EDITORIAL

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Guest editorial: Asking the right questions†

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I do not know who said it first. I have heard this statement several times from instructors and colleagues throughout the years. I myself have said it several times. 'The key to quality chemistry education is not teaching the right answers, but teaching how to ask the right questions.' Now, almost 25 years after first calling myself 'a chemist' I believe this more than ever.

I started out as an undergraduate chemistry student doing hands on research at my university. I was what they called a 'lab rat'... a 'research animal'. You know the type, spending more than 60 hours a week in the lab. I published 5 papers as an undergraduate student. I spoke at American Chemical Society National Meetings. I prided myself in my research prowess and productivity. I used to set up 7 or 8 reactions simultaneously. I would work most, if not all, of my reactions up… Isolate and characterize most of my products… I counted in my old laboratory notebooks that I synthesized over 150 compounds as an undergraduate. A large metropolitan area newspaper did a big story on me when I graduated. They called me one of the region's 'best and brightest' college graduates.

My graduate school career continued this productive trend. I started doing research in my first semester. I passed all of my cumulative exams in the first round. I was in a rush to pass into 'candidacy' and more importantly, to get into the lab… Of course, the purpose was to make more compounds. I remember my graduate school days with such fondness. I would get into the lab before the sun came up. I would leave, come back, leave and come back throughout the day, and night, working around the clock. My life and daily activities were aligned to reflux times. Meals, shopping and entertainment were scheduled around the thermodynamics of molecular synthesis. I published more than a dozen papers as a graduate student. I do not have an exact count, but I probably made over 1000 compounds.

I graduated and got a job in industry. I wanted to prove my self-worth. The metric I knew and embraced was measured in 12 dram to 10 dram glass vials with carefully written labels and correlated spectra and analyses. I synthesized more and more new compounds. I put methyl groups and ethyl groups in places where they had never been. This was my pathway to success. And I did it well. I got a bunch of patents. I cranked out countless compounds. I was so very proud of myself. Not only was I making complicated new molecules, whose syntheses were challenging and difficult, but a lot of the compounds that I made actually did what I wanted them to do! I was successful at making stuff and more importantly, I was 'asking the right questions'!

It's funny how things hit you.

I prided myself as being 'a family guy' through all of this. I identified myself first and foremost a member of a large family. My mom had 10 brothers and sisters. I grew up with 35 cousins all within a few miles of my house. Nearly all of my relatives entered the full time workforce immediately from high school, getting jobs and starting families by the time they were 25. I was no exception. My oldest daughter, Joanna was born in my third year of graduate school. My first son, Tom was born just after I started my job in industry. Son number two, John, was born a couple years later. But my son John was born with a serious liver disease. It was called Billiary Atresia. This is one of those diseases that no one quite knows what the cause is. John was born perfectly healthy and normal, but within a week after birth he began to show signs of jaundice. His billiary system was not functional, in fact, it wasn't even there! No bile secretions [necessary for adequate nutritional uptake] could pass from his liver to his GI tract. A surgical procedure called a 'Kasai Junction' was performed on him in order to artificially connect his liver to his small intestines. This 'fix' remained functional for a few months as we waited and waited on a liver transplant list. My son spent an enormous amount of time in the hospital. I stayed over night with him quite a bit. At this time I had several scientists reporting to me in my industrial job. I kept a laptop computer with me, to monitor the progress of 'my people' at work and to keep track of the molecules they were making and testing. I remember going back and forth between excel spreadsheet files in the wee hours of the night. One file showed my son's blood electrolyte levels and another file showed performance results of a series of compounds that were synthesized at work. By this time in my career I figure I must have synthesized over 2500 compounds.

This story doesn't have a happy ending. My son died after receiving his liver transplant. I can't begin to describe the anguish that followed. Lying awake at night, I would wonder 'what causes this kind of thing to happen? Could it possibly be that some chemical that I had previously worked with might have had something to do with this?' I understand that the physiological causes for this disease are complicated—and it is very likely that my son's illness and subsequent death had nothing to do with anything that I ever interacted with in the lab. But a father can come up with a great deal of methods to apply self-blame when an infant son dies.

I began to think more and more about this situation. I had prided myself with my ability to make compounds. I prided myself on my ability to solve complicated scientific problems. I prided myself on the ability 'to ask myself the right questions'. At no time in my chemistry education could I remember learning about toxicity or environmental impact of chemistry or chemicals. Sure I was constantly reminded about safe lab techniques and proper waste disposal protocols. But this was handled as a 'housekeeping' part of chemistry, like taking out the trash at home and filling out tax forms, something you had to do… but in the background.

I consider myself fortunate to have had the opportunity to study with a few of the most brilliant chemists I have ever known. And these people were of the most compassionate of human beings. I do not fault the education that I received or the people who educated me. 'We' as a science have somehow followed a path and got to the point where 'making stuff' is the focus of what we do. The 'right questions' involve the ingenuity of chemical synthesis and design. Issues such as toxicity and

†The opinions expressed in the following article are entirely those of the author and do not necessarily represent the views of either the Royal Society of Chemistry, the Editor or the Editorial Board of *Green Chemistry*.

environmental impact… Well, the EH&S people and the industrial engineers can handle that stuff! I think the most important question, the right question that has not been asked, a simple little question really…. 'Why?'

Isn't it funny that the people society entrusts with the job of inventing the next generation's materials and products are not taught how to make these materials safely? Isn't it strange that a really good chemist can develop dozens of synthetic schemes to prepare new and different molecules, but it is unlikely that they can assess, at any level, the relative risks of their methods and materials to human health and the environment? Why is this acceptable?

My guess is that chemical risk is very different from almost any other type of risk we might expose ourselves to. On occasion I try to do some cooking in the kitchen. Talk about risk! I use a knife to cut up my food. There is a good chance that I will cut myself! But I accept this risk because the function of the knife is to cut. Cut food, cut me. *The risk and function are intimately connected*. Same with the stove. It gets hot. I might burn the food. I might burn myself. But that is what the stove is supposed to do, heat things up. Again, the function and the risk are closely related. Chemistry is different. Lets say that I want to synthesize a red dye. I know that I will want to assemble a planar system with a few conjugated double bonds. I will want to have an electron donating group on one side, and an electron withdrawing group on the other side. If I put this molecule together correctly, it will have appreciable broad absorbance around 500 to 600 nm, and I will have a red dye. If the molecule that I make happens to also be carcinogenic, it will have nothing to do with the fact that it is red. The ability of the molecule to be red has no relationship with it being carcinogenic. *The risk and function are not intimately connected*. It is unlikely that there is some hidden scientific truth that states that all red molecules must be carcinogenic. I, as a synthetic organic chemist, know how to make a red molecule, but I do not know what makes a molecule carcinogenic.

We need to re-evaluate the 'machinery of chemistry'. We need to take a look at our relationship with the community we serve. We need to think about how we teach chemistry to future chemists and to the general community. I do not expect that we can convert all practicing chemists to fully functioning toxicologists. There is still a lot we do not know about mechanisms of toxicity. But we do know some things. And if we want to learn more, then we need to be placing a stronger emphasis on this. We need to link the function of making molecules with a better assessment of their risk. Maybe we need to ask ourselves some better questions, like 'Why do I make things the way I do?' Or perhaps, 'Is there a way to make these molecules that will not be harmful to human health or the environment?' I believe that there are answers. The growing field of Green Chemistry is testament to the interest in answering these questions. There are researchers who understand this quite well. Some may argue it is out of financial incentive. Obviously, it is much less expensive to work with, and manufacture, environmentally benign materials that do not have associated regulatory and disposal costs. I would like to think there is more to it than that.

Things really need to move more quickly. I worry that in some places these important questions are not being asked enough. And perhaps more troubling, the response to these important questions might remain unspoken, but ring through some research hallways…. 'But that's not the way we've always done it!' And that is exactly the point.

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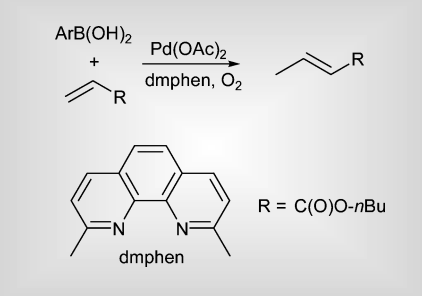
Highlights

Markus Hölscher reviews some of the recent literature in green chemistry

Ligand modulated Heck vinylation with molecular oxygen as oxidant

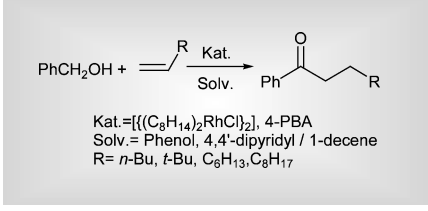
Palladium(II)-mediated vinylic substitutions of organoboronic acids are known as oxidative Heck reactions and up to now there has been no ligand-supported oxidative Heck protocol, which would help in the development of new selective and efficient reactions. Larhed *et al.* from the University of Uppsala have developed a novel protocol in which aryl boronic acids are coupled to a variety of olefins, employing a phenanthroline type ligand and molecular oxygen as reoxidant (*Chem. Commun.* 2004, 218–219).



In a comparison of this setup with other N- and P-based ligands the oxidatively stable 2,9-dimethyl-1,10-phenanthroline (dmphen) proved to be an oxidatively stable ligand resulting in product yields of up to 97%, whereas the other ligands yielded lower yields and were oxidized. Upon testing different aryl boronic acids under optimized conditions this protocol gave moderate to high yields with low catalyst loadings, a cheap ligand and molecular oxygen as a ″green reoxidant″ of the catalyst.

A new thermoregulated solvent system for recycling of catalysts

The hydroacylation of olefins with primary alcohols to yield ketones is an interesting example for C–H activation with organometallic catalysts. Jun *et al.* from Yonsei University, Korea have developed a novel two phase solvent system for this reaction (*J. Am. Chem. Soc.* 2004, **126**, 424–425), which is based on the temperature dependent stability of hydrogen bonds. Phenol and 4,4′-dipyridyl form a hydrogen bonded polar phase immiscible with 1-decene at room temperature. Upon heating to 150 °C the two phases mix, due to the instability of a H-bond network at elevated temperatures. This enables the reaction between benzyl alcohol and 1-hexene in the presence of a rhodium catalyst precursor and a phosphine as the ligand to take place in a homogenous phase at elevated temperatures followed by easy catalyst separation at low temperature.



Upon cooling the H-bonded network is re-established resulting in phase separation. The polar phase contains the catalyst and the nonpolar phase the ketone. When 4-diphenylphosphino-benzoic acid (4-PBA) is used as the ligand, the isolated yields of seven runs vary between 88 and 96%. ICP-MS analyses revealed the rhodium content in the nonpolar phase to be low (0.005 and 0.01% in two following runs). The amount of ketone in the polar phase also was low. Furthermore benzyl alcohol derivatives with CF_3 and OMe groups in *para* position performed as well as different olefins (1-octene, 1-decene, 2,2-dimethyl-1-butene) with isolated product yields in the 90% range.

Spectroscopic determination of Lewis and Brønsted acidity in ionic liquids

Much work in the field of ionic liquids has focused on commercial applications, while the establishment of a procedure for the determination of the acidity of ILs still is missing. Recently two groups have contributed fundamental research to solve this problem. The group of Kou *et al.* from Peking University, China has focused on Lewis acidity while Gilbert *et al.* from the University of Liège, Belgium, concentrated on Brønsted acidity. The work of Kou *et al.* describes by means of IR spectroscopic investigations the interaction between different IL/metal halide mixtures and probe molecules as pyridine and ethanenitrile (*Chem. Commun.* 2004, 236–237). The authors show that IR bands of the probe molecules associated with certain vibrations shift reliably and reproducibly when Lewis acidic centres are present. Depending on the mole fraction of the metal halide different aluminate ions are present in solution, which can also be distinguished by this method. In contrast, the work of Gilbert *et al.* uses UV/Vis spectroscopy as the analytical tool, which is used to describe Brønsted acidity in non-chloroaluminate ILs (*J. Am. Chem. Soc.* 2003, **125**, 5264–5265). In a typical experiment the acid strength of $HNTf_2$ ($NTf_2 = N(CF_3SO_2)_2$) dissolved in [bmim][NTf_2] could be described by the systematic decrease of a characteristic band of the unprotonated form of the probe molecule 2,4-dinitroaniline with regard to the concentration of $HNTf_2$. Also BF_4 containing ILs were studied as well as the influence of water in these systems. The authors come to the conclusion that in ILs based on the BF_4 and NTf_2 anions acidity levels between −3.35 and −7.00 (in terms of the Hammett function) can be reached. These media appear to be less solvating than water.

Silica-immobilized catalysts for asymmetric transfer hydrogenation of ketones

Optically active secondary alcohols are interesting intermediates for the synthesis of biologically active compounds. Asymmetric transfer hydrogenation of prochiral ketones consequently is an attractive method for the synthesis of these alcohols. Ruthenium catalysts containing N-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) type ligands are very selective and efficient catalysts for hydrogenations of ketones, which makes them attractive candidates for immobilization experiments. Tu *et al.* from Lanzhou University, China, have

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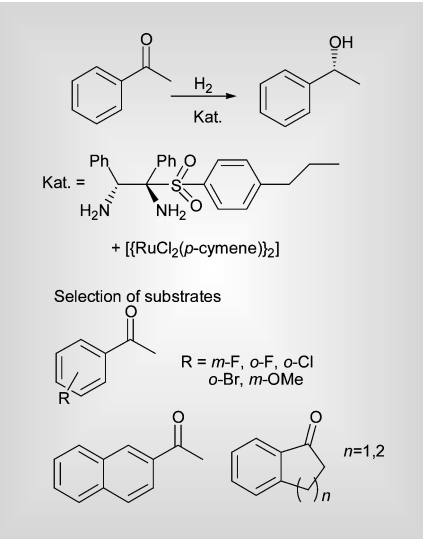
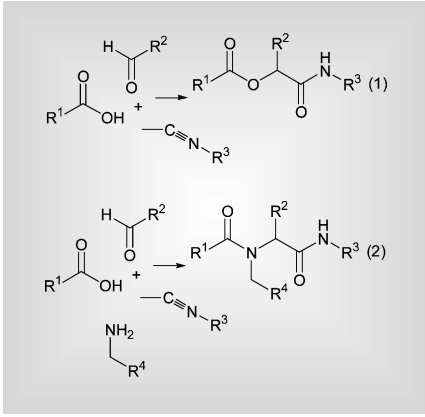
developed novel heterogeneous Ru-TsDPEN catalysts by grafting TsDPEN ligands directly on amorphous silica as well as mesoporous MCM-41 and SBA-15 material (*Org. Lett.* 2004, **6**, 169–172). Firstly the ligand was anchored to the support, then the catalyst was generated *in situ*.



The hydrogenation of acetophenone was chosen to optimize reaction conditions. Both conversion and enantioselectivity reached values of 99 and 97%, respectively, which could be reproduced in several recycling experiments. However, reaction times had to be increased due to a considerable leaching of Ru metal in the workup process. Also the catalyst's color changed markedly indicating irreversible decomposition or deactivation of the active catalyst species. Nevertheless grafted Ru-TsDPEN proved successful as catalyst for the hydrogenation of a variety of ketones. Under optimized reaction conditions most of the substrates were hydrogenated with conversions larger than 95% with *ee*'s varying between 93 and 99%.

Acceleration of multicomponent reactions in water

Being a 'green' solvent, water also helps in many other ways to improve the efficiency of chemical reactions. Multicomponent reactions such as the Passerini (1) and the Ugi reaction (2) for example benefit from the presence of water, as was shown by Pirrung *et al.* from Duke University, North Carolina (*J. Am. Chem. Soc.* 2004, **126**, 444–445).



The reaction becomes considerably faster and facilitates the isolation of the products due to their insolubility in water. Simply by switching from CH_2Cl_2 to water the Passerini reaction is accelerated by a factor of 18. The addition of LiCl (1.0 M) resulted in an additional 16-fold acceleration over pure water and also glucose (0.5 M) as additive increased the reaction rate by a factor of 7 relative to water. Conversions were 100% in all cases and the yields varied between 91 and 95% with reaction times between 30 min and 2 h at room temperature. The Ugi reaction is accelerated by roughly a factor of 50 when conducted in water. The syntheses of a library of 32 β-lactams after extraction of the reaction products yielded HPLC purities between 70 and 99%, which is sufficient for initial biological testing.

Sustainability – changes which pay

More than twenty years of growing concerns about modern industrial production with regard to the planet's resources have induced a general awareness of long term environmental risks, which in turn has led to the concept of sustainability. This was introduced in industrialized societies more than ten years ago, and it was the chemical industry which set the ball rolling. Sustainable has been defined by the World Commission on Environment and Development (WCED) as 'forms of progress that meet the needs of the present without compromising the ability of future generations to meet their needs.' A more precise and practical description defines financial, social and environmental issues as the core topics of sustainability. Michael Kenward has recently summarized the 'behaviour' of leading companies in this field (*Chemistry World*, January 2004). Nowadays chemical industries have to a large extent integrated sustainability into their driving forces and many companies succeeded even in gaining economical benefit. This was certainly supported by the introduction of official tools such as the Dow Jones Sustainability Index which were set up to monitor industrial performance on this issue. Even though quite a large number of companies have meanwhile established a reliable competence in sustainability there is still a lot to do. John Elkington, founder of the consultancy 'SustainAbility', sees an explosion of reports verifying companies efforts, however, he also states that the 'total number of reporting companies is still very small with regards to the estimated total of more than 50,000 multinational corporations and the millions of smaller companies operating everywhere in the world.' Obviously financial reports are much more significant at the immediate time, but sustainability reports are becoming more important as industries realize that it pays to be green.

COMMUNICATION

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Convenient and rapid microwave-assisted synthesis of pyrido-fused ring systems applying the *tert*-amino effect

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The microwave-assisted synthesis of pyrido-fused heterocycles was accomplished in an efficient, economically and environmentally friendly route by the application of the *tert*-amino effect as the key ring closure methodology.

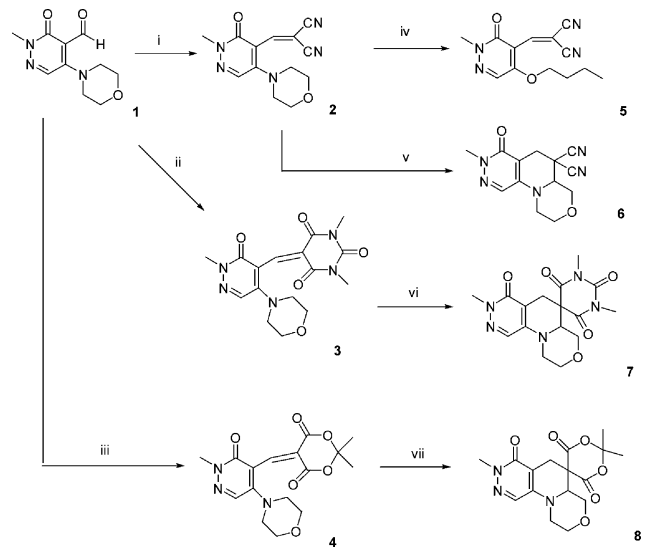
Introduction

Pyrido-fused ring systems are of great importance due to their valuable biological activities. One of the most efficient synthetic pathways to obtain angularly annelated derivatives of such systems involves a three step sequence starting from the easily available *ortho*-functionalized (hetero)aromatic aldehydes. The first step is a nucleophilic substitution to introduce a *tert*-amino group; in the second step the elaboration of a vinylic moiety, generally *via* a Knoevenagel condensation reaction, occurs; finally in the third step, the ring closure between the carbon atoms of the vinyl moiety and the *tert*-amino group is achieved applying the *tert*-amino effect.[1–4] This approach has apparently a serious limitation: the cyclization reaction is a rather slow process, and it often requires prolonged heating in organic solvents with high boiling points to achieve satisfactory conversion.[2,4] As it is known[5] that such processes could highly benefit from microwave irradiation, we were particularly interested in comparing the microwave irradiation protocol with the conventional heating conditions. In this paper we describe our attempts to develop a novel, convenient, rapid and eco-friendly procedure for the preparation of angularly annelated quinolines and pyridopyridazines, based on the microwave-assisted application of the *tert*-amino effect.

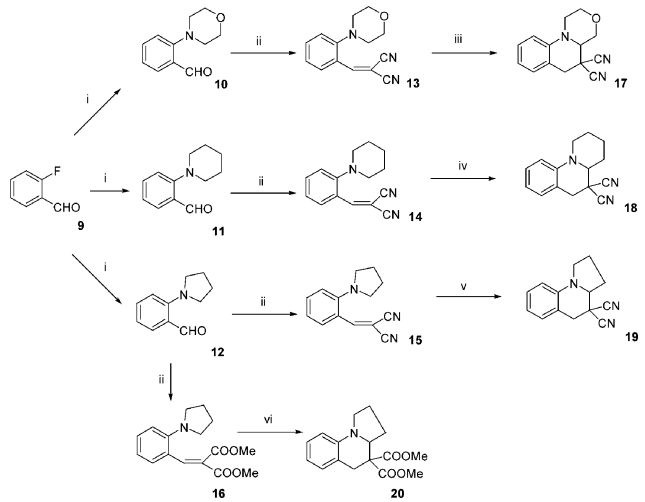
Results and discussion

Two series of (hetero)aromatic aldehydes with an *ortho*-*tert*-amino substituent were prepared in order to investigate the microwave methodology in compounds with significantly different cyclization tendency. These reactions have been studied previously under conventional heating conditions.[1–2] The 5-*tert*-amino-4-vinylpyridazinones **2–4** (Scheme 1), and their benzene analogues **13–16** (Scheme 2) were smoothly synthesized by Knoevenagel condensation of the aldehydes with the corresponding active methylene compounds, according to the procedures described before.[1–4]

In the next step, the cyclization was carried out by operation of the *tert*-amino effect. Under conventional conditions the pyridazino ring system can be obtained after heating at a high temperature for several hours or even days. We now found that the cyclization could be realized in a substantially shorter time upon microwave irradiation applying a dedicated monomode CEM-Discover microwave reactor. Thus, the dimethylbarbituric acid and Meldrum's acid derivatives **3** and **4** underwent ring closure in 5 and 30 min upon microwave irradiation at 230 °C and 200 °C to afford the expected spirocyclic ring systems **7** and **8** in 63% and 73% yields, respectively (Scheme 1, Table 1). Instead of xylene and DMF, *n*-butanol or dimethoxyethane (DME) could be used, making the isolation of the compounds easier. In accordance with our previous observations,[2] we found that the conversion of the acyclic malononitrile derivative **2** to the angularly annelated dinitrile **6** required a prolonged irradiation time (42 min) at 210 °C in DMSO; nevertheless the reaction was far faster compared to conventional heating conditions (44 h). It should be noted that the solvent plays a decisive role in the latter reaction: upon irradiation of compound



Scheme 1 (i) ref. 1; (ii) ref. 2; (iii) ref. 2; (iv) n-BuOH, MW, 240 °C, 40 min, 25%; (v) DMSO, MW, 210 °C, 42 min, 29%; (vi) n-BuOH, MW, 230 °C, 5 min, 63%; (vii) DME, MW, 200 °C, 30 min, 73%.



Scheme 2 (i) ref. 3; (ii) ref. 4; (iii) n-BuOH, MW, 220 °C, 30 min, 96%; (iv) n-BuOH, MW, 200 °C, 3 min, 80%; (v) n-BuOH, MW, 200 °C, 3 min, 84%; (vi) n-BuOH, MW, 220 °C, 15 min, 73%.

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Table 1 Comparison of the cyclization conditions applying the *tert*-amino effect under conventional heating and microwave irradiation conditions

	Conventional heating			Microwave irradiation		
Product	Temp (°C)/ time (h)	Yield (%)	Solvent	Temp (°C)/ time (min)	Yield (%)	Solvent
6	150/44	35	DMSO	210/42	29	DMSO
7	138/2	45	xylene[a]	230/5	63	*n*-BuOH
8	100/5	79	DMF	200/30	73	DME
17	117/35	84	*n*-BuOH	220/30	96	*n*-BuOH
18	117/2	78	*n*-BuOH	200/3	80	*n*-BuOH
19	117/2	82	*n*-BuOH	200/3	84	*n*-BuOH
20	117/22	67	*n*-BuOH	220/15	73	*n*-BuOH

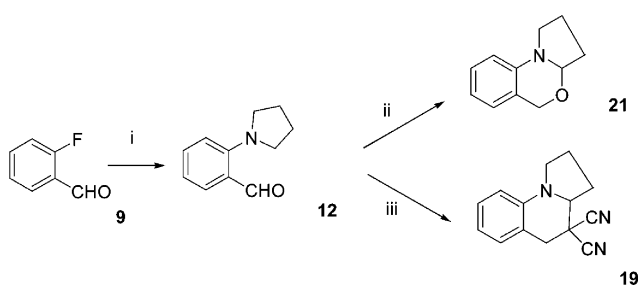
[a] With a catalytic amount of aluminium trichloride.

2 in *n*-butanol, the nucleophilic substitution of the morpholino group proceeded faster than the desired cyclization, and at 70% conversion of the starting compound **2**, the 5-butyloxy derivative **5** has been isolated in 25% yield.

The reaction rates of the cyclizations of the *ortho*-vinyl-*tert*-anilines were also significantly enhanced upon microwave irradiation. Moreover, in all cases the ring closure could be performed in *n*-butanol without the problem of simultanous nucleophilic exchange of the *tert*-amino group by *n*-butyloxy. Thus, the microwave irradiation of solutions of the piperidino and pyrrolidino derivatives **14** and **15** at 200 °C for 3 min afforded the fused products **18** and **19** in high yields (Scheme 2, Table 1). The cyclization of the morpholino analogue **13** required a slightly higher temperature of 220 °C for 30 min, compared to 35 h under conventional heating conditions, and the pyrido-fused ring system **17** was isolated in almost quantitative yield.

Replacement of the cyano groups by the less electron-withdrawing ester groups decreased the reaction rate as expected.[1,2] Accordingly, cyclization of **16** needed a higher temperature (220 °C) and a longer reaction time (15 min) compared to that of the malononitrile derivative **15** (200 °C, 3 min).

As the next step towards real green chemistry, we investigated the replacement of the organic solvent by water. This, in combination with microwave irradiation,[6] should render the procedure highly cost-effective and environmentally friendly. A survey of the literature revealed that both condensation and cyclization reactions, such as aldol-like condensations, Diels–Alder cyclizations, even a domino Knoevenagel–Diels–Alder process, could be performed in water as the sole solvent.[7] As a proof of concept, we investigated the conversion of the *ortho*-fluorobenzaldehyde **9** into the tricyclic **19**. The first intermediate, the *ortho*-pyrrolidinobenzaldehyde (**12**) could be obtained by substitution of the fluorine with pyrrolidine upon controlled microwave irradiation of an aqueous suspension of **9** in the presence of potassium carbonate (Scheme 3). Interestingly, it was found that



Scheme 3 (i) Pyrrolidine, K_2CO_3, H_2O, MW, 130 °C, 3 min; (ii) K_2CO_3, H_2O, MW, 210 °C, 50 min, 28%; (iii) $CH_2(CN)_2$, H_2O, MW, 100 °C, 10 min, then 1 drop of TFA, 200 °C, 3 min, 50%.

further irradiation of **12** at a higher temperature (210 °C) for 50 min afforded the pyrrolobenzoxazine **21** in 28% yield.[8] To obtain the desired tricyclic compound **19**, a powerful one-pot procedure was elaborated. After microwave irradiation of the mixture of the aldehyde **12** and malonitrile at 100 °C for 10 min, one drop of trifluoroacetic acid (TFA) was added to the reaction mixture and irradiation was continued at 200 °C for 3 min. The desired compound **19** could be isolated in 50% yield, starting from **12**.

Conclusions

The development of a new, cost-efficient, microwave-assisted procedure for the synthesis of pyrido-fused ring systems, applying the *tert*-amino effect, has been described. Typically, reactions that required hours or even days under conventional heating conditions, could be completed within 3–42 min under microwave irradiation conditions, with minimum energy demands. The isolated yields obtained with the microwave-assisted procedures, have been found to be at least comparable or even superior to those obtained under conventional heating conditions. Moreover, in a case study for the preparation of a tricyclic angularly annelated compound, an operationally very simple, environmentally friendly protocol was also elaborated, starting from a commercially available aldehyde, using water as the sole solvent in all reaction steps, and integrating the Knoevenagel condensation and the subsequent cyclization into a one-pot reaction.

Based on these results, the new protocols we have developed can be regarded as practical and viable green procedures.

Experimental

General

Melting points were determined using a Reichert–Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM 250, Bruker Avance 300 or on a Bruker AMX 400 instrument, using $CDCl_3$ as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane, or using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150–250 °C as required. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70–230 mesh silicagel (E.M.Merck)) were used. Pyridazinecarbaldehyde **1** was prepared according to the published procedure,[2] whereas *ortho*-fluorobenzaldehyde **9** was purchased from Aldrich. Compounds **2–4**, **6–8**, **10–20**, **21** have melting points and spectral data identical to the published values.[1–4,8]

Microwave irradiation experiments

A monomode CEM-Discover microwave reactor (CEM Corporation P.O. Box 200 Matthews, NC 28106) was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in sealed large (10 mL) microwave process vials.

Nucleophilic substitution reaction of 2

2-(5-Butyloxy-2-methyl-3-oxo-2*H*-pyridazin-4-ylmethylene)-malonitrile (5). A solution of **2** (0.2 mmol) in *n*-butanol (3 mL) was irradiated at 240 °C for 40 min at 300 W maximum power. The reaction mixture was cooled to ambient temperature and the solvent was evaporated *in vacuo*. The residue was subjected to flash chromatography on silica (eluent: dichloromethane–hexane 9 : 1) to give starting material **2** (30%) and **5** (25%). White needles, mp 151–153 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H), 8.19 (s, 1H), 4.59 (t, 2H, J = 7.6 Hz), 3.86 (s, 3H), 1.88 (m, 2H), 1.55 (m, 2H), 1.02 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 165.7, 158.4, 147.6, 143.5, 137.7, 118.6, 114.2, 102.0, 69.3, 40.1, 30.9, 19.5, 14.2. DEPT ($CDCl_3$): 143.5, 137.7, −69.3, 40.1, −30.9, −19.5, 14.1. MS (CI): m/z (%) = 259 (100) [MH^+]. HR-MS (EI): $C_{13}H_{14}N_4O_2$ Calcd. 258.11168, found 258.11177.

Ring closure reactions of vinylpyridazinones 2–4

2-Methyl-1-oxo-2,5,6,8,8a,10-hexahydro-1*H*-7-oxa-2,3,4b-triaza-phenanthrene-9,9-dicarbonitrile (6). A solution of **2** (0.2 mmol) in DMSO (3 mL) was irradiated at 210 °C for 42 min at 200 W maximum power. The reaction mixture was cooled to ambient temperature, extracted with ether (3 × 10 mL) and washed with brine. The combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo* and the residue was triturated with petroleum ether (bp 60–80 °C) to give **6** in 29% yield.

1′,3,3′-Trimethylspiro-(3,4,5,6,6a,7,9,10-octahydropyridazino[5′,4′:5,6]pyrido-[2,1-c][1,4]oxazine-6,5′-(hexahydropyrimidine)]-2′,4,4′,6′-tetraone (7). A solution of **3** (0.2 mmol) in *n*-butanol (3 mL) was irradiated at 230 °C for 5 min at 300 W maximum power. The reaction mixture was cooled to ambient temperature, the solvent was evaporated *in vacuo* and the residue was triturated with petroleum ether to give **7** in 63% yield.

2,2,3′-Trimethylspiro[dihydro-4*H*-[1,3]dioxane-5,6′-(3′,4′,5′,6′,6a′,7′,9′,10′-octahydropyridazino[5′,4′:5,6]pyrido[2,1-c][1,4]oxazine)]-4,4′,6-trione (8). A solution of **4** (0.2 mmol) in DME (3 mL) was irradiated at 200 °C for 30 min at 300 W maximum power. The reaction mixture was cooled to ambient temperature, the solvent was evaporated *in vacuo* and the residue was crystallized from ethanol to give **8** in 73% yield.

General procedure for the preparation of 17–20

A solution of a compound **13–16** (0.2 mmol) in *n*-butanol (3 mL) was irradiated under conditions described in Table 1 at 300 W maximum power. The reaction mixture was cooled to ambient temperature, the solvent was evaporated *in vacuo* and the residue was triturated with cold methanol to give **17–20**.

One-pot preparation of compound 19

1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (19). A mixture of *ortho*-fluorobenzaldehyde **9** (1 mmol), pyrrolidine (1 mmol) and potassium carbonate (1 mmol) in water (2 mL) was irradiated at 130 °C for 3 min at 50 W maximum power. The reaction mixture was cooled to room temperature, extracted with diethyl ether (3 × 10 mL), washed with a saturated ammonium chloride solution and then with water. The combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo*. The crude aldehyde **12** was suspended in water (3 mL), malononitrile (1 mmol) was added and the reaction mixture was irradiated at 100 °C for 10 min at 60 W maximum power. The vial was cooled down to ambient temperature, TFA (1 drop) was added and the suspension was irradiated at 200 °C for 3 min at 100 W maximum power. The reaction mixture was cooled down to room temperature, extracted with diethyl ether (3 × 10 mL), washed with a saturated ammonium chloride solution and then with water. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated *in vacuo* and the crude product was recrystallized from methanol to give **19** in 50% yield.

1,2,3,3a-Tetrahydro-5*H*-4-oxa-9b-aza-cyclopenta[*a*]naphthalene (21). A mixture of *ortho*-fluorobenzaldehyde **9** (1 mmol), pyrrolidine (1 mmol) and potassium carbonate (1 mmol) in water (2 mL) was irradiated at 130 °C for 3 min at 50 W maximum power and then at 210 °C for 50 min at 110 W maximum power. The reaction mixture was cooled to room temperature, extracted with diethyl ether (3 × 10 mL), washed with a saturated ammonium chloride solution and then with water. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography over silica gel (dichloromethane-*n*-hexane, 1 : 1) to afford **21** in 28% yield. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.16 (t, 1H, J = 7.3 Hz), 6.93 (d, 1H, J = 7.3 Hz), 6.75 (t, 1H, J = 7.3 Hz), 6.71 (d, 1H, J = 8 Hz), 4.96 (d, 1H, J = 14.6 Hz), 4.95 (m, 1H), 4.77 (d, 1H, J = 14.6 Hz), 3.62 (m, 1H), 3.27 (m, 1H), 2.35 (m, 1H), 2.01 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 143.6, 128.1, 125.1, 122.0, 118.3, 115.6, 89.9, 68.6, 50.1, 32.8, 23.0. DEPT ($CDCl_3$): 128. 1, 125.1, 118.3, 115.6, 89.9, −68.6, −50.1, −32.8, −23.0 MS (CI): *m*/*z* (%) = 176 (100) [MH^+].

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CRITICAL REVIEW

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Microwave assisted synthesis – a critical technology overview

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Since 1986, when Gedye and Giguere published their first articles in *Tetrahedron Letters* on microwave assisted syntheses in household microwave ovens, there has been a steadily growing interest in this research field. Since the use of microwaves comprises more than the simple application of a goal-oriented, innovative tool, it is crucial to be aware of the fundamentals of chemistry in the microwave field before investigating challenging reaction mechanisms. Therefore, the following overview focuses mostly on reaction engineering in the microwave field. Parallel reactions and scale-up are also discussed. The last section of this review is dedicated to the development of experimentally sound protocols on microwave-assisted syntheses and separations, which are illustrated through experiments.

1 Introduction

The use of microwaves as an energy source for chemical reactions and processes has been extensively investigated during recent years,[1–4] but has also led to many controversial discussions.[5–7] A great number of scientific publications cover this subject. An extensive but incomplete overview was previously published.[2g] The critical net result of recent publications leads to several common points:

– There is hardly any reaction type or name reaction that has not yet been tested in the microwave field.

– Independent of the impact factor of the scientific journal or its referee system, the experimental details and the microwave systems used are usually insufficiently described. Often, other research groups have great trouble reproducing the attractive reaction parameters such as conversion, selectivity and yield.

– No reaction exists that only proceeds in the microwave field. There are always similar reactions under classical conditions, *i.e.* thermal heating.

Recently, articles such as reference[8a] in the "highlights" section of a respected journal (*cf.* the correspondence letter[8b]) and [9–11] were published, which led to discussions on these and points of view presented in these articles. This article reviews the essential aspects of the use of non-classical energy input. The presented arguments will be supported through experimental evidence.

Fig. 1 summarizes the development of publications on microwave-assisted reactions since 1985.[12] The first chemical reactions relating to organic synthesis date back to 1986.[13,14]

Such a figure is often found in review articles, *cf.*[2g]. However, the number of papers published on a certain subject does not address the quality of those investigations. A quality criterion for the level of understanding of the subject has not yet been established.

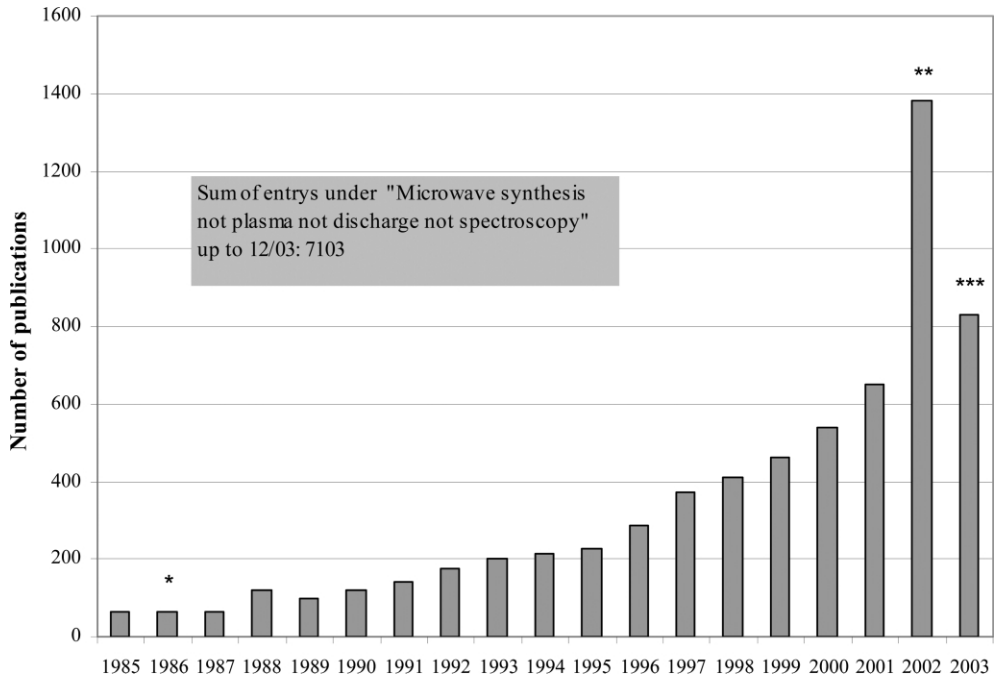

Fig. 1 Number of publications identified by keyword "microwave synthesis …"[12] plotted against publication year * Includes only two publications about organic synthesis. ** Includes 483 chinese patents concerning microwave assisted extraction of medicine plants. *** Search results up to December 2003.

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The use of microwaves for the activation of chemical reactions in a broader sense has been known for a long time. A great number of applications, such as sintering, drying, melting and defrosting have been reported. Rapid developments in those fields still prevail today. In contrast to many other subjects investigated during recent years, one cannot talk about a "temporary fashion" in this case. This is due to the presented, partly surprising, results and the innovations that require the use of microwave-activation.

As opposed to conventional thermal heating, the use of microwave radiation for the "activation" of chemical reactions requires a certain theoretical preparation. More than ever, the synthetic chemist experiences measurement problems and physical problems when using microwaves. This makes the connection of classical chemical synthesis to technical engineering sciences unavoidable. The fact that more measurement technology will be required is contradictory to the current trends in simplification and miniaturisation (making certain operations, *e.g.* stirring, superfluous) observed in organic synthesis. Many publications in the literature do not provide essential reaction parameters. While the analytical equipment (NMR, GC) used is often reported in detail, the description of the microwave devices employed are rarely documented (*e.g.*[15–17]). Often, the type of the microwave device, typically a domestic microwave oven, is not even mentioned. The power used is described in terms of "full power" or only the preset power step is given. Thus, it is impossible to draw conclusions about the achieved temperatures. Furthermore, the reactions performed are often only compared to literature data from reactions that were performed under completely different conditions. For scale-up of first laboratory results (in mmol scale), it is necessary to describe the experimental details, *e.g.* apparatus, reaction protocol, very carefully. This is a general rule for all process development, and not only connected to chemistry under microwave conditions. A disadvantage of microwave technology is perhaps the high investment costs.

Interestingly, microwaves, energy sources that have been previously used for decades for rather "trivial" applications such as cooking, heating of food, drying *etc.*, have also been used for research purposes.[18] The microwave devices utilized up to today have high security standards with respect to electromagnetic radiation, but are of limited use for chemical reactions. The control and setting of reaction parameters is limited to the energy input and the irradiation time. Pressure and temperature measurements are extremely problematic. This makes a comparison with classical reaction conditions difficult and leads to speculations about non-thermal (or microwave) effects.[19–24] Since the reaction control is only performed by energy input, temperature limitation is not possible by switching the power off.

In recent years, the technical developments, *e.g.* possibilities for temperature and pressure measurement, continuous processes, unpulsed energy entry, microwave leak sensors, in specialized systems that are adapted to chemical synthesis have extended the possibilities of microwave-assisted reaction engineering.

With these new advantages, there is a growing interest in scaling-up this method. When discussing the advantages of the microwave-assisted power input into chemical reactions and processes, one must always consider that the energy of microwave quanta is far too small to directly initiate a chemical reaction. Based on data for the bond energy it must be pointed out that microwave irradiation does not give a high enough energy to break typical chemical bonds commonly found in organic synthesis (C–C, C–O, or C–H, Table 1).

Table 1 Energies of chemical bonds[a] in comparison to different microwave energies

		Energy/eV [b]	Energy/kJ mol^{-1}
1	CC single bond	3.61[c]	347
2	CC double bond	6.35[c]	613
3	CO single bond	3.74[c]	361
4	CO double bond	7.71[c]	744
5	CH bond	4.28[c]	413
6	OH bond	4.80[c]	463
7	hydrogen bond	0.04–0.44[d]	4–42
8	MW 0.3 GHz	1.2×10^{-6}	0.00011
9	MW 2.45 GHz	1.0×10^{-5}	0.00096 $\approx$ 1 J mol^{-1}
10	MW 30 GHz	1.2×10^{-3}	0.11

[a] For more examples of strengths of chemical bonds see ref. 73. [b] 1 eV = 1.602177×10^{-19} J. [c] See ref. 74. [d] See ref. 75.

2 Principles of microwave irradiation

2.1 Physical principles – energy conversion – penetration depth

The physical principles of microwaves are based on relatively simple laws and are described briefly in the following paragraphs.

The wavelength λ_0 of a microwave (in this case 12.24 cm) is related to the frequency (2.45 GHz) *via* eqn. (1). The frequency indicates the number of oscillations of the electric or magnetic field in one second, *cf.*[1f]

$$\lambda_0 = \frac{c}{f} \tag{1}$$

The mechanism by which matter absorbs microwave energy is called dielectric heating.[3b] In this context, an important property is the mobility of the dipoles and the ability to orient them according to the direction of the electric field. The orientation of the dipoles changes with the magnitude and the direction of the electric field. Molecules that have a permanent dipole moment are able to align themselves through rotation completely or at least partly with the direction of the field. Molecules can rotate in time with field frequencies of 10^6 Hz in gases or liquids.[2c] However, they cannot follow the inversion of the electric field at an indefinite time. Phase shifts and dielectric losses are the results. In this case, besides the dielectric coefficient (permittivity), the size (mass) of the excited molecules is also relevant. Field energy is transferred to the medium and electrical energy is converted into kinetic or thermal energy. Molecular friction is often cited as a model for this behaviour. For numerous polar substances, dielectric losses are observed in the microwave range.[2c]

A simplified illustration of the heating mechanism of polar solvents by microwave radiation is provided in Fig. 2 for the example of a water molecule.

The fast changing electric field of the microwave radiation leads to a rotation of the water molecules. Due to this process, "internal friction" takes place in the polar medium, which leads to a direct and almost even heating of the reaction mixture. Because the change in the polarity of the electric field is faster than the rotation of the water molecules around its dipole centre, a phase shift results and energy is absorbed from the electric field.

Reflections and refractions on local boundaries yield "hot spots" and may result in a "super-heating" effect, which has been controversially discussed in the literature.[25,26] This effect can be described best as local overheating and is comparable to the delayed boiling of overheated liquids under conventional conditions. This effect is characteristically found only in unstirred solutions.

The coupling of microwave energy in the medium depends on the dielectric properties of the substance to be heated, *i.e.* it depends on the quantity of microwave radiation that fails to penetrate the substance.[2c] A measure of this behaviour is the dielectric coefficient ε_r that is characteristic for each substance and its state. ε_r is related to the capacity *C*, *i.e.* the ability to save electric energy, *via* eqn. (2) (capacitor model):

$$\varepsilon_r = \frac{C}{C_0} \tag{2}$$

For the electromagnetic field, ε_r is extended by the imaginary part $i\varepsilon_r''$ according to eqn. (3), where $i^2 = -1$:

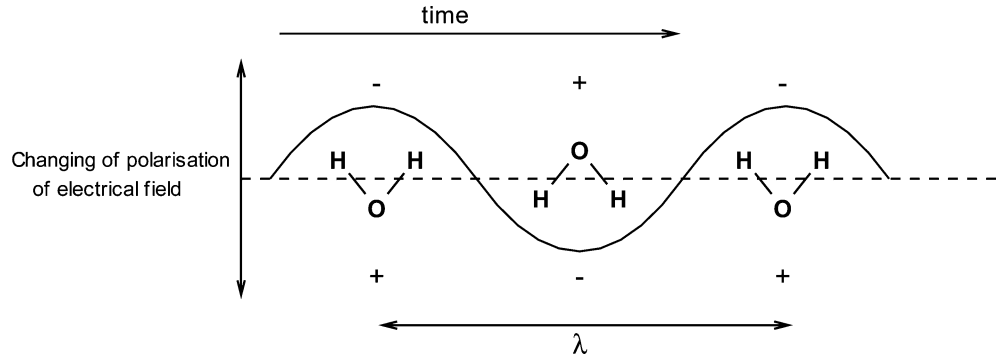


Fig. 2 Water in an alternating electrical field.

$$\varepsilon_r = \varepsilon_r' + i\varepsilon_r'' \quad (3)$$

The dielectric loss factor ε_r'' (also called dynamic dielectric coefficient) is obtained by comparing the irradiated microwave energy to the energy that has coupled with the sample. ε_r'' depends on the dielectric conductivity *s* and on the frequency *f* according to

$$\varepsilon_r'' = \frac{\sigma}{2\pi f} \quad (4)$$

The degree of energy coupling in the reaction system depends on both parameters ε_r' and ε_r'' and is called the dissipation factor $D = \tan \delta$, c.f. eqn. (5):

$$D = \tan \delta = \frac{\varepsilon_r''}{\varepsilon_r'} \quad (5)$$

$$\tan \delta \sim \frac{1}{x} \quad (6)$$

The dissipation factor defines the ability of a medium at a given frequency and temperature to convert electromagnetic energy into heat. It can also be regarded as a measure of the penetration depth *x* of microwave radiation into a material and is inversely proportional to *x* (eqn. (6)). According to the definition, the penetration depth is the point where only 37% (1/e) of the initially irradiated microwave power is still present. Penetration depths are only tabulated for a few materials and only for one temperature or for a small range of temperatures.[2g,3b] Because the penetration depth and the dissipation factor are both strongly dependent on temperature, this fact has to receive special attention for the scaling-up of chemical reactors for industrial applications.

According to the mechanism of energy input (ion conduction or dipole rotation), the dissipation factor additionally depends on other factors. It is directly proportional to the ion concentration, the ion size, the dielectric constant, the microwave frequency, and the viscosity of the reacting medium, *cf.*[2c] The dissipation factor of water and most organic solvents decreases with increasing temperature, *i.e.* the absorption of microwave radiation in water decreases at higher temperatures. In turn, the penetration depth of microwaves increases.

The dielectric coefficients for a number of substances such as organic and inorganic compounds, plastics, ceramics, waxes, glasses, and food are documented in the literature (*e.g.*[27]). For common organic compounds, the dependency of the dielectric coefficient on the temperature is known and tabulated.[1g,28,29] However, extensive knowledge is missing.

The interaction of electromagnetic radiation with matter is characterised by three different processes: absorption, transmission and reflection.[30]

Highly dielectric materials lead to a strong absorption of microwaves and consequently to a rapid heating of the medium. This means that ε_r'' and accordingly tan δ increase and the penetration depth of the microwaves in the medium decreases. Optimal energy absorption is reached in the system.

If microwave radiation is reflected by the material surface, there is no or only a small coupling of energy in the system. The temperature increase in the material is only marginal. This holds true especially for metals with high conductivity. Therefore, microwave devices are internally shielded with a metal surface (Faraday cage) to avoid any leakage of microwave radiation. Because interactions take place even with delimiting surfaces, irradiated energy is dissipated in empty microwave devices so quickly that no relaxation times can be measured.

Non-polar materials exhibit only small interactions with penetrating microwaves and can thus be used as construction materials for reactors. These materials are quartz, pure aluminium oxide (corundum), special glass types, and most common, plastics. Polyethylene and polypropylene have a low softening temperature and can only be used for external reactor parts. Due to their temperature and chemical resistance, fluorocarbon polymers can be used for parts that are in direct contact with hot reaction mixtures. Often combinations of these materials (PTFE + PEEK or PP + PTFE) or composites (*e.g.* glass fibre-reinforced plastics) are used.

Due to the wide use of microwaves in communication technology, international agreements greatly restrict the frequency domains that can be used for other applications.[1f,18] The so-called ISM frequencies are summarised in Table 2. The frequency used in most devices is 2.45 GHz, which is also used in the majority of household microwave ovens.

Table 2 According to international agreements allowed ISM-frequencies (ISM – frequencies for **i**ndustrial, **s**cientific and **m**edical use)

Frequency/MHz	Wavelength/cm
433.92 ± 0.2%	69.14
915 ± 13[a]	32.75
2450 ± 50	12.24
5800 ± 75	5.17
24125 ± 125	1.36

[a] Not allowed in Germany.

In the context of these basic principles, the following sections discuss the problems which must be considered in this research field. The microwave radiation is converted into thermal energy and quasi accumulated in the reaction medium. Reactions and processes taking place under the influence of the accumulated thermal energy have thus far always yielded similar results to classical reactions.[5,31–34]

2.2 Aspects of energy efficiency in microwave assisted reactions

In general, discussion about "energy efficiency" should always relate to comparable parameters. The question whether microwave energy can be used for the activation of chemical reactions more efficiently cannot be answered spontaneously. In ref. 8 and 9 as well as in most of the published work *e.g.*[35–37], investigations were only carried out with very small amounts of reaction mixture in the mmol range, which were then irradiated with comparatively high power (300 to 1000 W). A factor that describes the efficiency of the

microwave input was, in our opinion, too rarely included in investigations or discussions.[5] Such a discussion was and will be neglected as long as reactions are carried out on a millimolar scale. Considering a scale-up (mmol → mol → kmol), the limitation of this approach becomes obvious.

The determination of the energy input (eqn. (7)) and the energy that is required to reach a certain temperature (eqn. (8)) follows simple physical laws:

$$Q_{mw} = P_{mw}t \quad (7)$$

$$Q_{th} = mc_p\Delta T \quad (8)$$

$$\eta = \frac{Q_{th}}{Q_{mw}} \quad (9)$$

The efficiency factor η can be calculated from both the required and the used energy input (eqn. (9)). The efficiency factor is dimensionless and describes the effectiveness of the conversion of microwave energy into thermal energy. The available microwave power P_{mw} is determined by microwave device manufacturers according to standardised procedures.[38] Therefore, the values calculated from eqn. (7) seem quite reliable. If one checks the values of the microwave power cited in 8 and 9 it becomes obvious that in those investigations the microwave power use was unnecessarily large. For example, 2.5 ml reaction mixture was irradiated with 150–250 W microwave power for 4–9 minutes. At first glance, energies of only 32 and 120 kJ were employed. However, using the thermodynamic data for the materials used in eqn. (9), we find that only 1–1.5 kJ are required to heat the reaction mixture to the reported temperature. The efficiency factor is thus between 0.05 and 0.01 and is far from being an effective conversion of energy. For a more detailed investigation of the energy efficiency, we would like to refer to an article recently published by our group.[5] The relations reported in the literature that state the absorbed energy[39] and the quotient of the change in temperature and time[2c] are proportional to the square of the amount of the electric field strength could be verified through our own heating experiments for multiple polar substances in the microwave field. Furthermore, it must be considered that the conversion of electric energy into microwave energy has an efficiency of 0.5 to 0.65.[40]

The control of the energy input plays an important role in reaching the predefined reaction conditions for the treatment of reaction mixtures in organic chemistry. In household microwave ovens, only time and the power irradiated during this time can be varied as reaction parameters. Thus, the temperature is undetermined and increases steadily during irradiation. A possible but insufficient method to control the temperature is the on- and off-switching of the microwave field within a given time interval.[41] In modern laboratory microwave systems, however, computer controls, which allow setting of the attainable temperature or pressure as limiting parameters, are state of the art. This feature is important with regard to safety aspects of handling chemicals and is also crucial for both the reproducibility and the scale-up of reactions. After reaching the preset parameters, the energy input is reduced to a level necessary for keeping the preset values. This power control contributes essentially to the efficiency of the power input by microwaves. The microwave energy proceeds almost free from losses through the reactor walls into the reaction mixture and is then converted into heat. The heat is accumulated in the reaction mixture and remains there since the reactor materials are also good heat insulators.

This control enables the regulation of the temperature in the reaction mixture with a precision of ±1 K and the pressure with ±0.5 bar. With conventional heating, these values cannot be easily reached and represent exceptions. If the reaction parameters are not known, the uncontrolled energy input results in much higher temperatures than those used in conventional reactions. This leads to shorter reaction times and sometimes to higher yields. Those results then nourish the speculations about non-thermal effects. Also, large amounts of reaction mixtures cannot be processed since the explosion and ignition risks are too high. In addition, household microwave ovens are entirely closed systems due to security constraints concerning the complete shielding of electromagnetic radiation. Therefore, they require the use of rather simple laboratory glassware such as open beakers or GC-vials. This complicates the reproducibility of results from such experiments.

In conclusion, it is not surprising that 2.5 ml of reaction mixture are heated very rapidly when irradiated with 250 W microwave power. If one would apply the same controlled concentration of thermal energy to a small vial (*e.g.* by solar reflectors, Bunsen burner), comparable heating effects and reactions would also result. Comparable power (120–500 W) is used for conventional heating in 250–1000 ml heating mantles, however, for much larger substance quantities and with completely different heat transfer mechanisms, requiring substantially longer heating times.

In our opinion, this point precisely illustrates the advantage of power input by microwaves. High power can be applied to reaction mixtures which are able to absorb microwaves in a controlled and fast manner. The fact that reaction parameters, such as the batch and the vessel size, play an important role will certainly require the education of any synthetic chemists who wishes to employ microwave-assisted reactions.

3 Instrumentation technology

3.1 Aspects of the irradiation method

An often employed argument in the literature (also in 8–11) is the advantage associated with employing a focused energy input when using monomode microwave radiation for chemical reactions compared to using multimode radiation. However, even manufacturers of technical microwave systems do not give consistent definitions of "multimode" and "monomode" devices, *cf.*[5]

The term "focused" implies the use of optical systems (lenses or mirrors) and is not adequate in this context. Many publications use the term "focused" in an uncritical way without even adding the trademark symbol and without discussing the true meaning of the term. To date, no commercially available microwave system uses a focusing system. Some manufacturers of technical microwaves have registered the term "focused" as a trademark, which has created misunderstandings.[42] In a monomode microwave device, the reactor is directly inserted into the waveguide. Microwaves follow the physical laws of electromagnetic radiation. The waveguide is designed in such a way that in the empty waveguide microwaves are reflected in phase. Standing waves result, and the reactor is inserted exactly where a maximum of the electric field was calculated for the dielectric material air. Only the relatively small sample amounts (max. 100 ml, often less) are irradiated at one point from the side. As a result, great inhomogeneities of the electrical field and high temperature differences arise. Furthermore, the insertion of the reactor influences the field geometry and the application of reaction mixtures leads to even further changes, which can not be counteracted by the control mechanisms in the waveguide. New modes (wave kinds) are created by refraction, reflection and interference, which will eventually result in a system with high microwave power density (radiation intensity). This represents a multimode system with an undetermined amount of initial monomode radiation. The amount of monomode radiation apparently depends on numerous parameters such as the reactor size and material, the insertion position in the waveguide, and the constitution and amount of the reaction mixture. Every additional change over time leads to an increase in the amount of multimode radiation. In theory, it makes little sense to distinguish between monomode and multimode radiation. A classification according to their radiation intensity or power density should better characterise today's microwave devices. Table 3 summarises common microwave systems with their important specification parameters.

The second type of commercially available microwave system is multimode systems. In these devices, the radiation produced by the magnetron is directed through a waveguide and a mechanical field

Table 3 Comparison of the currently available microwave systems for synthetic applications

Manufacturer	Sharp[a]	Personal Chemistry[b]	CEM[c]	MLS/Milestone[d]
Type	domestic MW oven R-220A,	Emrys™ Creator	Discovery™	ETHOS™ MR
Irradiation modus	multimode	monomode	monomode	multimode
Max. power	800 W, pulsed	300 W, unpulsed	300 W, unpulsed	1000 W, pulsed or unpulsed
Cavity volume	15.7 L	< 1 L	< 1 L	42.8 L
Maximum power density in empty cavity	around 50 W L^{-1}	> 300 W L^{-1}	> 300 W L^{-1}	around 23 W L^{-1}
Reaction scale	max. 100 g in dry reactions	< 20 g	< 50 g	up to 3000 g depending on reactor

[a] Some other modified or unmodified domestic microwave ovens are used for chemical reactions, *e.g.* Panasonic NN-S740WA-1200 W, see also ref. 2e and 76. [b] See also ref. 77. [c] See also ref. 42*b*. [d] See also ref. 78.

distributor in a rather large volume (microwave cavity). In the cavity, radiation is in general homogeneously distributed, thus avoiding the formation of standing waves. While household microwave ovens exclusively operate with pulsed microwave radiation, technical systems also allow the use of continuous (unpulsed) irradiation. In the pulsed operation mode, pulses with the maximum available power (800–1000 W) are applied according to the preset irradiation power and time. In the unpulsed mode, the actual preset power is applied (Fig. 3, designed by W. Lautenschläger, MLS GmbH, Leutkirch, Germany).

Working with unpulsed microwave radiation exhibits advantages for refluxing, distilling and for photoreactions in the microwave field (*e.g.*[4]). Sensitive substances might not be overheated. The disadvantage of these unpulsed power supplies in comparison to conventional systems is their higher technical complexity. However, since the use of the full microwave power[5] did not seem advantageous for most of the investigated reaction, the use of unpulsed power supplies will result in advantages in the long run, also with respect to energy efficiency.

At this point, we would like to discuss the term "penetration depth" in more detail. The microwave cavity of the largest available synthetic microwave system has a volume of approximately 100 L and allows for reactions on the pilot plant-scale. Microwaves penetrate from all sides into the sample and lead to a mostly homogeneous energy input, which is additionally improved by stirring the reaction mixture. Considering the penetration depth of microwaves in water, 1.4 cm at 25 °C and 5.7 cm at 95 °C, the reactor dimensions are limited.[25] Currently a more precise prediction for organic solvents is impossible due to a lack of data. However, since water has a comparatively high dielectric coefficient, higher penetration depths can be expected at ambient temperature for the majority of substances used in organic synthesis.

Literature[5,32–34] reveals that for a series of investigations when other reaction parameters were kept constant (*e.g.* temperature, batch size, mol ratio), the irradiation method (monomode or multimode) did not influence the result of the experiment. Examples include the enzyme-catalysed transesterification of ethyl acetate or vinyl ester with racemic alcohols for enantiomeric separation,[32] the Hantzsch reaction of ethyl acetoacetate with formaldehyde and ammonia, the Knoevenagel reaction of salicylaldehyde with ethyl acetoacetate (Scheme 1),[5] hydrolysis of benzamide[33] and examples of the palladium-catalysed C–C-coupling.[34]

3.2 Aspects of the temperature measurement in the microwave field

Commonly employed mercury thermometers cannot be used for temperature measurements in the microwave field because they absorb microwaves (act as antenna). When the mercury heats up, it builds a self-potential, which creates feedback with the magnetron or the cavity walls. This can lead to a spark discharge (compensation of potential) that destroys the thermometer.

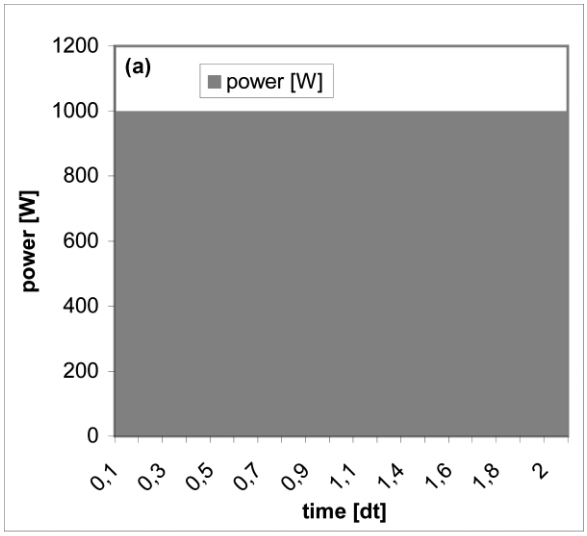
Due to a lack of alternatives, temperature measurement was often neglected during the first years of microwave-assisted reactions, *e.g.*[2e,13,14] The obtained results were compared with data in literature, which sometimes lead to incorrect estimations of the capability of microwave radiation for the activation of chemical reactions. Due to the comparatively high costs, new temperature measurement systems were only slowly introduced. These systems allowed for the temperature measurement directly inside the microwave field or the reaction mixture. Three essential methods for the measurement of temperature in the presence of microwaves exist:

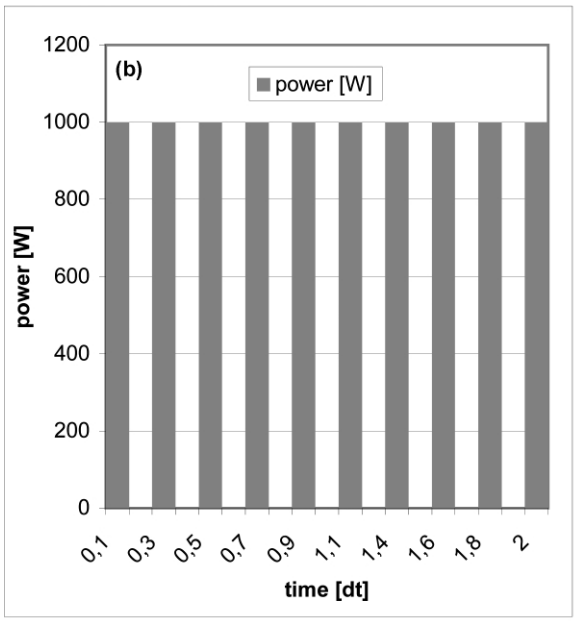
(i) shielded thermocouples
(ii) IR-sensors
(iii) fibre optics

3.2.1 Shielded thermocouples. The measurement with specially shielded thermocouples is currently the least expensive possibility. However, this method is inappropriate for more non-polar solvents such as dichloromethane or methyl-*tert*-butyl ether, because these solvents, even in well shielded thermocouples, act as antenna and are themselves heated. These thermocouples can be used up to 300 °C, which is a temperature higher than typically useful for organic synthesis. Furthermore, since those thermocouples have significant volume due to the shielding, reaction volumes should have a minimum size of approximately 30 ml. To our knowledge, this measurement method is to date only available from MLS GmbH/Milestone Ltd.

3.2.2 IR-sensors. Another widespread method is indirect temperature measurement with IR-sensors on the reactor wall. This method can be applied universally because the sensors are integrated into the wall of the microwave cavity and measurements are made from a certain distance. This, however, is also the biggest disadvantage of this method, because temperature is only measured on the outside wall of the reactor. The wall is the coldest spot of the reaction system due to air cooling in all modern synthesis systems. Measurement errors are thus unavoidable. Heat flux is inverted with regard to conventional reactions since the energy conversion takes place directly inside the reaction mixture. Thus, the reaction mixture will always be warmer than the reactor wall. This is an essential advantage of microwave-assisted reactions. Fig. 4 depicts the heating curve of 500 ml water heated from ambient temperature to 100 °C and measured with a shielded thermocouple, an IR-sensor and a fibre-optical sensor.

The investigated measurements with three different measurement methods exhibit a margin of error of ΔT = 30 K, especially when reaction mixtures were heated quickly and when reaction times were short (< 20 min). The IR-sensor always registers lower temperatures. This discrepancy explains many speculations about microwave effects in systems where only IR-sensors were employed.[20,21] For example, if an IR-sensor reads 220 °C for a microwave-assisted reaction (*cf.*[20] in[8]) and the same reaction is reproduced at exactly 220 °C when measured by a thermocouple or a mercury thermometer under conventional heating methods, any difference in the course of the reaction could stem from more than one parameter (temperature measurement or energy input). A questionable concept for temperature measurement and reaction processing using IR-sensors is propagated by the CEM Corp. under





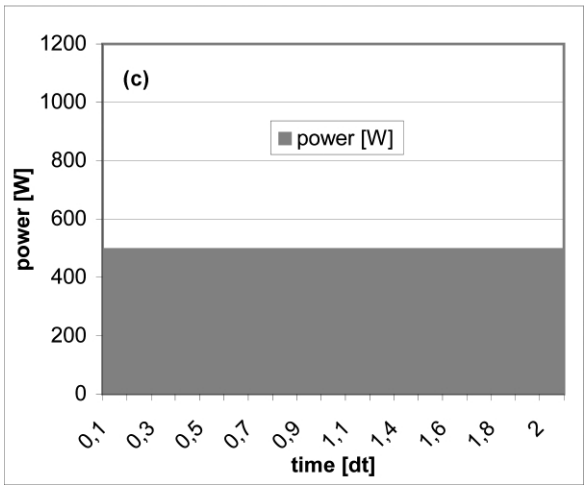
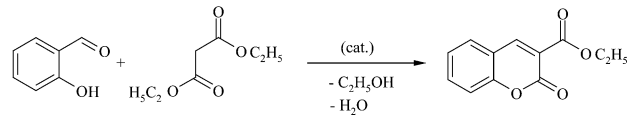
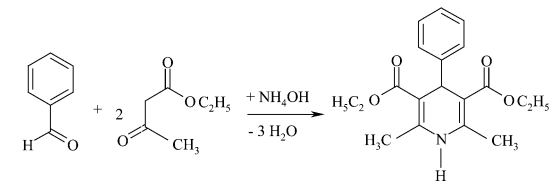


Fig. 3 Microwave power at work with pulsed and unpulsed power supply unit, maximum power of the discussed system: 1000 W (a) Irradiation of 1000 W. No differences are found between pulsed and unpulsed power supply units. (b) Irradiation of 500 W with pulsed power supply units. Irradiated with full power (1000 W) in 50% of predetermined time. (c) Irradiation of 500 W with unpulsed power supply units. Irradiated with 50% power in the complete predetermined time.

Knoevenagel condensation (ETHOS MR, 300 W, 10 mmol scale, 15 min, 140 °C)



Hantzsch reaction (ETHOS MR, 600 W, 20 mmol scale, 15 min, 90 °C)



Scheme 1

the name PowerMAX™.[42] In this concept, the reactor wall is cooled directly with a strong air stream and at the same time the power input of the microwave system is increased. The temperature at the reactor wall (measured with an IR-sensor) remains constant because the heat flux through the glass wall remains constant. The cooled air stream is able to keep the temperature of the reactor wall at the preset point. The temperature rise inside the reactor is undetected, and thus higher conversions for sample reactions can be obtained. Additionally, this cooling system contributes to energy dissipation and can incorrectly lead the operator to the conclusion that higher microwave power leads to higher conversions. The same result is obtained when one works without the intensified cooling by setting the temperature higher and applying regular microwave energy, *cf.*[43]

The measuring range of IR-Sensors currently used is between −40 and +1000 °C. Such sensors are used by all manufacturers of technical microwave systems and are fairly widespread. For devices from CEM and Personal Chemistry, the IR-sensor is the lead-sensor and controls the power input. MLS/Milestone uses the IR-sensors in several systems for secondary measurements that explicitly control the temperature on the reactor surface.

3.2.3 Fibre optics. The third, also widespread but cost-intensive method, is the temperature measurement by fibre-optic sensors. With this method, a fibre-optic sensor with gallium arsenide crystal on the tip is placed inside a protective tube directly into the reaction mixture. Minor errors in measurement can be electronically adjusted through comparison with NiCr/Ni-thermocouples and a precision of ΔT = 2 K can be achieved. A disadvantage compared to other measurement systems is the more narrow operating range of 0 to 330 °C. Permanent aging phenomena of the sensors are already observed above 250 °C after a few hours. Furthermore, fibre-optic sensors are very sensitive to mechanical stress. One reason for the lower temperature resistance of the fibre-optical sensors is the unavoidable use of plastics during their fabrication (*e.g.* for gluing the measuring crystal to the optical fibre).

Although there are disadvantages in the operating range and a reduced mechanical stability in fibre-optical sensors, they still have a broad range of applications for temperature measurement in the microwave field. Furthermore due to the low volume requirements, the sensors can also be applied to small scale reactions. At present, the commercial availability of fibre-optical measurement systems with a constant sensor quality remains a problem. The precision of the temperature is crucial for the reproducibility of the experiments and the comparison with conventional reactions.

It must be concluded that the problem of temperature measurement within the microwave field is mostly solved. However, a breakthrough in the precision of the working methods is still sought and until implementation there is still room for more speculations or discussions about non-thermal effects during a microwave

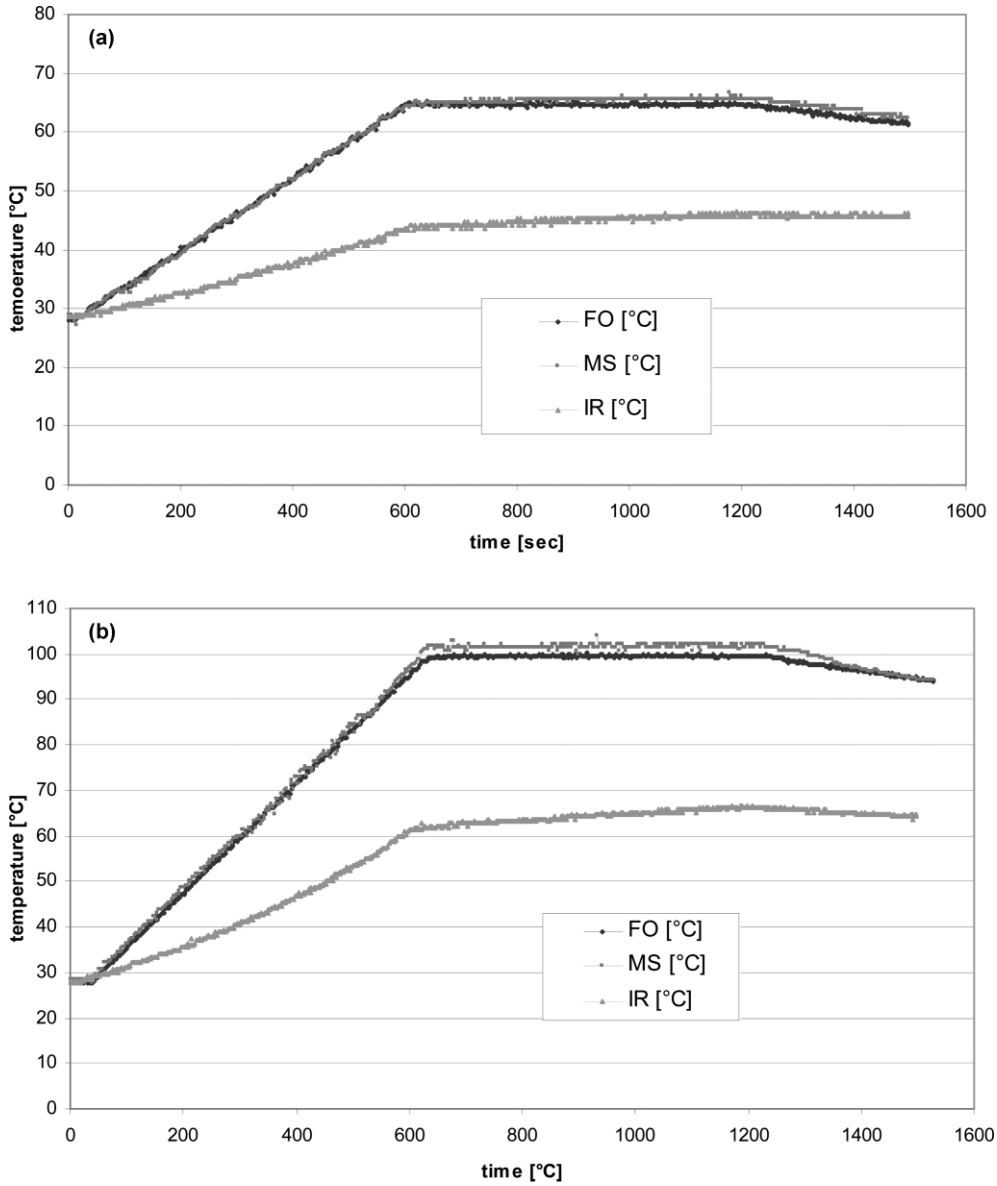


Fig. 4 Comparison of temperature measurement with different sensors. Irradiation of 500 g water with 500 W microwave power (ETHOS 1600 *, reflux apparatus) (a) Temperature range: 28 °C up to 65 °C. (b) Temperature range: 28 °C up to 100 °C. *The fibre optic sensor (FO) and the metal sensor (MS) are placed directly into the stirred medium and the precision of measurement for the FO-sensor and metal sensor are ±2 K. The IR-sensor measured the temperature on the outer surface of the reactor. The temperature increase is controlled by a programmed predetermined ramp step and controlled with FO-sensor.

reaction.[19–23,42] The possibility that all microwave effects found are due to incorrect temperature measurements and invalid comparisons with conventional reactions cannot be ruled out. The proof of this statement, however, requires a large number of reproducible experiments.

4 Applications – experiments – comparisons

4.1 Aspects of microwave-assisted synthesis as an interdisciplinary research field

The questions on generalisation, reproducibility and scale-up of microwave assisted reactions will always be centred on the reaction conditions. Additionally in microwave-assisted reactions, the medium plays a much more important role than in classical reactions. Also, the polarity of all components in the reaction mixture determines the absorption of microwave power. Since dielectric constants (static and dynamic) are only known for a few compounds, further complexity arises and contact with neighbouring disciplines, for example with electrical engineering in this case, is required in order to further study and ultimately, to better understand the reaction.

The concept of a "Comprehensive Chemistry" is not useful in the case of microwave-assisted reactions. Compared to conventional reactions, the reaction engineering and technical parameters play a much larger role in microwave-assisted reactions. Therefore, an improvement of the description of reaction parameters is crucial. These considerations lead us to develop a draft for a general experimental protocol for microwave-assisted reactions and processes. Its introduction and application in the sense of sustainability shall be presented later for some examples.

The batch sizes, the energy input, and especially the method of the temperature measurement are rarely described correctly or completely. Thus it is impossible to place a value on the described reaction and its reproducibility.

As a result of long-lasting effort between the microwave system manufacturers and the chemical engineers, a concept for the transfer of conventional reactions into the microwave field, which attempts to find solutions through "scale-down" and "numbering-

up" approaches as well as through "scale-up" concepts (Fig. 5), has been developed.

The following applications demonstrate the realisability of the concept and some possibilities of the developed complex microwave system. Some problems of scaling-up are discussed in Section 4.3.

4.2 Application examples

4.2.1 Microwave assisted extraction of raw materials from natural sources. As the search for finding new lead structures for pharmaceuticals and other active agents continues, extraction processes for compounds from natural materials have gained significant importance. While in the analytical sector a range of new methods were developed,[44] in the preparatory field the development of extraction processes has lagged behind. The isolation of preparative amounts of substances (solid extraction) is today still mostly performed using the more than 100 year old Soxhlet extraction method. Extractions in the laboratory on the kg-scale are possible and thus larger amounts of extract are obtainable. But with respect to temperature sensitive materials, Soxhlet extractions are limited because the extraction often requires several hours at the boiling temperature of the respective solvent.

Microwave technology provides an alternative source of energy that should be well suited for preparative extractions.[45] Not only is it possible to introduce energy quickly into the reaction system, but also the extract and the energy can be quickly removed from the system. After a series of preliminary experiments for analytical extractions,[46] the HEF 270 extraction system with a 6-fold segmented rotor was developed in cooperation with MLS.[47] This extraction system enables the heating of the extraction mixture in a controlled fashion. For example, the separation of trimyristine directly from the nutmeg powder was achievable.

With this system, even heat sensitive natural material can be isolated since the residence time at the elevated temperatures is very short (approx. 1 min). This simple and easy-to-operate system was used to study aspects of the non-classical energy input (in this case: microwaves) for chemical extractions and processes in the education of graduate chemistry students.[48]

As an introductory example, the extraction of trimyristine from nutmeg powder was chosen (Fig. 6).[49] Common unground nutmeg nuts contain between 10% and 40% of extractable substances. The main constituent of those substances is a triglyceride consisting of 90% myristic acid (saturated C_{14} carboxylic acid). Due to its solubility, trimyristine can be easily isolated by hot extraction with ethanol.

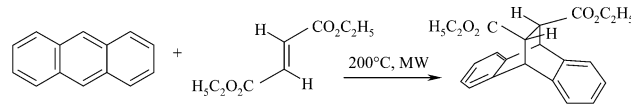
Comparative investigations were performed with Soxhlet apparatuses with additional attention paid to the choice of solvent, completeness of the extraction and the required amount of energy. While the conventional extraction was performed with 10 g nutmeg powder at approximately 80 °C and with a solvent volume of 300 ml over the course of 4 to 6 hours, in the microwave field, the extraction of 3 × 3.3 g nutmeg powder, each with 80 ml ethanol at 100 °C, only required 10 to 15 minutes of extraction time. The yields of trimyristine in the microwave experiments are approximately 10% higher than those under conventional techniques with comparable batches of raw product. With the microwave-assisted conditions, an almost quantitative extraction was obtained. Comparison of IR spectra of the raw product, trimyristine and the extraction residue (Fig. 6) from a second extraction step showed this high conversion.

A proposed protocol for the microwave-assisted extraction experimental is summarised in Table 3.

This protocol allows for an easy implementation of a non-classical experiment into the curriculum of chemistry students. The starting materials are known and the concept is practical. Students without any previous knowledge of microwave techniques and processes could, after a short introduction, operate the microwave system including the extraction rotor and perform the extraction of a natural product.

4.2.2 Solvent free reactions. In organic chemistry, Diels–Alder reactions are synthetically useful for the construction of six-membered rings.[50] This reaction type was one of the first performed in a microwave field.[14]

The reaction of fumaric acid diethyl ester with anthracene to the respective Diels–Alder adduct is a well-investigated[1e] and comparatively simple reaction. It proceeds in high yield under conventional conditions in the presence of equimolar amounts of anhydrous aluminium chloride as an activator (Scheme 2).[51] If no



Scheme 2 Diels–Alder reaction (*cf.* Table 4, entry b).

activator is used, heating for several days in dioxane or for several hours in *p*-xylene is required to achieve high yields.[52]

Surprisingly, results that have been described once with defined reaction conditions are rarely investigated further and are only revised in very few cases.[48] Moreover, they are usually carried out as described in the literature.

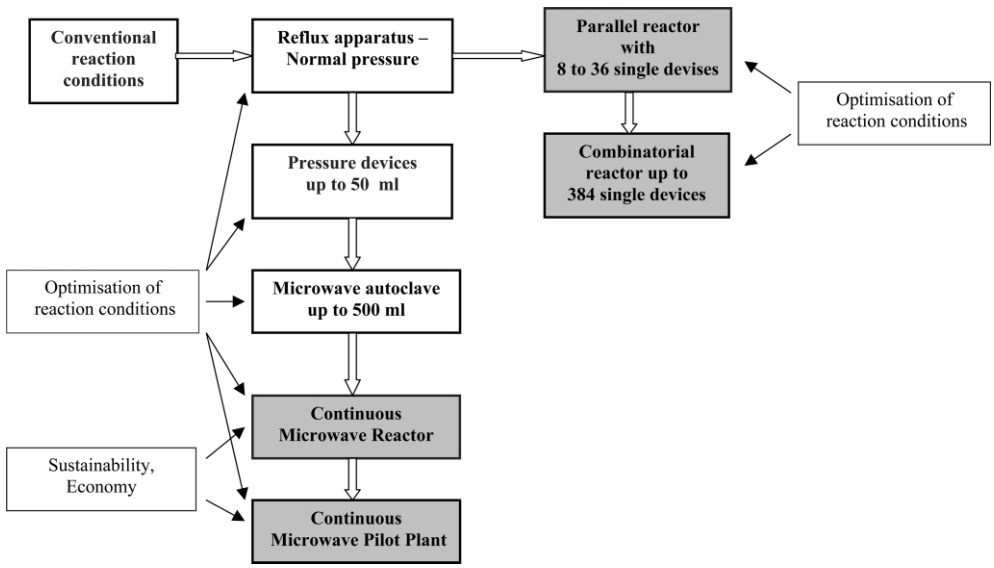


Fig. 5 Development concept for microwave assisted chemical reactions and processes.

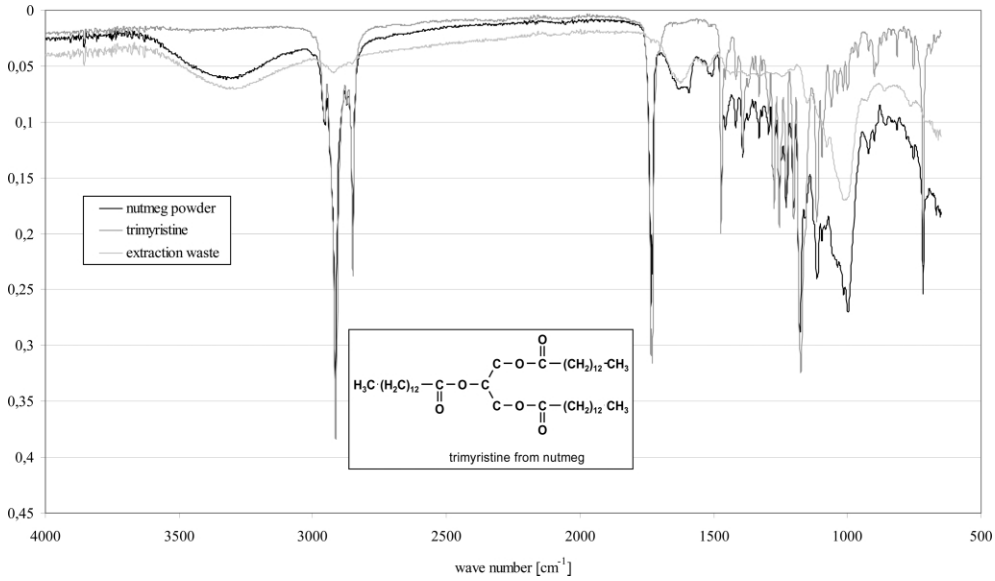


Fig. 6 Comparison of FTIR-spectra (ATR, TravelIR, Perkin Elmer Instruments, Sheldon, CT) of nutmeg powder, trimyristine and extraction waste.

If one takes a closer look at the selection of a solvent, this is mostly determined by the desired reaction temperature or perhaps the viscosity of the reaction mixture. Normally, especially with respect to scale-up, diluting of the reaction mixture is undesirable. For reactions at elevated temperatures, the solvent is often used in order to keep the reaction temperature constant for an extended period of time. If another control mechanism exists, the use of a solvent can perhaps be avoided. Without the solvent, the temperature range up to the boiling point of the reactants can be exploited. This in turn brings into question the necessity of an activator or catalyst.

The reaction represented in Scheme 3 was performed in the microwave field after extensive preliminary tests. As a result of the

$$\text{R-COOH} + \text{R}^1\text{-OH} \rightarrow \text{R-CO-O-R}^1 + \text{H}_2\text{O}$$

$$(\text{R-CO})_2\text{O} + \text{R}^1\text{-OH} \rightarrow \text{R-CO-O-R}^1 + \text{R-COOH}$$

$$\text{R-CO-O-R}^1 + \text{R}^2\text{-OH} \rightarrow \text{R-CO-O-R}^2 + \text{R}^1\text{-OH}$$

Scheme 3 Possibilities of esterification.

comparative experiments with the conventional reaction conditions, it was shown that without the solvent, reaction temperatures could easily be set to 150–250 °C. This led to a reduction of the reaction time to 10 minutes and rendered the activator superfluous. The temperature was reached within a few seconds for a 1 mol batch and kept constant with the modern automatic control technology of the technical microwave systems. Thus, the reaction conditions changed drastically: Two auxiliaries were not required and no aqueous work-up was needed. With these measures, a previously published classical reaction was improved and now the new possibilities of modern reaction engineering can be implemented. Reaction conditions are summarised in Table 4.

4.2.3 Parallel chemical reactions. The right hand side of Fig. 5 addresses the concept of parallel chemical reactions in the microwave field. The goal of this effort is to transfer the advantages associated with microwave-assisted reaction engineering to combinatorial chemistry. The technology of running parallel chemical reactions is an intensively investigated area of research,[53] and microwave irradiation was already used for the rationalisation of this process.[35,54–56] In general, there are two different methods for performing parallel synthesis in the microwave field (selected examples):

(i) EXPLORER-System (CEM) and EMRYS-Systems (Personal Chemistry)

(ii) ETHOS (MLS/Milestone) and Multiwave 3000 (PAAR)

(i) The first method allows for the use of small microwave cavities with high microwave density, for irradiation of solely the reactor (*e.g.* GC vial) and volumes of up to 50 ml. This approach is used by the companies CEM and Personal Chemistry (*cf.* Table 3). Short reaction times under controlled reaction conditions (temperature measurement *via* IR-sensor) are used for a step-by-step processing of a large number of assays.

(ii) The ETHOS system from the company MLS/Milestone takes a different approach which allows for the simultaneous irradiation of several assays (sample volumes: 1–100 ml) in a larger microwave cavity under identical reaction conditions. For this purpose, some rotor reactor racks that can accommodate up to 192 assays were developed in cooperation between the company MLS GmbH and the ITUC of Friedrich Schiller University of Jena. Test reactions performed in this reactor set-up have been published.[57] It is noteworthy that these tests confirmed that the reaction time itself is not the rate-determining step for combinatorial chemistry in the microwave field. It is rather the data management, sample preparation, work-up and sample analyses that consume the most time.

4.3 Aspects of process development

A common requirement associated with the introduction of a new technology is the possibility to scale-up the respective process, first to a pilot plant-scale and eventually to the production scale.

The aim of using microwave processing is to accelerate reactions in order to avoid disadvantageous reaction parameters (*i.e.* long reaction times, secondary reaction time, solvent use, excess components *etc.*). A further goal for process improvement is to transfer a batch operation to a continuous operation after they have undergone a process analysis. For this purpose, usually the first step is to repeat the known reaction conditions used in the conventional reactions in the microwave field. Often a similar experimental setup is used (reflux apparatus). Starting from this point, all conventional reaction conditions must be re-evaluated. The introduction of a new technology in organic technical synthesis allows for the questioning of old preparation protocols. It would be advantageous to produce a check list for each reaction that critically questions the known synthetic protocols, analyses them, and provides potential new solutions. When considering process development a variety of parameters should be addressed. A list of questions that could be asked follows:

- What is required temperature for the reaction?
- What is the influence of the temperature?
- Are the compounds in the reaction mixture thermally stable?

Table 4 Proposal of protocol for a microwave assisted extraction and a Diels–Alder reaction

1. General data	Microwave–assisted extraction: trimyristine from nutmeg powder	Solvent free – Diels–Alder reaction: anthracene with fumaric acid diethyl ester
Type of microwave system	ETHOS 1600;	ETHOS MR
Manufacturer	MLS GmbH Leutkirch	MLS GmbH Leutkirch
Construction year	2000	1998
2. System description		
Cavity volume	42 L	42 L
Max. microwave power	1000 W	1000 W
Characteristic of magnetron	2 industry magnetrons, power drop down from 800 to 500 W.	2 industry magnetrons, power drop down from 800 to 500 W.
Power dosage	10 W steps	10 W steps
Irradiation modus	multimode	multimode
Microwave irradiation	unpulsed	unpulsed
3. Reactor and program		
Type of reactor	HEF 270, segment rotor, 3 segments	reflux apparatus, 100 ml flask
Temperature measurement	fibre optic in one segment	fibre optic
Safety equipment	MW-leak sensor	MW-leak sensor
Control program	5 min/500 W/up to 100 °C – 10 min/400 W/at 100 °C	15 min/700W/up to 220 °C – 5 min/900 W/up to 250 °C – 15 min/900 W/at 250 °C
Max. temperature	110 °C	220–250 °C
Max. pressure	4–5 bar	1 bar
Average power	197 W	522 W
Energy entry	175 kJ (kWs)	1112 kJ (kWs)
Stirring in reactor	magnetic stirring bar, 14 mm	magnetic stirring bar, 30 mm cross form
4. Chemical data		
Scheduled quantity	10 g nutmeg powder	0.1 mol
Amount and ratio of all components	3.3 g nutmeg powder in each rotor segment	anthracene: 17.8 g, fumaric acid ethyl ester: 20.7 g (20% excess)
Solvent	80 ml ethanol in each rotor segment	
Dosage of reaction compounds	assembling of segments following construction manual[46] before installation of rotor in the microwave system.	mixing of components before installation of flask in microwave system.
Reaction behaviour	pressure extraction	solvent-free reaction at boiling point of fumaric acid ethyl ester (219 °C), after reaction time at 250 °C
Cooling method	Extract was taken hot.	air cooling
Cooling time	20 min	
Work-up	cooling of extract, filtration in vacuum, drying on air, transesterification of triglycerides	stirring with petrolether, washing, vacuum filtration
Yield	depended of quality of nutmeg powder	92%
Analyses	mp., IR, NMR, GC of FAME	mp., GC, NMR

• Is the reaction exothermic or endothermic; what is the energy balance?

• Do secondary reactions occur? Why?

• Is a solvent required? Why?

• How is the work-up? Do the work-up processes require (heat) energy?

• Is a catalyst required? Which catalyst and in what quantity?

• Can the catalyst be recycled? Is the recycling advantageous?

• Which reaction conditions influence each other?

• Is the stoichiometry optimum?

• What waste materials and/or by-products form and how can they be handled?

• Do toxicological/ecotoxicological data exist?

This list can be extended on the basis of the rules for sustainable development[10,58] in all areas and is not meant to be an exhaustive list. Microwave technology allows for the investigation of these questions with the present technology by changing reaction parameters and checking old reaction protocols.

Microwave systems that are currently commercially available were initially developed for chemical decomposition (complete mineralization as sample preparation for atomic adsorption spectroscopy). This development limited the size of the reactors that could potentially be used for chemical synthesis. With operating volumes of 25–50 ml, or in rare cases 250 ml, reactions on the 10–50 mmol scale could be performed. Relating to this, the concept of dry reactions has been reported,[5] and cited in the literature.

The development of microwave systems for further applications in organic chemistry is going in several directions: one trend is the development of small devices or devices that are tailored to a special application. The small devices (*cf.* Table 3) allow for the reaction of mmol-amounts in a short time (several minutes) with comparatively high power input. These devices posses a small microwave cavity ($\leq$1 L) and have a reactor installed directly in the waveguide, often only small and closed vessels similar to GC-vials can be used. These systems are advantageous for organic chemists if only a yes-or-no-answer with respect to the experimental result is expected (*i.e.* for screening conditions). If the investigatory scope is extended to questions about the reproducibility, the reaction kinetics, or the increase in the reaction scale up to 0.1 mol product (factor 100), such devices will fail. This product line was developed by three companies:

– Personal Chemistry (Sweden) – automated products of the EMRYS-systems

– Prolabo (F) (no longer existing) – "real" monomode systems (see section 3.1) of the "Synthewave"-series

– CEM (USA) – "Discovery"-series. CEM also produces a wide range of multimode devices, which are mainly used for sample preparation (digestion, drying, ashing) and sometimes also for carrying out organic syntheses.[59,60]

However, according to the previous explanations, the EMRYS and the Discovery systems do not represent real monomode systems, but rather are multimode systems with a high power density.[61]

The second development direction is the design of different reactor kits that can be integrated into the same basic system (ETHOS system, MLS/Milestone). This system allows for the realisation of a concept (see Fig. 5) for the comparative transition of classical thermal reactions into the microwave field. The use of different reactors for different requirements and applications allows for a flexible reaction engineering in which reaction parameters can

be precisely documented. Through the exact reproduction of conventional conditions, it is possible to simultaneously compare classical and microwave-assisted reactions. With this construction kit, reactions from the mmol-scale to the mol-scale can be performed. Furthermore, the transition from a batch operation to a continuous operation is also imaginable. This has already been described for some reaction types.[62]

Derived from the basic model, a robust beginner system (PRAKTIKA, MLS GmbH) is now available with simple measurement technology that allows for easy integration of microwave-assisted reactions into laboratory classes.

Further, a pilot plant device was derived from the base mode in which first studies on the real scale-up were performed.[63] The ETHOS 4000/4001 devices can already process reaction mixtures of 5–10 kg per hour and are thus already suitable for the production of high-priced fine chemicals, *e.g.* pharmaceuticals.

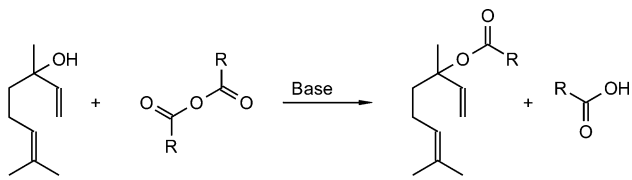
The goal of all these investigations was to obtain a holistic view and to question all reaction parameters employed so far in order to discover new unconventional ways for carrying out long-known reactions. Therefore, the description of all reaction parameter is absolutely necessary.

4.4 Application example – esterification of linalool with carboxylic acid anhydride

Various esterification reactions were repeatedly performed in the microwave field (Scheme 3).[64] It was found that if all reaction conditions were similar between the conventional and microwave-assisted reactions, no differences in the reaction kinetics were observed.[65]

The esterification of tertiary alcohols is a well established process that poses significant problems,[66] especially when other functional groups are present and when the process is to be transferred from the laboratory-scale into the pilot plant-scale and the production-scale.

In the realm of process design, the use of microwave energy for the esterification of linalool with different carboxylic acid anhydrides was investigated (Scheme 4).



Scheme 4 Formation of linalooyl ester (*cf.* Table 6, entry a and b).

First, the parameters for the batch process were analysed, and then in a second development step, the reaction was transferred into a continuous process. Table 5 summarises reaction parameters for the continuous esterification (1. step in Table 5) of linalool with carboxylic acid anhydrides in the continuous microwave system ETHOS contFLOW.

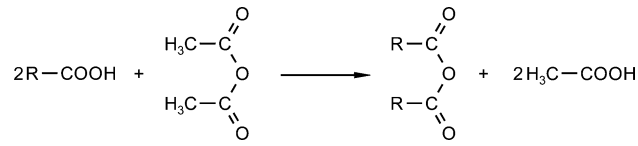
Table 5 Yield of linalyl propionate at various reaction duration in a 5-hour-experiment to the continuous esterification of linalool with propionic acid anhydride (ETHOS PILOT 4001, residence time 12 min, *i.e.* 2.2 L h^{-1}, 1000 W, 10 bar, *cf.* Table 6)

Reaction duration/min	Yield of linalyl propionate (GC, area-%)
42	49.7
120	52.2
215	50.8
Average yield	51.1

With these parameters, orienting experiments were carried out in the pilot plant microwave system ETHOS PILOT 4000. After a short starting-up phase, the reactions on the 25 kg-scale showed relatively constant conversion and product composition through the experiment (Table 5).

Parallel to the reaction, improvement of the whole process, especially with respect to the thermal steps in the work-up procedure and in the recycling of the secondary products, using microwave energy was made. For this purpose, the reaction mixture (conversion 50–60%) was submitted to a reactive distillation,[67,68] in which the carboxylic acids formed were distilled under vacuum at temperatures of 10–20 °C below the actual reaction temperature (2. step in Table 5). Thus, the reaction equilibrium could be completely shifted in favour of reaction products. The losses of linalool (dehydration to olefins, rearrangement to nerol and geraniol, and formation of isomeric esters) were less than 10%. Table 6 provides a proposal for the protocol for all steps in the continuous lab scale esterification.

The investigations of the reactive distillation show that distillation processes especially benefit from the use of microwave energy. The temperature measurement directly at the bottom of the distillation and the previously discussed advantages of the inversed heat flux in the microwave field, prevent overheating of the vessel walls, which may arise under external heating. Thus higher yields, suppression of decomposition reactions, and a longer stability during distillation result. The elimination of decomposition reactions is of great importance, for example in the fabrication of perfumes and is essential for improvements in the end product quality, since foreign odours can disturb the olfactory system. Besides the reactive distillation for the quantitative esterification of linalool, another reactive distillation was used for recycling the carboxylic acids to anhydrides (Scheme 5).



Scheme 5 Formation of acid anhydride (*cf.* Table 6, entry c).

Mixtures of higher carboxylic acids and acetic anhydride were heated in the microwave field to 120–125 °C (b. p. of acetic acid: 118 °C) and the formed acetic acid was distilled from the reaction under vacuum.

This method is suitable for producing larger amounts of carboxylic acid anhydrides (up to 2 kg), which are otherwise difficult to obtain from commercial suppliers. A comparatively short reaction time of 4–6 hours (3. step in Table 6) was used. Since acetic anhydride is a low-cost starting material and anhydrides of higher carboxylic acids are interesting intermediate products for the perfume industry, this procedure could be of economic interest.

Using an appropriate distillation column, the mixed anhydrides that form as intermediate products do not disturb the work-up of the carboxylic acid anhydride that remains in the distillation bottom. For these power input parameters, the microwave reaction system (ETHOS MR) was able to keep up to 2 L of reaction mixture at 135 °C, and thus only the capacity of the reaction column determines the effectiveness of the process.

It has to be noted, however, that the vacuum precision distillation of the perfume esters and the higher carboxylic acid anhydrides cannot be performed in the microwave field for safety reasons. At pressures below 100 mbar, microwave plasma might ignite and therefore it is too dangerous to perform reactions and processes in this domain.[69]

Another example for the beneficial application of microwaves is the acylation of tocopherols[70] to the main commercial form of vitamin E, (all-*rac*)-α-tocopheryl acetate. The acylation reactions, more particularly the synthesis of tocopheryl acetate, can be carried out in the absence or presence of a catalyst and solvent-free. Excellent yields and selectivities could be achieved (> 99% yield, total conversion of starting material). The reaction can be carried out continuously in kg scale and is of great commercial interest.

Table 6 Proposed protocol – esterification of linalool with carbonic acid anhydrides

1. General data	1. step: continuous reaction	2. step: reactive distillation	3. step: reactive distillation – reaction of carboxylic acid with acetic acid anhydride
Microwave system	ETHOS contFLOW,	ETHOS MR	ETHOS MR
Manufacturer	MLS GmbH Leutkirch	MLS GmbH Leutkirch	MLS GmbH Leutkirch
Construction year	1998	1997	1997
2. System description			
Cavity volume	42 L	42 L	42 L
Max. microwave power	1000 W	1000 W	1000 W
Characteristic of magnetron	2 industrial magnetrons; Power drop down from 800 to 500 W.		
Power dosage	10 W steps	10 W steps	10 W steps
Irradiation modus	multimode	multimode	multimode
Microwave irradiation	unpulsed	unpulsed	unpulsed
3. Reactor & program			
Type of reactor	contFLOW reactor; pump: KM281, Aldos Eichler GmbH	rectification apparatus with 2000 ml flask	rectification apparatus with 2000 ml flask
Temperature measurement	shielded thermocouple,	fibre optic	fibre optic
Safety equipment	MW leak sensor		
Control program	10 min/500 W/up to 150 °C – 300 min/500 W/at 150 °C	5 min/750 W/up to 135 °C – stepwise (1 K) to 142 °C depending on distillation behaviour/500 W/time: 600 min	5 min/750 W/up to 125 °C – stepwise (1 K) to 130 °C depending on distillation behaviour/500 W/time: 480 min
Maximum temperature	160 °C	145 °C	135 °C
Maximum pressure	15 bar		
Minimum pressure		80 mbar	100 mbar
Average power	500 W,	432 W,	482 W
Energy entry	4500 kJ (kWs)	10388 kJ (kWs)	9328 kJ (kWs)
Stirring in reactor		magnetic stirring bar, 30 mm cross form	magnetic stirring bar, 30 mm cross form
4. Chemical data			
Scheduled quantity	10 mol	1300 ml reaction mixture	1300 ml reaction mixture
Amount/ratio of components	linalool : carbon acid anhydride = 1 : 1.5; 10 : 15 mol	reaction mixture from 1. step	distillate from 2. step with equimolecular amounts of acetic acid anhydride
Catalyst	potassium carboxylate, 18 mmol/mol linalool		
Dosage of reaction compounds	mixed compounds pumped through the reactor		components mixed before placing flask in microwave system
Reaction behaviour	continuous reaction, residence time: 12 min	distillation of carbonic acid, carbonic acid anhydride and small amounts of terpene olefins from 1. step	distillation of acetic acid out of the reaction mixture
Cooling method	direct cooling	air cooling after end of distillation	air cooling after end of distillation
Work-up		after filtration of catalyst, washing with sodium carbonate solution and vacuum distillation	vacuum distillation of the raw carbonic acid anhydride
Yield	conversion around 50%	overall yield 85% linalyl carboxylate	95% of carbonic acid anhydride
Analyses	GC	GC, GC-MS, NMR	GC, GC-MS, NMR

5 Conclusions

"Simple heating with microwaves" has become a common laboratory practice for many preparative chemists. Microwave systems with integrated on-line control guarantee safe operation and open a vast field of applications, even on the technical scale. In this context, it seems worthwhile to critically assess all reaction parameters for syntheses and separations and to coordinate them with each other. In other words, besides the obvious need to learn more about microwave-assisted reactions, there are also promising challenges ahead.

For technical applications and implementation of a new method, it is necessary to have equipment available. For application in a synthetic pathway not only criteria like E-factor[71] or atom economy are important, the equipment factor also plays an important role:[72]

$$\text{Implementation} = \text{Atom Economy} \times \text{(weighted) E-Factor} \times \text{Equipment Factor}$$

For example, if the equipment is available around the world without any restrictions, the factor is 1. In the case of microwaves the factor is around 0.3 because for large scale industrial production (several 1000 tons), currently no equipment exists.

For further chemical applications of alternative energy entries in reactions systems the development of new apparatus and improvement in reactor design is strictly recommended.

6 Symbols

λ_0 wavelength at vacuum conditions [cm]
c speed of light [2.998×10^{10} cm s^{-1}]
f frequency [Hz]
ε_r relative dielectric coefficient
C capacity [F]
C_0 capacity under vacuum conditions [F]
ε_r'' dielectric loss factor (dynamic dielectric coefficient)
σ dielectric conductivity
D dissipitation factor ($= \tan \delta$)
x penetration depth [cm]
Q_{mw} microwave power input [kWs]
P_{mw} microwave power [W]
t time [sec]
Q_{th} required thermal energy [kJ = kWs]
T Temperature [°C = K + 273.15]
ΔT temperature difference [K]

c_p specific heat capacity [J K^{-1} kg^{-1}]
m mass [kg]
η efficiency

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PAPER

A practical improvement of odorless Corey–Kim and Swern oxidations†

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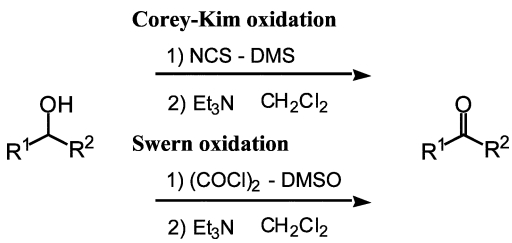
Methyl 6-morpholinohexyl sulfide (**3a**, MMS) and methyl 6-morpholinohexyl sulfoxide (**7**, MMSO) have been employed as efficient odorless substitutes for dimethyl sulfide (DMS) and dimethyl sulfoxide (DMSO) in Corey–Kim and Swern oxidations, respectively. The oxidation products and the byproduct **3a** are easily separable by simple aqueous extraction. The Corey–Kim oxidation was studied in various solvents. The utility of the odorless 6-morpholinohexan-1-thiol (**2a**) in the dealkylation of phenyl ethers and methyl esters is also presented.

Introduction

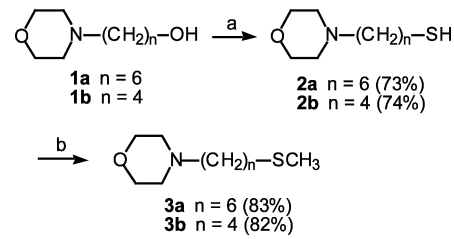
Thiols and sulfides are synthetically versatile functional groups.[1] They are essential reagents in making everything from coatings to pharmaceuticals to catalysts. However, they often have an unbearable and persistent stench. Working with thiol and sulfide reagents can be a very unpleasant experience, especially for those carrying out large-scale, industrial processes. Therefore, we designed a program to prepare odorless variants of the most common malodorous reagents such as ethanethiol, benzenethiol, benzyl mercaptan and dimethyl sulfide (DMS).[2–4] While studying the odor activity of alkane thiols[3] and sulfides (see Tables 1 and 2 in the ESI†), we observed that dodecanethiol and dodecyl methyl sulfide had no odor and thus could be used as odorless substitutes for ethanethiol and DMS, respectively. Prompted by the presidential recognition[5] of innovative syntheses, process improvements and new products that minimize or prevent pollution, chemical industries and academic groups are using the "green" approach to many fundamental synthetic transformations. For instance, in the oxidation of alcohols to aldehydes and ketones, the methods and reagents are constantly being refined and improved, and the largely metal based oxidations[6] are gradually being replaced with better, more efficient catalytic processes.[7] However, completely metal free conditions are of particular importance.[8] The Corey–Kim[9] [*N*-chlorosuccinimide (NCS)–DMS] and Swern[10] [$(COCl)_2$–DMSO] oxidations, which readily convert primary and secondary alcohols to aldehydes and ketones, have harmful environmental implications because both involve DMS either as a reagent (Corey–Kim) or as a byproduct (Swern).



Owing to the immense popularity of these oxidations, the Vederas group pioneered[11] the introduction of polymer supported and extractable reagents.[12] Crich and Neelamkavil addressed this issue using the fluorous extraction method,[13] and we have replaced DMS and DMSO with odorless dodecyl methyl sulfide and the corresponding sulfoxide.[14] However, the laborious separation of dodecyl methyl sulfide after the reaction led us to try to further improve upon the odorless Corey–Kim and Swern oxidations. Here, we present easy to prepare, inexpensive and recyclable amino sulfur reagents, which prove to be better alternatives to the commonly used thiols and sulfides. We discuss the versatility of these sulfur reagents in the Corey–Kim and Swern oxidations and also in dealkylation.

Results and discussion

The thiol **2a** was easily obtained in two steps by condensation of morpholine and commercially available 1-chloro-6-hexanol to give 6-morpholinohexan-1-ol (**1a**) in quantitative yield (> 97%), followed by direct thiolation (Scheme 1) using thiourea and HBr *via*



Scheme 1 (a) Thiourea, H_2O, 48% HBr, 120 °C, 8 h then 40% NaOH, 120 °C, 2 h; (b) 50% NaOH, EtOH, CH_3I, rt, 3 h.

the isothiouronium salt.[15] In order to have a relatively 'atom-economical' reagent, the 4-morpholinobutan-1-thiol (**2b**) was prepared in a similar manner from the alcohol **1b**.[16] The thiols **2** could be alkylated selectively using methyl iodide in aqueous alkali medium to give the corresponding methyl sulfides **3**.

Following the above procedure, the corresponding 3- and 5-carbon linked morpholino thiols were also prepared to check their relative odor profile (Table 1). The most malodorous in this group, the 3-morpholinopropan-1-thiol (entry 1 in Table 1), is indexed as 3, and the odorless 6-morpholinohexan-1-thiol, 0. The following data further support our earlier observation[3] that the foul smell of thiols on the human olfactory sense is closely related to the length of the carbon chain.

Our initial studies were aimed at the application of the morpholino methyl sulfides **3** as DMS equivalents in the Corey–Kim oxidation using various solvents (Table 2). For such oxidations, THF and acetonitrile as reaction solvents were as good as the commonly used toluene and dichloromethane, whereas ethyl acetate and acetone were ineffective. The reaction in the latter two

† Electronic supplementary information (ESI) available: experimental procedures and analytical data for other new compounds as well as copies of NMR spectra. See http://www.rsc.org/suppdata/gc/b3/b312849k/

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Table 1 Relative odor scale of morpholinoalkanethiols

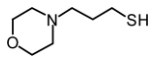
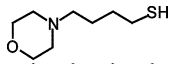
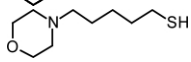
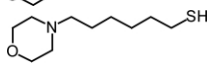
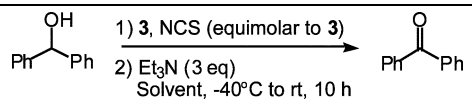
Entry	Thiol	Odor scale
1		3
2		2
3		1
4		0

Table 2 Screening of solvents and stoichiometry



Entry	**3**/equiv.	Solvent	Yield (%)
1	1.5[a]	Toluene	90
2	2[b]	Toluene	97
3	1.5[a,b]	CH_2Cl_2	96
4	1.5[a]	CH_3CN	91
5	2[b]	CH_3CN	93
6	2[a]	THF	92
7	1.5[a]	AcOEt	16[c]
8	1.5[a]	Acetone	10[c]

[a] Using **3a**. [b] Using **3b**. [c] NMR yield.

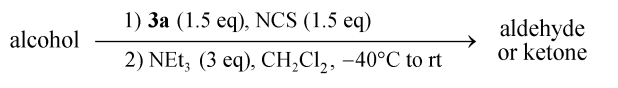
solvent systems looked turbid, apparently suggesting low solubility of the intermediate ylide probably due to the interaction between basic nitrogen on morpholine and carbonyl groups in these solvents, hence resulting in low yields. Most significantly, only 1.5 equivalents of the reagents **3** were enough for the complete conversion of benzhydrol to benzophenone in high isolated yield (96% with 86% recovery of reagent **3**; entry 3, Table 2). The use of a near stoichiometric reagent is important in order to achieve high recovery of **3** after the reaction, since any excess NCS is capable of oxidizing the remaining sulfide. While both of the sulfides **3a** and **3b** have been shown to be efficient alternatives to DMS in preliminary Corey–Kim oxidations, we chose **3a** because the corresponding thiol **2a** is odorless (Table 1).

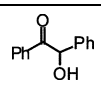
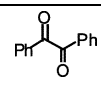
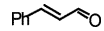
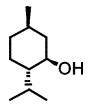
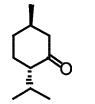
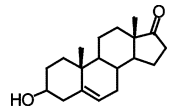
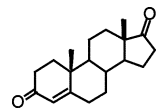
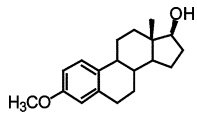
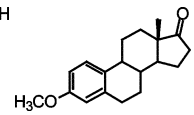
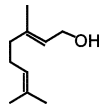
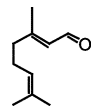
In order to further test the practicality of the sulfide **3a**,[17] several non-natural and naturally occurring alcohols were subjected to the standard Corey–Kim oxidation (Table 3). The reaction mixture after acidic (1 N HCl) work-up, followed by washing with water and brine, afforded the corresponding crude aldehydes and ketones (> 95% pure based on NMR) in very high yields with complete consumption of the starting alcohols. No foul smell was detected and the use of column chromatography was unnecessary. Moreover, the sulfide reagent **3a** could be recycled easily upon basification (pH = 10) using aq. NaOH followed by ethereal extraction. The recovered crude material was distilled (Kuegelruhr; 145 °C, 1.5 mmHg) to obtain the pure sulfide **3a** in high yields (70–90%).

Next we investigated the deuterium transfer experiment of the Corey–Kim oxidation using 2-deuterioisoborneol (**4**). Following the standard protocol, oxidation of **4** (1 equiv.) using **3a** and NCS (0.5 equiv. each) afforded camphor **5** (45%) and sulfide **6** (86%) after acid–base extraction (Scheme 2). Various spectral analyses, including ^2H NMR ($CHCl_3$) with $CDCl_3$ as the reference, confirmed selective deprotonation of the *S*-methyl group (95%) rather than the *S*-methylene group (5%) in **3a**.

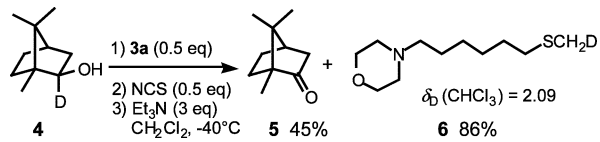
Encouraged by the excellent results of the Corey–Kim oxidation, we extended our approach to the more popular Swern oxidation, which employs the corresponding sulfoxide. In order to oxidize the morpholino methyl sulfide **3a**, we had to selectively oxidize the sulfide moiety rather than promote *N*-oxide formation. After

Table 3 Corey–Kim oxidations using **3a**



Entry	Substrate	Product	Yield (%)	Recd **3a** yield (%)
1			98, 94[a]	81
2			96, 90[b]	81
3			94, 90[a]	89
4			89, 85[c]	74[c]
5			91	77
6			99[c]	70
7			85, 89[c]	82

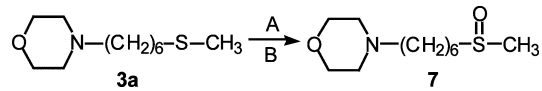
[a] Reaction performed in CH_3CN using 2 equiv. of reagents. [b] Reaction performed in CH_3CN. [c] Reaction performed in CH_3CN using 2.5 equiv. of reagents.



Scheme 2 A deuterio experiment of the Corey–Kim oxidation using **3a**.

several experiments with different reagents and conditions, we discovered that, in order to avoid unwanted *N*-oxidation as well as overoxidation of the sulfide, the best conditions (86% yield) turned out to be *m*-chloroperbenzoic acid (*m*-CPBA, 1.2 equiv.) at −60 °C for 30 min followed by 10 min at 0 °C.

In another attempt to control *N*-oxidation, addition of 1 equivalent of CH_3COX (X = Br, Cl) prior to *m*-CPBA also worked very well, providing more than 95% yield of the desired sulfoxide **7** (Scheme 3). Due to its high boiling range (over 180 °C at 1.5

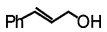
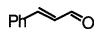
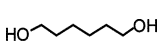
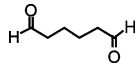
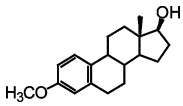
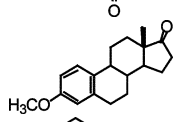
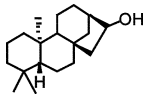
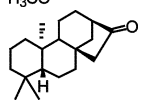


Scheme 3 *Method A*: *m*-CPBA (1.2 equiv.), $CHCl_3$, −60 °C (30 min), 0 °C (10 min), 86%; *Method B*: CH_3COCl (1 equiv.), *m*-CPBA (1.2 equiv.), $CHCl_3$, −60 °C (30 min), 0 °C (10 min), 95.5%.

mmHg), **7** was purified by passing it through a short silica gel column. Because of its hygroscopic nature, the sulfoxide **7** requires drying under Dean–Stark conditions for several hours before the Swern oxidation. Following the standard Swern protocol, but using the sulfoxide **7** as a DMSO equivalent, primary and secondary alcohols were oxidized to the corresponding aldehydes and ketones in very high yields (Table 4). In some cases, we found that using 2 equivalents of the sulfoxide **7** and 1.5 equivalents of oxalyl chloride

Table 4 Swern oxidations using **7**

alcohol —[1) **7** (2–3 eq), $(COCl)_2$ (1.5–2.5 eq); 2) NEt_3 (3–6 eq), CH_2Cl_2, −60°C to rt]→ aldehyde or ketone

Entry	Substrate	Product	Yield (%)	Recd **3a** yield (%)
1[a]			94	84
2[a]			94	87
3[a]			92	81
4[b]			91	76
5[a]			96	90
6[a]			95	83

[a] **7**, $(COCl)_2$, Et_3N (2, 1.5, and 3 equiv., respectively). [b] **7**, $(COCl)_2$, Et_3N (3, 2.5, and 6 equiv., respectively).

was necessary to avoid formation of the corresponding chloride. In the case of 1,6-hexanediol (entry 4 in Table 4), 3 equivalents of the sulfoxide **7** and 2.5 equivalents of oxalyl chloride were used for an optimum yield of 91%. In all cases, we employed the acid–base extraction principle to separate the products and to recover the sulfide **3a** so that it could be oxidized back to the sulfoxide **7**.

Next, we examined the utility of the modified odorless thiol **2a** in thiolate anion induced dealkylation reactions. Several phenyl ethers and methyl esters were subjected to dealkylation in the presence of the sodium salt of **2a** (5 equiv.) under the reaction conditions described in Table 5. Although the yields of the products varied, compared to the inherently toxic and malodorous ethanethiol, our reagent **2a** could nonetheless be quite useful because it is odorless and can be reused.

Conclusion

We have demonstrated the use of these modified, sulfur reagents **3a** (MMS) and **7** (MMSO) as odorless alternatives to DMS and DMSO in the Corey–Kim and the Swern oxidations, respectively. The morpholine based thiol **2a** could also act as an odorless alternative to the foul smelling ethanethiol commonly used in industrial settings. The products of these reactions can be easily purified using only acid–base extraction, thereby eliminating unpleasant odors, saving time and protecting the environment. In view of current environmental and economic factors, the utility of these simple reagents could be enormously beneficial.

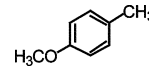
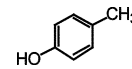
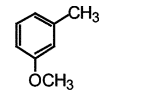
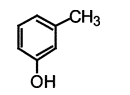
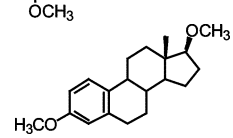
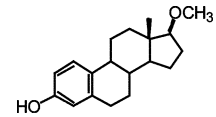
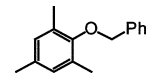
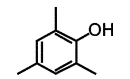
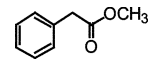
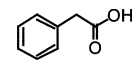
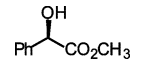
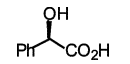
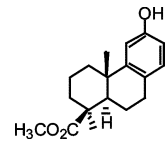
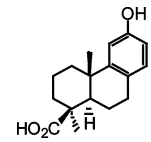
Experimental

General

All reagents were purchased from commercial sources and used as received. All reactions were performed under a dry N_2 atmosphere unless otherwise indicated. Reaction solvents such as toluene, CH_2Cl_2, acetone, acetonitrile, ethyl acetate and DMF were dried prior to use. Analytical TLC was done on precoated (0.25 mm) silica gel plates. Column chromatography was conducted with 230–400 mesh silica gel. Infrared (IR) spectra were measured on a FTIR spectrometer. The ^2H NMR (62 MHz) spectrum was recorded in chloroform using $CDCl_3$ (7.26 ppm) as the internal standard. All oxidation and dealkylation substrates were commercially available

Table 5 Dealkylation reactions using **2a**

phenyl ether or ester —[**2a** (5 eq), NaH (6 eq); DMF, 120°C, 3 h]→ phenolic alcohol or acid

Entry	Reactants	Product	Yield (%)
1[a]			77
2[a]			81
3[a]			72
4[a]			83
5			92
6[b]			92
7[b]			97

[a] Some starting material also recovered. [b] Reaction time, 2 h.

or prepared by known procedures and used as such and the products were identical to commercial samples.

Typical procedure for the preparation of methyl 6-morpholinohexyl sulfide (3a)

To a solution of thiol **2a** (8.34 g, 41.04 mmol) in ethanol (15 mL) was added 50% aqueous NaOH (30 mL). The solution was cooled to 5 °C and MeI (3.83 mL, 61.56 mmol) was added dropwise with stirring. The reaction mixture was stirred at ambient temperature for 3 h. Excess ethanol was distilled off under reduced pressure, the solution diluted with water (100 mL) and extracted with diethyl ether (5 × 75 mL), washed with brine and dried (Na_2SO_4) and concentrated. The crude colorless oil was distilled at 145 °C/1.5 mmHg to give pure sulfide **3a** (7.4 g, 83%): bp 145 °C (1.5 mmHg); IR ($CHCl_3$): 3030, 2930, 2860, 2815, 2485, 1600, 1460, 1310 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.71 (t, J = 4.6 Hz, 4H), 2.48 (t, J = 6.8 Hz, 2H), 2.42 (br s, 4H), 2.30 (dd, J = 7.1, 2.0 Hz, 2H), 2.08 (s, 3H), 1.52–1.28 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.9, 59.1, 53.8, 34.2, 29.1, 28.7, 27.1, 26.5, 15.6; MS (EI) m/z 217 (M^+, 3.4), 202 (20), 170 (100), 156 (9.4), 100 (98.1), 87 (19.2); HRMS calcd for $C_{11}H_{23}NOS$: 217.1503, found 217.1500.

Methyl 6-morpholinobutyl sulfide (3b)

Methyl 6-morpholinobutyl sulfide (**3b**) was prepared similarly from **2b** (6.90 g, 39.36 mmol) and MeI (3.67 mL, 59.04 mmol) in 82% yield (6.10 g) as colorless oil: IR ($CHCl_3$): 3005, 2920, 2860, 2815, 2480, 1600, 1460, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.70 (t, J = 4.7 Hz, 4H), 2.50 (t, J = 7.1 Hz, 2H), 2.42 (br dd, J = 4.4, 4.0 Hz, 4H), 2.34 (t, J = 7.7 Hz, 2H), 2.08 (s, 3H), 1.69–1.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.5, 58.1, 53.4, 33.7, 26.5, 25.2, 15.1; MS (EI) m/z 189 (M^+, 12.8), 142 (16.8), 100 (100), 156 (9.4), 100 (98.1), 83 (22.5); HRMS calcd for $C_9H_{19}NOS$: 189.1184, found 189.1187.

General procedure for the Corey–Kim oxidation using 3a

To a solution of *N*-chlorosuccinimide (63.76 mg, 0.48 mmol) in anhydrous dichloromethane (2 mL) under N_2 at −40 °C was added **3a** (104 mg, 0.48 mmol) in dichloromethane (2 mL) dropwise. The reaction mixture was stirred at −40 °C for 30 min before the addition of the alcohol (0.32 mmol) in dichloromethane (2 mL). After the reaction had been stirred for 2 h at −40 °C, freshly distilled Et_3N (0.14 mL, 0.95 mmol) was added and the reaction mixture was stirred at the same temperature for a further period of 2.5 h. It was then allowed to warm to rt for 8 h with continued stirring before being poured into aq. 1 N HCl (60 mL) and extracted with ethyl acetate (3 × 30 mL). The organic component was washed again with aq. 1 N HCl (50 mL), brine and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to afford the pure aldehyde or ketone.

General procedure for the recovery of 3a

The aq. 1 N HCl solution collected after work-up of Corey–Kim/Swern oxidation was made alkaline (pH > 9) using aq. 5 M NaOH and extracted with diethyl ether (3 × 30 mL), dried (Na_2SO_4) and concentrated followed by Kuegelruhr distillation (145 °C, 1.5 mmHg) to afford the pure **3a**.

Procedure for the synthesis of methyl 6-morpholinohexyl sulfoxide (7) using *m*-CPBA

Method A. To a stirred solution of the sulfide **3a** (518 mg, 2.39 mmol) in chloroform (10 mL) at −60 °C was added *m*-CPBA (642 mg from 77% *m*-CPBA, 2.86 mmol) in portions. The reaction mixture was stirred for 30 min followed by stirring at 0 °C (10 min). It was then quenched and washed with aq. sat. $NaHCO_3$, extracted with $CHCl_3$ and dried (Na_2SO_4). Purification of the crude sulfoxide by a short silica gel column using chloroform and methanol (10 : 1) as eluents afforded the title compound (482 mg, 86%) as a colorless oil.

Method B. To a stirred solution of the sulfide **3a** (1.46 g, 6.74 mmol) in chloroform (20 mL) at ambient temperature was added acetyl chloride (0.5 mL, 6.75 mmol). The reaction mixture was cooled to −60 °C and *m*-CPBA (1.81 g from 77% *m*-CPBA, 8.09 mmol) was added in portions. The reaction mixture was stirred for 30 min followed by warming to 0 °C (10 min). It was then quenched and washed with aq. $NaHCO_3$, extracted with $CHCl_3$ and dried (Na_2SO_4).The crude sulfoxide was purified by a short silica gel column using chloroform and methanol (10 : 1) as eluents to afford **7** (1.50 g, 95.5%): IR ($CHCl_3$): 3030, 2940, 2815, 2475, 1600, 1460, 1425, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.72 (t, J = 4.6 Hz, 4H), 2.74–2.62 (m, 2H), 2.57 (s, 3H), 2.44 (br s, 4H), 2.33 (dd, J = 7.3, 0.6 Hz, 2H), 1.78 (quint, J = 7.7 Hz, 2H), 1.56–1.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.9, 58.9, 54.6, 53.7, 38.5, 28.7, 27.1, 26.3, 22.5; MS (FAB) m/z 234 (M^++1, 100), 216 (15), 170 (25), 147 (20), 100 (45); HRMS calcd for $C_{11}H_{23}NO_2S$ (M^++H): 234.1540, found 234.1525.

General procedure for the Swern oxidation using 7

To a well-stirred solution of anhydrous CH_2Cl_2 (5 mL) under dry N_2 atmosphere at −60 °C was added oxalyl chloride (20.5 μL, 0.24 mmol). A solution of **7** (73.25 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) was then added dropwise and the reaction mixture was stirred for an additional 20 min. The alcohol (0.16 mmol) dissolved in CH_2Cl_2 (2 mL) was added to this solution followed, after an additional 30 min to 1 h, by freshly distilled Et_3N (66 μL, 0.48 mmol). The reaction mixture was stirred for 2 h at −60 °C and allowed to warm to rt where it was stirred for a further period of 1 h. The reaction mixture was then quenched with H_2O (5 mL), washed with aq. 1 N HCl (2 × 20 mL), extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (50 mL) followed by brine (50 mL) and dried (Na_2SO_4). After evaporation of the solvent under vacuum, the pure ketone or aldehyde was obtained.

General procedure for the dealkylation using 2a

To a stirred suspension of NaH (from 118 mg of 60% NaH dispersion in mineral oil, 2.46 mmol) in anhydrous DMF (2 mL) at ambient temperature was added **2a** (416 mg, 2.05 mmol) in DMF (2 mL) and the mixture was stirred for 5 min. A solution of the phenolic ether or the methyl ester (0.41 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at 120 °C for 3 h. Excess solvent was distilled off under low pressure. The residue was poured into aq. 1 N HCl and extracted with diethyl ether (2 × 50 mL). The ether layer was washed successively with aq. 1 N HCl and brine, and dried (Na_2SO_4). After evaporation of the solvent, the crude compound was purified either by a short silica gel column using hexane and ethyl acetate (5 : 1) as eluents or by recrystallization to afford the dealkylated products.

Acknowledgements

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17 The sulfide **3a** was dried under Dean–Stark conditions for several hours before using in the Corey–Kim oxidation.

PAPER

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Ionic liquid promoted novel and efficient one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones at ambient temperature under ultrasound irradiation

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3,4-Dihydropyrimidin-2-(1*H*)-ones have been synthesized in excellent yields in short reaction time at ambient temperature in the absence of any added catalyst by the reaction of aromatic or aliphatic aldehydes with ethyl acetoacetate (EAA) and urea (or thiourea) in room temperature ionic liquid (IL) under ultrasound irradiation. The evidence for the role of IL in promoting this multicomponent reaction has been given. Based on this evidence, a plausible mechanistic pathway has been postulated.

Introduction

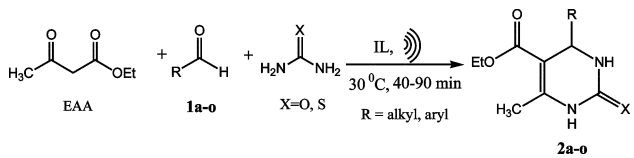
In recent years, 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their derivatives have attracted considerable interest because of their therapeutic and pharmacological properties.[1] They have emerged as integral backbones of several channel blockers, antihypertensive agents, α-1a antagonists and neuropeptide Y (NPY) antagonists.[2] Moreover several alkaloids containing the DHPM unit have been isolated from marine sources, which also exhibit interesting biological properties.[3] The synthesis of this important heterocyclic nucleus reported by Biginelli in 1893, involved a one pot condensation of ethyl acetoacetate, benzaldehyde and urea under strong acidic conditions.[1a] However, one serious drawback of the Biginelli reaction is low yields in the case of substituted aromatic and aliphatic aldehydes.[4] This has led to the development of multistep strategies resulting in marginally improved yields.[5] However, the multistep methods lack the simplicity of the one-pot, one-step procedure. Consequently, the Biginelli reaction for the synthesis of DHPMs has attracted renewed attention and many improved procedures have been reported. Many of these procedures employ catalysts such as $BF_3{\cdot}OEt_2$,[6a] polyphosphate ester,[6b] montmorillonite KSF,[6c] zeolites,[6d] $FeCl_3{\cdot}6H_20$,[6e] $LaCl_3{\cdot}7H_20$,[6f] $Yb(OTf)_3$,[6g] $InCl_3$.[6h] In addition methods employing microwave,[7] ultrasound,[8] solid and fluorous-phase syntheses[9] have been reported. Most of the methods reported above use expensive catalysts, strong acidic conditions, higher temperatures and require longer reaction times. Some of the methods resulted in unsatisfactory yields and involved cumbersome product isolation procedures. Consequently, we thought, there is scope for further innovation towards milder reaction conditions, absence of a catalyst, short reaction times and better yields which can possibly be achieved by a combination of 'green' room temperature ionic liquids (ILs) as solvents and ultrasound as energy source for this multicomponent reaction (MCR).

In recent times, the use of non-aqueous room temperature ILs as green solvents in organic synthetic processes has gained considerable importance due to their negligible vapour pressure, solvating ability and easy recyclability.[10] Additionally, some ILs possess inherent Lewis/Brønsted acidity, which can promote and catalyse organic transformations of commercial importance in excellent yields under ambient conditions such as bromination of aromatics and synthesis of 1,5-benzodiazepines recently reported by us.[11]

Likewise, the use of ultrasound in organic transformation is now well known to enhance the reaction rates and yields/selectivity of reactions and in several cases facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure.[12] The driving energy is provided by cavitation, the formation and collapse of bubbles, which liberates considerable energy in very short times. The use of ultrasound in these ILs, which have no vapour pressure, should change considerably the characteristics of cavitation in the bulk and force even less volatile substrates to undergo the cavitational activation. Indeed, by practising sonochemistry in ILs, we have succeeded in promoting Heck and Suzuki reactions at ambient condition, without the need for a phosphine ligand,[13] nitration of phenols in significantly enhanced reaction rates as well as high para selectivity[14] and acylation of alcohols.[15] Continuing our investigations in this area, herein we report for the first time a novel synthesis of DHPMs promoted by the combined use of ultrasound and the IL, 1-*n*-butylimidazolium tetrafluoroborate, $[Hbim]BF_4$ under ambient conditions in excellent isolated yields in short reaction times. The non-volatile IL can be efficiently recovered and reused, and the process does not require any additional catalyst.

Results and discussion

A variety of aldehydes including aliphatic, aromatic, cyclic and cinnamyl aldehydes were chosen to be condensed with ethyl acetoacetate and urea (or thiourea) as shown in the Scheme 1.



Scheme 1

Several ILs belonging to the 1,3-di-*n*-butylimidazolium [bbim] and 1-*n*-butylimidazolium [Hbim] series were screened for the typical sonochemical MCR of benzaldehyde, ethyl acetoacetate and urea to afford 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (**2a**). The results are recorded in Table 1. Evidently, the IL $[Hbim]BF_4$ afforded the best results. Hence all further reactions with other aldehydes were carried out using this IL. All the reactions were monitored by TLC and taken to completion. The results are recorded in Table 2. All the known and new compounds were well characterized by melting point, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. For the known compounds, the values were in agreement with those reported in literature. It can be observed that all the aldehydes have reacted in short reaction times under ambient conditions to afford the DHPMs in very good to excellent isolated yields. The process tolerates

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Table 1 The Biginelli reaction of **1a** with EAA and urea in various ILs

Entry	Ionic liquid	Time for complete conversion/min	Yield (%)[a]
1	[bbim]Br	80	92
2	[bbim]Cl	75	88
3	[bbim]ClO_4	95	87
4	[bbim]BF_4	110	86
5	[bbim]PF_6	125	83
6	[Hbim]Br	60	66
7	[Hbim]Cl	60	64
8	[Hbim]ClO_4	90	75
9	**[Hbim]BF_4**	**45**	**97**

[a] Isolated yields of **2a**.

Table 2 Condensation of aldehydes **1a–o** with EAA and urea–thiourea in [Hbim]BF_4

Entry	R-	Atom 'X'	Product **2**	Time/ min	Yield (%)[a]	Mp/°C (lit.)[b]
1	Ph–	O	**2a**	45	97	202–203[16]
2	4-NO_2–C_6H_4–	O	**2b**	70	98	207–209[16]
3	4-CH_3–C_6H_4–	O	**2c**	45	95	171–172[17]
4	2-F–C_6H_4–	O	**2d**	60	90	235–237[c]
5	2-Cl–C_6H_4–	O	**2e**	30	98	222–223[18]
6	2-Br–C_6H_4–	O	**2f**	60	90	205–207[19]
7	3-OMe-4-OH–C_6H_3–	O	**2g**	45	95	205–206[20]
8	C_6H_5–CH=CH–	O	**2h**	50	95	215–216[18]
9	2-Pyridyl-	O	**2i**	55	83	> 300[c]
10	2-Furyl-	O	**2j**	30	93	202–204[21]
11	c-C_6H_{11}–	O	**2k**	50	93	237–238[21]
12	n-C_9H_{19}–	O	**2l**	55	87	122–123[20]
13	Ph–	S	**2m**	50	93	191–193[18]
14	4-OMe–C_6H_5–	S	**2n**	55	97	151–153[18]
15	3,4,5-Trimethoxy-C_6H_2–	S	**2o**	70	92	202–204[c]

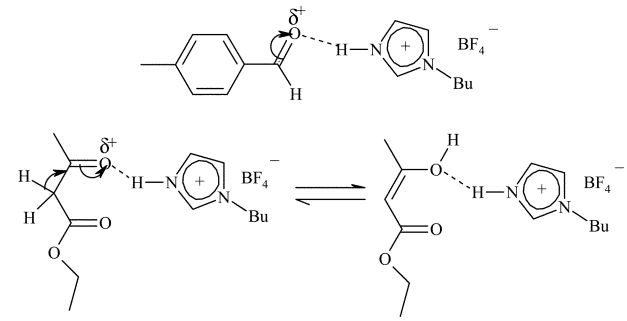
[a] Yields after recrystallisation. [b] Melting points are uncorrected. [c] New compounds.

aromatic aldehydes containing both electron donating and electron withdrawing substituents. The substituted aromatic, heterocyclic as well as aliphatic aldehydes all produced significantly improved yields as compared to the classical Biginelli protocol.[1a]

The products were easily isolated by dilution with water and filtration of the precipitated DHPM. The DHPMs, thus isolated were homogeneous on TLC and were pure enough for all practical purposes. However, they were subjected to further purification by recrystallisation for characterization and the yields reported are after this procedure. The combined aqueous filtrate was then subjected to distillation at 80 °C/10 mmHg for 4 h to remove water leaving behind [Hbim]BF_4 in near quantitative yield. The IL, thus recovered could be used at least three times for the sonochemical synthesis of **2a** without loss in yield. Furthermore, the stability of the IL under the sonochemical reaction conditions and recycle batches was investigated by recording the ^{19}F NMR spectra of the IL as such before the reaction, after recovery for recycle and after subjecting the IL to ultrasound irradiation for 60 min in the absence of any substrate respectively. The ^{19}F NMR spectra of the IL were recorded neat with an external lock of D_2O and using trifluoroacetic acid as an internal standard. The ^{19}F NMR spectra were identical and no changes were observed indicating the stability of the IL under these conditions.

It was observed that the reactions did not proceed even after several hours of sonication in molecular solvents such as acetonitrile, ethanol, THF and dichloromethane instead of the IL under otherwise similar conditions. Similarly, no formation of DHPMs was observed when the reactions were conducted in the IL under silent conditions (stirring at 30 °C without ultrasound irradiation). Thus it becomes evident that it is the synergic effect of the combined use of ultrasound and the IL as the reaction medium that has promoted this MCR at ambient conditions in the absence of any added catalyst. Previous reports[8] on the ultrasound promoted synthesis of DHPMs make use of catalysts such as sulfamic acid (0.8 equivalents) and ceric ammonium nitrate, and require higher reaction temperature (50–60 °C) and long reaction times (7 h).

The IL [Hbim]BF_4 has not only acted as a favorable medium with improved energetics of cavitation for the sonochemical MCR, but also promoted the reaction with its inherent Brønsted acidity thus obviating the necessity of using additional acid catalyst. The Brønsted acidity is conferred by the –NH proton of [Hbim]BF_4 (chemical shift of 14.59 ppm) capable of bonding with the carbonyl oxygen of the aldehydes as well as that of the β-keto ester EAA as shown in Scheme 2. Evidence for this was obtained by recording

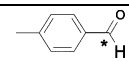
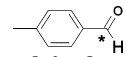
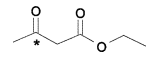
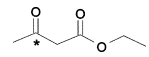


Scheme 2

the ^{13}C-NMR spectra of *p*-tolualdehyde and EAA (neat) with an external lock of D_2O and with one equivalent of the IL under similar conditions.

The results are recorded in Table 3. A significant shift of ~ 3 ppm for the carbonyl carbons of both the aldehyde and EAA by their

Table 3 The ^{13}C-NMR chemical shifts and IR data for the carbonyl group

Entry	Substrate	Chemical shift[a], ppm	IR values[b], ν, cm^{-1}
1		204.3	1703.2
2	 + [Hbim]BF_4	207.4	1685.3
3		214.1	1742.1
4	 + [Hbim]BF_4	217.1	1735.5

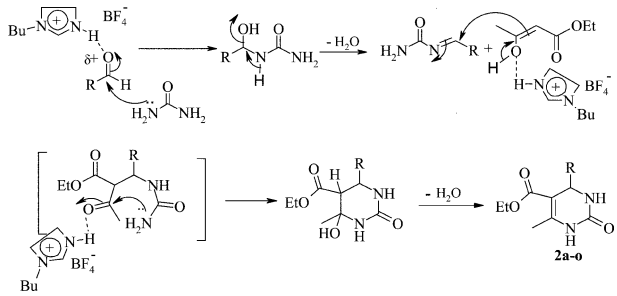
[a] Recorded neat with D_2O as external lock. [b] Recorded with neat sample.

interaction with the IL were observed. Additional evidence was obtained by recording their IR spectra neat wherein also a significant shift to a lower wave number by 7–18 cm^{-1} was observed (Table 3).

Based on this evidence, a plausible mechanism may be postulated for the reaction as outlined in Scheme 3.

Conclusion

Thus, this one pot MCR promoted by the synergy of combined use of IL and ultrasound offers an easy access to substituted DHPMs in excellent yields. The products can be easily isolated by simple work up procedures such as dilution and filtration of the precipitated product (DHPMs) leaving behind an aqueous filtrate from which the IL can be completely recovered and recycled. The role of IL in promoting this MCR has been established in terms of ^1H-NMR and IR spectral evidence. Based on this evidence, a plausible mecha-



Scheme 3

nistic pathway has been postulated. The ambient conditions, absence of a catalyst, high reaction rates, excellent isolated yields and easy work up procedures makes this methodology an improved practical alternative to the conventional acid/base catalyzed thermal processes and is environment friendly with minimal or no waste.

Experimental

General

All chemicals were of research grade and were used as obtained from Aldrich or Fluka. The reactions were carried out in a thermostated (30 ± 1 °C) ultrasonic cleaning bath (Branson 5200 E4) at 50 kHz. The ultrasonic cleaner had output power of 120 W and a power supply of 450 W. The tank dimensions were 290 mm × 240 mm × 150 mm with liquid holding capacity of 9.5 l. The reactions were carried out in a round-bottomed flask of 25 ml capacity suspended at the center of the cleaning bath, 5 cm below the surface of the liquid.

IR Spectra were recorded on a Mattson Research Series FT-IR spectrometer, mass spectra on a Finnigan Mat-1020 automated GC/MS spectrometer and NMR spectra were recorded on Bruker AC-500 spectrometer in $CDCl_3$/DMSO-d_6 with TMS as an internal standard. The melting points are uncorrected and are compared with the reported literature values.

Preparation of different ionic liquids

The ILs [bbim]Br and [bbim]BF_4 were prepared as per the methods reported by us.[11,12] The IL, [bbim]Cl was prepared using *n*-butyl chloride as an alkylating agent in a manner similar to the method described for [bbim]Br. The ILs [bbim]PF_6 and [bbim]ClO_4 were prepared by metathesis of [bbim]Br using the corresponding acid of the anion exactly as per the method reported by us for [bbim]BF_4.

1-Butylimidazolium tetrafluoroborate [Hbim]BF_4

Tetrafluoroboric acid (8.7 g, 0.1 mol) 40% solution in water was added slowly over a period of 30 min to 1-butylimidazole (12.4 g, 0.1 mol) at 0 °C under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water was removed from the reaction mixture by subjecting it to evaporation for 4 h at 80 °C under reduced pressure (10 mmHg) to give the product [Hbim]BF_4.

Viscous oil – (19.97 g; yield 96%); IR (KBr) ν = 3607, 3153, 2876, 1580, 1466, 894, 762 cm^{-1}; ^1H NMR δ = 0.55 (t, J = 7.0 Hz, 3H, CH_3); 0.95 (m, 2H, $CH_3CH_2(CH_2)_2N$); 1.47 (s, 2H, NCH_2CH_2); 3.87 (t, J = 7.0 Hz, 2H, NCH_2), 7.12 (s, 2H, NC*H*C*H*N), 8.16 (s, 1H, NC*H*N); 14.59 (br s, 1H, NH). ^{13}C NMR δ = 13.1, 19.2, 32.1, 48.5, 120.9, 122.8, 135.2 – MS: *m*/*z* (%):124 (M − X, 26), 109 (3), 97 (92), 81 (100), 68 (26), 55 (56) – $C_7H_{13}N_2BF_4$ (211): Anal. Calcd, for C, 39.81; H, 6.16; N, 13.27%. Found C, 39.77; H, 6.05; N, 13.18%.

General procedure for the synthesis of DHPMs

A mixture containing aldehyde **1** (10 mmol), ethyl acetoacetate (EAA, 10 mmol) and urea or thiourea (11 mmol) in [Hbim]BF_4 (2.0 g) was sonicated in an atmosphere of argon at ambient conditions in a thermostated (30 ± 1 °C) ultrasonic cleaning bath. After completion of the reaction (indicated by TLC), the reaction mixture was poured into crushed ice (20 g) and stirred for 10–15 min. The solid separated was filtered through a sintered funnel under suction, washed with ice-cold water (20 ml) and then recystallized from hot ethanol or *i*PrOH to afford pure DHPMs, **2a–o**. The combined aqueous filtrate was subjected to distillation at 80 °C under reduced pressure (10 mmHg) over 4 h to leave behind the IL in near complete recovery, pure enough for recycle. The recovered ionic liquid was found to be effective for at least 3 recycles in the synthesis of **2a**.

Characterization data of selected DHPMs

5-Ethoxycarbonyl-6-methyl-4-(2-fluorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (2d). Mp: 235–237 °C (recystallized from hot ethanol). ^1H-NMR (DMSO-d_6): δ (ppm) 9.43 (s, 1H, NH), 7.87 (s, 1H, NH), 7.48–7.28 (m, 4H, ArH), 5.62 (s, 1H, ArCHN), 4.07 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.44 (s, 3H, CH_3), 1.20 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ (ppm) 160.3, 158.3, 157.2, 154.7, 135.8, 129.3, 127.8, 124.0, 122.4, 115.2, 61.1, 54.5, 13.8; IR (Nujol): 3350, 3229, 3110, 2924, 2854, 1690, 1644, 1461, 1378, 1265, 1231, 1102, 754 cm^{-1}. Anal. Calcd for $C_{14}H_{15}FN_2O_3$: C, 60.42; H, 5.43; F, 6.83; N, 10.07%. Found: C, 60.22; H, 5.40; F, 6.79; N, 10.12%.

5-Ethoxycarbonyl-6-methyl-4-(2-pyridyl)-3,4-dihydropyrimidin-2(1*H*)-one (2i). Mp: > 300 °C (recystallized from hot ethanol). ^1H-NMR (DMSO-d_6): δ (ppm) 9.13 (s, 1H, NH), 8.47 (s, 1H, NH), 7.71 (m, 2H), 7.51 (d, 1H), 7.23 (m, 1H), 5.31 (s, ArCHN, 1H), 4.21 (q, J = 6.66 Hz, 2H, OCH_2CH_3), 2.44 (s, 3H, CH_3), 1.15 (t, J = 7.0 Hz, 3H, OCH_2CH_3). IR (Nujol): 3400, 2924, 2854, 1619, 1566, 1487, 1462, 1377, 1323, 1303, 1269, 1244, 1202, 1148, 1116, 1083, 1049, 976, 926, 861, 786 cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15; S, 11.56%. Found: C, 56.20; H, 5.50; N, 15.20; S, 11.50%.

5-Ethoxycarbonyl-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (2o). Mp 202–204 °C. (Recystallized from hot *i*PrOH); ^1H-NMR (DMSO-d^6): δ (ppm) 10.22 (s, 1H, NH), 9.49 (s, 1H, NH), 7.29 (m, 2H, ArH), 5.04 (s, 1H, ArCHN), 6.40 (s, 2H), 3.94 (q, J = 6.66 Hz, 2H, OCH_2CH_3), 3.53–3.62 (s, 9H, OCH_3), 2.12 (s, 3H, CH_3), 1.04 (t, J = 7.0 Hz, 3H, OCH_2CH_3). ^{13}C-NMR: δ (ppm) 174.9, 165.6, 153.3, 145.5, 139.5, 137.5, 103.9, 101.1, 60.4, 60.1, 56.2, 54.3, 17.6, 14.5. IR (Nujol): 3297, 3169, 2925, 2854, 1661, 1589, 1571, 1509, 1419, 1338, 1297, 1242, 1187, 1144, 1130, 999 cm^{-1}. Anal. Calcd. for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.64; S, 8.75%. Found: C, 55.55; H, 5.98; N, 7.59; S, 8.77%.

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PAPER

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Synthesis of novel polyurethane polyesters using the enzyme *Candida antarctica* lipase B

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There are significant health and environmental hazards associated with the synthesis of polyurethane polymers and the diisocyanate intermediates due to their toxicity and that of the phosgene used to produce the diisocyanate. The synthesis of polyurethane polymers avoiding or minimising the requirement for diisocyanate is reported. Using the *Candida antarctica* lipase B to catalyse the polyesterification, a series of polyurethanes based on *bis*-carbamate diols were synthesised. Several polyurethane polymers have been synthesised based on diamines for which no corresponding diisocyanate exists.

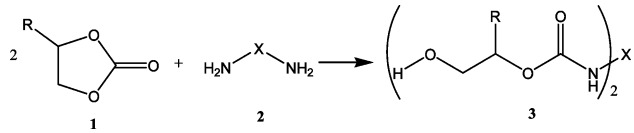
Introduction

Polyurethane polymers are extremely important and versatile materials having numerous applications in foams, surface and textile coatings, adhesives and elastomers. They are used in a wide variety of industries such as furniture, construction, aircraft and automobile manufacture and mining equipment. The total market size for urethane intermediates in Europe is in excess of 3×10^6 tonnes of which diisocyanates make up over half. These materials are manufactured from hydroxy terminated polyester resins made by the high temperature Lewis acid catalysed condensation of a diacid and diol,[1] or hydroxy terminated polyethers derived from propylene oxide, in both cases the subsequent reaction with highly toxic diisocyanates produces the polyurethane polymer.[2] The toxicity and environmental hazard of the diisocyanates is such that the maximum allowable concentration in the emissions to atmosphere is as low as 0.005 ppm. All companies using toluene diisocyanate and any company using in excess of 100 tonnes per annum of diphenyl methane diisocyanate is regarded as such a risk to the environment that it has to be a registered isocyanate works with the Department of the Environment.

The diisocyanates are synthesised by the reaction of phosgene and the corresponding diamine,[3] a process that involves the elimination of hydrogen chloride and uses a large volume of chlorinated solvent. The synthesis of 1,000,000 tonnes of diisocyanate in Europe creates approximately 330,000 tonnes of hydrogen chloride requiring treatment and disposal. Thus, the production of a narrow range of toxic diisocyanates is limited to only the few companies in the world who are capable of operating the process safely. While there have been many attempts at non-phosgenation routes to diisocyanates and to the synthesis of polyurethanes without using diisocyanates,[4–6] none have been successful commercially.

The majority of reported enzymatic syntheses using lipases are concerned either with the synthesis of optically active esters or alcohols, where the enantioselectivity of the enzyme steers the reaction product to a particular isomer,[7] or with the synthesis of polyesters.[8] Apart from the synthesis of sugar esters,[9] the hydrolysis[10] and transesterification[11] of sensitive esters (*e.g.* prostaglandin esters) and the work of Harffey *et al.*, with epoxide esters,[12] the mild, low temperature aspects of enzymatic synthesis have not been exploited to full advantage as yet. In the conventional synthesis of polyester based polyurethanes the addition of the isocyanate to the polyester polyol must occur after esterification because the carbamate group begins to decompose at 160–180 °C,[13,14] well below the esterification temperature (typically 220 °C). However, the use of enzymatic methods allows us to reverse the conventional process by creating the urethane first and then using a low temperature enzymatic polyester synthesis to build the polymer. Thus, we were able to synthesise a novel series of *bis*-carbamate esters and polyesters.

It was known from the work of Delaby *et al.*,[15] in the 1950s that the carbamate group could be synthesised by the ring opening addition of a cyclic carbonate, such as ethylene carbonate **1a**, with a primary diamine. The product of this reaction being the *bis*-(hydroxyethyl) carbamate (*e.g.* Scheme 1).



1 2 3

Scheme 1 Synthesis of diurethane diols.

These diols have been used to form polymers by reaction of the *bis*-carbamates with methylol melamine to give cross-linked urethane-containing polyether polymers.[16] These polymers had some of the properties of a polyurethane, but the need for high temperature stoving meant that some degradation took place.

Enzyme catalysed esterification of *bis*-(hydroxyethyl) carbamates derived from readily available diamines, gave the possibility of a low temperature route to polyester polyurethanes avoiding the use of diisocyanates. This idea suggested two possible applications, firstly more environmentally friendly syntheses of polymers that are analogues of existing polymers, secondly synthesis of novel polyester polyurethanes where the requisite diamine was available, but the diisocyanate was not, *e.g.* ethylenediamine **2b** is readily available, but ethylenediisocyanate is not as it is extremely toxic and hazardous due to its volatility. Although it is feasible to use both aromatic and aliphatic diamines in this reaction, reactions with aliphatic diamines were selected because aliphatic diisocyanates are much more expensive and hazardous than aromatic ones.

Delaby *et al.* synthesised *bis*-(hydroxyethyl) hexamethylene carbamate **3a** using ethylene carbonate **1a** and 1,6-hexamethylenediamine **2a**.[17] Their procedure was modified, instead of mixing the stoichiometric amounts of carbonate and diamine and reacting in ice, we chose to control the reaction by adding the diamine slowly in order to control the exotherm. Compound **3a** (mp 94 °C) was obtained in 60% yield and high purity; by gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy (Table 1). As the desired physical properties of the finished polyester polyurethane meant that the *bis*-carbamate **3a** was unlikely to be used as the only diol component of the polyester, a co-polyester **4a** with 1,4-butanediol **5** and adipic acid **6** was synthesised using the *bis*-carbamate as about 10% of the total diol (Scheme 2). The procedure adopted for the synthesis of the co-polymer was derived from the protocol developed by Harffey *et al.*[12] High initial pressures

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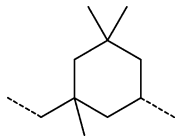
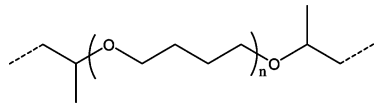
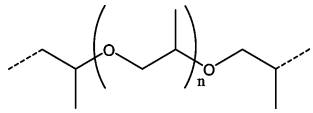
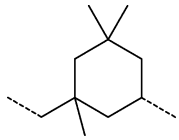
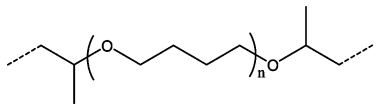
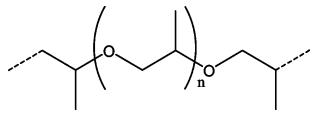
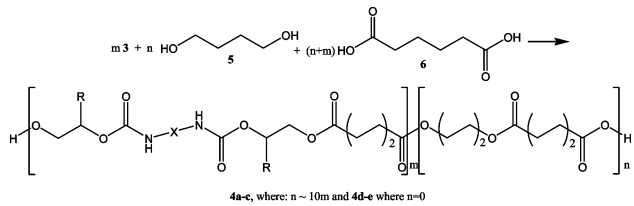
Table 1 Groups R and X present in the compounds **1–3** and polymers **4**

Compound	R	X
1a	H	—
1b	CH_3	—
2a	—	$-(CH_2)_6-$
2b	—	$-(CH_2)_2-$
2c	—	
2d	—	$n \sim 3$ 
2e	—	$n \sim 1$ or 2 
3a, 4a	H	$-(CH_2)_6-$
3b, 4b	H	$-(CH_2)_2-$
3c, 4c	CH_3	
3d, 4d	H	$n \sim 3$ 
3e, 4e	H	$n \sim 1$ or 2 



Scheme 2 Synthesis of a polyester polyurethane co-polymer.

(typically 400–200 mmHg for 12 hours and 100 mmHg for 24 hours) at low temperatures (60 °C) are employed initially to reduce loss of volatile 1,4-butanediol **5**. The pressure is reduced (80–50 and 50–10 mmHg for 12 hours each) and the temperature raised (80 °C) to complete the reaction (no more water given off). This procedure results in a polymer whose molecular weight range approaches the maximum attainable under these conditions and repeated runs have shown little deviation in molecular weight and dispersity (±10%). Thus, the *bis*-carbamate **3a** was dissolved in 1,4-butanediol **5** at 90 °C under nitrogen, cooled to 60 °C and reacted with adipic acid **6** using Novozyme 435, a commercial preparation of supported *Candida antarctica* lipase B, as catalyst. The only deviation from this protocol was that the adipic acid **6** was added in portions, as we had shown that too high an acidity inhibited the enzyme.[18] GPC analysis using a 1000 Å column gave the molecular weight of the resulting polyester polyurethane **4a** as 9350 Daltons, compared to a polystyrene standard, with a dispersity of 1.75.

The polyester polyurethane **4a** is the analogue of a polybutane adipate polyester that has been partially chain extended with hexamethylene diisocyanate and which could be chain extended once more by the addition of further diisocyanate.

Next, the method was extended to the synthesis of urethane polyesters for which no equivalent isocyanate is available. Ethylenediamine **2b** was reacted with ethylene carbonate **1a** to give *bis*-(hydroxyethyl) ethane carbamate **3b**, identical to a carbamate based on ethylene diisocyanate. The mp of the white crystalline compound was 93 °C. The yield was 60% after recrystallisation; losses being due to the slight solubility of the product during a cold ethanol wash. Chromatography showed a single product free from starting materials. Once again, a 1,4-butanediol, adipic acid co-polyester **4b** was synthesised using the *bis*-carbamate **3b** as 10% of the diol component. In the first instance the preparation was performed at 60 °C and 200 mmHg for 24 hours, then at 50 mmHg for 24 hours and finally at 70 °C at 10 mmHg for 24 hours. The polymer had an acid number of 33.8 mg KOH g^{-1} and M_w 4500 Daltons by GPC, with a dispersity of 2.4. Trying to speed up the procedure had obviously failed. Further 1,4-butanediol **5** was added and the reaction continued at 60 °C at 100 mmHg for 6 hours and 50 mmHg for 12 hours. The acid number improved to 8.5 mg KOH g^{-1} the M_w to 7300 and the dispersity to 1.8. Repetition of this reaction with 20% excess 1,4-butanediol **5** present initially gave a similar polymer M_w 7920, dispersity 1.9 and acid number 7.0 mg KOH g^{-1}. This novel polyester was found to be extremely water soluble, due to the preponderance of ethane groups in the polymer. Such a water soluble polymer may well have applications in water soluble polyurethane coatings or adhesives.

One major problem associated with the commercialisation of a new process using novel intermediates is the need for costly toxicological testing of the compounds. The EINECS regulations are relaxed if the novel compound does not leave the reactor and if the final product is a high molecular weight polymer. Thus, as 1,4-butanediol **5** does not react with either of the reactants, the toluene solvent can be replaced with 1,4-butanediol **5**. IR spectroscopy and GPC analysis confirmed completion of the reaction with diamine **2b**; the product **3b** being a clear solution at 60 °C and a white waxy solid on cooling. Novozyme 435 and the requisite amount of adipic acid **6** were added to the reaction product **3b** to give a polyester **4b**. GPC gave the molecular weight as M_w 4640, M_n 2200 dispersity 2.1 and acid number 0.7 mg KOH g^{-1}. Repetition of the synthesis of the hexamethylene *bis*-carbamate **3a** in 1,4-butanediol **5** as solvent and subsequent polymerisation gave the co-polymer **4a** with M_w 9350, M_n 5190, dispersity 2.0 and acid number 8.5 mg KOH g^{-1}. Thus it appears that there is no reason why this principle of using a diol from the second stage esterification as the diluent in the formation of the *bis*-carbamate cannot be extended to the synthesis of any *bis*-carbamate.

As it provides a useful polymer substituent, isophorone diamine **2c** was reacted with propylene carbonate **1b** to give the *bis*-carbamate **3c**. GPC analysis showed that the reaction had gone to completion with no reactants remaining. This *bis*-carbamate **3c** was converted to co-polyester polyurethane **4c** in the usual manner. GPC gave the molecular weight, M_w, as 6000 and the dispersity as 2.14. The acid number was 2.0 mg KOH g^{-1}.

α,ω-Polytetramethylene ether diols are used extensively in the manufacture of high performance polyurethane elastomers and coatings. There are no equivalent diisocyanates available, but the related diamine **2d** is available by the reaction of an α,ω-polytetramethylene ether diol with acrylonitrile followed by hydrogenation to give the *bis*-(1-aminoprop-2-yl)polytetramethylene ether **2d** of molecular weight 350. The *bis*-carbamate **3d** of diamine **2d** was synthesised by reaction with ethylene carbonate **1a**.

The product **3d** was a reddish viscous liquid. NMR analysis showed that all the ethylene carbonate **1a** had reacted, however there was a trace of un-reacted amine remaining. Because of the substantial polyether backbone of the diamine **2d** it was not thought necessary to add any 1,4-butanediol **5** to the *bis*-carbamate **3d** in order to form a useful polyester polyurethane. Therefore, adipic acid **6** and Novozyme 435 were added and after heating at 60 °C under reduced pressure for 48 hours the final polymer **4d** had a

molecular weight of 6500 by GPC and an acid number of 5.0 mg KOH g^{-1}. The combination of the ester groups and the ether backbone gave a polymer that was not soluble in any of the common solvents. It was thought that this material would make an excellent intermediate in the manufacture of solvent resistant coatings.

The above reaction was extended to the related polyoxypropyleneamine **2e**, Jeffamine D230. The amine was added to the ethylene carbonate **1a** as before, however, the exotherm was substantially less than with any of the previous amines and thus the reaction was maintained at 80 °C overnight. TLC and ^{1}H NMR spectroscopy indicated that the reaction had gone to completion with only a trace of residual amine remaining. This *bis*-carbamate **3e** was also converted to polyester in the same manner as the others and as for polymer **4d**, the finished polyester **4e** was a brown viscous liquid, the molecular weight was 6500 Daltons by GPC and the acid number was 2 mg KOH g^{-1}.

Experimental

All NMR spectra were obtained on a Bruker DPX250 spectrometer. The FTIR spectra were recorded using the Mattson Infinity 1 FTIR spectrometer. All urethane compounds decomposed in the gas chromatography/mass spectrometer and so no mass spectra could be obtained. Gel permeation chromatography was done using a Waters HPLC with a 510 pump and a Waters 410 refractive index detector together with a Waters 717 autosampler. The column used was a Polymer Labs, 1000A polystyrene copolymer packing. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected.

Di(hydroxyethyl)hexamethylene bis-carbamate (3a)

Ethylene carbonate **1a** (0.32 moles, 28.23 g) was heated in a flask to 50 °C and 1,6-hexamethylenediamine **2a** (0.69 moles, 8.0 g) added with stirring. An exotherm to 85 °C followed and after 40 minutes the mixture solidified. Toluene (25 g) was added as an adjuvant and the temperature increased to 60 °C. The remainder of the 1,6-hexamethylenediamine **2a** (0.09 moles, 10.42 g) was added, again producing an exotherm to 85 °C. The mixture solidified, hot toluene (15 g) was added to triturate and the crystalline product filtered off on cooling,, recrystallised twice from ethanol and dried to give the *bis*-carbamate as white crystals. (28 g, 70%), mp 94 °C. IR (ATR) cm^{-1} 3324, 2947, 2856, 1683, 1528, 1337, 1261, 1219, 1084. δ^1_H ($CDCl_3$, 250 MHz), ppm 1.27 (4H, t, *J* 7.0 Hz, –(NH–CH_2–CH_2–CH_2–CH_2)$_2$), 1.39 (4H, br m, –(NH–CH_2–CH_2–CH_2)$_2$), 1.58 (2H, br s, –OH), 3.21 (4H, q, *J* 6.5 Hz, (–NH–CH_2–CH_2–CH_2)$_2$), 3.79 (4H, br m, –O–CH_2–CH_2–OH), 4.23 (4H, br t, –O–CH_2–CH_2–OH), 4.89 (2H, br m, (–NH–CH_2–CH_2–CH_2)$_2$). δ^{13}_C ($CDCl_3$, 63 MHz), ppm 26.1 (t, NH–CH_2–CH_2–CH_2)$_2$), 29.1 (t, –(NH–CH_2–CH_2–CH_2)$_2$), 40.7 (t, –(NH–CH_2–CH_2–CH_2)$_2$), 61.8 (t, –O–CH_2–CH_2–OH), 66.6 (t, –O–CH_2–CH_2–OH), 157.3 (s, –O–CO–N–). $C_{12}H_{24}N_2O_6$ requires C, 49.32; H, 8.22; N, 9.58; found: C, 49.37; H, 8.30; N, 9.53%.

Synthesis of a polyester containing di(hydroxyethyl)hexamethylene bis-carbamate (4a)

Di(hydroxyethyl) hexamethylene *bis*-carbamate (0.264 moles, 7.25 g) **3a** and 1,4-butanediol **5** (0.253 moles, 22.72 g) were placed in a flask and heated to 90 °C under an atmosphere of nitrogen. Adipic acid **6** (0.055 moles, 8 g) was added and stirred until dissolved. The reactants were cooled to 60 °C and Novozyme 435 (0.7 g) was added. The pressure was reduced to 400 mmHg and after 2 hours, further adipic acid **6** (0.17 moles, 25 g) was added and left for 16 hours. The remainder of the adipic acid **6** (0.049 moles, 7.17 g) was added and the pressure reduced to 100 mmHg and left for 24 hours. A further amount of Novozyme 435 (0.5 g) was added, the reaction temperature raised to 70 °C and the pressure reduced to 50 mmHg for a further 24 hours. The polyester product **4a** had M_w 9350, M_n 5345, dispersity 1.75, determined by GPC, and acid number 16.1 mg KOH g^{-1}. δ^{13}_C ($CDCl_3$, 63 MHz), ppm 24.7 (t, *C*H_2–CH_2–CO_2), 25.7 (t, –*C*H_2–CH_2–OCO–), 26.9 (t, NH–CH_2–CH_2–*C*H_2)$_2$), 30.6 (t, –(NH–CH_2–*C*H_2–CH_2)$_2$), 34.1 (t, *C*H_2–CO_2–), 41.3 (t, –(NH–*C*H_2–CH_2–CH_2)$_2$), 62.5 (t, –*C*H_2–OCO–NH), 64.3 (t, –*C*H_2–OCO–), 71.0 (t, –OCO–*C*H_2–CH_2–OCO–), 156.7 (s, –O–*C*O–N–), 173.8 (s, –$(CH_2)_4$–O*C*O–), 176.9 (s, –O–$(CH_2)_2$–O*C*O–).

Di(hydroxyethyl)ethane bis-carbamate (3b)

Ethylene carbonate **1a** (1.216 moles, 107 g) was heated in a flask to 50 °C and ethylenediamine (0.604 moles, 36.26 g) added *via* a dropping funnel such that the exotherm maintained the temperature at approximately 60 °C. After the initial exotherm abated toluene (40 g) was added to reduce the viscosity. When all the ethylenediamine had been added the reaction was maintained at 65 °C for 4 hours. The white crystalline *bis*-carbamate product **3b** was recrystallised from ethanol, washed and dried (86.5 g, 60%), m.p. 93 °C.

IR (ATR) cm^{-1} 3324, 2944, 2874, 1685, 1537, 1448, 1321, 1271, 1226, 1149, 1078. δ^1_H ($CDCl_3$, 250MHz), ppm 3.22 (4H, q, *J* 6.5 Hz, (–NH–C*H*$_2$–)$_2$), 3.82 (4H, br m, (–O–CH_2–C*H*$_2$–OH)$_2$), 4.17 (4H, t, *J* 8.75 Hz, (–O–C*H*$_2$–CH_2–OH)$_2$), 5.28 (2H, br m, (–O–CH_2–CH_2–O*H*)$_2$), 7.35 (2H, br m, (–CO–N*H*)$_2$). δ^{13}_C ($CDCl_3$, 63 MHz), ppm 40.7 (t, *C*H_2–NCO), 61.7 (t, –O–CH_2–*C*H_2–OH), 66.7 (t, –O–*C*H_2–CH_2–OH), 157.2 (s, –C–N–*C*O–). $C_8H_{16}N_2O_6$ requires C, 40.68; H, 6.78; N, 11.86; found C, 40.75; H, 6.80; N, 11.76%.

Synthesis of a polyester containing di(hydroxyethyl)ethane bis-carbamate (4b)

Di(hydroxyethyl)ethane *bis*-carbamate **3b** (0.0508 moles, 12.0 g) was dissolved in 1,4-butanediol **5** (0.1997 moles, 18 g) at 70 °C and adipic acid **6** (0.068 moles, 10 g) was added and stirred until dissolved. Novozyme 435 (0.78 g) was added and the mixture heated at 200 mmHg at 60 °C for 6 hours. Further adipic acid **6** (0.0684 moles, 10 g) was added and the reaction was held for 18 hours at 60 °C and 200 mmHg. The final portion of adipic acid **6** (0.063 moles, 9.2 g) was added and heating continued at 70 °C at 50 mmHg for 18 hours and 10 mmHg for 24 hours. The product **4b** was an extremely water soluble polyester of molecular weight M_w 7920, dispersity of 1.9 and an acid number of 7 mg KOH g^{-1}. δ^{13}_C ($CDCl_3$, 63 MHz), ppm 24.7 (t, *C*H_2–CH_2–CO_2), 25.7 (t, –*C*H_2–CH_2–OCO–), 34.1 (t, *C*H_2–CO_2–), 41.4 (t, –(NH–*C*H_2–)$_2$), 62.9 (t, –*C*H_2–OCO–NH), 63.2 (t, –OCO–*C*H_2–CH_2–OCO–), 64.3 (t, –*C*H_2–OCO–), 156.9 (s, –O–*C*O–N–), 173.8 (s, –$(CH_2)_4$–O*C*O–), 174.0 (s, –O–$(CH_2)_2$–O*C*O–).

Di(hydroxypropyl)isophorone bis-carbamate (3c)

Propylene carbonate **1b** (0.5 moles, 51 g) was heated to 50 °C and isophorone diamine **2c** (0.059 moles, 10.0 g) added under nitrogen, no exotherm was observed. The remainder of the isophorone diamine **2c** (0.191 moles, 32.5 g) was added gradually and the reactants heated to 80 °C, when a slight exotherm was observed. The reaction was left overnight at 80 °C. Analysis by GPC (single peak) and NMR spectroscopy indicated that the reaction had gone to completion.[19] The *bis*-carbamate **3c** was a straw coloured liquid consisting mainly of a mixture of two of the four possible diastereoisomers (93.5 g, 100%). IR (neat) (ATR) cm^{-1} 3311, 2949, 1684, 1532, 1384, 1305, 1240, 1140, 1046, 843. δ^1_H ($CDCl_3$, 250 MHz), ppm 0.93 (s, 3H × 0.25, gem CH_3 minor isomer), 0.95 (s, 3H × 0.75, gem CH_3 major isomer), *ca.* 1 (br s, 2H, –OH), 1.02 (s, 3H × 0.25, gem CH_3 minor isomer), 1.08 (s, 3H × 0.75, gem CH_3 major isomer), 1.15–1.27 (8H, m, ring CH_2 & 2 × C*H*$_3$–CH–O), 1.5–1.8 (2H, br m, 2 × ring CH_2), 2.93 (2H, br d, C*H*$_2$NH), 3.5–4.2 (2 × 3H, 2 × br m, 2 × OCH_2CHO), 4.6 (1H, br m, CH–N), 4.88 (2H, br s, 2 × NH); the ^{13}C NMR spectrum shows a mixture of predominantly two diastereoisomers, the major peaks are: δ^{13}_C ($CDCl_3$, 63 MHz), ppm 17.0, 19.2, 19.5, 23.5, 23.6, 23.7,

26.0, 28.3, 30.0, 30.1, 31.4, 32.2, 35.5, 35.6, 36.8, 41.9, 44.4, 45.0, 45.1, 46.3, 46.5, 47.3, 48.6, 49.6, 54.9, 55.1, 66.2, 66.6, 68.3, 68.6, 70.3, 70.5, 72.7, 72.8, 156.6, 156.7, 157.9. $C_{18}H_{34}N_2O_6$ requires C, 57.75; H, 9.09; N, 7.48; found C, 57.52; H, 9.10; N, 7.43%

Synthesis of a polyester containing di(hydroxypropyl)isophorone bis-carbamate (4c)

Dihydroxypropylisophorone *bis*-carbamate **3c** (0.061 moles, 22.85 g) was dissolved in 1,4-butanediol **5** (0.454 moles, 40 g) at 70 °C, adipic acid **6** (0.21 moles, 30.15 g) added and after dissolution the reactants were cooled to 60 °C and Novozyme 435 (2.5 g) added. The mixture was heated at 60 °C at 400 mmHg for 4 hours, when the remaining adipic acid **6** (0.296 moles, 43.66 g) was added. The temperature was maintained at 60 °C and the pressure at 200 mmHg for 24 hours, the pressure was reduced to 10 mmHg for a further 24 hours. The product **4c** (117 g, 85.5%), a pale straw coloured resin, was filtered and analysed by GPC, M_w 6000, dispersity 2.14 and acid number 4.2 mg KOH g^{-1}.

Bis-[hydroxyethyl(3-carbamatopropyl)]polytetrahydrofuran (3d)

Ethylene carbonate **1a** (0.686 moles, 60.37 g) was heated to 60 °C and *bis*-(3-aminopropyl)polytetrahydrofuran **2d** (0.343 moles, 120.1 g) added, an immediate exotherm to 90 °C was observed. The reaction mixture was cooled to 60 °C and maintained at this temperature for 16 hours. Analysis by ^{1}H NMR spectroscopy showed that all the ethylene carbonate **1a** had been consumed with only a trace of starting amine remaining. The product **3d** was a reddish brown viscous liquid (180 g, 99.5%). IR (ATR) cm^{-1} 3324, 2944, 2860, 1685, 1530, 1258, 1200, 1079. δ^1_H ($CDCl_3$, 250 MHz), ppm 1.42 (4H, br m, –O–CH_2–CH_2–CH_2–NH–CO), 1.51 (4H × 4, br m, –O–[CH_2–(CH_2)$_2$–CH_2–O]$_4$), 1.61 (4H, br m, –O–CH_2–CH_2–CH_2–NH), 3.45 (4H × 4, t, ^3J 8, –O–[CH_2–CH_2–CH_2–CH_2–O]$_n$), 3.32 (4H, q, ^3J 6.7, (–CH_2–NH–CO–O)$_2$), 3.79 (4H, br m, (–O–CH_2–CH_2–OH)$_2$), 4.19 (4H, br m, (–O–CH_2–CH_2–OH)$_2$), 5.28 (2H, s, –CH_2–CH_2–O*H*), 5.52 (2H, br m, (–CH_2–N*H*–CO–O)$_2$). $C_{26}H_{52}N_2O_{10}$ requires C, 56.52; H, 9.42; N, 5.07; found C, 55.93; H, 9.37; N, 5.41%.

Synthesis of a polyester containing bis-[hydroxyethyl(3-carbamatopropyl)]-polytetrahydrofuran units (4d)

bis-[Hydroxyethyl(3-carbamatopropyl)]polytetrahydrofuran **3d** (0.153 moles, 70.32 g) was heated to 60 °C and Novozyme 435 (0.83 g) added. Adipic acid **6** (0.153 moles, 22.36 g) was added in 4 equal amounts over a period of 4 hours. The temperature was maintained at 60 °C and the pressure at 50 mmHg for 12 hours and then reduced to 10 mmHg for 12 hours. The pressure was then reduced to 2 mmHg for the final 12 hours. The polyester **4d** (78.6 g, 85%) had M_w 6500 and dispersity 2 by GPC. The acid number of the polyester was 5.0 mg KOH g^{-1}. δ^{13}_C ($CDCl_3$, 63 MHz), ppm 24.7 (t, *C*H_2–CH_2–CO_2), 26.9 (t, –*C*H_2–CH_2–O–), 30.1 (t, –NH–CH_2–*C*H_2–), 39.6 (t, *C*H_2–CO_2–), 39.6 (t, –NH–*C*H_2–), 62.8 (t, –*C*H_2–OCO–NH–), 63.1 (t, –OCO–*C*H_2–CH_2–OCO–), 69.3 (t, –O–*C*H_2–(CH_2)$_2$–N–), 71.0, 71.1, 71.3 (t's, polyTHF *C*H_2–O–), 156.6 (s, –O–*C*O–N–), 173.6 (s, –(CH_2)$_4$–O*C*O–).

Di(hydroxyethyl)polyoxypropylene bis-carbamate (3e)

Ethylene carbonate **1a** (0.466 moles, 41 g) was heated to 60 °C and polyoxypropyleneamine D230 **2e** (0.233 moles, 53.6 g) added in three portions over 3 hours; a slight exotherm being observed after each addition. The reaction was left at 80 °C under nitrogen for 16 hours. The usual work up gave the product as a pale yellow oil (94 g, 99.4%). IR (ATR) cm^{-1} 3320, 2934, 1695, 1531, 1455, 1310, 1233, 1072. δ^1_H ($CDCl_3$, 250 MHz) ppm 1.63 (4H × 3.6, br m, O–[CH_2–(CH_2)$_2$–CH_2–O]$_{3.6}$), 1.78 (4H, quin, *J* 6.0 Hz, O–CH_2–CH_2–CH_2–N), 2.84 (2H, br s, OH), 3.30 (4H, q, *J* 6.0 Hz, CH_2–CH_2–N), 3.43 (4H × 3.6, br m, O–[CH_2–(CH_2)$_2$–CH_2–O]$_{3.6}$), 3.51 (4H, t, *J* 5.9 Hz, CH_2–OH), 3.79 (4H, br s, O–CH_2–CH_2–CH_2–N), 4.18 (4H, br t, *J* 4.25 Hz, OCO–CH_2–CH_2), 5.47 (2H, br s, NH). $C_{18}H_{36}N_2O_9$ requires C, 50.94; H, 8.49; N, 6.60; found C, 51.10; H, 8.38; N, 6.54%.

Synthesis of a polyester containing di(hydroxyethyl)polyoxypropylene bis-carbamate units (4e)

Dihydroxyethyl polyoxypropylene *bis*-carbamate **3e** (0.075 moles, 30 g) and 1,4-butanediol **5** (0.074 moles, 6.7 g) were heated to 60 °C. Novozyme 435 (0.83 g) was added and adipic acid **6** (0.149 moles, 21.6 g) was added in three equal amounts over three hours whilst a pressure of 100 mmHg was applied. The pressure was maintained at 100 mmHg for 24 hours and 10 mmHg for a further 24 hours to give the product **4e** as a viscous brown resin (51 g, 87%) M_w 6750 and dispersity of 1.9 by GPC and acid number 4.8 mg KOH g^{-1}. δ^{13}_C ($CDCl_3$, 63 MHz), ppm 17.1 (q, *C*H_3–CH–N–), 18.2 (q, *C*H_3–CH–O–), 24.7 (t, *C*H_2–CH_2–CO_2), 34.2 (t, *C*H_2–CO_2–), 47.6 (t, –NH–*C*H_2–), 61.7 (t, –*C*H_2–OCO–NH–), 63.0 (t, –OCO–*C*H_2–CH_2–OCO–), 65.0 (d, –*C*H–N–), 66.9 (t, –O–*C*H_2–CH–N–), 72.5 (d, –N–CH_2–*C*H–O–), 74.7, 75.6 (d's, polypropylene oxide *C*H–O–), 156.2, 156.9 (s, –O–*C*O–N–), 173.7 (s, –(CH_2)$_4$–O*C*O–).

One pot process for the synthesis of polyesters containing urethane groups

Ethylene carbonate **1a** (0.50 moles, 44.32 g) and 1,4-butanediol **5** (0.44 moles, 40 g) were heated to 60 °C. 1,6-Hexamethylenediamine **2a** (0.25 moles, 29 g) was added over 1 hour making sure the exotherm did not exceed 88 °C. The reaction was maintained at 60 °C for 16 hours. The solution was a clear liquid at 60 °C, but crystallised rapidly on cooling to a white waxy solid. GPC showed that the reaction had gone to completion with only the peaks of the diol and the *bis*-carbamate remaining; the composition being 64.7% w/w *bis*-carbamate and 35.3% w/w 1,4-butanediol **5**. A portion of this mixture (25 g) was heated at 100 °C with adipic acid **6** (0.071 moles, 10.42 g) until the acid had dissolved. The reactants were cooled to 60 °C, Novozyme 435 (1.04 g) added and the pressure maintained at 200 mmHg. The remaining adipic acid **6** (0.102 moles, 14.86 g) was added in three equal amounts over 5 hours and the temperature maintained at 60 °C at 200 mmHg for a further 11 hours. The pressure was then reduced to 80 mmHg for 8 hours and finally to 2 mmHg for 24 hours. The polyester **3a** (43 g, 85.5%) had M_w 11,000, dispersity 2.0 by GPC and an acid number of 8.5 mg KOH g^{-1}.

Acknowledgments

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PAPER

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An expeditious synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines under solvent-free conditions using iodobenzene diacetate

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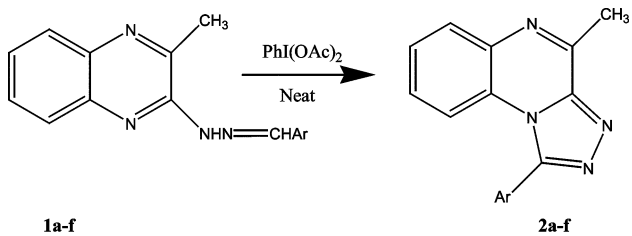
A solvent-free and expeditious synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines is described that utilizes a relatively benign non-metallic oxidant, iodobenzene diacetate.

Triazoles are an important class of heterocyclic compounds and specifically the 1,2,4-triazole nucleus has been found to be an integral part of therapeutically interesting compounds that display significant antibacterial, CNS stimulative, sedative, antifungal and antitumor activities.[1] Consequently, the synthesis of this heterocyclic nucleus has gained great importance in organic synthesis. Generally, syntheses of 1,2,4-triazoles are accomplished by the condensation of 2-hydrazinoquinoxaline with carboxylic acids at elevated temperature,[2] 1,3-dipolar cycloaddition reaction of aromatic nitriles in presence of strong base and followed by hydrogen elimination,[3] photolysis of triazole-3-thiones,[4] and oxidation of arylhydrazones.[5] However, these methods involve multi-step, harsh reaction conditions, toxic reagents and require longer reaction time.

Recently, organic reactions under solvent-free conditions have received much attention due to advantages over the conventional methods in terms of time, yields and relatively benign conditions.[6–8] In view of our initial successes on the utilization of hypervalent iodine reagents for the synthesis of various heterocyclic compounds under solvent-free conditions,[9] and because of the biological significance of 1,2,4-triazole derivatives, we decided to develop an efficient and environmentally benign synthesis of 1,2,4-triazoles that proceeds under solvent-free conditions. Herein, we report our results on oxidative transformation of arenecarbaldehyde 3-methylquinoxalin-2-yl-hydrazones to 1-aryl-4-methyl-1,2,4-triazolo[4, 3-a]quinoxalines (Scheme 1) with iodobenzene diacetate that leads to the expeditious formation of 1-aryl-4-methyl-1,2,4-triazolo[4, 3-a]quinoxalines in fairly good yields. This oxidative conversion simply involves a thorough mixing of substrates with iodobenzene diacetate at room temperature (slightly warming in some cases) *via* an exothermic reaction. Hydrazones form a yellowish eutectic melt with iodobenzene diacetate upon mixing prior to the occurrence of a mildly exothermic reaction. This is in accord with the recently postulated model for such solid–solid reactions.[6]



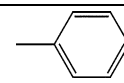
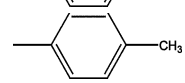
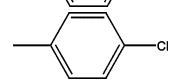
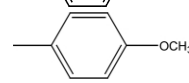
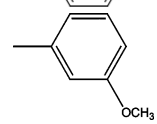
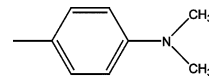
1a-f **2a-f**

Ar = C_6H_5, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-$OCH_3C_6H_4$, *m*-$OCH_3C_6H_4$, *p*-$N(CH_3)_2C_6H_4$

Scheme 1

Hydrazone derivatives of arenecarbaldehyde encompassing an electron-donating group undergo ready conversion without warming affording relatively high yields (Table 1). The formation of

Table 1 Synthesis of some 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines

Entry	Ar	mp/°C	Yield (%)[a]
2a		205–206 (203[2])	65
2b		212–213	76
2c		220–222	75
2d		186–187	74
2e		168–170	72
2f		258–260	69

[a] Unoptimized yields are for the isolated products.

1-aryl-4-methyl-1,2,4-triazolo[4, 3-a]quinoxalines are characterized by disappearance of a singlet in the ^{1}H NMR spectra ascribable to N=CH around δ 9.0. A plausible pathway for this transformation is depicted in Scheme 2. The initial electrophilic attack of iodobenzene diacetate followed by loss of iodobenzene and acetic acid generates the nitrile imine **A**. The final ring closure through quinoxaline ring nitrogen leads to the product.

In conclusion, we have developed a rapid, solvent-free and environmentally benign protocol which is fairly general for the synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines.

Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ using TMS as internal standard. All the arenecarbaldehyde 3-methylquinoxalin-2-yl-hydrazones were

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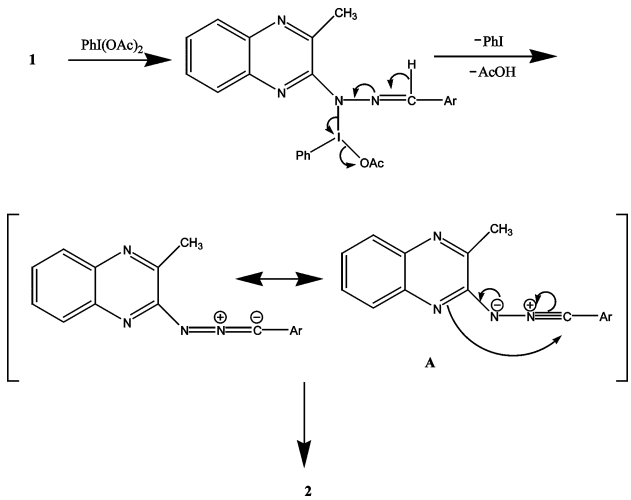

Scheme 2

prepared according to the literature procedure.[10] Iodobenzene diacetate was purchased from Aldrich.

General procedure

A mixture of arenecarbaldehyde 3-methylquinoxalin-2-yl-hydrazone (1 mmol) and iodobenzene diacetate (1.2 mmol) was ground thoroughly in a pestle and mortar. After 2–3 minutes an exothermic reaction ensued while in some cases slightly warming to ~40 °C for 2 min was required to initiate the reaction. The residue was washed with hexane and then recrystallized or filtered through a small pad of silica gel to afford analytically pure products.

4-Methyl-1-[(*p*-(methylphenyl)]-1,2,4-triazolo[4, 3-a]quinoxaline (**2b**) ^{1}H NMR ($CDCl_3$): δ 2.50(s, 3H, CH_3), 3.04(s, 3H, CH_3), 7.32(dd, 1H, *J* = 1.0, 8.0 Hz, H-7), 7.40(d, 2H, *J* = 7.0Hz, H-3′, H-5′), 7.51–7.58(m, 4H, H-aromatic), 8.02(dd, 1H, *J* = 1.0, 8.0 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 21.2, 21.7, 116, 125.2, 126, 127.5, 128.3, 129.9, 130, 136.4, 141.5, 144.90 150.4, 153. Anal. Calc. For $C_{17}H_{14}N_4$: N, 20.42. Found: N, 20.38%.

1-[(*p*-(Chlorophenyl)]-4-methyl-1,2,4-triazolo[4, 3-a]quinoxaline (**2c**) ^{1}H NMR ($CDCl_3$): δ 3.05(s, 3H, CH_3), 7.35(dd, 1H, *J* = 1.0, 8.0 Hz, H-7), 7.50–7.66(m, 6H, H-aromatic), 8.04(dd, 1H, *J* = 1.0 & 8.0 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 21.68, 116.09, 126.04, 127.08, 128.25, 128.73, 130.04, 130.74, 131.80, 137.02, 137.88, 145.52, 149.45, 153.33. Anal. Calc. For $C_{16}H_{11}N_4Cl$: N, 19.01. Found: N, 18.92%.

4-Methyl-1-[(*p*-(methoxyphenyl)]-1,2,4-triazolo[4, 3-a]quinoxaline (**2d**) ^{1}H NMR ($CDCl_3$): δ 3.03(s, 3H, CH_3), 3.92(s, 3H, OCH_3), 7.10(d, 2H, *J* = 8.0 Hz, H-3′, −5′), 7.32(dd, 1H, *J* = 1.0, 8.0Hz, H-7), 7.51–7.62(m, 4H, H-2′,-6′, −8, −9), 8.01(dd, 1H, *J* = 1.0 & 8.0Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 21.28, 55.57, 114.70, 115.85, 120.15, 125.98, 127.58, 128.17, 130.12, 131.51, 136.62, 145.00, 150.11, 152.96, 161.67. Anal. Calc. For $C_{17}H_{14}N_4O$: N, 19.30. Found: N, 19.18%.

4-Methyl-1-[(*o*-(methoxyphenyl)]-1,2,4-triazolo[4, 3-a]quinoxaline (**2e**) ^{1}H NMR ($CDCl_3$): δ 3.05(s, 3H, CH_3), 3.62(s, 3H, OCH_3), 7.07(dd, 1H, *J* = 1.0, 8.0 Hz, H-3′), 7.17–7.21(m, 1H, H-5′), 7.30–7.39(m, 2H, H-7, −8), 7.50–7.54(m, 1H, H-4′), 7.61–7.65(m, 2H, H-6′, −9), 8.01(dd, 1H, *J* = 1.0, 8.0 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 21.22, 55.44, 111.14, 115.53, 117.48, 121.28, 126.22, 127.33, 128.08, 129.58, 132.12, 132.91, 136.25, 144.98, 147.56, 152.84, 158.08. Anal. Calc. For $C_{17}H_{14}N_4O$: N, 19.30. Found: N, 19.15%.

1-[(*p*-(N,N-Dimethylphenyl)]-4-methyl-1,2,4-triazolo[4, 3-a]quinoxaline (**2f**) ^{1}H NMR ($CDCl_3$): δ 3.05(s, 3H, CH_3), 3.10(s, 6H, $N(CH_3)_2$), 6.86(d, 2H, *J* = 9.0 Hz, H-3′, −5′), 7.34(dd, 1H, *J* = 1.0, 8.0 Hz, H-7), 7.51–7.58(m, 3H, H-aromatic), 7.75(dd, 1H, *J* = 1.0, 8.0 Hz, H-9), 8.01(dd, 1H, *J* = 1.0, 8.0 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 19.46, 38.54, 110.25, 114.29, 124.48, 125.57, 126.24, 127.71, 128.13, 129.14, 134.84, 143.17, 149.25, 150.01, 151.23. Anal. Calc. For $C_{18}H_{17}N_5$: N, 23.09. Found: N, 22.85%.

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PAPER

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A more benign approach to the synthesis of calixarenes

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A more benign 'one pot' preparation of various *p*-substituted calixarenes in modest yields has been devised which involves simple and rapid solventless procedures with low waste generation.

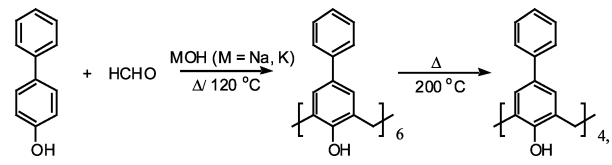
Minimisation of the use of organic solvents in chemical synthesis is of growing importance from both economical and environmental considerations.[1] In this context, solventless reactions are important and can be used in the syntheses of a wide range of compounds,[2] including cavitands (container molecules), by way of reactions involving the mixing of solids, and of solids and liquids.[3] Calixarenes are an extensively used class of cavitands, as macrocycles in supramolecular chemistry for example, and their syntheses are well established, involving the use of organic solvents as the reaction media, particularly for *p*-^{t}Bu substituted systems.[4] There are several reports on the synthesis of other *p*-substituted calixarenes which also use direct 'one pot' methods (single path reactions). However, the calixarenes are isolated in low yield, and the procedures involve reflux in high boiling noxious solvents such as tetralin and diphenyl ether, and require tedious workup.[5]

Molecules of large ring size and deep cavity are of interest in host–guest chemistry and inclusion studies involving the binding of large molecules and ions, and more. *p*-Phenylcalixarenes represent a family of such host molecules for which inclusion studies are limited. In the present study we report advances in developing more benign 'one pot' and efficient syntheses of these calixarenes. The phenyl groups of *p*-phenylcalixarenes provide potential site elaboration through aromatic substitution reactions, recently demonstrated by *p*-sulfonation using chlorosulfonic acid.[6] A limiting factor in developing the chemistry of *p*-phenylcalixarenes is the difficulty in preparing viable quantities on a routine basis. Some of this class of calixarenes have been prepared involving multi-step sequences starting with *p*-^{t}Bu-calixarenes, notably the syntheses of *p*-phenylcalix[4 and 5]arene, which generate waste through solvent utilisation, low atom efficiency, and the generation of byproducts.[7] We note that the supramolecular chemistry of *p*-phenylcalix[5]arene with C_{60} has recently been explored,[6] which nicely demonstrates at least the potential host–guest chemistry of this class of calixarenes.

p-^{t}Bu-phenol condensation with formaldehyde under basic or acidic catalysis conditions generates a mixture of calixarenes. However, the pathways by which these macrocycles are formed are still unsubstantiated. Over two decades Gutsche and co-workers have carried out extensive studies on base-catalysed reactions mainly involving *p*-^{t}Bu-phenols, gaining insight into the preferential formation of certain ring sizes.[8] Metal ion and solvent dependences have been established for controlling the formation of the major calixarenes for the *p*-^{t}Bu-phenol systems, where the octamer is believed to be the kinetically favoured product.[8]

Direct synthesis of *p*-phenylcalix[4]arene was first reported by Zinke in 1944 by a 'one-pot' method, although yields were not provided, and full characterization was not possible at the time.[9] Here the *p*-phenylphenol was treated with aqueous formaldehyde and sodium hydroxide at 50 °C for 45 hours, whereupon the mixture was acidified, heated, suspended in linseed oil at 130 °C, and heated further at 220 °C.

In using the solventless approach (no organic solvent in the reaction mixture), which worked well for preparing various calix[4]resorcinarenes[3] and indeed *p*-benzylcalix[8]arene,[10] we find that temperature is a critical factor in producing major *p*-phenylcalixarenes, regardless of the nature of base or the ratio of base to phenol. Calixarenes in general have high melting points and are thermally stable in excess of *ca.* 250 °C, an advantage using the solventless approach where the products can tolerate elevated temperatures without the need for high pressure equipment, and with minimal decomposition. Recently, we reported a 'one pot' synthesis of *p*-benzylcalix[8]arene, obtained as the sole calixarene product in moderate yield using the solventless approach.[10] Herein we report a dramatically improved synthesis for the smaller ring systems, *p*-phenylcalix[4,5,6]arene, without the use of environmentally unfriendly reaction media such as tetralin or diphenyl ether, with shorter reaction times, lower energy usage, and enhanced ease of reaction workup. Overall the solventless approach proved to be facile, leading to higher yields and with selectivity depending on the conditions of the reaction. In addition, similar reactions were carried out using organic solvents for comparative purposes, noting that only phenycalix[6]arene has been prepared in good yield thus far using this approach, involving refluxing the reaction mixture in xylene for 2.5 hours.[11] In contrast to the *p*-^{t}Bu-calixarene system, where the octamer is the favoured product, we find that for the phenylcalixarenes the hexamer is favoured (Scheme 1).



Scheme 1

The present preparation consisted of heating a slurry of *p*-phenylphenol and aqueous formaldehyde solution and, after reaching 120 °C, a catalytic amount of 1 M MOH (M = Na, K) was added, whereupon the mixture was heated rapidly under a stream of nitrogen to effect oligomerization (*ca.* 1 h). The resulting solid was broken down to a powder, stirred and heated at 200 °C for 1 hour under an inert atmosphere. After cooling to room temperature, the solid was suspended and stirred vigorously in a 1 : 1 mixture of methanol and 1 M HCl for 30 minutes. Filtration and air drying afforded a mixture of phenylcalix[4,5,6]arenes which were separated first by tituration with acetone to give phenylcalix[6]arene, followed by successive crystallisation from acetone to afford the remaining calixarenes. The yields are summarized in Table 1.

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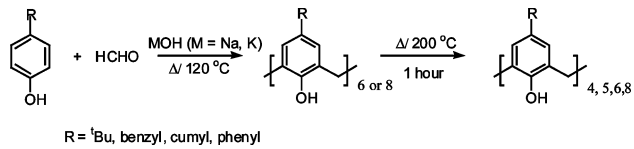
Table 1 *p*-Phenylcalix[*n*]arenes yields as a function of base : *p*-phenylphenol ratio

Molar ratio (base to phenol)	(%) yields[a]			
	n = 4	*n* = 5	*n* = 6	*n* = 8
NaOH (0.045)	0	5	20	15
KOH (0.045)	10	10	50	0
NaOH (0.18)	20	10	0	30
KOH (0.18)	0	0	40	0
NaOH (0.45)	5	0	20	30
KOH (0.45)	10	0	40	0

[a] Based on isolated yields.

With this success, the work was extended to investigate the synthesis of other calixarene systems using the same solventless approach, as detailed above for the synthesis of *p*-phenyl-calixarenes. This also proved successful in gaining access to various *p*-substituted-calixarenes, Scheme 2, with unprecedented



Scheme 2

convenience and in higher yields. It is noteworthy that extended heating beyond 1 hour alters the composition of the calixarene mixtures, generally tending to produce the thermodynamically favoured product but lowering the overall yield of the reaction.

The condensation reactions of *p*-benzylphenol, *p*-cumylphenol and *p*-^{t}Bu-phenol with formaldehyde proceeds in the same fashion as for *p*-phenylphenol. The ease of condensation is somewhat better for *p*-benzylcalix[*n*]arenes and *p*-cumylcalix[*n*]arenes while *p*-^{t}Bu-phenol lacks total conversion to the calixarene products. The results for *p*-benzylcalix[*n*]arene, *p*-cumylcalix[n]arene and *p*-^{t}Bu-calix[n]arene are summarised in Table 2.† It is important to stress that the data represented is based on one gram scale reactions for the starting phenol; scaling up the reaction to 5 grams of the phenolic monomer retains consistency of the results. Further scaling up was not attempted but clearly could have an effect on the ultimate mixing and heat transfer to the solid mixture and subsequently the yields. Comparing the yields with those from traditional methods, *p*-phenylcalix[4,5,6]arenes have been produced in higher yields.[5b,6b] Significant improvement was achieved for *p*-benzyl calix[4,6,8]arenes and for *p*-cumyl-calix[4,6]arenes[5a,12] while the *p*-^{t}Bu-calix[4,5,8]arenes were obtained in comparable yields.[4]

The potentially deep cavity calix[*n*]arenes based on *p*-benzyl and *p*-cumyl are of interest in respect of the orientation of the phenyl rings relative to the calixarene cavity, and it is of interest to establish their structures as a basis for understanding their potential host–guest chemistry. We were successful in growing suitable crystals from toluene of *p*-cumylcalix[4]arene for structural authentication using X-ray diffraction data.‡ The calixarene crystallised as a toluene disolvate, with one toluene embedded in the cavity of the calixarene and the other filling interstitial space, Fig. 1. There is a report on the structurally authenticated *p*-cumylcalix[6]arene as a dimethylformamide disolvate where each DMF molecule is bound to the pseudo cavities of the double partial cone conformation of the calixarene.[12]

In the present structure, the orientation of the *endo*-cavity toluene, with the methyl group directed inwards and residing on the principle axis of the calixarene is similar to that found in the structure of toluene complex of ^{t}Bu-calix[4]arene,[14] and also its 1,3-O,O′-dimethylated analogue.[13] The calixarene has quasi-*2* symmetry with two opposite phenyl rings directed away from the cavity. Their planes are aligned quasi-parallel to the plane of the toluene molecule residing in the cavity (the dihedral angle between the two phenyl rings is 5.9(3)° and their angles with the included toluene are 28.6 and 28.5(4)°). The other pair of opposite phenyl rings are orientated such that an *o*-hydrogen atom from each ring is directed towards the π-cloud of the included toluene ($C_{aryl}H\cdots$centroid of the *endo*-cavity toluene molecule 2.99 and 2.90(2) Å). For these arms of the calixarene the dihedral angle between the phenyl rings is 70.4(4)°, and their angles with the included toluene are 98.8 and 90(4)° so that the phenyl rings are essentially orthogonal to the toluene molecule. A methyl group from each of the same arms of the calixarene is directed away from the calixarene cavity rather than a phenyl group, as for the other opposed pairs of phenyl rings. The *endo*-cavity included toluene fits snugly into the cavity, Fig. 1, without the disorder found in the toluene included complex of *p*-^{t}Bu-calix[4]arene.[14]

The dihedral angles of the phenol calix[4]arene ring planes to the O_4 plane are of 51.2(1), 60.2(1), 50.6(1), 57.2(1)°, successively around the macrocycle, so that the calixarene has a slight pinched cone conformation, the pinching associated with the C–H···π interactions. Interestingly similar C_{aryl}–H···π interactions are prevalent in the C_{60} complex of *p*-benzylhexahomooxa-calix[3]arene.[15] At the base of the calixarene the OH groups are involved in a cyclic intramolecular hydrogen bonding array, as is usual for

† Compounds previously reported were characterised using ^{1}H NMR spectroscopy[5,6] All new compounds were characterised using ^{1}H, ^{13}C and mass spectrometry: *p*-cumylcalix[4]arene: M.p. 280 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 6H; CH_3), 3.27 (d, 1H; Ar–CH_2–Ar, J_{AB} = 14 Hz), 4.20 (d, 1H; Ar–CH_2–Ar, J_{AB} = 14 Hz), 6.85 (s, 2H; Ar–H), 7.11–7.25 (m, 5H; Ph), 9.51 (s, 1H; OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 30.5 (C^1H_3), 30.7 (C^2H_3), 30.8 (Ar–CH_2–Ar), 42.1 (Ar–$C(CH_3)_2$–Ph), 125.4 (Ar), 126.5 (Ar), 126.8 (Ar), 127.8 (Ar), 128.5 (Ar), 144.33 (Ar), 146.5 (Ar), 150.4 (Ar(C)–OH); MS (MALDI-TOF): *m*/*z* 896 [M·-H], $C_{64}H_{64}O_4$ (897.2).

‡ $(C_{64}H_{64}O_4\cdot C_7H_8)\cdot C_7H_8 \equiv C_{78}H_{80}O_4$, M = 1081.5. Monoclinic, space group $C2/c$, a = 27.15(2), b = 14.785(12), c = 31.33(2) Å, β = 91.02(5)°, V = 12574 Å^3. D_c (Z = 8) = 1.14$_2$ g cm^{-3}. μ_{Mo} = 0.6 cm^{-1} (no correction). Monochromatic Mo Kα radiation, λ = 0.7107$_3$ Å, $2\theta_{max}$ = 50°; 11001 unique single counter instrument data, 5153 with $I > 3\sigma(I)$ considered 'observed' and used in the full matrix least squares refinement, anisotropic displacement parameter forms refined for C, O, $(x,y,z,U_{iso})_H$ constrained at estimates, phenolic H observed in difference maps. *T ca.* 295 K. No disorder resolvable, solvent site occupancies constrained at unity after trial refinement. CCDC 225173. See http://www.rsc.org/suppdata/gc/b3/b315204a/ for crystallographic data in .cif or other electronic format.

Table 2 Molar ratio of base to *p*-R-phenol in Scheme 2 and the resulting yields of *p*-R-calix[*n*]arenes

Molar ratio (base to phenol)	(%) yields[a]		
	R = ^{t}Bu	R = benzyl	R = cumyl
NaOH (0.045)	*n* = 8 (40)	*n* = 8 (60), *n* = 4 (20)	*n* = 6 (60), *n* = 5 (10)
KOH (0.045)	*n* = 4 (16)	*n* = 8 (60), *n* = 4,5,6 (< 10)	*n* = 6 (60), *n* = 4,5,6,8 < (5)
NaOH (0.18)	*n* = 4 (20)	*n* = 4 (20), *n* = 8 (60)	*n* = 4 (40), *n* = 6 (30)
KOH (0.18)	*n* = 4 (30)	*n* = 4 (40), *n* = 8 (40)	*n* = 4 (40), *n* = 6 (40)
NaOH (0.45)	*n* = 4 (40), *n* = 8 (10)	*n* = 4 (20), *n* = 8 (50)	*n* = 4 (60), *n* = 6 (20)
KOH (0.45)	*n* = 8 (30), *n* = 4 (5), *n* = 5 (15)	*n* = 6,7 (50), *n* = 4 (10)	*n* = 4 (40), *n* = 6 (20)

[a] Based on NMR integrations.

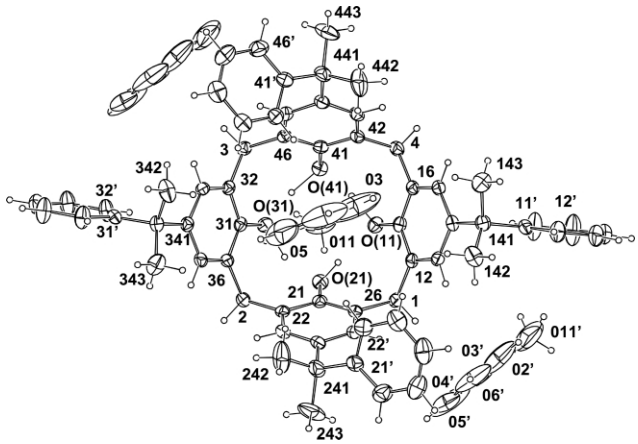


Fig. 1 Molecular projection of the structure of *p*-cumylcalix[4]arene, showing the disposition of the toluene molecule included within the calixarene cavity (CH_3 'in') on its quasi-*2* axis, and its relation to successive non-included toluenes. Non-hydrogen atoms are shown with 20% probability amplitude displacement ellipsoids, hydrogen atoms having arbitrary radii of 0.1 Å.

calix[4]arenes;[14] O···O distances around the ring are 2.666, 2.663, 2.664, 2.641(5) Å.

The unit cell packing shows a bilayer array where the calixarene molecules adopt head-to-head and back-to-back interplay which optimises the hydrophilic and hydrophobic domains, and cancels opposite dipoles, Fig. 2. Each bilayer can be viewed as the OH

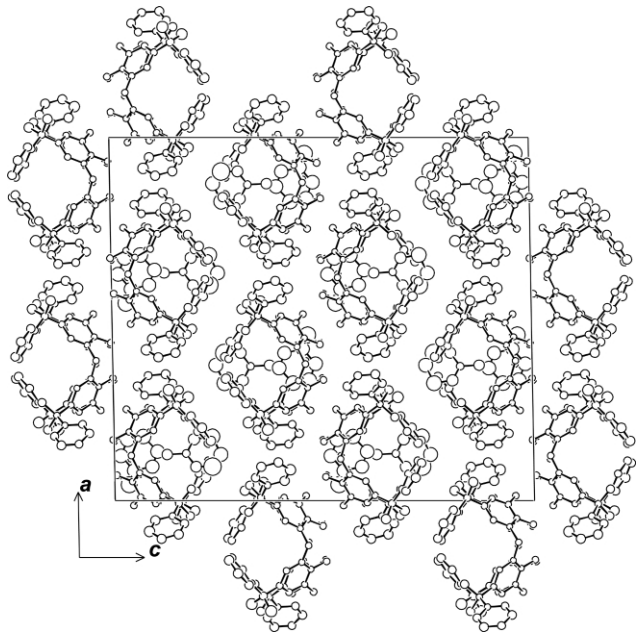


Fig. 2 Packing diagram for *p*-cumylcalix[4]arene: unit cell contents, excluding non-included toluene molecules for clarity, projected down the *b* axis.

groups arranged at the outer edges, with each calixarene π-interlocked through π-stacking involving phenol rings to two other calixarenes from the other side of the bilayer, and π-stacking through phenyl rings to adjacent calixarenes on the same side of the bilayer, Fig. 2. In the structure of the *p*-cumylcalix[6]arene, the packing is described as involving pairs of the calixarenes in the double cone conformation lying over centers of symmetry. The two DMF molecules are situated between these pairs, and residing in the cavity of the half cone of the calixarene with extended hydrogen-bonding to neighbouring calixarenes, the third DMF molecule being distorted and occupying space between the calixarenes.[12]

In conclusion this paper presents a proof of concept that *p*-phenylcalixarenes and other *p*-substituted calixarenes are readily accessible without the use of noxious high boiling point organic solvent, in modest yields. The yields may be further improved if engineering issues regarding solid mixing and heat control and transfer are addressed, a current theme of our research initiatives. Moreover, the structure determination of one of these new calixarenes further highlights their unusual structure and inclusion phenomena.

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PAPER

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Selective oxidation of alcohols by molecular oxygen over a Pd/MgO catalyst in the absence of any additives

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Selective oxidation of alcohols to the corresponding carbonyl products using molecular oxygen is achieved over a simple and easily recyclable 1% Pd/MgO impregnated heterogeneous catalyst in the presence of trifluorotoluene. A variety of activated and non-activated alcohols are effectively oxidized without the use of any additives under relatively mild reaction conditions. Other supported Pd catalysts such as Pd/Hydrotalcite (HT), Pd/Al_2O_3, Pd/SiO_2 and Pd/Zeolite-β are also studied for comparison. Pd/HT also shows a comparable oxidation activity to Pd/MgO whereas other supported catalysts were not found to be active for this reaction under the conditions studied. A mechanism of the reaction is also outlined.

Introduction

Oxidation of alcohols to aldehydes and ketones is a highly desirable and much sought after transformation both in industrial chemistry as well as in organic synthesis due to the wide ranging utility of the these products as important precursors and intermediates for many drugs, vitamins and fragrances.[1,2] Numerous methods are available for alcohol oxidation,[3] however, the development of newer methods and methodologies is gaining much attention currently due to the significance of this reaction. Traditional alcohol oxidations use toxic, corrosive and expensive oxidants such as chromium(VI) and manganese complexes, stringent conditions like high pressure or temperatures and use of strong mineral acids.[1,4] Some of the methods use O_2 in the presence of a stoichiometric amount of a reactive aldehyde, producing peracid as the actual oxidizing agent.[5] Due to the increasing environmental concerns, oxidation using environmentally friendly oxidants such as molecular oxygen and hydrogen peroxide are more desirable these days. Hydrogen peroxide oxidation, however, is relatively less economical due to its cost and comparatively poor efficiency.[6] Also, in industrial chemistry, heterogeneous catalyst systems are preferred over homogeneous system due to easy recyclability and separability. Therefore, development of an active and recyclable heterogeneous catalyst for alcohol oxidation using molecular oxygen is a highly attractive research area.

There are few aerobic oxidation methods that use copper,[7] palladium[8] and ruthenium compounds.[9] Some of these methods are limited to benzylic alcohols and also require two equivalents of the catalyst per equivalent of the alcohol[7] or the presence of a base[8] and additives like di(*tert*-butylazodihydrazine).[10] Notwithstanding the many studies on Pd systems, most of them are focused on palladium acetate in the presence of an organic solvent such as toluene and an additive. Aerobic oxidations of alcohols using Pd and Pt/C are also known.[8a] Aerobic oxidation of a variety of alcohols in the aqueous phase using water-soluble palladium(II) bathophenanthroline complex catalyst with high conversion and selectivity[8b] has also been reported recently but it involves moderate pressure (3 MPa) and an expensive and complex catalyst preparation. Another study reports a method for enantioselective aerobic oxidation of alcohols using a (−)-sparteine/Pd(II) complex catalyst.[11] The method is proved to be good for benzylic alcohols and its application to other substrates is being investigated. Recently, Yamaguchi and Mizuno have reported that Ru/Al_2O_3 is an efficient catalyst in the oxidation of a variety of alcohols using molecular oxygen.[12] A hydroxyapatite-supported palladium complex is demonstrated to be efficient catalyst for the aerobic oxidation of alcohols by Kaneda and co-workers.[13] Very recently they have expounded the design of another catalyst *viz.*, monodispersed palladium nanoclusters by the treatment of $Pd_4phen_2(CO)_2(OAc)_4$ with $Cu(NO_3)_2$ as efficient heterogeneous catalyst for the selective oxidation of primary aromatic allylic alcohols using molecular oxygen as the oxidant.[14] This reaction was, however, conducted in acetic acid medium.

Other heterogeneous catalyst systems reported include Ru/CeO_2,[15] $[RuCl_2(p\text{-cymene})]_2$ on activated carbon,[16] tetrapropylammonium perruthenate (TPAP)/MCM-41,[17] Ru-hydroxyapatite,[18] Ru-hydrotalcite,[19] Pd-hydrotalcite.[20] Nevertheless, most of these systems are effective for only activated and benzylic alcohols besides the use of additives such as pyridine in many cases. Herein we report a very effective aerobic oxidation of a variety of both activated and non-activated alcohols to their corresponding carbonyl products using a 1% Pd on MgO heterogeneous catalyst.

Results and discussion

X-Ray diffraction analysis of the calcined catalyst samples show characteristic peaks corresponding only to the support (for example MgO) and show no peaks corresponding to Pd species indicating the amorphous nature of the metallic species. The 1% Pd/MgO reduced catalyst shows a BET surface area of 39 $m^2\ g^{-1}$ and a metal area of 0.72 $m^2\ g^{-1}$ catalyst with a 16% metal dispersion and a crystallite size of 6.9 nm (Table 1). The catalysts Pd/Al_2O_3, Pd/SiO_2 and Pd/Zeolite-β show a relatively lower metal area and a higher crystallite size.

Table 1 Adsorption properties of supported palladium catalysts.

Catalyst	BET surface area/$m^2\ g^{-1}$cat	Metal area/m^2g^{-1}cat	% Dispersion of Pd	Crystallite size/nm
1% Pd/MgO	39	0.72	16	6.9
1% Pd/HT	136	0.94	21	5.3
1% Pd/Al_2O_3	32	0.41	9.2	12.2
1% Pd/SiO_2	240	0.15	3.3	33.0
1% Pd/Zeolite-β	432	0.17	3.7	30.1

Temperature programmed reduction (TPR) studies on the catalyst show multiple reduction peaks (Fig. 1). The peaks at temperatures lower than 150 °C indicate the reduction of the metal (Pd) whereas the peak at higher temperature (> 300 °C) shows the reduction of the support.[21] While the MgO and HT supported palladium catalysts show a high temperature support reduction

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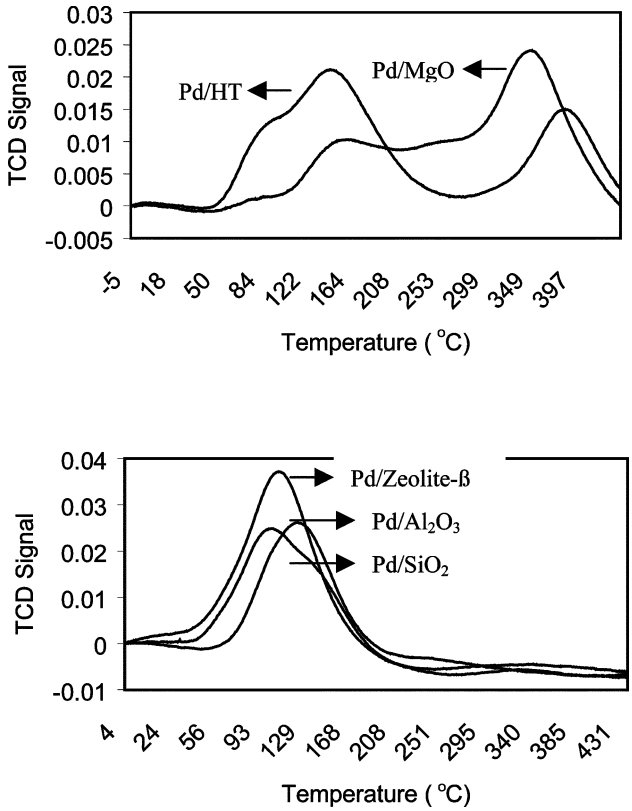


Fig. 1 Temperature programmed reduction (TPR) profiles of different supported palladium catalysts.

peak, no such support reduction is observed for other supports such as zeolite-β, Al_2O_3 or SiO_2. The TPR profiles also reveal that MgO reduces at a lower temperature than HT and the intensity of the high temperature hydrogen absorption peak is greater for MgO than HT. These observations suggest that MgO is a more reducible support than HT whereas other supports like Al_2O_3, SiO_2 and zeolite-β are non-reducible.

Table 2 shows the optimization results of various experimental parameters for the oxidation of cyclopentanol over 1% Pd/MgO catalyst using molecular oxygen. A variety of solvents and other experimental conditions are examined. Trifluorotoluene is found to be the most suitable solvent for the reaction followed by solvents such as cyclohexane (entry 13), toluene (entry 14) and dichloromethane (entry 15). Reactions in dimethyl sulfoxide, benzene, dimethyl carbonate and ethyl acetate are found to be less successful (entries 15–19). There is hardly any reaction in tetrahydrofuran and dioxane (entries 20 & 21). Reaction rate increases with time from 0–24 h. Nevertheless, a reaction time of 8 h is found to be suitable for the optimization studies of other parameters as presented in Table 1. Studies on the effect of temperature on the reaction (entries 3, 8 & 9) and substrate/metal ratio (entries 2, 3 & 4) shows that the conversion increases with temperature and a maximum product is obtained at 90 °C at an alcohol/Pd mol ratio of 133 (entry 9). The reaction has been found to be equally successful even at a 10 fold higher scale (entry 10). Air can also be used instead of molecular oxygen without any significant reduction in activity (entry 11). The reaction rate, however, is drastically reduced when the oxygen atmosphere is replaced by nitrogen (entry 12).

The 1% Pd/MgO catalyst is also found to exhibit good to excellent activity for the oxidation of a variety of alcohols using molecular oxygen as the oxidant at 70 °C as illustrated in Table 3. Even though maximum conversion is obtained at 90 °C for cyclopentanol (Table 1), the reactions of various substrates are studied at a moderate temperature of 70 °C to avoid the formation of other side products especially in the case of primary alcohols. The estimated turnover numbers (TON) have also been given. The selectivity for the corresponding carbonyl product is almost complete with no appreciable formation of any other side products. Even though the best conditions and therefore the maximum conversions obtainable for each individual alcohols are not optimized, the method is found to be useful in the oxidation of various types of alcohols such as primary, secondary, aliphatic, alicyclic, allylic and aromatic alcohols. Both activated and non-activated alcohols are converted to the corresponding carbonyls efficiently and selectively even though activated alcohols such as benzyl alcohol (entry 22), 1-phenylethanol (entry 23) and benzhydrol (entry 24) afford a much higher conversion than the non-activated alcohols such as 2-pentanol (entry 4), 3-pentanol (entry 5), 2-hexanol (entry 7), 3-hexanol (entry 8), 2-octanol (entry 16) *etc*. However, chloro and bromo substituted benzyl alcohols (entries 25–27) are not significantly oxidized due to the competitive reaction of fluorine substitution of the chlorine atoms. The electron withdrawing nature of these halogen substituents may also be responsible for their lower reactivity. This may be the reason for the

Table 2 Oxidation of cyclopentanol over 1% Pd/MgO catalyst using O_2.[a]

Entry	Solvent (conditions)	Solvent quantity/mL	Temperature/ °C	Catalyst amount/g	Conversion (%)	Cyclopentanone selectivity (%)
1	Trifluorotoluene (TFT)	1.5	70	0.01	12	100
2	TFT	1.5	70	0.05	44	100
3	TFT	1.5	70	0.10	50	100
4	TFT	1.5	70	0.20	45	100
5	TFT	1.0	70	0.10	20	100
6	TFT	2.0	70	0.10	46	100
7	TFT	3.0	70	0.10	37	100
8	TFT	1.5	50	0.10	33	100
9	TFT	1.5	90	0.10	69	100
10[b]	TFT	15	70	0.50	49	100
11[c]	TFT (Air)	1.5	70	0.10	45	100
12[d]	TFT (N_2)	1.5	70	0.10	11	100
13	Cyclohexane	1.5	70	0.10	37	100
14	Toluene	1.5	70	0.10	33	100
15	Dichloromethane	1.5	40[e]	0.10	32	100
16	Dimethyl sulfoxide	1.5	70	0.10	18	100
17	Benzene	1.5	70	0.10	14	100
18	Dimethyl carbonate	1.5	70	0.10	12	100
19	Ethyl acetate	1.5	70	0.10	12	100
20	Tetrahydrofuran	1.5	65[e]	0.10	05	100
21	Dioxane	1.5	70	0.10	03	100

[a] Reaction conditions: substrate (1 mmol), 8 h, O_2 atmosphere, stir. [b] 10 fold higher scale (10 mmol substrate). [c] Under air atmosphere. [d] Under N_2 atmosphere. [e] Maximum temperature limited by the boiling point of the solvent.

Table 3 Oxidation of various alcohols over 1% Pd/MgO catalyst using O_2[a]

Entry	Alcohol	Product	Time/h	Conversion (%)	Selectivity (%)	TON
1	2-Propanol	Acetone	8	40	100	43
			20	60	100	64
2	2-Butanol	2-Butanone	8	45	100	48
			20	75	100	80
3	1-Pentanol	Pentanal	8	08	100	09
			20	14	100	15
4	2-Pentanol	2-Pentanone	8	48	100	51
			20	87 (84)	100	93
5	3-Pentanol	3-Pentanone	8	60	100	64
			20	100 (95)	100	106
6	1-Hexanol	Hexanal	8	16	100	17
			20	18	100	19
7	2-Hexanol	2-Hexanone	8	24	100	26
			20	30	100	32
8	3-Hexanol	3-Hexanone	8	45	100	48
			20	51	100	54
9	Cyclohexanol	Cyclohexanone	8	16	100	17
			20	25	100	27
10	1-Methylcyclohexanol	1-Methylcyclohexanone	8	21	100	22
			20	47	100	50
11	2-Methylcyclohexanol	2-Methylcyclohexanone	8	41	100	44
			20	44	100	47
12	4-Methylcyclohexanol	4-Methylcyclohexanone	8	42	100	45
			20	48	100	51
13	4-*t*-Butylcyclohexanol	4-*t*-Butylcyclohexanone	8	51	100	54
			20	65	100	69
14	Cycloheptanol	Cycloheptanone	8	38	100	40
			20	56	100	60
15	1-Octanol	Octanal	8	18	100	19
			20	20	100	21
16	2-Octanol	2-Octanone	8	55	100	59
			20	65	100	69
17	Cyclooctanol	Cyclooctanone	8	58	100	62
			20	60	100	64
18	*exo*-Norborneol	2-Norbornanone	8	33	100	35
			20	58	100	62
19	Isoborneol	Isobornanone	8	56	100	60
			20	75	100	80
20	2-Adamantanol	2-Adamantanone	8	20	100	21
			20	35	100	37
21	1-Dodecanol	1-Dodecanal	8	20	100	21
			20	27	100	29
22	Benzyl alcohol	Benzaldehyde	8	64	100	68
			20	100	92[c]	106
23	1-Phenylethanol	Acetophenone	8	100 (96)	100	106
24	Benzhydrol	Benzophenone	8	100 (96)	100	106
25	3-Chlorobenzyl alcohol	3-Chlorobenzaldehyde	8	03	100	3
			20	05	100	5
26	4-Chlorobenzyl alcohol	4-Chlorobenzaldehyde	8	05	100	5
			20	11	100	12
27	2-Bromobenzyl alcohol	2-Bromobenzaldehyde	8	02	100	2
			20	03	100	3
28	4-Fluorobenzyl alcohol	4-Fluorobenzaldehyde	8	32	100	34
			20	37	100	39
29	5-Norbornene-2-methanol	5-Norbornene-2-carboxaldehyde	8	62	100	66
			20	72	100	77
30	Cinnamyl alcohol	Cinnamaldehyde	2	90	76[d]	96
31	Geraniol	Geranial	4	70	95[e]	74
			8	82	92[e]	87
32	3,5,5-Trimethyl-2-cyclohexene-1-ol	Isophorone	8	68	100	72
			20	75	100	80

[a] Reaction conditions: alcohol (1 mmol), catalyst (0.10 g, 0.0094 mmol Pd), TFT (1.5 mL), 70–80 °C, O_2 balloon, stir. TON = Turnover number = number of moles of product formed per mole of Pd. Values in parenthesis shows the isolated yield. Reaction products were analyzed by GC-MS. Identification of compounds was carried out by standards and GC-MS. Stereochemistry of compounds not identified. [b] Reaction in air. [c] Benzoic acid = 08%. [d] Ethyl benzene = 04%, 2-phenylethanol = 20%. [e] Remaining neral.

lower conversion of 4-fluorobenzyl alcohol (entry 28) than the benzyl alcohol (entry 22). The higher conversion of alkyl substituted cyclohexanols (entries 10–13) than cyclohexanol (entry 9) may also be attributed to the electron donating nature of alkyl groups. Alicyclic alcohols such as cyclopentanol (Table 1), cyclohexanols (entries 9–13), cycloheptanol (entry 14), cyclooctanol (entry 17), *exo*-norborneol (entry 18), isoborneol (entry 19) and 2-adamantanol (entry 20) are also successfully converted to their respective cyclic ketones with good to excellent yield. The lower conversion of cyclohexanol (entry 9) than the other cyclic alcohols may be due to the increased stability of the six-carbon ring structure.[22] It is interesting to note that less reactive primary alcohols such as 1-pentanol (entry 3), 1-hexanol (entry 6), 1-octanol (entry 15) and 1-dodecanol (entry 21) are also selectively oxidized to their respective aldehydes wherein the conversion generally increases with increase in the C-chain length. Oxidation of alkenic

alcohols such as 5-norbornene-2-methanol (entry 29), cinnamyl alcohol (entry 30), geraniol (entry 31) and 3,5,5-trimethyl-2-cyclohexen-1-ol (entry 32) also proceeded readily resulting in the formation of the corresponding enones. This is in contrast to other Pd systems where a large excess of base such as pyridine was required to afford a good conversion.[8]

The catalyst is easy to prepare and can readily be separated from the reaction mixture by simple filtration and recycled successfully without any significant loss of activity and selectivity (Fig. 2). The

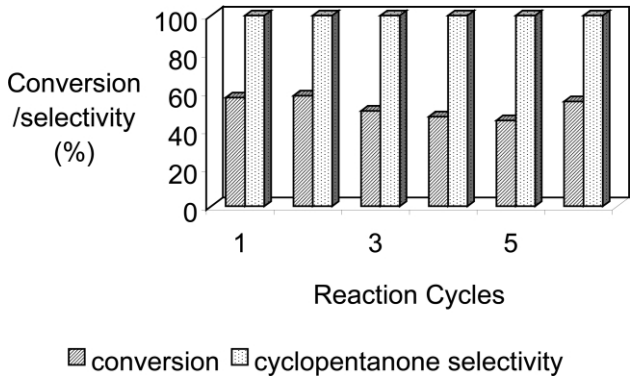


Fig. 2 Recyclability of 1% Pd/MgO catalyst for the oxidation of cyclopentanol using O_2 (reaction conditions: substrate (10 mmol), catalyst (0.50 g), TFT (15 mL), 20 h, stir).

solvent is also recyclable. The repeated use of the catalyst many times reduces its activity, which can, however, be regained by its regeneration (calcination and reduction) for further use.

Other supports such as hydrotalcite (HT), silica, alumina and zeolite-β were also examined (Fig. 3), however, none of them

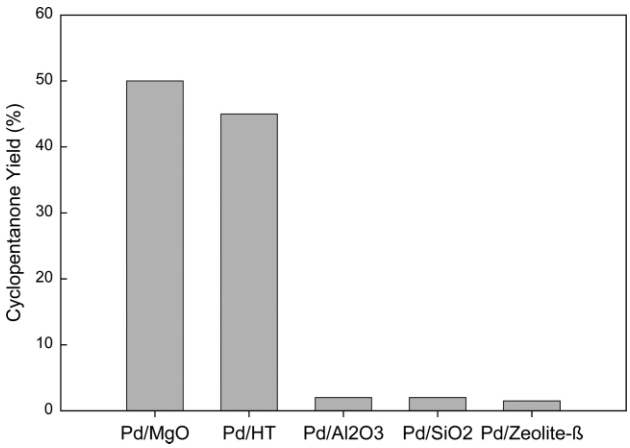


Fig. 3 Comparison of cyclopentanone oxidation using molecular oxygen over different supported palladium catalysts.

except Pd/HT afford any appreciable oxidation activity. Hydrotalcite (another basic material like MgO) supported palladium catalyst also shows comparable performance to that of Pd/MgO. It is also noteworthy here that no multiple organic solvent mixture is used in this oxidation protocol, further adding to its ecofriendly nature. It has also been confirmed that the reaction was not catalyzed by leached metal as another experiment, in which the catalyst is separated by filtration after 4 hours reaction and 30% conversion, does not show any further increase in the conversion value after 8 h of reaction. This also shows that the observed catalysis is clearly heterogeneous in nature. Addition of a free radical trap such as hydroquinone does not alter the activity or selectivity of the reaction indicating the non-radical nature of the reaction mechanism.

Yamaguchi and Mizuno[12] have proposed a reaction mechanism for Ru/Al_2O_3 system involving the formation of Ru-alcoholate intermediate, which undergoes a β-elimination to afford the carbonyl product and Ru^{n+}-hydride. This hydride species is further oxidized by molecular oxygen to form Ru^{n+}-OH. A similar mechanism is envisaged to be operating in this case (Scheme 1) as the reaction of a mixture of primary and secondary alcohols (0.5 mmol each) such as 1-hexanol and 2-hexanol shows a higher reaction rate (14% conversion) for the primary alcohol (1-hexanol) than the secondary alcohol (5% conversion for 2-hexanol) after 8 h of reaction suggesting that a metal–alcoholate species is formed as an intermediate. It is also known that a metal–alcoholate species is formed in the selective oxidation of primary hydroxy groups.[23] The higher reactivity of alkyl substituted alcohols (Table 3, compare entry 9 with entries 10–13) and lower reactivity of halogen-substituted alcohols (Table 3, compare entry 22 with entries 25–28) also support this mechanism. The electron donating alkyl groups increase the nucleophilicity of the alcohol and hence could accelerate the formation of the metal alcoholate intermediate whereas electron withdrawing substituents could inhibit its formation. TPR studies reveal that MgO and HT are reducible supports and therefore the reduced support species could have acted as a ligand for palladium metal and thereby helped in the formation of this metal–alcoholate species. This also explains the negligible reactivity observed for Pd/Al_2O_3, Pd/SiO_2 and Pd/zeolite-β catalysts. Further, formation of Pd-hydride is known to be a highly facile reaction.[24] In addition, no significant reaction is observed when a calcined, un-reduced catalyst is used for the reaction. It is also observed that a mixture of acetophenone (1 mmol) and 2-propanol (2 mL) under N_2 atmosphere affords equimolar amounts of 1-phenylethanol and acetone indicative of a transhydrogenation reaction which further supports the formation of a metal hydride species. The exact role of the solvent is not clear here and may be related to its solvation ability facilitating a redox cycle between different Pd oxidation states during the reaction. The reaction rate is found to be dependent on the oxygen pressure (not shown here) as well as on the Pd concentration (Table 2, entries 1–4) suggesting that the oxidation of Pd(0) by dioxygen may be the rate-limiting step.

Conclusions

In summary, 1% Pd/MgO catalyst is found to be a highly active heterogeneous catalyst for the oxidation of alcohols using molecular oxygen at a moderate temperature of 70–80 °C without the presence of any added base or excess organic solvents. This relatively cheap catalyst can be prepared easily and can be readily separated from the reaction mixture by simple filtration and reused without any appreciable loss of activity and product selectivity. The activity of the catalyst is ascribed to the reducible nature of the support, which can act as a ligand for the metal that helps in the oxygen transfer through the formation of a metal–alcoholate intermediate.

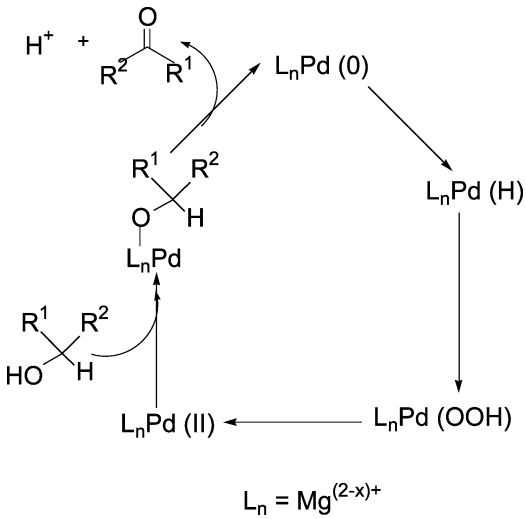
Experimental

Materials

All the alcohol substrates, $PdCl_2$ and $Mg(NO_3)_2{\cdot}6H_2O$, Al_2O_3, SiO_2, hydrotalcite (HT) were obtained from Aldrich Chemical Company and used as received without any further purification. Zeolite-β (Si/Al = 150) was obtained from Zeolist International (USA) and used as received.

Catalyst preparation

Magnesia (MgO) was prepared by calcination of $Mg(NO_3)_2{\cdot}6H_2O$ in air at 450 °C for 12 h. Magnesia supported Pd catalyst containing 1 wt% Pd was prepared by wet impregnation of the MgO powder using a 0.1 M acidified (dilute HCl) solution of $PdCl_2$. After impregnation, the catalyst was dried under vacuum at 110 °C overnight, calcined in air at 450 °C for 6 h and reduced in flowing hydrogen at 400 °C for 6 h before being cooled to room temperature and stored in a vacuum desiccator. Other supported Pd catalysts containing 1 wt% metal such as Pd/Hydrotalcite (HT), Pd/Al_2O_3,



Scheme 1

Pd/SiO_2 and Pd/zeolite-β (Si/Al = 150) were also prepared by the wet impregnation of respective support materials for comparison studies.

Catalyst characterization

Single point BET surface and the metal area of the catalyst were determined by N_2 adsorption at 77 K and CO chemisorption at room temperature respectively using a Micromeritics Autochem II (Model 2920) equipment. The same instrument was used for determining the metal surface areas, percentage dispersion of the metal and crystallite size of the catalysts by CO chemisorption at room temperature. A stoichiometry of Pd/CO = 1 and a Pd surface density of 1.27×10^{19} atoms m^{-2} were assumed for determining the metal surface area of the catalysts.[24] X-Ray diffraction analyses of the catalyst samples were carried out on a Siemens D5000 diffractometer with Cu-Kα radiation running at 40 KV/30 mA in the 2θ range 10° to 80° with a step size of 0.05°.

Temperature programmed reduction (TPR) studies on the catalysts were conducted using a Micromeritics Auto Chem. II Instrument (Model 2920). The calcined catalyst samples were reduced by a 10% H_2/Ar mixture in a temperature programmed reduction protocol from 0 to 450 °C at a rate of 10 °C min^{-1}. A liquid nitrogen containing cryocooler with temperature controller was used to bring the sample temperature to 0 °C.

Alcohol oxidation

Oxidation of alcohols was conducted in the liquid phase in a 25 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirrer. In a typical reaction procedure, 0.10 g catalyst was mixed with 1.5 mL of trifluorotoluene (TFT) at room temperature for 5 minutes. To this mixture was added 1 mmol of the alcohol and the suspension was purged with oxygen. The mixture was then heated to 70–80 °C under stirring in the presence of oxygen for a specified time. Samples were collected at different reaction intervals and analyzed by a Hewlett-Packard 6890 Gas Chromatograph using a HP-5 5% phenylmethylsiloxane capillary column (30 m × 320 μm × 0.25 μm) and a quadrupole mass filter equipped HP 5973 mass selective detector. Quantification of the oxygenated products was obtained from the peak area ratios of the reactant and corresponding products. This method was verified by comparing with the isolated yields obtained in some cases and also with the quantification results obtained using a multi-point calibration curve for some of the alcohols *viz.*, 2-pentanol, cyclopentanol, 1-hexanol, 2-hexanol, 3-hexanol, cyclohexanol, 1-phenylethanol, and benzyl alcohol which were found to be satisfactory with the quantification values calculated from the peak area ratio method.

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PAPER

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Biodegradable ionic liquids: Part I. Concept, preliminary targets and evaluation

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The design, preparation and evaluation of biodegradable ionic liquids containing ester or amide groups in the alkyl side chain are presented. Factors improving the biodegradation of surfactants were successfully applied to ionic liquids. These novel ionic liquids can be prepared from readily available starting materials in high yield. The introduction of a group susceptible to enzymatic hydrolysis greatly improves the biodegradation (OECD 301D 'Closed Bottle Test') compared with the commonly used dialkylimidazolium ionic liquids, bmimBF_4 and bmimPF_6. For the 3-methyl-1-(alkyloxycarbonylmethyl)imidazolium bromide series, the greatest biodegradation was observed when alkyl = butyl, pentyl, hexyl and octyl. The corresponding amide analogs proved to be poorly biodegradable.

Introduction

Ionic liquids (ILs) have been the subject of considerable interest as media for a wide range of synthetic and analytical processes.[1,2] They are considered in a 'green chemistry' context due to their low vapour pressure, ease of recovery facilitating recycling[3] and applicability to catalytic processes.[4] ILs possess a number of interesting properties such as high polarity and ionic conductivity, a wide window of electrochemical potential and excellent chemical and thermal stability. However, it is this stability that has lead us to question the potential for ILs to accumulate in the environment.[5] When the ionic liquid has served its operational use, disposal becomes an issue. As the pressure to reduce incineration and landfill waste increases the requirement for chemicals which are biodegradable increases.[6] Within the field of green chemistry it is unacceptable to produce large quantities of waste which have high ecotoxicity or biological activity.[7] Seddon reported the first industrial process where ionic liquids were used on a multi-tonne scale.[8] As ionic liquids advance from academic curiosities the need to study their toxicity and biodegradation is paramount.

Toxicity to humans and other organisms has obvious significance, while toxicity to micro organisms has the potential to limit biodegradation. Like biodegradability, the assessment of IL toxicity is only now being addressed. There have been a few articles stating that there is a need to test the biodegradation of ionic liquids[5] however experimental results to ascertain these properties have been surprisingly lacking.

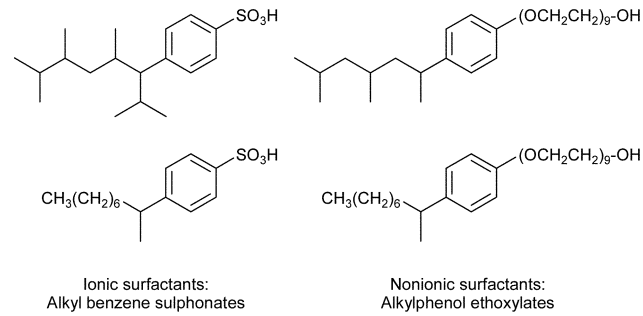
In a preliminary communication[9] we reported the first investigation into the biodegradability of the dialkylimidazolium ionic liquids. We chose the dialkylimidazolium ILs as a starting point and incorporated features which have been found to improve the biodegradability of other classes of compounds such as surfactants. Since this initial disclosure of our findings no biodegradation data on ILs has been published, although a few preliminary toxicology results have been reported.

Jastorff and co-workers subsequently reported a theoretical environment risk analysis on a test set of dialkylimidazolium ILs.[10] This multidimensional analysis was based on five ecotoxicological indicators; release, spatiotemporal range, bioaccumulation, biological activity and uncertainty. The current lack of detailed experimental data on the biodegradability of ILs complicated predictions on bioaccumulation and spatiotemporal range and resulted in a high uncertainty level.

Our inspiration for this work came from the development of biodegradable surfactants. We now report our progress towards preparing a readily biodegradable ionic liquid.

History of surfactants

The development of biodegradable surfactants[11] has been of significant commercial interest since the 1940's when synthetic surfactants were developed as a replacement for soap in many laundry products. Tetrapropylene alkyl benzene sulfonates (TPBS)[12] were manufactured extensively but due to their poor biodegradation lead to major problems in sewage treatment and contamination of river waters.[13]



Modification of the highly branched alkyl chain to the linear secondary alkyl group gave linear alkylbenzene sulfonate surfactants (LAS) with greatly improved biodegradation.[14] In the 1960's TPBS were phased out and replaced with LAS in the United States.[12]

On further examination of the literature regarding biodegradation of surfactant compounds we noticed a close resemblance between many quaternary ammonium compounds as well as surfactants based around an imidazolium core. These derivatives have a striking resemblance to the structure of many of the most important ILs prepared to date and we felt that much of the work developing biodegradable surfactants would be relevant to the design of a biodegradable ionic liquid. In particular is the development of biodegradable surface active quaternary ammo-

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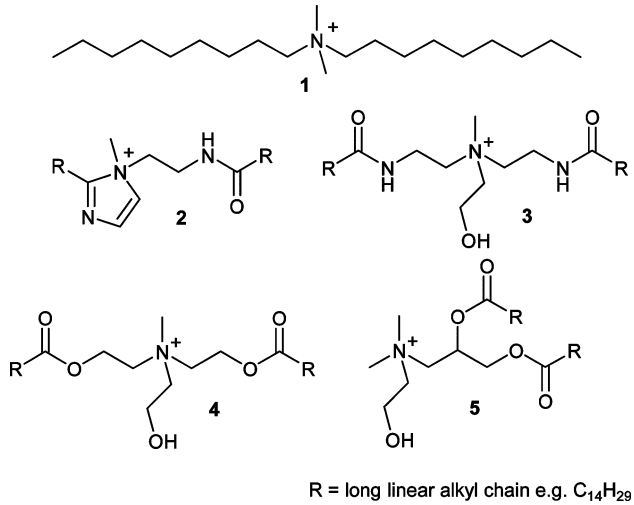
nium compounds (QACs). The most popular QAC used initially was the dialkyl dimethyl ammonium salt (**1**), however the biodegradation of **1** in aquatic sediments is low and this coupled to its ecotoxicity has led to its replacement by dialkyl QACs based on the imidazolium and ethoxylated ethanaminium QACs (compounds **2** and **3**).[15] The presence of the amide bonds led to improved biodegradation properties due to an extra hydrolysis degradation pathway. Ester derivatives (**4** and **5**) and related compounds have also been prepared and show good biodegradation.[15,16c]



Design

Boethling[15] identified three factors which are important in the design of biodegradable compounds; (i) the presence of potential sites of enzymatic hydrolysis (for example, esters and amides), (ii) the introduction of oxygen in the form of hydroxyl, aldehyde or carboxylic acid groups, and (iii) the presence of unsubstituted linear alkyl chains (especially ≥4 carbons) and phenyl rings, which represent possible sites for attack by oxygenases. These principles have been followed during the development of biodegradable surfactants.[16–18]

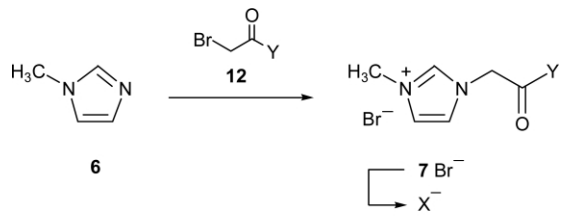
Not all of these structural features are appropriate for ILs. The incorporation of oxygen containing functional groups such as alcohols, aldehyde and carboxylic acids would severely limit the ILs usefulness as reaction media, while the introduction of phenyl groups is known to produce compounds with elevated melting points.[19] As a result, we chose to prepare dialkylimidazolium ILs with ester or amide functionality in one of the side chains. It was deemed important to limit branching in the side chains so only linear alkyl groups attached to the ester and amide were chosen. An important feature of this design is that although there are a very large number of possible ionic liquids that can theoretically be prepared based on the imidazolium core, within the limits suggested in the design segment of this paper, the number of potential hot targets is reasonably small. The incorporation of an ester or amide group was postulated to be a balance between reduced chemical stability and increased biodegradability.

A major concern at the design stage of this project was the physical properties of these modified imidazolium ionic liquids. Points which needed to be addressed were 1) melting points and 2) solubility and the effect of the ester/amide alkyl length on these properties. If the inclusion of an ester or amide bond into the side chain lead to increased order and crystallinity these target ionic liquids would only be liquids at elevated temperatures. A key property of PF_6 and NTf_2 based ILs is their hydrophobic nature. If the hydrogen bonding possible with the ester or amide in the side chain was sufficient to remove this hydrophobic character then their use as alternatives for $BmimPF_6$ and $BmimNTf_2$ would be compromised.

Results and discussion

Syntheses of the ILs described in this manuscript were based on standard approaches for the preparation of imidazolium ILs.[19,20] This process involved alkylation of methyl imidazole with the appropriate ester or amide derivative of bromoacetic acid.

The esters or amide derivatives of bromoacetic acid were either commercially available or formed in one step *via* the reaction of bromoacetyl bromide with the appropriate alcohol or amine.[21] An advantage of this route is that a wide range of ester and amide side chains can be prepared easily. For ionic liquids with anions other than bromide, a metathesis reaction was employed to introduce the counter ion of choice (Scheme 1). Metathesis of the halide anion to



Y =	X = Br	X = BF_4	X = PF_6	X = NTf_2	X = $N(CN)_2$
OMe	**[7a]**	**8a**	**[9a]**	**10a**	--
OEt	**7b**	**8b**	**9b**	**10b**	**11b**
O^{n}Pr	**7c**	**8c**	**9c**	**10c**	--
O^{n}Bu	**7d**	--	--	--	--
O^{n}Pt	**7e**	--	--	--	--
O^{n}Hex	**7f**	**8f**	**9f**	**10f**	--
O^{n}Oct	**7g**	**8g**	**9g**	**10g**	--
NH^{n}Bu	**[7h]**	**8h**	**[9h]**	--	--
NMe^{n}Bu	**7i**	**8i**	**[9i]**	**10i**	**11i**
NEt_2	**[7j]**	**8j**	**[9j]**	**[10j]**	--

Scheme 1 IL synthesis [compounds in parentheses are solids at room temperature].

BF_4^-, PF_6^-, NTf_2^- and $N(CN)_2^-$ proceeded in good to excellent yield. BF_4^- ionic liquids were prepared by counter-ion exchange with $NaBF_4$ in acetonitrile. Removal of the solvent gave IL contaminated with trace $NaBF_4$ as shown by ^{19}F NMR. Clean samples could be isolated after a simple work-up. Compound **9h** was prepared by counter-ion exchange with KPF_6 in acetonitrile. PF_6^- and NTf_2^- based ionic liquids (except **9h**) were prepared by mixing an aqueous solution of the bromide salt with KPF_6 or $LiNTf_2$, respectively. The hydrophobic IL phase was separated, washed and residual water removed under high vacuum to give pure samples. $N(CN)_2^-$ ionic liquids were prepared by counter-ion exchange with $NaN(CN)_2$ in acetonitrile analogously to the BF_4^- ionic liquid examples.[22]

Imidazolium salts with ester containing side chains were generally found to be liquids a room temperature; 21 of the 23 ester containing compounds proved to be liquids at room temperature, though compound **8a** and all ILs with the bromide counter ion were viscous at room temperature. ILs with amide containing side chains were less likely to be room temperature ionic liquids; 6 of the 12 examples prepared were solids at room temperature. The secondary amide derivatives **7h** and **9h** were solids, presumably due to increased intermolecular forces resulting from H-bonding. Imidazolium salts with *N*,*N*-diethyl amide side chains (compounds **7j**, **9j** and **10j**) were solids, while *N*-butyl-*N*-methyl amides (compounds **7i**, **8i**, **10i**, **11i**) were liquids at room temperature.

There are two main features of the *N*-butyl-*N*-methyl amides (**7i–11i**) which affect their macroscopic properties. Firstly, the unsymmetrical environment around the nitrogen of the amide (*cf.* with solid *N*,*N*-diethyl amide examples **7j**, **9j** and **10j**), as symmetry has previously been reported as important regarding melting point.[1,23] Secondly, the *N*-butyl-*N*-methyl amides (**7i–11i**) prepared exist as a 1 : 1.3 mixture of rotomers around the amide bond and it

is proposed that this isomeric mixture leads to a depression of the melting point.[24]

All the ionic liquids prepared in this paper have melting points below 100 °C, a benchmark which has been set to determine their classification as ILs.[8]

All PF_6 and NTf_2 ILs containing an ester or amide in the side chain were hydrophobic except for the secondary amide derivative **9h**. The introduction of the polar functional group did not significantly affect the water solubility of the IL. The use of PF_6 ionic liquids outside of the research laboratory has been questioned due to their propensity to evolve HF if not stored and handled carefully.[5c] The authors note that for the ionic liquids presented within, HF formation would lead to decomposition. The PF_6 ILs were prepared to study their properties however their suitability as industrial chemicals seems limited.

Biodegradation testing data

Two samples (**7b** and **8b**) were evaluated in a commercial laboratory[25] using a modified Sturm test (OECD 301B). In this test, the chemical being evaluated is added to aerobic aqueous medium inoculated with wastewater micro organisms and the evolution of CO_2 is measured for a defined period and reported as a percentage of the theoretical maximum. The Organisation for Economic Cooperation and Development (OECD) has approved this modified Sturm test as one means of assessing biodegradability.[26] Compounds which evolve more than 60% of the total CO_2 are considered to be a pass (OECD 301B). This test was applied to two dialkylimidazoles with ester containing side chains (compounds **7b** and **8b**) and bmimPF_6. All three examples appeared to be relatively close to the pass level (**7b** = 48%, **8b** = 59% and bmimPF_6 = 60%). After these preliminary results a more comprehensive biodegradation study was initiated.

A larger panel of ionic liquids with functionalised side chains were evaluated using the 'Closed Bottle Test' (OECD 301D).[27] In this test the IL was added to an aerobic aqueous medium inoculated with wastewater micro organisms and the depletion of dissolved molecular oxygen was measured for a defined period of time and reported as a percentage of the theoretical maximum. Duplicate bottles of each series were analysed at the start of the test for dissolved oxygen and the remaining bottles were incubated at 20 °C±1 °C in the dark. Bottles of all series were withdrawn in duplicate for dissolved oxygen analysis over the 28-day incubation period. A control with inoculum, but without test chemicals was run in parallel for the determination of oxygen blanks. Sodium *n*-dodecyl sulfate (SDS) was used as reference substance. Compounds which reached a biodegradation level higher than 60% are referred to as readily biodegradable. Readily biodegradable has been defined as "an arbitrary classification of chemicals which have passed certain specified screening tests for ultimate biodegradability; the conditions in these tests are so stringent – relatively low density of non-acclimatized bacteria, relatively short duration, absence of other compounds – that such chemicals will rapidly and completely biodegrade in aquatic environments under aerobic conditions".[11]

The data showed significant differences between the biodegradability of the ionic liquids incorporating an ester group and those containing an amide linker in the side chain. ILs incorporating different alkyl esters (from methyl to octyl) in the side chain presented similar biodegradation profiles (Fig. 1).

It appears that the biodegradation increased slightly with increasing alkyl chain length for the lowest alkyl esters and later remained relatively constant (Fig. 2). Regarding the structure of ionic liquids containing an ester group in the chain side, it seems reasonable that the biodegradation of these molecules may be initiated by enzymatic cleavage of the ester bond leading to the separation of the imidazolium fragment and the corresponding primary alcohol that can readily be metabolized *via* the pathway of fatty acid β-oxidation.[17]

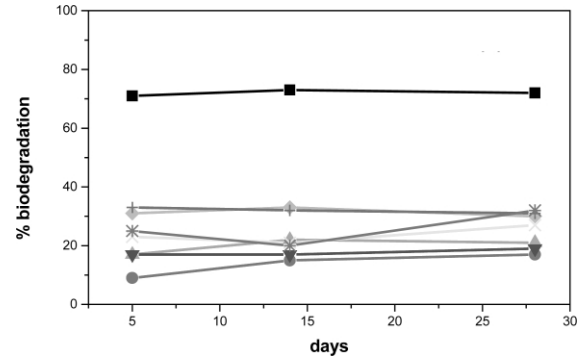


Fig. 1 Biodegradation curves of the ionic liquids containing an ester group in the cation side chain (3-methyl-1-(alkyloxymethylcarbonyl)-imidazolium bromides): Me (●), Et (▲), Pr (▼), Bu (◆), Pent (+), Hex (×), Oct (*); reference substance: SDS (■).

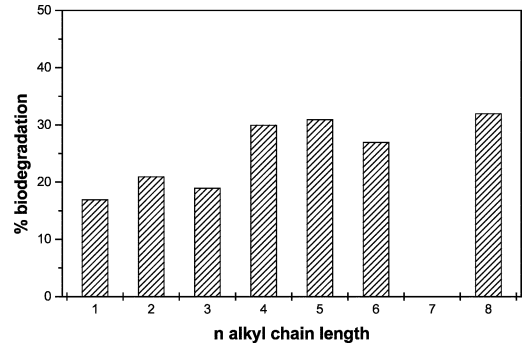


Fig. 2 Biodegradation (28-day period) of 3-methyl-1-(alkyloxycarbonylmethyl)imidazolium bromides as a function of the number of carbon atoms of the alkyl chain.

No evidence for some extent of ultimate biodegradation was detected for ILs containing an amide linker in the side chain (Fig. 3).

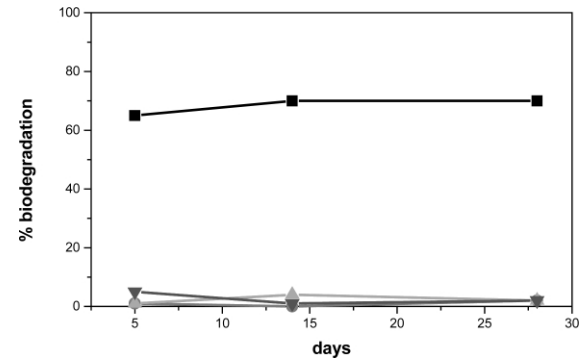


Fig. 3 Biodegradation curves of ionic liquids incorporating an amide group in the cation side chain: N(Et_2) (●), N(BuH) (▲), N(BuMe) (▼); reference substance: SDS (■).

The two most widely used ionic liquids in academia and industry are based on the 1-*n*-butyl-3-methylimidazolium core. *i.e.* bmimBF_4 and bmimPF_6. These ILs, with bmimBr, were also tested for biodegradation by the 'Closed Bottle Test' (OECD 301D). BmimBF_4 and bmim PF_6 were found to show no biodegradation (0%) in this test. BmimBr was found to have negligible biodegradation as measured by the Closed Bottle Test (1%). Comparison of compounds **7a–j** and bmimBr shows that the incorporation of the ester functional group has greatly improved the biodegradation properties of the IL. A more detailed study of counter-ion effect on biodegradation is in progress.

The results obtained from the Closed Bottle Test differed from those obtained using the modified Sturm test, with the latter

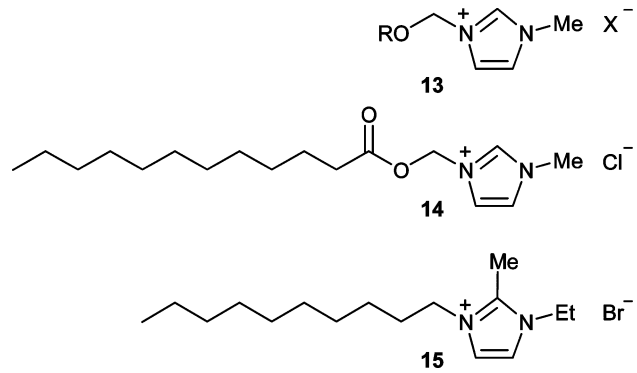
indicating higher levels of biodegradation. Such differences may be related to the inoculum that was used. Biodegradation is intimately bound up with bacterial growth, nutrition and metabolism, and factors which affect these bacterial functions will also affect the biodegradability assessments. The nature and quantity of the inoculum play an important role in biodegradability assessment; the inoculum is probably the biggest single factor in the success of the batch test. Although the Closed Bottle and modified Sturm test have a number of similarities, the inoculum cell densities in these tests methods vary considerably (Closed Bottle Test; 10^1–10^3 cells mL^{-1}, modified Sturm test; 10^4–10^6cells mL^{-1}). The bacterial cell density in the medium determines, to a large extent, the length of the lag period and also whether sufficient test substance is degraded within the duration of the test. If the number of cells capable of degrading the test substance is relatively high, the density will soon reach a value which makes a significant reduction in the concentration of the substance. However, when the initial cell density is relatively low, the lag period before a significant density is reached may be longer than the period of the test (28 days). Thus, the large differences found in the extent of ultimate biodegradation applying these two biodegradation methods could be reasonably attributed to significant variability in cell density.

The biodegradation data should be interpreted with caution taking into account the features both of the biodegradation test applied as well of the chemicals studied. Screening methods have been used in many studies on the biodegradability of quaternary ammonium compounds, namely surfactants such as alkyltrimethyl ammonium salts and benzylalkyldimethyl ammonium salts.[28,29] It has been found that degradation rates of these compounds in screening methods significantly underestimated the rate and the extent of degradation occurring in natural environmental systems.[30,31] Since imidazolium compounds are similarly charged ammonium ion-species similar results would be expected.

The toxicity of the ionic liquids may also have an negative impact on their biodegradation. Many quaternary ammonium salts are potential biocides and could inhibit growth of micro organisms capable of degrading quaternary ammonium salts.[32–35] Ranke *et al.*[36] recently conducted the first comprehensive study on the biological effects of dialkylimidazolium ionic liquids. Cytoxic effects of IL were determined against two mammalian cell lines (the promyeloctic leukaemia rat cell line IPC-18 and the rat glioma cell line C6) while acute toxicity was measured using a luminescent bacteria (*Vibrio fischeri*) assay. In general the toxicity of the ILs was found to be some orders of magnitude lower than that of the conventional solvents such as acetone, acetonitrile, methanol and methyl *tert*-butyl ether. The length of the alkyl chains was found to influence the toxicity of the dialkylimidazolium ILs, with longer chain lengths proving to be more toxic. A search of the literature shows that the biological properties of these biocides is related to their long alkyl chain length.[37,38]

The anti-microbial activity of a series of 3-alkoxymethyl-1-methylimidazolium ionic liquids (**13**, R = C_3H_7–$C_{16}H_{33}$, X = Cl, BF_4, PF_6) has also been investigated.[37] ILs with shorter alkoxy substituents lacked activity against cocci, rods and fungi, while those with longer alkoxy chains (> 10 carbon atoms) proved to be very active. These findings have implications for the use of such IL as media for biotransformations as well as their degradation by micro organisms. A study of soft antimicrobials including 1-[(*n*-dodecanoyloxy)methyl]-3-methylimidazolium chloride (**14**) by Bodor *et al.* showed that the long chain ester derivatives of methyl imidazole (including **14**) show effective antimicrobial activity at ppm concentrations.[39] Similarly, other alkyl substituted imidazolium compounds (*e.g.* **15**) have also been found to possess biological activity.[40]

Therefore, the biodegradation results found could be related to the inhibitory effects of the quaternary ammonium salts on the bacterial populations. In light of these results, further investigations on biodegradability and potential toxicity of ionic liquids should be carried out.



Conclusions

ILs containing an ester in the side-chain were generally found to be liquids at room temperature, independent of the counter-ion. The amide derivatives were solids at room temperature except for the *N*-butyl-*N*-methyl series. NTf_2 and PF_6 ILs containing an ester in the side chain exhibited the same hydrophobic character as bmimNTf_2 and bmimPF_6.

The Bmim derived ILs and examples containing an amide in the side chain were found to show poor to negligible biodegradation as measured by the Closed Bottle Test (OECD 301D). The incorporation of an ester in the side chain resulted in a significant increase in biodegradation. Esters of type **7** with an alkyl chain length of $\geq$4 proved to be the most biodegradable. It is postulated that this improved biodegradation is due in part to an enzymatic hydrolysis step which initiates a pathway to further breakdown products. Significant enhancement in the biodegradation of methylimidazolium ILs has been achieved. The factors which improved the biodegradation of surfactants have successfully been applied to ionic liquids.

Experimental

Methyl bromoacetate, ethyl bromoacetate, propyl bromoacetate were purchased from Aldrich and used without further purification. Butyl bromoacetate, pentyl bromoacetate, hexyl bromoacetate, octyl bromoacetate, *N*,*N*-diethyl-2-bromo-acetamide, *N*-butyl-2-bromoacetamide and *N*-butyl-*N*-methyl-2-bromoacetamide were prepared as described below, and purified by distillation. Ethyl chloroacetate was purchased from Fluka and used without further purification. 1-Methylimidazole (99%, Aldrich) was distilled before use to remove impurities detrimental to all ILs prepared. All organic solvents were dried and distilled before use. ILs were washed with distilled water. 3-Methyl-1-(methoxycarbonylmethyl)imidazolium bromide (**3a**) was prepared according to the literature [mp = 131–133 °C].[19] 1-*n*-Butyl-3-methylimidazolium BF_4, PF_6 and NTf_2 were prepared according to the literature. All NMR spectra of ILs were recorded in CD_3CN (Aldrich 15,180–7, 99.8 atom %D) on a Bruker Avance DPX 300 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75.4 MHz respectively. NMR spectra of the ester and amide derivatives of bromoacetic were recorded in $CDCl_3$. Melting points are uncorrected. All room temperature ionic liquids were placed in the fridge (2 °C) and freezer (−18 °C) to further evaluate their melting points. Unless indicated in the experimental data below (see **8g** and **9g**) all the room temperature ionic liquids did not crystallise at −18 °C. However, the viscosity of the ionic liquids at this temperature was significantly increased. A study of glass transition temperatures was not attempted with these materials. Determination of the physical properties of the ionic liquids prepared is still in progress (*e.g.* solubility, thermal stability, viscosity, density and stability to hydrolysis[41]) and will be reported in due course.

3-Methyl-1-(ethoxycarbonylmethyl)imidazolium bromide (7b)

To a stirred solution of 1-methylimidazole (4.1 g, 4.0 mL, 50 mmol) in THF (50 mL) at −5 °C under a nitrogen atmosphere was added dropwise ethyl bromoacetate (10.0 g, 6.7 mL, 60 mmol). The reaction mixture was stirred vigorously at −5 °C for 1 h, then at rt for 3 h. The THF top phase was decanted and the IL washed with diethyl ether (3 × 10 mL), then residual solvent removed *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous hygroscopic oil in 98% yield (12.2 g, 49 mmol). ^{1}H NMR (300 MHz, CD_3CN) 9.38 (s, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 5.30 (s, 2H), 4.23 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz) δ 167.80, 138.72, 124.82, 124.10, 63.23, 51.06, 37.40, 14.63. MS (ESI): *m*/*z*, 169.1 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(propoxycarbonylmethyl)imidazolium bromide (7c)

This compound was prepared analogously to **7b** using 1-methylimidazole (2.11 g, 2.05 mL, 25 mmol) and propyl bromoacetate (5.46 g, 3.90 mL, 30 mmol) to give a clear viscous hygroscopic oil in 96% yield (6.31 g, 24 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 9.57 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 5.42 (s, 2H), 4.10 (q, J = 7.0 Hz, 2H), 3.94 (s, 3H), 1.62 (tq, J = 7.0, 7.0 Hz, 2H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.93, 138.89, 124.81, 124.40, 68.73, 51.08, 37.40, 22.68, 10.75. MS (ESI): *m*/*z*, 183.1 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(butoxycarbonylmethyl)imidazolium bromide (7d)

This compound was prepared analogously to **7b** using 1-methylimidazole (3.86 g, 3.75 mL, 47 mmol) in diethyl ether (50 mL) and butyl bromoacetate (11.0 g, 56.4 mmol) to give a clear viscous hygroscopic oil in 98% yield (12.75 g, 47 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 9.44 (s, 1H), 7.66 (s, 1H), 7.53 (s, 1H), 5.33 (s, 2H), 4.18 (t, J = 7.0 Hz, 2H), 3.93 (s, 3H), 1.62 (tt, J = 7.5, 7.5 Hz, 2H), 1.38 (tt, J = 7.5, 7.5 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.58, 138.76, 124.66, 124.23, 66.94, 66.20, 50.90, 37.16, 31.15, 19.63, 13.89. MS (ESI): *m*/*z*, 197.2 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(pentoxycarbonylmethyl)imidazolium bromide (7e)

This compound was prepared analogously to **7b** using 1-methylimidazole (4.93 g, 4.78 mL, 60 mmol) in diethyl ether (50 mL) and pentyl bromoacetate (15.0 g, 71.8 mmol) to give a clear viscous hygroscopic oil in 97% yield (16.98 g, 58 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 9.49 (s, 1H), 7.69 (s, 1H), 7.55 (s, 1H), 5.36 (s, 2H), 4.16 (t, J = 7.0 Hz, 2H), 3.94 (s, 3H), 1.61 (tt, J = 7.5, 7.5 Hz, 2H), 1.38–1.28 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.56, 138.75, 124.62, 124.18, 67.16, 50.87, 37.13, 28.76, 28.48, 22.84, 14.17. MS (ESI): *m*/*z*, 211.1 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(hexoxycarbonylmethyl)imidazolium bromide (7f)

To a stirred solution of 1-methylimidazole (2.11 g, 2.05 mL, 25 mmol) in diethyl ether (25 mL) at −5 °C under a nitrogen atmosphere was added dropwise hexyl bromoacetate (6.70 g, 5.31 mL, 30 mmol). The reaction mixture was stirred vigorously at −5 °C for 1 h, then at rt for 3 h. The diethyl ether top phase was decanted and the IL washed with diethyl ether (3 × 10 mL) then residual solvent removed *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous hygroscopic oil in 92% yield (7.01 g, 23.0 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 9.49 (s, 1H), 7.69 (s, 1H), 7.56 (s, 1H), 5.36 (s, 2H), 4.15 (t, J = 7.0 Hz, 2H), 3.93 (s, 3H), 1.67–1.57 (m, 2H), 1.40–1.25 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.95, 139.03, 124.95, 124.54, 67.51, 51.20, 37.50, 32.32, 29.36, 26.35, 23.48, 14.60. MS (ESI): *m*/*z*, 225.2 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(octoxycarbonylmethyl)imidazolium bromide (7g)

This compound was prepared analogously to **7f** using 1-methylimidazole (0.84 g, 0.82 mL, 10.3 mmol) and octyl bromoacetate (3.01g, 12.0 mmol) to give a clear viscous hygroscopic oil in 95% yield (3.26 g, 9.8 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 9.41 (s, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 5.32 (s, 2H), 4.17 (t, J = 7.0 Hz, 2H). 3.94 (s, 3H), 1.70–1.60 (m, 2H), 1.40–1.20 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.97, 139.08, 125.00, 124.59, 67.58, 51.23, 37.52, 32.84, 30.23, 30.18, 29.48, 26.75, 23.68, 14.73. MS (ESI): *m*/*z*, 253.3 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(*N*-butylcarbamoylmethyl)imidazolium bromide (7h)

This compound was prepared analogously to **7f** using 1-methylimidazole (0.42 g, 0.41 mL, 5.0 mmol) and *N*-butyl-2-bromoacetamide (1.16 g, 6.0 mmol) to give an oil in 94% yield (1.30 g, 4.7 mmol). The oil slowly crystallised at room temperature. ^{1}H NMR (300 MHz, CD_3CN) δ 9.11 (s, 1H), 8.39 (bs, 1H, NH), 7.56 (s, 1H), 7.45 (s, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 3.15 (q, J = 7.0 Hz, 2H), 1.52–1.40 (m, 2H), 1.40–1.37 (m, 2H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz) δ 166.12, 138.89, 124.99, 124.58, 52.70, 40.48, 37.62, 32.55, 21.28, 14.57. MS (ESI): *m*/*z*, 196.1 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)-imidazolium bromide (7i)

To a stirred solution of 1-methylimidazole (821 mg, 0.80 mL, 10 mmol) in THF (15 mL) at −5 °C under a nitrogen atmosphere was added dropwise *N*-butyl-*N*-methyl-2-bromoacetamide (2.50 g, 12 mmol, 1 : 1.3 mixture of isomers) in THF (5 mL). The reaction mixture was stirred vigorously at −5 °C for 1 h, then at rt for 48 h. The THF top phase was decanted and the IL washed with THF (2 × 5 mL), then residual solvent removed *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous hygroscopic oil in 95% yield (2.76 g, 9.51 mmol). * denotes both isomers. ^{1}H NMR (300 MHz, CD_3CN) δ 8.78 (s, 1H, minor), 8.74 (s, 1H, major), 7.43–7.35 (m, 2H*), 5.22 (s, 2H, major), 5.19 (s, 2H, minor), 3.90 (s, 3H*), 3.37 (t, J = 7.0 Hz, 2H, major), 3.30 (t, J = 7.0 Hz, 2H, minor), 3.02 (s, 3H, major), 2.92 (s, 3H, minor), 1.70–1.25 (m, 4H*), 0.99 (t, J = 7.0 Hz, 3H, minor), 0.93 (t, J = 7.0 Hz, 3H, major). ^{13}C (75 MHz) δ 165.85 (major), 165.53 (minor), 138.89 (minor), 138.72 (major), 125.01 (minor), 124.91 (major), 123.75 (minor), 123.72 (major), 51.70 (major), 51.33 (minor), 49.64 (minor), 48.53 (major), 37.19*, 34.96 (major), 34.24 (minor), 30.86 (minor), 29.94 (major), 20.69 (minor), 20.58 (major), 14.25*. MS (ESI): *m*/*z*, 210.2 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(*N*,*N*-diethylcarbamoylmethyl)imidazolium bromide (7j)

This compound was prepared analogously to **7b** using 1-methylimidazole (1.05 g, 1.02 mL, 12.8 mmol) and *N*,*N*-diethyl-2-bromoacetamide (2.98 g, 15.4 mmol) to give a crystalline solid in 99% yield (3.51 g, 12.7 mmol). mp = 66–68 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 9.27 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 5.44 (s, 2H), 3.91 (s, 3H), 3.37 (q, J = 7.0 Hz, 2H), 3.34 (q, J = 7.0 Hz, 2H), 1.24 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 165.17, 139.25, 125.54, 124.14, 51.80, 42.60, 41.97, 37.55, 14.86, 13.67. MS (ESI): *m*/*z*, 196.1 $[M-Br^-]^+$; MS (ESI): *m*/*z*, 79 and 81 $[Br^-]$.

3-Methyl-1-(methoxycarbonylmethyl)imidazolium BF_4 (8a)

A dry flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide (**7a**) (702 mg, 3.0 mmol) and acetonitrile (2 mL) under a nitrogen atmosphere. $NaBF_4$ (362 mg, 3.3 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at rt. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (2 × 1 mL). The filtrate and washings were combined, solvent removed by rotary evaporation then *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous hygroscopic oil in 96% yield (0.70 g, 2.9 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.58 (s, 1H), 7.40 (s, 2H), 5.02 (s, 2H), 3.89 (s, 3H), 3.78 (s, 3H). ^{13}C (75 MHz) δ 168.33, 138.75, 125.15, 125.00, 54.33, 51.18, 37.63. ^{19}F (254 MHz) δ −151.6 (BF_4^-). MS (ESI): *m*/*z*, 155.1 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(ethoxycarbonylmethyl)imidazolium BF_4 (8b)

This compound was prepared analogously to **8a** using 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide **7b** (1.79 g, 6.3 mmol) and $NaBF_4$ (0.69 g, 6.3 mmol) to give a clear viscous hygroscopic oil in 92% yield (1.51 g, 5.9 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.66 (s, 1H), 7.44 (s, 1H), 7.40 (s, 1H), 5.30 (s, 2H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.83, 138.80, 125.16, 124.93, 63.90, 51.31, 37.64, 14.83. ^{19}F (254 MHz) δ −151.6 (BF_4^-). MS (ESI): *m*/*z*, 169.1 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(propoxycarbonylmethyl)imidazolium BF_4 (8c)

This compound was prepared analogously to **8a** using 3-methyl-1-(propoxycarbonylmethyl)imidazolium bromide **7c** (722 mg, 2.8 mmol) and $NaBF_4$ (333 mg, 3.0 mmol) to give a clear viscous hygroscopic oil in 98% yield (727 mg, 2.7 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.55 (s, 1H), 7.41 (s, 2H), 7.40 (s, 1H), 5.00 (s, 2H), 4.17 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 1.70 (qt, *J* = 7.0, 7.0 Hz, 2H), 0.95 (t, *J* = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.90, 138.76, 125.15, 124.9, 69.24, 51.22, 37.58, 23.00, 10.96. ^{19}F (254 MHz) δ −151.5 (BF_4^-). MS (ESI): *m*/*z*, 183.1 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(hexoxycarbonylmethyl)imidazolium BF_4 (8f)

This compound was prepared analogously to **8a** using 3-methyl-1-(hexoxycarbonylmethyl)imidazolium bromide **7f** (758 mg, 2.25 mmol) and $NaBF_4$ (247 mg, 2.50 mmol) to give a clear viscous hygroscopic oil in 90% yield (630 mg, 2.0 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.63 (s, 1H), 7.43 (s, 2H), 7.40 (s, 1H), 5.02 (s, 2H), 4.19 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 1.70–1.60 (m, 2H), 1.42–1.28 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.85, 138.76, 125.17, 124.94, 67.87, 51.30, 37.64, 32.55, 29.56, 26.58, 23.72, 14.77. ^{19}F (254 MHz) δ −151(BF_4^-). MS (ESI): *m*/*z*, 225.2 [M−BF_4^-]$^+$ MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(octoxycarbonylmethyl)imidazolium BF_4 (8g)

This compound was prepared analogously to **8a** using 3-methyl-1-(octoxycarbonylmethyl)imidazolium bromide **7g** (350 mg, 1.05 mmol) and $NaBF_4$ (127 mg, 1.16 mmol) to give a clear viscous hygroscopic oil in 97 % yield (346 mg, 1.02 mmol). The oil crystallised in the freezer at −18 °C. ^{1}H NMR (300 MHz, CD_3CN) δ 8.50 (s, 1H), 7.40 (s, 2H), 7.38 (s, 1H), 4.98 (s, 2H), 4.19 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 1.70–1.60 (m, 2H), 1.42–1.25 (m, 10H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.87, 138.79, 125.16, 124.95, 67.85, 51.25, 37.60, 33.00, 30.38, 30.32, 29.59, 26.89, 23.83, 14.88. ^{19}F (254 MHz) δ −151.4 (BF_4^-). MS (ESI): *m*/*z*, 253.3 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(*N*-butylcarbamoylmethyl)imidazolium BF_4 (8h)

This compound was prepared analogously to **8a** using 3-methyl-1-(*N*-butylcarbamoylmethyl)imidazolium bromide **7h** (128 mg, 0.45 mmol) and $NaBF_4$ (50 mg, 0.50 mmol) in acetonitrile (1 mL) to give a clear viscous hygroscopic oil in 86% yield (110 mg, 0.39 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.55 (s, 1H), 7.39 (s, 1H), 7.35 (s, 1H), 7.05 (bs, 1H, NH), 4.85 (s, 2H), 3.86 (s, 3H), 3.20 (q, *J* = 7.0 Hz, 2H), 1.55–1.40 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.40–1.28 (qt, *J* = 7.0, 7.0 Hz, 2H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 165.73, 138.65, 125.10, 124.59, 52.39, 20.54, 37.50, 32.52, 21.11, 14.45. ^{19}F (254 MHz) δ −151.7 (BF_4^-). MS (ESI): *m*/*z*, 196.1 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)-imidazolium BF_4 (8i)

This compound was prepared analogously to **8a** using 3-methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)imidazolium bromide **7i** (256 mg, 0.88 mmol, 1 : 1.3 mixture of isomers) and $NaBF_4$ (107 mg, 0.97 mmol) to give a clear viscous hygroscopic oil in 98% yield (256 mg, 0.86 mmol, 1 : 1.3 mixture of isomers). * denotes both isomers. ^{1}H NMR (300 MHz, CD_3CN) δ 8.46 (s, 1H, minor), 8.44 (s, 1H, major), 7.40–7.30 (m, 2H*), 5.08 (s, 2H, minor), 5.05 (s, 2H, major), 3.88 (s, 3H*), 3.37 (t, *J* = 7.0 Hz, 2H, major), 3.28 (t, *J* = 7.0 Hz, 2H, minor), 3.00 (s, 3H, major), 2.92 (s, 3H, minor), 1.70–1.25 (m, 4H*), 0.99 (t, *J* = 7.0 Hz, 3H, minor), 0.93 (t, *J* = 7.0 Hz, 3H, major). ^{13}C (75 MHz) δ 166.05 (major), 165.79 (minor), 139.14 (minor), 139.04 (major), 125.48 (minor), 125.44 (major), 124.43*, 121.42* (q, *J* = 320 Hz, CF_3), 51.76 (major), 51.51 (minor), 50.01 (minor), 49.15 (major), 37.41*, 35.07 (major), 34.65 (minor), 31.21 (minor), 30.35 (major), 21.10 (minor), 21.09 (major), 14.74 (major), 14.69 (minor). ^{19}F (254 MHz) δ −152.10 (BF_4^-). MS (ESI): *m*/*z*, 210.2 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(*N*,*N*-diethylcarbamoylmethyl)-imidazolium BF_4 (8j)

This compound was prepared analogously to **8a** using 3-methyl-1-(*N*,*N*-diethylcarbamoylmethyl)imidazolium bromide **7j** (552 mg, 2.0 mmol) and $NaBF_4$ (242 mg, 2.2 mmol) to give a clear viscous hygroscopic oil in 92% yield (520 mg, 1.84 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.55 (s, 1H), 7.38 (s, 2H), 5.10 (s, 2H), 3.83 (s, 3H), 3.30 (m, 4H), 1.19 (t, *J* = 7.0 Hz), 1.07 (t, *J* = 7.0 Hz).^{13}C (75 MHz) δ 163.72, 137.68, 124.10, 122.95, 50.22, 41.12, 40.58,, 36.01, 13.25, 12.21. ^{19}F (254 MHz) δ −150.8 (BF_4^-). MS (ESI): *m*/*z*, 196.1 [M−BF_4^-]$^+$; MS (ESI): *m*/*z*, 87.0 [BF_4^-].

3-Methyl-1-(methoxycarbonylmethyl)imidazolium PF_6 (9a)

A flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide **7a** (702 mg, 3.0 mmol) and distilled water (2 mL). KPF_6 (607 mg, 3.3 mmol) in distilled water (1 mL) was added in one portion and the suspension was stirred vigorously for 4 h at rt. The top aqueous layer was removed, the IL washed with water (3 × 1 mL) then the solvent removed *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a crystalline solid in 67% yield (0.61 g, 2.0 mmol). mp = 76–78 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 8.49 (s, 1H), 7.39 (s, 2H), 4.99 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H). ^{13}C (75 MHz) δ 168.32, 138.67, 125.14, 125.02, 54.35, 51.18, 37.64; ^{19}F (254 MHz) δ −73.0 (d, J_{P-F} = 707 Hz, PF_6^-); MS (ESI): *m*/*z*, 155.1 [M−PF_6^-]$^+$; MS (ESI): *m*/*z*, 144.9 [PF_6^-].

3-Methyl-1-(ethoxycarbonylmethyl)imidazolium PF_6 (9b)

This compound was prepared analogously to **9a** using 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide **7b** (0.55 g, 2.2 mmol) and KPF_6 (0.41 g, 2.2 mmol) to give a clear viscous oil in

68% yield (0.47 g, 1.5 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.47 (s, 1H), 7.39 (s, 2H), 4.97 (s, 2H), 4.26 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.80, 138.65, 125.18, 125.00, 63.98, 51.30, 37.63, 14.84. ^{19}F (254 MHz) δ −72.5 (d, J_{P-F} = 707 Hz, PF_6^-). MS (ESI): m/z, 169.1 $[M-PF_6^-]^+$; MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(propoxycarbonylmethyl)imidazolium PF_6 (9c)

This compound was prepared analogously to **9a** using 3-methyl-1-(propoxycarbonylmethyl)imidazolium bromide **7c** (0.60 g, 2.3 mmol) and KPF_6 (464 mg, 2.5 mmol) to give a clear viscous oil in 78% yield (585 mg, 1.8 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.47 (s, 1H), 7.39 (s, 2H), 4.98 (s, 2H), 4.17 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.69 (qt, J = 7.0, 7.0 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C (75 MHz) δ 167.84, 138.65, 125.18, 124.99, 69.32, 51.28, 37.64, 23.03, 10.98; ^{19}F (254 MHz) δ −72.7 (d, J_{P-F} = 707 Hz, PF_6^-); MS (ESI): m/z, 183.1 $[M-PF_6^-]^+$; MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(hexoxycarbonylmethyl)imidazolium PF_6 (9d)

This compound was prepared analogously to **9a** using 3-methyl-1-(hexoxycarbonylmethyl)imidazolium bromide **7d** (762 mg, 2.3 mmol) and KPF_6 (458 mg, 2.5 mmol) to give a clear viscous oil in 89% yield (0.76 g, 2.1 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.49 (s, 1H), 7.39 (s, 2H), 4.98 (s, 2H), 4.20 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.70–1.60 (m, 2H), 1.40–1.30 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.78, 138.62, 125.17, 124.97, 67.89, 51.28, 37.62, 32.54, 29.56, 26.57, 23.71, 14.77. ^{19}F (254 MHz) δ −71.94 (d, J_{P-F} = 707 Hz, PF_6^-). MS (ESI): m/z, 225.2 $[M-PF_6^-]^+$ MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(octoxycarbonylmethyl)imidazolium PF_6 (9g)

This compound was prepared analogously to **9a** using 3-methyl-1-(octoxycarbonylmethyl)imidazolium bromide **7g** (528 mg, 1.58 mmol) and KPF_6 (321 mg, 1.74 mmol) to give a colourless oil in 81% yield (508 mg, 1.27 mmol). The oil crystallised in the fridge at 2 °C. ^{1}H NMR (300 MHz, CD_3CN) δ 8.46 (s, 1H), 7.39 (s, 2H), 4.96 (s, 2H), 4.19 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.72–1.60 (m, 2H), 1.42–1.25 (m, 10H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.77, 138.57, 125.15, 124.96, 67.88, 51.26, 37.62, 32.99, 30.38, 30.31, 29.58, 26.89, 23.84, 14.86. ^{19}F (254 MHz) δ −72.67 (d, J_{P-F} = 707 Hz, PF_6^-); MS (ESI): m/z, 253.3 $[M-PF_6^-]^+$; MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(*N*-butylcarbamoylmethyl)imidazolium PF_6 (9h)

A dry flask was charged with 3-methyl-1-(*N*-butylcarbamoylmethyl)imidazolium bromide **7h** (120 mg, 0.43 mmol) and acetonitrile (1 mL) under a nitrogen atmosphere. KPF_6 (96 mg, 0.52 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at rt. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (2 × 1 mL). The filtrate and washings were combined, solvent removed by rotary evaporation then *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear crystalline solid in 99% yield (145 mg, 0.42 mmol). mp = 64–66 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 8.46 (s, 1H), 7.36 (s, 2H), 6.78 (bs, 1H, NH), 4.80 (s, 2H), 3.87 (s, 3H), 3.21 (q, J = 7.0 Hz, 2H), 1.60–1.30 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 165.87, 138.66, 125.15, 124.69, 52.36, 40.68, 37.51, 32.53, 21.14, 14.55. ^{19}F (254 MHz) δ −72.46 (d, J_{P-F} = 707 Hz, PF_6^-); MS (ESI): m/z, 196.1 $[M-PF_6^-]^+$; MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)-imidazolium PF_6 (9i)

This compound was prepared analogously to **9a** using 3-methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)imidazolium bromide **7i** (265 mg, 0.91 mmol, 1:1.3 mixture of isomers) and KPF_6 (185 mg, 1.0 mmol) to give a crystalline solid in 70% yield (225 mg, 0.63 mmol, 1 : 1.3 mixture of isomers). mp = 62–64 °C; * denotes both isomers. ^{1}H NMR (300 MHz, CD_3CN) δ 8.42 (s, 1H, minor), 8.40 (s, 1H, major), 7.40–7.30 (m, 2H*), 5.06 (s, 2H, major), 5.03 (s, 2H, minor), 3.88 (s, 3H*), 3.37 (t, J = 7.0 Hz, 2H, major), 3.28 (t, J = 7.0 Hz, 2H, minor), 3.00 (s, 3H, major), 2.92 (s, 3H, minor), 1.70–1.25 (m, 4H*), 0.99 (t, J = 7.0 Hz, 3H, minor), 0.93 (t, J = 7.0 Hz, 3H, major); ^{13}C (75 MHz) δ 165.75 (major), 165.48 (minor), 138.93 (minor), 138.85 (major), 125.51 (minor), 125.45 (major), 124.42*, 51.86 (major), 51.61 (minor), 50.00 (minor), 49.18 (major), 37.50*, 35.05 (major), 34.59 (minor), 31.28 (minor), 30.36 (major), 21.11*, 14.69 (major), 14.65 (minor). ^{19}F (254 MHz) δ −72.38 (d, J_{P-F} = 710 Hz, PF_6^-); MS (ESI): m/z, 210.2 $[M-PF_6^-]^+$; MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(*N*,*N*-diethylcarbamoylmethyl)imidazolium PF_6 (9j)

This compound was prepared analogously to **9a** using 3-methyl-1-(*N*,*N*-diethylcarbamoylmethyl)imidazolium bromide **7j** (828 mg, 3.0 mmol) and KPF_6 (607 mg, 3.3 mmol) to give a crystalline solid in 66% yield (0.68 g, 2.0 mmol). mp = 64–66 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 8.43 (s, 1H), 7.33 (s, 2H), 5.04 (s, 2H), 3.88 (s, 3H), 3.37 (q, J = 7.0 Hz, 2H), 3.34 (q, J = 7.0 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C (75 MHz) δ 164.80, 138.85, 125.47, 124.34, 51.71, 42.50, 42.00, 37.54, 14.65, 13.55; ^{19}F (254 MHz) δ −72.8 (d, J_{P-F} = 707 Hz, PF_6^-); MS (ESI): m/z, 196.1 $[M-PF_6^-]^+$; MS (ESI): m/z, 144.9 $[PF_6^-]$.

3-Methyl-1-(methoxycarbonylmethyl)imidazolium NTf_2 (10a)

A flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide **7a** (702 mg, 3.0 mmol) and distilled water (2 mL). $LiNTf_2$ (947 mg, 3.3 mmol) in distilled water (1 mL) was added in one portion and the suspension was stirred vigorously for 4 h at rt. The top aqueous layer was removed, the IL washed with water (3 × 1 mL) then the solvent removed *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous oil in 93% yield (1.21 g, 2.8 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.49 (s, 1H), 7.39 (bs, 2H), 4.99 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H). ^{13}C (75 MHz) δ 168.23, 138.59, 125.22, 125.09, 121.39 (q, J = 320 Hz, CF_3), 54.31, 51.19, 37.64. ^{19}F (254 MHz) δ −80.15 (CF_3). MS (ESI): m/z, 155.1 $[M-NTf_2^-]^+$; MS (ESI): m/z, 279.9 $[NTf_2^-]$.

3-Methyl-1-(ethoxycarbonylmethyl)imidazolium NTf_2 (10b)

This compound was prepared analogously to **10a** using 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide **7b** (0.53 g, 2.1 mmol) and $LiNTf_2$ (0.60 g, 2.1 mmol) to give a clear viscous oil in 90% yield (0.85 g, 1.9 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.46 (s, 1H), 7.39 (s, 2H), 4.96 (s, 2H), 4.26 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.70, 138.66, 125.19, 124.98, 123.53 (q, J = 320 Hz, CF_3), 63.98, 51.33, 37.64, 14.81. ^{19}F (254 MHz) δ −80.05 (CF_3). MS (ESI): m/z, 169.1 $[M-NTf_2^-]^+$; MS (ESI): m/z, 279.9 $[NTf_2^-]$.

3-Methyl-1-(propoxycarbonylmethyl)imidazolium NTf_2 (10c)

This compound was prepared analogously to **10a** using 3-methyl-1-(propoxycarbonylmethyl)imidazolium bromide **7c** (0.95 g, 3.6 mmol) and $LiNTf_2$ (1.15 g, 4.0 mmol) to give a clear viscous oil in 92% yield (1.55 g, 3.4 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.49 (s, 1H), 7.39 (s, 2H), 4.99 (s, 2H), 4.17 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.68 (tq, J = 7.0, 7.0 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.89, 138.82, 125.27, 125.02, 121.44 (q, J = 320 Hz, CF_3), 69.44, 51.32, 37.63, 23.03, 11.03. ^{19}F (254 MHz) δ −80.06 (CF_3). MS (ESI): m/z, 183.1 $[M-NTf_2^-]^+$; MS (ESI): m/z, 279.9 $[NTf_2^-]$.

3-Methyl-1-(hexoxycarbonylmethyl)imidazolium NTf_2 (10d)

This compound was prepared analogously to **10a** using 3-methyl-1-(hexoxycarbonylmethyl)imidazolium bromide **7d** (680 mg, 2.0 mmol) and $LiNTf_2$ (637 mg, 2.2 mmol) to give a clear viscous oil in 89% yield (0.90 g, 1.8 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.47 (s, 1H), 7.39 (s, 2H), 4.97 (s, 2H), 4.19 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.70–1.60 (m, 2H), 1.40–1.30 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.74, 138.60, 125.16, 124.97, 121.39 (q, J = 320 Hz, CF_3), 67.90, 51.30, 37.65, 32.53, 29.55, 26.57, 23.70, 14.74. ^{19}F (254 MHz) δ −80.20 (CF_3). MS (ESI): m/z, 225.2 [M−NTf_2^-]$^+$; MS (ESI): m/z, 279.9 [NTf_2^-].

3-Methyl-1-(octoxycarbonylmethyl)imidazolium NTf_2 (10g)

This compound was prepared analogously to **10a** using 3-methyl-1-(octoxycarbonylmethyl)imidazolium bromide **7g** (548 mg, 1.64 mmol) and $LiNTf_2$ (520 mg, 1.81 mmol) to give a clear viscous oil in 93% yield (0.81 g, 1.52 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 8.48 (s, 1H), 7.39 (s, 2H), 4.97 (s, 2H), 4.20 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.70–1.60 (m, 2H), 1.40–1.20 (m, 10H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.76, 138.72, 125.21, 124.27, 121.20 (q, J = 320 Hz, CF_3), 67.95, 51.28, 37.60, 33.06, 30.43, 30.40, 29.62, 26.96, 23.89, 14.95. ^{19}F (254 MHz) δ −80.05 (CF_3); MS (ESI): m/z, 253.3 [M−NTf_2^-]$^+$; MS (ESI): m/z, 279.9 [NTf_2^-].

3-Methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)-imidazolium NTf_2 (10i)

This compound was prepared analogously to **10a** using 3-methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)imidazolium bromide **7i** (302 mg, 1.04 mmol, 1 : 1.3 mixture of isomers) and $LiNTf_2$ (329 mg, 1.15 mmol) to give a clear viscous oil in 80% yield (410 mg, 0.84 mmol, 1 : 1.3 mixture of isomers). * denotes both isomers. ^{1}H NMR (300 MHz, CD_3CN) δ 8.42 (s, 1H, minor), 8.40 (s, 1H, major), 7.40–7.30 (m, 2H*), 5.06 (s, 2H, minor), 5.02 (s, 2H, major), 3.88 (s, 3H*), 3.37 (t, J = 7.0 Hz, 2H, major), 3.28 (t, J = 7.0 Hz, 2H, minor), 3.00 (s, 3H, major), 2.92 (s, 3H, minor), 1.70–1.25 (m, 4H*), 0.99 (t, J = 7.0 Hz, 3H, minor), 0.93 (t, J = 7.0 Hz, 3H, major). ^{13}C (75 MHz) δ 165.72 (major), 165.47 (minor), 139.01 (minor), 138.93 (major), 125.55 (minor), 125.48 (major), 124.38*, 121.42* (q, J = 320 Hz, CF_3), 51.90 (major), 51.65 (minor), 50.07 (minor), 49.24 (major), 37.49*, 35.07 (major), 34.62 (minor), 31.29 (minor), 30.36 (major), 21.10*, 14.67 (major), 14.61 (minor). ^{19}F (254 MHz) δ −79.90 (CF_3); MS (ESI): m/z, 210.2 [M−NTf_2^-]$^+$; MS (ESI): m/z, 279.9 [NTf_2^-].

3-Methyl-1-(*N*,*N*-diethylcarbamoylmethyl)imidazolium NTf_2 (10j)

This compound was prepared analogously to **10a** using 3-methyl-1-(*N*,*N*-diethylcarbamoylmethyl)imidazolium bromide **7j** (828 mg, 3.0 mmol) and $LiNTf_2$ (947 mg, 3.3 mmol) to give a crystalline solid in 83% yield (1.18 g, 2.48 mmol). mp = 43–45 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 8.47 (s, 1H), 7.34 (s, 2H), 5.06 (s, 2H), 3.88 (s, 3H), 3.37 (q, J = 7.0 Hz, 2H), 3.34 (q, J = 7.0 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 164.81, 138.89, 125.47, 124.33, 121.39 (q, J = 320 Hz, CF_3), 51.72, 42.51, 42.00, 37.53, 14.65, 13.55. ^{19}F (254 MHz) δ −80.03 (CF_3); MS (ESI): m/z, 196.1 [M−NTf_2^-]$^+$; MS (ESI): m/z, 279.9 [NTf_2^-].

3-Methyl-1-(ethoxycarbonylmethyl)imidazolium $N(CN)_2$ (11b)

A dry flask was charged with 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide (**7b**) (1.50 g, 6.0 mmol) and acetonitrile (3 mL) under a nitrogen atmosphere. NaNCNCN (641 mg, 7.2 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at rt. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (2 × 1 mL). The filtrate and washings were combined, solvent removed by rotary evaporation then *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous hygroscopic oil in 96% yield (1.35 g, 5.73 mmol). ^{1}H NMR (300 MHz, CD_3CN) δ 9.06 (s, 1H), 7.53 (s, 1H), 7.45 (s, 1H), 5.18 (s, 2H), 4.25 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.90, 138.99, 125.02, 124.64, 63.67, 51.26, 37.53, 14.77. Peaks for $NCNCN^-$ not cited. MS (ESI): m/z, 169.1 [M−$NCNCN^-$]$^+$; MS (ESI): m/z, 66.0 [$NCNCN^-$].

3-Methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)-imidazolium $N(CN)_2$ (11i)

This compound was prepared analogously to **11b** using 3-methyl-1-(*N*-butyl-*N*-methylcarbamoylmethyl)imidazolium bromide **7i** (208 mg, 0.71 mmol, 1:1.3 mixture of isomers) and NaNCNCN (77 mg, 0.86 mmol) to give a clear viscous hygroscopic oil in 96% yield (189 mg, 0.68 mmol, 1 : 1.3 mixture of isomers). * denotes both isomers. ^{1}H NMR (300 MHz, CD_3CN) δ 8.75 (s, 1H, minor), 8.71 (s, 1H, major), 7.50–7.35 (m, 2H*), 5.20 (s, 2H, major), 5.18 (s, 2H, minor), 3.90 (s, 3H*), 3.37 (t, J = 7.0 Hz, 2H, major), 3.30 (t, J = 7.0 Hz, 2H, minor), 3.02 (s, 3H, major), 2.92 (s, 3H, minor), 1.70–1.25 (m, 4H*), 0.99 (t, J = 7.0 Hz, 3H, minor), 0.93 (t, J = 7.0 Hz, 3H, major). ^{13}C (75 MHz) δ 165.85 (major), 165.54 (minor), 138.99 (minor), 138.85 (major), 125.19 (minor), 125.11 (major), 123.94*, 51.78 (major), 51.43 (minor), 49.78 (minor), 48.75 (major), 37.29*, 35.03 (major), 34.36 (minor), 31.02 (minor), 30.09 (major), 20.85 (minor), 20.77 (major), 14.41*. Peaks for $NCNCN^-$ not cited. MS (ESI): m/z, 210.2 [M−$NCNCN^-$]$^+$; MS (ESI): m/z, 66.0 [$NCNCN^-$].

Butyl bromoacetate (12d)[42]

To a stirred solution of triethylamine (41.6 mL, 300 mmol), butan-1-ol (18.3 mL, 14.82 g, 200 mmol) and dichloromethane (300 mL) at −78 °C under a nitrogen atmosphere was added dropwise bromoacetyl bromide (17.4 mL, 40.37 g, 200 mmol). After stirring at −78 °C for 3 h the reaction mixture was allowed to warm up to −20 °C and quenched by addition of water (50 mL). The organic phase was washed with distilled water (3 × 50 mL), saturated ammonium chloride (3 × 50 mL), saturated sodium bicarbonate (3 × 50 mL) and brine (2 × 50 mL) then dried over magnesium sulfate, filtered and solvents removed *via* rotary evaporation. The crude product (28 g, clean by ^{1}H NMR) was distilled to give a pale yellow oil in 59% yield (23.1 g, 118 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (t, J = 7.0 Hz, 2H), 3.81 (s, 3H), 1.64 (tt, J = 7.0, 7.0 Hz, 2H), 1.40 (tt, J = 7.0, 7.0 Hz, 2H), 0.93 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ. 167.17, 66.01, 30.33, 25.77, 18.87, 13.49.

Pentylbromoacetate (12e)[42,43]

This compound was prepared analogously to butylbromoacetate using pentan-1-ol (21.7 mL, 17.6 g, 200 mmol) to give a pale yellow oil in 72% yield (29.9 g, 143 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (t, J = 7.0 Hz, 2H), 3.81 (s, 3H), 1.64 (tt, J = 7.0, 7.0 Hz, 2H), 1.45–1.25 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ. 167.16, 66.28, 27.99, 27.76, 25.77, 22.12, 13.79.

Hexylbromoacetate (12f)

This compound was prepared analogously to butylbromoacetate using triethylamine (20.8 mL, 150 mmol), hexan-1-ol (12.4 mL, 10.2 g, 100 mmol), dichloromethane (200 mL) and bromoacetyl bromide (8.7 mL, 20.2 g, 100 mmol) to give a crude product (21.6 g) which was distilled to give a colourless oil in 65% yield (14.5 g, 65 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (t, J = 7.0 Hz, 2H), 3.82 (s, 3H), 1.64 (tt, J = 7.0, 7.0 Hz, 2H), 1.40–1.20 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ. 167.20, 66.34, 31.24, 28.28, 25.77, 25.30, 22.38, 13.84. NMR data in agreement with literature.[44]

Octylbromoacetate (12g)

This compound was prepared analogously to butylbromoacetate using triethylamine (20.8 mL, 150 mmol), octan-1-ol (15.8 mL, 13.0 g, 100 mmol), dichloromethane (200 mL) and bromoacetyl bromide (8.7 mL, 20.2 g, 100 mmol) to give a crude product (18.7 g) which was distilled to give a colourless oil in 24% yield (6.0 g, 24 mmol). ^{1}H NMR (300 MHz, $CDCl_3$ δ 4.16 (t, J = 7.0 Hz, 2H), 3.82 (s, 3H), 1.64 (tt, J = 7.0, 7.0 Hz, 2H), 1.40–1.20 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 167.13, 66.27, 31.62, 29.00, 29.01, 28.30, 25.74, 25.62, 22.48, 13.91. NMR data in agreement with literature.[45]

N-Butyl-2-bromoacetamide (12h)[46]

This compound was prepared analogously to butylbromoacetate using triethylamine (20.8 mL, 150 mmol), butylamine (9.8 mL, 7.3 g, 100 mmol), dichloromethane (200 mL) and bromoacetyl bromide (8.7 mL, 20.2 g, 100 mmol) to give a crude product (18.0 g) which was distilled to give a light brown oil, which crystallized on standing, in 39% yield (7.5 g, 39 mmol). Mp = 35–37 °C. Lit. Mp = 38–39 °C.[46] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (bs, 1H, NH), 3.87 (s, 2H), 3.28 (q, J = 7.0 Hz, 2H), 1.52 (tt, J = 7.0, 7.0 Hz, 2H), 1.37 (tt, J = 7.0, 7.0 Hz, 2H), 0.93 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 165.35, 39.85, 31.18, 29.17, 19.86, 13.55.

N-Butyl-*N*-methyl-2-bromoacetamide (12i)[42]

This compound was prepared analogously to butylbromoacetate using triethylamine (20.8 mL, 150 mmol), *N*-methyl-butylamine (11.8 mL, 8.72 g, 100 mmol), dichloromethane (200 mL) and bromoacetyl bromide (8.7 mL, 20.2 g, 100 mmol) to give a crude product (21.0 g) which was distilled to give a pale yellow oil in 54% yield (11.37 g, 54 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 2H, minor), 3.83 (s, 2H, major), 3.35 (t, J = 7.0 Hz, 2H, major), 3.30 (t, J = 7.0 Hz, 2H, minor), 3.04 (s, 3H, major), 2.92 (s, 3H, minor), 1.65–1.25 (m, 4H, major and minor), 0.94 (t, J = 7.0 Hz, 3H, minor), 0.91 (t, J = 7.0 Hz, 3H, major). ^{13}C (75 MHz) δ 166.30, 50.55, 47.88, 35.89, 33.61, 30.41, 28.84, 26.57, 25.89, 19.75, 13.66.

N,*N*-Diethyl-2-bromoacetamide (12j)

This compound was prepared analogously to butylbromoacetate using triethylamine (20.8 mL, 150 mmol), diethylamine (10.4 mL, 7.30 g, 100 mmol), dichloromethane (200 mL) and bromoacetyl bromide (8.7 mL, 20.2 g, 100 mmol) to give a crude product (14.5 g) which was distilled to give a pale yellow oil in 31% yield (6.01 g, 31 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 2H), 3.378 (q, J = 7.0 Hz, 2H), 3.383 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H). ^{13}C (75 MHz) δ 165.65, 42.78, 40.36, 26.39, 14.20, 12.34. NMR data in agreement with literature.[47]

Closed Bottle Test

Sodium *n*-dodecyl sulfate (SDS) was used as reference substance. Solutions containing 2 mg L^{-1} of the test ionic liquids and the reference chemical as sole sources of organic carbon were prepared, separately, in previously aerated mineral medium. The solutions were then inoculated with secondary effluent collected from an activated sludge treatment plant and each well-mixed solution was carefully dispensed into a series of BOD bottles so that all the bottles were completely full. A control with inoculum, but without test chemicals was run parallel for the determination of oxygen blanks. Duplicate bottles of each series were analysed immediately for dissolved oxygen and the remaining bottles were incubated at 20 °C±1 °C in the dark. Bottles of all series were withdrawn in duplicate for dissolved oxygen analysis over the 28-day incubation period. The biodegradation after *n* days was expressed as the ratio of the biochemical oxygen demand (BOD) to the chemical oxygen demand (COD) both of them expressed as mg O_2/mg compound. The chemical oxygen demand was determined by the dichromate reflux method.[48] For the calculation of the biochemical oxygen demand the determined oxygen depletions were divided by the concentration of ionic liquid.

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PAPER

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Recovery of various phenols and phenylamines by micellar enhanced ultrafiltration and cloud point separation

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The recovery of organic pollutants by micellar enhanced ultrafiltration and cloud point technique was studied. It was found that micellar enhanced ultrafiltration and cloud point technique enable high recovery of some organic pollutants without using any hydrocarbon solvents. The cloud point technique gives higher recovery than ultrafiltration. Appropriate surfactants having low critical micelle concentration and low cloud point must be used. Oxyethylated fatty acid methyl esters are the most appropriate for cloud point separation as, having ester groups, they are quickly hydrolyzed in sewage systems. CTAB and SDS are appropriate for ultrafiltration. The recovery of pollutants in both considered techniques can be estimated from the micelle binding constants or from linear solvation free energy relationships according to the Abraham model. The efficiency of separation increases with an increase of pollutant hydrophobicity and excess molar refraction. Hydrogen bond acidity of pollutants improves separation from systems containing nonionic surfactants and CTAB but it does not affect separation in the presence of SDS. Hydrogen bond basicity and dipolarity of pollutants decrease the recovery. The derived models enable the selection of pollutants which can be efficiently removed from aqueous streams by the cloud point technique and micellar enhanced ultrafiltration.

Introduction

Nowadays, there is a strong concern to protect the environment, and despite major progress achieved over the last three decades in the field of separation techniques, the removal of organic pollutants from aqueous industrial streams and wastewaters remains an important challenge. The use of new surfactant supported processes, including micellar enhanced ultrafiltration (MEUF)[1–5] and cloud point separation[6–9] is proposed. In this way, the use of hydrocarbon diluents and organic extractants used in classical extraction is avoided. These components of extraction systems are always slightly soluble in aqueous streams and may be the source of induced secondary pollution.[10]

Membrane ultrafiltration has been successfully used as an effective process for the treatment of a large number of industrial wastewaters. MEUF has been proposed for water clean-up. The effectiveness of MEUF in removing organic compounds from aqueous stream owes to the fact that surfactant micelles containing these contaminants are too large to pass through the pores of the ultrafilter.[2–4] In this process a surfactant is added to the aqueous stream and forms micelles which solubilize pollutants, so that the subsequent ultrafiltration step produces a permeate stream, passing through the membrane nearly free from impurities, while most of the target solutes and the added surfactant are retained in the retentate. However, an at least monomeric surfactant with a concentration close to the critical micelle concentration is not retained by the membrane. Thus, such surfactants may cause an additional environmental problem connected with their biodegradability and toxicity. This means that appropriate surfactants must be selected. The problem was broadly discussed in the papers of Sabate *et al.*[11] who used surfactants for ground-water remediation. Successful laboratory studies and field demonstrations have been carried out and the technology is moving rapidly toward commercialization.

Cloud point separation is connected with the phase phenomenon of nonionic and zwitterionic surfactant micelle systems. Under appropriate conditions (*i.e.*, temperature, addition of salt or other additives), separation of an aqueous surfactant micellar solution into a concentrated phase containing most of the surfactant (surfactant-rich phase) and a dilute aqueous phase containing low concentration of surfactant is observed.[6–9] Solutions containing nonionic or zwitterionic surfactants become turbid in a narrow range of temperature, referred to as the cloud point. Above the cloud point the system separates into two isotropic phases. This process is reversible, and on cooling the separated phases form once again a clear solution. A surfactant-rich phase and a micellar phase can co-exist in equilibrium. These phases differ in their hydrophilicity and in the basicity and acidity of the hydrogen bond. As a result, organic solutes can be transferred to the surfactant-rich phase. The concentration of surfactants in the initial aqueous feed is only a few percent. As a result, the separated surfactant-rich phase has a relatively small volume in comparison with the volume of the initial feed. Thus, the method enables both the separation and enrichment of the solute.

It was the aim of this work to study the efficiency of removal of organic pollutants by the MEUF and CP separation. Thirteen different pollutants, mainly phenols and phenylamines with various substituents changing their acid–base properties were considered. Sodium dodecylsulfate (SDS), hexadecyltrimethylammonium bromide (CTAB) and alkylpolyglucoside (APG) were used as representatives of anionic, cationic and nonionic surfactants in MEUF separations, and oxyethylated methyl dodecanoate (OMD) in CP technique. These surfactants seem to be non-hazardous for the environment. Oxyethylated methyl dodecanoates are new biodegradable surfactants[12] which hydrolyze easily in sewage systems to non-toxic and non-surface active components.

Oxyethylated fatty acid methyl esters show higher biodegradability and lower aquatic toxicity compared to oxyethylated alcohols. Generally, aquatic toxicity of oxyethylated fatty acid methyl esters is one order lower compared to that of oxyethylated alcohols.[13,14] According to the European Union Directive No. 67/548/EEC with the respective amendment No. 7, hydrophobic oxyethylated alcohols are classified to the IInd toxicity class (R51) regarded as toxic against aquatic life, while hydrophilic oxyethylated alcohols having an average degree of oxyethylation above 12 belong to the IIIrd toxicity class (R52) and are marked as harmful. Oxyethylated fatty acid methyl esters are classified to the third toxicity class according to the test on *Daphnia magna* and they fall out of the classification of the EU regarding toxicity against water organisms, as determined on fish. Biodegradability tests performed on activated sludge following the OECD Confirmatory Test procedure No. 82/242/EEC at the certified laboratory show the

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biodegradation level of oxyethylated fatty acid methyl esters and oxyethylated alcohols is equal to 88.4–93.3 and 83.2–90.4%, respectively.

The ratio of prognostic concentration of oxyethylated fatty acid methyl esters in wasted water, used as detergents in washing powders in a region with 1.6 million population, to the acute toxicity is in the range 400–510 estimated for *Daphnia magna* and 1240–2130 for *Lebistes reticulates*.[13,14] Thus, the ratio is a few–20 times higher than the threshold value and indicates that the replacement of oxyethylated alcohols by oxyethylated fatty acid methyl ester equivalent can decrease the expected risk of negative environmental impact 7 times. Additionally, oxyethylated fatty acid methyl esters do not show any allergic action towards human skin, contrary to the other surfactants.[15]

APG is non-toxic and is easy biodegradable as it contains an oligoglucose moiety. SDS hydrolyzes quickly in aqueous solutions giving dodecanol, especially in acidic and neutral solutions. Cationic surfactants are used in small quantities, compared with anionic surfactants present in detergent compositions, and they precipitate in the form of salts with anionic surfactants.

The aim of this work was also an attempt to use the Abraham model[16,17] to predict the parameters that affect micellar enhanced ultrafiltration and cloud point separation of organic toxic pollutants. Up to now, the model was used to estimate the binding of solutes by micelles of various surfactants[18] and the efficiency of cloud point separation.[8,19] However, no such attempt was discussed in the literature concerning MEUF.

Experimental

Thirteen different organic pollutants, mainly from the group consisting of phenols and phenylamines, were used. Table 1 presents pK_a values in distilled water, in a few cases also in CTAB and SDS, octanol/water partition coefficients calculated according to the Hansch and Leo method[20] and the Abraham parameters for twelve compounds. The Abraham parameters for 2,2-bis(4-hydroxyphenyl)propane were not found. Sodium dodecylsulfate (SDS) from BDH (Great Britain), hexadecyltrimethylammonium bromide (CTAB) from Chemapol (Czech Republic), alkylpolyglucoside – Glucopon 215 CSUP from Henkel (Germany) and oxyethylated methyl dodecanoate (OMD) with an average degree of oxyethylation equal to 11, from the Institute of Heavy Organic Synthesis (Poland) were used as surfactants. APG contained 8–10 carbon atoms in the alkyl chain and the degree of glucose oligomerization was 1.4.[21]

Ultrafiltration experiments were carried out at 22 ± 1 °C, with an Amicon 8010 (USA) stirred cell having a volume of 10 ml. A nitrogen pressure of 0.35 MPa was applied. The hydrophilic Millipore membrane (PLGC type) with a micellar weight cut-off of 10,000 Da was made of regenerated cellulose. Equal volumes of pollutant and surfactant solutions (5 ml each) were introduced into a filtration module and pH was adjusted to 3, 7 or 10. The solution present in the module was stirred for 5 minutes with a magnetic stirrer and then it was filtered until 5 ml of permeate was obtained while stirring vigorously. The concentrations of the surfactants amounted to 9.7×10^{-2}, 9.2×10^{-3} and 1.1×10^{-2} M for SDS, CTAB and APG and were equivalent to 10 cmc in distilled water. The concentrations of pollutants in the permeate and retentate were determined by UV at the maximum wavelength, using surfactant solutions of appropriate concentrations (1 cmc and 19 cmc for permeate and retentate, respectively) as a reference. Prior to measurements pH was adjusted to 11. Thus, the ionic form of phenols and the nonionic form of amines were registered. A Secomam 750 (France) spectrophotometer was used. Continuous UV/VIS spectra were recorded on a Shimadzu 215 spectrophotometer (Japan).

The value of the cloud point (CP) was determined in the classical way by heating the solution above the cloud point, *i.e.*, to cause the solution to become turbid, and then cooling it slowly while stirring vigorously. The temperature at which the solution became transparent was assumed to be the cloud point. The determination was repeated at least six times for each solution and the error on the average values of CP did not exceed 1 °C. The concentration of oxyethylated methyl dodecanoate was equal 3.6×10^{-2} M. The initial concentration of pollutants was always 10^{-3} M. The concentration of sodium chloride was zero or 1 M. The pH of the aqueous solutions was below 3.5. The solutions of pollutants in pure water or in the presence of 1 M NaCl and surfactant solutions were introduced into calibrated tubes of 10 ml capacity, mixed by shaking by hand, then overheated 20 °C over the CP. The separation of the surfactant-rich phase is a slow process and about 12 hours is needed to achieve complete and reproducible separations. The concentration of the pollutants in the aqueous phase after separation was determined spectrophotometrically. The analytical procedure was analogous to the analysis in MEUF. The efficiency of phase separation was estimated from the measure of the surface tension of OMD in the aqueous phase, as measured by a tensiometer Tracker, I.T. Concept (France). The concentrations of OMD in the aqueous phase were estimated from the linear parts of surface tension isotherms and were equal to 2 cmc and 20 cmc for the solution with and without the electrolyte, respectively.

Results and discussion

Acid–base equilibrium

Phenols (PhOH) are weak acids and can dissociate at adequately high pH.

Table 1 Recovered pollutants and their pK_a values, Abraham parameters and octanol/water partition coefficients

No.	Pollutant	Producer	pK_a[a]	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	π^2	R_2	$V_X/100$	log$P_{o/w}$
1	4-methylphenol	POCH, Poland	10.28	0.57	0.32	0.87	0.82	0.916	1.97
2	phenol	Loba Chemie, Austria	9.92	0.60	0.31	0.89	0.81	0.755	1.47
3	4-fluorophenol	Aldrich, Germany	9.6	0.63	0.23	0.97	0.67	0.793	1.92
4	4-methoxyphenol	Aldrich, Germany	9.48	0.57	0.48	1.17	0.90	0.975	1.57
5	4-chlorophenol	Aldrich, Germany	9.02	0.67	0.21	1.08	0.92	0.898	2.49
6	2,2-bis(4-hydroxyphenol) propane	ICSO Kędzierzyn Koźle, Poland	8.0	—	—	—	—	—	3.67
7	2,4-dichlorophenol	Aldrich, Germany	7.87	0.53	0.19	0.84	0.96	1.02	2.97
8	4-nitrophenol	POCH, Poland	7.23 6.5^{SDS}	0.82	0.26	1.72	1.07	0.95	1.85
9	4-ethylphenylamine	Aldrich, Germany	5.9^{CTAB} 6.5^{SDS}	0.23	0.56	0.91	0.94	1.098	1.94
10	4-isopropylphenylamine	Aldrich, Germany	5.8^{CTAB}	0.23	0.6	0.87	0.92	1.239	2.34
11	4-methoxyphenylamine	Aldrich, Germany	5.39 4.6 5.4^{SDS}	0.23	0.72	1.1	1.05	1.016	1.00
12	phenylamine	Aldrich, Germany	4.8^{CTAB}	0.26	0.5	0.96	0.96	0.816	0.92
13	4-aminobenzonitrile	Aldrich, Germany	—	0.4	0.5	1.78	1.09	0.971	1.00

[a] Values in distilled water are given; superscripts *SDS* or *CTAB* indicate that the values were determined in surfactant solutions.

$$PhOH = PhO^- + H^+ \qquad K_a = \frac{[PhO^-][H^+]}{[PhOH]} \qquad (1)$$

Amines (A) having basic nitrogen can be protonated at low pH.

$$AH^+ = A + H^+ \qquad K_a = \frac{[A][H^+]}{[AH^+]} \qquad (2)$$

pK_a values for considered phenols are in the range 7.23–10.28 in water. This means that at the pH values considered in this paper (3, 7 and 10), phenolic pollutants in pure water are present only in nonionic forms at the pH of 3 (Fig. 1). At the same time, each amine

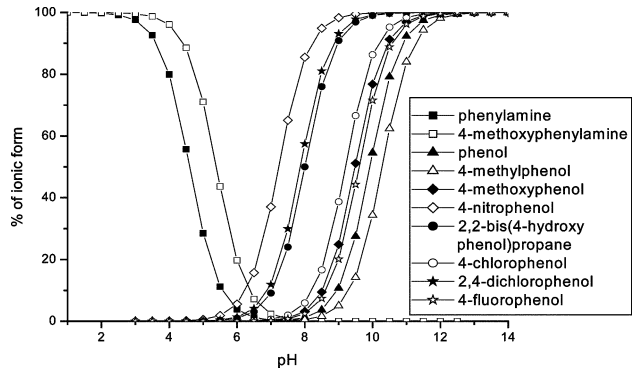

Fig. 1 pH effect on the concentration of pollutant ionic species in pure aqueous solutions.

is almost completely protonated. Thus, that pH is very convenient because the pollutants are only in one form.

The situation is more complicated at the pH of 7. In this case only phenols **1**–**4** are present in nonionic forms. The nonionic species are dominant for **5**–**7**, but the concentration of phenolates can be estimated at the level of 10–20% in pure water and near 40% for **8**, **13** and **12** are in nonionic forms but small amounts of protonated forms (a few percent) are observed for **9**–**11**.

Compounds **9**–**13** are in neutral forms at pH 10. However, only compounds **5**–**7** are completely dissociated. Other phenols, **1**–**4**, exist both in nonionic and anionic forms.

Actually, the situation is more complicated in micellar solutions containing CTAB and SDS. Charged micelles of the cationic surfactant accumulate hydroxyl groups in the Stern layer. Thus, the local pH at the micelle interface is higher, compared with the one measured in solution. As a result, the apparent K_A value increases and enhanced dissociation of weak acids (phenols) and protonated amines is observed. The opposite effect is observed in micellar solutions of anionic surfactants.[22–24]

All this means that, depending on the pH and on the pollutant, one can expect the binding by the micelles of nonionic or ionic species or the binding of both forms.

In acidic media, which are very convenient from the point of view of the pollutant acid–base equilibrium, the hydrolysis of SDS and APG can occur.[21,25,26] To eliminate the hydrolysis, separation was made directly after pH adjustment.

Recovery of pollutants in MEUF

Recovery of pollutants and/or binding of pollutants (Table 2) can be characterized by several parameters, including rejection $R_{A,UF}$ and micelle binding constant $K_{A,UF}$.

$$R_{A,UF} = \left(1 - \frac{[A]_P}{[A]_R}\right) \times 100\% \qquad (3)$$

$$K_{A,UF} = \frac{[A]_M}{[A]_W([S] - cmc)} \qquad (4)$$

where A and S denote the pollutant and the surfactant respectively, and the subscripts P, R, M and W stand for the permeate, retentate, micellar pseudophase and aqueous pseudophase, respectively. [S] – cmc is the concentration of the surfactant which contributes to the surfactant pseudophase, and $[A]_M$ and $[A]_W$ are the concentrations expressed in the total volume of the solution.

Table 2 Rejection $R_{A,UF}$ (%) and binding constant $K_{A,UF}$ calculated from ultrafiltration experiments

		CTAB		SDS		APG	
Pollutant	pH	$R_{A,UF}$	log $K_{A,UF}$	$R_{A,UF}$	log $K_{A,UF}$	$R_{A,UF}$	log $K_{A,UF}$
4-Methylphenol	3	72.8	2.20	86.2	1.55	39.8	1.52
	7	72.3	2.20	85.3	1.52	29.8	1.33
	10	88.1	2.65	78.0	1.31	26.3	1.26
Phenol	3	33.6	1.49	66.2	1.05	20.3	1.11
	7	34.2	1.50	65.8	1.04	19.2	1.08
	10	95.8	3.14	33.1	0.45	8.7	0.68
4-Fluorophenol	3	64.0	2.03	74.9	1.23	19.4	1.09
	7	61.2	1.98	74.0	1.21	21.0	1.13
	10	89.2	2.70	67.0	1.07	10.3	0.76
4-Methoxyphenol	3	44.7	1.69	71.1	1.15	20.3	1.11
	7	43.4	1.67	72.2	1.17	22.0	1.15
	10	75.7	2.27	63.4	1.00	19.6	1.09
4-Chlorophenol	3	91.1	2.79	92.7	1.86	53.3	1.76
	7	90.5	2.76	90.2	1.72	49.7	1.70
	10	97.8	2.43	76.7	1.28	34.1	1.42
2,4-Dichlorophenol	3	96.5	3.22	88.5	1.64	39.8	1.52
	7	96.0	3.16	86.2	1.55	29.8	1.33
	10	99.1	3.82	85.3	1.52	26.3	1.26
	3	99.4	4.00	78.0	1.31	60.3	1.89
4-Nitrophenol	7	99.2	3.87	86.2	1.55	59.2	1.87
	10	99.8	4.48	85.3	1.52	34.6	1.43
4-Ethylphenylamine	3	22.0	1.23	97.3	2.32	14.3	0.93
	7	47.0	1.73	91.8	1.81	42.1	1.57
	10	69.6	2.14	89.7	1.70	43.1	1.58
4-Isopropylphenylamine	3	60.7	1.97	96.3	2.17	88.7	2.60
	7	86.7	2.60	95.9	2.13	97.2	3.24
	10	88.1	2.65	91.3	1.78	97.0	3.21
4-Methoxyphenylamine	3	17.9	1.12	61.6	0.96	11.1	0.80
	7	28.3	1.38	42.3	0.62	14.5	0.93
	10	37.1	1.55	47.9	0.72	18.8	1.068
Phenylamine	3	11.1	0.88	48.0	0.72	1.0	−0.29
	7	37.9	1.57	38.5	0.56	7.8	0.63
	10	37.9	1.57	38.8	0.56	11.1	0.80
4-Aminobenzonitrile	3	17.9	1.12	80.3	1.37	1.8	−0.03
	7	21.5	1.22	64.5	1.02	1.2	−0.21
	10	24.7	1.30	39.9	0.58	3.6	0.28

Rejection can be correlated with the binding constant according to the linear relationship $R_{A,UF} = a + b \log K_{A,UF}$. Actually, the relationship has an S-shape approaching two asymptotic values of rejection equal to 0 and 100%, respectively. However, the results below 10% and above 90% can be rejected as they concern the extreme cases of negative and positive recoveries. The following relationships were obtained irrespective of the acidity of the surfactant solution:

– for SDS:

$$R_{A,UF} = 14.67 + 47.03 \log K_{A,UF} \quad R = 0.992; \log K_{A,UF} \in (0.5, 1.7) \qquad (5)$$

– for CTAB:

$$R_{A,UF} = -34.84 + 47.29 \log K_{A,UF} \quad R = 0.996; \log K_{A,UF} \in (0.8, 2.7) \qquad (6)$$

– for APG:

$$R_{A,UF} = -27.23 + 44.44 \log K_{A,UF} \quad R = 0.992; \log K_{A,UF} \in (0.6, 1.9) \qquad (7)$$

where R denotes the regression coefficient.

As is seen in Fig. 2, similar relationships were obtained for CTAB and APG. Thus, the following relationship was obtained

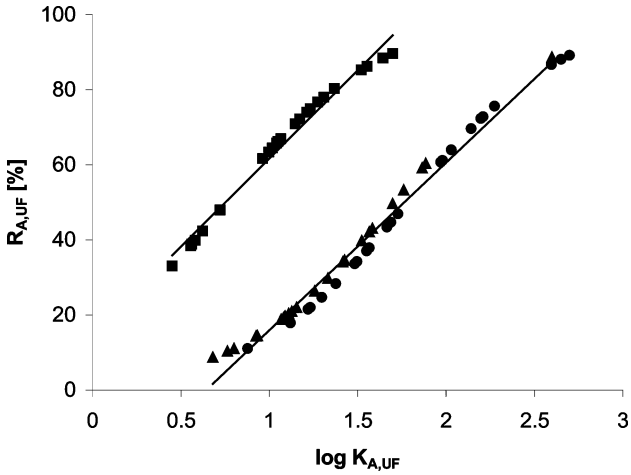

Fig. 2 Rejection of pollutants *versus* log $K_{A,UF}$ (●, CTAB; ■, SDS; ▲, APG).

when the results obtained for CTAB and APG were taken into consideration:

– for CTAB + APG:

$$R_{A,UF} = -28.75 + 44.45 \log K_{A,UF} R = 0.993 \quad (8)$$

The mass balance equations can be described as follows:

$$V_o[A]_o = V_R[A]_R + V_P[A]_P \quad (9)$$

$$V_o[S]_o = V_R[S]_R + V_P[S]_P \quad (10)$$

where V_o, V_R and V_P indicate the volumes of the feed, retentate and permeate, respectively. In the case considered $V_R = V_P = 0.5V_o$, $[A]_o = 10^{-2}$ M, $[S]_o = 10$ cmc, $[S]_P \approx 1$ cmc and $[S]_R = 19$ cmc.

The values of $R_{A,UF}$ and log $K_{A,UF}$, calculated from ultrafiltration experiments (Table 2), indicate that CTAB micelles bind phenols well both in their anionic and nonionic forms, although the anionic forms are better rejected in ultrafiltration than the nonionic ones. As a result, the highest rejections of phenols are obtained for alkaline aqueous solutions. The highest rejections are obtained for 4-nitrophenol, 2,4-dichlorophenol and 4-chlorophenol, while the lowest rejections are obtained for phenol and 4-methoxyphenol.

Amines are not so well bound by CTAB micelles as phenols. The worst results are obtained for acidic solutions where amines are almost entirely protonated. However, even in this case, the rejection of 4-isopropylphenylamine is above 60%. Amines **9**, **10** and **12** have different hydrophobicities due to the presence of the alkyl chain. The hydrophobicities change in the range **10** > **9** > **12** which agrees with the order of the observed rejections $R_{A,UF}$[**10**] > $R_{A,UF}$[**9**] > $R_{A,UF}$[**12**]. All this means that the hydrophobicity of the pollutants is the second important factor.

Hydrophobicity may be characterized by several parameters. The octanol/water partitioning parameter is often used as it can be estimated from the molecular structure. However, it is impossible to derive any statistically valid relationship correlating $R_{A,UF}$ and $K_{A,UF}$ with the octanol/water partitioning coefficient (log $P_{o/w}$) or with molecular volume. The results are scattered and the correlation coefficients are low (0.1–0.7).

Satisfactory rejections of both phenols and amines are observed for SDS solutions. The exception is the rejection of 4-nitrophenol from neutral and alkaline solutions. It is interesting that at the pH of 10, the rejections of phenols are above 60%. Therefore, although anionic forms of phenols are rejected by the micelles, the bonding occurs. This means phenol nonionic forms, bound by micelles, are formed due to the shifting of the equilibrium of reaction 1. SDS micelles bind amines better than CTAB micelles and higher rejections are observed.

Alkylpolyglucoside is not an appropriate surfactant for the recovery of the considered pollutants. High rejection of 4-isopropylphenylamine only is observed.

All this means that CTAB or SDS solutions can be used for the recovery of pollutants. The former and the latter are preferred for recovery of phenol and amine, respectively.

Recovery of pollutants in CP

The extraction of the studied pollutants to the surfactant-rich phase can be expressed by the percentage of extraction $\%E_{CP}$ and distribution ratio D_{CP}:

$$\%E_{CP} = \left(\frac{[A]_0 V_0 - [A]_W V_W}{[A]_0 V_0} \right) \times 100 \quad (11)$$

$$D_{CP} = \frac{[A]_S}{[A]_W} \quad (12)$$

where A denotes the pollutant, and the subscripts 0, S, W stand for the initial solution, surfactant-rich phase and aqueous phase, respectively; V is the volume of the solution, dm^3.

The values of these parameters (Table 3) depend upon the pollutant and the presence of electrolyte. The effect of the electrolyte upon the extraction is different for phenols and amines.

Addition of electrolyte (1 M NaCl) causes an increase in the concentration of OMD-11 in the surfactant-rich phase (Table 4). Sodium chloride effectively breaks the hydrogen bonds between water molecules and both the polyoxyethylene chain and phenol molecules. However, remaining in the aqueous phase, the NaCl present does not affect the hydrogen bonding in the surfactant-rich phase. The salting-out effect is dominant for phenols, while the reaction equilibrium seems to become dominant for amines. As a result, the addition of sodium chloride increases the extraction of phenols and decreases the transfer of amines to the surfactant-rich phase.

The recovery of pollutants by the cloud point technique also depends on the concentration of the surfactant, overheating and type of pollutants.[7,8] The percentage of phenols recovery changes

Table 3 The percent of extraction ($\%E_{CP}$) and distribution coefficients (log D_{CP}) for solutions with and without electrolyte (1 M NaCl); [OMD-11] = 3.6 × 10^{-2} M, [pollutant] = 10^{-3} M, ΔCP = t − CP = 20 °C (s.d. – standard deviation)

	Deionized water				With 1 M NaCl			
Pollutant	$\%E_{CP}$	s.d.	log D_{CP}	s.d.	$\%E_{CP}$	s.d.	log D_{CP}	s.d.
4-Methylphenol	64.9	1.6	1.78	0.07	69.1	1.5	1.82	0.06
Phenol	52.0	1.4	1.59	0.10	65.1	1.3	1.64	0.11
4-Fluorophenol	38.0	3.2	1.35	0.06	71.1	3.2	1.90	0.07
4-Methoxyphenol	21.4	3.6	0.94	0.09	61.3	1.7	1.71	0.03
4-Chlorophenol	80.9	1.9	2.14	0.05	89.6	1.4	2.45	0.06
2,4-Dichlorophenol	70.4	5.5	1.89	0.11	90.2	3.1	2.49	0.15
4-Nitrophenol	72.2	2.5	1.98	0.03	79.6	2.3	2.12	0.05
4-Ethylphenylamine	58.1	6.9	1.77	0.13	45.6	7.2	1.43	0.21
4-Isopropylphenylamine	58.2	6.6	1.66	0.12	45.3	4.0	1.43	0.07
4-Aminobenzonitrile	42.9	3.3	1.39	0.06	40.5	4.2	1.34	0.08

Table 4 Content of OMD-11 in the surfactant-rich phase (CP extraction); $\Delta CP = t - CP$, [OMD-11] = 3.6×10^{-2} M

[NaCl]	ΔCP/°C	%OMD-11
0	5	42.9
	10	56.6
	15	67.6
	20	75.8
	25	81.2
	30	83.9
1 M	5	80.0
	10	84.2
	15	87.5
	20	90.1
	25	91.7
	30	92.6

approximately linearly with the surfactant concentration. The overheating of the system in the range from 10 to 40 °C has a negligible effect on the kinetics of phase separation. However, an effect of overheating on the efficiency of phenols separation is observed. The overheating of 20 °C was selected to compare the efficiencies of separations. The recovery of pollutants depends on the type of pollutants, *i.e.*, their hydrogen bond acidity and hydrophobicity. The best separations are obtained for the most acidic and hydrophobic compounds.

The comparison with ultrafiltration experiments (Table 5) indicate that the cloud point technique is able to cause better separation of the considered pollutants than ultrafiltration. The comparison is, however, only qualitative as different surfactants were used in the cloud point and ultrafiltration experiments.

Table 5 Distribution coefficients (log *D*) for cloud point technique (CP) and ultrafiltration (UF), (CP: [OMD-11] = 3.6×10^{-2} M, [pollutant] = 10^{-3} M, $\Delta CP = t - CP = 20$ °C; UF: pH = 3, [SDS] = 9.7×10^{-2} M, [CTAB] = 9.6×10^{-3} M and [APG] = 1.1×10^{-2} M, equivalent to 10 cmc)

Pollutant	OMD-11 CP	SDS UF	CTAB UF	APG UF
4-Methylphenol	1.78	0.86	0.57	0.22
Phenol	1.59	0.18	0.47	0.10
4-Fluorophenol	1.35	0.60	0.44	0.09
4-Methoxyphenol	0.94	0.54	0.26	0.10
4-Chlorophenol	2.14	1.14	1.05	0.33
2,4-Dichlorophenol	1.89	0.94	1.46	0.22
4-Nitrophenol	1.98	0.66	2.22	0.40
4-Ethylphenylamine	1.77	1.57	0.11	0.07
4-Isopropylphenylamine	1.66	1.43	0.41	0.95
4-Aminobenzonitrile	1.39	0.71	0.09	0.01

The advantage of cloud point separation over the surfactant enhanced ultrafiltration is also demonstrated when the amounts of surfactants released per tons of phenols removed are compared. For example they are as follows: 0.6 ton OMD-11/ton 4-chlorophenol, 1.3 ton CTAB/ton 4-chlorophenol and 11.2 ton SDS/ton 4-chlorophenol. The very high value determined for SDS is caused by the high hydrophilicity of this compound, reflected then in the cmc value. However, more hydrophobic surfactants can be used, *e.g.*, oxyethylated fatty acid methyl esters with a shorter polyoxyethylene chain and sodium alkylsulfate containing 16–18 carbon atoms in the alkyl group. In such a case the considered parameter decreases and assumes the following values: 0.2 ton OMD-5/ton 4-chlorophenol and 0.3 ton sodium octadecylsulfate/ton 4-chlorophenol.

Effect of pollutant structure upon its recovery in ultrafiltration

The recovery of pollutants in MEUF can be predicted from the micelle binding constants which can be found in the literature for a broad range of compounds.[18] However, such estimation can be carried out only under comparable conditions, including the acidity of the aqueous phase, electrolyte concentration and temperature.

The linear solvation free energy relationship (LSER) has proven to be useful for understanding processes that involve the transfer of solutes between two phases. The following linear model was proposed by Abraham:[16,17]

$$\log SP = c + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + s\pi_2^H + rR_2 + vV_x/100 \quad (13)$$

where SP refers to the property of interest for a series of solutes, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ account for solute hydrogen bond acidity and basicity, respectively, π_2 stands for solute dipolarity, R_2 is excess molar refraction and V_x is solute molar volume; *c*, *a*, *b*, *s*, *r*, and *v* are regression coefficients. The value of $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$, π_2 and R_2 can be found in the literature, and the value of V_X can be calculated from solute structure.[16,17] Among other applications of LSER, Abraham[16] has shown that octanol/water partitioning coefficients satisfy the relationship:

$$\log P_{oct/w} = 0.08 + 0.03\,\Sigma\alpha_2^H - 3.4\,\Sigma\beta_2^H - 1.09\,\pi_2^H + 0.58\,R_2 + 3.81\,V_x/100 \quad (14)$$

It has also been demonstrated that $\log P_{mic/w}$ (between micellar and water pseudophase) correlate reasonably well with $\log P_{o/w}$.[27–29]

Quina *et al.*[18] have derived the following equations, correlating micelle binding constant with Abraham parameters:

– for CTAB:

$$\log K_{A,appr} = -0.76 \pm 1.02\,\Sigma\alpha_2^H - 3.78\,\Sigma\beta_2^H - 0.32\pi_2^H + 0.76R_2 + 3.57V_x/100 \quad (15)$$

– for SDS:

$$\log K_{A,appr} = -0.62 \pm 0.08\,\Sigma\alpha_2^H - 1.84\,\Sigma\beta_2^H - 0.57\pi_2^H + 0.32R_2 + 3.25V_x/100 \quad (16)$$

– for Brij-35 (oxyethylated alcohol):

$$\log K_{A,appr} = -1.39 \pm 1.62\,\Sigma\alpha_2^H - 3.83\,\Sigma\beta_2^H - 0.37\pi_2^H + 1.63R_2 + 3.65V_x/100 \quad (17)$$

The values of log $K_{A,appr}$, calculated from equations derived by Quina *et al.*,[18] are in satisfactory agreement with those estimated in the ultrafiltration experiment by the present authors (Fig. 3 and 4).

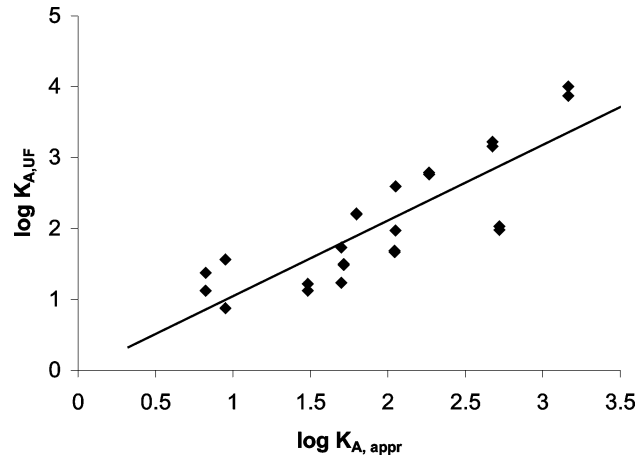

Fig. 3 Comparison of binding constants obtained from ultrafiltration experiments (CTAB, pH = 3 and 7) with those estimated from eqn. 15.

The presence of some deviations is observed as the data were obtained using different analytical techniques and the experimental conditions were not the same.[18] The experimental and estimated results coincide for CTAB. As a result, the linear relationship:

$$\log K_{A,UF}^{CTAB} = 1.068 \log K_{A,appr}^{CTAB} - 0.024 \quad (18)$$

with a slope near 1 was obtained.

A systematic deviation is observed for SDS as it is reflected in the slope equal to 0.886:

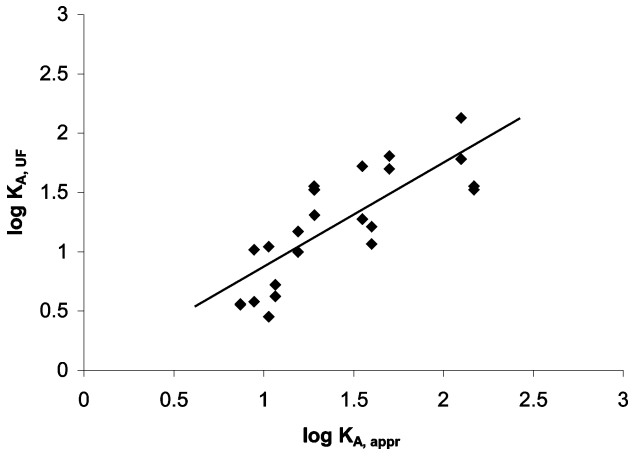

Fig. 4 Comparison of binding constants obtained from ultrafiltration experiments (SDS, pH = 7 and 10) with those estimated from eqn. 16.

$$\log K_{A,UF}^{SDS} = 0.886 \log K_{A,appr}^{SDS} - 0.015 \quad (19)$$

Taking into account that rejection $R_{A,UF}$ is a linear function of log $K_{A,appr}$, and can be correlated with solute structure parameters, the following effects of solute structure parameters upon the efficiency of ultrafiltration can be postulated. The dominant contributions to the solute binding and then rejection in ultrafiltration experiments arise from the terms in V_x and $\Sigma\beta_2^H$. The former reflects the hydrophobic effect. As a result, more hydrophobic solutes are better bound by micelles and better rejected in ultrafiltration. The effect is clearly observed when a homologous series of solutes is considered, *i.e.*, the first homologues of alcohol series are too hydrophilic to be incorporated into the micelles. Moreover, they increase the cmc of the surfactants. High binding is observed for alcohols containing at least 5 carbon atoms. $K_{A,appr}$ values are equal to 0.1, 0.3, 1.3, 3.2, and 14 M^{-1} for methanol, ethanol, 2-propanol, butanol and pentanol, respectively, as determined for SDS solutions by NMR technique.[30]

The high negative coefficients at the $\Sigma\beta_2^H$ terms imply that solute hydrogen bond basicity strongly favors partitioning to the aqueous pseudophase, *i.e.* that bulk water is a much better hydrogen bond donor that the solubilization sites in the micelles. Phenols have a higher proton bond donating ability and lower proton bond accepting ability than amines (Table 1). As a result, lower rejections are obtained for the amines, compared with the phenols.

The values of $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ depend upon the substituent and they change in a typical way, *i.e.*, $\Sigma\alpha_2^H$ increases and $\Sigma\beta_2^H$ decreases in the presence of electron withdrawing substituents. The strongest effect is observed for the nitro group. The opposite changes are observed in the presence of electron donating substituents, *e.g.*, alkyl group. The values of π_2^H and β_2^H are comparable for the considered compounds. The exceptions are high values of π_2^H registered for 4-nitrophenol and 4-aminobenzonitrile. The molar volume is sensitive to the substituent and it increases in the presence of any substituent but especially strongly in the presence of the bulky, branched isopropyl group.

The effect of solute dipolarity is negative but relatively weak, indicating that the dipolarity of the bulk water is only slightly lower than that of the micelle solubilization sites. The effect of solute excess molar refraction is positive but also weak in CTAB and SDS solutions. This means that neither water nor the micelles of these surfactants provide a polarizable solubilization environment. The parameter is important for nonionic surfactant because polyoxyethylene chain contributes to the polarizability of micellar solubilization sites.

Hydrogen bond acidity makes little or no contribution to micellar solubilization in SDS, indicating that the hydrogen bond basicity of the micellar solubilization environment is comparable to that of bulk water. Thus, the hydrogen bond acidity of the solute makes little or no contribution to micellar solubilization and then rejection in ultrafiltration. The effect is positive and relatively strong for CTAB and nonionic surfactant solutions, *i.e.*, solute hydrogen bond acidity favors pollutant incorporation into micelles and rejection in ultrafiltration.

All this means that strongly hydrophobic pollutants can be easily bound by micelles and their high rejections can be achieved in ultrafiltration, irrespective of the choice of micelles. Low hydrophobic pollutants can also be rejected in ultrafiltration but only in the presence of attractive electrostatic interactions. Thus, the use of cationic and anionic surfactants is favored for rejections of pollutants having acidic and basic group(s), respectively. Nonionic polyglucoside is not suitable for separations.

Using eqns. 5, 6, 15, 16, 18 and 19, the following equation for $R_{A,UF}$ is obtained:

– for CTAB

$$R_{A,UF} = -74.3 + 51.5\,\Sigma\alpha_2^H - 191.1\,\Sigma\beta_2^H - 16.1\pi_2^H + 38.3R_2 + 180.2V_x/100 \quad (20)$$

– for SDS

$$R_{A,UF} = -11.9 - 0.33\,\Sigma\alpha_2^H - 76.6\,\Sigma\beta_2^H - 24.0\pi_2^H + 13.2R_2 + 135.4V_x/100 \quad (21)$$

The equations enable the estimation of rejections of organic pollutants in ultrafiltration from the Abraham parameters with the average errors equal to 9.5 ± 4.8 and 8.4 ± 2.9 for CTAB and SDS natural solutions (*i.e.*, acidic for CTAB and alkaline for SDS).

Effect of pollutant structure upon its recovery in CP separation

The surfactant-rich phase shows a higher hydrogen-bond accepting ability than the aqueous phase. As a result, an increase in the solute hydrogen-bond donating power increases the transfer of solute to the surfactant-rich phase. The effect of the solute hydrogen-bond ability is the opposite, *i.e.* negative, as the aqueous phase has a significantly higher ability to donate protons than the surfactant-rich phase. That ability depends upon the water content in the aqueous and surfactant-rich phase. The aqueous phase contains the surfactant in the concentration near cmc. The content of water in the surfactant-rich phase depends upon the temperature (*i.e.*, the overheating over the cloud point − ΔCP) and the electrolyte content.[9] In the case considered (ΔCP = 20 °C) the surfactant-rich phase contains 15 and 5% water for the NaCl concentrations equal to 0 and 1 M, respectively. Thus, the surfactant-rich phase formed in the presence of sodium chloride is a weaker hydrogen-bond donor than the phase separated from the solution without NaCl. All this means, even in the case of phenol, that the effect of electrolyte upon the extraction of phenol is more comprehensive than could be expected when only the salting out effect is considered. The electrolyte also modifies the relative proton accepting and proton donating abilities of the separated phases.

The surfactant-rich phase is less hydrophilic than the aqueous phase. Moreover, the hydrophilicity of the surfactant-rich phase decreases with increased overheating over CP and increased concentration of electrolyte. Thus, the separation depends most upon the solute hydrophobicity, which can be roughly quantified by the solute molar volume or by the octanol–water partition coefficient.

The following statistically valid equations were obtained:

– the set of phenols and amines in the absence of electrolyte:

$$\log D_{CP} = 0.54\Sigma\alpha_2^H - 1.11\,\Sigma\beta_2^H - 0.74\pi_2^H + 2.22R_2 + 0.68V_x/100R^2 = 0.999;\ \text{s.d.} = 0.07;\ F = 1631.1;\ N = 11 \quad (22)$$

$$\log D_{CP} = 0.38\Sigma\alpha_2^H - 0.92\Sigma\beta_2^H - 0{,}26\pi_2^H + 1.83R + 0.29 \log PR^2 = 0.999;\ \text{s.d.} = 0.06;\ F = 1742;\ N = 11 \quad (23)$$

– the set of phenols and amines in the presence of 1 M NaCl:

$$\log D_{CP} = 0.84\Sigma\alpha_2^H - 2.97\Sigma\beta_2^H + 2.58V_x/100R^2 = 0.994;\ \text{s.d.} = 0.15;\ F = 552.7;\ N = 11 \quad (24)$$

$$\log D_{CP} = 0.83\Sigma\alpha_2^H - 1.33\Sigma\beta_2^H + 0.19\pi_2^H + 0.97R_2 + 0.42\log PR^2 = 0.997;\ \text{s.d.} = 0.11;\ F = 604.1;\ N = 11 \quad (25)$$

where R^2 denotes the determination coefficient, s.d. is standard deviation, F stands for the Fischer–Snedecor function and N is the number of pollutants.

The equations enable the estimation of the distribution and recovery of pollutants from solutions containing 0 and 1 M NaCl with the average error of log D_{CP} equal to 0.21 ± 0.14 and 0.11 ± 0.09, respectively.

Similar equations are obtained for the percentage of extraction. The comparison of eqns. 22–25 with eqns. 15–17 and 20–21 indicates that the surfactant-rich phase exhibits a great similarity to the micellar phase. The effects of the considered parameters are similar. The hydrogen bond acidity and hydrophobicity of pollutants increases the recovery of pollutants, *i.e.* their distribution to the surfactant-rich phase. The hydrogen bond basicity and the excess molar refraction have negative effects.

Oxyethylated methyl dodecanoates show similar surfactant properties to oxyethylated alcohols.[8,9,31,32] Although they have the terminal hydroxyl group blocked with the methyl group, a relationship between log D_{CP} or $\%E_{CP}$ and $K_{A,appr}$ calculated from eqn. 17 can be derived (Fig. 5), the deviations of results are not great.

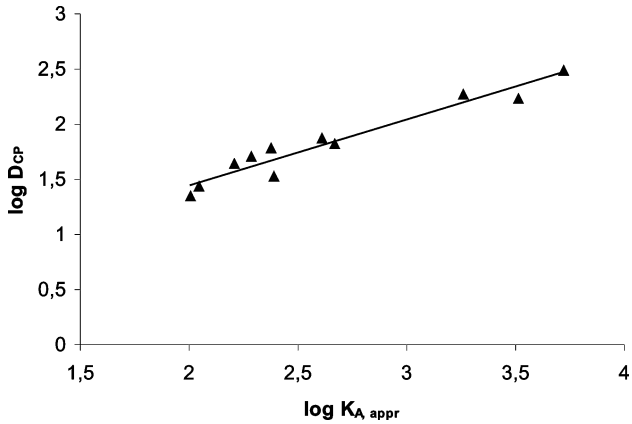

Fig. 5 Effect of micelle binding constant upon the distribution of pollutants between the surfactant-rich phase and micellar aqueous phase (1 M NaCl).

Conclusions

Micellar enhanced ultrafiltration and cloud point technique enable high recovery of some organic pollutants without using any hydrocarbon solvents. The cloud point technique gives higher recovery than ultrafiltration. Appropriate surfactants having low critical micelle concentrations and low cloud points must be used. Oxyethylated fatty acid methyl esters are the most appropriate for the cloud point separation, as having ester groups they are quickly hydrolyzed in sewage systems. CTAB and SDS are appropriate for ultrafiltration. The recovery of pollutants in both considered techniques can be estimated from the micelle binding constants or from linear solvation free-energy relationships according to the Abraham model. The efficiency of separation increases with an increase of pollutant hydrophobicity and excess molar refraction. The hydrogen bond acidity of pollutants improves separation from systems containing nonionic surfactants and CTAB, but it does not affect the separation in the presence of SDS. Hydrogen bond basicity and dipolarity of pollutants decrease the recovery. The derived models enable the selection of pollutants, which can be efficiently removed from aqueous streams by the cloud point technique and micellar enhanced ultrafiltration.

Acknowledgements

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PAPER

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Solvent-free synthesis of melamines under microwave irradiation

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A fast, highly efficient and environmentally friendly solvent-free procedure under microwave irradiation, using silica gel supported reagents, for the synthesis of melamines, including ones with a broad range of biological activities, is developed. The main advantages of the synthetic approach presented here are the cheap and easily available starting material, cyanuric chloride, and the considerable rate enhancement in comparison with a thermal reaction. The scope of the reaction, towards the amine used, is also studied and it is shown that the method is valid as a highly effective one when moderately bulk amines are used. The by-product of the reaction, hydrogen chloride, is quenched as ammonium salts, preventing its release into the environment.

Introduction

Melamines are an important class of organic compounds since they have demonstrated a wide range of biological activities such as anti-angiogenesis,[1] anti-tumour activity for breast[2] and ovarian[3] cancer treatment, effective treatments for menopausal symptoms and postmenopausal osteoporosis,[4] anti-metastatic activities,[5] herbicidal effects,[6] and many others. In addition, some of them are also useful as chemoselective building blocks for dendrimers[7] and porous hydrogen-bonded networks,[8] chromophores in probes for the absolute configuration determination by circular dichroism,[9] *etc.*

Among the broad synthetic pathways known for melamine preparation,[10] an efficient and expedite method is based on the nucleophilic substitution of chlorine atoms in cyanuric chloride (**1**), a rather cheap and easily available material, with different amines.[11]

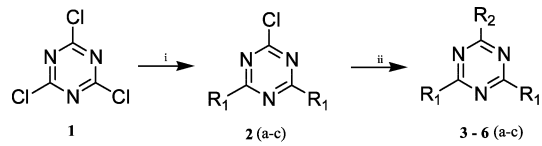
While an amine replaces the first chlorine atom spontaneously and the second under mild conditions, relatively hard conditions have to be used to achieve complete substitution,[12] which represents a serious problem if hindered amino groups, like 1-adamantyl amino,[13] have to be introduced in the molecule. Applying spot-synthesis technique, one of the most effective synthetic protocols in combinatorial chemistry, on cellulose and polypropylene membranes, a microwave irradiated reaction, using DMF solutions of piperidine, has been found to be a highly efficient substitution procedure at membrane-bond monochlorotriazines.[14] An *N*-alkylation of pyrazole by cyanuric chloride, leading to *tris*-pyrazolyl triazine,[15] has been performed in a solvent-free procedure under microwave irradiation in the absence of any additives, starting from *N*-benzyl pyrazole, where the problems, related with quaternisation and isomerisation of the substrate as well as with hydrogen halide elimination from the reagent, have been devoided. Providing a solventless microwave assisted synthesis of pyrazoylphenylamino triazines, resulting in a low yield of trisubstituted product,[16] the occurrence of restricted rotations and triazine tautomerism have been observed and the equilibrium constants and the activating free energies of the restricted rotations have been calculated.

Microwave assisted reactions have become an established tool in organic synthesis, since they achieve rate enhancement, higher yields and better selectivity in respect to the conventional heating.[17] The efficient, clean and economic solventless technique,[18] which avoids the hazards of solution phase reactions, where high pressures are created in a microwave oven at elevated temperatures, is an environmentally benign condition preventing release of reaction products into the environment.

Here we report a simple, facile and effective solvent-free microwave accelerated procedure for melamines preparation, using solid-supported reagents.

Results and discussion

The starting 2-chloro-4,6-di(dialkylamino)-1,3,5-triazines were prepared by replacing the chlorine atoms of cyanuric chloride with different amines, according to a known procedure,[19] in high



R_1 = morpholino (a) ; 1-adamantyl amino (b) ; diethylamino (c)

R_2 = dibenzyl amino (**3**) ; morpholino (**4**) ; 1-adamantyl amino (**5**) ; dicyclohexyl amino (**6**)

Scheme 1 General method used for the preparation of melamines **3–6**. (i) amine (4 equiv.), dichloromethane; (ii) silica gel (2 g per mmol of **2**), amine (3 equiv.), MWI (800 W).

isolated yields (87–96%) after flash chromatography (Scheme 1). These products, initially impregnated onto silica gel support by solvent removal of the preliminary prepared dichloromethane solutions, were irradiated in a domestic household microwave oven in open vessels with a power of 800 W, to give the corresponding melamines **3–6** in different yields, depending mainly on the bulk of the amine used (Scheme 1, Table 1). The by-product of both reactions, hydrogen chloride, was quenched by the amine, used as a nucleophile and as a base, forming an ammonium salt, thus avoiding its release into the environment. When neutral Al_2O_3 was tested as a solid support in the case of **3c** melamine formation from **2c**, lower conversion was observed even after 20 min irradiation (entry 13, 43% after 20 min *vs* entry 12, 94% after 10 min), therefore the silica gel was used in all experiments.

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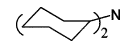
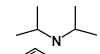
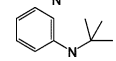
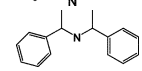
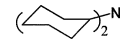
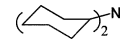
Table 1 Solvent-free preparation of melamines **3–6** under microwave irradiation

Entry	Starting chloride	React. time/min	Melamine			Yield[a] (%)
			Comp.	R_1	R_2	
1	**2a**	10	**3a**		$(PhCH_2)_2N$	96
2	**2a**	5	**4a**			93
3	**2a**	15	**5a**			87
4	**2a**	45	**6a**			10
5	**2a**	10	—			—[b]
6	**2a**	10	—			—[b]
7	**2a**	10	—			—[b]
8	**2b**	10	**3b**		$(PhCH_2)_2N$	93
9	**2b**	5	**4b**			91
10	**2b**	15	**5b**			78
11	**1**	15	**5b**			82
12	**2c**	10	**3c**	$(C_2H_5)_2N$	$(PhCH_2)_2N$	94
13	**2c**[c]	20	**3c**	$(C_2H_5)_2N$	$(PhCH_2)_2N$	43
14	**2c**	5	**4c**	$(C_2H_5)_2N$		96
15	**2c**	15	**5c**	$(C_2H_5)_2N$		94
16	**2c**	15	**6c**	$(C_2H_5)_2N$		1.5
17	**2c**	60	**6c**	$(C_2H_5)_2N$		16

[a] Isolated yield after purification by preparative TLC. [b] No reaction occurs. [c] Neutral Al_2O_3 was used as a solid support.

As can be seen in Table 1, no reaction occurred with di-isopropyl amine (entry 5), which could be due to reagent evaporation as no amine was detected inside the crude reaction mixture by chromatography. However, since the same reaction, performed in a closed vessel, where the presence of the amine was detected at the end of the reaction, showed again the starting chloride only, it gives an indication that di-isopropyl amine is rather hindered in replacing the last chlorine atom of triazine **2a** under these conditions. Additionally, no substitution products were observed when other bulky amines were used; *N*-t-butyl-*N*-phenyl amine (entry 6) and *N*,*N*-di-(1-phenylethyl)amine (entry 7). The limitation of the method, due to the bulk of the amino group inserted, can also be clearly seen when moderately hindered amines were used in the substitution of substrates **2a–c**.

Thus, while morpholine and dibenzyl amine reacted almost completely after 5 min and 10 min respectively, the relatively hindered 1-adamantyl amine needed 15 min irradiation. As dicyclohexyl amine is more bulky than 1-adamantyl amine, it showed the lowest reactivity in the series tested, giving 10–16% products only (entries 4, 16 and 17) even after 1 h irradiation. Nevertheless, compared with a thermal reaction in solution in the case of **5b** formation, where very high temperatures have been used (285 °C) to reach 53% conversion[13] *vs*. 78% after 15 min (entry 10), the method presented here shows considerable rate enhancement and it presents a fast and simple procedure for melamine synthesis when moderately hindered amino groups have to be introduced into the molecule.

As the tris-adamantyl melamine (**5b**) appears as a frontier case, giving high conversion but in longer reaction times in respect to the less bulky amines tested, the direct transformation of cyanuric chloride into this compound was also performed, resulting in a high reaction yield in the same time scale (82% from **1**, entry 11 *vs*. 78% from **2b**, entry 10), which shows that if melamines with three equal substituents have to be synthesised, cyanuric chloride can be used directly, without preliminary preparation of the bisubstituted compound.

The microwave accelerated transformation, reported here, showed clean conversion in high yields when moderately hindered amines were used. In order to compare this method with the thermal conversion, the reaction of **2c** was carried out in refluxing decaline (193 °C) as a reaction media, using dibenzyl amine and morpholine as nucleophiles, followed by ^{1}H NMR spectra of the crude reaction mixtures. As can be seen in Table 2, while the dibenzyl amine reacted slower than in solventless conditions in a microwave, giving a similar conversion but in longer time (Table 2, entries 1–3, 86% after 9 h *vs.* Table 1, entry 12, 94% after 10 min), the more hindered adamantyl amine showed even slower conversion, leading to a relatively low reaction yield after 9 h reflux (Table 2, entries 4–6, 48% after 9 h *vs.* Table 1, entry 15, 94% after 15 min), thus appearing as a good candidate for a more detailed investigation of the role of the microwaves. Irradiating a decaline solution of **2c** and adamantyl amine in a microwave oven with a power of 800 W on the same scale, where a temperature of 153 °C was measured at the end of the reaction, a considerable rate enhancement was observed in comparison with the conventional heating (Table 2, entries 7–8 *vs.* entries 4–6), which demonstrates that microwaves accelerate the transformation studied. Additionally, the same reagents, impregnated onto silica gel, were heated at the same temperature as the solutions, 193 °C, on the same time scale and the rate enhancement observed (Table 2, entries 9–11, 63–98.5% *vs.* entries 4–6, 28–48%), gives an indication that silica gel promoted the transformation investigated.

In conclusion, despite limitations due to the bulk of the amine used, the microwave accelerated solventless procedure, presented

Table 2 Melamine **3c** and **5c** synthesis from **2c** in different reaction conditions

Entry	Reaction conditions	Reaction time	Melamine	Conversion[a] (%)
1	Thermal reaction in a decaline solution[b]	2 h	**3c**	71
2		6 h	**3c**	82
3		9 h	**3c**	86
4	Thermal reaction in a decaline solution[b]	2 h	**5c**	28
5		6 h	**5c**	42
6		9 h	**5c**	48
7	MWI reaction in a decaline solution[c]	15 min	**5c**	67
8		45 min	**5c**	71
9	Thermal heating on silica gel supported reagents[d]	2 h	**5c**	63
10		6 h	**5c**	89
11		9 h	**5c**	98.5

[a] Followed by ^{1}H NMR spectra of the crude reaction mixtures by comparing the integrals of the signals for CH_2 protons of the diethyl amino groups with those for benzylic CH_2 group in **3c** and for CH_2 group bonded with the quaternary carbon and CH protons, which appear as overlapped signals, in **5c**. [b] The reactions were carried out in refluxing decaline, 193 °C, using 0.5 mmol **2c** and 1 mmol amine in 5 ml decaline. [c] The solutions (the same concentrations and proportions described in footnote b) were irradiated in a microwave oven with a power of 800 W. A temperature of 153 °C was measured at the end of the reaction. [d] The reagents, impregnated on silica gel (1 g per 0.5 mmol **2c**), were heated at 193 °C.

here, is a simple, fast and highly effective method for the synthesis of melamines with moderately hindered amino substituents in the molecule. As the by-product, hydrogen chloride, is quenched as an ammonium salt in the course of the reaction, avoiding its liberation into the air, the method presents an additional environmentally benign synthetic advantage.

Experimental

All reagents were purchased from Aldrich and Fluka and were used without any further purification. The dichloromethane was dried over P_2O_5. MN Kieselgel 60 M was used for MWI transformations as well as for the column chromatograpgy isolation of the products **2a–c** and MN Kieselgel G/UV_{254} was applied for preparative TLC of the products **3–6**. The microwave irradiated reactions (MWI) were made in a domestic household oven Balay 3WM-2121 in open vessels. The melting points were determined with an Electrothermal Mod. IA6304 in capillary tubes without correction. The NMR spectra were recorded on a Bruker AMX 400 in deuterochloroform, the chemical shifts were quoted in ppm in δ-value against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The IR spectra were recorded on an Unicam ATI Mattson Genesis Series FTIR as films, obtained by evaporation of dichloromethane solutions on the NaCl plates, and were quoted in cm^{-1}. The microanalyses were taken on a CHNS Analyser Thermo Finnigan model Flash 1112 Series. High and low resolution mass spectra (EI, FAB+) were carried out by the mass spectrometry service of the University of Santiago de Compostela, Spain.

Substituted 2,4-diamino-6-chloro-1,3,5-triazines. General procedure

To a stirred solution of 10 mmols of cyanuric chloride in dry dichloromethane (100 ml) 40 mmols of amine were slowly added at 0 °C. After stirring for 1 h under cooling and 1 h at room temperature, the amine hydrochloride was filtered, the solvent was removed *in vacuo* and the crude reaction mixture was purified by flash chromatography on silica gel using hexane–ethyl acetate as a mobile phase.

2,4-Bis-(morpholino)-6-chloro-1,3,5-triazine[20] 2a. Flash chromatography (ethyl acetate–hexane 1 : 3), R_f 0.29; 96% yield; m.p. 175–6 °C (lit.[20] 173–4 °C); IR 3054.7, 2985.3, 2908.1, 2858.0, 2306.5, 1569.8, 1496.5, 1446.4, 1365.4, 1307.5, 1265.1, 1114.7, 979.7, 744.4, 705.8; ^{1}H NMR 3.755 (m, 16H); ^{13}C NMR 43.82 (CH_2–N), 66.57 (CH_2–O), 164.33 (C_{quat}), 169.53 (C_{quat}).

2,4-Bis-(1-adamantylamino)-6-chloro-1,3,5-triazine[13] 2b. Flash chromatography (ethyl acetate–hexane 1 : 4), R_f 0.61; 87% yield; m.p. 213–5 °C (lit.[13] 214–5 °C); IR 3405.7, 3054.7, 2985.3, 2915.9, 2684.4, 2306.5, 1581.4, 1515.8, 1423.2, 1265.1, 894.8, 748.2, 705.8; ^{1}H NMR 1.675 (m, 12H, CH–*CH*$_2$–CH), 2.083 (m, 18H, CH and CH–*CH*$_2$–C_{quat}), 4.702 (br s, 2H, NH); ^{13}C NMR 29.54 (CH), 36.42 (CH–*CH*$_2$–CH), 42.04 (CH–*CH*$_2$–C_{quat}), 51.03 (C_{quat}, Ad), 164.59 (C_{quat}, triazine ring), 164.71 (C_{quat}, triazine ring).

2,4-Bis-(diethylamino)-6-chloro-1,3,5-triazine[19] 2c. Flash chromatography (ethyl acetate–hexane 1 : 9), R_f 0.54; 94% yield; colourless oil; IR 3054.7, 2981.4, 2935.1, 2873.4, 2306.5, 1569.8, 1511.9, 1488.8, 1438.6, 1376.9, 1326.8, 1265.1, 1184.1, 1083.8, 1029.8, 975.8, 894.8, 802.2, 748.2, 705.8; ^{1}H NMR 1.170 (t, 12H, *J* 6.8, CH_3), 3.562 (q, 8H, *J* 6.8, CH_2); ^{13}C NMR 13.26 (CH_3), 41.55 (CH_2), 163.90 (C_{quat}), 168.89 (C_{quat}).

Substituted 2,4,6-triamino-1,3,5-triazines. General procedure

To a solution of 0.5 mmol of substituted 2,4-diamino-6-chloro-1,3,5-triazines (**2a–c**) in dichloromethane (10 ml) 1.5 mmols of amine and then 1 g of silica gel were added, the solvent was removed and the mixture was heated in a MW oven at 800 W. When cyanuric chloride **1** was used as a starting material, 3.5 mmols of adamantyl amine were added in the same reaction scale. The products were extracted from silica gel with ethyl acetate (2 × 10 ml) and were purified by preparative TLC (PTLC) on silica gel using hexane–ethyl acetate as a mobile phase. The analytically pure samples were obtained after recrystallisation from an appropriate solvent, depending on the solubility of the products. As the products **4c**, **5c** and **6c** are soluble in all solvents, even in hexene, and can not be recrystallised, their mass spectral data were given instead of microanalyses.

2,4-Bis-(morpholino)-6-dibenzylamino-1,3,5-triazine 3a

Reaction time −10 min; PTLC (ethyl acetate–hexane 1 : 3), R_f 0.58; 96% yield; recrystallisation from heptane: m.p. 133–4 °C; IR 3054.7, 2962.1, 2896.6, 2854.1, 2306.5, 1535.1, 1481.1, 1438.6, 1361.5, 1303.6, 1253.5, 1114.7, 1006.7, 987.4, 863.9, 806.1, 740.5, 702.0; ^{1}H NMR 3.723 (m, 16H, morpholine), 4.746 (s, 4H, CH_2–Ph), 7.234–7.320 (m, 10H, Ph); ^{13}C NMR 43.71 (CH_2–N), 48.34 (CH_2–Ph), 66.80 (CH_2–O), 126.93 (*p*-Ph), 127.78 (*o*-Ph), 128.33 (*m*-Ph), 138.67 (*i*-Ph), 164.45 (C_{quat}), 165.66 (C_{quat}); Anal Calc. for $C_{25}H_{30}N_6O_2$ C 67.24, H 6.77, N 18.82; Found C 67.18, H 6.79, N 19.03%.

2,4,6-Tris-(morpholino)-1,3,5-triazine[21] 4a

Reaction time – 5 min; PTLC (ethyl acetate–hexane 1 : 3), R_f 0.31; 93% yield; recrystallisation from heptane: m.p. 285–8 °C (lit.[21] 284–9 °C); IR 3054.7, 2985.3, 2306.5, 1538.9, 1438.6, 1423.2,

1265.1, 894.8, 748.2, 705.8; ^{1}H NMR 3.730 (m, 24H); ^{13}C NMR 43.59 (CH_2–N), 66.65 (CH_2–O), 164.69 (C_{quat}).

2,4-Bis-(morpholino)-6-(1-adamantylamino)-1,3,5-triazine 5a

Reaction time – 15 min; PTLC (ethyl acetate–hexane 1 : 3), R_f 0.62; 87% yield; recrystallisation from heptane: m.p. 142–4 °C; IR 3421.1, 3054.7, 2985.3, 2912.0, 2854.1, 2306.5, 1562.1, 1538.9, 1488.8, 1442.5, 1265.1, 1114.7, 894.8, 744.4, 705.8; ^{1}H NMR 1.674 (m, 6H, CH–*CH*$_2$–CH), 2.085 (m, 9H, CH and CH–*CH*$_2$–C_{quat}), 3.718 (m, 16H, morpholine), 4.700 (br s, 1H, NH); ^{13}C NMR 29.45 (CH), 36.53 (CH–*CH*$_2$–CH), 41.92 (CH–*CH*$_2$–C_{quat}), 43.64 (CH_2–N), 52.41 (C_{quat}, Ad), 66.79 (CH_2–O), 164.59 (C_{quat}, triazine ring), 164.74 (C_{quat}, triazine ring); Anal Calc. for $C_{21}H_{32}N_6O_2$ C 62.97, H 8.05, N 20.98; Found C 63.27, H 8.19, N 21.24%.

2,4-Bis-(morpholino)-6-dicyclohexylamino-1,3,5-triazine 6a

Reaction time – 45 min; PTLC (ethyl acetate–hexane 1 : 3), R_f 0.78; 10% yield; recrystallisation from ethanol: m.p. 180–1 °C; IR 3054.7, 2985.3, 2306.5, 1531.2, 1423.2, 1265.1, 894.8, 748.2, 705.8; ^{1}H NMR 1.106 (m, 2H, CH_2-4, axial), 1.277 (m, 4H, CH_2-2, axial), 1.310 (m, 4H, CH_2-3, axial), 1.582 (m, 4H, CH_2-2, equatorial), 1.653 (m, 2H, CH_2-4, equatorial), 1.798 (m, 4H, CH_2-3, equatorial), 3.718 (18H, morpholine and CH-1); ^{13}C NMR 25.90 (CH_2-4), 26.52 (CH_2-3), 30.60 (CH_2-2), 43.76 (CH_2–N), 54.98 (CH-1), 66.88 (CH_2–O), 164.79 (C_{quat}), 165.09 (C_{quat}); Anal Calc. for $C_{23}H_{283}N_6O_2$ C 64.15, H 8.90, N 19.52; Found C 63.82, H 8.73, N 19.42%.

2,4-Bis-(1-adamantylamino)-6-dibenzylamino-1,3,5-triazine 3b

Reaction time – 10 min; PTLC (ethyl acetate–hexane 1 : 4), R_f 0.58; 93% yield; recrystallisation from heptane: m.p. 135–6 °C; IR 3421.1, 3054.7, 2985.3, 2912.0, 2850.3, 2306.5, 1550.5, 1492.6, 1423.2, 1265.1, 894.8, 748.2, 705.8; ^{1}H NMR 1.558 (m, 12H, CH–*CH*$_2$–CH), 1.978 (m, 18H, CH–*CH*$_2$–C_{quat}), 4.736 (s, 4H, CH_2–Ph), 4.761 (br s, 2H, NH), 7.215–7.305 (m, 10H, Ph); ^{13}C NMR 29.51 (CH), 36.45 (CH–*CH*$_2$–CH), 42.01 (CH–*CH*$_2$–C_{quat}), 48.84 (CH_2–Ph), 51.04 (C_{quat}, Ad), 126.68 (*o*-Ph), 127.27 (*p*-Ph), 128.26 (*m*-Ph), 138.59 (*i*-Ph), 164.89 (C_{quat}, triazine ring), 165.43 (C_{quat}, triazine ring); Anal Calc. for $C_{37}H_{46}N_6$ C 77.31, H 8.07, N 14.62; Found C 77.56, H 8.40, N 14.22%.

2,4-Bis-(1-adamantylamino)-6-morpholino-1,3,5-triazine 4b

Reaction time – 5 min; PTLC (ethyl acetate–hexane 1 : 4), R_f 0.42; 91% yield; recrystallisation from heptane: m.p. 213–4 °C; IR 3421.1, 3054.7, 2985.3, 2908.1, 2850.3, 2306.5, 1550.5, 1492.6, 1442.5, 1265.1, 748.2, 705.8; ^{1}H NMR 1.673 (m, 12H, CH–*CH*$_2$–CH), 2.082 (m, 18H, CH–*CH*$_2$–C_{quat}), 3.696 (m, 8H, morpholine), 4.782 (br s, 2H, NH); ^{13}C NMR 29.51 (CH), 36.47 (CH–*CH*$_2$–CH), 41.99 (CH–*CH*$_2$–C_{quat}), 43.64 (CH_2–N), 51.08 (C_{quat}, Ad), 66.82 (CH_2–O), 164.56 (C_{quat}, triazine ring), 164.72 (C_{quat}, triazine ring); Anal Calc. for $C_{27}H_{40}N_6O$ C 69.79, H 8.68, N 18.09; Found C 69.58, H 8.83, N 18.12%.

2,4,6-Tris-(1-adamantylamino)-1,3,5-triazine[13] 5b

(a) Starting material – 2,4-Bis-(1-adamantylamino)-6-chloro-1,3,5-triazine; reaction time – 15 min; PTLC (ethyl acetate–hexane 1 : 4), R_f 0.38; 78% yield; recrystallisation from heptane: m.p. 277–8 °C (lit.[13] 276–8 °C); IR 3417.3, 3054.7, 2908.1, 2850.3, 2306.5, 1558.2, 1484.9, 1430.9, 1357.6, 1307.5, 1265.1, 1160.9, 894.8, 813.8, 748.2, 705.8; ^{1}H NMR 1.675 (m, 18H, CH–*CH*$_2$–CH), 2.084 (m, 27H, CH and CH–*CH*$_2$–C_{quat}), 4.744 (br s, 3H, NH); ^{13}C NMR 29.54 (CH), 36.41 (CH–*CH*$_2$–CH), 42.04 (CH–*CH*$_2$–C_{quat}), 51.20 (C_{quat}, Ad), 164.01 (C_{quat}, triazine ring);

(b) Starting material – cyanuric chloride **1**; reaction time – 15 min; 82% yield.

2,4-Bis-(diethylamino)-6-dibenzylamino-1,3,5-triazine 3c

Reaction time – 10 min; PTLC (ethyl acetate–hexane 1 : 9), R_f 0.69; 94% yield; recrystallisation from ethanol–water: m.p. 61–2 °C; IR 3054.7, 2985.3, 2306.5, 1535.1, 1492.6, 1427.1, 1265.1, 894.8, 744.4, 705.8; ^{1}H NMR 1.093 (t, 12H, *J* 6.8, *CH*$_3$–CH_2), 3.547 (q, 8H, *J* 6.8, *CH*$_2$–CH_3), 4.754 (s, 4H, CH_2–Ph), 7.170–7.413 (m, 10H, Ph); ^{13}C NMR 13.54 (*CH*$_3$–CH_2), 41.15 (*CH*$_2$–CH_3), 48.29 (CH_2–Ph), 126.70 (*p*-Ph), 127.99 (*o*-Ph), 128.26 (*m*-Ph), 139.66 (*i*-Ph), 164.91 (C_{quat}), 166.15 (C_{quat}); Anal Calc. for $C_{25}H_{34}N_6$ C 71.73, H 8.19, N 20.08; Found C 71.87, H 8.33, N 20.53%.

2,4-Bis-(diethylamino)-6-morpholino-1,3,5-triazine 4c

Reaction time – 5 min; PTLC (ethyl acetate–hexane 1 : 9), R_f 0.49; 96% yield; non-crystallisable colourless oil; IR 3054.7, 2973.7, 2931.3, 2858.0, 2306.5, 1535.1, 1496.5, 1434.8, 1373.1, 1326.8, 1268.9, 1222.6, 1114.7, 1083.8, 1029.8, 810.0, 744.4, 705.8; ^{1}H NMR 1.141 (t, 12H, *J* 6.8, *CH*$_3$–CH_2), 3.536 (q, 8H, *J* 6.8, *CH*$_2$–CH_3), 3.727 (m, 8H, morpholine); ^{13}C NMR 13.34 (*CH*$_3$–CH_2), 41.00 (*CH*$_2$–CH_3), 43.58 (CH_2–N), 66.92 (CH_2–O), 164.61 (C_{quat}), 165.51 (C_{quat}); MS (EI) *m*/*z* 308 (M, 33), 279 (M − Et, 100), 265 (M − NEt, 27); HRMS (EI+) *m*/*z* calcd for $C_{15}H_{28}N_6O$ 308.2324, found 308.2321.

2,4-Bis-(diethylamino)-6-(1-adamantylamino)-1,3,5-triazine 5c

Reaction time – 15 min; PTLC (ethyl acetate–hexane 1 : 9), R_f 0.48; 94% yield; m.p. 68–70 °C (without recrystallisation); IR 3425.0, 3050.8, 2973.7, 2908.1, 2854.1, 2306.5, 1565.9, 1531.2, 1500.4, 1434.8, 1373.1, 1307.5, 1272.8, 1230.4, 1184.1, 1145.5, 1083.8, 1029.8, 975.8, 813.8, 748.2, 705.8; ^{1}H NMR 1.142 (t, 12H, *J* 6.9, *CH*$_3$–CH_2), 1.670 (m, 6H, CH–*CH*$_2$–CH), 2.115 (m, 9H, CH and CH–*CH*$_2$–C_{quat}), 3.517 (q, 8H, *J* 6.9, *CH*$_2$–CH_3), 4.557 (br s, 1H, NH); ^{13}C NMR 13.50 (*CH*$_3$–CH_2), 29.63 (CH), 36.69 (CH–*CH*$_2$–CH), 40.85 (*CH*$_2$–CH_3), 42.14 (CH–*CH*$_2$–C_{quat}), 50.75 (C_{quat}, Ad), 164.44 (C_{quat}, triazine ring), 165.66 (C_{quat}, triazine ring); MS (EI) *m*/*z* 372 (M, 33), 343 (M − Et, 100), 329 (M − NEt, 31), 300 (M − NEt_2, 8), 257 (M − NEt–NEt_2, 28), 228 (M−2 × NEt_2, 80), 135 (adamanthyl, 16), 72 (NEt_2, 52; FAB+ *m*/*z* 373 (M^+, 100), 343 (M − Et, 20), 329 (M − NEt, 9), 135 (adamanthyl, 49); HRMS (EI+) *m*/*z* calc. for $C_{21}H_{36}N_6$ 372.3001, found 372.2993.

2,4-Bis-(diethylamino)-6-dicyclohexylamino-1,3,5-triazine 6c

Reaction time – 60 min; PTLC (ethyl acetate–hexane 1 : 9), R_f 0.45; 16% yield; m.p. 216–9 °C (without recrystallisation); IR 3054.7, 2981.4, 2931.3, 2854.1,2306.5, 1562.1, 1531.2, 1504.2, 1430.9, 1373.1, 1265.1, 1087.7, 894.8, 748.2, 705.8; ^{1}H NMR 1.214 (m, 4H, CH_2-2, axial), 1.273 (m, 4H, CH_2-3, axial), 1.339 (m, 2H, CH_2-4, axial), 1.445 (t, 12H, *J* 7.0, *CH*$_3$–CH_2), 1.598 (m, 2H, CH_2-4, equatorial), 1.729 (m, 4H, CH_2-3, equatorial), 2.009 (m, 4H, CH_2-2, equatorial), 3.531 (q, 8H, *J* 7.0, *CH*$_2$–CH_3), 3.788 (m, 2H, CH-1); ^{13}C NMR 13.89 (*CH*$_3$–CH_2), 24.90 (CH_2-3), 25.80 (CH_2-4), 33.21 (CH_2-2), 41.01 (*CH*$_2$–CH_3), 49.24 (CH-1), 163.48 (C_{quat}), 164.62 (C_{quat}); MS (EI) *m*/*z* 320 (M–:C_6H_{10}, 10), 291 (M–:C_6H_{10}-Et, 100), 209 (M–:C_6H_{10}–Et–:C_6H_{10}, 66), 55 (:C=N–Et, 62); FAB+ *m*/*z* 321 (M^+–:C_6H_{10}, 100), 291 (M–:C_6H_{10}-Et, 4), 209 (M–:C_6H_{10}-Et–

:C_6H_{10}, 3); HRMS (EI+) *m*/*z* calc. for $C_{17}H_{32}N_6$ 320.2688, found 320.2694.

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