials of $Me_3NCH_2C_6H_5Cl$ and $ZnCl_2$ and used as extractant in ODS of DBT.

Results and discussion

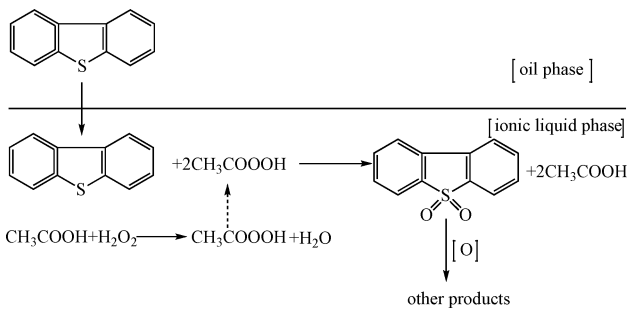
Structures of anions in $ZnCl_2$-based ionic liquid

To identify the Zn^{2+} species of BTMAC·$x$$ZnCl_2$ ionic liquid and verify its stability to air, electrospray ionization tandem mass (ESI-MS) spectral analysis was carried out. ESI-MS spectrum of BTMAC·2$ZnCl_2$ ionic liquid, as typical representative of BTMAC·$x$$ZnCl_2$, is shown in Fig. 1. Intensive peaks are observed at m/z 171, 309 and 442, which correspond to $ZnCl_3^-$, $Zn_2Cl_5^-$ and $Zn_3Cl_7^-$, respectively, using the atomic weights of Zn and Cl.

Wicelinski *et al.*[33] prepared ionic liquids composed of $AlCl_3$ with 1-butylpyridinium chloride (BPC) or l-methyl-3-ethylimidazolium chloride (MEIC) and found there were hydroxychloro and oxychloro anionic species (such as $Al_2Cl_6OH^-$, $Al_3Cl_7O_2H^-$) in the ionic liquids because of the strong Lewis acidity of anions. It indicated that the $AlCl_3$-based ionic liquids are moisture sensitive. Whereas there were no obvious oxygen-containing anionic species in Fig. 1, which showed that BTMAC·2$ZnCl_2$ was stable to moisture and air.

The process and mechanism of ODS/extraction by BTMAC·2$ZnCl_2$

There are two steps in the process of the oil–ionic liquid phase system of oxidation of DBT, containing the extractive equilibrium and the oxidative reaction.[34] In the first step, DBT is extracted from oil phase into ionic liquid until the extractive equilibrium is stabled. The second step is oxidation of DBT. In presence of H_2O_2, the acetic acid (AcOH) gives peracetic acid (CH_3COOOH), which is a strong oxidant and its oxidative ability is stronger than that of H_2O_2.[35] DBT in ionic liquid phase is oxidized to its corresponding sulfone ($DBTO_2$) by CH_3COOOH. The decrease of DBT concentration in ionic liquid promotes the extraction process and the sulfur content in the oil phase decreases continuously. On the basis of this and the combined oxidative process developed by Wei and coworkers,[29] the process of extraction and oxidation mechanism of DBT is proposed, as shown in Scheme 1.



Scheme 1 The process of extraction and oxidation mechanism of DBT using H_2O_2 and AcOH as the oxidants in an oil–ionic liquid system.

Extraction desulfurization performance of ILs for DBT in *n*-octane

Table 1 shows the Nernst partition coefficients k_N sulfur of DBT with BTMAC·$x$$ZnCl_2$ ILs. For comparison, some results of k_N with other ILs from literature are also listed.

As can be seen by the Nernst partition coefficients k_N listed in Table 1, all of the BTMAC·$x$$ZnCl_2$ ionic liquids show remarkable ability for sulfur removal. It is found that sulfur removal of model oil can reach above 23.3% after extraction with BTMAC·$x$$ZnCl_2$ ionic liquids, whereas the sulfur removal of DBT with imidazolium-based ILs are all below 20%. The reason for the difference of extraction capabilities is that the desulfurization mechanism with $ZnCl_2$-based ionic liquids is different from that with imidazolium-based ionic liquids. Hernández-Maldonado and Yang *et al.*[37] found there was π-complexation between DBT with Zn^{2+} when performing desulfurization with Zn(II)–X and Y zeolite sorbents. The mechanism for the extraction of sulfur-containing compounds with imidazolium-based IL is likely relevant to the formation of liquid clathrate due to the π–π interaction between the unsaturated bonds of the S-compound and the imidazolium ring of ILs.[22,36] In reference 19, Zhang *et al.* compared the absorption capacities of several ILs, including trimethylammonium chloride salt-aluminium trichloride ($AlCl_3$-TMAC),

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Table 1 Nernst partition coefficients k_N for extraction of DBT with ILs

IL	k_N [mg of S (L of IL)$^{-1}$/mg of S (L of oil)$^{-1}$]	IL	k_N [mg of S (L of IL)$^{-1}$/mg of S (L of oil)$^{-1}$]
BTMAC·$ZnCl_2$[a]	1.52	BTMAC·$3ZnCl_2$[a]	1.68
BTMAC·$1.5ZnCl_2$[a]	1.82	[BMIm]BF[b]	0.96
BTMAC·$2ZnCl_2$[a]	2.03	[BMIm]TA[b]	0.79
BTMAC·$2.5ZnCl_2$[a]	1.89	[OMIm]TA[b]	1.02

[a] Reaction conditions: model oil = 10 mL, IL = 2 mL, the mixture was stirred at 30 °C for 10 min. [b] Results from Li and coworkers.[27] Model oil was prepared by dissolving DBT in *n*-octane to give a solution with S-content of 1000 ppm. Reaction conditions: model oil = 5 mL, IL = 1 mL, the mixture was stirred at 30 °C for 15 min.

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[BMIm]PF_6, [BMIm]BF_4 and [EMIm]BF_4 for model organosulfur compounds and found that the absorption capacity of $AlCl_3$-TMAC was higher than that of others. So the π-complexation between lone pair electrons on organosulfur compounds and the unoccupied orbital on transition metal ions was higher than the π–π interaction between the unsaturated bonds of the S-compound and the imidazolium ring of IL. Compared to ionic liquids, the organic solvents show lower k_N. For example, Shiraishi *et al.*[8] reported that acetonitrile was considered to be the most suitable solvent for the extraction of the sulfur-containing compounds. As a result, the k_N was 1.32 and 0.19 when acetonitrile was employed as extractant to extract DBT from *n*-octane at 60 °C[38] and commercial light oil at ambient temperature,[8] respectively.

The high sulfur removal ability of BTMAC·$x$$ZnCl_2$ ionic liquids make them good extraction solvents for desulfurization. Although the Nernst partition coefficients are lower than that of DBT in *n*-dodecane with [BMIm]Cl/$AlCl_3$ (4.09),[16] BTMAC·$x$$ZnCl_2$ are also competitive ILs with wide developing prospect because they are cheap and insensitive to moisture and air. It also can be seen that the highest Nernst partition coefficient was 2.03 when BTMAC·$2ZnCl_2$ was used as extractant. That is, BTMAC·$2ZnCl_2$ is the ideal ionic liquid.

Relative Lewis acidity and viscosities of ionic liquids

The Lewis acidic strength of [HSO_3–$(CH_2)_3$–NEt_3]Cl–$ZnCl_2$ ionic liquids could be adjusted by varying the molar fraction of $ZnCl_2$ reported by previous literature.[39] Here the relative acidity of BTMAC·$x$$ZnCl_2$ ionic liquids is compared by FT-IR to investigate the reason why the molar ratio of $ZnCl_2$ to BTMAC affects the extraction performance. As shown in Fig. 2, pure acetonitrile shows two characteristic bands around 2292 and 2253 cm^{-1}, which are assigned to CN stretching vibrations. When acetonitrile is mixed with ionic liquids, a higher wavenumber around 2313 cm^{-1} appears. The band at around 2313 cm^{-1} is indicative of the existence of Lewis acidic sites. It is known that the higher intensity of characteristic band means the stronger Lewis acidity of the corresponding ionic liquid, so the Lewis acidity strength of the ionic liquids increased with the increase of the fraction of $ZnCl_2$. Zhang *et al.*[19] reported that the acidity change did not have a significant effect on the sulfur removal efficiency with ionic liquids and our extraction desulfurization results are in agreement with them. That is, Lewis acidity is not the only factor affecting the sulfur removal.

The viscosities of liquids always have a greater effect on their extraction ability. The viscosities of BTMAC·$x$$ZnCl_2$ ionic liquids are shown in Table 2.

The viscosities of the ionic liquids appear to be governed essentially by H-bonding.[40] When the molar ratio of $ZnCl_2$ to BTMAC increased from 1 to 1.5 or 2, the H-bonding between H^+ on the cation and Cl^- on the anion weakened and the viscosity decreased because of the existence of the large anion[41] of $ZnCl_3^-$, $Zn_2Cl_5^-$ and $Zn_3Cl_7^-$. However, when the molar ratio of $ZnCl_2$ to BTMAC exceeded 1.5 or 2, some $ZnCl_2$ could not fully react with BTMAC and the ionic liquid was not really pure, so the viscosity increased. It can be seen that the extraction performance of ionic liquids depends on both Lewis acidity and viscosity. That is, the extraction ability increases with the increase of Lewis acidity and the decrease of viscosity. By combining the influence of the two factors on the extraction ability of ionic liquid, BTMAC·$2ZnCl_2$ is the ideal ionic liquid.

Effect of H_2O_2/DBT molar ratio and IL/oil volume ratio on sulfur removal of DBT

To investigate the effect of the amount of oxidizing agent and extractant on the sulfur removal properties, the oxidation/extraction of DBT in *n*-octane under different H_2O_2/DBT (O/S) molar ratios and IL/oil volume ratios is carried out at 30 °C. The results are shown in Fig. 3 when BTMAC·$2ZnCl_2$, H_2O_2 and an equal volume of AcOH are employed as extractant and oxidants in the system, respectively. As can be seen, the sulfur removal of model gasoline increases with the increase of IL/oil volume ratio. When the IL/oil volume ratio is low (below 1 : 5), the extraction effect of IL for model gasoline is bad. As the IL/oil volume ratio goes above 1 : 5, *i.e.* 1 : 1, the sulfur removal of model gasoline increases slightly and much IL is wasted. So the most appropriate IL/oil volume ratio is 1 : 5.

In the presence of H_2O_2 and AcOH, DBT was oxidized chemically to $DBTO_2$ *etc.* and the remaining DBT in *n*-octane phase was further extracted into the IL phase. As shown in Fig. 3, the sulfur removal of DBT in oil phase continued to increase at different IL/oil volume ratios when the O/S molar ratio was increased from 2 : 1 to 10 : 1. According to the stoichiometric reaction, 2 mol of hydrogen peroxide are consumed for oxidation of 1 mol of DBT to $DBTO_2$. With the increase of H_2O_2, the oxidant had more opportunity to react with DBT and the desulfurization yield increased. It can be seen that when V(IL)/V(oil) = 1 : 5, the sulfur removal of DBT increased from 75.9% at a molar ratio of O/S = 2 to 94% at a molar ratio of O/S = 6. When the O/S molar ratio reached 8, 10 and 12, the sulfur removal of DBT increased slowly to 98, 98.5 and 99.1%, respectively. The results indicated that the optimal O/S molar ratio was 6 because less H_2O_2 was used, it is not economical to use excess amounts of oxidant.

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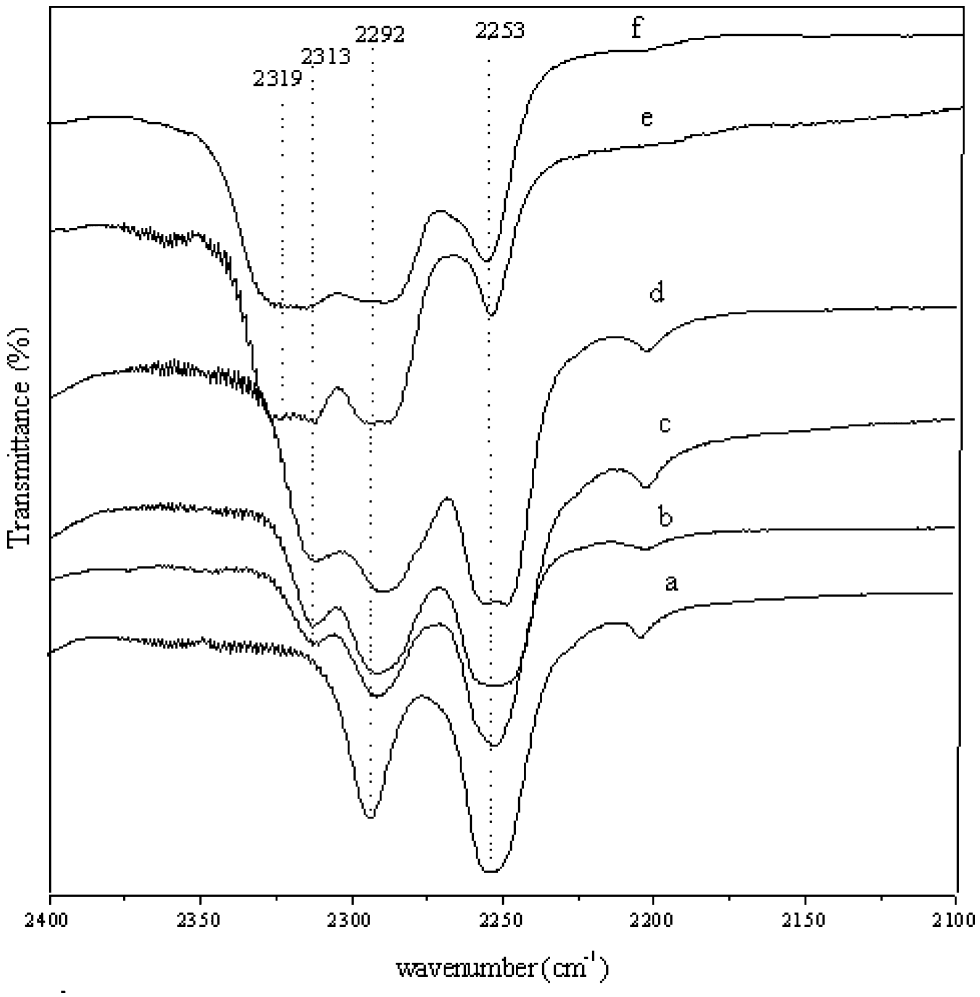

Fig. 2 FT-IR spectra of mixtures of acetonitrile and ionic liquids. (a) Pure acetonitrile, (b) molar ratio of $ZnCl_2$ to BTMAC = 1.0, (c) molar ratio of $ZnCl_2$ to BTMAC = 1.5, (d) molar ratio of $ZnCl_2$ to BTMAC = 2.0, (e) molar ratio of $ZnCl_2$ to BTMAC = 2.5 and (f) molar ratio of $ZnCl_2$ to BTMAC = 3.0.

Table 2 Dynamic viscosities at 30 °C (Pa s) of the BTMAC·$x$$ZnCl_2$ ionic liquids

BTMAC·$ZnCl_2$	BTMAC·1.5$ZnCl_2$	BTMAC·2$ZnCl_2$	BTMAC·2.5$ZnCl_2$	BTMAC·3$ZnCl_2$
3.548	3.067	3.112	3.358	3.649

Kinetics of oxidation of DBT in *n*-octane by H_2O_2 and AcOH

To study kinetics of oxidation of DBT, samples (10 μL) were taken out from *n*-octane phase and measured with a micro coulometer to determine sulfur content every 5 min in the reaction course. The results are shown in Fig. 4.

The oxidation of DBT in tetradecane has been studied by Wei and coworkers[29], who found that the rate of DBT oxidation was first-order when excess H_2O_2 and AcOH were employed as oxidants and [BMIm]BF_4 or [BMIm]PF_6 was used as extractant. In this experiment, when the oxidation of DBT in *n*-octane by H_2O_2 and AcOH is assumed to be the first-order reaction, the sulfur content of model gasoline will meet eqn (1):[7]

$$\ln(C_0/C_t) = kt \quad (1)$$

Where C_0 and C_t are the sulfur content of model gasoline at time zero and time t (s), respectively, and k is the first-order rate constant (min^{-1}). Half-life ($t_{1/2}$ (min)) is calculated using eqn (2), which is derived from eqn (1) by replacing C_t with $C_0/2$

$$t_{1/2} = 0.693/k \quad (2)$$

Fig. 5 illustrates the time-course variation in $\ln(C_0/C_t)$ which was obtained from data shown in Fig. 4. k and $t_{1/2}$ could be calculated. k and $t_{1/2}$ were 0.0842 min^{-1} and 8.23 min, respectively. Here, the results of the experiments strongly supported the first-order reaction of oxidation kinetics of DBT.

Regeneration/recycling of ionic liquid

The recycling of the BTMAC·2$ZnCl_2$ was investigated in ODS of DBT in *n*-octane. After the reaction, the ionic liquid phase was recycled and residual oxidizing agents (H_2O_2 and AcOH) were evaporated from the ionic liquid. Then the system was charged again with fresh H_2O_2 and AcOH for the next run.

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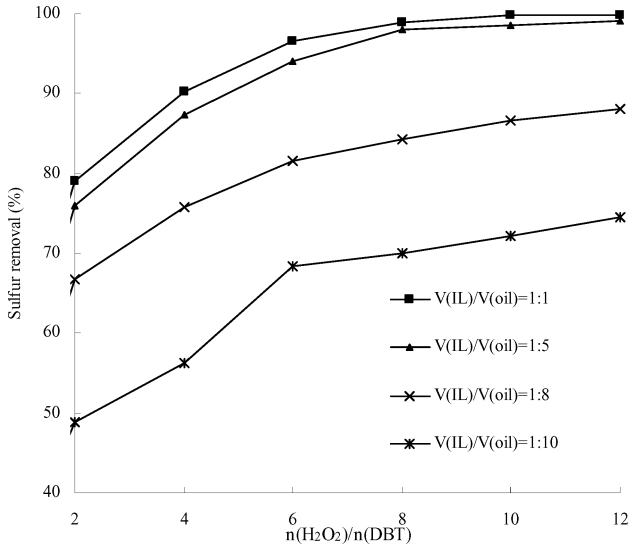

Fig. 3 Effect of H_2O_2/DBT molar ratio and IL/oil volume ratio on sulfur removal of DBT. Reaction conditions: model oil = 10 mL, t = 30 min, 30 °C.

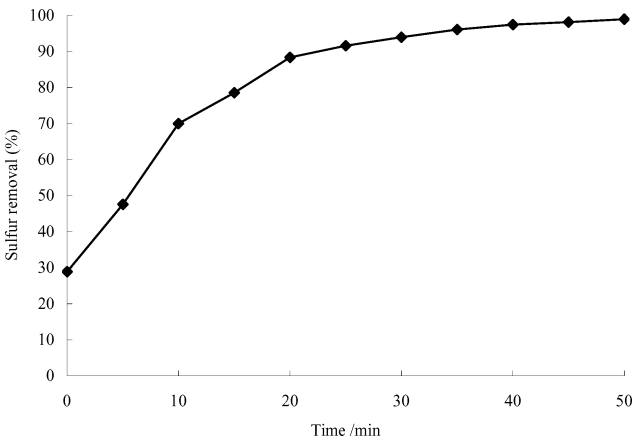

Fig. 4 Time-course variation of sulfur removal of DBT in *n*-octane. Reaction conditions: T = 30 °C; model oil = 10 mL, IL = 2 mL; molar ratio of O/S = 6.

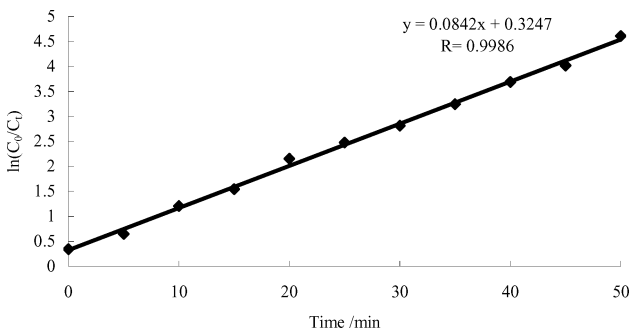

Fig. 5 Time-course variation of $\ln(C_0/C_t)$. Reaction conditions: T = 30 °C; model oil = 10 mL, IL = 2 mL; molar ratio of O/S = 6.

After four times, $DBTO_2$ was precipitated in the ionic liquid phase and reclaimed from the ionic liquid by centrifugation. The data shown in Table 3 indicated that the BTMAC·2$ZnCl_2$ ionic liquid could be recycled six times without a significant decrease in activity. When six cycles had finished, the desulfurization yield decreased slightly with the increase of the cycle. The reason was that $DBTO_2$ in the ionic liquid was more and more and the extraction performance of ionic liquid decreased.

Table 3 Recycle of BTMAC·2$ZnCl_2$ in desulfurization of model oil[a]

Cycle	Sulfur removal (%)	Cycle	Sulfur removal (%)
1	94	5	93.8
2	93.7	6	93.0
3	93.2	7	92.1
4	92.5	8	91.2

[a] Reaction onditions: T = 30 °C; t = 30 min; model oil = 10 mL, IL = 2 mL; molar ratio of O/S = 6.

Conclusion

BTMAC·2$ZnCl_2$ ionic liquid is an excellent extraction solvent because it is not only stable to moisture and air, but also exhibits remarkable extraction desulfurization for DBT in *n*-octane, which may be attributed to the π-complexing interaction of DBT and Zn(II). In the presence of H_2O_2 and AcOH, DBT is extracted from oil phase and oxidized to its corresponding sulfone. The desulfurization yield of DBT can reach 94% at 30 min and 99% at 50 min. The BTMAC·2$ZnCl_2$ ionic liquid can be recycled six times without a significant decrease in activity. The kinetics of oxidative desulfurization of DBT by H_2O_2 and AcOH is first-order with an apparent rate constant of 0.0842 min^{-1} and half-time of 8.23 min. All the experiments were conducted at room temperature and it was easy to handle. The study on extraction/oxidation desulfurization of DBT can guide the desulfurization of light oils.

Experimental

Preparation of ionic liquids and detection of the structure of anions in ionic liquid

Anhydrous $ZnCl_2$ and $Me_3NCH_2C_6H_5Cl$ were used as received. $Me_3NCH_2C_6H_5Cl$ (0.1 mol) was mixed with $ZnCl_2$ (0.1 $x$mol, x = 1–3) and heated to *ca.* 120 °C in air with stirring until a clear colorless liquid was obtained.

Structure of anions in ionic liquid was detected *via* ESI-MS, which had been confirmed by Ko *et al.*[25] to be an ideal analytical tool in characterizing the structure of negative ions in IL. ESI-MS spectrum of BTMAC·2$ZnCl_2$ was collected on Shimadzu 2010EV LC-MS.

Evaluation of the Lewis acidity and measurement of viscosity of ionic liquids

FT-IR spectra were obtained on Shimadzu IRPrestige 21 spectrometer. Acetonitrile was used as a base probe molecule to determine the acidity of ionic liquids. The detail process was similar to that outlined in the previous literature.[42] The measurement of viscosity was carried out using an NDJ-8S rotational viscometer.

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Oxidative desulfurization of DBT in *n*-octane

0.056 g DBT was dissolved in 10 mL *n*-octane to form the model oil, the sulfur content of which was 1000 μg mL^{-1}. IL (1–10 mL) was then added and mixed with the oil. The sulfur content of oil was detected using a micro coulometer with the process of extraction. After 10 min, the sulfur content of oil did not change which meant that the extraction equilibrium of DBT in oil and ionic liquid phase was reached. 30 wt% H_2O_2 and an equal volume of AcOH were added to the mixture, which was then stirred vigorously. The upper phase (model oil) was periodically withdrawn and analyzed for sulfur content using a micro coulometer.

Recovery/regeneration of used ionic liquid

At the end of each run, the ionic liquid phase was separated by decantation from the oil phase. The oxidizing agents were then evaporated from the ionic liquid phase at 100 °C for 3 h by rotary evaporation. The $DBTO_2$ was not removed from the ionic liquid. The fresh H_2O_2, AcOH and model oil were introduced for the next reaction under the same conditions as described above. By this procedure, the $DBTO_2$ was accumulated in the ionic liquid successively. The solubility of $DBTO_2$ in BTMAC·2$ZnCl_2$ ionic liquid is about 1805 ppm calculated by S-content and $DBTO_2$ is insoluble in *n*-octane. After four times, there was yellow solid, *i.e.* $DBTO_2$ in the ionic liquid phase. Then $DBTO_2$ was reclaimed from the ionic liquid by centrifugation and the ionic liquid was reused.[27,29]

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Exploring fungal activity in the presence of ionic liquids

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In this work, the toxicological assessment towards filamentous fungi (*Penicillium* sp.) as model eukaryotic organisms of sixteen ionic liquids (containing an imidazolium, pyridinium, or cholinium cation) is presented. Amongst these fungi are members which show much higher tolerance towards ionic liquids than any other microorganism so far studied. Furthermore, guided by the paradigm that the choice of an ionic liquid as catalyst can alter the outcome of a given chemical reaction, the ability of ionic liquids to alter the metabolic profile in fungi was studied. The metabolic footprint, as investigated by electrospray ionisation mass spectrometry, revealed that fungal cultures respond to specific ionic liquids by changing their cell biochemistry, resulting in an altered pattern of secondary metabolites.

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Introduction

In the last two decades, ionic liquids have attracted a lot of scientific and commercial interest, as demonstrated in numerous publications and patents. They are, by definition, salts that are liquid at, or near, room temperature, completely composed of ions.[1,2] Their negligible vapour pressure and usual non-flammability are the basis for them sometimes being classified as "green" solvents.[3] In addition, ionic liquids can be, by design, chemically and thermally stable, recyclable, and with tunable physical and chemical properties. Integration with their outstanding solvation ability opens doors for numerous industrial applications as replacements for conventional organic solvents.[1] Further to remarkable developments in their core chemical properties and applications, ionic liquids are now providing unexpected opportunities at the interface of chemistry with the life sciences, *e.g.* acting as solvents in enzymatic[4] and whole-cell[5] biocatalysis. In order to move ionic liquids beyond being an academic curiosity, their environmental, health, and safety impacts must be fully determined.[6] Although this field is still in its infancy, significant efforts are being made to obtain ecotoxicological data and design ionic liquids composed of naturally-derived materials for reduced toxicity and increased biodegradability.[7] Reports that ionic liquids can be used as active pharmaceutical ingredients (APIs) serve to further emphasise their potential for *in vitro* biochemical studies.[8,9]

Filamentous fungi are significant members of the Mycota kingdom, widespread in nature, especially in soil.[10] They play an important role in the carbon cycle on Earth, food spoilage, and as pathogens. On the other hand, due to the enormous diversity of species and their rich enzymatic systems, resulting in a broad range of secondary metabolites, they are widely used in biotechnological processes for production of chemicals, pharmaceuticals, food ingredients, and enzymes.[11] Many secondary metabolites of filamentous fungi have found application as therapeutic and/or bioactive compounds (*e.g.* antibiotics, cholesterol-lowering agents, anti-tumour agents, and immunosuppressors).[12,13] Their ability to adapt to extreme environmental conditions and to degrade some of the most recalcitrant materials (such as lignin and aromatic xenobiotics) makes them a very attractive model for screening the toxicity of chemicals with an unknown risk factor. In this work, for the first time, filamentous fungi were used as model eukaryotic organisms to assess the possible impact of ionic liquids whenever they are released into the environment.

Metabolic profiling using mass spectrometry (MS) has become one of the most important techniques in fields ranging from diagnostics to functional genomics,[14] from taxonomy of filamentous fungi,[15] to screening of new compounds for biological activity. Here, metabolic footprinting is focussed on qualitative scanning of metabolites secreted by the cells. Components of the substrate that were transformed by the organism are also a part of the footprint.[14]

The cell chemodiversity strongly depends on inherited phylogenetic information (genomics), as well as on environmental conditions. Here, a relationship is proposed between the phylogenetic origin of fungal species, their specific response to the presence of ionic liquids, and the modification of the metabolic profile caused by it.

Experimental

Chemicals

All ionic liquids used in this study (see Fig. 1) were prepared by QUILL (Queen's University Ionic Liquids Laboratory, Belfast, UK), except for cholinium chloride (Sigma, Germany), 1-ethyl-3-methylimidazolium thiocyanate, [C_2mim][SCN]

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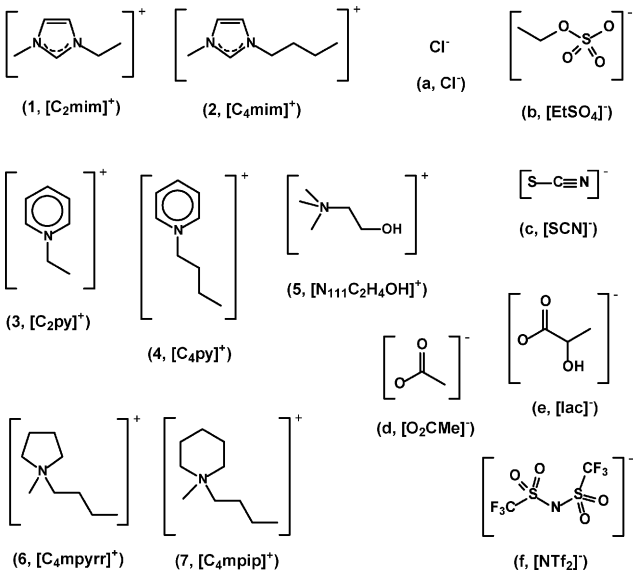

Fig. 1 Chemical structures of all ionic liquids used (cations and anions, numbers and letters, respectively). (1a) 1-ethyl-3-methylimidazolium chloride ([C_2mim]Cl); (1b) 1-ethyl-3-methylimidazolium ethyl sulfate [C_2mim][$EtSO_4$]); (1c) 1-ethyl-3-methylimidazolium thiocyanate ([C_2-mim][SCN]); (1d) 1-ethyl-3-methylimidazolium ethanoate ([C_2mim][O_2CMe]); (1e) 1-ethyl-3-methylimidazolium DL-lactate ([C_2mim][lac]); (2a) 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl); (4a) 1-butyl-pyridinium chloride ([C_4py]Cl); (3d) 1-ethylpyridinium ethanoate ([C_2-py][O_2CMe]); (3e) 1-ethylpyridinium DL-lactate ([C_2py][lac]); (5a) cholinium chloride ([$N_{111}C_2H_4OH$]Cl); (5d) cholinium ethanoate ([$N_{111}C_2H_4OH$][O_2CMe]); (5e) cholinium DL-lactate ([$N_{111}C_2H_4OH$][lac]); (5f) cholinium bis((trifluoromethyl)sulfonyl)amide ([$N_{111}C_2H_4$-OH][NTf_2]); (6a) 1-butyl-1-methylpyrrolidinium chloride ([C_4mpyrr]-Cl); (6e) 1-butyl-1-methylpyrrolidinium DL-lactate ([C_4mpyrr][lac]); (7d) 1-butyl-1-methylpiperidinium ethanoate ([C_4mpip][O_2CMe]).

(Fluka, Switzerland) and 1-ethyl-3-methylimidazolium ethyl sulfate, [C_2mim][$EtSO_4$] (Solvent Innovation, Germany). D(+)-glucose, $K_2[HPO_4]$, $ZnSO_4{\cdot}7H_2O$, $CuSO_4{\cdot}5H_2O$, $FeSO_4{\cdot}7H_2O$, KCl, and ethyl ethanoate were purchased from Sigma Aldrich (Germany). CsCl, $MgSO_4{\cdot}7H_2O$, $NaNO_3$, 1-methylimidazole, and pyridine were purchased from Fluka (Switzerland). NaCl was purchased from Panreac (Spain), and ethanenitrile from Merck (Germany).

Ionic liquids prepared at QUILL were characterised by a combination of ^{1}H NMR, ^{13}C NMR, electrospray ionisation mass spectrometry, halide content, CHN elemental analysis, and water content. Typical halide content was <0.1%, and the maximum amount in one sample was 1.2%.

Fungal isolates

The following fungal isolates were used, all belonging to the Instituto de Biologia Experimental e Tecnológica (IBET) culture collection: *Penicillium brevicompactum* Dierckx (IBET-PeA), *P. olsonii* Bainier and Sartory (DSM 16515), *P. janczewskii* K.M. Zalessky (IBETF5), *P. glandicola* (Oudem) Seifert and Samson (IBETPeB), *P. corylophilum* Dierckx (IBETF6), *P. glabrum* (Wehmer) Westling (DSM 16516), *P. restrictum* J.C. Gilman and E.V. Abbot (IBETF4), *P. adametzii* Zaleski (IBETF2), *P. variabile* Sopp (IBETF2), *P. diversum* Raper and Fennell (IBETPeE). They had previously been isolated from cork samples purchased from several Portuguese cork industries.[16,17]

Toxicity tests

The toxicity of ionic liquids towards filamentous fungi was determined by measuring the absorbance of the culture medium at 600 nm.

The minimal culture medium containing glucose (1.0 g l^{-1}), K_2HPO_4 (1.0 g l^{-1}), $NaNO_3$ (3.0 g l^{-1}), $ZnSO_4{\cdot}7H_2O$, (0.01 g l^{-1}), $CuSO_4{\cdot}5H_2O$ (0.005 g l^{-1}), $MgSO_4{\cdot}7H_2O$ (0.5 g l^{-1}), $FeSO_4{\cdot}7H_2O$ (0.01 g l^{-1}), and KCl (0.5 g l^{-1}) was dissolved in distilled water and sterilised in an autoclave (20 min; 121 °C), and supplemented with ionic liquids in order to obtain a final concentration of 50 mM (corresponding to 7–20 g l^{-1}, depending on the molecular weight of the ionic liquid).

Each liquid medium (2 cm^3) was inoculated with a suspension of fungal spores, prepared as previously described,[18] in order to obtain the final concentration of 10^5 spores per cm^3, and divided into eight wells (0.25 cm^3 each) of a 96 well microtitre plate. Cultures were incubated in the dark at 25 °C.

The control samples (inoculated) and the blanks (non-inoculated) were produced and incubated under the same conditions: negative control (an ionic liquid free medium), osmotic stress controls (media supplemented with either aqueous NaCl (50 mM) or aqueous CsCl (50 mM): high charge density and low polarisability, or low charge density and high polarisability, respectively), organic function controls (media with aqueous 1-methylimidazole (50 mM) or aqueous pyridine (50 mM)), and blank samples (media with addition of the selected substances).

Fungal growth (or lack thereof) was followed daily by measuring the absorbance (600 nm) of the medium. Increase of absorbance was taken as indication of growth. Spore formation (gauged by eye) and/or the absorbance approaching a constant value indicated that the culture entered a stationary growth phase. The culture supernatant liquid was separated from the mycelium by centrifuging (4 °C) and filtration (0.2 μm nylon membrane), and stored at −20 °C awaiting further analysis.

Toxicity data analysis

The toxicity data were analysed using scripts written in the R language, version 2.7.1 (for review see ref. 19 and 20). The relation between any two toxicity profiles was quantified by the Jaccard distance, which measures dissimilarity between sample sets consisting of binary data. The obtained distance matrix was used to assess the existence of groups of fungal species with similar toxicity profiles by means of hierarchical cluster analysis (HCA). Results are presented based on Ward's method for cluster linkage, which is designed to minimise the variance of distances within each cluster.[20] The robustness of the resulting dendrogram was validated using several other linkage methods as well. Given the binary nature of the data (growth or its inhibition), the distance measured between species is equivalent to the number of different cases between two fungal species.

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Metabolites extraction

Fungal secondary metabolites (fSM, ionic liquid free) were extracted from the fungal cultures. The mycelium-free cultures (1 cm^3) were lyophilised (freeze-dried) in order to remove water, and ethyl ethanoate (1 cm^3) was added to the residue. Ethyl ethanoate was selected, due to its common use for extraction of fSM and to its limited miscibility with the ionic liquids studied. The upper layer (ethyl ethanoate) contains the fSM. This extraction was repeated once more and the combined ethyl ethanoate extracts were evaporated in a vacuum concentrator. The residue was dissolved in ethanenitrile (0.4 cm^3) and ultrasonicated (10 min). The same procedure was applied on blank samples previously prepared (see Toxicity Tests).

ESI-MS analysis

The electrospray mass spectra were recorded on a Bruker Esquire 3000 plus ion trap mass spectrometer in the positive and negative polarity modes (Bruker Daltonics, Billerica, MA, USA). The samples (fSM in ethanenitrile) were injected at a rate of 0.1 $cm^3\ h^{-1}$ into the electrospray ionisation (ESI) probe. The capillary temperature was set to 250 °C. All spectra were acquired using the Esquire Control Programme (Bruker Daltonics, Billerica, MA, USA) and then converted to ASCII file format for computational interpretation.

Computational interpretation of MS data

Mass spectrometry data were analysed with the same software as the toxicity data. After binning the intensities of mass spectra to integral m/z values, spectra pre-processing, peak detection and alignment of the spectra were performed using the msProcess package.[21] Peak intensities were normalised by their total, and values below 0.001 were set to zero. Peaks of the sample spectra were compared with the spectra from corresponding solvents and blanks, and coinciding peaks were eliminated from the peak matrix. To eliminate ionic liquid cations or anions with $z = 1$, only m/z values between 150 and 1100 were considered in the analysis. Ionic liquid solubility in ethyl ethanoate (see Metabolites Extraction) is very limited but its nature may lead to an intense m/z peak even at a negligible concentration. The resulting binary matrices, peaks present or absent, were further analysed by HCA in an analogous manner to the toxicity data.

Results and discussion

Toxicological assessment

In this work, an examination of the toxicity of ionic liquids to filamentous fungi, belonging to the *Penicillium* genus, is presented. The selection of sixteen ionic liquids as test compounds was made by combining seven different cations and six different anions (see Fig. 1). This approach enabled us to investigate *inter alia* the toxic effect of the head group in the cation. Focussing on chloride, ethanoate, and DL-lactate anions (herein depicted as lactate) enabled the toxic effect of the anion to be studied.

In order to prove that the ionic liquids are not causing a toxic effect solely due to osmotic stress, the effects of sodium chloride and caesium chloride were tested. The latter loosely approximates the low-charge density and high polarisability of ionic liquids. Its addition to the growth medium has inhibited fungal growth (except for the case of *P. adametzii*), causing a stronger growth inhibitory effect than all the tested ionic liquids. These data were not used in the hierarchical clusters presented (see Fig. 2 and 3), but their inclusion does not alter the cluster profile. 1-Methylimidazole and pyridine, as commonly used building blocks in ionic liquid chemistry, were also tested to assess whether their unsaturated nature had a deciding role to play in the antifungal activity of the ionic liquids.

The HCA of the inhibitory effect of twenty selected compounds at 50 mM upon the growth of ten *Penicillium* species is illustrated in Fig. 2. The ionic liquid growth inhibitory effect was simplified to a binary matrix of fungal growth inhibition or no inhibition. It became evident that the chemical nature of the cationic head group influenced the overall toxicity of the ionic liquid, which has been demonstrated in numerous other studies.[22,23,24,25,26]

The imidazolium-based ionic liquids have the highest toxicity rankings of those studied, with an average of three toxic cases. Comparison of $[C_2mim]Cl$ and $[C_4mim]Cl$ showed the expected tendency[25] of increased toxicity with increasing alkyl side chain length. The $[N_{111}(C_2H_4OH)]^+$ cation elicited the lowest toxic effect, and choline chloride, $[N_{111}(C_2H_4OH)]Cl$, failed to inhibit growth in any of the fungal species. With the exception of $[C_2py][lac]$, which showed no toxicity, the remaining ionic liquids (containing pyridinium, pyrrolidinium, or piperidinium cations) lay in between these extremes.

The control compounds, 1-methylimidazole and pyridine, inhibited growth in 100% and 60% of the cases, respectively, proving to be significantly more toxic to fungi than any of their derived ionic liquids (studied herein).

Within the two groups of ionic liquids containing $[C_2mim]^+$ or $[N_{111}(C_2H_4OH)]^+$ combined with Cl^-, $[O_2CMe]^-$ or $[lac]^-$, the $[O_2CMe]^-$ anion was the most toxic. None of the other ionic liquids tested showed any significant correlation with the nature of the selected anion. This suggests that a more extensive study would be of great value. Here, it is noted that, while the cation has the more predictable effect, the anion also contributes toward the antifungal activity (*cf.* with rat leukaemia cell line).[24]

The HCA of the toxicity profiles (Fig. 2) revealed four groups of fungal species with similar growth behaviours. The group {A, B} showed the highest ionic liquid susceptibility. The group {C, D} showed intermediate, and the remaining groups {E, F, G} and {H, I, J} low susceptibility. It was interesting to compare and correlate these data with the clusters in a phylogenetic study on *Penicillium* species by Wang and Zhuang, which they based on calmodulin gene partial sequences (about 600 nucleotides).[27] Their study distinguished eleven clusters and covered all the species featured in our work, except {A} and {I}, and a high degree of correlation between the phylogenetic background of the species and their response to the ionic liquid environment was observed (see Table 1).

This detected correlation between the genetic proximity of the species and their susceptibility to different environmental conditions can be used in the rationalisation of toxicological studies, and in the prediction of the behaviour of different species.

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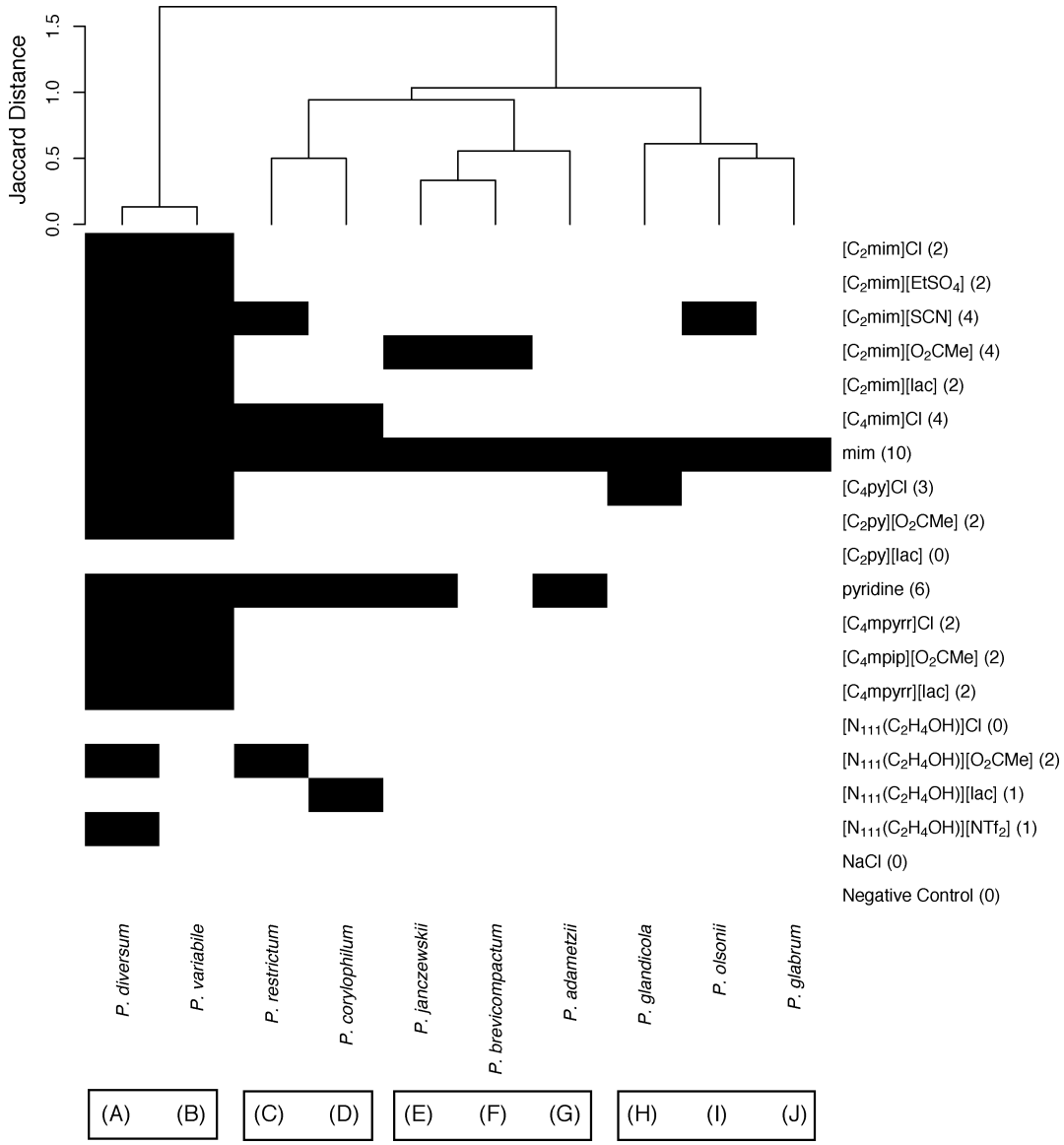

Fig. 2 Hierarchical cluster analysis of the growth behaviour of *Penicillium* species in the ionic liquid containing media and controls (see Experimental section for details). Black fields show cases of growth inhibition; row labels indicate the tested ionic liquids (ordered by common cation group) and control substances; the number in brackets corresponds to the toxicity ranking (from 0 to 10).

Table 1 Comparison of the results of this work with those of Wang and Zhuang[27]

Toxicity study (this work)	Phylogenetic study
{B}	{XI}
{C, D}	{VIII}
{E, F, G}, {H, J}	{I, II}

Metabolic footprinting

In order to assess the ability of ionic liquids to alter the metabolism of fungi, fungal culture extracts (fSM extracts, ionic liquid free) were analysed by ESI-MS, the spectra being interpreted qualitatively according to the presence or absence of peaks.

The selection of samples (combinations of fungal species and ionic liquids) was made based on the analysis of the toxicological data presented above. The species {B}-{H} were used, including one or more species from each cluster. The ionic liquids, $[C_2mim]Cl$, $[C_2mim][lac]$, $[C_4py]Cl$, $[C_2py][lac]$, $[N_{111}(C_2H_4OH)]Cl$ and $[N_{111}(C_2H_4OH)][lac]$, were selected according to Fig. 2, comprising all cationic groups which have shown distinct effects, imidazolium and cholinium, as the most and the least toxic, respectively, and pyridinium, with intermediate toxic effect. In addition, negative and sodium chloride controls were included.

After growth, extraction of fungal metabolites, and collection of their ±ESI-MS spectra, the HCA of these "metabolic footprints" for all ionic liquids tested per species showed no discernable pattern (data not shown). However, the metabolic footprints induced by $[C_2mim]Cl$ and $[C_2mim][lac]$ were

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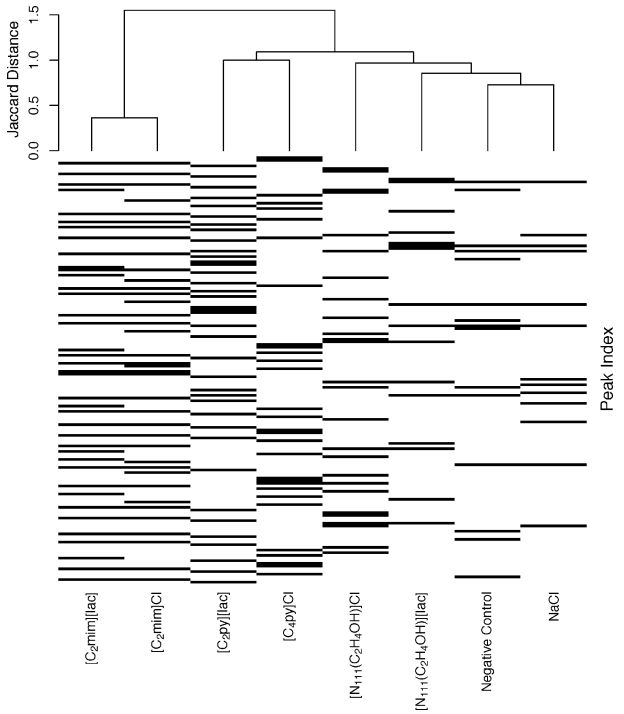

Fig. 3 Hierarchical cluster analysis of the joint peak lists, uniting all individual peak matrices of positive and negative mode, detected by ESI-MS after fungal growth in the ionic liquid containing media and controls (see Experimental section for details). Black fields indicate the presence of a peak at a given m/z value.

clustered together for all fungal species, and were disassociated from the metabolic footprints induced by the other ionic liquids (data not shown). This observation is confirmed in the integrated assessment of the joint peak lists, uniting all individual peak matrices (depicted in Fig. 3), and this result was robust against variations of the clustering algorithm. The remaining metabolic footprints produced a single cluster divided into two subclusters: those induced by $[C_4py]Cl$ and $[C_2py][lac]$, and those induced by $[N_{111}(C_2H_4OH)]Cl$, $[N_{111}(C_2H_4OH)][lac]$ and controls. In the latter, the metabolic footprints induced by the cholinium-based ionic liquids showed weak correlation with controls and between themselves.

Distinct groups are also revealed when one merely accounts for the number of the peaks in the metabolic profiles. The correlation between the number of detectable mass species in the extracts and the toxicity of the corresponding ionic liquids is apparent. $[C_2mim]Cl$ and $[C_2mim][lac]$ induced the highest number of peaks (≥38), significantly different from the controls (≤15). Interestingly, despite the fact that $[C_2py][lac]$ and $[N_{111}(C_2H_4OH)]Cl$ showed no inhibition to fungal growth, both have still induced significant metabolic alterations.

In order to provide a more complete picture of the specific events in the metabolic network (species and ionic liquid dependency), quantitative analysis will be attempted in the future.

Conclusion

This is the first time that filamentous fungi have been used in a toxicological study on ionic liquids. The most significant observation is the very high tolerance of *Penicillium* species towards the ionic liquids. Complete inhibition of growth was noted in only 20% of ionic liquids/species cases. The concentration of ionic liquids that was tested in this study (50 mM) is much higher, by several orders of magnitude, than in any other testing system reported so far.[22,26] In addition, we have observed that fungi can tolerate, in some cases, even higher ionic liquid concentrations, *e.g. P. olsonii* can grow in the presence of 0.375 M of $[C_2mim]Cl$ (data not shown).

Testing a vast number of ionic liquids and organisms is rather time-consuming and costly, but the cluster strategy presented here, along with the concept of QSAR (quantitative structure–activity relationship), which refers to estimation of the hazard potential of ionic liquids based on structure, simplifies their risk evaluation.

These data show that the ionic liquid induced effects on fungal metabolism cannot be simply explained by the ionic liquid toxicity. Moreover, the metabolic footprints induced by the ionic liquids do not correlate with those induced by common salts, such as sodium chloride. Even caesium chloride, in the specific case of *P. adametzii*, clustered closer to the controls than to the ionic liquids. This is supported by preliminary data on the fungal secretome (bidimensional electrophoresis analysis) induced by the different ionic liquids.[28] Results suggest that some ionic liquids, *e.g.* $[N_{111}(C_2H_4OH)]Cl$ and $[C_4mpyrr]Cl$, have induced the expression of a distinct set of fungal extracellular proteins, which could be grouped into ionic liquid responsive, ionic liquid specific or non-specific, and inorganic salt responsive proteins. In addition, these metabolic alterations cannot be, in the case of all ionic liquids, a result of their co- or direct metabolism by the fungi. That would certainly not be the case of imidazolium cation, which is resistant to microbial degradation.[29,30]

The behaviour of fungi, and any other organisms, is highly linked to different omes (genome, transcriptome, proteome and metabolome) and influenced by environmental conditions. Transcriptional profiling and proteomic analysis are becoming routine techniques and, joined with metabolite analysis, could build a platform applicable in many areas. Going beyond ecotoxicological studies to describe the effect of toxic compounds on living cells, could be useful in the discovery of novel natural compounds and in the development of efficient and environmentally friendly bioprocesses.

The test systems described in this work are highly promising, especially considering that filamentous fungi have the ability to produce biologically active secondary metabolites.[13,12] Further studies are necessary to prove whether or not ionic liquids have the ability to induce a tailored metabolic alteration. Should this be observed, it would be a significant breakthrough in whole-cell biocatalysis, creating a new concept: an ionic liquid controlled bio-tool for designing targeted end products.

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