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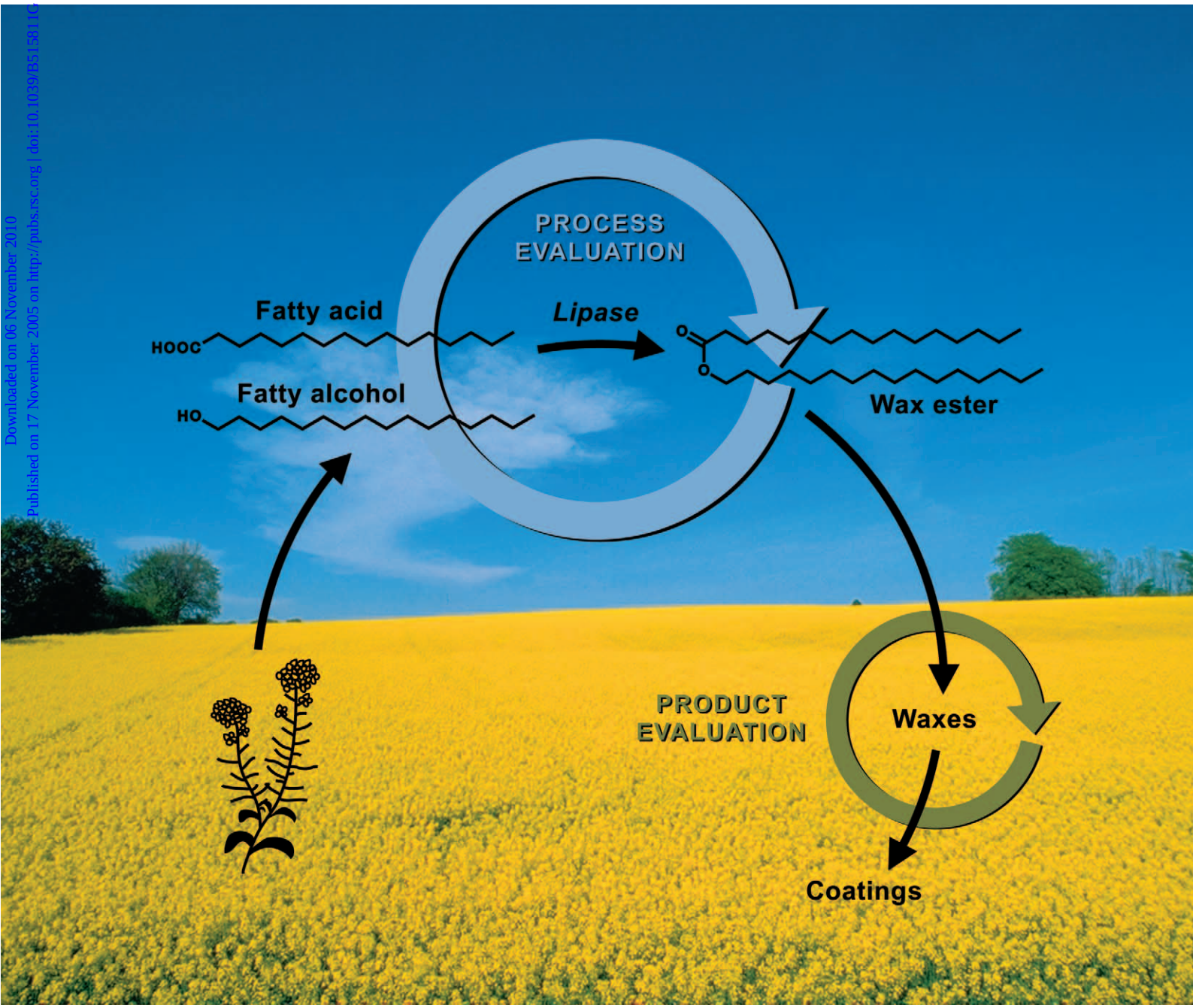

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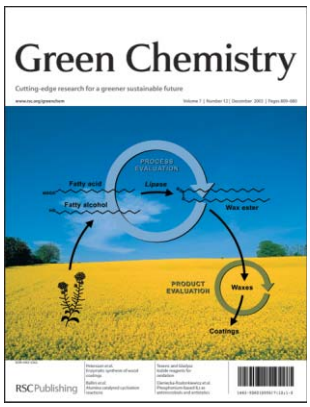
Akichika Itoh *et al.* discuss the facile solar oxidation of alcohols with molecular oxygen



Cover

Illustration shows a field of rapeseed, a source of fatty acids and fatty alcohols. The conceptual scheme depicts the synthesis of wood coatings from these raw materials.
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CHEMICAL TECHNOLOGY

T45

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Chemical Technology

December 2005/Volume 2/Issue 12

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Report on the Eighth Summer School on Green Chemistry

I. Correia, J. M. Kremsner, V. Llopis Mestre and A. Rickers

The Eighth Summer School on Green Chemistry was held on the island of San Servolo, Italy, September 4–9, 2005.

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2005 EuCheMS lectureship

Roger Sheldon delivered the 2005 EuCheMS lecture entitled 'Combining Organometallic Catalysis and Biocatalysis in Catalytic Cascade Processes' at the XVIth FECHEM Conference on Organometallic Chemistry held at Eötvos University in Budapest, 3–8 September, 2005.

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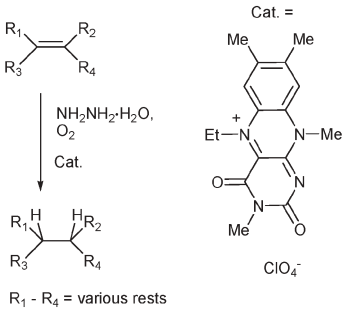
Highlights

Markus Hölscher reviews some of the recent literature in green chemistry.



COMMUNICATIONS

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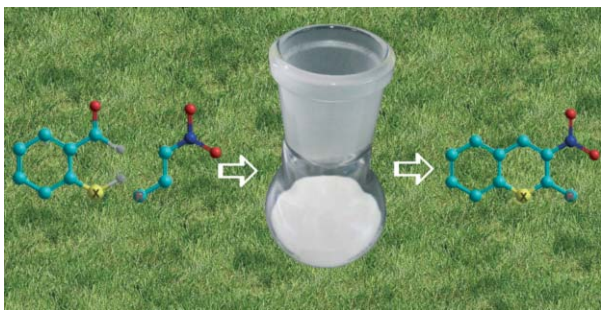
Neutral alumina catalysed synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes, under solvent-free conditions, *via* tandem process

Roberto Ballini,* Giovanna Bosica, Dennis Fiorini and Alessandro Palmieri

Neutral alumina carries out the solvent-free reaction of 2-aminobenzaldehyde and salicylaldehyde over nitroalkenes allowing the one-pot synthesis of 3-nitroquinolines and 3-nitrochromenes, respectively.



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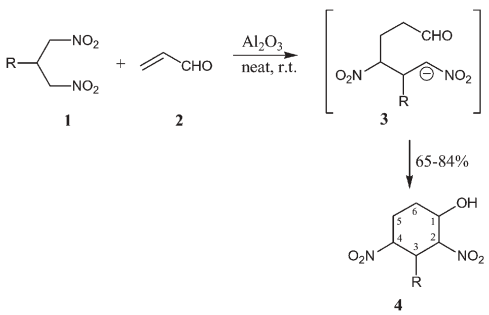
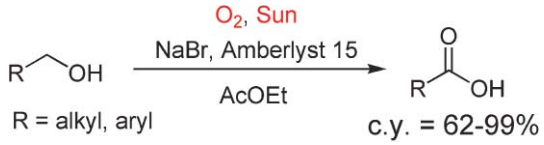
One-pot synthesis of 3-alkyl-2,4-dinitrocyclohexanols, under solventless conditions using basic alumina

Roberto Ballini,* Luciano Barboni, Dennis Fiorini, Guido Giarlo and Alessandro Palmieri

3-Alkyl-2,4-dinitrocyclohexanols can be prepared in a one-pot procedure by reaction of 1,3-dinitroalkanes with acrolein, catalysed by basic alumina and in the absence of any solvent.



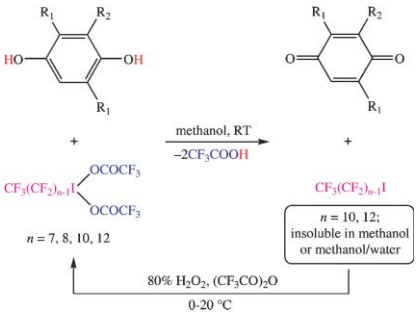
COMMUNICATIONS



Facile solar oxidation of alcohols with molecular oxygen

Akichika Itoh,* Shouei Hashimoto, Kiyoto Kuwabara, Tomohiro Kodama and Yukio Masaki

A useful method for the aerobic oxidation of alcohols directly to the corresponding carboxylic acid or ketone with combination of sodium bromide and Amberlyst 15 (safe and inexpensive reagents) under solar radiation is reported.

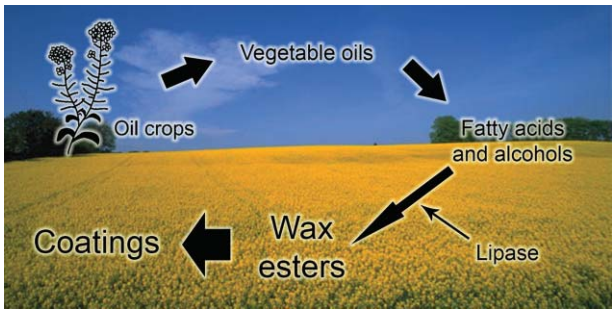


An easily accessed class of recyclable hypervalent iodide reagents for functional group oxidations: bis(trifluoroacetate) adducts of fluorous alkyl iodides, $CF_3(CF_2)_{n-1}I(OCOCF_3)_2$

Verona Tesevic and J. A. Gladysz*

The title compounds readily convert hydroquinones to quinones, and the coproducts $CF_3(CF_2)_{n-1}I$ are easily recovered under fluorous/organic liquid/liquid or solid/liquid biphase conditions and reoxidized (80% H_2O_2, $(CF_3CO)_2O$) to the title compounds.

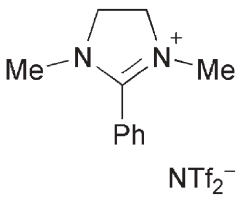
PAPERS



Wax esters produced by solvent-free energy-efficient enzymatic synthesis and their applicability as wood coatings

Anna E. V. Petersson,* Linda M. Gustafsson, Mathias Nordblad, Pål Börjesson, Bo Mattiasson and Patrick Adlercreutz

Enzymatic production of wax esters is environmentally benign, energy-efficient, solvent-free, highly efficient atom-wise, and consistent with the principles of green chemistry. An energy analysis and a product evaluation are presented.

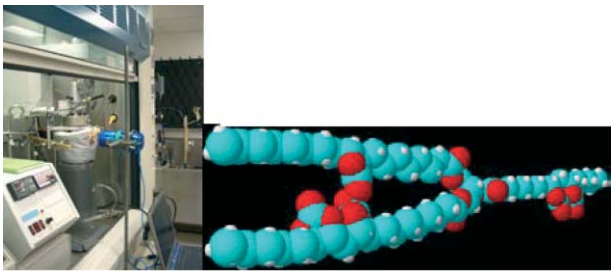


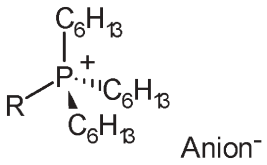
An imidazolinium salt as ionic liquid for medium and strong bases

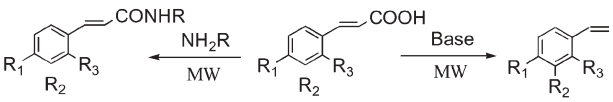
Václav Jurčík and René Wilhelm*

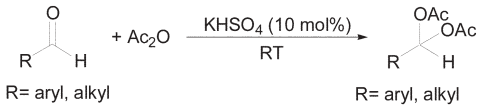
An imidazolinium salt with a phenyl ring at the C-2 position has been found to be an ionic liquid suitable as a solvent for reactions involving medium and strong bases like quinuclidine and Grignard reagents.

PAPERS









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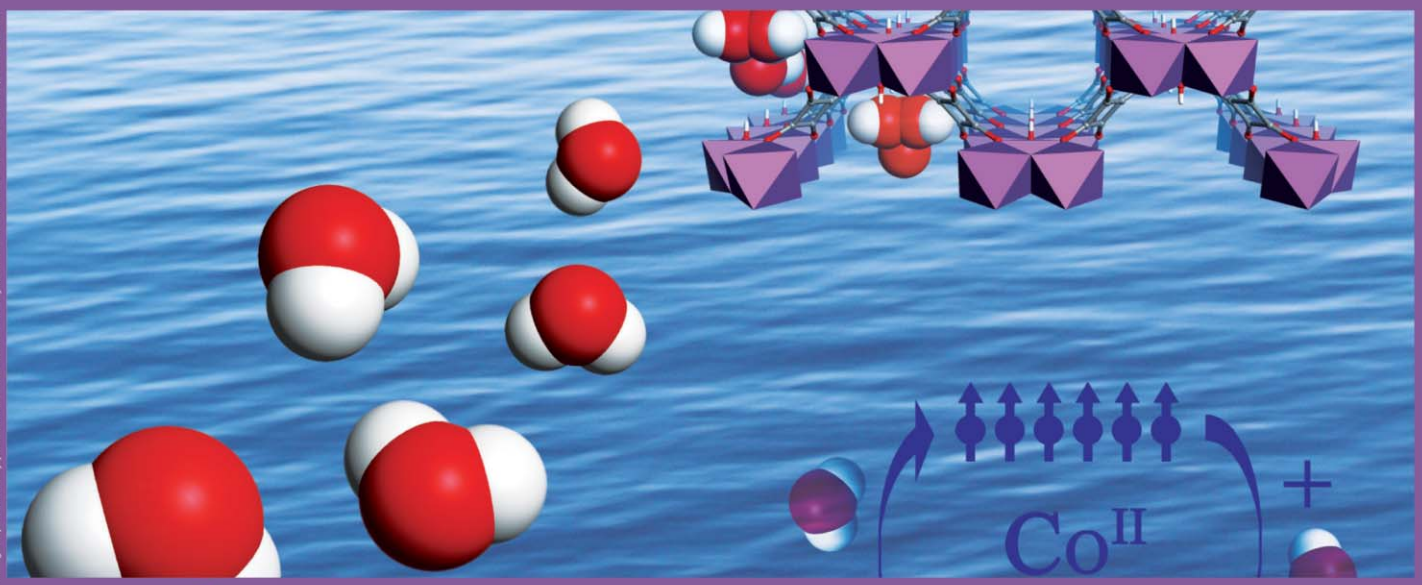

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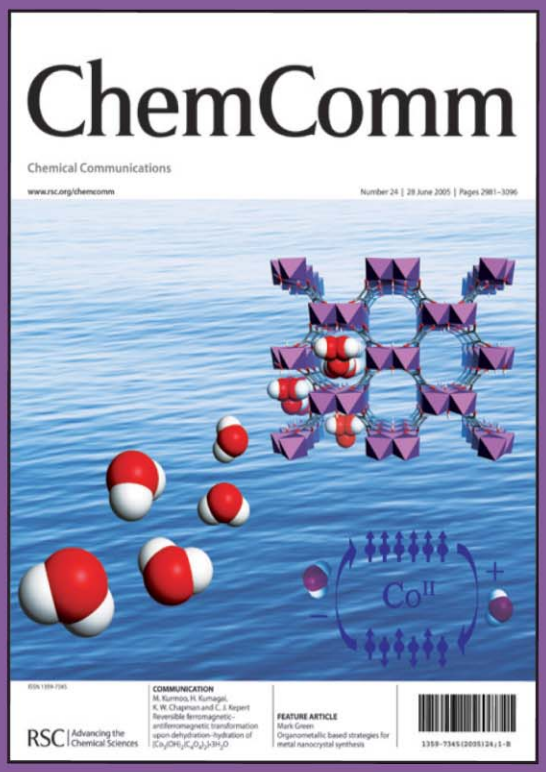

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Report on the Eighth Summer School on Green Chemistry

I. Correia,[a] J. M. Kremsner,[b] V. Llopis Mestre[c] and A. Rickers[d]

DOI: 10.1039/b514986j

A small island in the lagune, the impressive scenery of Venice in the background, 13 teachers and about 40 students coming from around 20 different countries, mild late summer temperatures: what place other than the green island of San Servolo could offer a better ambiance for a five-day visit to learn, discuss and reflect on new ideas in green chemistry?

The Summer School on Green Chemistry (SSGC) is a high level training school for young European chemists organized by the Consorzio Interuniversitario La chimica per l'Ambiente (INCA). The school became a reality in 1998 when a grant from the European Commission's IV Framework Programme (FP) Training and Mobility of Researchers (TMR) provided the financial support needed. Its goal: to teach the design of intrinsically clean processes that can prevent pollution concerns at the source, and develop alternative routes to produce new chemicals from renewable resources. A collection of the lectures from the summer schools held between 1998 and 2003 has been published by INCA as a text book, which was distributed to the students and is also available for free download (http://venus.unive.it/inca/publications/gcbooks.php).

The Eighth Summer School, comprising lectures, tutorials and poster sessions, took place from September 4–9, 2005. The informal atmosphere among the PhD students, post-docs and several teachers (from various areas of green chemistry) was created by living together on the small island, which afforded many occasions for useful and open discussions. The welcoming dinner on the first evening gave the participants a chance to get to know each other, that further social activities (like the sightseeing trip to San Lazzaro followed by a barbecue) would reinforce.

Lectures on alternative solvents and feedstocks, catalysis and alternative reaction conditions were presented by the respective experts in each field. All sessions were characterized by a high variety of specialized lectures which allowed the students to see the bigger picture and also to get different views on the application of green chemistry's concepts—that it is not possible to always apply all the principles of green chemistry but that it is important to find the right combination for a certain process. Furthermore, they showed how academia, industry and government interact and influence each other and that the so-called "Triple bottom line" philosophy, which states that an enterprise will only be sustainable if it takes into account not just financial outcomes but also environmental and social performance is a key factor for evaluating the success of benign technologies.

The Summer School started smoothly on Monday morning with a welcome speech from **Alvise Perosa** and a general introductory lecture from **Pietro Tundo** on "Progress in Green Chemistry", followed by a group picture on San Servolo's garden.

Afterwards, **David Black**, secretary general of the IUPAC, gave the 1st lecture on "Green Chemistry in the International Context" in which he spoke about IUPAC's goals and activities, focusing on the relevant events related to green chemistry. The afternoon session was split between two German lecturers: Wolfgang Hölderich from RWTH-Aachen and Dieter Lenoir from GSF-Research Center Neuherberg. **Wolfgang Hölderich** spoke about "New Heterogeneously Catalyzed Processes for Environmentally Benign Sustainable Chemical Production" showing several examples of successful heterogeneous acid–base catalysts, which follow the green chemistry principles, namely, avoidance of salt formation, low E-factor, high atom-efficiency and ease of separation as well as low investment and capital costs. **Dieter Lenoir** started with an introduction on the estimation of the sustainability of oxidation processes and then focused on the "Formation, Mechanism and Minimization of Chlorinated Micropolutants (Dioxins) Formed in Incineration Processes", emphasizing the need for primary

[a]*Centro de Química Estrutural, Instituto Superior Técnico, Av Rovisco Pais 1, 1049-01, Lisbon, Portugal*
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[d]*Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Worringer Weg 1, 52074, Aachen, Germany*

measures in technical chemical processes and for knowledge on the formation mechanisms of the micropolutants.

Pietro Tundo, director of the SSGC and president of INCA, was the first lecturer of the second day speaking about ''The Chemistry of Dimethyl Carbonate (DMC), a Green Reagent''. After a general introduction he gave an interesting lecture about the versatility of DMC as a methylating and cabonylating agent including its activation by bases and zeolites for oxidations, presenting several processes and focusing on the mechanistic approach. Subsequently, **Howard Moore**, the director of the UNESCO office in Venice—Regional Bureau for Science in Europe (ROSTE), presented the organization and its activities. The morning session ended with a challenging lecture by **Chris Adams** from Queens University of Belfast on ''Innovating with Green Chemical Technologies''. He spoke about the drivers and barriers for innovation, green chemistry and sustainability and presented sagas of (unsuccessful) innovations. In his opinion the ''Triple bottom line'' model (economic, social and environmental) is 'hopelessly flawed' and 'new economic concepts are needed'. **Jennifer Young**, from the Green Chemistry Institute (GCI) (from the group of Paul Anastas, USA) was the only afternoon lecturer, which ended with the 1st poster session. After presenting the GCI she gave an overview on ''Green Polymer Chemistry''. Different green processes were presented: polymerizations with renewable monomers (sources), alternative solvents, recoverable catalysts and biodegradable polymers. Young ended her lecture with a group activity, which resulted in a lively class discussion.

Michel Guisnet from Université de Poitiers (France) started the third day with a comprehensive lecture on ''Zeolites for Cleaner Technologies''. He emphasized the versatility and efficiency of zeolites as adsorbents and catalysts, due to their shape selectivity and remarkable acid properties, and showed several examples of new green processes along with the increase of the application of zeolites in depollution and fine chemicals industry. **Jean Luc Guillaume** from DOW Chemical brought the industry perspective to the Summer School with a talk entitled ''Seamless Chemistry for Sustainability''. He focused on the industry key challenges: feedstock, energy cost, reinvestment of capital and new materials based on renewable sources. In his opinion 'sustainable technology is here to stay', and the ''Triple bottom line'' principle will enable a balanced and multidisciplinary approach.

The third day started with **Jan Engberts** from the University of Groningen (Netherlands), who gave an insight into the field of ''Organic Chemistry in Water'', explaining the anomalies of this green solvent and presenting chemistry done in water, which explores the hydrophobic effect. **David Black** gave his second lecture, this time about ''Enantioselective Metal Catalysed Oxidation Processes''. It was a very detailed explanation of oxidation reactions performed by transition metal catalysts, in which he pointed out the difficulty of having good conversions and selectivities. In his opinion this is a field which has been based on 'trial and error', since it is very difficult to predict the outcome of reactions catalysed by transition metal complexes. In the afternoon session **Frieder Lichtenthaler** from the Technical University of Darmstadt (Germany) gave a talk about ''Carbohydrates as Green Raw Materials for the Chemical Industry'' before the day ended with the 2nd poster session. Lichtenthaler showed industrial processes based on sugars, sugar derivatives and cellulose, and spoke about the need for the 'systematic chemical and biochemical exploitation of carbohydrates towards industrial viable products'.

The last day started with **Walter Leitner** from the Technical University of Aachen (Germany) who gave a lecture on ''Supercritical Carbon Dioxide as a Green Solvent''. This very comprehensive lecture presented the advantages and properties of $scCO_2$, concerning health, safety, activity and reactivity issues, as well as *in situ* protection, separation and immobilization.

Leitner's talk was followed by **Ken Seddon**'s (QUILL Research Center in Belfast, UK) presentation on ''Ionic Liquids''. Among many examples where ionic liquids proved to be indispensable alternative solvents, he showed some thought-provoking pictures (like the *chemistry bear* in the picture) to point out the need of not only talking about but also practising sustainable chemistry. **Bernd Jastorff** from the University of Bremen (Germany) was the very last speaker talking about ''Sustainable Industrial Chemicals''. He focused on the T-SAR methodology (structure–activity relations) and on the need for an interdisciplinary collaboration between chemists, biologists and environmental scientists, in order to design safer chemicals.

Besides the lectures, *tutorial* and *poster sessions* allowed the students to interact closely with each other and with the teachers. In the *tutorial sessions* the students were divided into small groups and discussed selected topics with tutors that worked on each field. The students were allowed to choose between alternative solvents, catalysis, industry and general green chemistry and overall the tutorial sessions ended with lively discussions. The *poster sessions* were an opportunity for the students to present their own results, establish new contacts and exchange knowledge about their research, as well as presenting and defending their work to the jury. The posters were presented and evaluated during two sessions and four awards were made for the best posters of the 8th Summer School in Green Chemistry. The awards were presented by Pietro Tundo (Director of the School) and Alvise Perosa (Scientific Organizer of the School) on behalf of the jury of instructors. The four prizes were awarded to the following students, who afterwards presented a short lecture: **Veronica Llopis Mestre** from Imperial College London (UK) was awarded one of the first prizes with the scientific poster entitled ''Environmental Control of Chemical Reactivity: Diels–Alder Reactions in Ionic Liquids''. **Jennifer M. Kremsner** from Karl-Franzens-University Graz (Austria) also received the first prize with

"Microwave-Assisted Organic Synthesis in Near-Critical Water at 300 °C". **Isabel Correia** from Centro de Química Estrutural in Lisbon (Portugal) and **Annika Rickers** from Institute of Technical and Macromolecular Chemistry RWTH-Aachen (Germany) shared the second prize with scientific posters entitled: "Vanadium Substituted Phytase-CLEA: Oxidative Catalysis and Structural Characterization" and "Polymer-Supported Pauson–Khand Reaction in $scCO_2$", respectively. The quality and diversity of the prized scientific work reflects the overall trend of the research presented by the students: many of them are working with alternative reaction media, such as ionic liquids and supercritical CO_2, as well as microwave assisted processes and catalysis.

On the last day of the summer school everybody had the chance to relax in the beautiful Venice island, before getting back to their own countries and research. This was surely a week that the students will not forget, since the opportunity to meet and have contact with known experts on green chemistry in such an informal ambiance and spectacular setting is not so frequent.

In 2006 the 9th Summer School on Green Chemistry will take place in Venice the first week of September, details will be published on the web site: http://venus.unive.it/inca/education/summer_school_on_green_chemistry/.

2005 EuCheMS lectureship

DOI: 10.1039/b514396a

Roger Sheldon delivered the 2005 EuCheMS lecture entitled 'Combining Organometallic Catalysis and Biocatalysis in Catalytic Cascade Processes' at the XVIth FECHEM Conference on Organometallic Chemistry held at Eötvos University in Budapest, 3–8 September, 2005.

The EuCheMS lecture honours outstanding achievements by a European chemist and serves to enhance the image of European chemistry and to promote scientific cooperation in Europe. It rotates among EuCheMS member societies and is delivered at a scientific event outside the lecturer's own country.

Roger Sheldon is Professor of Biocatalysis and Organic Chemistry at Delft University of Technology and was the first Chairman of the Editorial Board of Green Chemistry. He was awarded the EuCheMS lectureship in recognition of his pioneering and important contributions to green chemistry and catalysis. His primary research interests encompass the application of green catalytic methodologies—homogeneous, heterogeneous and enzymatic—in organic synthesis, particularly in relation to fine chemicals manufacture. He is widely known for developing the concept of E Factors for assessing the environmental footprint of chemical processes. This concept is currently applied by chemical companies on a worldwide basis.

To commemorate the occasion he was presented with a 'wise owl' of Swarovski silver crystal by Prof. Jozsef Bakos of the University of Veszprem, Veszprem, Hungary.

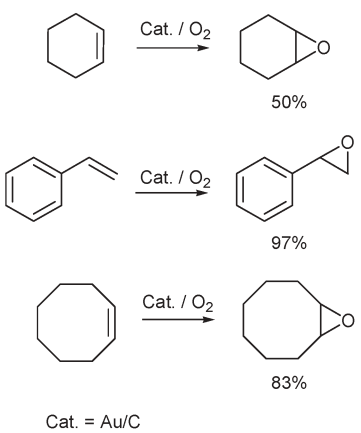
Highlights

DOI: 10.1039/b515519n

Markus Hölscher reviews some of the recent literature in green chemistry

Selective hydrocarbon oxidations with tunable gold catalysts

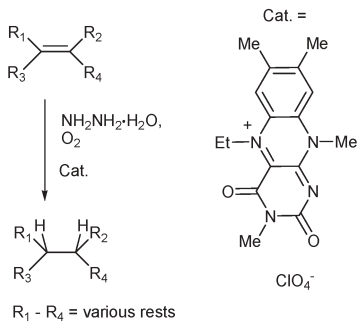
The direct electrophilic addition of molecular oxygen to alkenes yielding an epoxide is still a major challenge for organic syntheses. Epoxidation of ethylene using heterogeneous silver catalysts is carried out on an industrial scale, however, this is the exception to the rule, that higher alkenes cannot be epoxidized directly and satisfyingly with O_2. Hutchings *et al.* from Cardiff university recently challenged the dogma by using nanocrystalline gold that serves as an efficient catalyst for the conversion of different alkenes to the corresponding epoxides by simply using molecular oxygen and no sacrificial reductants.[1] The only coreagents used were small amounts of a hydroperoxide initiator, either hydrogen peroxide or *t*-butyl hydroperoxide. The initial experiments revealed a strong solvent dependancy showing the best results to be achieved with nonpolar solvents. As a result cyclohexene oxide could be obtained with a selectivity of 50% using 1,2,3,5-tetramethylbenzene with 1% Au/C as catalyst. Styrene was epoxidized to styrene oxide with a selectivity of 97% using the same catalyst, while the selectivity for the conversion of *cis*-cyclooctene amounted to 83%.



Doping of the catalyst with other metals such as bismuth was shown to open promising routes for further enhancement of selectivity, which is desirable, since for practical application the yields obtained must be increased significantly.

Diimide as reagent for catalytic environmentally friendly aerobic hydrogenation of olefins

The search for new hydrogenation methods as alternatives for established techniques has been extended to organocatalysis with the result that in many cases a new reaction/catalyst can be found, but at the expense of creating considerable waste. In an attempt to use an environmentally friendly reducing agent for the C–C double bond, the utilization of diimide NH=NH could be an interesting solution as only N_2 is formed during the hydrogenation. However, the use of diimide is problematic due to its tendency to disproportionate to hydrazine and nitrogen. The ideal approach would be the catalytic aerobic oxidation of hydrazine, resulting in the *in situ* formation of diimide, which subsequently hydrogenates the C–C double bond. Imada *et al.* from the university of Osaka recently reported about a flavin based solution to this problem.[2]



A variety of olefins were hydrogenated by mixing the olefin with an appropriate flavin such as 5-ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate and $NH_2NH_2{\cdot}H_2O$. Reaction times of 4 to 8 h at 25 °C afforded the corresponding hydrogenated products with yields between 90 and 99%. Though the method in itself is highly efficient, facile and safe, the solvents used for the reaction (CH_3CN, DMSO, DMF) don't easily go along with the idea of green chemistry. However, as many sustainable polar solvents are available this new method might be improved in the future.

Au^{III}/La_2O_3 catalysts oxidize CO at 298 K with no need for Au^0

Highly dispersed gold is an active catalyst for important reactions such as CO oxidation and the water gas shift reaction. As the nature of the catalytically active gold species has been a matter of controversal debate many studies have adressed the issue. A clear insight into the nature of the active catalyst would help in rational catalyst development. Gates *et al.* from the university of California studied the behaviour of Au^{III} complexes adsorbed on La_2O_3.[3] The authors found these catalyst to be highly active for the oxidation of CO at a temperature of 298 K with no deactivation in continuous operation in flow reactors for more than 50 h. EXAFS spectra of the as prepared gold sample gave no evidence for Au–Au interactions, *i.e.* the absence of gold nanoclusters and XANES spectra indicated the presence of Au^{III}. EXAFS and XANES analyses after the reaction again showed mononuclear Au^{III} to be present, while the pure La_2O_3 support showed no catalytic activity. These data indicate the Au^{III} to be the catalytically active species and that the presence of Au^0 in this particular case is not a necessary prerequisite for catalysis. With an equimolar mixture of CO and O_2 the catalyst yielded a CO conversion to CO_2 of *ca.* 10% at 298 K under steady

state conditions, which corresponds to a turnover frequency of 1.0×10^{-2} s^{-1}. These types of Au/La_2O_3 catalysts are among the most stable catalysts of this kind reported to date.

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Neutral alumina catalysed synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes, under solvent-free conditions, *via* tandem process†

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It has been found that neutral alumina carries out the solvent-free reaction of 2-aminobenzaldehyde or salicylaldehyde over a range of nitroalkenes, under mild and convenient conditions, allowing the one pot synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes, respectively.

Introduction

Quinolines are widely used heterocyclic compounds in organic chemistry,[1–5] and three general methods are typically used to prepare nitroquinolines:[2] (i) nitration of quinolines,[2e–g] with the formation of several regioisomers, (ii) reaction of 3-nitroquinoline *N*-oxide with a limited number of reactants,[2d] (iii) condensation of certain nitro compounds with 2-amino carbonyl compounds.[2a–c,g] The preparation of 3-nitro-1,2-dihydroquinolines *via* reaction of conjugate nitroalkenes with 2-aminobenzaldehyde and 1,4-diazabicyclo[2.2.2]octane (DABCO) as base, in refluxing benzene, has also been recently reported by Yao and coworkers.[2g] The latter procedure needs long reaction times, the products are polluted by the formation of 3-nitroquinolines, the basic conditions partially convert the starting aliphatic conjugate nitroalkenes to β,γ-unsaturated alkenes, and highly dangerous solvents such as benzene are required making the methods of little interest, especially from the industrial point of view.

3-Nitrochromenes are another important class of heterocyclic compounds due to their biological activity[6] and their importance as precursors of flavonols,[7] amines,[8] and other important targets.[9] 3-Nitrochromenes can be prepared from different sources[10] including the reaction of conjugate nitroalkenes with salicylaldehyde, catalysed under basic conditions by DABCO[11] or by basic alumina.[10d] However, the latter procedures show some important drawbacks, since DABCO catalysis demands a large excess of salicylaldehyde (4–10 times) and a significant amount of catalyst (0.5–1 equiv.), while basic alumina needs the help of ultrasonication and seems to work well just with aromatic nitroalkenes (styrene derivatives). Moreover, both the methodologies, due to their basic conditions, present some problems of isomerization with aliphatic nitroalkenes (conjugate nitroalkenes convert to β,γ-unsaturated ones).

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† Electronic Supplementary Information (ESI) available: analytical data for compounds 5a–5l. See DOI: 10.1039/b511003c

Considering that α,β-unsaturated nitroalkenes are easily available starting materials,[12] we wish here to report a unique methodology for the efficient synthesis of both 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes through nitroalkenes. The use of solvent-free conditions (SFC) in combination with heterogeneous catalysts represents one of the more powerful green chemical technology procedures.[13]

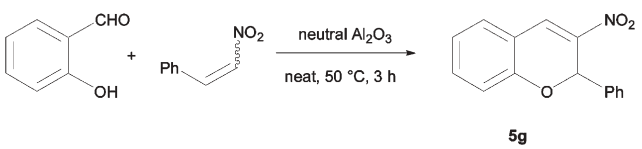
Alumina is a particularly interesting metal oxide as it is widely used industrially as filler, adsorbent, drying agent, catalyst, catalyst support and reagent. γ-Alumina is the transition alumina most commonly utilised to carry out surface organic chemistry.[14] In contrast to clays and zeolites, this material does not contain accessible channels or cavities and shows large surface area and highly porous exteriors available to substrates.

Results and discussion

In continuation of our investigations on the use of heterogeneous catalysts for fine chemicals preparations,[15,16] we have studied the synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes by reaction of conjugate nitroalkenes with 2-aminobenzaldehyde or salicylaldehyde, respectively, using γ-alumina as common, cheap and neutral heterogeneous catalyst under solventless conditions.

In order to test the effect of the catalyst amount we chose to carry out the reaction by mixing salicylaldehyde (1 mmol) and β-nitrostyrene (1 mmol) with a varying amounts of neutral alumina, then leaving the mixture at 50 °C for 3h.[17] As reported in Table 1 we found the best yield (83%) by using the ratio Al_2O_3 g/mmol of substrate = 1. The decrease of the yield (71%) by employing a ratio of 1.5 can probably be explained by the

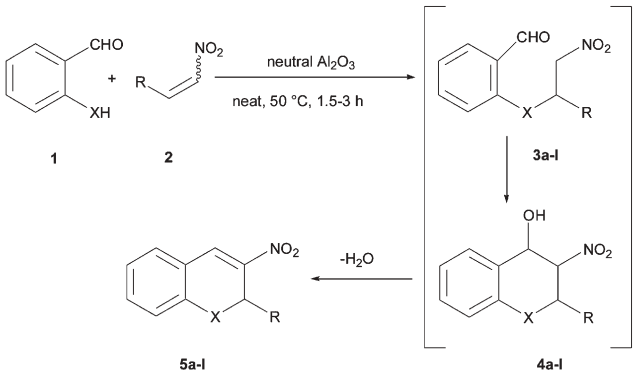
Table 1 Trend of the model reaction with different amounts of neutral alumina



5g

Al_2O_3[a] g/mmol of salicylaldehyde	Yield of **5g** (%)
0.5	69
1	83 (71)[b]
1.5	71

[a] Available from Baker Reagents and activated by MW, 500 W, 4 min. [b] Yield obtained with unactivated alumina.



Scheme 1

increased dilution of the solid mixture. Moreover, the activation of alumina (MW, 500 W, 4 min) gives better yield (83% *vs.* 71%, Table 1).

2-Aminobenzaldehyde and salicylaldehyde were subjected to reactions with different nitroalkenes under the optimised reaction conditions (Scheme 1). Satisfactory to good product yields were obtained from the reactions in very short reaction times and the nature of nitroolefins has little influence on the efficiency. Other functionalities such as cyano, ether and chlorine can be preserved under our conditions (Table 2).

Conclusions

The procedure evidences several advantages such as: (i) short reaction times, (ii) no excess of the reactants is demanded, (iii) no solvent is employed, (iv) cheap catalyst is applied, (v) three steps can be performed one-pot, (vi) no isomerization of the starting conjugate nitroalkenes is observed, (vii) mild and neutral reaction conditions are required, (vii) no work up is needed, since the crude mixture can be directly charged to a chromatographic column for immediate purification. Thus, our method, compared with the reported ones, shows very important advantages from both ecological and economic point of view.

Experimental

Typical procedure for the synthesis of 3-nitro-1,2-dihydroquinolines 5a–f

To a stirred heterogeneous mixture of neutral alumina (1 g) and 2-aminobenzaldehyde (1 mmol), 1 mmol of the appropriate nitroalkene was added and the obtained mixture was warmed at 50 °C under stirring for 1.5 hours. Then, the mixture was cooled at room temperature and directly charged on a chromatography column to give the pure product **5a–f**.

Typical procedure for the synthesis of 3-nitrochromenes 5g–l

To a stirred heterogeneous mixture of neutral alumina (1 g) and salicylaldehyde (1 mmol), 0.5 mmol of the appropriate nitroalkene was added and the mixture was warmed at 50 °C under stirring for 1.5 hours. Then a further 0.5 mmol of nitroalkene was added and the mixture left at 50 °C for another 1.5 h. The mixture was cooled at room temperature and directly charged on a chromatography column to give the pure product **5g–l**.

Table 2 One-pot synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes catalysed by neutral alumina[a]

Entry		R	X	Yield (%)[b] of **5**	Reaction time/h
1	**a**	n-C_4H_9	NH	71	1.5
2	**b**	n-C_5H_{11}	NH	75	1.5
3	**c**	Ph	NH	85	1.5
4	**d**	p-Cl-C_6H_4	NH	72	1.5
5	**e**	c-C_6H_{11}	NH	55	1.5
6	**f**	$Ph(CH_2)_2$	NH	60	1.5
7	**g**	Ph	O	83	3
8	**h**	n-C_4H_9	O	81	3
9	**i**	n-C_5H_{11}	O	82	3
10	**j**	$Ph(CH_2)_2$	O	75	3
11	**k**	p-CN-C_6H_4	O	72	3
12	**l**	p-CH_3O-C_6H_4	O	72	3

[a] Reaction conditions: 1 mmol of aldehyde, 1 mmol of nitroalkene, 1 g of neutral Al_2O_3, 50 °C. [b] Isolated yields.

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17 The reaction temperature of 50 °C is needed since at room temperature just the cyclic nitroalkanols **4** are obtained.

One-pot synthesis of 3-alkyl-2,4-dinitrocyclohexanols, under solventless conditions using basic alumina†

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3-Alkyl-2,4-dinitrocyclohexanols can be prepared in a one-pot procedure by reaction of 1,3-dinitroalkanes with acrolein, catalysed by basic alumina and in the absence of any solvent. The synthesis proceeds using tandem Michael/nitroaldol (Henry) reactions and allows satisfactory to good yields of the title compounds. Moreover, several functionalities can be preserved under our conditions.

Introduction

Cyclohexanols are useful intermediates in organic synthesis,[1] because they serve as building blocks in several synthetic transformations and in this context the polyfunctionalized ones are of special interest.[2] Dinitrocyclohexanols are a new class of molecules in which the presence of two nitro-functionalities offers a variety of synthetic opportunities due to the great versatility of the nitro group. In fact, the proton α to the nitro group is fairly acidic and can be easily removed under mild conditions thus permitting C–C bond formation,[3,4] and after, C–C bond formation of the nitro group can be removed or converted into amino functionalities, to a carbonyl group or to many other functionalities.[5–9]

The use of solventless conditions in combination with heterogeneous catalysts represents one of the more powerful green chemical technology procedures,[10] and the environmental acceptability of the process is improved if the one-pot strategy is applied.

Alumina is a particularly interesting metal oxide as it is widely used industrially as filler, adsorbent, drying agent, catalyst, catalyst support and reagent. γ-Alumina is the transition alumina most commonly utilised to carry out surface organic chemistry.[11] In contrast to clays and zeolites, this material does not contain accessible channels or cavities and shows large surface area and highly porous exteriors available to substrates.

Results and discussion

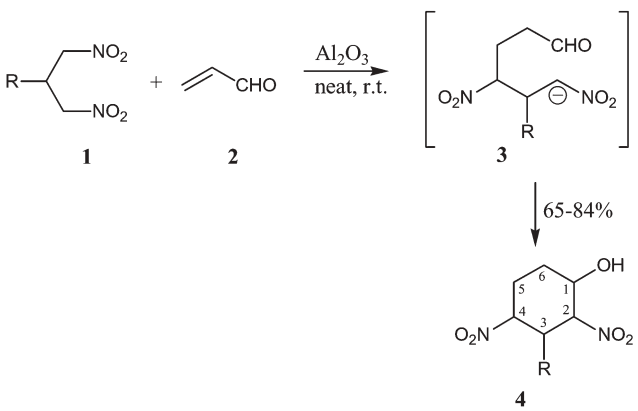
During our studies devoted to the use of ecofriendly conditions for the synthesis of fine chemicals,[12,13] we planned the first synthesis of 3-alkyl-2,4-dinitrocyclohexanols in a one-pot procedure, under solventless conditions using basic alumina as a heterogeneous catalyst. Thus, by treating a mixture of 1,3-dinitroalkanes **1**[14] and acrolein **2** with basic alumina (activity I), at 0 °C, without any solvent, then stirring at 0 °C for 15 min and at room temperature for 4–48 h, the target 3-alkylated-2,4-dinitrocyclohexanol derivatives **4** are obtained with satisfactory to good yields (65–84%) and in a one-pot procedure (Scheme 1). The synthesis proceeds by a tandem process in which the first step is the conjugate addition of **1** to **2** yielding the intermediate **3** that is prone to give **4** through an intramolecular nitroaldol (Henry)[3] reaction. Although four stereogenic centers are present in the compounds **4**, the stereoisomers **4′** (±) (1*R**, 2*S**, 3*R**, 4*R**) and **4″** (±) (1*S**, 2*S**, 3*R**, 4*R**) are predominant (>95%). Their structures were estabilished on the basis of the H–H coupling constants and COSY and NOESY spectra.

The synthetic results and the diastereomer ratios are presented in Table 1. By following these mild conditions, several dinitrocyclohexanol derivatives can be obtained and other important functionalities, such as furanyl, phenyl, ether, C–C double bond, cyano, heteroaromatic and phenol, can be introduced and preserved.

Because the reaction can be performed using a solventless procedure, at the end of the reaction (checked by TLC) the crude mixture can be charged on a chromatographic column to give the pure product **4**, avoiding any tedious and dangerous work up.

Conclusions

We have reported the one-pot synthesis of a new class of polyfunctionalized cyclohexanols from easily available starting materials, through a tandem Michael–Henry process. This procedure works under solvent-free conditions and affords good yields of the title compounds without the need of any solvent and of a work up, since the crude mixture can be directly charged to a chromatographic column for immediate purification.



1 **2** **3** **4**

Scheme 1

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† Electronic supplementary information (ESI) available: Characterisation of diastereomers. See DOI: 10.1039/b512617g

Table 1 Synthesis of 3-alkyl-2,4-dinitrocyclohexanols **4**

	R	Reaction time/h	Yield[a] % of **4**	Diastereomer ratio of **4′** : **4″**
a	Furyl	7	72	51 : 49
b	Ph	4	71	61 : 39
c	*n*-Pr	5	83	15 : 85
d	*i*-Pr	9	65	20 : 80
e	*n*-C_8H_{17}	6	87	53 : 47
f	*o*-$NO_2C_6H_4$	5	70	51 : 49
g	*p*-$MeOC_6H_4$	18	76	54 : 46
h	*p*-$CF_3C_6H_4$	5	71	56 : 44
i	*cis*-$CH_3(CH_2)_4CH{=}CH(CH_2)_2$	5	71	30 : 70
j	*cis*-C_6H_{11}	6	84	22 : 78
k	*m*-$NO_2C_6H_4$	48	68	53 : 47
l	*m*-CNC_6H_4	20	70	50 : 50
m	$PhCH_2CH_2$	6	74	35 : 65
n	*o*-Py	6	71	63 : 37
o	*m*-(OH)-*p*-$MeOC_6H_3$	4	72	48 : 52

[a] Yield of pure isolated product.

Experimental

Typical procedure

To a stirred mixture of dinitroalkane **1** (2 mmol) and acrolein **2** (2.6 mmol, 0.174 mL), 2 g of basic alumina (activity I) was added, at 0 °C. The resulting mixture was stirred at the same temperature for 15 min, then at room temperature for the appropriate reaction times (Table 1). The heterogeneous mixture was directly charged on a chromatographic column (EtOAc/hexane as eluent) giving the pure products **4**.†

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Facile solar oxidation of alcohols with molecular oxygen†

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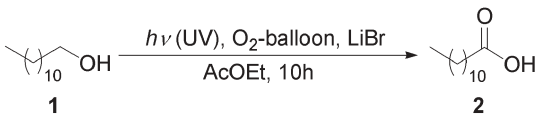
A useful method for the aerobic oxidation of alcohols directly to the corresponding carboxylic acid or ketone with combination of sodium bromide and Amberlyst 15 (safe and inexpensive reagents) under solar radiation is reported.

The oxidation of alcohols is an extremely important reaction in organic synthesis.[1] Recently, efficient systems using molecular oxygen have been developed for the catalytic aerobic oxidation of alcohols.[2–5] Unfortunately many of these reactions use transition metals and halogenated solvents, which are detrimental to the environment. In the course of our investigation into photo-oxidation reactions, we found that alcohols were readily oxidized to the corresponding carboxylic acids with molecular oxygen as a terminal oxidant in the presence of catalytic alkali metal halides, such as lithium bromide, under irradiation of a high pressure mercury lamp.[6]



1 **2**

Of the alkali metal halides examined in this study, we found lithium bromide was the most suitable. The product was barely detectable in typical organic solvents, such as acetone, THF, MeCN, H_2O, other than ethyl acetate. Surprisingly, we also found that the reaction proceeded even under irradiation from a xenon lamp after addition of the mesoporous silica, Ti-HMS.[7] This reaction afforded the product **2** in 95% yield within 10 h. It occurred to us that this reaction might proceed under solar radiation because the spectral distribution curve of a xenon lamp is similar to that of sunlight. Furthermore, in accordance with the concept of "green chemistry" solar radiation is an infinite source of clean energy.

Although a synthetic reaction using solar energy was reported about 50 years ago, the rate was very slow and the yield of product poor.[8] To alleviate these problems, strong UV light (*e.g.* from a high pressure mercury lamp) has been used to accelerate the reaction. Unfortunately, this source of radiation consumes a large amount of energy. If solar radiation can be used to mediate the efficient oxidation of alcohols, an environmentally benign process will be established. Here we report the solar oxidation of alcohols with molecular oxygen in the presence of alkali metal halides and solid catalysts.

Our initial study of the reaction conditions of solar oxidation were carried out using 1-dodecanol (**1**, 50 mg, 0.269 mmol) as test substrate with a combination of Amberlyst 15 (100 mg) and several alkali metal halides (0.107 mmol) in various solvents. The reactions were performed for 10 h (from 7 a.m. to 5 p.m. on a clear day) in a pyrex glass test tube fitted with an oxygen balloon. Among the solvents and the alkali metal halides examined, ethyl acetate and sodium bromide were found to be suitable for the reaction.† No product, **2**, was detected if the reaction was carried out in the absence of solar radiation or sodium bromide.

Fig. 1 shows the results for the study of solid phase catalysis. The catalysts we examined included mesoporous silica FSM-16[9] and 10%Ti-HMS, the zeolites NaY and H-ZSM-5, ion-exchange resins Amberlyst 15 and Dowex 50Wx8, TiO_2 (a known photo-catalyst) and silica gel (230–400 mesh from Merk). The oxidation of **1** (50 mg) using a variety of different catalysts (100 mg) was carried out in parallel on the same day (experiments performed from October to April). The yield of **2** was then compared. Amberlyst 15, a strong acidic ion exchange resin, was consistently found to afford the best results.

Further studies into the reaction conditions revealed a combination of 0.2 equiv. of sodium bromide and 25 mg of Amberlyst 15 afforded the highest yield of product, **2**, from the oxidation of 50 mg of **1**.†

Table 1 shows the results for the oxidation of several alcohols under the reaction conditions outlined above.[10] Primary alcohols generally gave the corresponding carboxylic acids in high yield (entries 1–5), whereas secondary alcohols gave the corresponding carbonyl compounds in low yield (entries 6 and 7).

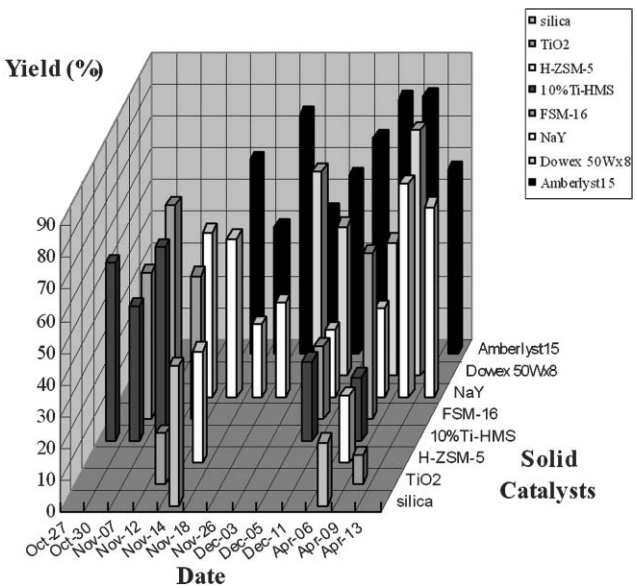


Fig. 1 Study of solid phase catalysis.

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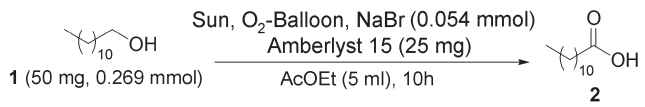
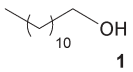
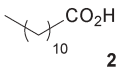
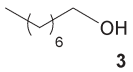
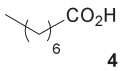
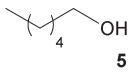
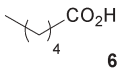
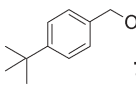
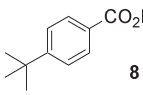
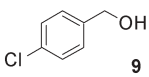
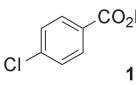
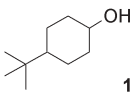
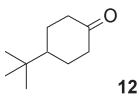
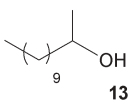
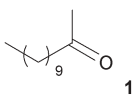
† Electronic supplementary information (ESI) available: Optimization procedure of solar oxidation. See DOI: 10.1039/b511780a

Table 1 Solar oxidation of alcohol substrates with a combination of NaBr and Amberlyst 15[a]

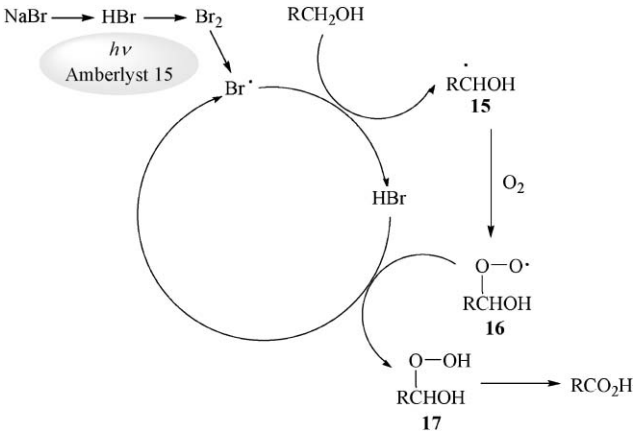


Entry	Substrate	Product	Yield (%)
1	 **1**	 **2**	97
2	 **3**	 **4**	83
3	 **5**	 **6**	62[b]
4	 **7**	 **8**	99
5	 **9**	 **10**	95
6	 **11**	 **12**	21[c]
7	 **13**	 **14**	3[d]

[a] A typical procedure was as follows: A suspension of alcohol (0.269 mmol), sodium bromide (5.5 mg, 0.054 mmol) and Amberlyst 15 (25 mg) in dry ethyl acetate (5 mL) in pyrex glass test tube was irradiated with sunlight for 10 h (from 7 a.m. to 5 p.m. on a clear day). Solid reagents were filtered off and washed with ethyl acetate, and the filtrate was concentrated under reduced pressure. All yields are for pure, isolated products. [b] The product **6** is volatile. [c] Some extent of Baeyer–Villiger oxidation products were formed. [d] 80% of starting **13** was recovered.

The mechanism of this reaction has not yet been determined. However, the pale yellow coloration of the suspension suggests that bromine is generated *in situ* from sodium bromide and Amberlyst 15 under solar-radiation. Bromine oxidizes **1** to **2** in 76% yield.[11] Because the color fades as the reaction proceedes, we believe that the alkyl radical species **15** is generated by abstraction of a hydrogen radical with a bromo radical, formed under solar radiation from bromine. The radical species traps molecular oxygen to afford the peroxyradical **16**, which gives hydroperoxide **17** and regenerates the bromo radical (Scheme 1).

In conclusion, we have found a useful method for aerobic oxidation of alcohols directly to the corresponding carboxylic acid with a combination of sodium bromide and Amberlyst 15, which are safety and inexpensive reagents, under solar radiation, which is clean and infinite energy. This novel method is thought to be convenient in view of the use of solid catalyst, easy work-up,



Scheme 1 Working hypothesis.

and non-requirement of environmentally detrimental heavy metals and halogenated solvents.

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10 This oxidation method is also applicable to gram scale conditions, and **2** was obtained in 80% yield when using **1** as substrate under similar conditions mentioned above.
11 A solution of **1** (50 mg, 0.269 mmol) and bromine (0.027 mmol) in dry ethyl acetate (5 mL) in a pyrex glass test tube was irradiated in the sun for 10 h. The work-up was the same as in the Experimental section.

An easily accessed class of recyclable hypervalent iodide reagents for functional group oxidations: bis(trifluoroacetate) adducts of fluorous alkyl iodides, $CF_3(CF_2)_{n-1}I(OCOCF_3)_2$†

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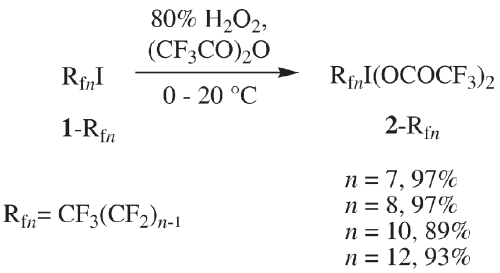
Reactions of commercial fluorous alkyl iodides $R_{fn}I$ (1-R_{fn}; R_{fn} = $CF_3(CF_2)_{n-1}$; *n* = 7, 8, 10, 12) with 80% H_2O_2 and trifluoroacetic anhydride give $R_{fn}I(OCOCF_3)_2$ (2-R_{fn}; 89–97%). These rapidly oxidize 1,4-hydroquinones in methanol. Subsequent additions of $CF_3C_6F_{11}$ or FC-72 give liquid/liquid biphase systems. The product quinones are generally isolated in ⩾95% yields from the methanol phases, and 1-R_{fn} in ⩾95% yields from the fluorous phases. Alternatively, the very low solubilities of 1-R_{f10} in 10 : 1 v/v methanol : water or 1-R_{f12} in methanol allow efficient recovery *via* solid/liquid phase separations without recourse to fluorous solvents. The recovered 1-R_{fn} may be reoxidized to 2-R_{fn} and reused.

Hypervalent iodide reagents continue to play an increasingly important role in organic synthesis.[1] However, many of the most frequently utilized compounds—for instance IBX or the Dess–Martin reagent—rate poorly from the standpoint of atom economy. Stoichiometric amounts of iodine-containing arene waste products are commonly produced. Accordingly, a number of approaches to recyclable hypervalent iodide reagents, involving both polymeric and molecular species, have recently appeared.[2–9]

However, many of these require multistep syntheses. For example, in our own first efforts, we prepared several fluorous aryl iodides of the formula $(R_{f8}(CH_2)_3)_xC_6H_{5-x}I$ (*x* = 2, 3; R_{fn} = $CF_3(CF_2)_{n-1}$), and the corresponding iodine(III) bis(acetate) adducts $(R_{f8}(CH_2)_3)_xC_6H_{5-x}I(OCOCH_3)_2$.[7] The latter were excellent reagents for oxidations of hydroquinones to quinones. The aryl iodide coproducts could be recovered in 98 to >99% yields *via* fluorous/organic liquid/liquid biphase workups and reoxidized. Nonetheless, syntheses of these iodine(III) reagents required four steps from the corresponding aromatic aldehydes $(O{=}CH)_xC_6H_{6-x}$.

We therefore sought fluorous hypervalent iodide compounds that could be more readily accessed. Notably, many fluorous *aliphatic* iodides $R_{fn}I$ (1-R_{fn}) are commercially available. Furthermore, they can be oxidized to iodine(III) bis(trifluoroacetate) adducts, $R_{fn}I(OCOCF_3)_2$ (2-R_{fn}),[10,11] as demonstrated earlier for *n* = 2, 3, 4, 6, 8.[11b] Although these have seen extensive use for the derivatization of arenes,[10] they have not to our knowledge been applied in functional group oxidations. Furthermore, the trifluoroacetate moieties might be replaced with heavier fluorous carboxylates (*e.g.*, $OCOR_{f10}$), such that all coproducts would be fluorophilic. In this communication, we report the successful use of these compounds for oxidations of hydroxylic substrates, employing hydroquinones for test purposes.

As shown in eqn (1), 1-R_{f7}, 1-R_{f8}, 1-R_{f10}, and 1-R_{f12} were oxidized with 80% H_2O_2 (an ideal oxidant from the green chemistry standpoint)[12,13] in trifluoroacetic anhydride. These conditions generate the peracid CF_3CO_3H, and were used for 1-R_{f8} previously.[11b] Workups gave 2-R_{fn} in 89–97% yields as white solids with melting points of *ca.* 110 °C. Their spectroscopic features, which included two IR υ_{CO} bands and ^{13}C NMR signals diagnostic of the $OCCF_3$ groups, were routine (see supporting information†). The absolute solubilities of 2-R_{fn}, like those of 1-R_{fn} and many other fluorous compounds,[14] decreased with the length of the pony tail. As summarized in Table 1, DMSO, acetone, methanol, and ether were the best organic solvents.



(1)

In contrast to 1-R_{fn}, 2-R_{fn} were not very soluble in fluorous solvents (*e.g.*, $CF_3C_6F_{11}$ or perfluoro(methylcyclohexane)), and fluorous/organic partition coefficients could not be measured. However, since 2-R_{fn} are more polar than 1-R_{fn}, they should be less fluorophilic. The $CF_3C_6F_{11}$/toluene partition coefficients of 1-R_{f8} and 1-R_{f10} have been reported as 88.5 : 11.5 and 94.5 : 5.5 (GLC).[15] As described in the supporting information†, we measured 87.7 : 12.3 and 94.3 : 5.7, which we consider good agreement. When $CF_3C_6F_{11}$/methanol was used—two solvents with a greater polarity difference—the ratios increased to 89.4 : 10.6 and 97.6 : 2.4, respectively.

Next, 2-R_{fn} and hydroquinones **3a–d** were combined in 1 : 1 mole ratios in methanol as summarized in Table 2. Although 2-R_{fn} were sparingly soluble, the mixtures immediately turned the characteristic yellow color of the quinone products **4a–d**. In four cases, $CF_3C_6F_{11}$ was added, and the fluorous and organic phases separated. Solvent removal (rotary evaporation) gave 1-R_{fn} and **4**–**3** mixtures in ⩾95% yields.[16] In another four cases, the samples were directly analyzed by ^1H NMR. The conversions of **3** to **4** in the eight reactions ranged from 91 to >99%.

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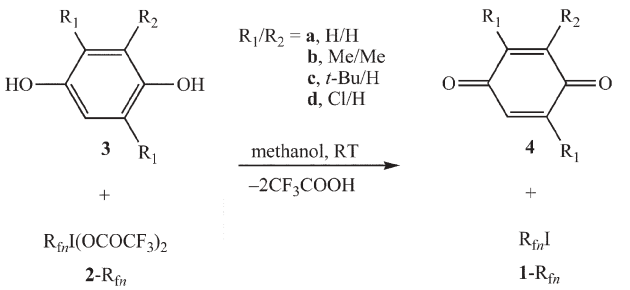
† Electronic supplementary information (ESI) available: Experimental details and analytical data. See DOI: 10.1039/b511951k

Table 1 Qualitative solubility data

Solvent	Solubility, $R_{fn}I(OCOCF_3)_2$ (**2**-R_{fn})				Solubility, $R_{fn}I$ (**1**-R_{fn})			
	n = 7	n = 8	n = 10	n = 12	n = 7	n = 8	n = 10	n = 12
DMSO	High	High	Low	Low	High	High	Low	V. low
Acetone	High	High	High	Medium	High	High	High	Medium
Methanol	High	High	Low	Low	High	High	Low	V. low
CH_2Cl_2	Medium	Medium	V. low	V. low	High	High	Medium	Medium
Hexane	Low	Low	V. low	V. low	High	High	High	Medium
Ether	High	High	Medium	Medium	High	High	High	Medium
$CHCl_3$	Medium	Medium	V. low	V. low	High	High	High	Medium
Toluene	Low	Low	V. low	V. low	High	High	High	V. low
$CF_3C_6F_{11}$	Low	Low	V. low	V. low	High	High	High	Medium
$CF_3C_6F_5$	High	High	Medium	Medium	High	High	High	Medium

Table 2 Oxidations of hydroquinones to quinones: screening reactions



Entry[a]	Oxidant[b]	Hydroquinone/ quinone	**4/3** (% isolated; conversion[c])	**1**-R_{fn} (% isolated)
1	**2**-R_{f8}	**3a/4a**	>99; 99 : 1	>99
2	**2**-R_{f10}	**3a/4a**	—; >99 : <1	—
3	**2**-R_{f12}	**3a/4a**	>99; 91 : 9	95
4	**2**-R_{f8}	**3b/4b**	>99; 91 : 9	>99
5	**2**-R_{f10}	**3b/4b**	—; >99 : <1	—
6	**2**-R_{f8}	**3c/4c**	—; 95 : 5	—
7	**2**-R_{f10}	**3c/4c**	—; >99 : <1	—
8	**2**-R_{f8}	**3d/4d**	95; 96 : 4	98

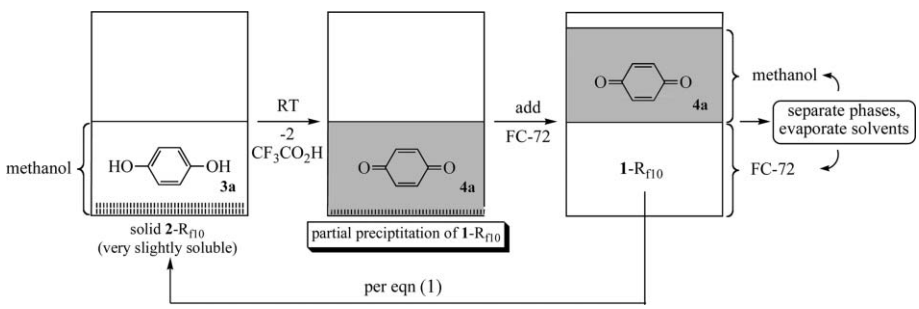
[a] Reactions 2, 5, 6, and 7 were conducted in NMR tubes in methanol-d_4 and analyzed after 10 min. The others were conducted in flasks (2–3 h) and analyzed after $CF_3C_6F_{11}$/methanol workups. However, similar reactions in NMR tubes were complete within 10 min. [b] 1 : 1 **2**-R_{fn} : **3** mole ratio. [c] As assayed by ^{1}H NMR. No species were detected other than **3a–d** or **4a–d**.

We sought to optimize these oxidations from the standpoint of convenience and recycling, using **3a** as the substrate. It proved somewhat tedious to efficiently separate the relatively volatile **1**-R_{f8} (bp 160–161 °C) from $CF_3C_6F_{11}$ (bp 76 °C) by rotary evaporation. Mass losses inevitably occurred over multiple cycles. Obvious solutions would include switching to a heavier **2**-R_{fn} reagent (bp of **1**-R_{f10}, 195–200 °C) or a more volatile fluorous solvent (*e.g.*, FC-72, bp 56–60 °C), or modifying the protocol to eliminate the fluorous solvent altogether. These were investigated in turn.

First, **2**-R_{f10} and **3a** were combined in a 1 : 1 mole ratio in methanol. After 1 h, an equal volume of FC-72 was added. As summarized in Table 3 and the supporting information†, phase separation followed by solvent removal gave **1**-R_{f10} (99%) and a **4a**–**3a** mixture (>99%; 91% conversion). The **1**-R_{f10} was reoxidized per eqn (1), and the exact same sample was used to conduct a second cycle. The results were similar (the **4a** was purified by chromatography), and comparable data were obtained for a third cycle (Table 3). The yields of **2**-R_{f10} were lower than those in eqn (1), which are for optimized larger-scale reactions.

Next, the limited solubilities of the higher **1**-R_{fn} species in methanol (Table 1) were exploited. As shown in Table 4 (which summarizes duplicate runs), the reaction of **2**-R_{f10} and **3a** (1 : 1 mole ratio) was conducted in 10 : 1 v/v methanol : water. The coproduct **1**-R_{f10} precipitated essentially quantitatively from this more polar medium and was recovered in 97% yield. The quinone **4a** remained soluble, and 98–99 : 1–2 **4a** : **3a** mixtures

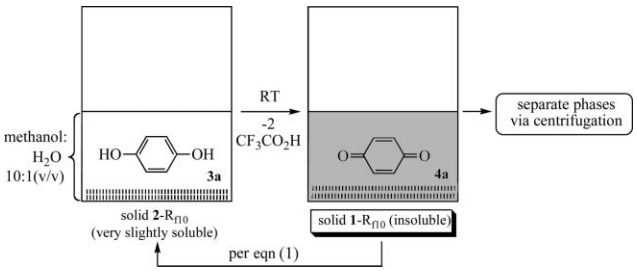
Table 3 Recycling of **2**-R_{f10} *via* fluorous/organic liquid/liquid phase separation



Cycle	**4a/3a** (% isolated; conversion[a])	**1**-R_{f10} (% isolated)	**2**-R_{f10} (% isolated[b])
I	>99; 91 : 9	99	71
II	90; >99 : 1[c]	99	69
III	92; >99 : 1[c]	99	—

[a] As assayed by ^{1}H NMR. No species were detected other than **3a** and **4a**. [b] For reoxidation of isolated **1**-R_{f10} using the procedure in eqn (1). [c] These yields and ratios are following column chromatography to remove the **3a**.

Table 4 Recycling of **2**-R_{f10} *via* fluorous/organic solid/liquid phase separation



Cycle	**4a**/**3a** (% isolated; conversion[a])	**1**-R_{f10} (% isolated)	**2**-R_{f10} (% isolated[b])
Ia	>99; 98 : 2	97	63
IIa	>99; 88 : 12	93	66
IIIa	>99; 92 : 8	98	—
Ib	>99; 99 : 1	97	69
IIb	>99; 90 : 10	92	61
IIIb	>99; 89 : 11	99	—

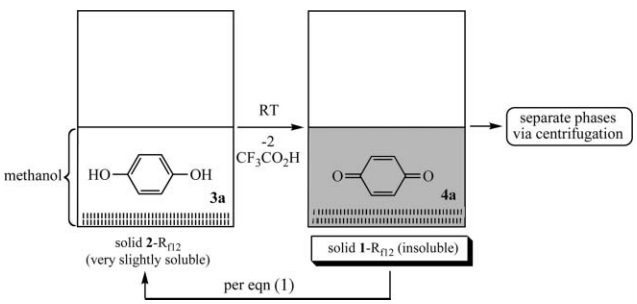
[a] As assayed by ^{1}H NMR. No species were detected other than **3a** and **4a**. [b] For reoxidation of isolated **1**-R_{f10} using the procedure in eqn (1).

were isolated in >99% yields. The **1**-R_{f10} was reoxidized and applied in subsequent cycles with similar results. Similar liquid/solid phase separations are seeing increasing use for the recovery of fluorous catalysts.[17,18]

Lastly, a similar sequence was conducted with **2**-R_{f12}. Since the coproduct **1**-R_{f12} is less soluble than **1**-R_{f10}, pure methanol could be used as the solvent. As summarized in Table 5, **1**-R_{f12} was recovered following precipitation in 95% yield, and reoxidized to **1**-R_{f12} in 90% yield. The results over three cycles were similar to those above, except that conversion of **3a** to **4a** dropped somewhat more as a function of cycle.

In summary, we have shown that the title compounds are excellent reagents for oxidations of hydroquinones to quinones,

Table 5 Recycling of **2**-R_{f12} *via* fluorous/organic solid/liquid phase separation.



Cycle	**4a**/**3a** (% isolated; conversion[a])	**1**-R_{f12} (% isolated)	**2**-R_{f12} (% isolated[b])
I	>99; 91 : 9	95	90
II	>99; 85 : 15	90	89
III	>99; 75 : 25	95	—

[a] As assayed by ^{1}H NMR. No species were detected other than **3a** and **4a**. [b] For reoxidation of isolated **1**-R_{f12} using the procedure in eqn (1).

affording quantitative yields under the best conditions. With **2**-R_{f10} and **2**-R_{f12}, the coproducts **1**-R_{fn} are easily recovered *via* fluorous/organic liquid/liquid or solid/liquid phase separations, and recycled. Extensions to other hydroxylic substrates such as alcohols will be described in future reports,[19] and a number of nitrogen-containing functional groups can also be oxidized.[20] Also, note that in fluorous chemistry, one often insulates the R_{fn} segment from the active site with methylene groups or other spacers in order to dampen the electron-withdrawing effect. However, as previously emphasized and exploited by Crich and coworkers with sulfur and selenium reagents,[21] R_{fn} substituents normally *enhance* oxidizing strengths.

Finally, this study may have even greater value as a paradigm for the optimization of recoverable fluorous reagents. Tables 3–5 depict a transition from protocols that depend upon somewhat costly and persistent fluorous solvents to those that do not. There is a reasonable likelihood that still less soluble fluorous alkyl iodides will be available in the future. Furthermore, the carboxylic acid coproduct (Tables 2–5) could likely be recycled using analogous reagents with longer and more fluorophilic $OCOR_{fn}$ substituents. Dehydration would give a fluorous anhydride that might mediate the reoxidation of recovered **1**-R_{fn} (eqn (1)). The obvious conceptual extension—an oxidation of a hydroquinone or other functional group using H_2O_2, with water as the only non-recycled coproduct—represents the ultimate in atom economy and a fluorous-based green process worthy of considerable future attention.

Acknowledgements

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Wax esters produced by solvent-free energy-efficient enzymatic synthesis and their applicability as wood coatings

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The study aimed at developing a process for making a wood coating wax based on the principles of green chemistry. The research was conducted within the Swedish interdisciplinary research programme Greenchem. Wax esters are attractive since they are non-hazardous, biodegradable and can be produced in an atom-efficient process from building blocks obtained from renewable resources. Four wax esters were prepared in a solvent-free process using an immobilised lipase as catalyst. When the water was removed during the process from what was initially an equimolar mixture of the starting materials carboxylic acid and alcohol by a stream of dry air passed through the reactor, there was a 95–99% conversion to the ester. The enzymatic process consumed 34% less energy and generated less waste than chemical esterification using a strong acid as catalyst. Two of the esters worked well in the industrial wood coating equipment employed and produced surfaces resistant to water and somewhat less to fat stains.

Introduction

Industrial interest in biotransformation processes, long a subject of research within academia, has been increasing recently. This has been shown by the increasing number of industrial-scale bioprocesses started during the last decade[1] and by the chemical industry's exploring possibilities of using renewable resources to replace crude oil and improve sustainability.[2] Two factors contributing to the expanding interest in this area have been the desire to utilise more environmentally benign processes and the fact that crude oil is a finite resource that there eventually will be a shortage of, with an accompanying of increasing costs. Most of today's commercial enzymatic processes possess a variety of positive characteristics, such as high productivity, high product concentrations, and a lack of undesirable by-products,[3] characteristics particularly evident in certain enzymatic processes, such as in esterification catalysed by lipases, which typically gives clean products with little need of downstream processing.

The research programme "Speciality Chemicals from Renewable Resources—Greenchem" is a Swedish interdisciplinary research programme concerned with the development and application of biocatalysts for the production of fine chemical products from renewable raw materials. The programme includes research activities within both biotechnology and environmental systems analysis and involves cooperation with several industrial partners.

Consumer and industrial desire for more environmentally benign paints and coatings is growing rapidly.[4] There is a strong interest here in developing waxes to serve as ingredients in coatings for wooden surfaces, with a minimum of pollutants and with substrates from renewable resources. The use of wax esters (esters of long-chain carboxylic acids and long-chain alcohols) is attractive since these are non-hazardous compounds with good biodegradability. Wax esters can be made from renewable feedstocks, such as vegetable oils. High atom economy can also be achieved, one molecule of water being the only side-product in the key production step, that of condensation of the carboxylic acid and the alcohol. The reaction can be carried out catalytically, either using a chemical catalyst such as a strong acid or using an enzyme. The enzymatic process presented in this work thus fulfils several of the twelve principles of green chemistry formulated by Anastas and Warner in 1998.[5] A conceptual picture of our work can be seen in Fig. 1. In the present study we make a theoretical comparison of the chemical and the enzymatic alternatives from a green chemistry perspective.

Life cycle assessment (LCA) has been recognised as a tool for the environmental evaluation of new, green alternative processes. This involves quantifying the benefits these have compared to the traditional chemical processes. In an ordinary LCA, the total environmental impact is calculated for the complete life cycle of the product, from cradle-to-grave. Such LCAs include feedstock production and the manufacturing, use and final disposal of the product. In considering only the processes, a gate-to-gate perspective can be employed. This is relevant when the systems compared utilise the same raw material and the product they result in are the same. One important parameter of LCA is the input of energy, which is analysed here for the processes involved.

A schematic diagram of the chemical and the enzymatic processes is shown in Fig. 2. Because of the advantages of the enzymatic processes, the laboratory work was concentrated on this alternative.

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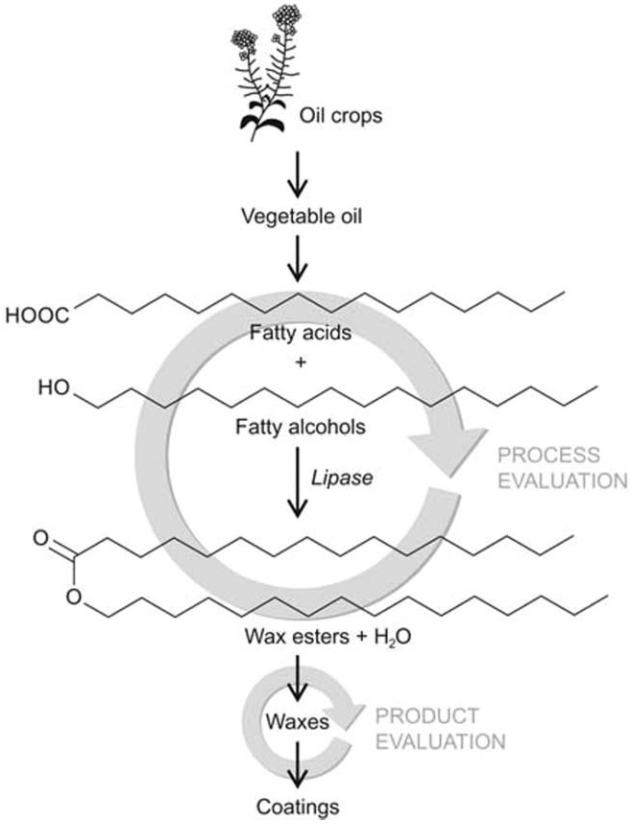

Fig. 1 Illustration of wax production from renewable resources.

In efforts to develop an attractive, green process for the enzymatic production of wax esters, key points to address were the evaluation of possibilities for use of a solvent-free process and of finding methods for achieving sufficiently high conversion levels to allow the product to be used with only a minimum of purification. From an economic point of view, the process had to be efficient enough to prevent the enzyme costs from becoming prohibitive. To this end, a particular process methodology was developed, one allowing four different wax esters to be produced enzymatically in a litre-scale reactor. Their properties as wood coating waxes were investigated by the industrial partners that participated.

Results and discussion

Choice of the solvent to be used in a process is a key issue, from a green chemistry perspective. Supercritical carbon dioxide and ionic liquids are often referred to as ''green solvents'', but use of a solvent-free process is the most attractive alternative. Solvent-free enzymatic esterification processes, having been thoroughly described previously, were a natural choice in the present study. The solvent-free synthesis of cetyl palmitate was performed in a 25 ml round-bottomed flask. Two different methods were used for monitoring the reaction, the one being analysis of cetyl alcohol by GC and the other titration of the acid groups. These methods produced similar results. A conversion of more than 98% of the cetyl alcohol was achieved.

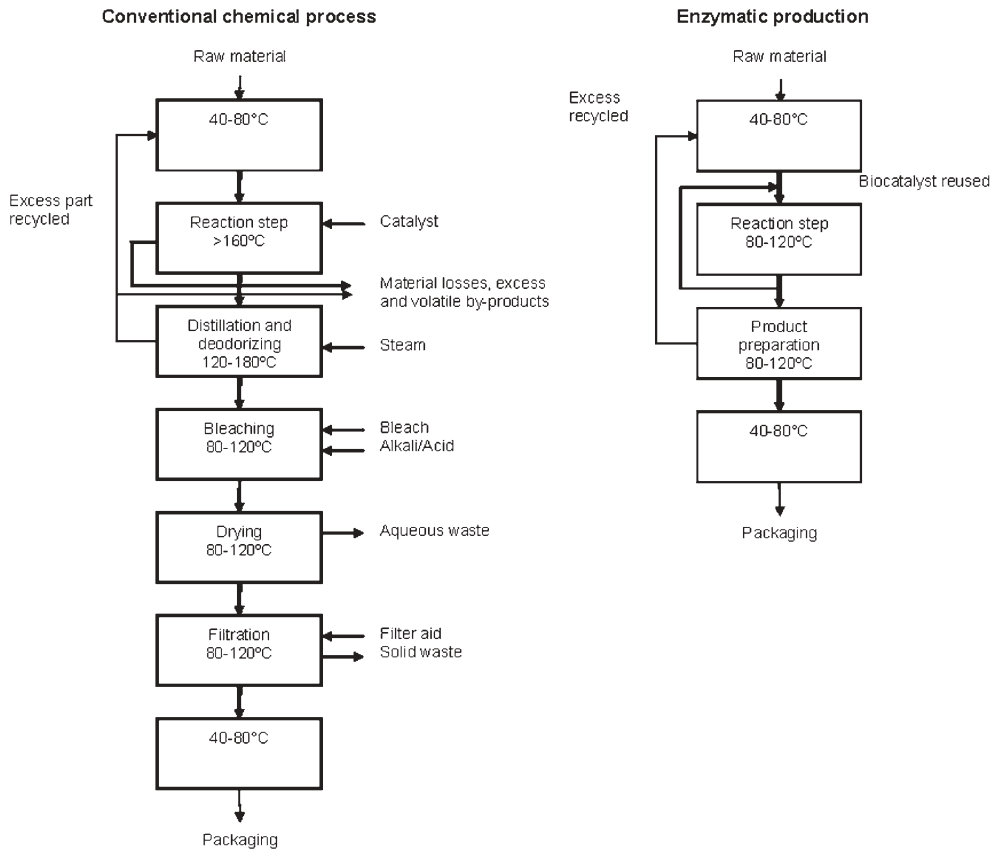

Fig. 2 Schematic diagrams of conventional chemical ester synthesis and the corresponding enzymatic process.[26]

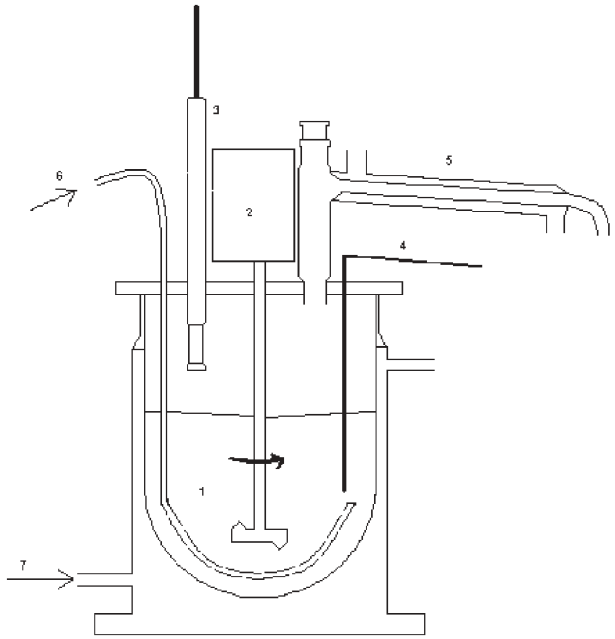

Fig. 3 Litre scale reactor for enzymatic esterification. 1—reaction liquid, 2—stirrer, 3—water activity sensor, 4—thermometer, 5—condenser, 6—dry air inlet, 7—heating medium, glycerol, inlet.

Since esterification reactions are reversible, it is advantageous, in order to achieve a high ester yield, that the reaction mixture contain as little water as possible. In concentrated systems, such as solvent-free reaction mixtures, water formed by the reaction should preferably be removed. Several means of water removal have been suggested, such as vacuum evaporation,[6] pervaporation,[7,8] addition of cation-exchange resins,[9] use of molecular sieves[10,11] and azeotropic distillation.[12] Some enzymes need a certain amount of water in order to display acceptable catalytic activity. In such cases, water removal at a fixed water activity (relative humidity) is better than extensive drying. Methods to control the water activity of the reaction mixture involve use of salt hydrate pairs[13–15] or saturated salt solutions, either for pre-equilibration[13,16] or for continuous control.[17–20] These alternatives have mainly been used in small-scale synthesis. Use of a vacuum for drying purposes has been studied extensively and is also applicable on a large scale. It has been shown that the water activity can be controlled by air-bleeding in a vacuum reactor,[6] although this method requires rather complicated equipment. A practical way of controlling the water activity in a reactor is to measure it continuously with a sensor and to adjust it to a set value by passing air (or nitrogen) through the reaction mixture. Dry air is used to remove water from the reactor and humid air to add it.[21–24] This can be carried out on a small and a large scale. If needed, the water activity can also be set at different values for separate stages of the reaction. A further advantage of this approach is that the gas bubbles produced improve the mixing in the reactor so that stirring can be reduced or even be avoided entirely, lowering the energy consumption.[22] This method has the drawback, however, that volatile substrates and products can be lost in the gas stream, although this is not of major concern when dealing with non-volatile substances, such as in the present study. For the synthesis of wax esters, a one litre reactor containing a water activity sensor and equipment for the automatic adjustment of water activity by use of dry or humid air was constructed (Fig. 3).

In the 25 ml-scale, removal of water occurred by simple evaporation to the surrounding air, but when the synthesis of cetyl palmitate was performed in the litre-scale reactor without any deliberate water removal, only ~65% conversion was obtained (Fig. 4). Thereafter, drying by the passing of dry air through the reactor was started and ~95% conversion was achieved. When the reaction mixture was dried by use of dry air from the start, almost complete conversion to cetyl palmitate was achieved (Fig. 5). Similar levels of conversion for this reaction have been reported using water activity adjustment involving the pumping of saturated salt solutions through silicone tubing in the reactor.[17] However, this method has certain drawbacks, such as the relatively slow transfer of

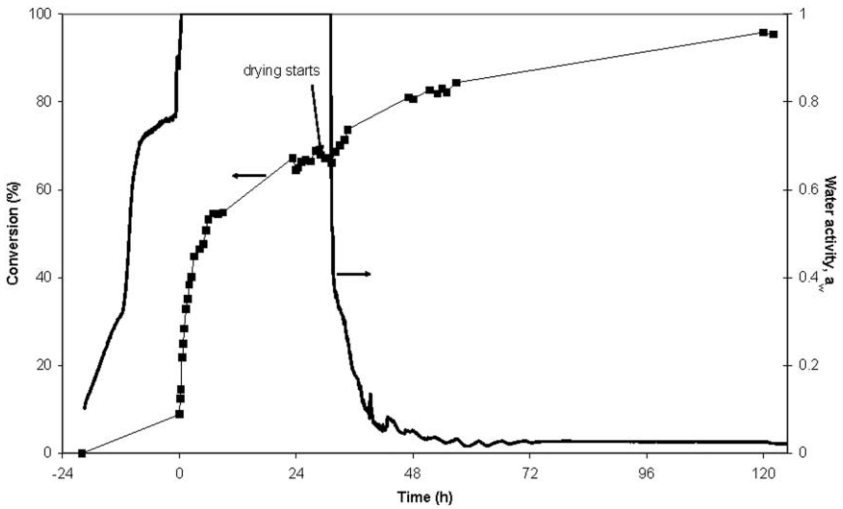

Fig. 4 Conversion (■) and water activity during the reaction of cetyl alcohol and palmitic acid 1 : 1, using Novozym® 435 as a catalyst, 0.5 g mol^{-1} substrate. The enzyme was added at time 0 and drying started after 29.5 h.

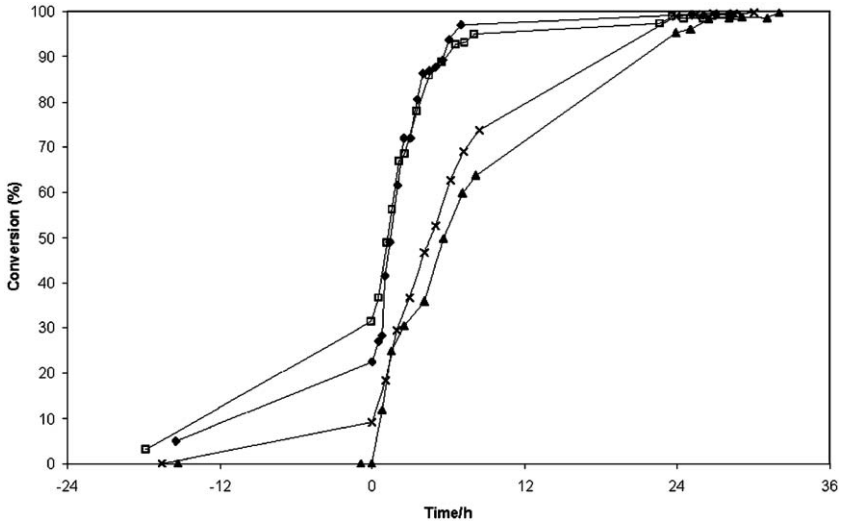

Fig. 5 Comparisons of the conversion levels achieved for the four wax esters produced: cetyl palmitate (◆), behenyl behenate (□), dibehenyl adipate (▲) and dibehenyl sebacate (×). The syntheses were performed using equimolar amounts of the reactive groups catalysed by Novozym® 435, 1 g mol^{-1} reactive group. The substrates were melted and dried before the enzyme was added at time 0. The reaction temperatures are listed in Table 2.

Table 1 Molecular formulae of the synthesised wax esters

Cetyl palmitate	$H_3C(CH_2)_{15}OOC(CH_2)_{14}CH_3$
Behenyl behenate	$H_3C(CH_2)_{21}OOC(CH_2)_{20}CH_3$
Dibehenyl adipate	$H_3C(CH_2)_{21}OOC(CH_2)_4COO(CH_2)_{21}CH_3$
Dibehenyl sebacate	$H_3C(CH_2)_{21}OOC(CH_2)_8COO(CH_2)_{21}CH_3$

water between the two phases and the limited suitability of it for large-scale processes.

Two monoesters, cetyl palmitate and behenyl behenate, and two diesters, dibehenyl adipate and dibehenyl sebacate, were produced (Tables 1 and 2) in the one litre reactor. The reaction temperatures were chosen so that all the substrates (monoester synthesis) or a major part of them (diester synthesis) were in liquid form. An increase in temperature leads to an increase in reaction rates, but also to an increase in enzyme inactivation rates as well as an increase of the energy consumption.

All four esters were synthesised at high conversions, see Table 2. In most cases, as can be seen in Fig. 4 and 5, some conversion could be observed before addition of enzyme, which could be explained by spontaneous esterification during the drying of the substrates. The various reactions differed in initial reaction rate after enzyme was added, as can be seen in Fig. 5. The initial reaction rate was highest for cetyl palmitate, despite this reaction being run at a lower temperature than the others. It has been shown earlier that between 65 and 75 °C the reaction rate for isopropyl palmitate synthesis increases with increasing temperature.[25] According to the manufacturer, the optimal temperature of this immobilised enzyme is 70–80 °C. The initial reaction rates for the monoesters were approximately twice as high as those for the diesters, dibehenyl adipate and dibehenyl sebacate. This might possibly be due to the fact that at the reaction temperature employed the diacids were not completely melted or dissolved initially. As the reactions proceeded, they dissolved, the reaction mixtures then becoming clear.

The energy requirements for the large-scale production of wax esters (25 tonnes annually) were estimated, both for batch and for continuous reactor systems using two different types of water removal systems: air-stripping or evaporation. In addition, estimates were made of the energy requirements of a conventional process. The results of the calculations on the best enzymatic and the conventional alternative are shown in detail in Table 3. The reactor system most similar to the reactor used in the laboratory-scale experiments described in the present study is a batch reactor employing air stripping. There are certain differences between the laboratory- and the large-scale systems, however, in large-scale production there are separate heating of the ingoing air and the reactor, and drying by heated air from the surroundings rather than by dried air and heat exchange between the in- and outgoing air. These differences contribute to increasing the energy efficiency of large-scale production.

Table 2 Concluding results from ester synthesis. Conversion results from titration. The initial reaction rate is based on mmol ester bonds formed

Ester	Temperature/°C	Initial reaction rate/mmol min^{-1} g^{-1}	Melting point product/°C	Final conversion of	
				alcohol (%)	acid (%)
Cetyl palmitate	65–67	3.4	50–51	98	99
Behenyl behenate	85–88	2.9	69–73	99	98
Dibehenyl adipate	90–93	1.4	70–73	99	99
Dibehenyl sebacate	88–90	1.4	71–74	95	99

Table 3 Comparison of the energy requirements for the best enzymatic method and for the conventional production method

Energy demand/MJ tonne^{-1}	Enzymatic	Conventional
Preheating	300	540
Heat losses from reactor	40	105
Air heating	55	n/a
Mixing and water removal	25	40
Heat demand for reactor	80	80
Total	500	765

The energy requirements for the large-scale reactor systems vary between 500 and 1500 MJ tonne^{-1}, the different batch reactors being the most efficient. On the basis of calculations concerning the best enzymatic process (batch reactor), the conventional method had an estimated energy requirement of 765 MJ tonne^{-1}, which is one and a half times that of the enzymatic process. The preheating of the substrates is the most energy-consuming step in the process, representing 60% (300 MJ tonne^{-1}) of the total energy requirement for the enzymatic process. For a chemical process conducted at 150 °C, the preheating step would require 70% (540 MJ tonne^{-1}) of the total energy requirements, which is 80% greater than for the enzymatic process. Several post-production steps are needed for the conventional method, although these have not been included in the calculations. Calculations performed by Hills[26] show that the chemical method, due to the higher temperature and the post-reaction purification steps, has energy requirements up to two and a half times as high as for enzymatic production.

Measurements of the litre-scale synthesis of wax esters indicate energy requirements of 125–160 GJ tonne^{-1} of the product, depending on the wax ester involved. The large difference as compared with the calculations for large-scale production (two orders of magnitude, in fact) clearly demonstrates the need of adequate insulation and energy recirculation for an acceptable level of energy efficiency to be achieved.

The large-scale enzymatic production of wax esters commercially is still under development, and there are only few companies utilising these reactions, Degussa being one. The enzymatic process has several advantages over the conventional chemical methods, which usually involve use of temperatures above 150 °C, the reaction thus being unselective and the waste and catalyst residues needing to be removed in post-reaction purification. According to Hills, the amount of waste (such as solvents, bleaching residues and by-products) generated in conventional chemical production is up to five times as high as in enzymatic production. In addition, for the chemical methods neutralisation of the acid, steam treatment for distillation, and both deodorizing and bleaching are needed, steps that involve use of a strong acid, and an alkaline or an acid, together with a catalyst. For the chemical method, drying of the product is also needed, as well as larger amounts of raw materials due to the unselectiveness of the process. During the post-reaction stages there is a loss in product yield as well, up to five percent according to Hills.[26] Martinez[27] has performed studies similar to Hills'. She has found that the enzymatic production of wax esters is more environmentally benign than the conventional chemical one. The lesser amount of refining needed also results in higher yield. Products made with use of such enzymatic reactions have a higher consumer appeal than those made using the conventional processes, due to the environmental benefits that result. The presented study yielded results similar to Hills' in showing energy use and waste to be less in the enzymatic processes.

Table 4 Evaluation of the use of wax esters as components in wood coatings, as performed by Akzo Nobel Industrial Coatings. Evaluation scale 1–5, 5 being the best

	Vaxoline	Cetyl palmitate	Behenyl behenate	Dibehenyl adipate	Dibehenyl sebacate
Performance in coating equipment	5	5	5	1	1
Water 16 h	5	4	4	n/a	n/a
Fat 6 h	5	2	3	n/a	n/a
Fat 24 h	4	1	2	n/a	n/a

The wax esters were emulsified in water using a surfactant, the emulsions being treated further to allow them to be used in industrial wood coating equipment. The monoesters cetyl palmitate and behenyl behenate behaved well in the wood coating equipment and produced waxy surfaces on pine wood, whereas the diesters formed precipitates in the coating equipment, making further evaluation of them impossible. Since the melting points of the diesters were only slightly higher than the melting point of the behenyl behenate, it was probably some other property of the diesters that caused this behaviour. The monoesters produced surfaces with good resistance to water, almost as good as the existing product, Vaxoline (Table 4). However, the resistance to fat achieved was relatively poor. In order to improve the fat resistance, it is likely that the size of the molecules needs to be increased. Work in this direction is continuing with polyesters. Additionally more additives may be needed to gain the desired properties. The wax esters produced in the study will be evaluated for other applications as well.

Experimental

Enzymatic solvent-free synthesis of wax esters

Chemicals and enzyme preparation

Cetyl alcohol (96%), palmitic acid (98%), adipic acid (>99%) and sebacic acid (>95%) were purchased from Sigma Aldrich. The following chemicals were generously donated by the companies referred to: behenyl alcohol (80–85%), Cognis (Boussens, France); behenic acid (85–90%), Croda Chemicals (East Yorkshire, England); Novozym® 435 (immobilised *Candida antarctica* lipase B), Novozymes A/S (Bagsværd, Denmark); glycerol, Karlshamns AB (Karlshamn, Sweden); and the surfactant, Bermodol 2525, Akzo Nobel Surfactants AB (Stenungsund, Sweden). All the other chemicals were of analytical grade.

Small-scale enzymatic synthesis of cetyl palmitate

Small scale synthesis of cetyl palmitate was performed at 65 °C in a three-necked round-bottomed flask. The alcohol and the acid were mixed in equimolar amounts and, when the

substrates had been melted, an immobilised enzyme, Novozym® 435, was added to start the reaction. During the reaction, water activity and temperature were measured in the air above the reaction liquid by a relative humidity sensor, Hygroflex 3 (Rotronic AG, Basseldorf, Germany). The reaction mixture was analysed by gas chromatography.

Litre-scale enzymatic synthesis of wax esters

Litre-scale synthesis of the wax esters was performed in a jacketed glass reactor using glycerol as the heating medium, see Fig. 3. The reaction was carried out at elevated temperatures, the exact temperature depending upon the product to be synthesised. To dry the reaction, air was bubbled through two gas-washing bottles containing blue silica gel, before it was sent to the reactor through small holes in narrow steel tubes. During the reaction, the water activity and the temperature were measured by a sensor, Hygroflex 3 (Rotronic AG, Basseldorf, Germany), which was present in the air above the reaction liquid. The reaction was followed by gas chromatography and/or titration of the remaining acid. Final samples were also analysed by titration of the hydroxyl groups. Following the reaction, the enzyme can be filtered from the product and be reused, approximately 5–6 times altogether.

Gas chromatography

Wax ester production was analysed by a gas chromatography device (GC-14A, Shimadzu Corp., Kyoto Japan) equipped with a flame-ionisation detector and a capillary column, DB5 (Supelco SPB5 15 m, 0.32 mm i.d., 25 μm film), purchased from Sigma Aldrich. Helium served as the carrier gas. The temperature of the injector and the detector was 350 °C. A temperature program between 225 °C and 320 °C was employed. Samples, taken by weight (20–90 mg), were diluted ($\times$1000) in cyclohexane:methyl ethyl ketone (11 : 1).

Titration of acid groups

A sample was dissolved in a cyclohexane : methyl ethyl ketone mixture (11 : 1), 20 drops phenolphthalein (1% in ethanol) being added. The solution was then titrated with a KOH solution in ethanol until a shift in colour was achieved. The amount of acid left was calculated in accordance with the equimolar relationship between the amount of potassium hydroxide added and the amount of acid in the sample.

Titration of hydroxyl groups

A sample was dissolved in 40 ml tetrahydrofuran, 10 ml of 4-dimethylaminopyridine solution (2.5% in acetone) being added, the mixture being stirred for one minute, and 2 ml of acetic acid anhydride solution (25% in methyl ethyl ketone) being added. The sample was stirred then for 5–10 min, after which 30 drops of phenolphthalein (1% in ethanol) were added. This solution was titrated with 1 M KOH in water until a colour shift was achieved. The amount of alcohol in the sample was calculated on the basis of the difference in the amount of potassium hydroxide between the sample and a blank, *i.e.* a titrated solution without the sample.

Emulsification of wax esters and application and evaluation as a wood coating ingredient

The coating in which the wax esters were tested is water based, with a dry content of approximately 20%. The commercial Vaxoline product contains an acrylate in combination with a wax emulsion, whereof approximately 40% of the dry weight is acrylate and the rest is wax. The wax ester tested was melted and 150 ml of it was mixed with 330 ml water and 20 ml Bermodol SPS 2525 using a homogeniser, Yellowline DI 25 basic, IKA (Staufen, Germany) to get an emulsion.

The wax ester emulsion was then mixed with small amounts of additives, and sprayed on solid glued samples of planed Scots pine, 8 $\times$ 200 $\times$ 250 mm in size. The emulsions were applied in one layer, 70 g m^{-2}, and then dried at 40 °C overnight.

Assessment of the surface resistance to water and paraffin oil (fat) was performed according to EN 12720 (European Standard EN 12720 (1997) Furniture—Assessment of surface resistance to cold liquids), a filter paper immersed in a liquid, being placed on the test surface and being covered by an inverted glass basin. After a specified period of time, the paper was removed and the surface was washed and dried. The surface was then examined for possible damages such as discolouration, change in gloss or colour, blistering *etc*. The assessment of the test results was performed in terms of a descriptive numerical rating code.

Energy analysis—a comparison between conventional chemical process and enzymatic production

The product investigated is a wax ester produced, in the first alternative, by conventional chemical method, and in the second alternative, by biocatalysis using enzymes.

Enzymatic process—biocatalytic synthesis of wax ester

Calculations for a large-scale production facility have been conducted for a total of six reactor systems, using air-stripping or evaporation for water removal. Heating of the reactor was achieved by circulating hot water in a mantle around the reactor and/or by preheating the air used for water removal. Both batch and continuously stirred tank reactors were evaluated. The calculations were based on suitable reactor volumes for an annual productivity of 25 tonnes, which were estimated to be 102 L for batch and 22 L for the continuous systems. For the reactor 20 mm of insulation was used and a heat exchanger was assumed for in- and outgoing air flows when applicable, with an efficiency of 83%. The efficiency of the air heating was assumed to be 90%. The ambient temperature was assumed to be 20 °C in all cases. In addition to the calculations on large-scale processes, measurements were made on the energy requirements for the litre-scale lab reactor. For a more detailed description of the system see Table 5. To calculate the energy needed to heat the substrates to the reaction temperature, literature data and models for c_p-values and ΔH_{fus} were used.

Conventional chemical process

Calculations for the conventional process have been made for the preheating step in the same way as for the enzymatic

Table 5 Details of the large-scale reactor systems used in the energy calculations

	Batch			Continuous		
Mode of operation	Air stripping and water heating	Air stripping only	Evaporation and water heating	Air stripping and water heating	Air stripping only	Evaporation and water heating
Height of reactor/m	1.13	1.13	0.71	0.68	0.68	0.206
Diameter/m	0.34	0.34	0.43	0.21	0.21	0.371
Height of liquid/m	1.02	1.02	0.64	0.612	0.612	0.185
Volume of reactor/L	102.2	102.2	102.2	22.2	22.2	22.2
Insulation/m	0.02	0.02	0.02	0.02	0.02	0.02
Heat exchanger area/m^2	4.4	4.0	n/a	5.2	5.2	n/a
Air flow/L min^{-1}	963	963	n/a	1262	1262	n/a
Temperature of ingoing air/°C	70	85	n/a	70	85	n/a

process using literature data for c_p-values.. An estimation of the energy requirements for a conventional process has been made using the data from the calculations for the enzymatic reactor, using a reaction temperature of 150 °C.

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An imidazolinium salt as ionic liquid for medium and strong bases

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An imidazolinium salt incorporating a phenyl ring at the C-2 position has been found to be an ionic liquid suitable as a solvent for reactions involving medium and strong bases like quinuclidine and Grignard reagents.

Introduction

Ionic liquids, having by definition a melting point below 100 °C, and especially room temperature ionic liquids (RTIL) have attracted much interest in recent years as novel solvents for reactions and electrochemical processes.[1] They are considered to be "green solvents".[2] The scope of ionic liquids based on various combinations of cations and anions has dramatically increased and new salts[3–5] and solvent mixtures[6] are continually being discovered. The most commonly used liquids are based on imidazolium cations like [BMIM] (1-butyl-3-methylimidazolium) with an appropriate counter anion.

However, it has been observed that imidazolium salts, incorporating a hydrogen substituent at the C-2 position, are, in some applications where bases are involved, deprotonated. The corresponding carbenes are formed, which can cause undesired side reactions,[7] such as in the case of the Baylis–Hillman reaction.[8] Nevertheless, there are also cases where this behavior has a positive effect. In reactions where metals are used as catalysts the carbenes formed are acting as ligands and stabilizing the metal catalyst, *e.g.*, in the Suzuki reaction.[9,10] The undesired deprotonation has been partly overcome by the application of imidazolium salts with a methyl group at the C-2 position, *e.g.*, [BDMIM][PF_6] (1-butyl-2,3-dimethylimidazolium) in a Baylis–Hillman reaction.[11] Recently, it has been shown that also the C-2 methyl group of these cations can be deprotonated under mild conditions,[12] which would make these cations unsuitable for reactions involving strong bases. Therefore, Clyburne and co-workers showed for the first time that an ionic liquid, based on a phosphonium salt, can be used in reactions involving highly basic organometallic reagents giving good GC yields.[13]

Here we would like to present a second possible alternative salt for reactions involving strong bases. The novel salt can be easily prepared on a large scale from commercially available sources. During our investigation of imidazolinium salts[14] we found that some of these salts qualify as novel ionic liquids. To the best of our knowledge imidazolinium based ionic liquids with a phenyl substituent at the C-2 carbon have not been used as solvents in reactions so far. Therefore, we would like to present here an example of this new type of ionic liquid salt and its application in reactions involving medium and strong bases.

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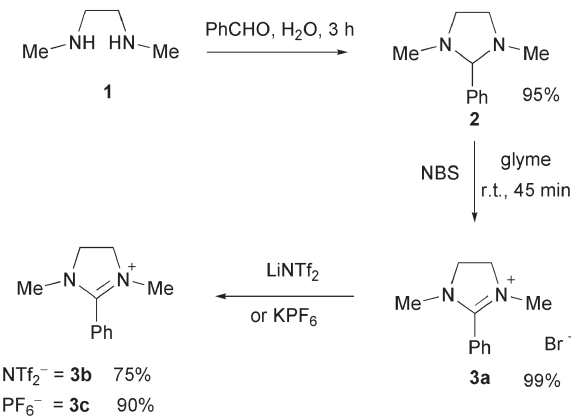
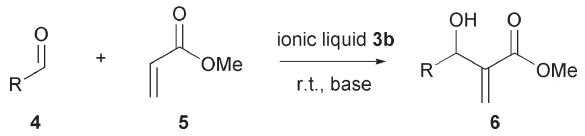
Results and discussion

In order to prepare the salt (Scheme 1), aminal **2** was synthesised according to a literature procedure from diamine **1** and benzaldehyde (**4a**) in water in 95% yield.[15] Compound **2** was oxidised with NBS to the corresponding imidazolinium bromide salt **3a** in 99% yield. Comparatively cheap NBS was chosen as the oxidation reagent instead of NBA (*N*-bromoacetamide), which is often the superior reagent since the product can be purified more easily. Nevertheless, no contamination by succinamide could be detected in the final product. **3a** was hygroscopic and was transformed into the salts **3b** and **3c** by vigorously stirring in the presence of $LiNTf_2$ or KPF_6 in a mixture of water and chloroform for 1 hour. After the aqueous phase had been removed, the chloroform phase was washed three times with water and dried over molecular sieves to furnish the salts **3b** and **3c** in 75% and 90% yield, respectively. The new salts were not hygroscopic. In one run 15 g of salt **3b** was prepared. In the procedure, chloroform can also be replaced with ethyl acetate without decreasing the yield and purity of the product. While **3c** had a melting point of 105 °C, the salt **3b** was a liquid at room temperature. The water content of **3b** was 0.065%, while the bromide impurity was 0.13%, which is comparable with commercially available ionic liquids. Spectral NMR data and CHN analysis demonstrated the purity of the salt. Only after some days did it



Scheme 1



Scheme 2

Table 1 Baylis–Hillman reaction with methyl acrylate[a]

Run	Aldehyde	Base	Time[b]/h	Product	Yield[c] (%)
1	R = Ph, **4a**	DABCO[d]	72	**6a**	53
2	**4a**	Quinuclidinol[d]	24	**6a**	41
3	**4a**	Quinuclidine[d]	48	**6a**	66
4	R = 4-Cl-C_6H_4, **4b**	Quinuclidinol[d]	48	**6b**	52
5	**4b**	Quinuclidine[d]	48	**6b**	66
6	R = 2-C_5H_4N, **4c**	Quinuclidine[d]	48	**6c**	69
7	R = 4-MeO-C_6H_4, **4d**	Quinuclidine[d]	48	**6d**	38
8	R = $PhCH_2CH_2$, **4e**	Quinuclidine[d]	48	**6e**	44
9	**4a**	Quinuclidine[e]	48	**6a**	52
10	**4b**	Quinuclidine[e]	48	**6b**	52
11	**4a**	Quinuclidine[f]	48	**6a**	Traces
12	**4a**	—	48	**6a**	0

[a] 1 equiv. **4**, 1.5 equiv **5**, **3b** (0.4 mL); for a complete procedure see experimental section. [b] Reaction times were not optimised. [c] Isolated yields after column chromatography. [d] 1 equiv. [e] 10 mol%. [f] 1 mol%.

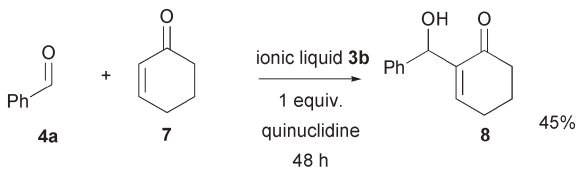
crystallize and a melting point of 35 °C was detected. Prior to use it was melted and it remained a liquid for several hours at room temperature. In the reaction mixture it remained permanently a liquid.

First, salt **3b** was tested as a solvent in the Baylis–Hillman reaction with methyl acrylate (**5**) and various aldehydes (Scheme 2). The results are shown in Table 1. When 1 equiv. of DABCO was used as a catalyst, benzaldehyde (**4a**) and methyl acrylate (**5**) formed the desired product **6a** in 53% yield after 72 h (Table 1, Run 1). Switching to quinuclidinol, the product **6a** was isolated at 52% yield after 24 h, while use of quinuclidine led, in 48 h, to a yield of 66% (Table 1, Runs 2 and 3). With the electron deficient 4-chlorobenzaldehyde (**4b**) and quinuclidinol a yield of 52% after 48 h was achieved, while with quinuclidine 66% was isolated (Table 1 Runs 4 and 5). 2-Pyridinecarbaldehyde (**4c**) gave a yield of 69% after 48 h (Table 1, Run 6). With the electron rich 4-methoxybenzaldehyde (**4c**) and quinuclidine, a yield of 38% was found (Table 1, Run 6). The aliphatic aldehyde, 3-phenylpropionaldehyde (**4d**), gave a yield of 44%. A repeat of the reaction with benzaldehyde and only 10 mol% of quinuclidine gave a slightly lower yield of 52% compared with 1 equiv. of the base (Table 1, Run 9). Aldehyde **4b** yielded, with 10 mol% quinuclidine, the product **6b** at 52% (Table 1, Run 10). However, when only 1 mol% of quinuclidine was used, just traces of the product were isolated after 48 h (Table 1, Run 11). In a control reaction with the absence of base, no product formation could be detected (Table 1, Run 12). The reaction times were not optimized and before the workup, unreacted starting material was still present in the reaction mixture. The ionic liquid was recovered in 93% yield and could be re-used after the work up with no changes in the reactivity: NMR data proved the purity of **3b**. Use of this recovered ionic liquid led to the same yield in the reaction of **4a** with **5**.

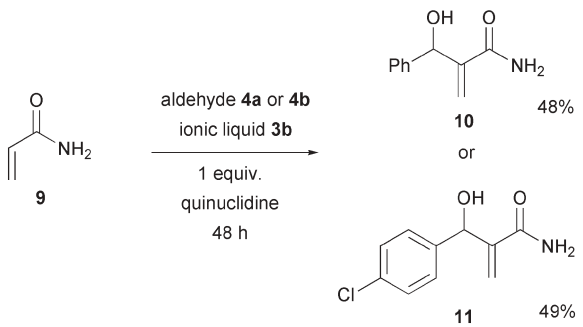
In addition, 2-cyclohexen-1-one (**7**) was applied in a reaction with benzaldehyde (**4a**) in the ionic liquid **3b** with quinuclidine and product **8** was isolated in 45% yield after 48 h (Scheme 3).

Moreover, the behaviour of acrylamide (**9**), which is best soluble in polar solvents, was tested in the reaction as shown in Scheme 4. When acrylamide (**9**) was treated in the ionic liquid **3b** with 1 equiv. of quinuclidine and benzaldehyde (**4a**) the product **10** was isolated in 48% yield after 48 h. The application of 4-chlorobenzaldehyde (**4b**) in the reaction led to the isolated product **11** in 48% yield. The last case is an example in which all reactants were solids, and were all dissolved in the ionic liquid.

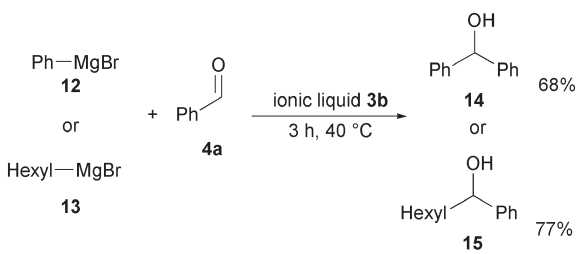
Next, we were interested to see if **3b** would be also suitable as a solvent in reactions involving Grignard reagents, as shown in Scheme 5. Therefore, 3 equiv. of **12** or **13** were placed in a dry vessel and the solvents were evaporated under high vacuum. 2 equiv. of **3b** (0.6 mL) were added in each case and it was observed that the Grignard reagents were dissolved in the ionic liquid. 1 equiv. of benzaldehyde was added and after 3 h at 40 °C, the desired products **14** and **15** were isolated at 68% and 77%, respectively. The ionic liquid was recovered after the workup in 93% yield and NMR data proved the purity of the recovered compound. The reaction temperature of 40 °C was chosen to compare with the standard procedure of adding Grignard reagents to aldehydes in refluxing diethyl ether.[16,17] When recovered ionic liquid was used in the



Scheme 3



Scheme 4



Scheme 5

Grignard reactions, the same yields were obtained with **12** and **13**. During the work up, a triphasic system (hexane, water, ionic liquid) was observed. When **12** was replaced with phenyl lithium, a complex mixture was isolated and no product was detected.

In order to prove the absence of any possible deprotonation in the ionic liquid **3b**, the reaction was repeated with **13**, lacking the addition of benzaldehyde, and after 1 h the mixture was quenched with deuterium oxide. A ^{1}H-NMR spectrum proved the absence of a possible deprotonation. In a second run **13** was replaced with LDA, which led to a complex mixture of compounds.

Conclusions

In conclusion, we have presented a novel ionic liquid based on a 1,3-dimethyl-2-phenylimidazolinium cation. The salt can be used in reactions involving strong bases. The preparation of analogues of these cations should be easy in order to tune the behaviour of these salts, including chiral analogues. A few limits for the ionic liquid in some other applications may be possible. The ionic liquid presented starts to degrade at −1 V measured against ferrocene/ferrocinium, which makes it less suitable for electrochemical applications.[18] Due to the incorporation of an arene ring in the salt, its use in aromatic nitrations[19] might be limited.

Experimental

General experimental

DABCO was purchased from Merck and was used without further purification. Quinuclidine and quinuclidinol were purchased from Fluka and used without further purification. Anhydrous glyme, $LiN(CF_3SO_2)_2$, hexylmagnesium bromide (2 M solution in Et_2O) and phenylmagnesium bromide (1 M solution in THF) were purchased from Aldrich. Benzaldehyde was distilled prior to use. All other reagents were purchased from commercial sources and used without further purification.

Chromatography was performed on a Buechi Sepacore system, using unmodified silica gel as a stationary phase. All reactions were monitored by TLC with Merck Silica gel 60 F_{254} plates. Elemental analyses were carried out by the Microanalytical Laboratory of the Institut für Pharmazeutische Chemie der Universität Braunschweig. Infrared spectra were recorded on a PerkinElmer 2000 FT-IR System. NMR spectra were performed at ambient temperature on a Bruker AC 200F. Mass spectra were recorded on Hewlett–Packard 5898B (at 70 eV). Melting points were taken with an apparatus after the design of Dr. Tottoli and are uncorrected. Water content was determined *via* the Karl Fischer method and bromide content *via* anion chromatography. The two measurements were carried out by the company IoLiTec.

1,3-Dimethyl-2-phenylimidazolidine (2). *N,N*-Dimethylethylenediamine (**1**) (4.15 g, 46.16 mmol) and benzaldehyde (**4a**) (4.90 g, 4.67 mL, 46.16 mmol) were added to a reaction flask filled with water (60 mL). The reaction mixture was vigorously stirred at r.t. for 3 h. The mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was distilled off under reduced pressure and the crude product was distilled under reduced pressure, giving the 1,3-dimethyl-2-phenylimidazolidine (**2**) as a colorless liquid (7.71 g, 95%). Spectral data were consistent with literature values.[20]

1,3-Dimethyl-2-phenylimidazolinium bromide (3a). 1,3-Dimethyl-2-phenylimidazolidine (**2**) (7.71 g, 43.74 mmol) was dissolved in glyme (40 mL) and NBS (7.79 g, 43.74 mmol) was added in two portions with an interval of 15 min. An exothermic reaction was observed. After addition of the second portion, the reaction mixture was stirred at r.t. for 30 min and then Et_2O (50 mL) was added in order to precipitate the bromide salt. The solvent was decanted and the oily product was washed with Et_2O (20 mL). The salt was dried *in vacuo*, giving the 1,3-dimethyl-2-phenylimidazolinium bromide (**3a**) as a yellow oil (11.15 g, 99%). This was used directly in the subsequent step. Hygroscopic. ESI-MS: *m/z* 175.1 (cation); IR(KBr) 3417 s, 1710 s, 1616 vs, 1576 m, 1353 m, 1302 m, 1183s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) 7.80–7.60 (m, 5 H), 4.32 (s, 4 H), 3.06 (s, 6 H); ^{13}C-NMR (50 MHz, $CDCl_3$) 166.3 (C-2), 132.7, 129.7, 128.7, 121.7, 50.8, 35.0.

1,3-Dimethyl-2-phenylimidazolinium bis(trifluoromethyl-sulfonyl)imide (3b). 1,3-Dimethyl-2-phenylimidazolinium bromide (**3a**) (11.16 g, 43.74 mmol) was dissolved in $CHCl_3$ (10 mL) and it was vigorously stirred with a solution of $LiNTf_2$ (13.81 g, 48.11 mmol) in water (10 mL) for 1 h. The organic layer was washed with a saturated solution of $Na_2S_2O_3$ (20 mL), water (3 × 20 mL) and dried over molar sieves (3Å). The solvent was evaporated, giving the 1,3-dimethyl-2-(phenyl)imidazolinium bis(trifluoromethyl-sulfonyl)imide (**3b**) as a colourless liquid (15 g, 75%) which solidified after a couple of days. m.p. 35 °C; ESI-MS: *m/z* 175.1 (cation); IR (KBr) 1623s, 1578s, 1357vs, 1180vs, 1051vs, 773s, 707s, 614vs 570s, 516s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) 7.61–7.49 (m, 5 H, H-Ar), 4.11 (s, 4 H, CH_2–CH_2), 2.96 (s, 6 H, H-Me); ^{13}C-NMR (50 MHz, $CDCl_3$) 166.3, 133.0, 129.8, 128.3, 121.4, 119.9 (q, J = 319.3 Hz), 50.1, 34.5. Formula mass 455.39. Calculated for $C_{13}H_{15}F_6N_3O_4S_2$: C, 34.29; H, 3.32; N, 9.23%; found: C, 34.26, N, 9.14, H, 3.40%. The water content of **3b** was 0.065%, while the bromide impurity was 0.13%.

1,3-Dimethyl-2-phenylimidazolinium hexafluorophosphate (3c). 1,3-Dimethyl-2-(phenyl)imidazolinium bromide (**3a**) (4.27 g, 16.72 mmol) was dissolved in $CHCl_3$ (10 mL) and vigorously stirred with a solution of KPF_6 (3.10 g, 16.72 mmol) in water (5 mL) for 1 h. The organic layer was washed with a saturated solution of $Na_2S_2O_3$ (10 mL), water (3 × 10 mL) and dried over molar sieves (3 Å). The solvent was evaporated, giving the 1,3-dimethyl-2-phenylimidazolinium hexafluorophosphate (**3c**) as a white solid (2.16 g, 90%). m.p. 105 °C; ESI-MS: *m/z* 175.1 (cation); IR (KBr) 3426s, 1623s, 835vs, 557s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) 7.70–8.40 (m, 5 H), 4.03 (s, 4 H), 2.86 (s, 6 H); ^{13}C-NMR (50 MHz, $CDCl_3$) 165.1, 131.8, 128.8, 127.3, 120.8, 49.1, 33.4.

General procedure for Baylis–Hillman reaction in ionic liquid. The amine catalyst (1 mmol) was placed in a dry Schlenk flask and ionic liquid **3b** (400 μL, *ca*. 600 mg) was added. An aldehyde (1 mmol) and methyl acrylate (**5**) (135 μL, 1.5 mmol, 1.5 equiv.) were added sequentially. The reaction was stirred at r.t. for 48 h. The reaction mixture was extracted with Et_2O (4 × 5 mL) and the combined ether fractions were evaporated. The crude product was purified by FCC (petrol ether/ethyl acetate, 95/5), giving the desired product.

Regeneration of ionic liquid. The remaining ionic liquid after the extraction was dissolved in $CHCl_3$ (5 mL), washed with 0.5 M HCl (5 mL), water (3 × 5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The ionic liquid was further dried *in vacuo*, giving 1,3-dimethyl-2-(phenyl)-imidazolinium bis(trifluoromethylsulfonyl)imide (**3b**) (470 mg, 78%), The NMR data were identical with the reference sample **3b**. Additional ionic liquid (80 mg, 15%) was obtained from the flash column chromatography by elution with DCM–MeOH (95/5) after separating the Baylis–Hillman product.

Methyl 2-[hydroxy(phenyl)methyl]acrylate (6a). From benzaldehyde (**4a**) (102 μL, 1 mmol), methyl acrylate (**5**) (135 μL, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as colorless oil (127 mg, 66%). Spectral data were consistent with literature values.[21]

Methyl 2-[(4-chlorophenyl)(hydroxy)methyl]acrylate (6b). From 4-chlorobenzaldehyde (**4b**) (145 mg, 1 mmol), methyl acrylate (**5**) (135 μL, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as colorless oil (127 mg, 66%). Spectral data were consistent with literature values.[22]

Methyl 2-[hydroxy(pyridin-2-yl)methyl]acrylate (6c). From 2-pyridinecarbaldehyde (**4c**) (96 μL, 1 mmol), methyl acrylate (**5**) (135 μL, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as colorless oil (133 mg, 69%). Spectral data were consistent with literature values.[23]

Methyl 2-[(4-methoxyphenyl)(hydroxy)methyl]acrylate (6d). From 4-methoxybenzaldehyde (**4d**) (122 μL, 1 mmol), methyl acrylate (**5**) (135 μL, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as colorless oil (84 mg, 38%). Spectral data were consistent with literature values.[21]

Methyl 3-hydroxy-2-methylene-5-phenylpentanoate (6e). From phenylpropionaldehyde (**4e**) (137 μL, 1 mmol), methyl acrylate (**5**) (135 μL, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as colorless oil (97 mg, 44%). Spectral data were consistent with literature values.[24]

2-[Hydroxy(phenyl)methyl]cyclohex-2-enone (8). From benzaldehyde (**4a**) (102 μL, 1 mmol), 1-cyclohexen-2-one (**7**) (147 μL, 1.5 mmol), ionic liquid **3b** (400 μL) and quinuclidine (115 mg, 1 mmol) as colorless oil (92 mg, 46%). Spectral data were consistent with literature values.[25]

2-[Hydroxy(phenyl)methyl]acrylamide (10). From benzaldehyde (**4a**) (102 μL, 1 mmol), acrylamide (**9**) (106 mg, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as a white solid (85 mg, 48%). Spectral data were consistent with literature values.[26]

2-[(4-Chlorophenyl)(hydroxy)methyl]acrylamide (11). From 4-chlorobenzaldehyde (**4b**) (145 mg, 1 mmol) and acrylamide (**9**) (106 mg, 1.5 mmol) and quinuclidine (115 mg, 1 mmol) in ionic liquid **3b** (400 μL) as a white solid (105 mg, 49%). m.p. 111–112 °C, MS (EI), *m*/*z* 210 ($M^+ - H$, 40%), 166 (40), 139 (95), 77 (100), 71 (50), 55 (60); IR (KBr) 3385vs, 3189s, 1658vs, 1624s, 1604s, 1491m, 1198m, 606m cm^{-1}; ^{1}H-NMR (200 MHz, DMSO) 7.47 (s, 1 H) 7.39–7.28 (m, 4 H, H-Ar), 7.01 (s, 1 H), 5.82–5.77 (m, 2 H), 5.62–5.60 (m, 1 H), 5.50–5.48 (m, 1 H); ^{13}C-NMR (50 MHz, DMSO) 168.4, 147.0, 142.3, 131.4, 128.5, 127.8, 117.5, 70.3; HRMS (EI) calculated for $C_{10}H_{10}NO_2ClNa$ 234.0297, found 234.0292.

General procedure for Grignard addition to carbonyl compound in ionic liquid. Commercially available Grignard compound (phenylmagnesium bromide (1 M in THF) or hexylmagnesium bromide (2 M in Et_2O) (3 mmol) was placed in a dry Schlenk flask under nitrogen and the solvent was removed *in vacuo*. Ionic liquid **3b** (600 mL, *ca*. 900 mg) was added and the reaction mixture formed a clear solution. Benzaldehyde (101 μL, 1 mmol) was added at once. The reaction mixture warmed up spontaneously. After the exothermic reaction ended, the reaction mixture was heated up to 40 °C for 3 h. The reaction mixture was quenched with saturated solution of NH_4Cl and extracted with hexane (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was distilled off under reduced pressure. The crude product was purified by FCC (petroleum ether–ethyl acetate, 95/5), giving the corresponding alcohol.

Regeneration of ionic liquid. The ionic liquid remained after extraction with hexane as a phase below the aqueous phase. It was dissolved in $CHCl_3$ (5 mL), washed with water (3 × 5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the ionic liquid was further dried *in vacuo*, giving 1,3-dimethyl-2-phenylimidazolinium bis(trifluoromethylsulfonyl)imide (**3b**) (837 mg, 93%), NMR data were identical with the reference sample **3b**.

Diphenylmethanol (14). From phenylmagnesium bromide (**12**) (3 ml 1 M THF solution, 3 mmol) and benzaldehyde (**4a**) (102 μL, 1 mmol) in ionic liquid **3b** (600 μL) as a white solid (125 mg, 68%). Spectral data were consistent with literature values.[27]

1-Phenylheptan-1-ol (15). From hexylmagnesium bromide (**13**) (1.5 mL 2 M Et_2O solution, 3 mmol) and benzaldehyde (**4a**) (102 μL, 1 mmol) in ionic liquid **3b** (600 μL) as a colorless oil (150 mg, 77%). Spectral data were consistent with literature values.[28]

Deuterium exchange experiment using ionic liquid and hexylmagnesium bromide. Hexylmagnesium bromide (**13**) (1 mL, 2 mmol) was placed in a Schlenk flask and the solvent was evaporated *in vacuo*. Ionic liquid **3b** (300 mg, 0.75 mmol)

was added and the reaction mixture stirred at 40 °C for 1 hour before being quenched by addition of D_2O. The ionic liquid was separated from the aqueous phase and dissolved in $CHCl_3$. The organic phase was washed with water (3 × 3 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The ionic liquid was dried *in vacuo*. ^{1}H-NMR was recorded and shown to be identical with the original sample of **3b**.

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The improved synthesis of carbonated soybean oil using supercritical carbon dioxide at a reduced reaction time†‡

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We have demonstrated an improved synthesis of a cyclic carbonate of soybean oil (CSO) utilizing supercritical carbon dioxide (CO_2) as the solvent. Because the mutual solubility of supercritical CO_2 and soybean oil is significantly higher than that of gaseous CO_2 and soybean oil, our method synthesizes the material in ~1/3 of the reaction time reported in the literature. We have also demonstrated a catalyst removal method for our system based on the simple Hofmann elimination reaction, reducing the need for organic solvent extraction. CSO is a potential petroleum replacement, and may be useful in the synthesis of polymers based on bio-resources.

Introduction

As petroleum prices surge to ~$70/barrel,[1,2] the use of bio-based alternatives continues to be necessary for both economic and environmental reasons. Energy absorbing materials from soybean oil are one area of high specific interest.[3,4] Bio-based polyurethane foams have been developed with mechanical and thermoinsulating properties comparable to foams of petrochemical origin.[5–8] These polymers are synthesized from soy based polyols and various di-isocyanates. One problem with these polymers is in making sure the di-isocyanate reacts completely as any unreacted isocyanate left in the polymer will react with ambient humidity and form voids in the material, reducing strength.[8] The alternative synthesis using a carbonate pathway avoids this disadvantage.

There are several methods to prepare carbonates, with one of the most attractive being the catalyzed reaction between carbon dioxide (CO_2) and an epoxide. Using this reaction, polycarbonates have been formed from small epoxides such as propylene oxide[9–11] and cyclohexene oxide.[11] Carbonates of oleochemical origin were patented as a plasticizing agent[12] and reported as a therapeutic agent[13] more than 30 years ago. Older synthetic methods required environmentally unfriendly solvents and phosgene as a reactant. Recently, there has been renewed interest in a more environmentally friendly synthesis of carbonates[14–16] brought on by a variety of new applications. Carbonates have physical and chemical properties which make them useful in the personal care, lubricant, fuel additive, and chemical feedstock industries.[17] Shorter chain linear carbonates are useful as emollients,[14] where longer chain carbonates have been used as lubricants, plasticizers, and fuel additives.[15,18] The cyclic carbonate, glycerol carbonate, has also found use as a highly polar solvent.[14,18]

Conversion of various triglycerides and fatty acids to epoxides was reported by Swern ~60 years ago.[19,20] Processes based on this reaction have been studied,[21,22] improved[23,24] and patented over the years,[25–28] to the point where epoxidized soybean oil (ESO) is now available commercially. Other useful vegetable oil monomers have also been synthesized through an epoxide route.[29–31] Following the epoxidation reaction, it is possible to form a cyclic carbonate with the addition of CO_2 and halide catalyst (Scheme 1).

The synthesis of carbonated soybean oil (CSO) has been reported by Tamami and co-workers, where they used CSO in the synthesis of polyurethanes.[32,33] However, CSO could also be used as a synthetic building block for other products as well, including possible bio-based polyesters which may show better bio-degradation behavior than the polyurethane systems.[34] The longest step in Tamami's synthesis is the conversion of ESO to CSO with a reported conversion of 94% after 70 h. The reaction time in this step needs to be shortened for these materials to be commercially viable. Additionally, the catalyst is removed using an extraction method involving ethyl acetate. Herein we report that the synthesis of CSO can be accomplished in ~1/3 of the time reported in the literature by the use of supercritical CO_2. Further, we report two simple methods for catalyst removal which do not require organic solvent.

Results and discussion

Carbonation of epoxidized soybean oil in supercritical CO_2

We synthesized CSO by reacting ESO with supercritical CO_2 at 100 °C with 5% (mol percent per oxirane moiety) catalyst. The reaction was run under 10.3 MPa of CO_2 for a variety of reaction times. The reaction was also attempted at 35 °C, however, no detectable reaction was observed at that temperature. The product from each of the successful reactions was studied by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy

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† Electronic supplementary information (ESI) available: Section S-1: The NMR data for carbonated soybean oil. Section S-2: A plot to obtain the apparent 1st order kinetic rate constant. See DOI: 10.1039/b511014a

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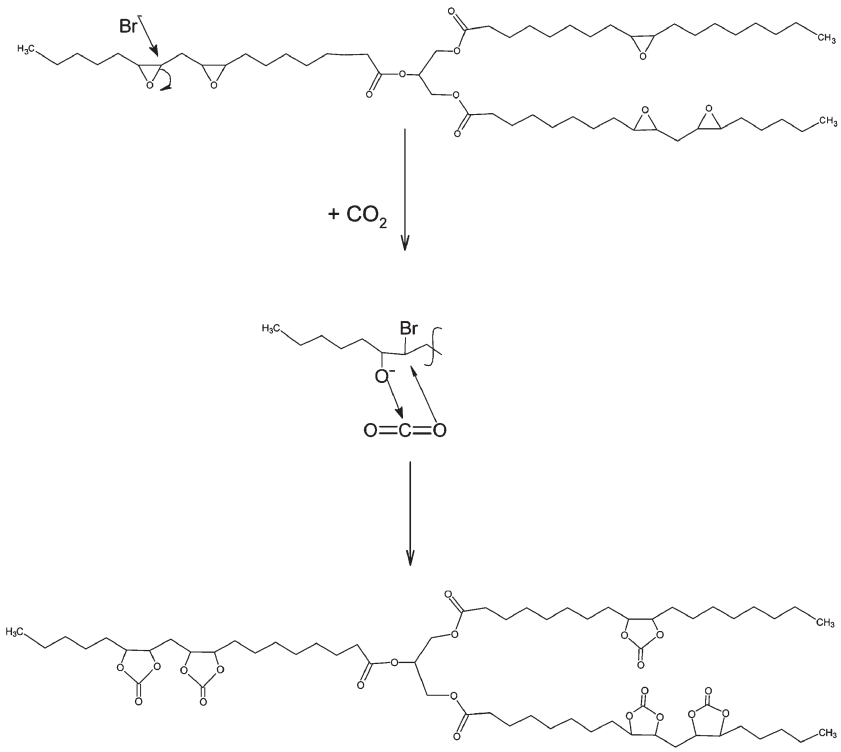


Scheme 1 The TBA^+Br^- catalyzed reaction on epoxidized soybean oil (ESO) to form carbonated soybean oil (CSO). There are an average of 4.2 oxirane moieties on each triglyceride.

(see ESI† Section S1), viscometry and thermogravometric analysis (TGA).

Infrared spectra

The reaction products of the reaction at different reaction times were studied by IR spectroscopy. The IR spectra (Fig. 1) clearly show the conversion of ESO to CSO. The appearance of an additional band in the carbonyl region at 1793 cm^{-1} (C=O stretch) was the most apparent. It was larger than the carbonyl band associated with the triglyceride backbone as expected for the epoxy material with ~4.2 epoxides per triglyceride. Also present is a new peak at 1047 cm^{-1} (C–O). The loss of epoxide bands at 823 cm^{-1} and 842 cm^{-1} indicates the consumption of the oxirane further confirming reaction. The inherent weakness of these epoxide bands does somewhat limit quantitation, so ^1H NMR and ^{13}C NMR spectroscopies were also used. Both the ^1H NMR and ^{13}C NMR spectra (see ESI† Section S1) show the conversion to the expected product in the 40 hour reaction time and about 82% conversion in the 10 h reaction sample.

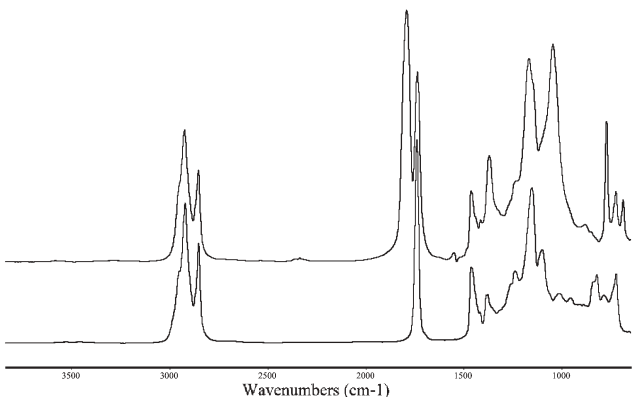


Fig. 1 The IR spectra of epoxidized soybean oil (ESO, lower spectrum) and carbonated soybean oil (CSO, upper spectrum). The disappearance of the spectroscopic peaks at 842–822 cm^{-1} shows the reaction progress. A new infrared spectroscopic peak at 1793 cm^{-1} shows the conversion to the carbonated product.

Viscosity and gel permeation chromatography

The viscosity of the product was also studied. The materials synthesized ranged from a moderately viscous light brown oil to a darker brown very viscous and sticky material. This is consistent with the literature reports of this compound (Table 1).[33] However, to investigate the high viscosity, we ran solution gel permeation chromatography (GPC) of the product (Fig. 2). The resultant Mw (Table 1) was within error of the expected value of ~1123 Daltons. The highest concentration of any higher Mw material was only 2.5%.

Table 1 The measured extent of reaction, viscosity, and Mw of the carbonation reaction of ESO in supercritical CO_2 catalyzed by 5 mol% TBA^+Br^- catalyst at 100 °C

Reaction time/h	% Reaction by ^1H NMR	Viscosity/Pa s−	Mw by GPC
0	0	0.396 ± 0.007	868
10	82	69.6 ± 6.9	1180
20	94	144.8 ± 6.8	1255
40	100	169.6 ± 12.0	1274

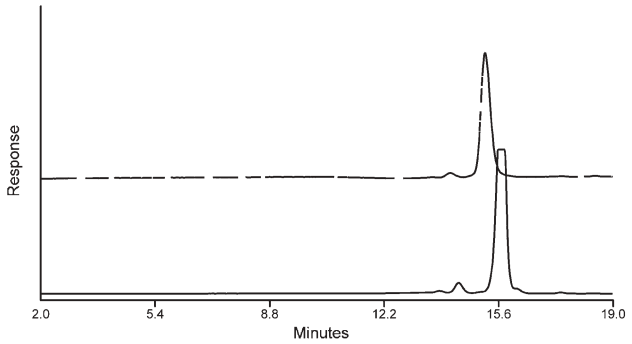


Fig. 2 The GPC analysis of CSO (top) and ESO (bottom). The GPC show that there is no significant polymerization formed during the carbonation reaction.

GPC of the starting material shows a similar amount (4.16%) of higher Mw material. There was clearly not sufficient polymerization to cause the noted viscosity increase. More likely, the viscosity increase is caused by the polar interaction of the carbonate moiety. This phenomenon has been recently observed and modeled for acrylated triglycerides, including soybean oil,[35] where Arrhenius viscosity behavior is observed.

Discussion of the reaction rate enhancement in supercritical carbon dioxide

There are two explanations for the observed rate enhancement in supercritical CO_2. The first hypothesis for the rate enhancement is the formation of a CO_2 expanded liquid,[36] which would reduce the viscosity of the oil increasing the diffusion of the reactant CO_2.[37] Although this would easily explain the rate enhancement shown in this work, there were no observations consistent with the expanded liquid formation. The second simpler hypothesis is a solubility effect. The mutual solubilities of CO_2 and the oil have been studied in the literature[38–40] and shown to vary significantly with both pressure and temperature. Solubility parameters for CO_2 with a variety of oils and other liquids have been estimated.[41] Non-polar liquids, such as soy oil, jojoba oil, and castor oil, have mutual solubilities which increase with increasing pressure. Soybean oil and supercritical CO_2 are considered completely miscible at 80 °C and at 95.0 MPa.[42] The solubilities of fatty materials at the pressures used in our system have also been studied in the literature. For example, the solubility of a fish oil ethyl ester in supercritical CO_2 at 5.13 MPa and 70 °C is 0.064 $Nm^3\ kg^{-1}$. When the pressure is increased to 10.04 MPa maintaining constant temperature, the solubility increases almost three fold to 0.170 $Nm^3\ kg^{-1}$.[40]

Table 2 The catalysts studied for the carbonation of ESO in supercritical CO_2 at 100 °C with a 40 h reaction time. Only the TBA^+Br^- system showed significant reactivity

Reaction catalyst (0.5 mol%)	% Reaction by ^1H NMR
None	0
TBA^+Br^-	100
K^+Br^-	6
Li^+Br^-	0
TBA^+OH^-	0

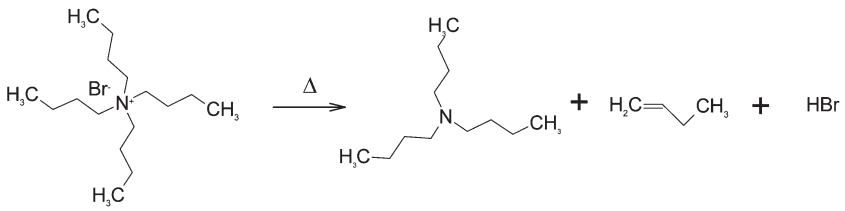
Because we ran the system at constant CO_2 concentration, an apparent 1st order kinetic rate constant can be calculated from a plot kinetic plot of ln $[ESO]_{initial}/[ESO]$. A value of 0.1118 h^{-1} was calculated, giving a $t_{1/2}$ of 6.2 h (see ESI† Section S-2). From literature synthesis, a rate of ~0.0402 h^{-1} and $t_{1/2}$ of 17.2 h can be calculated in a similar manner. In other words, we have increased the observed reaction rate by a factor of three. This closely matches the expected difference in the mutual solubility of the reactants and can explain the enhanced rate.

Other catalysts

We ran similar experiments with a variety of other catalysts in order to determine if the TBA^+Br^- salt was necessary for the reaction (Table 2). We used TBA^+OH^- solution, Li^+Br^-, and K^+Br^- all at 5 mol% as well as a catalyst free system. Both ^1H NMR and IR of the resultant products were taken, and all of these systems showed little or no reactivity. This is especially interesting in the Li^+Br^- case where reactivity has been shown in other carbonate systems.[43,44] The lack of activity is probably due to poor solubility of these catalysts in both the epoxidized soybean oil and in supercritical CO_2. Further catalyst studies for CO_2 soluble systems of higher reactivity may be of interest, as was found in polymerization[45,46] and hydrogenation reactions.[47] However, the TBA^+Br^- system has an advantage in that it can be removed by thermal breakdown into volatile products by the Hofmann elimination reaction (Scheme 2).

Catalyst removal and TGA analysis

In order to take advantage of the catalyst breakdown reaction, we heated the material with catalyst still present (Fig. 3), and noticed a temperature where the catalyst breakdown occurs but the carbonated oil product is still stable: 190 °C. We treated material at this temperature under a nitrogen atmosphere for 2 hours. The material lost the expected 8.6% mass within error of the 7.5% observed in the TGA experiment. The volatile mass lost from the sample was trapped and determined



Scheme 2 The well studied Hofmann elimination of TBA^+Br^- under heating. TGA analysis of pure material shows complete catalyst removal by this decomposition to volatile products which occurs from 150–190 °C.

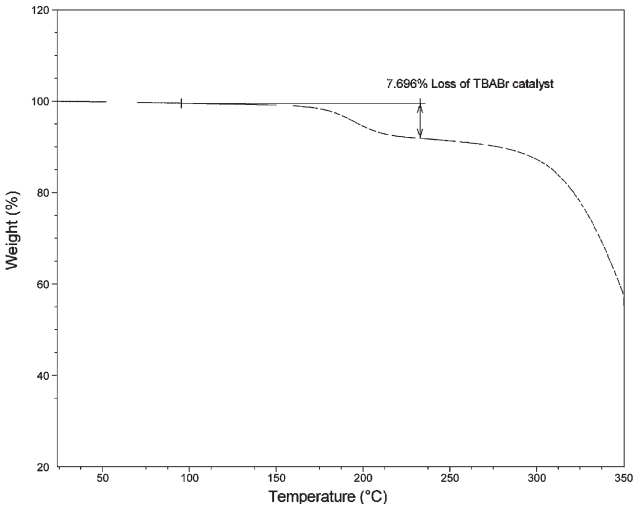


Fig. 3 The TGA trace of CSO with catalyst still present. The initial loss of material, ~8%, is evidence of the decomposition of the catalyst (TBA^+Br^-) to volatile material.

to be the expected tributylamine by GC analysis and comparison to a standard solution. The resultant CSO was compared and found to be identical to CSO which had catalyst removed by a washing and sonication method. TGA analyses of both samples (Fig. 4) show identical behavior, and ^1H NMR analysis confirmed complete removal of the catalyst. It is of note that the oil stability is not a complicating issue as the temperature employed here is significantly below the 288–306 °C temperature where thermal decomposition[48] of vegetable oil occurs and well below the 325–335 °C preferred for thermal viscosity modification of soybean oil.[49,50]

Overall, our synthesis is a step in making a potentially useful chemical material available for use. The potential to use the Hofmann reaction allows for an easy catalyst removal mechanism, or the material can be washed and the catalyst reused. The potential of using supercritical CO_2 in a continuous flow system for carbonation of propylene oxide has been demonstrated.[43] Extension of this type of reaction to oleochemical epoxides may allow the synthesis of a variety of useful materials. Further work may include trying this reaction at even higher pressure to further reduce the reaction time.

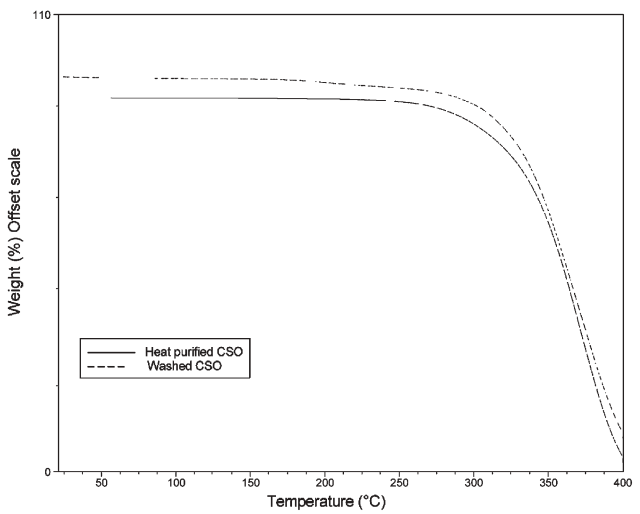


Fig. 4 The TGA traces for samples of CSO which have had catalyst removed by washing and sonication (top) and by heat purification (bottom). The material shows no change with respect to the different purification methods.

Experimental

Materials

Epoxidized soybean oil (Atofina, VIKOFLEX 7170, 4.2 oxirane moieties per triglyceride); tetrabutylammonium bromide (Sigma, 99%); tetrabutylammonium hydroxide (Sigma, ACS reagent); potassium hydroxide (Barns, Analytical); lithium hydroxide (Sigma-Aldrich, 99%); carbon dioxide (AirGas 50 lb syphon type high pressure cylinder, UN1013); tetrahydrofuran (Sigma-Aldrich, 99 + % ACS reagent); and tributylamine (Fluka, >99.0%) were used as received.

Instrumentation and equipment

The reactor employed was a Parr 4560 mini benchtop controlled by a thermocouple equipped Parr 4843 controller. A 300 mL reactor body equipped with quartz viewing windows was used.

FTIR spectra were recorded on a Thermonicolet Nexus 470 FTIR with a Smart ARK accessory containing a 45° ZeSe trough. Data were collected and processed on a Windows 2000 equipped Dell Optiplex GX260 Pentium 4, 2.46 GHz computer running Omnic 6.2 software.

Gel permeation chromatography was performed on a Polymer Labs PL-GPC 120 high temperature chromatograph through a Polymer Labs PLgel 5 uM guard (50 × 7.5 mm) and 2 Polymer Labs Plgel 3 uM MIXED-E (300 × 7.5 mm) columns using a Refractive Index detector. A Holland spark Midas autosampler was employed. Data were collected and processed on a Windows 98 Micron Pentium 2 computer running Cirrus GPC online GPC/SEC software version 1.11. Chromatographic runs were made using an isocratic flow rate (1 mL min^{-1}) of tetrahydrofuran at 40 °C. The Mw were calculated by the Cirrus software using a third order polynomial derived from a standard curve. The standard curve was generated from a series of polystyrene Mw standards (Polymerlabs easycal A) and a series of mono, di, and tri oleins and palmitates (Nu-Chek Prep, Inc.)

NMR spectroscopy (See ESI† Section S-1) was performed on a Bruker Avance 500 NMR. It was operating at 500 MHz for ^1H and 125 MHz for ^{13}C. Viscosity measurements were performed on a TA Instruments ARES controlled strain rheometer with 1 K FRTN1 transducer using TA Orchestrator software package 7.0.

Viscosity was measured at 25 °C using a rate sweep method where the sheer rate was increased until a constant viscosity was measured. The sheer rate had to be varied from 0.1 s^{-1} to 500 s^{-1} depending on the sample studied.

Freeze drying was performed with a Labconco Freezone 1. Samples were pre-frozen in a dry ice/ethanol bath using standard laboratory procedures.

Thermogravimetric analysis (TGA) was performed on a TA TGA Q500. Data were collected and processed on a Windows 2000 × 86 Family6 Model 8 IBM computer with Advantage for Q series version 1.5.0.208 Thermal Advantage release 3.2.0 software. Samples were heated under nitrogen using a heating ramp of 2.0 °C min^{-1} from 25 °C to 350 °C.

Gas chromatography was performed on a Hewlett Packard 6890 GC system equipped with a 6890 series injector and a 5973 mass detector. Samples were collected using a solid phase micro-extraction PDMS fiber over the headspace of the trapped sample for 1 h.

Synthesis of carbonated soybean oil

Epoxidized soybean oil (ESO) was heated in a warm water bath until fluid and ~30 g (0.0311 mol triglyceride, 0.131 mol of oxirane functionality) poured into a 300 mL high pressure reactor vessel. Next, ~2.11 g (0.0065 mol, 5.0 molar percent, 6.6 weight percent) tetrabutylammonium bromide (TBA^+Br^-) was dissolved into the oil with stirring. The reactor was closed and pressurized with CO_2 to ~3.4 MPa. The reactor was then heated to 100 °C causing the pressure to rise. Once the reaction temperature was reached, the CO_2 pressure was further increased to 10.3 MPa and maintained there throughout the reaction with the necessary addition of CO_2 by the pressure controlling pump. After the reaction time was complete, the reactor was de-pressurized slowly to allow dissolved CO_2 to leave the carbonated product. Typical isolated yield was ~29 g, ~81% based on a product of Mw 1150 g mol^{-1}, with the loss caused by difficulty in recovering the viscous light brown liquid from the reactor.

Removal of tetrabutylammonium bromide from the product

Catalyst removal could be accomplished by either of the following two methods. The first allows the recovery, characterization, and possible reuse of the catalyst, the second method takes advantage of the Hofmann elimination reaction possible for TBA^+Br^-. In the first method, 5 g of carbonated soybean oil was suspended in ~50 mL of warm (50 °C) water. The mixture was sonicated for two hours in order to obtain a dispersion. After sonication, the mixture was separated using a separatory funnel, and the process repeated two more times. All of the water washings were saved and freeze dried yielding 0.308 g (96% recovery) of white powder. This white powder was verified to be TBA^+Br^- by NMR and TGA analysis. The carbonated soybean oil solution was dried in a Kugel-Rohr® and characterized by IR (Fig. 1) and TGA (Fig. 3) as well as by ^1H NMR, ^{13}C NMR (see ESI† Section S-1). The second method of catalyst removal involved heating of the carbonated soybean oil to 190 °C for ~2½ hours. TGA analysis shows that the carbonated soybean oil is stable at this temperature, however the catalyst decomposes into volatile Hofmann elimination products which are removed in the nitrogen stream. The volatile products were trapped in a dry ice/ethanol trap and verified to be the expected tributylamine by GC analysis. The final product was comparable to the washed product by TGA, IR, and ^1H NMR spectroscopy.

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Synthesis, anti-microbial activities and anti-electrostatic properties of phosphonium-based ionic liquids

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A range of phosphonium ionic liquids having the generic formula $[PR_3R']X$ (R and R′ are alkyl groups; X is halide, trifluoromethanesulfonate, bis(trifluoromethylsulfonyl)imide, nitrate, dialkylphosphinate, dicyanamide, decanoate, tetrafluoroborate, hexafluorophosphate, or diisobutyldithiophosphinate have been prepared, characterised, and tested for anti-microbial activity and anti-electrostatic properties. Within this group of phosphonium salts, in contrast to their 1-alkyl-3-methylimidazolium analogues, both cation structure and the type of anion have effects on their biological activity. The ionic liquids also showed high anti-electrostatic effect.

Introduction

Ionic liquids have been defined as salts which are liquid at, or below, room temperature or more broadly as salts which melt at, below, or around 100 °C. Over the past ten years, there has been an exponential growth in publications and patents relating to ionic liquids.[1,2] Many of the key publications are covered in numerous excellent reviews,[3–11] and Wilkes has also reviewed ionic liquids from an historical point of view.[12] With the exception of significant early work by Parshall[13] and Knifton *et al.*[14–19] and, more recently, by Clyburne *et al.*,[20] Kaufmann,[21] Garayt *et al.*,[22] and McNulty *et al.*,[23] there has been a noticeable absence of reports using phosphonium-based ionic liquids. This is surprising, since phosphonium salts are commercially available and can be readily converted to a wide range of ionic liquids.[24]

While, initially, chloroaluminate-based ionic liquids were used as media for electrodeposition of aluminium,[25] and later for their electrolyte properties for use in batteries,[26] the range of applications has widened considerably to include using air-stable ionic liquids as solvents for a wide range of chemical reactions,[11] separation media,[27] light-emitting cells,[28] lubricants,[29] liquid crystals,[30,31] and even embalming fluids.[32] Because of the wide variety of potentially available cations and ions, an ionic liquid can be specifically tailored to suit the application—"designer solvents".[33]

Ionic liquids have now moved from laboratory curiosities to industrial application.[2] It is increasingly important to now understand not only their chemical properties, but also their physical and biological properties and environmental impact. Knowledge of ionic liquid properties such as density and viscosity[34] are essential when designing an application. The liquid range, colligative properties, and thermally-induced physical transformations within the liquid region also play a role in any potential application.[30,31]

Because of their nature, ionic liquids do not boil at elevated temperatures, but they do have upper thermal stability limits. TGA is a useful tool to obtain relative thermal stability. However, TGA data in which weight losses are reported for samples that are heated at modest 5 to 10 °C min^{-1} rates can be deceiving. Data from these tests would indicate that, depending on the anion, imidazolium and phosphonium salts are generally stable to 300 °C or even higher. However, tests carried out under static temperatures have shown that while most ionic liquids are still quite thermally stable, the upper temperature limit is significantly lower than 300 °C.[24,34] Indeed, a rough rule of thumb is that the static decomposition temperature is between 75–100 °C lower than the temperature derived from dynamic TGA experiments. Thus, a more realistic thermal stability range is between 175 and 220 °C, still adequate for most applications.

In addition to thermal stability, chemical stability is equally important. Hexafluorophosphate and tetrafluoroborate salts have long been known to be hydrolytically unstable, and will release HF, which is both hazardous to personnel and equipment.[35]

Biological properties of ionic liquids are also important. Recently the anti-microbial activities and biodegradability of a series of imidazolium based ionic liquids was reported.[36] Not unexpectedly, many of the salts showed biocidal activity against several aquatic organisms. None of the dialkylimidazolium salts could be classified as "readily biodegradable". Here, we report a parallel study on the microbial activities and anti-electrostatic effect of a series of phosphonium-based ionic liquids. The phosphonium ionic liquids have the generic formula $[PR_3R']X$, where both R and R′ are alkyl groups, and X is halide, trifluoromethanesulfonate, bis(trifluoromethylsulfonyl)imid, nitrate, dialkylphosphinate, dicyanamide, decanoate, tetrafluoroborate, hexafluorophosphate, or diisobutyldithiophosphinate.

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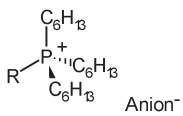
Experimental

The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Brucker Avance series 300 MHz NMR spectrometer; values for ^{1}H and ^{13}C are given in ppm relative to TMS in $CDCl_3$, for ^{31}P are given in ppm relative to external 85% H_3PO_4. LC/MS data were obtained using an "Applied Biosystems Mariner LC/MS" system. IR spectra were run on a Nicolet Impact 4000D FTIR spectrometer using liquid film between KBr discs. The melting points and yields for the prepared phosphonium salts are summarized in Table 1.

Preparation of trihexyl(tetradecyl)phosphonium chloride (2f)

A 2 l round-bottomed flask fitted with a condenser was charged with trihexylphosphine (286.0 g, 1.0 mol) and was heated to 145 °C, whence 1-chlorotetradecane (261.0 g, 1.20 mol) was added over 2.75 h. The temperature was maintained at 140 °C overnight (approximately 16 h of post-addition reaction). The progress of the reaction was monitored by ^{31}P NMR spectroscopy. The mixture was then vacuum stripped at 180 °C (22 mm Hg) to remove the excess of 1-chlorotetradecane and volatile by-product impurities (mainly tetradecene isomers). The product (495.0 g) was obtained as a colourless oil (97.2% $[PR_3R]Cl$, 2.1% $[PHR_3]Cl$, 0.2% HCl and 0.12% tetradecene isomers). ^{1}H NMR (δ/ppm; $CDCl_3$): 0.80 (q, 12H), 1.2 (m, 32H), 1.42 (m, 16H), 2.34 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 13.76, 13.95, 18.77, 19.40, 21.70, 21.75, 22.17, 22.50, 28.81, 29.13, 29.17, 29.49, 30.20, 30.39, 30.91, 31.73. The two signals at 13.76 and 13.95 ppm were in a approximate 3 : 1 ratio and were determined to be methyl carbons by the J mod experiment and were assigned to the terminal methyl carbons of the hexyl and tetradecyl alkyl groups respectively. Due to the complex P/C coupling it was difficult to assign the remaining individual signals. ^{31}P NMR (δ/ppm; $CDCl_3$): δ 33.43 which is very typical of tetraalkylphosphonium salts. The LC/MS indicated an intense molecular ion with m/z 483.6 which is indicative of the trihexyl(tetradecyl)phosphonium cation. IR ν_{max} (KBr disc)/cm^{-1}: 2955 (s), 2924 (s), 2854 (s,), 1465 (s), 1414 (w), 1378 (w), 720 (m).

Table 1 Alkyltrihexylphosphonium salts



Salt	R	Anion	Mp/°C	Yield (%)
1a	C_2H_5	Br	59.5	96
1b	C_3H_7	Br	Liquid	94
1c	C_4H_9	Br	30	87
1d	C_6H_{13}	Br	70	98
2a	C_6H_{13}	Cl	Liquid	97
2b	C_7H_{15}	Cl	Liquid	95
2c	C_8H_{17}	Cl	Liquid	94
2d	$C_{10}H_{21}$	Cl	Liquid	96
2e	$C_{12}H_{25}$	Cl	Liquid	98
2f	$C_{14}H_{29}$	Cl	Liquid	98
2g	$C_{16}H_{33}$	Cl	Liquid	97
3a	$C_{14}H_{29}$	[OTf]	Liquid	98
3b	$C_{14}H_{29}$	$[NTf_2]$	Liquid	98
3c	$C_{14}H_{29}$	$[N(CN)_2]$	Liquid	98
3d	$C_{14}H_{29}$	$[NO_3]$	Liquid	96
3e	$C_{14}H_{29}$	$[(^{i}C_8H_{17})_2PO_2]$	Liquid	95
3f	$C_{14}H_{29}$	$[C_9H_{19}CO_2]$	Liquid	95
3g	$C_{14}H_{29}$	$[PF_6]$	39.5	87
3h	$C_{14}H_{29}$	$[BF_4]$	38.5	88
3i	$C_{14}H_{29}$	$[(cyc\text{-}C_6H_{11})_2PO_2]$	Liquid	95
3j	$C_{14}H_{29}$	$[(^{i}C_4H_9)_2PS_2]$	Liquid	93

Trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)-phosphinate (3e)

Bis(2,4,4-trimethylpentyl)phosphinic acid (CYANEX® 272 {Cytec Industries}, 29.0 g, 100 mmol), trihexyl(tetradecyl)-phosphonium chloride (51.9 g, 100 mmol) and water (1 l) were stirred together at 55 °C. Sodium hydroxide (100 mmol; 25% aqueous solution) was added over a period of 30 min, and the reaction mixture was then stirred for a further hour at 55 °C. The aqueous phase was decanted and the organic layer was then washed with water three times and during each wash cycle, the phases were agitated for 1 h at 55 °C. Finally, the ionic layer was vacuum stripped at 125–135 °C (4–5 mm Hg). The density was found to be 0.88 g cm^{-3} at 25 °C. ^{1}H NMR (δ/ppm; $CDCl_3$): 1.0 (m, 12H), 1.15 (m, 4H), 1.4 (m, 70H), 1.7 (m, 8H), 2.6(m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.2, 14.4, 18.9, 19.5, 22.2, 22.3, 22.6, 22.9, 24.8, 25.9, 29.3, 29.6, 29.8, 29.9, 30.4, 30.6, 30.7, 31.5, 32.2, 43.3. ^{31}P NMR (δ/ppm; $CDCl_3$): 33.39. IR ν_{max} (KBr disc)/cm^{-1}: 2954 (s), 2927(s), 2857(s), 1466 (s), 1407 (w), 1362(s), 1048 (s), 1030 (s), 720 (m).

Trihexyl(tetradecyl)phosphonium dicyanamide (3c)

Trihexyl(tetradecyl)phosphonium chloride (5.2 g, 10 mmol) and sodium dicyanamide (1.1 g, 12.4 mmol) was added to a mixture of water (25 cm^3) and propanone (25 cm^3). The reaction mixture was stirred at ambient temperature for 6 h and then the propanone was removed by evaporation. The aqueous layer was extracted with chloroform (4 × 50 cm^3), and the combined organic layers were washed with deionised water (10 × 15 cm^3). The solvent was evaporated to give a colourless free-flowing oily liquid (5.2 g, 96.4%). ^{1}H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 12 H), 1.40 (m, 40 H), 1.70 (m, 8 H), 2.35 (m, 8 H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.3, 14.4, 18.9, 19.6, 21.9, 22.0, 22.6, 22.7, 23.0, 29.2, 29.62, 29.67, 29.8, 30.0, 30.6, 30.8, 31.3, 32.2, 120.3 $\{[N(CN)_2]^-\}$. ^{31}P NMR (δ/ppm; $CDCl_3$): 33.39. IR ν_{max} (KBr disc)/cm^{-1}: 2955 (s), 2925 (s), 2854 (s), 2225 (s), 2188(s), 2126 (s), 1465 (s), 1412 (w), 1378 (w), 720 (m).

Trihexyl(tetradecyl)phosphonium diisobutylphosphinate

Trihexyl(tetradecyl) phosphonium chloride (5.6 g, 10.8 mmol) and diisobutylphosphinic acid (1.9 g, 10.8 mmol) were added to a round bottomed flask (100 cm^3), water (6 cm^3) was added and heated to 55 °C. Sodium hydroxide (10.8 mmol; 25% aqueous solution) was added over a period of 30 min, and the mixture was stirred for an additional hour at 55 °C, whence the phases were allowed to separate. The lower aqueous phase was decanted and the organic layer was then washed three times with water (3 × 20 cm^3). During each wash cycle, the phases were agitated for 1 h at 55 °C. The aqueous phases were tested for the presence of chloride ion using aqueous silver nitrate

solution. Finally, the organic layer was vacuum stripped to remove the bulk of the dissolved water by heating the organic layers to 125–135 °C (4–5 mm Hg) to give trihexyl(tetradecyl)-phosphonium diisobutylphosphinate. ^{1}H NMR (δ/ppm; $CDCl_3$): 0.92 (m, 12H), 1.05 (m, 12H), 1.35 (m, 44H), 1.65 (m, 8H), 2.01 (m, 2H), 2.6 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 13.9, 14.1, 18.7, 19.3, 21.8, 21.9, 22.3, 22.6, 25.1, 25.2, 28.9, 29.3, 29.4, 29.6, 30.3, 30.5, 31.9, 33.8, 41.8. IR ν_{max} (KBr disc)/cm^{-1}: 2925 (s), 2856(s), 1465 (s), 1407 (w), 1362 (s), 1232 (w), 1056 (m), 1029 (s), 720 (m).

Trihexyl(tetradecyl)phosphonium dicyclohexylphosphinate (3i)

This ionic liquid is prepared using the procedure for trihexyl(tetradecyl)phosphonium diisobutylphosphinate, but using dicyclohexylphosphinic acid in place of diisobutyl-phosphinic acid. ^{1}H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 12H), 1.40 (m, 62H), 1.70 (m, 8H), 2.35 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.0, 14.2, 18.8, 19.4, 22.1, 22.2, 22.5, 22.8, 26.6, 26.9, 27.3, 29.2, 29.5, 29.6, 29.75, 30.6, 30.8, 30.9, 32.0, 36.98. IR ν_{max} (KBr disc)/cm^{-1}: 2925 (s), 2856 (s), 1465 (s), 1407 (w), 1362 (s), 1232 (w), 1056 (m), 1029 (s), 720 (m).

Trihexyl(tetradecyl)phosphonium diisobutyldithiobutylphos-phinate (3j)

This ionic liquid is prepared using the procedure for trihexyl(tetradecyl)phosphonium diisobutylphosphinate, but using sodium diisobutyldithiophosphinate rather than diiso-butylphosphinic acid. ^{1}H NMR (δ/ppm; $CDCl_3$): 0.92 (m, 12H), 1.05 (m, 12H), 1.35 (m, 46H), 1.65 (m, 8H), 2.01 (m, 2H), 2.6 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.3, 14.42, 19.44, 20.0, 22.3, 22.7, 23.0, 25.4, 25.5, 29.3, 29.6, 29.8, 29.9, 30.7, 30.9, 31.4, 32.2, 53.2. ^{31}P NMR (δ/ppm; $CDCl_3$): 33.39 (cation), 65.8 (anion). IR ν_{max} (KBr disc)/cm^{-1}: 2925 (s), 2858(s), 1465 (s), 1401(w), 1378 (w), 1361 (vw), 1215 (w), 1165 (w), 1061 (w), 721 (m).

Trihexyl(tetradecyl)phosphonium decanoate (3f)

Trihexyl(tetradecyl)phosphonium chloride (5.6 g, 10.8 mmol) and 1-decanoic acid (2.06 g, 12 mmol) were added to a round-bottomed flask (100 cm^3). Water (*ca.* 6 cm^3) was added and heated to 55 °C, and then sodium hydroxide (12 mmol; 25% aqueous solution) was added over a period of 30 min. The mixture was stirred for an additional hour at 55 °C and the phases were allowed to separate, the lower aqueous phase was removed by decantation. The organic layer was then washed with water (3 × 20 cm^3): during each wash cycle; the phases were agitated for 1 h at 55 °C. The aqueous phases were tested for the presence of chloride ion using aqueous silver nitrate solution. Finally, the organic layer was vacuum stripped to remove the bulk of the dissolved water by heating the organic layers to 125–135 °C (4–5 mm Hg) to give trihexyl(tetradecyl)-phosphonium decanoate as a viscous liquid.

^{1}H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 15H), 1.40 (m, 50H), 1.70 (m, 10H), 2.35 (m, 12H). ^{13}C NMR (δ/ppm; $CDCl_3$): 13.8, 14.1, 18.5, 19.1, 21.8, 22.3, 22.6, 27.4, 28.9, 29.2, 29.3, 29.5, 29.6, 29.8, 30.2, 30.3, 30.5, 31.0, 31.8, 39.6, 178.8 ($[RCO_2]^-$). ^{31}P NMR (δ/ppm; $CDCl_3$): 33.39. IR ν_{max} (KBr disc)/cm^{-1}: 2956 (s), 2925 (s), 2855 (s), 1579 (s), 1465 (s), 1418 (w), 1377 (s), 720 (m).

Trihexyl(tetradecyl)phosphonium trifluoromethanesulfonate (3a)

Sodium trifluoromethanesulfonate (2.06 g, 12.0 mmol, pre-pared by the neutralisation of triflic acid, *ex* Aldrich) was added to trihexyl(tetradecyl)phosphonium chloride (5.1 g, 10 mmol) in propanone (100 cm^3) and stirred magnetically for 6 h at ambient temperature, whence the reaction mixture was filtered. The filtrate was concentrated and the residue was dissolved in diethyl ether (150 cm^3). The ethereal layer was washed with distilled water (6 × 50 cm^3), and the aqueous phases were tested for the presence of chloride ion using aqueous silver nitrate solution. Then the ether was stripped off, and the residue was vacuum stripped to remove the bulk of the dissolved water by heating at 125–135 °C (4–5 mm Hg) to give trihexyl(tetradecyl)phosphonium triflate as a colourless free-flowing liquid. ^{1}H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 12H), 1.40 (m, 40H), 1.70 (m, 8H), 2.35 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.2, 14.4, 18.7, 19.3, 21.8, 21.9, 22.6, 23.0, 29.2, 29.7, 29.8, 30.0, 30.5, 30.7, 30.8, 31.2, 32.2, 121.2 (anion; q, J_{CF} = 321.9 Hz). ^{31}P NMR (δ/ppm; $CDCl_3$): 33.39. IR ν_{max} (KBr disc)/cm^{-1}: 2957 (s), 2928 (s), 2855 (s), 1466 (s), 1418(w), 1261 (s), 1223 (m), 1153 (s), 1030 (s), 721 (m).

Trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)-imide (3b)

Lithium bis(trifluoromethylsulfonyl)imide (3 M Belgium N.V.; 3.44 g, 12 mmol) was added to trihexyl(tetradecyl)phos-phonium chloride (5.1 g, 10 mmol) in propanone (100 cm^3) and stirred magnetically for 6 h at ambient temperature, during which time solid lithium chloride precipitates: the reaction mixture was then filtered. The filtrate was concen-trated and the residue was dissolved in diethyl ether (250 cm^3). The ethereal layer was washed with water (6 × 50 cm^3), and the aqueous phases were tested for the presence of chloride ion using aqueous silver nitrate solution. Then the diethyl ether was stripped off, and the residue was vacuum stripped to remove the bulk of the dissolved water by heating 125–135 °C (4–5 mm Hg) to give trihexyl(tetradecyl)phosphonium bis(tri-fluoromethylsulfonyl)imide as a colourless free-flowing liquid. ^{1}H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 12H), 1.40 (m, 40H), 1.70 (m, 8H), 2.35 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.2, 14.5, 18.7, 19.3, 21.8, 21.9, 22.6, 23.0, 29.2, 29.6, 29.9, 30.99, 30.03, 30.06, 30.5, 30.6, 31.0, 31.2, 32.3, 120.5 (anion; q, J_{CF} = 321.5 Hz). ^{31}P NMR (δ/ppm; $CDCl_3$): 33.39. IR ν_{max} (KBr disc)/cm^{-1}: 2929 (s), 2858 (s), 1467 (s), 1412 (w), 1352 (s), 1332 (s), 1112 (s), 720 (m).

Trihexyl(tetradecyl)phosphonium tetrafluoroborate (3h)

A solution of sodium tetrafluoroborate (13.2 g, 120 mmol) in water (100 cm^3) was added slowly to a cooled, rapidly stirring solution of trihexyl(tetradecyl)phosphonium chloride (51.9 g, 100 mmol) in water (150 cm^3). The reaction mixture stirred at 0 °C for 6 h. The reaction mixture was extracted with diethyl ether (4 × 250 cm^3), and the combined organic layers were washed with cooled aqueous sodium hydroxide solution (1%;

2 × 75 cm^3) and then with water (6 × 50 cm^3), dried over $MgSO_4$, and the solvent removed in vacuum to yield the tetrafluoroborate salt (50.25 g, 88% yield). ^1H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 12H), 1.40 (m, 40H), 1.70 (m, 8H), 2.35 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.3, 14.5, 18.7, 19.3, 21.89, 21.95, 22.0, 22.7, 23.0, 29.3, 29.7, 29.9, 30.01, 30.06, 31.2, 31.3, 32.3. ^{31}P NMR (δ/ppm; $CDCl_3$): 33.25. IR ν_{max} (KBr disc)/cm^{-1}: 2857 (s), 1467 (s), 1412 (s), 1379 (w), 1300 (w), 844 (b), 720 (m).

Trihexyl(tetradecyl)phosphonium hexafluorophosphate (3g)

Trihexyl(tetradecyl)phosphonium chloride (3.32 g, 6.4 mmol) was dissolved in water (60 cm^3), and then cooled in an ice bath. The mixture was stirred vigorously and aqueous HPF_6 solution (60% w/w; 2.0 cm^3, 13.6 mmol) was added using a glass syringe. The reaction mixture was stirred at ambient temperature for 6 h. The total reaction mixture was extracted with diethyl ether (4 × 25 cm^3), and the combined organic layers were washed with cooled aqueous sodium hydroxide solution (1%; 2 × 7.5 cm^3) and then with water (6 × 15 cm^3), dried over $MgSO_4$, and the solvent removed in vacuum to yield the trihexyl(tetradecyl)phosphonium hexafluorophosphate salt (3.49 g, 87% yield). ^1H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 12H), 1.40 (m, 40H), 1.70 (m, 8H), 2.35 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.3, 14.5, 18.6, 19.2, 21.8, 22.7, 23.0, 29.2, 29.7, 30.0, 30.5, 30.7, 31.25, 32.28. ^{31}P NMR (δ/ppm; $CDCl_3$): 33.25. IR ν_{max} (KBr disc)/cm^{-1}: 2852 (s), 1466 (s), 1410 (w), 1380 (w), 1230 (w), 1112 (s), 1099 (w), 1001 (w), 967 (w), 910 (b), 793 (w), 753 (s), 717 (m).

Ethyltrihexylphosphonium bromide (1a)

A round-bottomed flask (250 cm^3) fitted with a condenser was charged with trihexylphosphine (28.60 g, 0.1 mol) and was heated to 60 °C; bromoethane (21.7 g, 0.2 mol) was then added over 2.75 h. The reaction mixture was then further heated for 12 h, and the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After the reaction was complete, the mixture was concentrated and then vacuum stripped at 180 °C (22 mm Hg) to remove the excess of any volatile by-products, and solid ethyltrihexylphosphonium bromide (38.6 g, 98%) was obtained. ^1H NMR (δ/ppm; $CDCl_3$): 1.00 (m, 9H), 1.40 (m, 15H), 1.70 (m, 12H), 2.35 (m, 8H). ^{13}C NMR (δ/ppm; $CDCl_3$): 14.2, 16.0, 18.9, 19.5, 22.0, 22.1, 22.6, 30.6, 30.8, 31.3. ^{31}P NMR (δ/ppm; $CDCl_3$): 33.25. IR ν_{max} (KBr disc)/cm^{-1}: 2926(s), 2858 (s), 1466 (s), 1414 (w), 1379 (w), 823(m), 726 (m).

Test microorganisms

Microorganisms used: *Micrococcus luteus* NCTC 7743, *Staphylococcus aureus* NCTC 4163, *Staphylococcus epidermidis* ATCC 49134, *Moraxella catarrhalis* ATCC 25238, *Enterococcus faecium* ATCC 49474, *Pseudomonas aeruginosa* NCTC 6749, *Escherichia coli* ATCC 25922, *Serratia marcescens* ATCC 8100, *Proteus vulgaris* NCTC 4635, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC 10231, *Rhodothorula rubra* Demml 1889, Lodder 1934). Standard strains were supplied by the National Collection of Type Cultures (NCTC) London and American Type Culture Collection (ATCC). *Rhodothorula rubra* was obtained from the Department of Pharmaceutical Bacteriology, University of Medical Sciences, Poznań.

Anti-microbial activity test procedure

Anti-microbial activity was determined by the tube dilution method. Bacteria strains were cultured on a Müller-Hinton broth for 24 h and fungi on Sabouraud agar for 48 h. A suspension of the microorganisms at a concentration of 10^6 cfu cm^{-3} (cfu = colony forming units), were prepared from each culture. Then to each dilution the broth medium inoculated with the suspension mentioned above was added in a 1 : 1 ratio. Growth (or lack thereof) of the microorganisms was determined visually after incubation for 24 h at 37 °C (bacteria) or 48 h at 28–30 °C (fungi). The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC (minimal inhibitory concentration). Then, an aliquot taken from each tube in a sample loop was cultured in an agar medium with inactivates (0.3% lecithin, 3% polysorbate 80 and 0.1% cysteine L) and incubated for 48 h at 37 °C (bacteria) or for 5 d at 28–30 °C (fungi). The lowest concentration of the phosphonium salt supporting no colony formation was defined as the MBC (minimum bactericidal or fungicidal concentration). The test results are summarized in Tables 2 and 3 and Fig. 1 and 2.

Anti-electrostatic properties

The anti-electrostatic effect was measured on a Wigofil polyethylene film with a density of 150 g m^{-2} that did not contain any lubricants or antioxidants. From this 0.25 mm film, 12.5 mm diameter disks were cut out. The disks were washed in acetone and then dried by placing them in an air-conditioned room. A disk was rubbed on the surface with a cotton-swab soaked with a 0.5% chloroform solution of studied salts. Then, the disk was hung up so that the chloroform could evaporate spontaneously. The disks, covered with phosphonium salts, were stored for 24 h in an air-conditioned room at 20 ± 2 °C and a relative humidity of 55 ± 5%. Finally, the surface resistance and half charge decay time were measured. The measuring apparatus and the method have recently been described elsewhere.[37] The relative error in the determination of these two quantities did not exceed 5%.

Results and discussion

Synthesis of phosphonium ionic liquids or salts involves the initial quaternisation of trialkylphosphines with haloalkanes.[38] Quaternisation of trihexylphosphine occurred within 12–16 h for chloroalkanes at 145 °C, bromoalkanes at 110 °C, and iodoalkanes at 90 °C (under solvent-free conditions or in toluene). The progress of the reaction was monitored using ^{31}P NMR spectroscopy. The tetraalkylphosphonium halides thus obtained were converted into other phosphonium ionic liquids by metathesis. Tetraalkylphosphonium dialkylphosphinates $[PR_3R'][R''_2PO_2]$, tetraalkylphosphonium dithiophosphinates $[PR_3R'][R''_2PS_2]$, and tetraalkylphosphonium decanoate ionic liquids were synthesised by using the sodium salt of the corresponding acid (prepared *in situ* in water). After the

Table 2 MIC and MBC[a] values for phosphonium bromides (**1a–d**), chlorides (**2a–g**) and BAC[b]

		Salts											
Strain		**1a**	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	BAC
Cocci													
M. luteus	MIC	2.5	1.2	2.4	2.2	0.5	0.5	0.5	2.2	2.0	1.9	3.7	1.4
	MBC	40.5	1.2	4.7	35	1.2	1.2	2.3	17	4.1	7.7	14.6	11
S. epidermidis	MIC	78	19.5	9.4	8.9	4.9	4.7	2.3	4.3	2.0	3.9	29	1.4
	MBC	157	151	73	35	9.8	38	18.4	270	254	241	457	5.6
S. aureus	MIC	20	19.5	9.4	8.9	2.5	4.7	2.3	8.6	33	119	228	2.8
	MBC	157	76	9.4	35	9.8	38	4.6	270	254	481	>913	23
M. catarrhalis	MIC	20	10	9.4	4.4	1.2	1.2	2.3	17	16	15.4	56.6	0.6
	MBC	20	10	9.4	4.4	2.5	1.2	9.2	17	16	15.4	56.6	1.4
E. faecium	MIC	157	10	18.9	17.7	9.8	9.5	9.2	17	33	119	228	5.6
	MBC	632	305	73	137	39	74	9.2	270	254	241	>913	23
Rods													
E. coli	MIC	20	10	4.7	17.7	2.5	4.7	9.2	17	16	31	113	2.8
	MBC	40.5	10	4.7	17.7	4.9	9.5	9.2	17	33	60	457	2.8
P. aeruginosa	MIC	>1264	>1220	>1180	>1107	>1228	>1187	1149	540	254	>963	>913	175
	MBC	>1264	>1220	>1180	>1107	>1228	>1187	>1149	>1080	1018	>963	>913	175
S. marcescens	MIC	>1264	>1220	>1180	>1107	>1228	1187	287	134	254	481	913	175
	MBC	>1264	>1220	>1180	>1107	>1228	1187	575	540	1018	>963	>913	175
P. vulgaris	MIC	>1264	>1220	>1180	1107	307	297	71	35	63	119	913	88
	MBC	>1264	>1220	>1180	1107	614	297	142	67	126	963	>913	88
Bacillus													
B. subtilis	MIC	10	39	18.9	8.9	4.9	4.7	4.6	17	33	7.7	913	2.8
	MBC	78	151	18.9	17.7	9.8	4.7	4.6	35	33	60	913	2.8
Fungi													
C. albicans	MIC	1264	>1220	>1180	554	152	594	71	134	33	241	913	11
	MBC	>1264	>1220	>1180	1107	1228	594	287	270	126	481	>913	88
R. rubra	MIC	>1264	>1220	>1180	554	152	147	71	134	63	241	913	23
	MBC	>1264	>1220	>1180	>1107	1228	594	575	540	126	>963	913	88

[a] In μM. [b] BAC—benzalkonium chloride.

Table 3 MIC and MBC[a] values for phosphonium salts (**3a–j**)

		Salts									
Strain		**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**
Cocci											
M. luteus	MIC	25	322	56	7.3	81	47	99	876	5.6	>721
	MBC	98	322	227	29	326	382	199	>876	11	>721
S. epidermidis	MIC	197	644	113	229	652	95	99	876	87	>721
	MBC	>790	>644	>909	>916	>652	382	795	>876	701	>721
S. aureus	MIC	790	>644	227	229	>652	191	199	876	87	>721
	MBC	>790	>644	909	916	>652	382	>795	>876	701	>721
M. catarrhalis	MIC	49	644	113	57	652	382	398	>876	43	>721
	MBC	98	>644	>909	114	652	382	398	>876	87	>721
E. faecium	MIC	790	>644	455	916	652	191	398	>876	175	>721
	MBC	790	>644	>909	>916	>652	763	398	>876	175	>721
Rods											
E. coli	MIC	>790	644	227	229	>652	382	49	876	175	>721
	MBC	>790	>644	909	458	>652	382	99	>876	175	>721
P. aeruginosa	MIC	>790	>644	>909	>916	>652	>763	>795	>876	701	>721
	MBC	>790	>644	>909	>916	>652	>763	>795	>876	>701	>721
S. marcescens	MIC	>790	>644	>909	916	>652	191	795	>876	>701	>721
	MBC	>790	>644	>909	>916	>652	>763	>795	>876	>701	>721
P. vulgaris	MIC	790	>644	>909	>916	>652	763	795	>876	701	>721
	MBC	>790	>644	>909	>916	>652	>763	>795	>876	>701	>721
Bacillus											
B. subtilis	MIC	395	>644	909	916	>652	382	398	>876	350	>721
	MBC	>790	>644	909	458	>652	382	398	>876	350	>721
Fungi											
C. albicans	MIC	>790	>644	>909	>916	>652	>763	795	>876	87	>721
	MBC	>790	>644	>909	>916	>652	>763	795	>876	350	>721
R. rubra	MIC	>790	>644	>909	>916	>652	763	795	>876	175	>721
	MBC	>790	>644	>909	>916	>652	>763	795	>876	350	>721

[a] In μM.

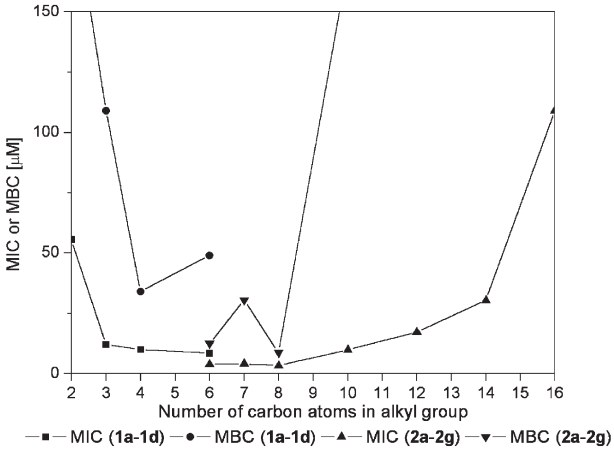


Fig. 1 Mean MIC and MBC values for *cocci*

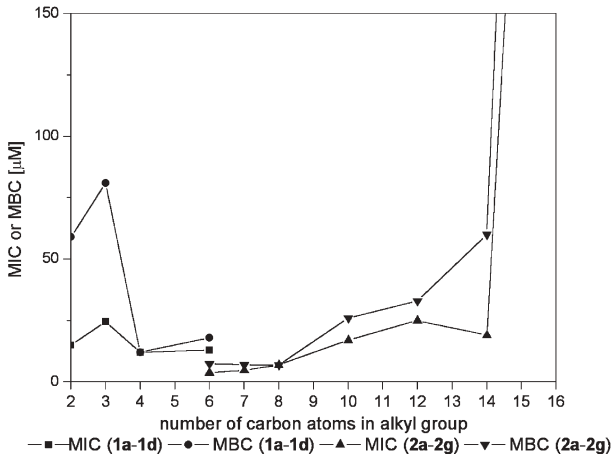


Fig. 2 Mean MIC and MBC values for *Escherichia coli* and *Bacillus subtilis*

reaction was complete, the ionic liquids were extracted and usual work-up procedures yielded the product. $[PR_3R']$-$[NTf_2]$,[39] $[PR_3R'][N(CN)_2]$,[40] $[PR_3R'][OTf]$,[38] $[PR_3R'][BF_4]$[41] and $[PR_3R'][PF_6]$[42] were prepared (adapting known procedures for the 1-alkyl-3-methylimidazolium analogues) by stirring the sodium salt of the anion with a tetraalkylphosphonium halide in water, propanone, or a mixture of both between 20 and 55 °C, followed by the extraction with chloroform or diethyl ether, followed by the usual work-up procedure. The obtained salts are listed in Table 1.

Minimal inhibitory concentration (MIC) and minimum bactericidal or fungicidal concentration (MBC) values, determined for 21 phosphonium salts, are given in Tables 2 and 3. The calculated average MIC and MBC values for cocci are presented in Fig. 1 and for *Escherichia coli* and *Bacillus subtilis* in Fig. 2. Alkyltrihexylphosphonium chlorides and bromides are active against microorganisms. The activity is selective: strong effects are observed against cocci and bacillus, but they are insignificant against fungi. In the case of rods, high activity has been observed only against *Escherichia coli*. The chlorides and bromides exert insignificant effects against the remaining rods.

Efficiency of their action reflects the length of alkyl substituent, as presented in Fig. 1 and 2. Highly bacteriostatic effects against cocci (Fig. 1), expressed by the low MIC values, have been demonstrated by halides with pentyl to tetradecyl cationic substituents. On the other hand, bacteriocidal effects, expressed by low values of MBC, have been exerted by halides having butyl to octyl cationic groups. On the other hand, against *Escherichia coli* and *Bacillus subtilis*, the bacteriostatic and bacteriocidal effects have overlapped. The most effective halides are those having butyl to tetradecyl cationic substituents. Chlorides **2a** and **2c** have proved most effective in their anti-bacterial activity. Their action against cocci is comparable to that of generally applied benzalkonium chloride (BAC, Aldrich, in which alkyl represents a mixture of alkyl from C_8H_{17} to $C_{18}H_{37}$), as shown in Table 2.

The halides examined have behaved in the distinctive manner of quaternary ammonium chlorides, (alkoxymethyl)-triphenylphosphonium chlorides,[43] and (alkylthiomethyl)-triphenylphosphonium chlorides,[44] which are equally effective against cocci, rods, bacillus and fungi. Loss of activity against a wide spectrum of microbes can be explained by the presence of four large substituents around the phosphorus atom. The more symmetrical anion is bound to be less adsorbed at the surface of cell membrane. Exchange of the halide by other anions has resulted in a loss of an anti-microbial activity of the salts. Indeed, salts **3h** and **3j** demonstrate no anti-microbial activity. In practice, the non-halogen containing salts destroy only *Micrococcus luteus*, and then only when present in relatively high concentrations. MIC and MBC values for the salts are listed in Table 3, where the symbol "$>$" indicates that actual MIC and MBC are higher than indicated. In the studies, original concentrations amounted to 500 mg l^{-1}.

The anion exerts practically no effect on anti-microbial activity in the case of a series of imidazolium ionic liquids[36] whereas this is not the case for alkyltrihexylphosphonium salts. Within the group of phosphonium salts of this investigation, both cation structure and the type of anion have effects on the biological activity.

The anti-electrostatic effect of phosphonium based ILs is a result of two quantities: the surface resistance and the half-life decay time. The surface resistance has been calculated from the formula

$$R_s = \frac{Ul}{is} \quad [\Omega]$$

in which U is the applied voltage (U = 100 V), l is the length of electrodes (l = 100 mm), i is the measured current intensity, and s is the distance between the electrodes (s = 10 mm).

The half-life decay time was found from relation

$$\tau_{1/2} = \sqrt{\frac{\tau_+^2 + \tau_-^2}{2}} \quad [s]$$

in which τ_+ and τ_- are the mean half-decay times of positive and negative charges, respectively.

The anti-electrostatic effect was determined following the criteria listed in Table 4 and presented in Table 5.

Generally, the studied bromides and chlorides have presented excellent anti-electrostatic properties. Only the bromide

Table 4 Criteria for the estimation of the anti-electrostatic effect based on the surface resistance R_s[a] and half charge decay time $\tau_{1/2}$[b]

log R_s	$\tau_{1/2}$	Anti-electrostatic effect
<9	<0.5	Excellent
9–9.99	0.51–2	Very good
10–10.99	2.1–10	Good
11–11.99	10.1–100	Sufficient
12–12.99	>100	Insufficient
>13	>600	Lack of anti-electrostatic properties

[a] In Ω. [b] In s.

Table 5 Surface resistance R_s[a], half charge decay time $\tau_{1/2}$[b] and anti-electristatic effect for the prepared salts

Salt	log R_s	$\tau_{1/2}$	Effect
1a	9.9	0.5	Very good
1b	8.8	0.25	Excellent
1c	8.3	0.25	Excellent
1d	8.3	0.25	Excellent
2a	8.3	0.25	Excellent
2b	8.8	0.2	Excellent
2c	8.6	0.25	Excellent
2d	8.6	0.2	Excellent
2e	8.8	0.1	Excellent
2f	8.9	0.2	Excellent
2g	8.9	0.25	Excellent
3a	9.5	0.5	Very good
3b	9.3	0.5	Very good
3c	9.3	0.5	Very good
3d	9.3	0.5	Very good
3e	8.5	0.1	Excellent
3f	8.5	0.2	Excellent
3g	>13	>600	Lack
3h	9.5	0.5	Very good
3i	9.3	0.5	Very good
3j	9.9	0.5	Very good

[a] In Ω. [b] In s.

1a with a short alkyl group, has shown a very good effect. Substitution of the anion in the studied trihexyl(tetradecyl)-phosphonium chloride demonstrated its excellent and very good effect. The obtained hexafluorophosphate **3g** lost its potential for draining the charge and showed no anti-electrostatic properties. Identical phenomenon was noted for ILs with symmetrical dialkoxymethyl imidazolium cation.[45]

Conclusion

A range of phosphonium ionic liquids having the generic formula $[PR_3R']X$ (R and R′ are alkyl groups; X is halide, trifluoromethanesulfonate, bis(trifluoromethylsulfonyl)imide, nitrate, dialkylphosphinate, dicyanamide, decanoate, tetrafluoroborate, hexafluorophosphate, or diisobutyldithiophosphinate have been prepared. The reaction conditions are mild, the workup procedure is simple and the yields are high. All of the obtained phosphonium ionic liquids are air- and moisture-stable under ambient conditions.

Alkyltrihexylphosphonium halides with alkyl ranging from pentyl to tetradecyl showed anti-microbial activities. They are strongly effective against cocci. This activity is comparable to that of a standard commercial biocide—benzalkonium chloride. Exchange of the halide to other anions has resulted in a loss of an anti-microbial activity. The fact that the non-halide phosphonium ionic liquids have relatively low bio-activity can be considered as a positive atribute.

This work shows that alkylphosphonium ionic liquids also have anti-electrostatic properties. This activity is dependent on the structure of the anion. Generally, halides have presented excellent anti-microbial properties and hexafluorophosphate lost its potential for draining the charge and showed no anti-electrostatic properties.

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Rapid base-catalyzed decarboxylation and amide-forming reaction of substituted cinnamic acids *via* microwave heating

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Decarboxylation of substituted cinnamic acids having a hydroxyl group at the *para* position gave predominantly the corresponding styrene derivatives in the presence of base with microwave heating. The reaction was conducted either under solvent-free conditions or using a solvent. When a primary amine was used as a base, the yield of the styrene or amide depended on the substituent of the cinnamic acid. Microwave heating for this reaction suppressed the side reactions compared with conventional heating.

Introduction

Various types of substituted cinnamic acids are known to be precursors of aroma compounds in plants.[1] Ferulic acid **1a** is a kind of cinnamic acid for which we have recently developed a mass production method from rice bran.[2,3] Therefore, interest in industrial usage of **1a** and its derivatives has intensified in recent years: for example, as cancer preventive agents,[4] agents for control of germination,[5] UV-absorbers,[6] and so on. In particular, it was found that amide compounds obtained from **1a** had potential as hypoglycemic agents.[7] A conventional synthesis of amide compounds has been performed by a condensation between carboxylic acid and amine with heating.[8] This reaction seemed to be suitable for microwave-assisted rapid synthesis.

Microwave-assisted organic reactions have been of growing interest as a type of environmentally friendly process.[9] In many cases, the reactions are performed under solvent-free heterogeneous conditions or homogeneous catalytic conditions. The salient feature of microwave irradiation is that often a decrease in reaction time is observed.

We tried to prepare the amide compounds of ferulic acid with alkylamines by microwave irradiation. However, the amide **3a** was not obtained but rather the styrene **2a** was produced instead.[10] Although the pH dependent decarboxylation of substituted cinnamic acids has been studied in aqueous media,[11] a convenient laboratory method for the preparation of substituted styrenes such as **2a** and **2b** was not reported due to the instability of the products.[12,13]

It is worthwhile to prepare styrene derivatives from a bio-natural resource for industrial usage as a functional polymer. For example, it was reported that the styrene **2a** could be useful for biodegradable polymers.[14] In this paper, we report our investigations into base-catalyzed decarboxylation and amide-forming reactions of various substituted cinnamic acids to produce the corresponding styrenes or amides using microwave heating (Scheme 1).

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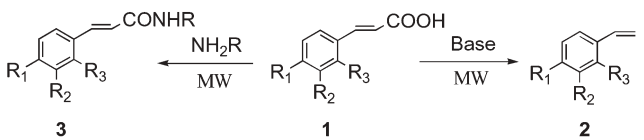
Results and discussion

The reactions using **1a** under solvent-free conditions were investigated. A typical reaction procedure is as follows. To 500 mg of **1a** in a 30 ml flask equipped with a condenser was added an equimolar amount of an amine, followed by heating with a 500 W modified household microwave oven until the evolution of carbon dioxide subsided (entries no. 3, 10, 12, and 19 in Table 1). The styrene **2a** was obtained in moderate yields using various bases such as alkyl amines or pyridine. No amide compound **3a** was produced in these reactions.

Next, we examined the reaction using solvents. No reaction was observed when solvents alone were used such as ethylene glycol (EG) and dimethylformamide (DMF) with microwave heating (entries no. 1 and 2 in Table 1). In some cases, when a small amount of solvent (0.5 mL) was used in a wetted condition, the yields increased with decreasing amount of base (entries no. 5–7 in Table 1). An amount of 10 mol% of base to **1a** was enough to produce the styrene in good yields. Solvents such as EG, diethylene glycol (DEG), and DMF, which have higher dielectric constants, seem to work well in this reaction. In our study, when DEG was used as solvent in the presence of Et_3N as base, the styrene was obtained in high yield (75%, entry no. 16 in Table 1). In these reactions the formation of the amide was not observed.

The relationship between the yield of **2a** and pK_a of the base is plotted in Fig. 1. This reaction depended on the basicity of



a: R_1 = OH, R_2 = OCH_3, R_3 = H
b: R_1 = OH, R_2 = R_3 = H
c: R_2 = OH, R_1 = R_3 = H
d: R_3 = OH, R_1 = R_2 = H
e: R_2 = OH, R_1 = OCH_3, R_3 = H
f : R_1 = OH, R_2 = OH, R_3 = H
g: R_1 = R_2 = OCH_3, R_3 = H
h: R_1 = R_2 = R_3 = H

Scheme 1

Table 1 Microwave-assisted decarboxylation of **1a**[a]

Entry	Base (mol%)	Solvent	Time/min	Recovery (%)	Yield (%) of **2a**
1	none	EG	2	>99	0
2	none	DMF	3	>99	0
3	$BuNH_2$ (100)	none	4	0	43
4	$BuNH_2$ (100)	water	1.5	0	40
5	$BuNH_2$ (100)	EG	2	0	30
6	$BuNH_2$ (50)	EG	2	0	36
7	$BuNH_2$ (10)	EG	2	4	61
8	$BuNH_2$ (1)	EG	4	54	30
9	$HexNH_2$ (10)	EG	2.5	0	56
10	$OcNH_2$ (100)	none	4	14	58
11	Quinoline (10)	EG	4	37	35
12	Pyridine (100)	none	4	34	41
13	Pyridine (100)	EG	4	63	16
14	Et_3N (10)	EG	2.5	0	62
15	Et_3N (5)	EG	4	3	55
16	Et_3N (10)	DEG	2.5	9	75
17	Et_3N (10)	DMF	2.5	13	63
18	Et_2NH (10)	EG	2.5	0	57
19	Piperidine (100)	none	4	0	27
20	Piperidine (10)	EG	2.5	0	48

[a] 2.57 mmol (0.5 g) of **1a**, 0.257–2.57 mmol of base and 0.5 mL of solvent were placed in the flask.

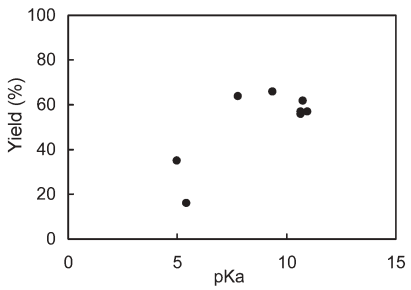


Fig. 1 Dependence of yields of **2a** on the pK_a of the base. Reaction conditions: 2.57 mmol (0.5 g) of **1a**, 0.257 mmol of base, and 0.5 mL of EG were heated with microwave irraditaion (500 W, 2–4 min, upper operating temperature was around 200 °C).

the amine and higher yield of **2a** was obtained by use of a base having higher basicity (pK_a > *ca.* 7).

It is noted that the styrene produced is reactive and easily forms polymeric products. When the reaction was performed under conventional heating (oil bath) using 0.5 g of **1a**, 10 mol% of triethylamine, and 0.5 mL of EG, the styrene was obtained in 22% yield (20 h heating at 100 °C), 31% (1 h at 150 °C), and 38% (10 min at 200 °C). It was assumed that such longer reaction times yielded polymeric products to reduce the yield during oil bath heating.

Various substituted cinnamic acids **1b–h** and ethyl ferulate **4** were used for the reaction to investigate the formation of amides or styrenes. The reactions were performed under two sets of conditions: A) two equivalents of *n*-butylamine were used in the amide-forming reaction; B) triethylamine or pyridine was used in the decarboxylation reaction. The reactions were performed under both solvent and solvent-free conditions. The results are summarized in Table 2. The acids **1b** and **1f** gave only styrenes under both sets of conditions. The acids **1c**, **1d**, and **1g** gave predominantly the corresponding amides in 63%, 22%, and 22% yield, respectively and a small amount of styrenes under conditions A. Among those, only the acid **1d** gave the styrene in 23% yield under conditions B. Very small amount of styrene from the acid **1e** was obtained under both sets of conditions. The acid **1f** gave only styrene in 30% yield. The cinnamic acid **1h** gave only amide in 69% yield. Ethyl ferulate **4** did not give any products. These results show that the production of amide or styrene depends on the substituent of cinnamic acid. It is noteworthy that a hydroxyl group at the *para* position of the benzene ring and a free carboxyl group are important to produce styrene derivatives.

A modern microwave apparatus for organic synthesis is able to control reaction conditions such as temperature, pressure, *etc*. We used this apparatus to monitor the temperature profiles of this reaction and the results are shown in Fig. 2. While a solid of ferulic acid **1a** was not only heated but also melted, adding EG to the solid caused its temperature to increase beyond the boiling point of EG by microwave heating with no reaction. Further, upon the addition of triethylamine, the reaction mixture was rapidly heated to the boiling point of EG to produce the styrene.

This base-catalyzed decarboxylation was explained by the mechanism suggested by Cohen and Jones,[11] who studied the decarboxylation of *p*-hydroxycinnamic acid in aqueous media and proposed that a produced dianion leads to the

Table 2 Microwave-assisted decarboxylation and amide-forming reaction of various substituted cinnamic acids[a]

Entry	Cinnamic acid	Base (mol%)	Solvent	Time/min	Recovery (%)	Yield (%) of **3**	Yield (%) of **2**
1	**1b**	$BuNH_2$ (200)	DMF	3	0	0	61
2	**1b**	Et_3N (10)	DMF	2	22	—	63
3	**1c**	$BuNH_2$ (200)	none	3.5	27	63	6
4	**1c**	Et_3N (10)	EG	4	66	—	trace
5	**1d**	$BuNH_2$ (200)	DEG	2	52	22	4
6	**1d**	Et_3N (50)	DEG	2.5	62	—	23
7	**1e**	$BuNH_2$ (200)	DEG	2	97	0	trace
8	**1e**	Et_3N (10)	EG	4	92	—	3
9	**1f**	$BuNH_2$ (200)	none	4	47	0	trace
10	**1f**	Pyridine (10)	DMF	1.5	4	—	30
11	**1g**	$BuNH_2$ (200)	DEG	3	72	22	2
12	**1g**	Et_3N (10)	EG	4	>99	—	0
13	**4**	$BuNH_2$ (200)	none	4	>99	0	0
14	**4**	Et_3N (10)	EG	4	>99	—	0
15	**1h**	$BuNH_2$ (200)	none	5	26	69	0
16	**1h**	Et_3N (10)	EG	3	92	—	0

[a] 2.57 mmol (0.5 g) of **1**, 0.257–2.57 mmol of base and 0.5 mL of solvent were placed in the flask.

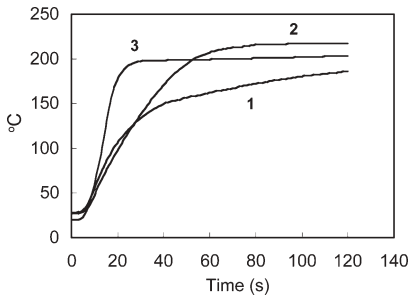
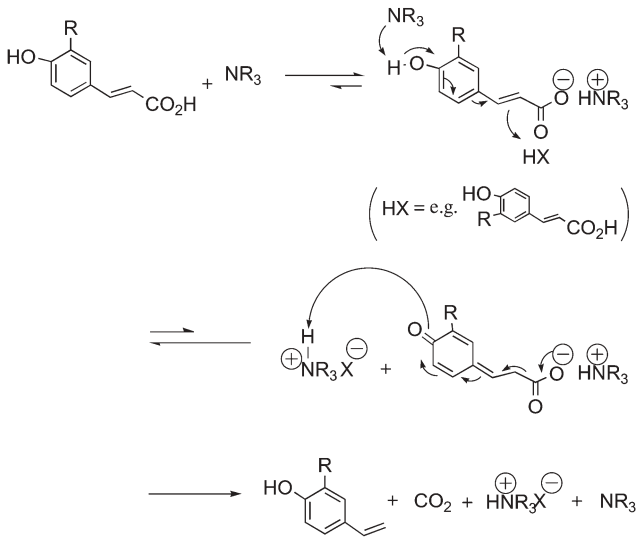


Fig. 2 Temperature profiles for EG (1), EG–**1a** (2), EG–**1a**–Et_3N (3). 2.57 mmol of **1a**; 0.257 mmol of Et_3N; 0.5 mL of EG, 300 W full-time microwave irradiation.



Scheme 2 Mechanism of base-catalyzed decarboxylation.

quinomethine which undergoes rapid decarboxylation. We propose a similar mechanism as shown in Scheme 2. The ester **4** did not yield the corresponding styrene but also only starting material was recovered. This indicates that decarboxylation proceeds *via* the formation of ammonium salts. This is supported by the reaction under solvent-free conditions, in which an exothermic reaction occurred immediately in solid state when an alkylamine was added to the powder of **1a**.

Experimental

General

A 500 W modified household microwave oven (2.45 GHz) was used for microwave heating and the microwave irradiation was continuous at full power. Temperature profiles of the reactions with microwave heating were monitored by a CEM Discover Focused Microwave Synthesis System equipped with a non-contact infrared sensor. NMR spectra were recorded on a Varian Unity-plus 400 spectrometer and the residual resonance of deuterated solvent was used as an internal reference.

Typical procedure

To 500 mg of **1a** and 0.5 mL of ethylene glycol in a 30 ml flask equipped with a condenser was added 10 mol% of triethylamine. The mixture was heated with a 500 W modified household microwave oven until the evolution of carbon dioxide subsided (*ca.* 2–4 min). After the reaction, the mixture was cooled immediately in a water bath and then dissolved in ethyl acetate. The solution was washed with 0.1 M aq. HCl, water, and brine, and then the organic portion was dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the product was purified by SiO_2 flash column chromatography using chloroform–MeOH.

3-Methoxy-4-hydroxylstyrene (2a)[14]

Oil; δ_H(400 MHz; $CDCl_3$) 3.90 (3 H, s, OCH_2), 5.11 (1 H, dd, *J* 0.9 and 10.8, $=CH_2$), 5.73 (1 H, dd, *J* 0.9 and 17.6, =CH), 5.63 (1 H, s, OH), 6.62 (1 H, dd, *J* 10.8 and 17.6, $=CH_2$), 6.85–6.93 (3 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 55.8, 108.0, 111.4, 114.3, 120.6, 130.2, 136.6, 145.6, 146.5; *m/z* (ESI-TOF) 151.06 $(M + H)^+$, $C_9H_{10}O_2$ requires $(M + H)^+$ 151.08.

4-Hydroxystyrene (2b)

Solid (plates); mp 67–69 °C (lit.[13] 72–73.5 °C); δ_H(400 MHz; $CDCl_3$) 5.04 (1 H, s, OH), 5.11 (1 H, dd, *J* 0.9 and 11.0, $=CH_2$), 5.59 (1 H, dd, *J* 0.9 and 17.6, =CH), 6.64 (1 H, dd, *J* 10.8 and 17.6, $=CH_2$), 6.76–6.80 (2 H, m, ArH), 7.27–7.31 (2 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 111.7, 115.4, 127.6, 130.7, 136.1, 155.2: *m/z* (ESI-TOF) 121.06 $(M + H)^+$, C_8H_8O requires $(M + H)^+$ 121.06.

3-Hydroxystyrene (2c)[12]

Oil; δ_H(400 MHz; $CDCl_3$) 4.82 (1 H, s, OH), 5.23 (1 H, dd, *J* 0.7 and 11.1, $=CH_2$), 5.71 (1 H, dd, *J* 0.9 and 17.6, =CH), 6.64 (1 H, dd, *J* 10.8 and 17.6, $=CH_2$), 6.71–6.73 (1 H, dd, *J* 2.1 and 7.6, ArH), 6.87 (1 H, t, *J* 2.1, ArH), 6.97 (1 H, d, *J* 7.5, ArH), 7.18 (1 H, t, *J* 7.9, ArH); δ_C(100 MHz; $CDCl_3$) 112.7, 114.3, 114.8, 119.1, 129.7, 136.4, 139.3, 155.7; *m/z* (ESI-TOF) 143.07 $(M + Na)^+$, C_8H_8O requires $(M + Na)^+$ 143.05.

2-Hydroxystyrene (2d)[12]

Oil; δ_H(400 MHz; $CDCl_3$) 5.06 (1 H, s, OH), 5.35 (1 H, dd, *J* 1.4 and 11.2, $=CH_2$), 5.76 (1 H, dd, *J* 1.4 and 17.6, =CH), 6.78 (1 H, dd, *J* 1.1 and 8.1, ArH), 6.93 (1 H, dd, *J* 11.2 and 17.6, $=CH_2$), 6.89–6.93 (1 H, m, ArH), 7.11–7.15 (1 H, m, ArH), 7.38 (1 H, dd, *J* 1.7 and 7.7, ArH); δ_C(100 MHz; $CDCl_3$) 115.82, 115.86, 120.9, 124.8, 127.3, 128.9, 131.5, 152.8; *m/z* (ESI-TOF) 121.05 $(M + H)^+$, C_8H_8O requires $(M + H)^+$ 121.06.

3-Hydroxy-4-methoxystyrene (2e)

Solid (plates); mp 57–58 °C; δ_H(400 MHz; $CDCl_3$) 3.87 (3 H, s, OCH_2), 5.11 (1 H, dd, *J* 0.9 and 10.8, $=CH_2$), 5.57 (1 H, s, OH), 5.58 (1 H, dd, *J* 0.9 and 17.6, =CH), 6.60 (1 H, dd, *J* 10.8 and 17.6, $=CH_2$), 6.78(1 H, d, *J* 8.2, ArH), 6.86 (1 H, dd, *J* 2.0 and 8.2, ArH), 7.03(1 H, d, *J* 2.0, ArH); δ_C(100 MHz; $CDCl_3$) 56.0, 110.4, 111.6, 112.1, 118.8, 131.4, 136.3, 145.6, 146.4; *m/z* (ESI-TOF) 151.12 $(M + H)^+$, $C_9H_{10}O_2$ requires $(M + H)^+$ 151.08.

3,4-Dihydroxystyrene (2f)

Solid; mp 50–53 °C; δ_H(400 MHz; DMSO-d_6) 4.99 (1 H, dd, *J* 1.2 and 10.9, =CH_2), 5.48 (1 H, dd, *J* 1.2 and 17.5, =CH), 6.52 (1 H, dd, *J* 10.9 and 17.5, =CH_2), 6.66–6.71(2 H, m, ArH), 6.84 (1 H, d, ArH), 8.94 (2 H, br s, OH); δ_C(100 MHz; DMSO-d_6) 110.6, 113.1, 115.7, 118.3, 129.0, 137.0, 145.5, 145.8; *m*/*z* (ESI-TOF) 137.11 $(M + H)^+$, $C_8H_8O_2$ requires $(M + H)^+$ 137.06.

3,4-Dimethoxystyrene (2g)

Oil; δ_H(400 MHz; $CDCl_3$) 3.87 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 5.13 (1 H, dd, *J* 0.9 and 10.8, =CH_2), 5.60 (1 H, dd, *J* 0.9 and 17.6, =CH), 6.63 (1 H, dd, *J* 10.8 and 17.6, =CH_2), 6.81 (1 H, d, *J* 7.6, ArH), 6.91–6.96 (2 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 55.8, 55.9, 108.5, 111.0, 111.8, 119.4, 130.7, 136.5, 148.9, 149.0; *m*/*z* (ESI-TOF) 187.13 $(M + Na)^+$, $C_{10}H_{13}O_2$ requires $(M + Na)^+$ 187.07.

3-Hydroxycinnamoyl *n*-butylamide (3c)

Solid; mp 104–106 °C; δ_H(400 MHz; DMSO-d_6) 0.88 (3 H, t, *J* 7.3, CH_3), 1.27–1.34 (2 H, m, CH_2), 1.39–1.46 (2 H, m, CH_2), 3.13–3.18 (2 H, m, CH_2), 6.52 (1 H, d, *J* 15.7, =CH), 6.74–6.77 (1 H, m, ArH), 6.90–6.96 (2 H, m, ArH), 7.16–7.20 (1 H, m, ArH), 7.29 (1 H, d, *J* 15.7, =CH), 8.05 (1 H, t, NH), 9.56 (1 H, s, OH); δ_C(100 MHz; DMSO-d_6) 13.9, 19.8, 31.4, 38.5, 113.8, 116.7, 118.8, 122.3, 130.1, 136.4, 138.7, 157.9, 165.0; *m*/*z* (ESI-TOF) 220.12 $(M + H)^+$, $C_{13}H_{17}NO_2$ requires $(M + H)^+$ 220.13.

2-Hydroxycinnamoyl *n*-butylamide (3d)

Solid; mp 151–154 °C; δ_H(400 MHz; DMSO-d_6) 0.88 (3 H, t, *J* 7.3, CH_3), 1.25–1.34 (2 H, m, CH_2), 1.38–1.45 (2 H, m, CH_2), 3.12–3.17 (2 H, m, CH_2), 6.63 (1 H, d, *J* 15.7, =CH), 6.78–6.88 (2 H, m, ArH), 7.13–7.18 (1 H, m, ArH), 7.38–7.58 (1 H, m, ArH), 7.60 (1 H, d, *J* 15.9, =CH), 8.01 (1 H, t, NH), 10.00 (1 H, br s, OH); δ_C(100 MHz; DMSO-d_6) 13.7, 20.1, 31.7, 39.5, 120.8, 127.7, 128.8, 129.6, 134.9, 140.8, 165.8; *m*/*z* (ESI-TOF) 220.12 $(M + H)^+$, $C_{13}H_{17}NO_2$ requires $(M + H)^+$ 220.13.

3,4-Dimethoxycinnamoyl *n*-butylamide (3g)

Solid; mp 114–117 °C; δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J*7.3 , CH_3), 1.32–1.41 (2 H, m, CH_2), 1.49–1.56 (2 H, m, CH_2), 3.34–3.39 (2 H, m, CH_2),3.87 (3 H, s, OCH_3), 3.88(3 H, s, OCH_3), 5.59 (1 H, t, NH), 6.24 (1 H, d, *J* 15.6, =CH), 6.82 (1 H, d, *J* 8.2, ArH), 6.99 (1 H, d, *J* 2.0, ArH), 7.05 (1 H, dd, *J* 2.0 and 8.3, ArH), 7.53 (1 H, d, *J* 15.6, =CH); δ_C(100 MHz; $CDCl_3$) 13.7, 20.1, 31.8, 39.4, 55.8, 55.9, 109.6, 111.0, 118.6, 121.8, 127.8, 140.6, 149.1, 150.5, 166.1; *m*/*z* (ESI-TOF) 264.23 $(M + H)^+$, $C_{15}H_{21}NO_3$ requires $(M + H)^+$ 264.16.

Cinnamoyl *n*-butylamide (3h)

Solid; mp 75–78 °C; δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.3, CH_3), 1.32–1.42 (2 H, m, CH_2), 1.50–1.57 (2 H, m, CH_2), 3.35–3.40 (2 H, m, CH_2), 5.72 (1 H, br s, NH), 6.37 (1 H, d, *J* 15.6, =CH), 7.31–7.36 (3 H, m, ArH), 7.46–7.48 (2 H, m, ArH), 7.60 (1 H, d, *J* 15.6, =CH); δ_C(100 MHz; $CDCl_3$) 13.7, 20.1, 31.7, 39.5, 120.8, 127.7, 128.8, 129.6, 134.9, 140.8, 165.8; *m*/*z* (ESI-TOF) 204.12 $(M + H)^+$, $C_{13}H_{17}NO$ requires $(M + H)^+$ 204.14.

Conclusions

In conclusion, base-catalyzed decarboxylation or amide-forming reactions of various types of substituted cinnamic acids using microwave heating were investigated. The styrenes were obtained predominantly from cinnamic acids having a hydroxyl group at the *para* position. The reaction can be performed under both solvent and solvent-free conditions and suppressed side reactions comparing with conventional heating. Microwave heating is suitable for this type of reaction in which an unstable product is produced. Furthermore, we believe it is important to develop a green process to obtain fundamental products from a renewable natural product.

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$KHSO_4$: a catalyst for the chemo-selective preparation of 1,1-diacetates from aldehydes under solvent-free conditions

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A simple, mild, effective and green method to form acylals from aliphatic and aromatic aldehydes in good to excellent yields in the presence of potassium hydrogen sulfate, $KHSO_4$, as catalyst under solvent-free conditions is described. Ketones are not affected under the reaction conditions.

The protection of carbonyl groups is often necessary during the synthesis of multi-functional complex molecules and natural products. Acylal formation is one of the most useful methods to protect carbonyl groups due to the stability of the resulting 1,1-diacetates. They are stable in neutral and basic media.[1] Geminal diacetates or 1,1-diacetates are synthetically important precursors for the preparation of 1-acetoxydienes for Diels–Alder reaction.[2] Chiral allylic esters have been obtained using palladium catalysts by an asymmetric allylic alkylation of *gem*-diesters.[3] The preparation of homoallyl acetates by allylation of 1,1-diacetates has also been reported.[4]

Generally, 1,1-diacetates have been prepared by the reaction of carbonyl compounds with acetic anhydride catalyzed with protic acids such as sulfuric acid, methanesulfonic acid or phosphoric acid,[5] NH_2SO_3H,[6] Nafion-H,[7] Lewis acids such as $ZnCl_2$,[8] $FeCl_3/SiO_2$,[1,9] I_2,[10] WCl_6,[11] LiOTf,[12] $LiBF_4$,[13] $Sc(OTf)_3$,[14] and neutral condition such as NBS.[15]

Some of these procedures have some drawbacks such as low yield, requirement for organic solvents, involvement of expensive, moisture and air sensitive catalysts and high temperatures.

Although a number of different methods have been reported for the preparation of 1,1-diacetates, there is still a need to search for better catalysts with regard to their toxicity, handling, availability, economic viability and operational simplicity. In view of the recent trend in catalytic processes towards the development of clean and green chemical processes, investigations for new and less hazardous catalyst has become a priority in synthetic organic chemistry.

In recent years the use of inorganic reagents in solvent-free conditions has rapidly increased, as these reactions often need milder reaction conditions, easier work-up and provide higher selectivity than similar reactions using organic reagents in solution.[16,17]

In continuation of our program to develop reactions in solvent-free systems[18–23] and in catalytic manner,[24,25] herein we report a simple, convenient and efficient process for preparation of acylals from aliphatic and aromatic aldehydes, in which only a catalytic amount of $KHSO_4$, a relatively green chemical, is required.

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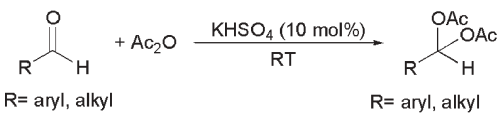
The reaction of benzaldehyde with acetic anhydride in the presence of 10 mol% $KHSO_4$ at room temperature afforded the corresponding 1,1-diacetates in less than 1 minute. The reaction is conducted simply by mixing the benzaldehyde with acetic anhydride and $KHSO_4$ in a beaker using a spatula. The progress of the reaction was monitored by TLC. To establish the generality of the method, several aliphatic and aromatic aldehydes were reacted similarly. The reaction gave substituted 1,1-diacetates (Scheme 1) in good to excellent yields (Table 1). Reactions were carried out in the absence of solvent. It should be mentioned that substrates having electron-donating groups in the *para* position in the aromatic ring underwent the reactions in a short period of time (Table 1, entries 4 and 5) and gave excellent yields of products. Ketones are found to be unaffected under the reaction conditions.

In order to show the high selectivity of the procedure, we investigated competitive reactions for the preparation of the 1,1-diacetates from benzaldehyde in the presence of benzophenone or acetophenone using a catalytic amount of $KHSO_4$ under solvent-free conditions at room temperature. We found that ketones did not produce any acylals under the reaction conditions. This result suggested that chemo-selective protection of aldehydes in the presence of ketones could be achieved with this procedure (Scheme 2).

In conclusion, a very simple and convenient catalytic method has been developed for the synthesis of 1,1-diacetates from a variety of aldehydes under solvent-free conditions. The method has advantages in terms of high yields, high selectivity, short reaction times, ease of operation, and use of a relatively non-toxic, available and inexpensive catalyst. We believe this protocol will be a useful addition to the modern synthetic methodologies.

Experimental

Melting points were measured by using the capillary tube method with electrothermal 9100 apparatus. ^1H NMR spectra were recorded on a Bruker DRX-90 AVANCE by using TMS

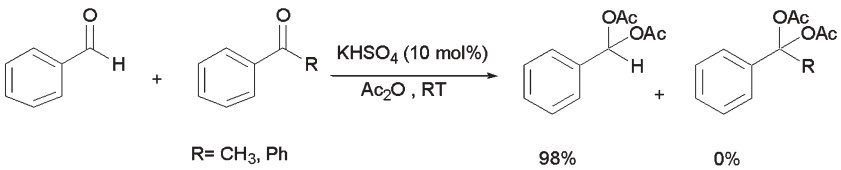


Scheme 1

Table 1 Synthesis of 1,1-diacetates using $KHSO_4$ as catalyst

Entry	Substrate	Time/min	Yield[a] (%)	Mp/°C	
				Found	Reported[ref]
1	Isobutyraldehyde	10	85	[b]	—
2	Butyraldehyde	15	87	[b]	—
3	Benzaldehyde	1	99	44	44–45[5]
4	4-Methyl-benzaldehyde	2	99	81	81–82[29]
5	4-Methoxy-benzaldehyde	2	86	63	64–65[30]
6	4-Chloro-benaldehyde	3	99	81	81–82[31]
7	2-Nitro-benzaldehye	90	92	89	90[32]
8	3-Nitro-benzaldehye	70	96	65	64–66[30]
9	4-Nitro-benzaldehye	90	96	125	125–126[30]
10	Cinnamaldehyde	20	90	86	84–86[1]
11	Furfuraldehyde	5	98	53	52–54[33]
12	Acetophenone	No reaction	—	—	—
13	Benzophenone	No reaction	—	—	—

[a] Yields refer to isolated pure products. [b] Oily products were obtained.



Scheme 2

as an internal standard ($CDCl_3$ solution). IR spectra were recorded as KBr disks on a FT-IR Bruker Tensor 27. All products are known compounds, which were satisfactorily characterized by physical and spectral data.[5,9,26–33]

Preparation of 1,1-diacetates using $KHSO_4$ as catalyst: general procedure

$KHSO_4$ (10 mol%) was treated with an appropriate aldehyde (10 mmol) and acetic anhydride (20 mmol). The slurry mixture was stirred for the indicated time (Table 1) at room temperature. After completion of the reaction (controlled by TLC), the reaction was quenched with 10 mol% aqueous solution of $NaHCO_3$ (5 mL), and the mixture was continuously extracted with Et_2O (5 mL). The organic layer was isolated and washed with brine (2 × 5 mL) and dried over $MgSO_4$. Evaporation of the solvent gave almost pure product. Further purification was performed by column chromatography on silica gel using petroleum ether–ethyl acetate as eluent to afford the desired pure products in good to excellent yields. The results are summarized in Table 1.

Physical and spectra data of selected products

Entry 2. Oil; ^{1}H NMR δ(ppm): 0.94 (t, 3H, J = 3.5 Hz, CH_3), 1.42–1.45 (m, 2H, CH_2), 1.77–1.79 (m, 2H, CH_2), 2.06 (s, 6H, $2COCH_3$), 6.81 (t, 1H, J = 5.5 Hz, CH); IR (KBr) ν/cm^{-1}: 2956,2880, 1755, 1250, 1225,1080.

Entry 3. Mp 44 °C (44–45 °C),[5] ^{1}H NMR δ(ppm): 2.10 (s, 6H, $2COCH_3$), 7.40–7.42 (m, 3H, Ar-H), 7.52–7.55 (m, 2H, Ar-H), 7.69 (s, 1H, CH); IR (KBr) ν/cm^{-1}: 1756, 1510, 1440, 1250, 1220, 1010.

Entry 4. Mp 81 °C (81–82 °C),[29] ^{1}H NMR δ(ppm): 2.12 (s, 6H, $2COCH_3$), 2.38 (s, 3H, CH_3), 7.20 (d, 2H, J = 8.0 Hz, Ar-H), 7.40 (d, 2H, J = 8.2 Hz, Ar-H), 7.65 (s, 1H, CH); IR (KBr) ν/cm^{-1}: 2940, 1770, 1715, 1520, 1400, 1250, 1210, 1010, 960, 920.

Entry 6. Mp 81 °C (81–82 °C),[31] ^{1}H NMR δ(ppm): 2.10 (s, 6H, $2COCH_3$), 7.36–7.40 (m, 2H, Ar-H), 7.45–7.49 (m, 2H, Ar-H), 7.64 (s, 1H, CH); IR (KBr) ν/cm^{-1}: 1760, 1600, 1525, 1385, 1245, 1205, 980, 910.

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Esterification of carboxylic acids by tributyl borate under solvent- and catalyst-free conditions

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A new method for esterification of mono- and dicarboxylic acids by tributyl borate has been reported. The esterification reactions have been cleanly carried out in the absence of any solvent under catalyst-free conditions. Boric acid is the only side product, which precipitates during the reaction and can be re-used in the production of tributyl borate. Important mono- and dibutylesters, which have found wide applications as plasticizers and ester base lubricants, were prepared by this manner.

Introduction

Plasticizers are important class of low molecular weight non-volatile compounds that are widely used in the polymer industries. Some commercially available plasticizers such as dibutyl phthalate (DBP), di-*iso*-butyl phthalate (DIBP), di-*iso*-pentyl phthalate (DIPP), di-*iso*-heptyl phthalate (DIHP), and dioctyl phthalate (DOP) are normally prepared *via* the esterification reaction of phthalic anhydride by the corresponding alcohols in the presence of acidic catalysts.[1,2] Among plasticizers, dioctyl phthalate (DOP), DOA (dioctyl adipate), and dioctyl terephthalate (DOTP) have been found wide applications due their biocompatibility. Biodegradations of these compounds have been recently shown by S. Nalli and co-workers.[3]

Esterification and transesterification reactions usually carry out in hydrocarbon solvents, such as toluene. Homogeneous acid catalysts such as, sulfuric acid, methane sulfonic acid, and *p*-toluene sulfonic acid are the most conventional catalysts for this purpose. Application of these catalysts causes some difficulties such as corrosion, and environment problems. Therefore, development of new methods involving more efficient catalysts without needing for solvent has been noted. It is well known that the use of heterogeneous catalysts for liquid phase organic reactions can give a lot of benefits.[4] In such reactions, a clean reaction product solution is obtained after simple filtration, and the catalyst can be easily recovered. For this reason, some attention has been paid to the use of heterogeneous catalysts in esterification reactions.[5–8] The use of heteropolyacids,[9,10] silicoaluminophosphate molecular sieves,[11–12] and sulfated zirconia[13] as heterogeneous catalysts for esterification and/or transesterification reactions has been reported earlier.

In this paper, we report a new method for production of mono- and dibutylesters of carboxylic acids. This work was originally performed with the aim of simplifying the esterification process by omitting any acid catalyst and solvent, easier work-up, cleaner reaction, lower cost, and reducing the amount of acidic waste, which has great importance from environmental and economical points of view. The method is based on esterification reaction of mono- and dicarboxylic acids by tributyl borate. The reactions were cleanly carried out in the absence of any solvent under catalyst-free conditions. Boric acid is the only side product, which precipitates during the reaction and can be re-used in the production of tributyl borate. The prepared ester/diester compounds have widespread applications as plasticizers and synthetic ester base lubricants.

Results and discussion

Esterification and transesterification reactions are normally carried out under acid or base catalysis in hydrocarbon solvents. In the present work, the esterification reaction of mono- and dicarboxylic acids by tributyl borate has been investigated. The reactions were carried out under solvent- and catalyst-free conditions. As the esterification reaction progress, boric acid (by-product) precipitates as white crystals and separates from the reaction mixture by simple filtration at the end of the reaction. The precipitated boric acid can be re-used in the production of tributyl borate. The reaction conditions, results, and physical properties of the obtained products are summarized in Table 1. The physical properties (refractive indices and boiling points) of the prepared diesters are compatible with the literature reported values. All prepared compounds are industrially valuable and most of them have been found wide applications as plasticizers and synthetic ester base lubricants.

It has been found that the diesters of long chain dicarboxylic acids can be considered as excellent base lubricants due to: (a) good properties at high and low temperatures, (b) excellent viscosity *vs.* temperature relationship, (c) low volatility (d) lubricity, (e) additive solubility, (f) frictional properties, and (g) biodegradability.[14–17] Dibutyl esters of maleic acid (entry 1), adipic acid (entry 2), and sebacic acid (entry 3), have prepared by this method according the reaction shown in Scheme 1.

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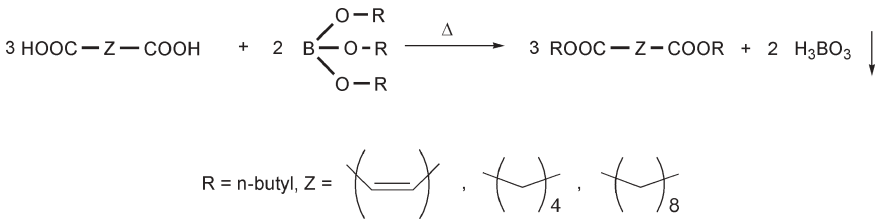
Table 1 Reaction conditions and yields of esterification reactions by tributyl borate

Entry	Product	N_D^{20} [a]	Bp/°C [b]	Temp./°C	Time/h	Yield (%) [c]
1	Dibutyl maleate	1.446 (1.445)	140–145[d] (280)	160–175	15	71.6
2	Dibutyl adipate	1.437 (1.436)	135–140[d] (305)	180–200	11	64.8
3	Dibutyl sebacate	1.443 (1.441)	160–170[d] (344)	180–200	14	73.0
4	Butyl 2-ethylhexyl phthalate	1.489(1.484)[e]	190–200[d] (210)[f]	165–170	12	75.2
5	Butyl benzoate	1.498(1.498)	90–95[d] (249)	170–190	21	70.0
6	Butyl acetate	—[g]	124–126[h] (124)	117–125	8	67.0
7	Butyl formate	—[g]	106–107[h] (106)[h]	100–105	18	54.3
8	Butyl propionate	—[g]	145–146[h] (146)	140–145	11	71.7

[a] Values in parentheses are reported in literature. [b] Values in parentheses are literature reported boiling points at atmospheric pressure. [c] Calculated based on acid number measurements. [d] Boiling point at 2–3 mmHg. [e] At 25 °C. [f] At 5 mmHg. [g] Not determined. [h] At atmosphere pressure.



Scheme 1

Butyl 2-ethylhexyl phthalate (entry 4), which is a commercially available plasticizer, was prepared by this method in two steps. In the first step phthalic anhydride was half-esterified by 2-ethylhexanol (1 : 1 molar ratios) in the absence of any catalyst and solvent. The obtained product was then subjected to esterification reaction by tributyl borate to give butyl 2-ethylhexyl phthalate.

The capability of tributyl borate toward esterification of mono carboxylic acids was also investigated (entries 5–8). Benzoic acid, acetic acid, formic acid, and propionic acid were successfully esterified by tributyl borate. The reaction work-up for low boiling point carboxylic acids is deferent from dicarboxylic acids and benzoic acid. Butyl esters of dicarboxylic acids and also benzoic acid were easily separated from reaction mixture by vacuum distillation after filtration of boric acid, whereas additional washing steps with 5% NaOH solution and water are required prior to vacuum distillation for low boiling point carboxylic acids (entries 6–8, see Experimental).

On the basis of obtained results, it can be concluded that because of the simplicity of the reaction process, absence of solvent and catalyst, easy work-up, and no waste production, the method is very useful for esterification of dicarboxylic acids as well as high boiling point mono carboxylic acids. This method can make the industrial processes less complicated. Boric acid (the only by-product) separates from the reaction mixture by filtration and can be re-used in the preparation of tributyl borate. Although the overall reactions yields (around 70%) are relatively lower than conventional methods, it must be noted that in our method the reaction takes place under solvent- and catalyst-free conditions, which are very important from environmental, economical, and industrial points of view. Furthermore, unreacted materials, which separate by simple distillation, and also boric acid, can be fed back into the reaction process and so re-used. It seems that our procedure is not suitable for esterification of low boiling point carboxylic acids and industrial processes will be complicated because of additional steps.

The extent of esterification reaction progress as a function of time for maleic acid, sebacic acid, adipic acid, 2-((2-ethylhexyloxy)carbonyl) benzoic acid, and benzoic acid are shown in Fig. 1. As is clear from this curve, all reactions achieve more than 60% conversion within 8 hours. The maximum rate belongs to sebacic acid, which reaches 65% and 73% conversions within 6.5 and 14 hours, respectively.

Experimental

Materials

Phthalic anhydride (technical grade, 99% purity) was obtained from Farabi Petrochemical Co. (Iran). Acetic acid (99.0%),

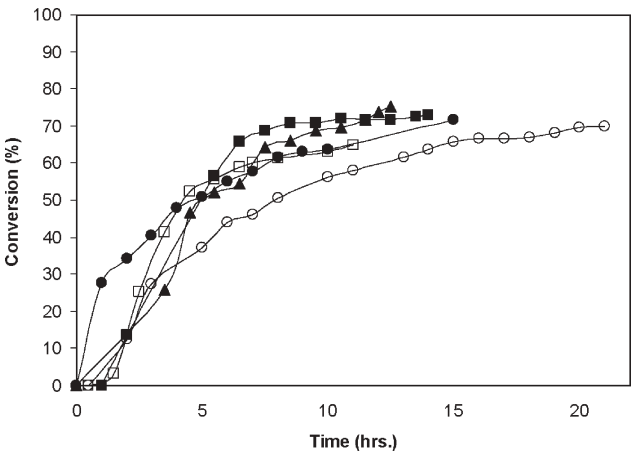


Fig. 1 Esterification reaction of mono- and dicarboxylic acids by tributyl borate as a function of time; (●) maleic acid, (■) sebacic acid, (□) adipic acid, (○) benzoic acid. (▲) 2-((2-ethylhexyloxy)carbonyl) benzoic acid.

2-ethyl-1-hexanol, and n-butanol (98.9%) were technical grades and derived from Arak Petrochemical Co. (Iran). All other chemicals are from laboratory grade and obtained from Merck Chemical Co.

Instruments

^{1}H NMR ($CDCl_3$) and FT-IR (neat) spectra were recorded on a Bruker-spectrospin-Avance 400-ultra shield spectrometer and a Shimadzu 200-91527 spectrophotometer, respectively.

Synthesis

Tributyl borate. The borate ester was prepared according to the literature.[14] In a 2 l three-necked round-bottom flask, equipped with an efficient mechanical stirrer, a reflux condenser, and Dean–Stark trap, n-butanol (444 g, 6 mole), and boric acid (124 g, 2 mole) were heated up to 90–110 °C while stirring for 11 h. During this time the reaction temperature raised up to 118 °C. After completion of the reaction, the mixture was cooled to room temperature and then filtered. The reaction yield was quantitative (230 g, 99.9%, based on collected water).

2-((2-Ethylhexyloxy)carbonyl)benzoic acid. In a 1 l three-necked round-bottom flask, equipped with an efficient mechanical stirrer, a reflux condenser, and Dean–Stark trap, phthalic anhydride (65 g, 0.5 moles), and 2-ethyl-1-hexanol (74 g, 0.5 mole) were heated up to 118 °C while stirring for 5 h. After quantitative completion of the reaction, it was allowed to cool to room temperature and the product used in the preparation of butyl 2-ethylhexyl phthalate without further treatment.

Butyl-2-ethylhexyl phthalate. To 2-((2-ethylhexyloxy)carbonyl)benzoic acid prepared in the previous section, tributyl borate (39 g, 0.169 moles) was added. The mixture was heated up to 165–170 °C while stirring and the reaction progress was followed by measuring the acid number at different time intervals. The reaction was completed in 12 h. Boric acid precipitates as the reaction progress. After completion of the reaction, the mixture was filtered. The filtrate was subjected to distillation and the low boiling point materials were removed under atmosphere pressure. The main product was obtained by continuing the distillation at 190–200 °C/2–3 mmHg (69.3 g, 75.2%).

General procedure for the preparation of dibutyl esters. In a 1 l three-necked round-bottom flask, equipped with an efficient mechanical stirrer, and a reflux condenser dicarboxylic acid and tributyl borate were charged in the molar ratios of 3 : 2. The third neck was sealed by a rubber septum and used for sampling. The mixture was heated up to the appropriate temperature for the appropriate time (Table 1) and the reaction progress was followed by measuring the acid number at different time intervals. Boric acid precipitates as the reaction progress. After completion of reaction, the mixture was filtered. The filtrate was subjected to distillation and the low boiling point materials were removed under atmosphere pressure. The main product was obtained by continuing the distillation at the appropriate temperature and pressure (Table 1). The reaction conditions and yields are also summarized in Table 1.

Butyl benzoate. In a 1 l three-necked round-bottom flask, equipped with an efficient mechanical stirrer, a reflux condenser, and Dean–Stark trap, benzoic acid (183 g, 1.5 mole), and tributyl borate (115 g, 0.5 mole) were refluxed while stirring. Boric acid precipitates as the reaction progress. After completion of the reactions (followed by measuring the acid number), the mixture was filtered. The filtrate was subjected to distillation and the low boiling point materials were removed under atmosphere pressure. The main product was obtained by continuing the distillation at 90–95 °C/2–3 mmHg (125 g, 70.0%).

General procedure for the preparation of butyl esters of low boiling point carboxylic acids (entries 6-8). The reaction was taken place same as procedure described for the preparation of butyl benzoate with the same molar ratios. The reaction mixture was refluxed while stirring for appropriate time (Table 1) and the reaction yields were determined by measuring the pH at the end of the reactions. Boric acid precipitates as the reaction progress. After completion of reactions, the mixture was filtered. The filtrate was successively washed with 200 ml of 5% NaOH solution, 200 ml of water, dried over anhydrous $CaCl_2$, and then filtered. The main product was obtained by distillation of the obtained mixture at the appropriate temperatures and pressures (Table 1). The reaction yields are summarized in Table 1.

Conclusions

A new method for esterification of mono- and dicarboxylic acids by tributyl borate has been reported. The esterification reactions have been cleanly carried out under solvent- and catalyst-free conditions. The reaction has easy work-up for dicarboxylic acids as well as high boiling point monocarboxylic acids, but additional steps are required for low boiling point carboxylic acids. Boric acid, which forms during the reaction, easily separates by filtration and can be re-used in the production of tributyl borate. Important mono- and dibutylesters, which have wide applications as plasticizers and ester base lubricants, were prepared by this method. Sebacic acid showed the maximum reactivity toward esterification reaction and reaches to 65% conversion by tributyl borate within 6.5 hours.

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TBAF-catalyzed [3 + 2]cycloaddition of $TMSN_3$ to 3-nitrocoumarins under SFC: an effective green route to chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-ones

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Tetrabutylammonium fluoride (TBAF) has been shown to catalyze very efficiently the [3 + 2] cycloaddition of trimethylsilyl azide ($TMSN_3$) to variously substituted 3-nitrocoumarins under SFC. A novel class of chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-ones has been prepared in high yields and following an environmentally-friendly protocol.

The synthesis of new heterocyclic small-molecules is a challenging topic in organic chemistry. These compounds play a pivotal role in the search for new therapeutic and drug candidates,[1] in the elucidation of the chemistry of living processes,[2] and are important substrates for the preparation of new materials necessary to improve the quality of life at a sustainable environmental cost.

The environmental cost of the organic synthesis can be significantly reduced by realizing one-pot multistep processes in alternative reaction media[3] and using environmentally-compatible catalysts (*e.g.*, organocatalyst and polymer supported catalysts).[3,4] A solvent-free condition (SFC), has proved to be very effective both in terms of selectivities and reactivity, due to the intimacy of the reactants.[5,6]

We have contributed to the development of green organic chemistry by performing organic processes in water as the reaction medium[7] and under SFC,[6] focusing our attention on the recovery and reuse of both aqueous medium (when used) and catalyst,[6a,7a,b,e–g,i,j] and on the definition of one-pot protocols for the preparation of target molecules.[6b–d,f,7a,b,f,i]

We are currently involved in the use of ammonium salts in the role of environmentally safe organic catalysts to access new classes of heterocyclic small molecules. We have recently defined a new synthetic approach for the preparation of 1*H*-tetrazoles *via* tetrabutylammonium fluoride (TBAF)-catalyzed [3 + 2] cycloaddition of trimethylsilyl azide ($TMSN_3$) to organic nitriles under SFC.[6c] Tetrabutylammonium bromide (TBABr) was also used as an effective ammonium salt to promote the silylation of alcohols by $TMSN_3$ under SFC.[6g]

Recently 1,2,3-triazoles have been receiving growing attention due to their wide range of applications[8] and consequently significant advances have been achieved in their preparation.[9] Some new *Click conditions* protocols based on the Huisgen 1,3-dipolar cycloaddition, have been disclosed by Sharpless *et al.*[9] and in particular a very efficient Cu(I)-catalyzed addition of azides to organic alkynes has been used for preparing a wide range of 1,2,3-triazoles. Adopting this approach the preparation of fluorescent 3-triazolylcoumarin for bioimaging applications has been reported.[10]

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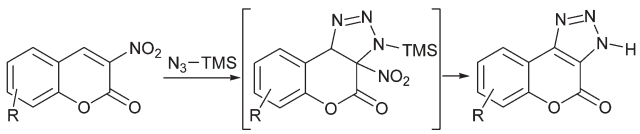
Considering that we have been investigating the synthetic utility of 3-nitrocoumarins,[7i,11] we prepared chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-ones by a [3 + 2] cycloaddition of 3-nitrocoumarins **1** with $TMSN_3$ under SFC (Scheme 1). Our intention was to define a straightforward and green protocol for accessing a new class of triazoles such as **2**, where fused triazole and chromen-2-one heterocyclic systems constitute a novel class of very promising compounds. This class of triazole is almost unknown except in a few very rare cases.[12]

We have preliminary performed the reaction of nitrocoumarin (**1a**) (R = H) with $TMSN_3$ (2 equivs) under SFC at 80 °C and after 24 h no conversion to **2a** was observed (Table 1, entry 1). The same result was achieved in the presence of 50 mol% of $TiCl_4$·2THF, chosen as a representative classical Lewis acid (Table 1, entry 2).

A good result was obtained by using tetrabutylammonium bromide (TBABr) (20 mol%), and the conversion of **1a** to **2a** was complete after 4.5 h at 80 °C under SFC (Table 1, entry 3). The best result was obtained by using TBAF which in terms of 10 mol% catalyzed the transformation of **1a** to **2a** in only 0.75 h and at 50 °C under SFC (Table 1, entry 4). The same reaction performed in THF as reaction medium gave a lower conversion (57%) after the same time (Table 1, entry 5). It is important to notice that chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one **2a** was isolated and no desilylation step was required.

These results confirmed that ammonium halogen salts can be efficaciously employed as non-metallic catalysts for activating the silicon–nitrogen bond under SFC. TBAF was then used to catalyze the cycloadditions of $TMSN_3$ to a variety of 3-nitrocoumarins **1**. The results are reported in Table 2.

Under SFC, [3 + 2] cycloadditions proceeded smoothly to completeness at 50 °C with 2–4 equivalents of $TMSN_3$ after 0.75–12 h and gave the corresponding 3*H*-triazoles derivatives in 70–94% isolated yields. Two exceptions were observed in the



1 2

Scheme 1 Coumarin-triazole derivatives **2** through $TMSN_3$ cycloaddition to coumarins **1**.

Table 1 Cycloaddition of 3-nitrocoumarin (**1a**) with $TMSN_3$ (2 equiv.)

Entry	Medium	Catalyst (mol%)	*T*/°C	*t*/h	*C*[a] (%)
1	SFC	—	80	24	—
2	SFC	$TiCl_4$·2THF (50)	80	24	—
3	SFC	TBABr (20)	80	4.5	>99
4	SFC	TBAF (10)	50	0.75	>99
5	THF	TBAF (10)	50	0.75	57

[a] Conversion measured by ^{1}H NMR analyses.

case of poorly reactive 7,8-dihydroxy-3-nitrocoumarin (**1f**) which required 24 h to give **2f** in 83% yield, and of 3-nitrobenzo[*g*]chromen-2-one **1k** where 80 °C were necessary to give after 31 h **2k** in 92% isolated yield.

Products **2a, b, g–k**, were isolated after charging the reaction mixtures on a silica gel chromatographic column and eluting with petroleum ether/ethyl acetate 8/2 (gradient). In the case of hydroxy-substituted chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-ones **2c–f**, *O*-trimethylsilylation of the phenolic hydroxy group occurred and after completion of the [3 + 2] cycloaddition process the reaction mixture was treated with 1 M HCl in H_2O/MeOH 1/4 solution for 30 min at 50 °C. After evaporating the aqueous phase under reduced pressure, the crude residue was washed with acetone at −20 °C, and the compounds **2c–f** were isolated in pure form with the yields reported in Table 2.

In conclusion TBAF proved to be an effective catalyst in the [3 + 2] cycloaddition of $TMSN_3$ to electron poor olefins such as 3-nitrocoumarins **1**. $TMSN_3$ under SFC is a safer source of azide ion and the basic TBAF catalyst helps prevent toxic gaseous hydrazoic acid being liberated.

By a very simple procedure not requiring any drying of the glassware, a new and very promising class of coumarinotriazole compounds have been prepared in good yields.

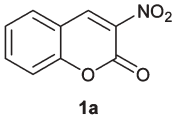
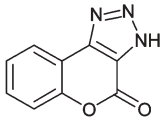
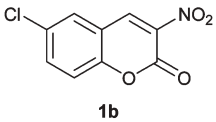
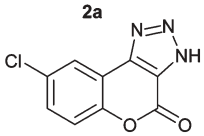
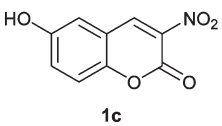
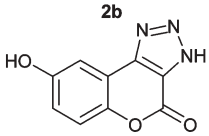
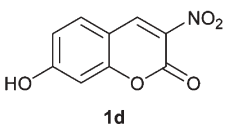
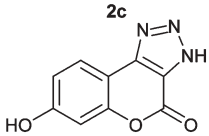
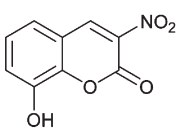
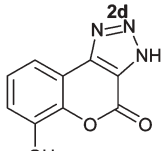
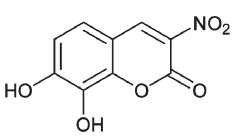
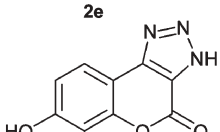
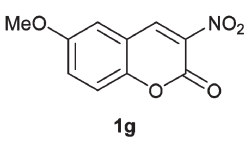
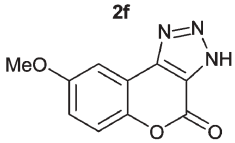
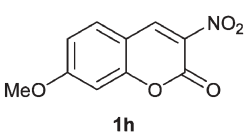
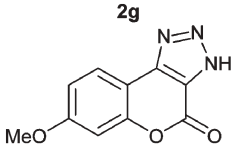
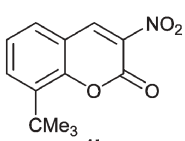
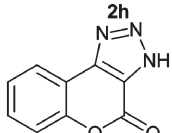
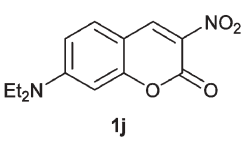
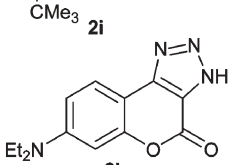
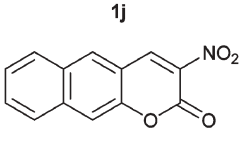
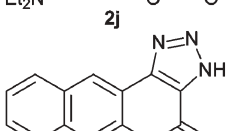
These results demonstrate once more that SFC is a very efficient synthetic tool allowing chemically efficient and environmentally friendly green organic processes to be realized.

Experimental

General

CAUTION: *Azides can be explosive compounds and should be handled with great care. During our study we encountered no problems*.[13] All chemicals were purchased and used without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz or 400 MHz, and at 50.3 or 100.6 MHz respectively, using a convenient deuterated solvent (reported below) and the residual peak as internal standard, or TMS in the case of $CDCl_3$. All melting points are uncorrected. Thin layer chromatography analyses were performed on silica gel on aluminium plates. Column chromatography were performed by using silica gel 230–400 mesh and eluting with petroleum ether/ethyl acetate 8/2 (gradient). 3-Nitrocoumarins **1a–e**,[7d,14] **1j**,[12] **1g–h**[15] and triazole **2a**[12] are known compounds. 3-Nitrocoumarins **1f**, **1i**, **1k** are new compounds and have been prepared following a reported procedure.[14] Triazoles **2b–k** are new compounds and their physical and spectral properties are reported below.

Table 2 (10 mol%) TBAF-catalyzed cycloadditions of 3-nitrocoumarins **1** with $TMSN_3$ (2 equiv.) under SFC at 50 °C

Coumarin	*t*/h	Triazole	Yield[a] (%)
 **1a**	0.75	 **2a**	88
 **1b**	1.5	 **2b**	91
 **1c**	6[b]	 **2c**	70
 **1d**	12[c]	 **2d**	94
 **1e**	2[b]	 **2e**	76
 **1f**	24[c]	 **2f**	83
 **1g**	8	 **2g**	90
 **1h**	10	 **2h**	92
 **1i**	2	 **2i**	90
 **1j**	12	 **2j**	91
 **1k**	31[c,d]	 **2k**	92

[a] Isolated yield of the pure product **2**. [b] 3 equiv. of $TMSN_3$. [c] 4 equiv. of $TMSN_3$. [d] Reaction performed at 80 °C.

7,8-Dihydroxy-3-nitro-2*H*-chromen-2-one (1f)

Isolated in 84% yield. Solid, mp = 243–244 °C (methanol). ^{1}H NMR (acetone-d_6) δ = 7.04 (d, 1H, J = 8.6 Hz); 7.45 (d, 1H, J = 8.6 Hz); 8.99 (s, 1H). ^{13}C NMR (DMSO-d_6) δ = 110.1, 114.4, 123.6, 130.26, 132.2, 144.8, 145.2, 152.5, 154.7. Anal. calc. for $C_9H_5NO_6$ (FW 223): C, 48.44; H, 2.26; N, 6.28. Found: C, 48.33; H, 2.13; N, 6.12.

8-*t*-Butyl-3-nitro-2*H*-chromen-2-one (1i)

Isolated in 83% yield. Solid, mp = 120–121 °C (petroleum ether/ethyl acetate 1/1). ^{1}H NMR ($CDCl_3$) δ = 1.52 (s, 9H); 7.38 (t, 1H, J = 7.7 Hz); 7.59 (dd, 1H, J = 1.6, 7.7 Hz); 7.78 (dd, 1H, J = 1.6, 7.7 Hz); 8.74 (s, 1H). ^{13}C NMR ($CDCl_3$) δ = 29.6, 35.1, 116.8, 129.0, 133.9, 138.6, 143.3, 151.5, 153.7 (one carbon not detected). Anal. calc. for $C_{13}H_{13}NO_4$ (FW 247): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.13; H, 5.24; N, 5.59.

3-Nitro-2*H*-benzo[*g*]chromen-2-one (1k)

Isolated in 87% yield. Solid, mp = 252–253 °C (methanol). ^{1}H NMR (DMSO-d_6) δ = 7.60–7.85 (m, 3H); 8.10 (d, 1H, J = 8.0 Hz); 8.41 (d, 1H, J = 9.1 Hz); 8.67 (d, 1H, J = 8.3 Hz); 9.82 (s, 1H). ^{13}C NMR (DMSO-d_6 at 42 °C) δ = 110.8, 115.8, 122.1, 126.4, 128.7, 129.0, 129.1, 129.6, 133.9, 137.3, 138.2, 151.5, 155.1. Anal. calc. for $C_{13}H_7NO_4$ (FW 241): C, 64.73; H, 2.93; N, 5.81. Found: C, 64.63; H, 2.96; N, 5.71.

TBAF-catalyzed [3 + 2] cycloaddition of $TMSN_3$ to coumarins 1. Typical procedure: 8-chlorochromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2b)

In a screw capped vial equipped with a magnetic stirrer, TBAF·3H_2O (0.064 g, 0.2 mmol), 6-chloro-coumarin (**1b**) (0. 448 g, 2.0 mmol) and $TMSN_3$ (0.460 g, 4.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 50 °C for 1.5 h. The crude reaction mixture was charged on a silica gel column chromatography (petroleum ether/AcOEt 8/2, gradient; silica/sample: 15 : 1). Pure 8-chlorochromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one was isolated in 91% yield (0.402 g). Solid, mp > 290 (dec.) (acetone). ^{1}H NMR (DMSO-d_6) δ = 7.59 (d, 1H, J = 8.9 Hz); 7.70 (dd, 1H, J = 2.5, 8.9 Hz); 8.07 (d, 1H, J = 2.5 Hz). ^{13}C NMR (DMSO-d_6) δ = 113.3, 119.4, 122.7, 128.9, 129.5, 131.2, 141.0, 150.9, 154.2. Anal. calc. for $C_9H_4ClN_3O_2$ (FW 221): C, 48.78; H, 1.82; N, 18.96. Found: C, 48.65; H, 1.80; N, 18.88.

8-Hydroxychromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2c)

After the typical cycloaddition procedure, the reaction mixture was treated with 1 M HCl in H_2O/MeOH 1/4 solution for 30 min at 50 °C. After evaporating the aqueous phase under reduced pressure, the crude residue was washed with acetone at −20 °C, and **2c** was isolated in pure form. Solid, mp 350 °C (dec.) (methanol). ^{1}H NMR (DMSO-d_6) δ = 7.00–7.10 (m, 1H); 7.31–7.35 (m, 1H); 7.35–7.42 (m, 1H). ^{13}C NMR (DMSO-d_6) δ = 108.0, 111.8, 118.5, 119.4, 130.5, 141.1, 145.5, 154.3, 154.9. Anal. calc. for $C_9H_5N_3O_3$ (FW 203): C, 53.21; H, 2.48; N, 20.68. Found: C, 53.32; H, 2.40; N, 20.63.

7-Hydroxychromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2d)

After the typical cycloaddition procedure, the reaction mixture was treated with 1 M HCl in H_2O/MeOH 1/4 solution for 30 min at 50 °C. After evaporating the aqueous phase under reduced pressure, the crude residue was washed with acetone at −20 °C, and **2d** was isolated in pure form. Solid, mp 290 °C (dec.) (acetone). ^{1}H NMR (DMSO-d_6) δ = 6.86 (d, 1H, J = 2.24 Hz); 6.90 (dd, 1H, J = 2.2, 8.5 Hz); 7.83 (d, 1H, J = 6.90 Hz). ^{13}C NMR (DMSO-d_6) δ = 102.5, 103.3, 113.6, 124.8, 140.7, 154.0, 154.9, 160.8. Anal. calc. for $C_9H_5N_3O_3$ (FW 203): C, 53.21; H, 2.48; N, 20.68. Found: C, 53.26; H, 2.43; N, 20.70.

6-Hydroxychromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2e)

After the typical cycloaddition procedure, the reaction mixture was treated with 1 M HCl in H_2O/MeOH 1/4 solution for 30 min at 50 °C. After evaporating the aqueous phase under reduced pressure, the crude residue was washed with acetone at −20 °C, and **2e** was isolated in pure form. Solid, mp 350 °C (dec.) (methanol). ^{1}H NMR (DMSO-d_6) δ = 7.13 (dd, 1H, J = 1.6, 8.0 Hz); 7.27 (t, 1H, J = 8.0 Hz); 7.44 (dd, 1H, J = 1.6, 8.0 Hz). ^{13}C NMR (DMSO-d_6) δ = 112.2, 113.2, 118.0, 125.3, 130.4, 141.0, 145.7, 146.7, 154.6. Anal. calc. for $C_9H_5N_3O_3$ (FW 203): C, 53.21; H, 2.48; N, 20.68. Found: C, 53.43; H, 2.46; N, 20.46.

6,7-Dihydroxychromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2f)

After the typical cycloaddition procedure, the reaction mixture was treated with 1 M HCl in H_2O/MeOH 1/4 solution for 30 min at 50 °C. After evaporating the aqueous phase under reduced pressure, the crude residue was washed with acetone at −20 °C, and **2f** was isolated in pure form. Solid, mp 400 °C (dec.) (methanol). ^{1}H NMR (DMSO-d_6) δ = 6.91 (dd, 1H, J = 2.1, 8.2 Hz); 7.31 (dd, 1H, J = 2.1, 8.2 Hz). ^{13}C NMR (DMSO-d_6) δ = 103.3, 113.1, 113.7, 128.8, 133.5, 141.0, 142.5, 149.3, 155.1. Anal. calc. for $C_9H_5N_3O_4$ (FW 219): C, 49.32; H, 2.30; N, 29.20. Found: C, 49.22; H, 2.37; N, 19.13.

8-Methoxychromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2g)

Solid, mp = 297–298 °C (methanol). ^{1}H NMR (DMSO-d_6) δ = 3.85 (s, 3H); 7.21 (dd, 1H, J = 2.8, 9.1 Hz); 7.47 (d, 1H, J = 9.1 Hz); 7.49 (s, 1H). ^{13}C NMR (DMSO-d_6) δ = 55.8, 106.0, 111.7, 118.5, 118.7, 130.5, 141.0, 146.4, 154.7, 155.9. Anal. calc. for $C_{10}H_7N_3O_3$ (FW 217): C, 53.30; H, 3.25; N, 19.35. Found: C, 53.22; H, 3.30; N, 19.33.

7-Methoxychromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2h)

Solid, mp 290 °C (dec.) (methanol). ^{1}H NMR (DMSO-d_6) δ = 3.87 (s, 3H); 7.07 (dd, 1H, J = 2.4, 8.7 Hz); 7.13 (d, 1H, J = 2.4 Hz); 7.89 (d, 1H, J = 8.7 Hz). ^{13}C NMR (DMSO-d_6) δ = 55.9, 101.7, 103.7, 112.7, 124.4, 129.0, 144.1, 153.8, 154.7, 162.0. Anal. calc. for $C_{10}H_7N_3O_3$ (FW 217): C, 53.30; H, 3.25; N, 19.35. Found: C, 53.22; H, 3.30; N, 19.33.

6-*t*-Butylchromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2i)

Solid, mp 312–313 °C (methanol). ^{1}H NMR (DMSO-d_6) δ = 1.47 (s, 9H); 7.41 (t, 1H, J = 7.7 Hz); 7.60 (dd, 1H, J = 1.5, 7.7 Hz); 7.92 (dd, 1H, J = 1.5, 7.7 Hz). ^{13}C NMR (DMSO-d_6) δ = 29.6, 34.9, 111.6, 121.8, 124.7, 128.9, 129.7, 137.8, 141.4, 150.7, 154.1. Anal. calc. for $C_{13}H_{13}N_3O_2$ (FW 243): C, 64.19; H, 5.39; N, 17.27. Found: C, 64.22; H, 5.30; N, 17.23.

7-Dimethylaminochromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2j)

Solid, mp 265–266 °C (methanol). ^{1}H NMR (DMSO-d_6) δ = 1.10 (t, 6H, J = 6.9); 3.40 (q, 4H, J = 6.9 Hz); 6.64 (s, 1H); 6.80 (bd, 1H, J = 8.8 Hz); 7.70 (bd, 1H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6) δ = 12.2, 48.6, 97.4, 109.0, 124.4, 128.0, 147.2, 154.6, 155.1 (2 carbons not detected). Anal. calc. for $C_{13}H_{14}N_4O_2$ (FW 217): C, 53.30; H, 3.25; N, 19.35. Found: C, 53.22; H, 3.30; N, 19.33.

Benzo[*g*]chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-one (2k)

Solid, mp 276–277 °C (methanol). ^{1}H NMR (DMSO-d_6) δ = 7.50–7.70 (m, 2H); 7.70–7.82 (m, 1H); 8.33 (d, 1H, J = 8.4 Hz); 8.13 (d, 1H, J = 9.0 Hz); 9.22 (d, 1H, J = 8.5 Hz). ^{13}C NMR (DMSO-d_6) δ = 106.9, 110.7, 116.7, 124.8, 125.8, 127.4, 128.0, 128.2, 129.7, 131.3, 145.0, 150.9, 154.5. Anal. calc. for $C_{13}H_7N_3O_2$ (FW 237): C, 65.82; H, 2.97; N, 17.71. Found: C, 65.72; H, 2.90; N, 17.73.

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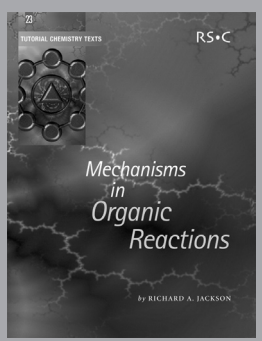

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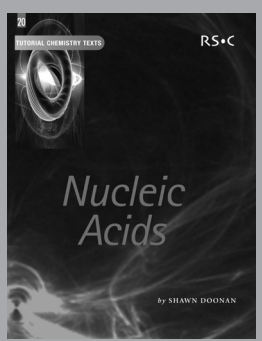

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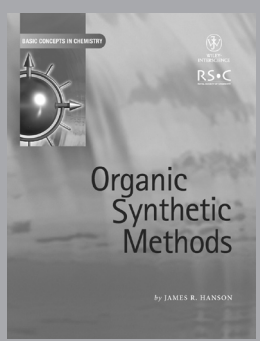

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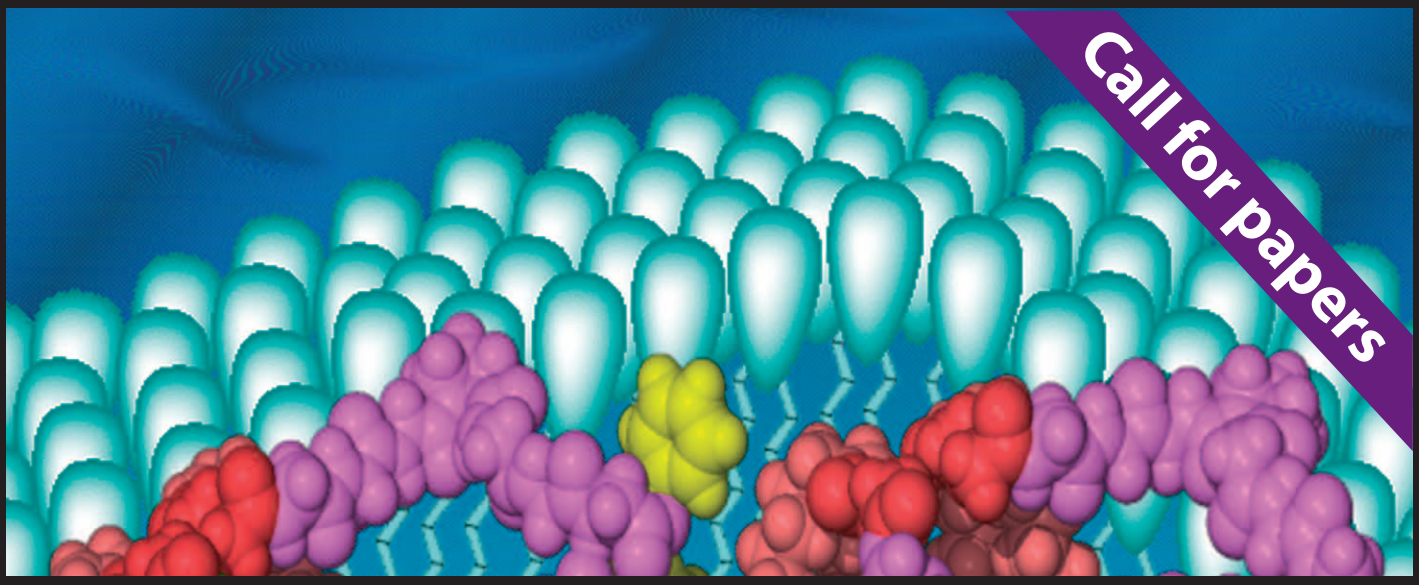

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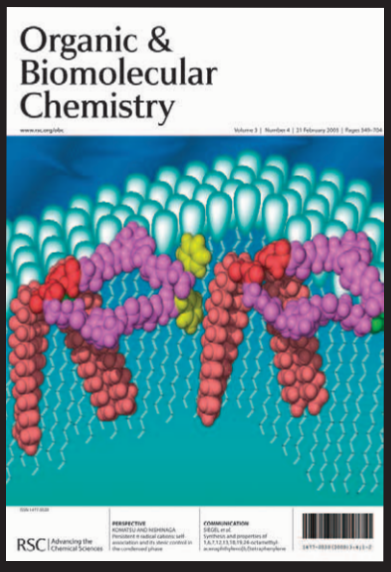

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