New Green Chemistry initiatives

The UK Government's Minister for Science and Technology David Sainsbury spent half a day with some of the UK's leading Green Chemists and Chemical Engineers at the Royal Society of Arts to help launch a major new national initiative in Green Chemistry. The so-called Faraday Partnership on 'Green Chemical Technology' is one of 18 such activities and seeks to bring together the academic science base with industry so as to significantly enhance the rate of green technology transfer from the laboratory to commercial-scale practice as well as increase awareness of best practice for sustainable products and processes. Technology Translators will visit industry and match industrial needs to university innovations. They will also promote activities where there are mismatches and recommend courses and seminars to companies with the aim of helping change the cultural climate in favour of green chemical technology. The Faraday will be run by the Institute of Chemical Engineers in collaboration with the Royal Society of Chemistry and the Chemical Industries Association. The Faraday will build on existing activities notably the Green Chemistry Network although its educational brief will be limited to postgraduate activities. This includes the existing Masters courses at the Universities of Newcastle and York ('Responsive Processing' and 'Clean Chemical Technology' and the Engineering doctorate programme on 'Environmental Technology' at the University of Surrey and new training courses which will be developed by the Faraday in collaboration with the Green Chemistry Network based here at York (http://www.chemsoc.org/gcn) and the Centre for Environmental Studies at the University of Surrey (http://www.surrey.ac.uk/eng/ces.htm).

Another exciting development in Green Chemistry in the UK is the announcement of a new undergraduate degree at the University of Nottingham on Green Chemistry and Process Engineering (http://www.nottingham.ac.uk/chemistry/studentopportunities/courses/greenchem.html). This combined Honours Degree will produce quality graduates with a unique blend of Chemistry and Chemical Engineering skills combined with an in-depth knowledge of the practice of Green processing contributing to sustainable development.

In Europe the newly approved COST programme on Green Chemistry represents a major new long-term development for the green chemistry research and application as well as the integration of green chemistry activities across the community. The COST programme will operate by:

- providing a mechanism to establish a common understanding of the current status and the future research, development, and educational needs of sustainable and green chemistry and chemical technology for Europe
- establishing and managing a selection process for identifying potential industrial chemicals and chemical based consumer products that would be considered sustainable/green according to information available at the time of selection
- co-ordinating new joint research efforts for designing and developing environmentally friendly processes for the production of sustainable/green products.

James Clark, York
November 2001

DOI: 10.1039/b110186m

Twelve more green chemistry principles†

Neil Winterton of the Leverhulme Centre for Innovative Catalysis‡ suggests that laboratory and research chemists should consider twelve more green chemistry principles, objectives and requirements to help them plan and carry out their work and to help them assess the relative 'greenness' of a process

Introduction

Chemical technology has achieved much in relation to waste minimisation even before sustainable development was ever conceived and is a major success story. Indeed, many of the major benefits in public health and our standard of life have arisen, in large measure, as a consequence of the application of chemistry, such as in the provision of clean drinking water, plentiful food and treatments for disease. There is, nevertheless, much still to do and the potential exists for chemical technology to continue to build on these earlier successes through the greater use of renewable resources and the development of cleaner products and processes. Some will arise by the continued application of existing methods and ways of working, whether consciously, coincidentally or unexpectedly—the potential benefits of serendipity in any scientific enterprise should not be underestimated! In addition, new approaches, consciously planned using the principles of sustainable development, industrial ecology, clean technology, life cycle analysis and green chemistry, are needed to bring about additional environmental and societal benefits.

Chemistry, being concerned with understanding the way the material world works, has become, to an extent greater than in the past, a central science relevant to technology, the environment and the understanding of human impact on the latter. Green chemistry, not simply being a subdivision of chemistry like organic or organometallic chemistry, has environmental, technological and societal goals and is linked to the wider sustainability movement. There is, thus, a wider context in which green chemistry is being developed and this requires awareness, clear thinking and pragmatism[1] to target the most critical problems as well as sound science to help resolve them.

Green chemistry has set itself the goal of making chemicals technology more environmentally benign by, in Roger Sheldon's words[2] *'efficiently using (preferably renewable) raw materials, eliminating waste and avoiding the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products'*.

To help it achieve this Anastas and Warner[3] set down the 12 well-known principles of green chemistry. These are summarised in Table 1. They are difficult to fault.

Most chemists, including those working in industry, recognise these as worthwhile ideals and acknowledge that most of them already guide their work. The failure to adopt them perfectly in every case does not arise from innate perversity or from indifference to environmental considerations. It arises from technological, economic and other factors that chemists do not always address.

William H. Glaze, the editor of the American Chemical Society publication, *Environmental Science & Technology* has indeed suggested[4] that the 'greenness' of a chemical transformation can only be assessed in the context of its scale-up, its application and its practice. This will usually involve some trade-off between conflicting factors, often driven by valid technical, economic and commercial considerations.

To complement and build on those formulated by Anastas and Warner and to address Glaze's concerns, twelve more green chemistry principles, objectives and requirements are suggested (Table 2). They are proposed to aid laboratory and research chemists, interested in applying green chemistry, to plan and carry out their work to include the collection of data that are of particular use to those, usually process chemists, chemical engineers and chemical technologists, wishing to assess the potential for waste minimisation. These groups will recognise and already work to these

Table 1 Anastas and Warner's green chemistry principles

1. It is better to prevent waste formation than to treat it after it is formed
2. Design synthetic methods to maximise incorporation of all material used in the process into the final Product
3. Synthetic methods should, where practicable, use or generate materials of low human toxicity and environmental impact
4. Chemical product design should aim to preserve efficacy whilst reducing toxicity
5. Auxiliary materials (solvents, extractants *etc.*) should be avoided if possible or otherwise made innocuous
6. Energy requirements should be minimised: syntheses should be conducted at ambient temperature/pressure
7. A raw material should, where practicable, be renewable
8. Unnecessary derivatisation (such as protection/deprotection) should be avoided, where possible
9. Selectively catalysed processes are superior to stoichiometric processes
10. Chemical products should be designed to be degradable to innocuous products when disposed of and not be environmentally persistent
11. Process monitoring should be used to avoid excursions leading to the formation of hazardous materials
12. Materials used in a chemical process should be chosen to minimise hazard and risk.

---

† Part of a presentation '*Sense and Sustainability: The Role of Chemistry, Green or Otherwise*', given at the BA Festival of Science, University of Glasgow, September 2001.

‡ Leverhulme Centre for Innovative Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD.

DOI: 10.1039/b110187k

Table 2 Twelve more principles of green chemistry

1.	Identify and quantify by-products
2.	Report conversions, selectivities and productivities
3.	Establish full mass-balance for process
4.	Measure catalyst and solvent losses in air and aqueous effluent
5.	Investigate basic thermochemistry
6.	Anticipate heat and mass transfer limitations
7.	Consult a chemical or process engineer
8.	Consider effect of overall process on choice of chemistry
9.	Help develop and apply sustainability measures
10.	Quantify and minimise use of utilities
11.	Recognise where safety and waste minimisation are incompatible
12.	Monitor, report and minimise laboratory waste emitted.

principles. They are all intended to help demonstrate and assess the potential 'greenness' of a process and, just as important, its relative 'greenness' when compared with other processes; additional background is discussed in more detail elsewhere:[5–9]

1. Identify by-products and, if possible, quantify them

Separation and disposal of by-products can be both expensive and resource consuming and indeed may determine the economic viability of a process or product. This may even be true of by-products formed in quite small amounts. Rarely do chemical processes give the targeted product with perfect specificity even after much effort. Because by-products may be recycled in a scaled-up process, it will also be informative to examine the effect on reaction outcome of adding each by-product at the beginning of the reaction.

2. Report conversions, selectivities, productivities

A product formed in high yield may be produced in an overall very inefficient and wasteful process, requiring stoichiometric co-reagents producing a range of co-products requiring separation or post-treatment for recycle or disposal. To aid process design, therefore, more informative metrics than yields should be reported. These should include conversions, selectivities, productivities (and related measures, such as atom efficiency[10] or productivity[11] functions) and rates.

3. Establish a full mass balance for the process

All the material used in producing and isolating the desired material should be identified, quantified and account for. In addition, all materials, including solvents, used in the recovery of the final product in its pure state should be specified and quantified.

4. Quantify catalyst and solvent losses

A much more useful estimate of catalyst and solvent losses is obtained by measuring their concentration in the (measured volume of) solid waste, aqueous or gaseous effluent you dispose of, rather than by simply weighing the recovered catalyst or solvent.

5. Investigate basic thermochemistry to identify potentially hazardous exotherms

A reaction operated on the small scale in the laboratory may be perfectly safe. However, surface-to-volume ratios decrease on scale-up leading to significant and unanticipated constraints on heat transfer. The design engineer would rather know about such effects before a pilot-plant or semi-tech unit is built.

6. Anticipate other potential mass and energy transfer limitations

Check other factors affecting heat and mass transfer and the consequences for reaction outcome. These might include stirring rates, gas dispersion, solid–liquid contacting. Can these be managed on scale up?

7. Consult a chemical or process engineer

Get the perspective of someone involved in scale-up to comment on your reaction. Examine some of the published literature. Identify and understand further likely constraints on process chemistry and take account of these in your laboratory investigations, as far as possible.

8. Consider the effect of the overall process on choice of chemistry

A range of options for the operation of a process on the large scale will arise from the choice of raw material, feedstock, reactor, by-product separation, purity and purification, energy and utilities utilisation, catalyst and solvent recovery and waste disposal. These should be considered pragmatically to establish the impact of your new chemistry on these options. This may be especially relevant to novel chemistry being considered for a well-established process. It makes sense to be aware of the current manufacturing technology. How many steps are used to obtain feedstock from a primary raw material, like oil? An alcohol may be made from the hydration of an olefin which itself is produced by cracking or dehydrogenation of a saturated hydrocarbon. Why not start using the hydrocarbon itself? Would your use of a very pure feedstock be ruled out on cost grounds? Would you create a waste-stream requiring disposal elsewhere in the product-chain in so doing? What would the effect be of using the commercial-grade rather than the research-grade material in your laboratory experiment?

9. Help develop and apply sustainability measures

Attempt to evaluate the sustainability of your process using, for example, the parameters described by J. Dewulf *et al.*[12]

10. Quantify and minimise use of utilities and other inputs

These are often neglected in laboratory studies. However, the use of water (*e.g.*, for cooling and extraction), electricity or inerting gases may be a significant element in emissions. For example, compression and recompression of CO_2 for use in supercritical fluid processing is very energy intensive.

11. Recognise where operator safety and waste minimisation may be incompatible

Partial oxidation of hydrocarbons using dioxygen must avoid explosive regimes.

12. Monitor, report and minimise **all** *waste emitted to air, water and as solids, from individual experiments or from laboratory overall*

This would represent a real and direct demonstration of your green credentials.

The application of these principles, in itself, will not guarantee that clean chemical processes will be developed. However, it is hoped that they will aid in their earlier selection as well as directing the attention of green chemists into the most productive of areas of investigation. However, there is no substitute for an awareness of the wider technological factors, beyond the chemical, that affect the efficiency of chemical processing and the choices made whether or not to develop new processes arising from green chemistry. Having said all this, the wholly novel, arising unanticipated from research done for its own sake, may also be the basis of innovative and waste-eliminating chemical technology.

References

1 *The Skeptical Environmentalist—Measuring the Real State of the World*, B. Lomborg, Cambridge University Press, 2001, ISBN 0 521 01068 3.
2 'Atom utilisation, *E* factors and the catalytic solution', R. A. Sheldon, *Comptes Rendus de l'Académie des Sciences—Series IIC - Chemistry*, 2000, **3**, 541.
3 *Green Chemistry: Theory and Practice*, P. T. Anastas and J. C. Warner, Oxford University Press, 1998.
4 'Sustainability engineering and green chemistry', W. H. Glaze, *Environmental Science & Technology*, 2000, **34**, 449A.
5 'So you think your process is green, how do you know?—Using principles of sustainability to determine what is green—a corporate perspective', A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1.
6 Green chemistry measures for process research and development, D. J. C. Constable, A. D. Curzons, L. M. Freitas dos Santos, G. R. Green, R. E. Hannah, J. D. Hayler, J. Kitteringham, M. A. McGuire, J. E. Richardson, P. Smith, R. L. Webb and M. Yu, *Green Chem.*, 2001, **3**, 7.
7 'Chemical process design using heuristics in the context of pollution prevention', D. W. Pennington, *Clean Prod. Process.*, 1999, **1**, 170.
8 'A screening-level prototype for the synthesis or analysis of separation systems to support identification of inherently cleaner chemical processes', D. W. Pennington and P. L. Yue, *Clean Prod. Proc.*, 2000, **2**, 82.
9 'Process design for the environment: a multi-objective framework under uncertainty', Y. Fu, M. Diwekar, D. Young and H. Cabezas, *Clean Prod. Proc.*, 2000, **2**, 92.
10 R. Sheldon, *Chem. Ind.*, 7 December, 1992, 903.
11 'Choosing Processes for their Productivity', A. Steinbach and R. Winkenbach, *Chem. Eng.*, April 2000, 94.
12 'Illustrations towards quantifying the sustainability of technology', J. Dewulf, H. Vangenhove, J. Mulder, M. M. D. van den Berg, H. J. van der Kooi and J. de Swaan Arons, *Green Chem.*, 2000, **2**, 108.

The greening of explosives and propellants using high-energy nitrogen chemistry†

Thomas M. Klapötke and Gerhard Holl of the Ludwid-Maximilians University of Munich and the Bundeswehr Research Institute for Materials in Swisttal, Germany, describe their work on reducing the toxicity of environmental impact of military explosives and propellants

Our aspiration is to serve the interest of the Federal Armed Forces and the general public. The main focus of our work is to ensure safety in the handling of military explosives and to guarantee a safe environment for a better and brighter future.

Areas we are particularly interested in are the following:

- Emission-reduced ammunition
- Primary and secondary explosives
- High energy density materials (HEDM)
- Rocket propulsion

Emission-reduced ammunition

In a test we used conventional (DAG) and emission-reduced ammunition (SINCO). The conventional propellant charge is based on nitroglycerine and a nitrocellulose binder and shows a negative oxygen balance. The propellant charge of the emission-reduced ammunition on the other hand is based on nitroguanidine and also on a nitrocellulose binder. The latter combination is very close to exhibiting oxygen balance and therefore the emission gases of the conventional and emission reduced ammunition are different (Table 1). Whereas the conventional-ammunition (DAG) shows a very high level of highly toxic carbon monoxide (CO) and high levels of NO, the emission-reduced ammunition (SINCO) shows CO levels that are 60% lower in comparison with conventional ammunition and NO levels that are reduced by over 65% thus greatly reducing the amounts of the toxic CO and NO gases produced.

Table 1

	mel[a]	conventional ammunition (DAG)	emission-reduced ammunition (SINCO)
NO [ppm]	25	14	5
NO_2 [ppm]	5	0.3	24
CO [ppm]	30	675	269
O_2 [vol-%]	—	21	21

[a] mel = maximum exposure limit.

Primary and secondary explosives

Primary explosives

- show very rapid transition from burning to detonation
- have the ability to transmit the detonation to less sensitive explosives

---

† Based on a lecture presented at the British Association for the Advancement of Science Festival of Science, 'Green Chemistry' section, Glasgow, UK, 1–7 September, 2001.

- will detonate when they are subjected to heat or shock
- on detonation, produce a tremendous amount of heat and/or shock
- have a **high degree of sensitivity to initiation through shock, friction electric spark or high temperatures**
- are used in initiating devices
- heat of detonation comparable (to smaller) to that of secondary explosives
- typical detonation velocities range from 3500–5500 m s^{-1}

A typical example of a primary explosive is lead azide, $Pb(N_3)_2$, some decomposition reactions of which are shown below [eqns. (1) and (2)].

$$\tfrac{1}{2}\,Pb(N_3)_2\,(s) \rightarrow \{\tfrac{1}{2}Pb^{2+} + N_3^-\} \rightarrow \tfrac{1}{2}\,Pb\,(s) + N_2\,(g) + N\,(g) \qquad \Delta H(1) = +56 \text{ kcal mol}^{-1} \qquad (1)$$

$$Pb(N_3)_2\,(s) \rightarrow Pb\,(s) + 3\,N_2\,(g) \qquad \Delta H(2) = -114 \text{ kcal mol}^{-1} \qquad (2)$$

Although $Pb(N_3)_2$ has undoubtedly many superior properties, the toxic heavy metal lead (Pb) is formed during the explosive decomposition. Consequently, we are interested in finding replacements for $Pb(N_3)_2$ which do not contain heavy metals *e.g.* lead. We have undertaken research in the area of hydrazinium azide chemistry, and particularly interesting results came not only from the compound $[N_2H_5][N_3]$ (hydrazinium azide) but also from its hydrazinate adduct $[N_2H_5][N_3]{\cdot}N_2H_4$.

Hydrazinium azide hydrazinate, $[N_2H_5][N_3]{\cdot}N_2H_4$ was synthesized from equimolar amounts of hydrazinium azide and hydrazine and was characterized by single crystal X-ray diffraction: density $\rho = 1.320$ g cm^{-3}. A particularly useful property of $[N_2H_5][N_3]{\cdot}N_2H_4$ is that it is less hygroscopic and less volatile than hydrazinium azide. Explosion of $[N_2H_5]^+[N_3]^-{\cdot}N_2H_4$ yielded dinitrogen (N_2), ammonia (NH_3) and dihydrogen (H_2). Compared to hydrazinium azide [eqn. (3)], the hydrazine adduct produces larger amounts of ammonia in the explosion [eqn. (4)].

$$[N_2H_5]^+[N_3]^- \rightarrow 2.18\,N_2 + 1.52\,H_2 + 0.65\,NH_3 \qquad (3)$$

$$[N_2H_5]^+[N_3]^-{\cdot}N_2H_4 \rightarrow 2.68\,N_2 + 2.02\,H_2 + 1.65\,NH_3 \qquad (4)$$

Secondary explosives

- cannot be detonated readily by heat or shock
- are usually more powerful than primary explosives
- are less sensitive than primary explosives and can only be initiated to detonation by the shock produced by the explosion of a primary explosive
- typical detonation velocities range from 5000–9000 m s^{-1}

Typical examples of secondary explosives are: HMX; RDX; TNT (*cf.* Fig. 1); nitroglycerine, $CH_2(ONO_2)–CH(ONO_2)–CH_2(ONO_2)$ [eqn. (5)]

$$CH_2(ONO_2)–CH(ONO_2)–CH_2(ONO_2) \rightarrow \tfrac{5}{2}\,H_2O(g) + 3\,CO_2(g) + \tfrac{3}{2}\,N_2(g) + \tfrac{1}{2}\,O_2(g) \qquad \Delta H(5) = -337 \text{ kcal mol}^{-1} \qquad (5)$$

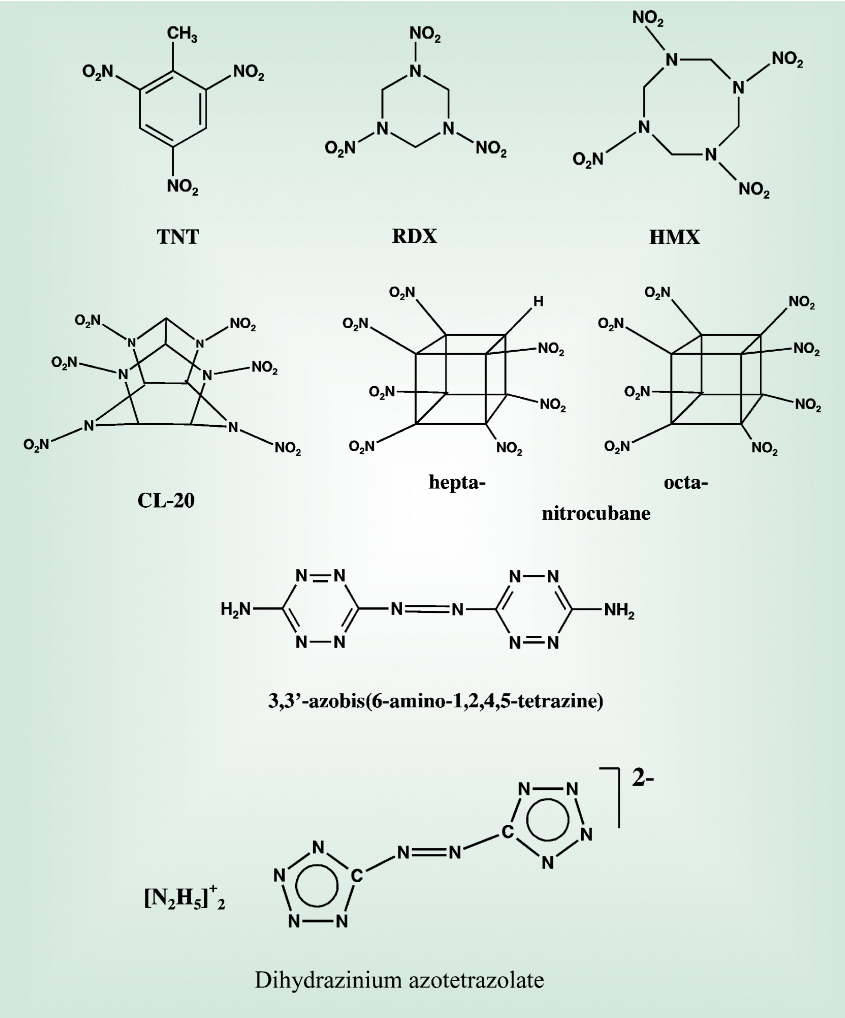


Fig. 1 High-energy density materials (HEDM).

High energy density materials (HEDM)

Modern research in the area of secondary explosives is often closely linked to research in the area of high energy density materials (HEDM) and propulsion. In order to create highly energetic materials which could be used both as explosives and for propulsion, the following requirements have to be met (as well as economic considerations):

- All products (explosion and/or combustion products) have to be environmentally compatible and, if possible, non-toxic.
- The HEDMs should be based on metal-free compounds since metals and metal containing products in the trace of a rocket can easily be detected by radar.
- upon explosion or combustion the materials should release a tremendous amount of energy, but should be safe to handle, *i.e.* high to very high activation barriers are required.

Typical HEDMs are shown in Fig. 1. Modern HEDMs derive most of their energy from either oxidation of the carbon backbone or their very high positive heat of formation. Examples of the first class are traditional explosives such as TNT, RDX and HMX. Modern nitro compounds such as CL-20 or the recently reported hepta- and octanitrocubanes possess very high densities and enhance the energies by possessing substantial cage strain. The most recent and most exciting members of the second class of compounds are 3,3′-azobis(6-amino-1,2,4,5-tetrazine) and dihydrazinium azotetrazolate which show the desired insensitivity to electrostatic discharge, friction and impact making these compounds able to be handled while having very high heats of formation of $\Delta H°_f$ = 940 kcal kg^{-1} and 1150 kcal kg^{-1}, respectively.

Rocket propulsion

Typical characteristics for solid rocket propellants are:

- combustible materials containing within themselves all the oxygen needed for their full combustion
- burn violently (flame, sparks, crackling sound) but do not explode (sharp, loud bang)

The most frequently used solid propellants (for many military missiles and rockets, as well as for Ariane 4 and 5 and the space shuttle boosters) consists of a mixture of ammonium perchlorate, $[NH_4][ClO_4]$ (7%), aluminium (Al, 16%) and epoxy resins (14%). The main combustion products are (apart from water and dinitrogen) hydrochloric acid (HCl) and aluminium oxides (Al_2O_3). While HCl contributes to both acid rain and to ozone depletion, Al compounds are in general toxic to wildlife and plants. Research is underway to replace this fuel by an environmentally friendly substance, for example ammonium dinitramide, $[NH_4][N(NO_2)_2]$, which consists only of nitrogen (N), oxygen (O) and hydrogen (H) and would consequently form dinitrogen (N_2) and water (H_2O) as the main combustion products and contains no metals or halides.

Liquid fuel, especially for the upper stage engines of civil spacecraft, usually consists of an oxidizer (N_2O_4) and a fuel (hydrazine or monomethylhydrazine, MMH) [eqns. (6), (7)]. Whereas N_2O_4 is toxic and also contributes to many environmental problems, the fuel based on hydrazine compounds is carcinogenic. Research is underway to replace both the oxidizer [eqns. (8)–(10)] and the fuel [eqn. (10)] with environmentally friendly and less toxic substances. Possible examples for the oxidizer are hydrogen peroxide (H_2O_2 > 90%) and hydrocarbons (HC) for the fuel side [eqn. (10)]:

$$2\,N_2H_4 + N_2O_4 \rightarrow 4\,H_2O + 3\,N_2 \tag{6}$$

$$(H_3C)HN\text{–}NH_2 + N_2O_4 \rightarrow 3\,H_2O + CO + 2\,N_2 \tag{7}$$

$$N_2H_4 + H_2O_2 \rightarrow 4\,H_2O + N_2 \tag{8}$$

$$(H_3C)HN\text{–}NH_2 + 4\,H_2O_2 \rightarrow 7\,H_2O + CO + N_2 \tag{9}$$

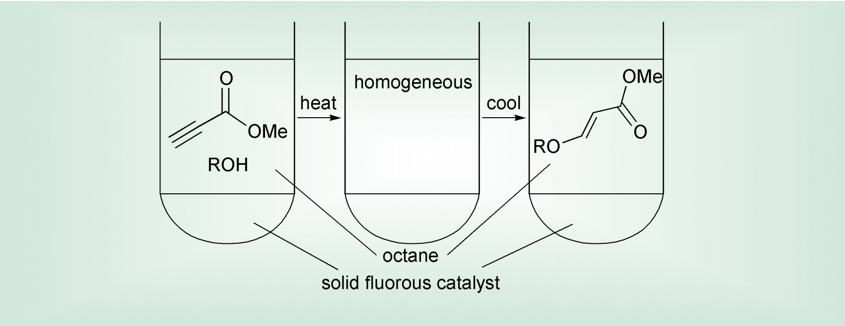
$$\text{HC's} + H_2O_2 \rightarrow H_2O + CO_{(2)} \tag{10}$$

Highlights

Duncan Macquarrie reviews the latest research in green chemistry

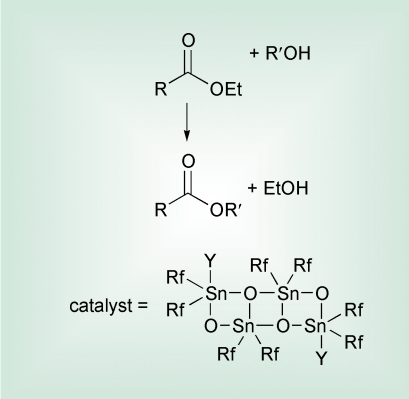
Fluorous biphase systems

The use of fluorous biphase systems has received considerable attention recently. Here, a fluorous phase typically consisting of a perfluorinated small molecule displays dramatic miscibility changes with a hydrocarbon as a function of temperature. This has been exploited by using a fluorous soluble catalyst to catalyse transformations of hydrocarbon soluble species. Thus, in the miscible range, the catalysis will occur homogeneously, after which the temperature is reduced to separate products and catalysts into the two phases. One drawback is that the fluorous solvents can be expensive, and doubts exist over their environmental acceptability. In a very significant development, John Gladysz and colleagues from the University of Erlangen have shown that using fluorous solvents may not be necessary (*J. Am. Chem. Soc.*, 2001, **123**, 11490). They have found that fluorous catalysts can be used directly, and that they display a similar solubility profile to the fluorous solvents' miscibility. In other words, at low temperatures, fluorous catalysts are insoluble in hydrocarbon solvents, but as



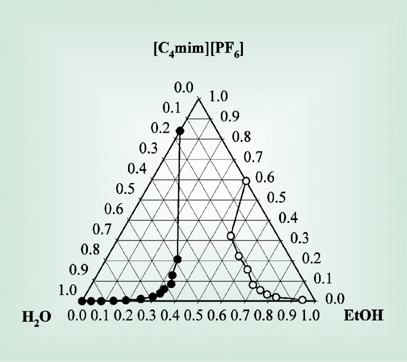
the temperature of the solvent approaches the melting point of the fluorous catalyst, the solubility shoots up. This means that the catalyst can be used directly, obviating the need for the expensive fluorous solvent. They have proved their concept using the phosphine-catalysed addition of alcohols to alkynes, demonstrating excellent performance and easy recovery and reuse.

Fluorous biphase catalysis has also been demonstrated for transesterifications. This important class of reaction is often tricky to push to completion without the use of a large excess of solvent, or the removal of the product alcohol in a continuous manner. The development of fluorous-soluble stannoxanes has allowed these obstacles to be overcome. Junzo Otera and co-workers from Okayama University (*Angew. Chem., Int. Ed.*, 2001, **40**, 3670) have shown that a neat 1 : 1 mixture of alcohol and ester can be transesterified quantitatively using the fluorous-soluble stannoxanes as catalyst in a perfluorohexane mixture at 150 °C. Catalyst recycling was also found to be very simple.

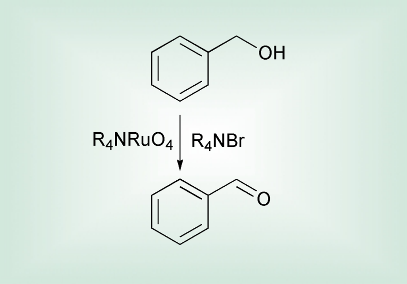


Ionic liquids

One of the benefits of ionic liquids is that they are non-volatile solvents, and thus avoid the production of VOCs. However, this lack of volatility means that they cannot undergo many of the simple evaporative processes required for, for example, drying products which are solvent-wet, or for cleaning reaction vessels after use. In particular, [C_4mim][PF_6], which is one of the commonest ionic liquids, is soluble in many hazardous solvents (hence reintroducing the VOC problem) but not in less difficult media, such as water or ethanol. Robin Rogers and colleagues at the Department of Chemistry and the Centre for Clean Manufacturing at the University of Alabama, USA, have shown that despite complete immiscibility in water or ethanol, the ionic liquid is freely soluble in mixtures of both, leading to a simple and relatively benign method for removing this ionic liquid from various systems (*Chem. Commun.*, 2001, 2070).

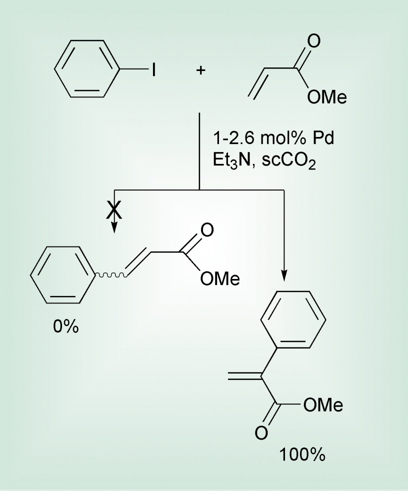


A second application of ionic liquid technology has been provided by the group of Steven Ley at Cambridge University (*Chem. Commun.*, 2001, 2278). Here they use tetrapropylammonium perruthenate as an oxidation catalyst in either ethylmethylimidazolium hexafluorophosphate or in Et_4NBr as an ionic liquid medium for the oxidation of alcohols to aldehydes or ketones. The oxidations proceed to give excellent yields of product, and isolation is effected by precipitation of the quaternary species by addition of a suitable organic solvent, which also solubilises the product. The precipitated species can be used again directly after removal of the organic solvent.



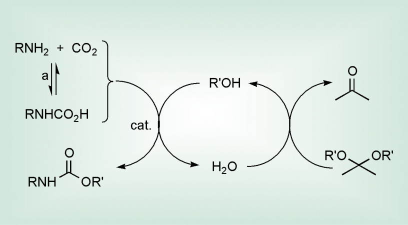
Supercritical CO_2

Supercritical CO_2 has been used as a solvent for two reactions catalysed by dendrimers containing Pd nanoparticles. Keith Johnstone of the University of Texas and Richard Crooks of Texas A + M University, USA, along with their co-workers have shown that these novel materials are effective catalysts for the hydrogenation of styrene, and the Heck reaction of iodobenzene and methyl acrylate (*Chem. Commun.*, 2001, 2290). Hydrogenation was achieved without evidence for catalyst decomposition. The Heck reaction gave a relatively low turnover number of 22 (moles product/mole Pd) but interestingly, only methyl 2-phenylacrylate was observed.



Urethane production

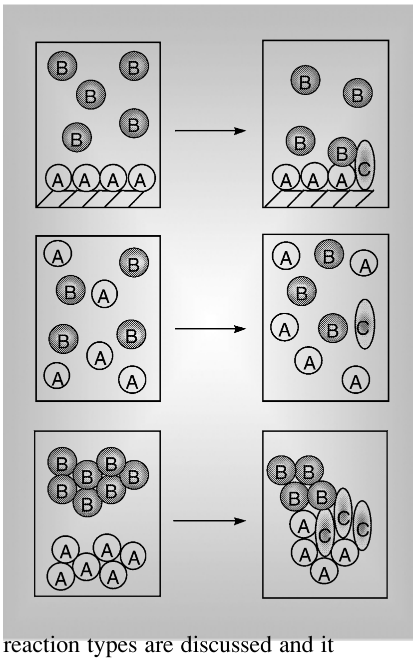
The replacement of reactions involving the liberation of halogens is of great importance. A recent contribution has been published by a group from the AIST in Ibaraki, Japan, led by Toshiyasu Sakakura (*Chem. Commun.*, 2001, 2238). They have investigated the production of urethanes, an enormously important class of compounds, traditionally made using phosgene. More recently, routes involving the reaction of an amine with CO_2, followed by alkylation of the carbamic acid with an alkyl halide have been developed. Sakakura's new development involves the conversion of the carbamic acid into the urethane using an alcohol and a tin catalyst in dense phase CO_2. They found that, in order to achieve acceptable yields, the presence of a water scavenger was necessary, and they found that acetals were excellent for this purpose (the water formed seems to deactivate the catalyst). Whether the tin catalyst described above (Otera) would be



more tolerant of the water produced would be interesting to know.

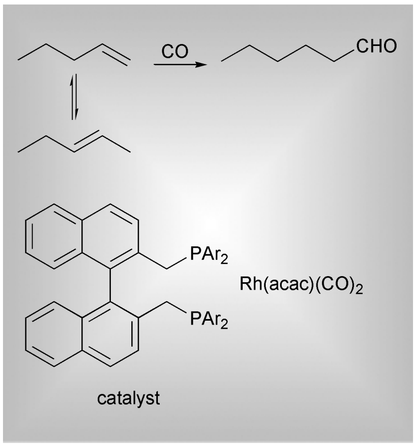
Solventless organic transformations

The best solvent is no solvent, and a mini-review of some solventless organic transformations has been provided by Colin Raston of the University of Leeds, UK, and his collaborators at Monash University in Melbourne, Australia (*Chem. Commun.*, 2001, 2159). Several reaction types are discussed and it emerges that the kinetic behaviour of these systems can best be explained by the formation of a eutectic mixture in which the reaction takes place.



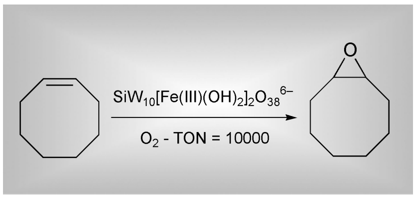
Hydroformylations

Hydroformylation continues to be studied with great vigour. The group led by Matthias Beller of the University of Rostock has now described a new catalytic system which allows the selective formation of the desired *n*-aldehydes directly from mixtures of terminal and internal alkenes (*Angew. Chem., Int. Ed.*, 2001, **40**, 3408). The catalyst is based on the combination of Rh and a range of NAPHOS bidentate diphosphines. The best of these allow the conversion of internal alkenes (*via* isomerisation to the thermodynamically disfavoured terminal alkene) to linear aldehydes with a selectivity (*n*:*i*) of typically >90%.



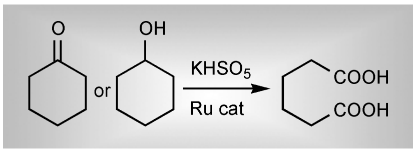
Epoxidation of alkenes

The epoxidation of alkenes using molecular oxygen is a challenging reaction, and is often achieved using greater than stoichiometric quantities of aldehydes as sacrificial oxygen carriers. Now a team led by Noritaka Mizuno at the University of Tokyo, Japan, has shown that a combination of oxygen and an iron-containing polyoxometallate is an extremely efficient catalyst for such reactions (*Angew. Chem., Int. Ed.*, 2001, **40**, 3639). The catalyst, which has two Fe(III) ions at the centre of two adjacent octahedra in a SiW_{10} Keggin ion promotes the epoxidation of linear and cyclic alkenes (with some formation of allylic oxidation products) with turnover numbers of 10,000 when the reaction was carried out under an atmosphere of oxygen. This turnover number is at least 100 times higher than that achieved using just oxygen and catalysts, but without oxygen carriers.



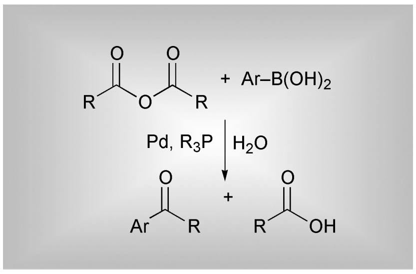
Adipic acid formation

Adipic acid is a major product, formed from the oxidation of cyclohexanone and/or cyclohexanol, with much of it being produced by nitric acid oxidation, leading to major problems with NO_x emissions. Cleaner alternatives are being sought, and work has now been published by a team led by Mario Bressan at the University of Pescara, and colleagues at the University of Padova (*New J. Chem.*, 2001, **25**, 1319). They have shown that Oxone® can oxidise both cyclohexanone and cyclohexanol to adipic acid using a Ru- or Fe-porphyrin catalyst in water. Conversions were high and selectivities very good in the best cases, and even cyclohexane could be oxidised to adipic acid in 22% conversion and good selectivity. Hydrogen peroxide also catalysed the oxidation of the alcohol and the ketone, but considerable decomposition of the oxidant was seen, contrary to the excellent utilisation of the Oxone®.

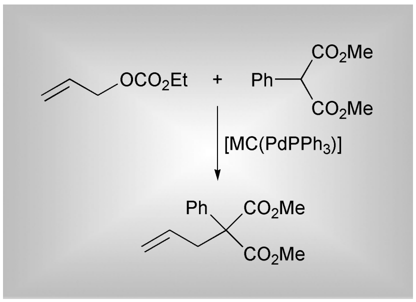


Palladium catalysis

Lukas Goossen and K Ghosh of the Max-Planck Institute in Mülheim, Germany, have described a new route to aryl ketones based on Pd-catalysed coupling (*Angew. Chem., Int. Ed.*, 2001, **40**, 3458). They have found that reaction of aryl boronic acids with anhydrides in the presence of palladium acetate and two equivalents of phosphine proceeded smoothly to give the aryl ketone and an equivalent of acid. Interestingly, in the absence of water, yields were quite low, but the addition of *ca.* 10 equivalents of water allowed yields up to 97% to be attained. Both aryl and alkyl ketones were amenable using this methodology. This route has the advantage over other related systems (which use very strongly nucleophilic aryl sources, or require acid chlorides) of being more tolerant of functional groups–CN, nitro, ester and other ketones are not affected).

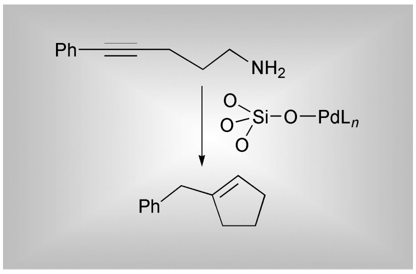


The ability to easily recover and reuse the expensive palladium catalysts which are displaying such versatility has been explored using several techniques. Shu Kobayashi and Ryo Akiyama of the University of Tokyo, Japan, have now extended their microencapsulation methodology from scandium and osmium to palladium (*Angew Chem., Int Ed.*, 2001, **40**, 3469). In this technique, the metal catalyst is stirred in a polystyrene solution, and then a controlled precipitation of the polymer is carried out. This encapsulates the palladium in the polymer, while allowing it to be



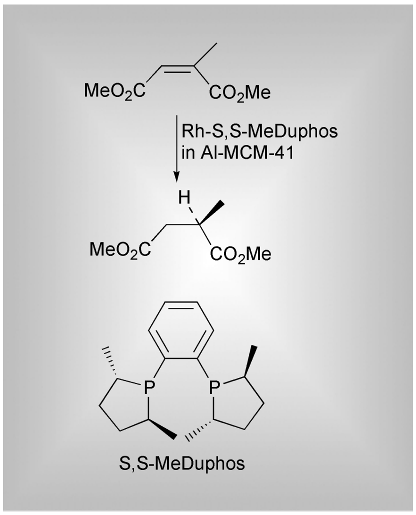
accessible and function as a catalyst. Results on allylic substitution and Suzuki reactions are impressive and reuse is easily achieved.

Immobilising palladium complexes on silica has been reported to be another good method for recovery and reuse of Pd complexes (*e.g. Green Chem.*, 2000, **2**, 53). Normally this is carried out using organic ligands bound to the silica surface, but Howard Alper and co-workers at the University of Ottawa, Canada, have found a more direct method (*J. Am. Chem. Soc.*, 2001, **123**, 10521). They have found that Pd–Me groups will react with silanols on the surface of silica to give Si–O–Pd species, which are active catalysts for the cyclisation of aminoalkynes. The catalysts give high conversions, are comparable to similar homogeneous catalysts (sometimes faster), and the air stability of the catalysts is also good, making them more easily handled than the more active but very air and moisture sensitive early transition metal complexes.



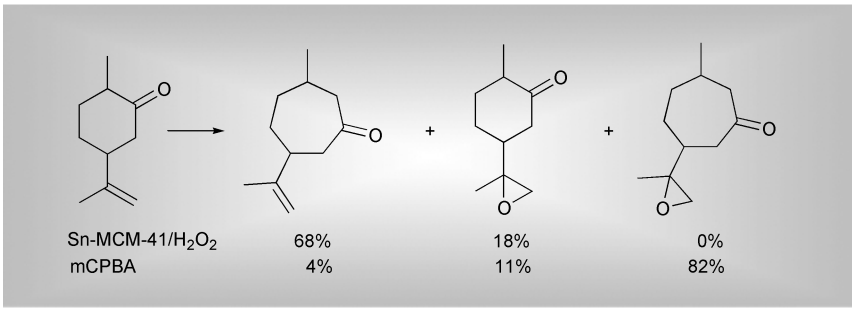
Enantioselective catalysis

Enantioselective catalysis using immobilised metal complexes is the subject of much activity, with some excellent results being reported recently. Wolfgang Hoelderich and colleagues at the RWTH Aachen, Germany, have now published details of a chiral Rh complex immobilised into Al-MCM-41, which displays excellent activity and very good enantioselectivity in the hydrogenation of alkenes (*J. Catal.*, 2001, **203**, 150). They found that the best catalyst was based on the *S*, *S*-Me-Duphos ligand. The supported catalyst gave quantitative conversion and a 92% ee in the hydrogenation of dimethyl itaconate. Turnover numbers were >16 000, and no leaching was observed.



Baeyer–Villiger reaction

Avelino Corma and co-workers at the University of Valencia and UOP in Des Plaines Illinois, have described a Sn-substituted MCM-41 catalyst which displays excellent activity in the Baeyer–Villiger reaction of cyclohexanone (*Chem. Commun.*, 2001, 2190). At reasonable conversions (using hydrogen peroxide as oxidant) they found excellent selectivities towards the lactone. Moderate catalyst lifetimes were observed, but an interesting selectivity was seen with reactions involving double bonds. Here, the selectivity towards lactonisation was much greater than with conventional peroxidic materials, where both lactone and epoxide are formed.



3M wins Business in the Environment award

3M UK plc had been awarded the ‘Example of Excellence’ for the 2001 Business in the Environment award.

3M UK plc is one of the largest subsidiaries outside the USA involved in engineering, manufacturing, distribution, sales, marketing and administration of almost 50,000 products. The Business in the Environment award recognises innovative environmental performance integrated into a company’s sustainable development strategy, demonstrated in 3M through their pollution prevention programme.

3M established the world’s first such programme, known as Pollution Prevention Pays (3P), in 1975. This programme was based on the then novel approach that pollution prevention is both an environmental and a competitive/financial strategy. Preventing pollution at source has fundamentally changed the UK operation, with environmental and business benefits. Highlights over the last 10 years include:

- Air emissions cut by 97%
- Waste generated cut by 33%
- Energy consumption reduced by 25%

The 3P program depends directly on the voluntary participation of 3M employees. Since the 3P programme started more than 4700 projects have been initiated by employees world-wide, 150 in the UK. Tony Bellis, Corporate Communications Manager at 3M, believes ‘What differentiates 3M’s approach from that of any other UK organisation is that because of the innovation ethos, all employees are empowered to make a difference.’

3M products include:

- Fuel cells
- 3M multilayer films—the world's most efficient reflectors of light
- Smart tapes which add more intelligence to products with less material and energy consumption
- 3M Intelligent Transportation—a first step toward safer, self-steering automobiles
- 3M inventory management systems, 3M library products and other products use smart tape technology to help customers reduce waste and material loss
- Tapes and adhesives made without solvents reduce volatile organic air emissions

‘3M’s record on the Environment is possible unequalled amongst companies in the UK. It is most impressive because it demonstrated total integration of environmental responsibility with the company’s whole approach to business.’

3M faced competition from Severn Trent Plc and Union Railways (South) Ltd, the Channel Tunnel Rail Link Company.

Severn Trent Plc have grown from a regional, state-owned water authority based in Birmingham, into an international environmental services company. It operates in the UK, the US and Europe, employs almost 15 000 people and generated sales last year of approx. £1.6bn.

In 1991 Severn Trent Plc extended the group portfolio by acquiring Biffa, now the UK’s largest single supplier of integrated waste management services in the UK and a leading player in Belgium. The recently recognised Severn Trent services division was formed in 1998 and now leads the UK and American markets in its core business of environmental laboratories and analysis.

The group is committed to environmental leadership. It achieves this by:

- Adopting exemplary standards of environmental performance in their operations
- Encouraging and supporting others to do the same
- Understanding new environmental challenges and developing the services that will address them
- Taking part in debate on key environmental issues, especially with 5 other businesses and with environmental experts

Union Railways (South) Ltd were formed as a Government-owned company to develop the Channel Tunnel link, and are a subsidiary of London & Continental Railways Limited (LCR). The company earned its nomination through its policy of selecting contractors on the basis of environmental criteria and minimising environmental risk early in the planning process.

Union Railways focused on minimising environmental effects by using existing transport corridors. Route alternatives, including more than one hundred local route variations, were assessed. In addition to the environmental impact, the five-hundred-strong project team also evaluated cost and local economic benefits.

See the following web sites for further information:
3M: http://www.3M.com
Severn Trent Plc: http://www.severn-trent.com
Information on Union Railways (South) Ltd.: http://www.ctrl.co.uk

Solventless syntheses of mesotetraphenylporphyrin: new experiments for a greener organic chemistry laboratory curriculum

Marvin G. Warner, Gary L. Succaw and James E. Hutchison*

Department of Chemistry, University of Oregon, Eugene, Oregon 97403-1253, USA.
E-mail: hutch@oregon.uoregon.edu

Received 4th September 2001
First published as an Advance Article on the web 19th November 2001

Two solvent-free syntheses of the macrocycle mesotetraphenylporphyrin are presented that are optimized to teach greener chemistry in the undergraduate teaching labs. The preparations are examples of a greener organic chemistry laboratory curriculum being developed at the University of Oregon that strives to teach fundamental chemical concepts and essential laboratory skills in the context of green chemistry. These examples provide students the opportunity to explore the green chemical concepts of solventless chemical synthesis (solid-supported and gas-phase reactions) and use of microwaves in chemical synthesis. At the same time the students learn essential laboratory skills such as column and thin layer chromatographies as well as optical spectroscopy.

Introduction

The practice of green chemistry has become increasingly important in both industrial and academic settings. Thus far, few materials are available for teaching students the strategies and techniques of green chemistry. For this reason we developed a greener organic chemistry laboratory curriculum at the University of Oregon that teaches the tools and strategies of green chemistry. The use of greener methods in the teaching laboratory makes possible the use of macroscale techniques on the bench top and greatly improves laboratory safety by eliminating hazards to human health and the environment. In addition, the green curriculum provides an excellent platform for practical discussion of chemical hazards and the effects of chemicals on human health and the environment.

During the development of the green organic chemistry curriculum, criteria were conceived to guide the design of new experiments.[1] Experiments were selected if they reduce laboratory waste and hazards, illustrate green chemical concepts, teach modern reaction chemistry, provide a platform for the discussion of environmental issues in the classroom, can be accomplished in the requisite laboratory period, use inexpensive, greener solvents and reagents, and are adaptable to either macroscale or microscale methods. In the cases where an existing experiment was modified, we sought to minimize hazardous solvents, utilize the most benign reagents and solvents possible, and develop and use efficient reaction chemistry.[2]

The gas-phase and solid-supported microwave porphyrin syntheses presented here (Fig. 1) are two in a series of green organic laboratory experiments developed at the University of Oregon under the constraints of the criteria set forth above. They were performed during the past three academic years in the seventh laboratory session of the first term (gas-phase synthesis) and the seventh laboratory session of the second term (microwave synthesis) of the green organic chemistry laboratory sequence.

The experiments were adapted from the recent literature[3,4] to fit into a 3 h laboratory period. Students are able to simply and quickly synthesize one of the most important biologically relevant macromolecules, the heme, reinforcing the discussion of bioorganic and coordination chemistries in the lecture class. In addition to the syntheses, the lab exercises introduces the students to column and thin layer chromatographies as well as UV–VIS spectroscopy. Alternatively, they can be used as a multi-period exercise to introduce more advanced techniques and concepts (described later).

The laboratory experiments *'Gas-phase synthesis and column chromatography of mesotetraphenylporphyrin'* and *'Rapid synthesis of tetraarylporphyrins on silica under microwave irradiation'* are excellent opportunities to discuss/practice strategies and techniques for eliminating hazards due to solvents and reagents. They introduce the important strategies of solventless synthesis, the use of more benign reagents, the use

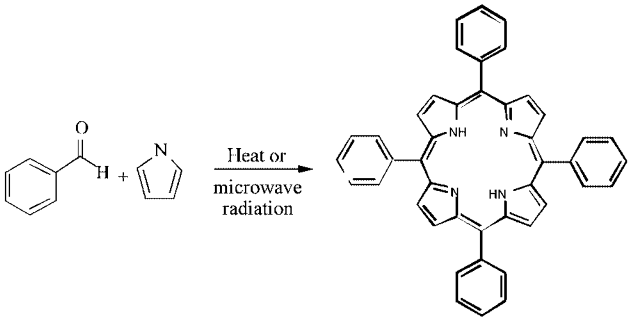


Fig. 1 Synthesis of mesotetraphenylporphyrin (TPP) is accomplished by high temperature reaction in the gas phase or by microwave irradiation on silica gel.

Green Context

The development of suitable green teaching lab experiments is extremely important in demonstrating the concepts of clean synthesis on a practical level, but can be time-consuming and difficult. Here are described two experiments which are currently used, and have been designed specifically with green chemistry in mind. In these experiments two routes to tetraarylporphyrins are investigated, molecules which have traditionally been prepared in a wasteful manner. The experiments could easily be carried out in most teaching laboratories. ***DJM***

DOI: 10.1039/b107999a

of air as a milder oxidizing agent, and the use of energy-efficient microwaves for synthesis.[5] The traditional porphyrin syntheses popularized by Adler, Longo and Lindsey use corrosive reagents (*e.g.* propionic, acetic and trifluoroacetic acids) and toxic solvents (*e.g.* benzene or chloroform) for chromatography and spectroscopic analysis.[6,7] On the other hand, the methods presented here[3,4] avoid the use of corrosive acids and halogenated solvents in the synthesis by performing the reaction in the gas phase or on a solid-phase support medium, essentially eliminating all waste produced during the synthesis. Additionally, the chromatography and spectroscopy solvent, hexanes and ethyl acetate (7 : 1), provides improved safety and reduced hazardous waste disposal issues compared to the traditionally used halogenated solvents.[8]

Results and discussion

The experimental procedures described herein are adaptations of syntheses of mesotetraphenylporphyrin (TPP) (Fig. 1) described in the recent literature.[3,4] Although the literature procedures provided positive results for some of our students with very little modification, the experiments needed further optimization before they could be reliably employed in the teaching laboratory. Refinement of the gas-phase synthesis focused on the method of heating the reaction vessel and the appropriate reaction temperatures for injection of the reactants. The new procedure can be carried out in standard teaching lab glassware shown in Fig. 2. In the case of the microwave synthesis, new chromatography conditions were needed in order to successfully separate the porphyrin product. Although no specialized glassware or laboratory apparatus is required to carry out the microwave reaction, it is important for the students to pay close attention to the reported reaction conditions and experimental set-up in order to successfully synthesize the product.

For the gas-phase reaction, injection of benzaldehyde at 170 °C followed closely by injection of pyrrole (immediately upon noticing the formation of droplets of benzaldehyde on the side of the reaction vessel at *ca.* 180 °C) led to the best results. Subsequent heating to a maximum temperature of 235 °C provided the best yields.[9] It is worth noting that in order to achieve even heating within the reaction vessel the height of the sand bath around the vial is important. The best results are observed when the 3-inch vial is immersed 1.5 inches in the sand bath.

In the case of the microwave synthesis, it is necessary to mix the benzaldehyde and pyrrole starting reagents immediately prior to absorption on the silica gel to assure good mixing and even coverage of the solid support medium. The reaction affords the best results when the reaction mixture is microwaved in five 2-min intervals at 1000 W to prevent overheating of the microwave oven.[10] Once the reaction is complete, the best results are obtained by first eluting the crude product mixture from the silica gel with ethyl acetate, removing solvent and extracting the crude product mixture in 1 mL of CH_2Cl_2 that is subsequently loaded on the silica gel column.

Chromatography of the crude reaction mixture employs a 7 : 1 hexanes–ethyl acetate mixture as the mobile phase for both thin layer and column chromatography. The lead fraction in both instances is the desired product, making identification and separation feasible for the beginning student. Because the porphyrin product is a good chromophore, it is easy for the novice to keep track of the product and evaluate the success of the reaction without spectroscopic means. If a student fails to inject each of the reactants at the appropriate temperatures in the case of the gas-phase reaction or if the reaction vial does not proceed to completion in either case, the lead fraction of the column is a green compound (that was not further characterized) rather than the porphyrin. Thus, the student can quickly determine success or failure of the synthesis and can repeat the experiment if necessary. Once the lead column fraction has been collected, the student can move directly to spectroscopic analysis without changing solvents.

Visible spectroscopy of the porphyrin product is provided here as both an introduction to the technique and a means for product identification. The absorption spectrum of mesotetraphenylporphyrin is very distinct and is shown in Fig. 3. The spectrum contains a strong absorbance at 420 nm (the Soret band) and four comparatively weak intensity absorbances at 510, 550, 590 and 645 nm (the Q bands). Students can calculate the relative extinction coefficient of each absorption band and determine the porphyrin concentration in their sample using the known extinction coefficient for the Soret band. When one compares the extinction coefficient ratios between the Soret band and Q bands for the purified products from both reactions they are found to be nearly identical suggesting that the product is the same in both instances.

A number of extensions to the experiment discussed above give the laboratory instructor flexibility when choosing the depth and breadth of the exercise. One possible extension involves the metallation of the porphyrin using $Zn(OAc)_2$. We focused on this metallation reaction because it can be monitored using visible spectroscopy by observing changes in the Q bands (Fig. 4). Here we replaced the typically used solvents (halogenated solvents or dimethylformamide) with more the benign solvents *N*-methylpyrrolidinone and dimethylsulfoxide.

Another possible extension involves the synthesis and ^{1}H NMR analysis of *ortho*-substituted tetraphenylporphyrins. The NMR spectroscopy is especially interesting in this case due to atropisomerism[11] and provides a platform for teaching/discussing more advanced topics in spectroscopy, such as observing temperature dependent phenomena and measuring rates of interconversion by line-broadening methods. Finally, the porphyrin product can also be used to construct functioning solar cells according to a procedure published in the recent literature.[12]

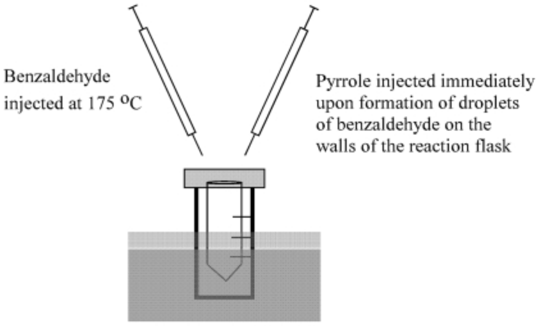


Fig. 2 Schematic representation of the experimental apparatus used for the gas-phase synthesis of mesotetraphenylporphyrin.

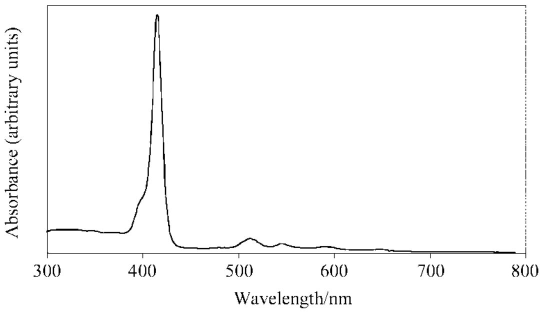


Fig. 3 UV–VIS spectrum of mesotetraphenylporphyrin in 7 : 1 hexanes–ethyl acetate.

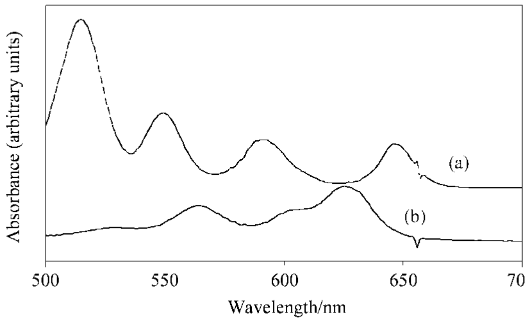


Fig. 4 Visible spectrum of the Q-band regions of mesotetraphenylporphyrin (a) before and (b) after metallation with $Zn(OAc)_2$. Spectra were collected in DMSO.

Conclusions

The experiments described effectively demonstrate strategies of green chemistry including solventless reaction conditions, more benign reagents and the use of microwave irradiation during synthesis. In addition, the halogenated and aromatic solvents often used to purify, spectroscopically characterize and metallate the product have been replaced with greener alternatives. The experiments have undergone extensive optimization and have been tested in the undergraduate teaching laboratory. The conditions reported here are optimized so that the synthesis and chromatographic purification work reliably in the teaching lab. During the past academic year the experiments has been tested by 35 students and we have found that whenever the procedures described herein are followed the experiments yield isolable product. Finally, these experiments are easily extendable to introduce topics such as NMR spectroscopy, organic materials chemistry, the construction of photochemical systems,[12] and coordination chemistry within the scope of a greener laboratory.

Experimental

General considerations

Prior to carrying out these reactions it is necessary to pass the pyrrole through basic alumina (or vacuum distill it) to remove polymeric impurities that interfere with successful formation or purification of the porphyrin product. All other solvents and reagents can be used as received.

Gas-phase synthesis of mesotetraphenylporphyrin (TPP)

A 3 inch tall 5 mL conical vial is placed in a sand bath so that the bottom 1.5 inches is immersed in the sand. When the sand bath reaches 170 °C, benzaldehyde (10 μL, 0.1 mmol) is injected *via* 20 μL syringe and allowed to vaporize. Once droplets of benzaldehyde form on the vessel walls and the temperature has reached approximately 180 °C, pyrrole (7 μL, 0.1 mmol) is injected *via* a 10 μL syringe and the temperature raised to 235 °C. After 15 min at 235 °C the vial is cooled to room temperature on the bench top. The reaction flask and cap liner are washed with 1 mL of CH_2Cl_2 to collect the product. The product mixture is now ready for chromatographic analysis and purification.

Microwave synthesis of TPP

A 25 mL Erlenmeyer flask, a standard Pyrex watch glass and a 1000 W microwave are used to carry out the microwave synthesis. 0.43 mL of benzaldehyde and 0.3 mL of pyrrole and mixed in the flask. Once the reactants are thoroughly mixed 0.63 g of silica gel is added, the flask stoppered, and the reagents mixed well until the silica gel is evenly and completely covered with the reactant mixture. The flask containing the reaction mixture is then placed in the microwave oven, covered with the watch glass and heated for 10 min in five 2-min intervals. Once the reaction is complete, it is allowed to cool to room temperature and *ca.* 15 mL of ethyl acetate added. The solution is filtered to remove the silica gel and then the ethyl acetate is removed using a rotary evaporator. Prior to chromatographic separation, the crude reaction mixture is extracted into 1 mL of CH_2Cl_2.[13] It is this fraction that is used in subsequent purification.

Thin layer chromatography. Thin layer chromatography of the product mixture was performed on silica TLC plates using a 7 : 1 hexanes–ethyl acetate mobile phase. TLC is then performed according to established procedures.[14] TPP appears as the leading spot on the silica plate (R_f = 0.46). The remaining impurities appear as a broad band with an R_f range of 0.0–0.3.

Column chromatography. A silica gel column is prepared in a column (3–5 cm *id*) fitted with a Teflon stopcock. A glass frit or a layer of glass wool covered with a 2 cm layer of sand provides a flat base for pouring the silica column. A slurry is prepared with between 6.5 and 8.5 g of silica gel in the mobile phase (30 mL 7 : 1 hexanes–ethyl acetate) resulting in a column height of ~ 32–40 cm. A 1 cm layer of sand is then placed on the top of the settled silica gel to protect the top surface of the column. The entire 1 mL solution of the product mixture in CH_2Cl_2 is carefully loaded on the top of the column and eluted until the solvent level has reached the top of the sand. The column is eluted with 7 : 1 hexanes:ethyl acetate at a flow rate of *ca.* 30 drops min^{-1} until the leading purple TPP band eluted. No other bands precede the TPP band, and the entire sample is collected in *ca.* 7–8 mL of solvent after *ca.* 20–25 min.

Visible spectroscopy. Spectra were collected on a Hewlett-Packard HP 8453 diode array instrument with a fixed slit width of 1 nm using 1 cm quartz cuvettes. For product identification, visible spectroscopy samples are prepared by placing 1–2 drops of the highly colored TPP solution collected during column chromatography in a scintillation vial and diluting to 4 mL with additional 7 : 1 hexanes–ethyl acetate. A few drops of triethylamine are added to the solution to maintain the free-base form of the porphyrin. The absorption spectrum of TPP shows a strong absorbance at 420 nm along with four weaker absorbances at 510, 550, 590 and 645 nm. Visible spectroscopy samples used for yield determinations are prepared by first removing the solvent under a stream of nitrogen and then drying on a vacuum line for 2–3 h. The purple crystals are then redissolved in a known amount of CH_2Cl_2 and spectra recorded and yields determined using previously reported extinction coefficient values for TPP.[2]

Metallation of TPP. A saturated solution of $Zn(OAc)_2$ (0.400 g, 2.2 mmol) in DMSO is prepared. The metallation is performed in a cleaned, dried glass UV cell. Three drops of the lead fraction from the column chromatography experiment are evaporated to dryness then diluted to 4 mL using *N*-methylpyrrolidinone (NMP). An initial spectrum is then collected. After addition of 5 drops of the $Zn(OAc)_2$ solution, spectra are collected every 25 min to monitor the progress of the metallation reaction. The metallation was complete in *ca.* 4 h at room temperature.

Acknowledgment

We thank Kathyrn Parent, Gerd Wöhrle, Scott Reed, the members of Fall and Winter term CH337G and CH338G (1999–2001 academic years) at the University of Oregon, John Thompson at Lane Community College, and Anne Glenn at Guilford College for their assistance in optimizing and testing these experiments. J.E.H. is an Alfred P. Sloan Research Fellow and a Camille Dreyfus Teacher-Scholar. M.G.W. and G.L.S. are Department of Education GAANN fellows. This work was supported by the University of Oregon and the National Science Foundation (CHE-9702726 and DUE-0088986).

References

1 S. M. Reed and J. E. Hutchison, *J. Chem. Ed.*, 2000, **77**, 1627.
2 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
3 C. M. Drain and X. Gong, *Chem. Commun.*, 1997, 2117.
4 A. Petit, A. Loupy, P. Maillard and M. Momenteau, *Synth. Commun.*, 1992, **22**, 1137.
5 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1998, **9**, 1213.
6 A. D. Adler, F. R. Longo and W. Shergalis, *J. Am. Chem. Soc.*, 1964, **86**, 3145; A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour and L. Korsakoff, *J. Org. Chem.*, 1967, **32**, 476.
7 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.
8 Chromatography is one of the requisite laboratory skills taught at sophomore level of organic chemistry. Therefore, even though the amount of solvent waste is increased, both thin-layer and column chromatography are included in these exercises to teach this important skill. (b) Efforts to eliminate the use of the small amount of CH_2Cl_2 in the initial extraction of the crude product were not successful. Elimination of the crude extraction step or the replacement of CH_2Cl_2 with a greener solvent led to poor chromatographic separation.
9 The yields for these reactions were determined using published extinction coefficient data in benzene; J. B. Kim, J. J. Leonard and F. R. Longo, *J. Am. Chem. Soc.*, 1972, **94**, 3986.
10 The time and microwave power will depend on the number of reaction vessels that are simultaneously placed in the oven. Our results indicated that longer reaction times are required to achieve the same results when more than one reaction is carried out in the same oven.
11 R. F. Beeston, S. E. Stitzel and M. A. Rhea, *J. Chem. Ed.*, 1997, **74**, 1468.
12 E. N. Durantini and L. Otero, *Chem. Educator*, 1999, **4**, 144.
13 The procedure as reported here provides porphyrin product in approximately 85% purity as determined by relative ^1H NMR integration. The major impurity can be seen in the NMR spectrum as a broad multiplet around 7.3 ppm. The impurity does not effect the UV–VIS spectrum of the porphyrin product nor does it effect ones ability to use the product in any of the further experiments reported.
14 R. Curtright, R. Emry and J. Markwell, *J. Chem. Ed.*, 1999, **76**, 249.

Modified natural phosphates: easily accessible basic catalysts for the epoxidation of electron-deficient alkenes

José M. Fraile,[a] José I. García,[a] José A. Mayoral,*[a] Said Sebti*[b] and Rachid Tahir[b]

[a] *Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón,*
Facultad de Ciencias, Universidad de Zaragoza-C.S.I.C., E-50009 Zaragoza, Spain.
E-mail: mayoral@posta.unizar.es
[b] *Laboratoire de Chimie Organique Appliquée, Université Hassan II, Faculté des Sciences,*
Ben M'Sik., B.P. 7955 Casablanca, Morocco

Received 14th May 2001
First published as an Advance Article on the web 8th October 2001

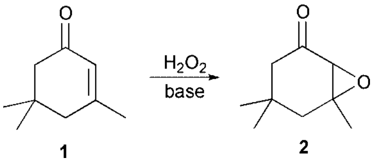
Natural phosphate is basic enough to promote the epoxidation of electron-deficient alkenes with dilute aqueous hydrogen peroxide. A simple modification with sodium nitrate leads to the probably most active, water compatible and recyclable basic catalyst described for this reaction. It promotes the epoxidation of a large variety of alkenes.

Introduction

Within the field of sustainable chemistry, the reduction in waste disposal through the development of cleaner catalytic processes is one of the main areas of interest.[1] In this kind of process the use of environmentally friendly reagents and recoverable heterogeneous catalysts is a key goal. Indeed, solid acid catalysts are being increasingly used in the synthesis of fine chemicals, which is not the case with basic catalysts. One of the reasons for this situation is that a large number of basic catalysts consist of basic compounds supported on metal oxides.[2] In this form the catalysts cannot be used in aqueous or alcoholic solvents due to leaching of the active species. Hydrotalcites and alkaline earth oxides do not suffer from this problem but, unlike clays, they are synthetic materials whose properties are closely related to very strict synthetic conditions.[3] Given these circumstances, the search for easily accessible materials, able to act as basic heterogeneous catalysts, is an area of great interest.

Epoxidation is among the most important oxidation reactions. Taking into account sustainable chemistry principles, aqueous hydrogen peroxide is one of the oxidants of choice because of its ease of handling, its high active oxygen content and the formation of water as the only by-product.[4] Basic catalysts are the most efficient ones for the epoxidation of electron-deficient alkenes and several examples of basic solids[5] have been described for this kind of reaction using dilute hydrogen peroxide. In all the cases hydrotalcites have been used as the starting material for the preparation of these basic catalysts. Calcined hydrotalcites were the first solids used in this epoxidation reaction,[6,7] with moderate to good results and some limitations arising from the relatively low basicity of these solids. The basicity can be tailored through modification in composition.[8] Kaneda and coworkers have recently reported the use of non-calcined hydrotalcites (in contrast with our own experience) with no clear advantages over the previous results.[9] Only the addition of the expensive and non-recyclable dodecyltrimethylammonium bromide improves the results using a biphasic hydrocarbon–water solvent system. The exchange of the hydrotalcite with *tert*-butoxide anions is clearly advantageous with regard to the hydrotalcite basicity,[10] but its use has only been described with chalcones and the highly reactive cycloalkenones. Furthermore, *tert*-butoxide anions are transformed into hydroxide and *tert*-butanol in aqueous media, which accounts for the need of preparation in anhydrous conditions and for the non-recyclability of the original catalyst. In any case, hydrotalcites suffer the drawback of the need for strict synthetic conditions[3] and they are not available either commercially or in a great scale.

In contrast with the artificial origin of hydrotalcites, phosphates are natural resources in many areas of the Maghrib and, in addition, they are easy to obtain and inexpensive. Considerable effort is currently focused on expanding the application of such materials in the field of catalysis. These phosphates show interesting basic properties and have been applied to different organic reactions, such as the Knoevenagel condensation,[11] addition of phosphites to carbonyls[12] or the Claisen–Schmidt condensation.[13] With these precedents in mind, we decided to test the activity of phosphates as catalysts for the epoxidation of



Scheme 1 Epoxidation of α-isophorone.

Green Context

Epoxides are extremely versatile intermediates in organic and pharmaceutical chemistry. Numerous methods are available for their synthesis but traditional methods such as the dehydrochlorination of epichlorohydrine and the use of peracids for the direct oxidation of alkenes suffer from problems due to large volumes of waste formation and, in the latter case, dangerous reagents. A number of more environmentally acceptable and safer alternatives are becoming available and this paper adds a new catalyst to this 'green toolkit' for epoxidations, notably the direct oxidation of electron-deficient alkenes. A simple modification of natural phosphate with sodium nitrate leads to a remarkably active and recyclable basic catalyst for expoxidising various alkenes using aqueous hydrogen peroxide. The water stability of this new solid base is a particularly significant and useful feature of the material.

JHC

DOI: 10.1039/b104201g

electron-deficient alkenes with dilute hydrogen peroxide, a more demanding reaction with regard to basicity than the aforementioned condensations.

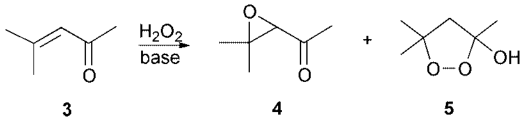
Results and discussion

The epoxidation of α-isophorone **1** was chosen as a test reaction (Scheme 1). Different amounts of natural phosphate (Table 1) were tested in order to find the optimal conditions. Low to moderate conversions were obtained with 100 and 300 mg of phosphate and a maximum of 60% conversion, similar to that reported with hydrotalcites,[8] was attained with 500 mg. The lower degree of conversion observed with smaller amounts of catalyst seem to be due to the very low surface area of the solid. In fact, higher conversions can be reached with longer reaction times, showing that the catalyst is not completely deactivated. The amount of basic centres in the natural phosphate was determined by adsorption of phenol at different initial concentrations. The extrapolation at zero concentration was carried out to minimise the effect of physisorption. A value of 0.54 mmol g^{-1} was obtained, showing that in all the cases the phosphate was used in a substoichiometric amount. This catalyst is recoverable, at least once, although it shows a slightly lower activity after recovery. An additional reaction, the epoxidation of mesityl oxide (**3**, Scheme 2), was tested because of the two possible products obtained upon using hydrotalcite catalysts, *i.e.* the epoxide **4** and the 3-hydroxy-1,2-dioxolane **5**. As described for hydrotalcites,[8] the degree of conversion of mesityl oxide is greater than that of isophorone under the same conditions, reaching up to 83%. Once again the phosphate is recoverable, although with a slight decrease in catalytic activity. The selectivity of epoxide/dioxolane (**4**/**5**) in this case is 40/60 and slightly favours the dioxolane in comparison to hydrotalcite.[6,8] It is worth noting that synthetic fluoroapatite and hydroxyapatite are not active under the same conditions despite the similarity in the structures with natural phosphate.

Table 1 Epoxidation of isophorone and mesityl oxide with hydrogen peroxide catalysed by natural phosphate[a]

Ketone	Phosphate/ mg	t/h	Conversion (%)[b]	Epoxide/ dioxolane[c]
α-Isophorone **1**	100	24	27	—
	100	96	41	—
	300	24	43	—
	500	1	26	—
		24	63	—
	500[d]	24	55	—
	100[e]	1	35	—
		24	62	—
	100[d,e]	24	40	—
Mesityl oxide **3**	500	1	23	—
		24	83	40/60
	500[d]	24	69	42/58
	100[e]	24	76	15/85

[a] *Reaction conditions*: ketone (0.75 mmol), 30% H_2O_2 (0.35 ml), methanol (1 ml) and phosphate at room temperature. [b] Determined by GC. [c] Determined by ^1H NMR spectroscopy. Unless it is indicated, epoxide is the only product. [d] Recovered catalyst. [e] Natural phosphate doped with benzyltriethylammonium chloride (15 mg).



Scheme 2 Epoxidation of mesityl oxide.

In previous research it was shown that the addition of a phase transfer agent to the phosphate, both natural[13] and fluoroapatite,[14] increases the activity of the solid. This strategy was tested in the same epoxidation reactions (Table 1), but in contrast with previous work[9] the inexpensive benzyltriethylammonium chloride was used and no hydrocarbon solvent was needed. The same maximal conversion of isophorone was obtained with only 100 mg of catalyst doped with 15 mg (0.066 mmol) of benzyltriethylammonium chloride. The same effect is observed for mesityl oxide, thus confirming the increase in activity. This activity is not due to any catalytic effect of the ammonium salt, as demonstrated by the lack of activity of benzyltriethylammonium chloride in a control experiment. However, a noticeable loss of activity is observed after recovery of the catalyst because of leaching of the phase transfer agent, which is partially soluble in the methanolic reaction medium. One solution for this problem would be the addition of a new portion of transfer agent to the reaction mixture. Another interesting effect observed in the reaction of mesityl oxide is the increase in the dioxolane selectivity to 15/85, a situation that occurs despite the higher catalytic activity. This result is in contrast with those obtained with hydrotalcites, where the final selectivity to dioxolane was lower in the cases where more active catalysts were employed.[8]This treatment with a phase transfer agent is also positive in the case of fluoroapatite and hydroxyapatite, although the conversions of isophorone are much lower than those obtained with the natural phosphate.

Another method to increase the activity of this type of solid is the impregnation of the phosphate with a solution of sodium nitrate ($NaNO_3$/phosphate = 1/2 w/w) followed by drying and calcination. In this way the structure of the solid is changed, as shown by the X-ray diffraction pattern of the sample calcined at 1073 K (Fig. 1), in a way that does not occur after calcination at lower temperature. This calcination produces a reaction in the solid phase that results in the formation at least of two new phases, which can be attributed to sodium phosphate and calcium oxide, although this point deserves further investigation. The decomposition of the nitrate was also detected by IR spectroscopy (disappearance of the band at 1365 cm^{-1}) and thermal analysis (loss of weight from 873 to 1073 K). This solid presents a similar surface area at about 0.66 m^2g^{-1}.

The modified phosphate is much more active than the natural one, as shown by the results gathered in Table 2. Total conversion of isophorone after 24 h is obtained with only 100 mg of catalyst. Moreover, the catalyst is partially recoverable without further re-activation (72% conversion) and retains almost complete activity after re-calcination at 773 K (87%). With mesityl oxide, the higher reactivity of the substrate leads to complete conversion after 12 h and, in this case, the catalyst is completely recoverable. This result shows that the modification introduced in the phosphate by treatment with sodium nitrate and calcination is permanent. One interesting result is

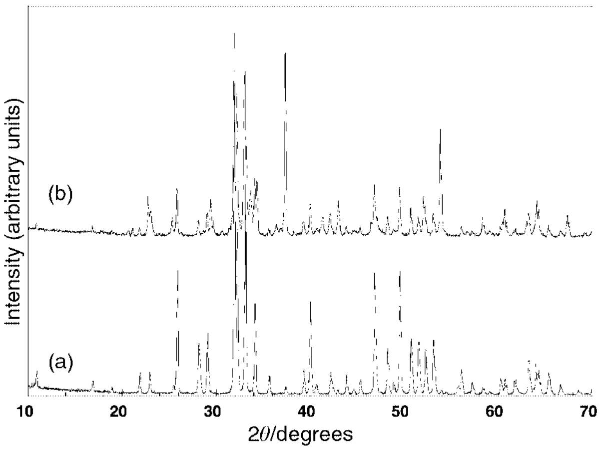


Fig. 1 X-Ray diffraction patterns of (a) natural phosphate and (b) natural phosphate modified with $NaNO_3$ and calcined at 1073 K.

again the high selectivity to dioxolane obtained with this catalyst, even after long reaction times. This situation is in contrast to previous findings concerning the use of hydrotalcite catalysts.[8] For $NaNO_3$/NP, high dioxolane selectivity is observed from the beginning, as is the case for very active hydrotalcite catalysts, but it is also maintained until the end of the reaction. This particular behaviour may be of use in the synthesis of 1,2-dioxolanes, which are difficult to prepare by other procedures.[15]

In view of these results a question arises, namely which new phase is responsible for the enhanced catalytic activity. In order to clarify this point, the epoxidation of isophorone was carried out in the presence of CaO or Na_3PO_4. Whereas CaO is not an active catalyst, with 28 mg of sodium phosphate a 95% yield is obtained after 24 h. It seems then clear that the sodium phosphate phase must be responsible for the increase in catalytic activity.

Some other electron-deficient alkenes were tested in order to check the general character of this methodology (Chart 1 and Table 2). In general, total conversion was obtained in the case of ketones with disubstituted (hexenone, chalcone, cyclohexenone, cyclopentenone) or trisubstituted (isophorone, mesityl oxide, carvone, phorone) C–C double bonds. Some lower conversions can be attributed to steric hindrance, as for the bicyclic terpene verbenone. Pulegone is less reactive, which is due to the tetrasubstitution of the double bond and the enforced *s-cis* disposition of the enoate. In spite of this, $NaNO_3$/NP catalyses the reaction, and the use of a higher amount of solid allows a very high conversion to the epoxide. This result is in strong contrast with the non-reaction described with hydrotalcite.[9] With hex-4-en-3-one the phosphate-based catalyst shows the same tendency to increase the selectivity as found for dioxolane, in this case from 73/27 with hydrotalcite[6] to 60/40. Finally, methyl cyanocinnamate also gives total conversion without ester or nitrile hydrolysis.

In conclusion, natural phosphate is a basic catalyst that is able to promote the epoxidation of electron-deficient alkenes with dilute hydrogen peroxide. However, its very low surface area gives rise to kinetic problems, leading to a reduction in the catalytic activity. This activity can be increased by the use of a phase transfer agent, although this modification is not permanent with the methanolic reaction medium used in the epoxidation reaction. The solid prepared by impregnation of the natural phosphate with sodium nitrate, followed by calcination at 1073 K, is a highly efficient basic catalyst for the epoxidation of electron-deficient alkenes with dilute hydrogen peroxide. The advantages of this solid over other basic heterogeneous catalysts are the high activity, the ready availability and low price of the precursors, the simplicity of the preparation method and the easy reuse. In fact this is probably the most active among the water compatible and recoverable solid catalysts for this reaction. Particularly interesting behaviour was observed with regard to the selectivity to 3-hydroxy-1,2-dioxolanes, and this case warrants further investigation.

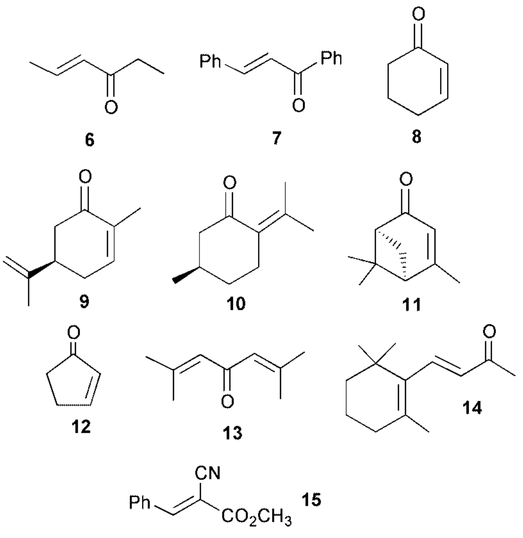


Chart 1 Electron-deficient alkenes used in this work.

Table 2 Epoxidation of electron-deficient alkenes with hydrogen peroxide catalysed by natural phosphate modified with sodium nitrate.[a]

Alkene	Catalyst/mg	*t*/h	Conversion (%)[b]	Epoxide/dioxolane[c]
α-Isophorone **1**	100	1	35	—
		24	98	—
	100[d]	24	72	—
	100[d,e]	24	87	—
Mesityl oxide **3**	100	1	55	23/77
		3	76	12/88
		12	99	10/90
	100[d,e]	12	98	15/85
Hex-4-en-3-one **6**	100	1	99	60/40
	100[d,e]	12	98	63/37
Chalcone **7**	100	1	76	—
		12	99	—
	100[d,e]	12	99	—
Cyclohex-2-en-1-one **8**	100	24	99	—
(*R*)-Carvone **9**	100	24	98	—
(*R*)-Pulegone **10**	100	24	44	—
	300	24	86	—
(1*S*)-Verbenone **11**	100	24	71	—
Cyclopent-2-en-1-one **12**	100	24	99	—
Phorone (**13**)	100	24	100[f]	96/4
β-Ionone **14**	200	24[g]	0	—
Methyl (*E*)-2-cyanocinnamate **15**	100	24	99	—

[a] Same reaction conditions as in Table 1. [b] Determined by GC and/or ^1H NMR spectroscopy. [c] Determined by ^1H NMR spectroscopy. Unless indicated, epoxide is the only product. [d] Recovered catalyst. [e] Reactivated at 500 °C. [f] Both C–C double bonds react. [g] Reaction carried out under reflux.

Experimental

Preparation of the catalysts

Natural phosphate was obtained in the Khouribga region (Morocco). The fraction of particle size 100–400 μm was isolated, washed with water, calcined at 1173 K for 2 h and sieved. The samples were re-activated at 773 K prior to use as catalysts.[12] The structure of the material is similar to that of fluoroapatite, as shown by the X-ray diffraction pattern. This solid presented a very low surface area (BET) at *ca.* 1 m^2g^{-1}. The chemical composition was determined as: P_2O_5 (34.24%), CaO (54.12%), F^- (3.37%), SiO_2 (2.42%), SO_3 (2.21%), CO_2 (1.13%), Na_2O (0.92%), MgO (0.68%), Al_2O_3 (0.46%), Fe_2O_3 (0.36%), K_2O (0.04%) and several metals (Cd, Zn, Cu, V, Cr, U) in the range of ppm.

Natural phosphate was doped with benzyltrimethylammonium chloride by impregnation of the solid with the required amount of a solution of the phase transfer agent and solvent evaporation.[13,14]

$NaNO_3$/NP was prepared by addition of natural phosphate (10 g) on a aqueous sodium nitrate solution (50 ml, 1.17 M). The mixture was stirred at room temperature for 30 min and water was evaporated under reduced pressure. The resulting solid was calcined under air at different temperatures. This solid was characterised by XRD, IR and BET measurements.

Epoxidation reactions

To a solution of the alkene (0.75 mmol) in methanol (1 mL) was added the catalyst (see Tables 1 and 2 for amounts) and 30% hydrogen peroxide (0.35 mL). The reaction mixture was stirred at room temperature for the appropriate time (see Tables 1 and

2), filtered and the catalyst washed with methanol (5 mL). Ethylene glycol dimethyl ether (100 mg) as an internal standard was added and the solution was analysed by gas chromatography. The nature of the products and the epoxide/dioxolane ratio were determined by ^{1}H NMR spectroscopy. For pulegone, the epoxide was also characterised by MS.

Control experiments were carried out in the same conditions using benzyltriethylammonium chloride (15 mg), CaO (47 mg) or Na_3PO_4 (28 mg).

Acknowledgements

We are indebted to CICYT (Project MAT99-1175-C03-01), Agencia Española de Cooperación Internacional (Project 2001MA0005), PROTARS (Project P2T3/59) and OCP ('Office Chérifien des Phosphates') for financial support.

References

1 P. T. Anastas, L. B. Bartlett, M. M. Kirchhoff and T. C. Williamson, *Catal. Today*, 2000, **55**, 11.

2 See, for example: G. W. Kabalka and R. M. Pagni, *Tetrahedron*, 1997, **53**, 7999.

3 F. Cavani, F. Trifirò and A. Vaccari, *Catal. Today*, 1991, **11**, 173; H. Hattori, *Chem. Rev.*, 1995, **95**, 537.

4 *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*, ed. G. Strukul, Kluwer, Dordrecht, 1992.

5 For a review, see: J. M. Fraile, J. I. García and J. A. Mayoral, *Catal. Today*, 2000, **57**, 3.

6 C. Cativiela, F. Figueras, J. M. Fraile, J. I. García and J. A. Mayoral, *Tetrahedron Lett.*, 1995, **36**, 4125.

7 J. M. Fraile, J. I. García, J. A. Mayoral and F. Figueras, *Tetrahedron Lett.*, 1996, **37**, 5995.

8 J. M. Fraile, J. I. García, D. Marco, J. A. Mayoral, E. Sánchez, A. Monzón and E. Romeo, *Stud. Surf. Sci. Catal.*, 2000, **130**, 1673.

9 K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Org. Chem.*, 2000, **65**, 6897.

10 B. M. Choudary, M. L. Kantam, B. Bharathi and C. V. Reddy, *Synlett*, 1998, 1203.

11 S. Sebti, A. Saber and A. Rhihil, *Tetrahedron Lett.*, 1994, **35**, 9399.

12 S. Sebti, A. Rhihil, A. Saber, M. Laghrissi and S. Boulaajaj, *Tetrahedron Lett.*, 1996, **37**, 3999.

13 S. Sebti, A. Saber, A. Rhihil, R. Nazih and R. Tahir, *Appl. Catal. A*, 2001, **206**, 217.

14 S. Sebti, R. Nazih, R. Tahir, L. Salhi and A. Saber, *Appl. Catal. A*, 2000, **197**, L187.

15 P. H. Dussault and X. Liu, *Org. Lett.*, 1999, **1**, 1391 and references therein.

Solventless preparation of oximes in the solid state and *via* microwave irradiation

Goverdhan L. Kad,* Monica Bhandari, Jasamrit Kaur, Raman Rathee and Jasvinder Singh

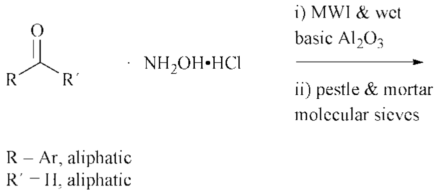
Department of Chemistry, Panjab University, Chandigarh 160014, India.
E-mail: kadgl@rediffmail.com

Received 14th August 2001
First published as an Advance Article on the web 17th October 2001

Effective methodologies for the preparation of oximes from aldehydes and ketones are presented, which have the advantage of being eco-friendly, easy to handle, employ shorter reaction times and solventless conditions.

Conversion of carbonyl functionalities into oximes is important in synthetic organic chemistry, not only for protection, purification and characterization of carbonyl groups, but also for various functional group transformations such as into nitriles,[1] nitro compounds,[2] nitrones,[3] amines[4] and isoxazolines.[5] Ketones are poor radical acceptors in reactions involving unimolecular chain transfer mechanisms as compared to acylgermanes,[6] furthermore, it has been noted that reactions involving oxime derivatives of acylgermanes lead to much greater enhancement in cyclization rate constants. Such studies have led to the development of better methods for the preparation of oximes. Conventionally, oximes are prepared[7] by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. More recently[8] oximes have been synthesized from nitriles,[9] phosphinium compounds[10] and *via* microwave irradiation (MWI)[11] of ketones, $NH_2OH{\cdot}HCl$ and NaOAc in EtOH.

In continuation of our earlier work[12] on the application of MWI in organic synthesis, we have recently developed a novel, environmentally safe and clean synthesis of aldoximes and ketoximes using MWI or grinding in a mortar (Scheme 1). The former method employs irradiation of reactants impregnated on wet basic Al_2O_3, in a domestic microwave oven and generally at power level (P.L.) 1 or 5 for 1 to 10 min (reaction under similar conditions using dry basic Al_2O_3 gave poor yields of the products). The latter method makes use of local heat produced by grinding of the reactants in the presence of molecular sieves for driving the chemical reactions. Both the techniques used, namely MWI or grinding in a mortar, utilize solvent-free conditions, easy work up and furnish the oximes in excellent to moderate yields (as shown in Table 1). This minimizes waste disposal problems and provide a simple yet efficient examples of unconventional methodologies which may be used at the undergraduate level. It is also interesting to note that ketoximes are not obtained when grinding in a mortar, whereas microwave exposure provide them in good to moderate yields, probably due to the specific effect of microwave radiation.



Scheme 1

Experimental

Basic Al_2O_3 used in the reactions was procured from Sd. Fine Chemicals Ltd, Mumbai, India. Optimum results were obtained when *ca.* 0.5 mL of water was added to 0.15 g of basic Al_2O_3 for wetting.

Typical procedure: (A) utilizing MWI

A mixture of aldehyde/ketone (1 mmol) and hydroxylamine hydrochloride (2 mmol) was impregnated on wet basic Al_2O_3, (1.5 equiv.) placed in a 25 mL Erlenmeyer flask and subjected to microwave irradiation at the required power level for 1–10 min. On cooling, the reaction mixture was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were washed with water (2 × 10 mL), brine and dried over anhydous Na_2SO_4. Evaporation of the solvent *in vacuo* afforded pure oximes in 47–99% yield (as shown in Table 1).

(B) Utilizing pestle and mortar (P/M)

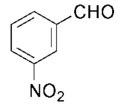
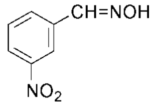
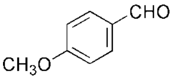
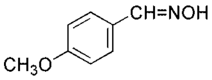
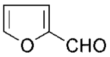
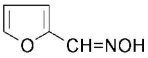
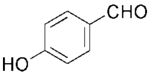
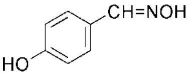
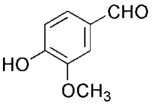
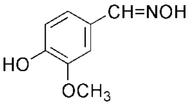
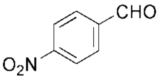
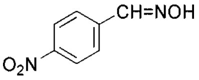
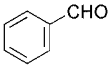
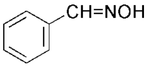
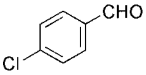
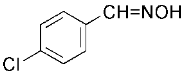
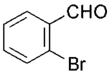
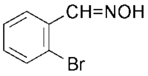
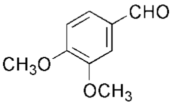
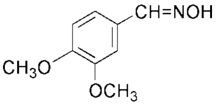
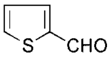
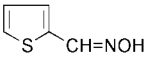
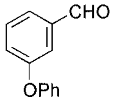
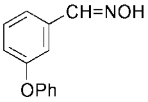
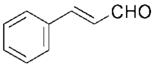
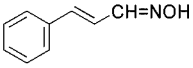
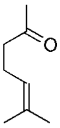
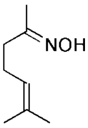
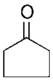
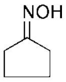
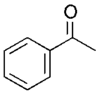
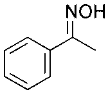
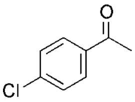
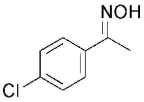
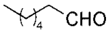
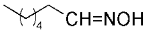
A mixture of aldehyde/ketone (1 mmol), hydroxylamine hydrochloride (2.5 mmol) and molecular sieves (4A, 2.5 g) were

Green Context

Oximes are very useful organic compounds. They are used for purification, characterisation and as intermediates en route to important functional groups including nitro, nitrile and nitrone. The oxime function is also used as a protecting group. Thus, if we are to use such compounds, it is important that we employ highly efficient, environmentally benign methods. Here a solvent-free method, based on innocuous alumina is described. The method is efficient, versatile and generates little waste. ***JHC***

DOI: 10.1039/b107356g

Table 1 Preparation of aldoximes and ketoximes[a]

					MWI		Pestle and mortar	
Entry	Reactant	Product	Mp/°C	P.L.	*t*/min	Yield (%)	*t*/min	Yield (%)
1			121–123[b]	1	5	96	50	52
2			45–52[c]	5	1	82	45	63
3			83–85[c]	1	5	83	40	66
4			—	1	5	94	95	74
5			98–100[c]	1	5	87	60	51
6			123–127[b]	1	5	83	50	48
7			—	1	5	79	30	60
8			87–95[c]	5	7	64	30	54
9			88–90[b]	1	5	67	30	88
10			—	1	5	55	30	31
11			—	1	6	50	40	74
12			—	1	5	47	45	70
13			—	1	5	99	30	79
14			—	5	5	98	30	No reaction
15			53–56[a]	1	5	91	30	No reaction
16			—	5	7	58	30	No reaction
17			—	5	0	64	30	No reaction
18			—	5	5	80	30	12

[a] All compounds are characterized on the basis of IR and ^{1}H NMR spectral data. [b] Melting points have been correlated literature values. [c] Not found in the literature.

ground in a pestle and mortar for the required time. On completion of the reaction as monitored *via* TLC, the reaction mixture was taken up in diethyl ether (2 × 15 mL) and filtered. The filtrate was washed with water (2 × 10 mL), brine dried over anhydous Na_2SO_4 followed by evaporation of solvent *in vacuo* to furnish the pure aldoxime in 12–79% yield (as shown in Table 1). Ketones were recovered as such, without any change.

Acknowledgement

We are highly grateful to the CSIR and UGC, New Delhi for financial assistance to carry out this piece of research.

References

1 H. M. S. Kumar, T. P. Reddy and J. S. Yadav, *Synthesis*, 1999, 586; B. Das, P. Madhusudhan and B. Venkataiah, *Synlett*, 1999, 1569.

2 P. R. Dave and F. Forshar, *J. Org. Chem.*, 1996, **61**, 8897; F. P. Ballistreni, E. Barbuzzi, G. A. Tomaselli and R. M. Toscano, *Synlett*, 1996, 1093.

3 M. E. Xenikaki, X. N. Stamplos, T. A. Charalambis and C. C. Karapostolon, *Tetrahedron*, 1997, **53**, 747.

4 S. Sasatani, T. Miyazak, K. Maruoka and H. Yamamoto, *Tetrahedron Lett.*, 1983, **24**, 4711; S. Negi, M. Matsukura, M. Mizuno and K. Miyake, *Synthesis*, 1996, 991.

5 J. T. Pulkkiner and J. J. Vepsalainen, *J. Org. Chem.*, 1996, **61**, 8604.

6 A. L. J. Beckwith and B. P. Hay, *J. Am. Chem. Soc.*, 1989, **111**, 2674; U. Iserloh and D. P. Curran, *J. Org. Chem.*, 1998, **63**, 4711.

7 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edn., John Wiley & Sons, Inc., New York, 1991, p. 214.

8 G. M. Robertson, *Comprehensive Organic Functional Group Transformations*, Elsevier, Cambridge, UK, 1995, vol. 3, p. 443 and 733.

9 M. Kizil and J. A. Murphy, *Tetrahedron*, 1997, **53**, 16847.

10 F. Palacios, D. Aparicio, J. M. De Los Santos and E. Rodriguez, *Tetrahedron*, 1998, **54**, 599.

11 A. K. Mitra , A. De and N. Karchaudhuri, *J. Indian Chem. Soc.*, 1999, **76**, 218.

12 G. L. Kad, J. Kaur, P. Bansal and J. Singh, *J. Chem. Res. (S)*, 1996, 188; G. L. Kad, K. Kaur, V. Singh and J. Singh, *Tetrahedron Lett.*, 1997, **38**, 1079; G. L. Kad, M. Sharma, J. Singh and B. R. Chhabra, *J. Chem. Res. (S)*, 1997, 264; G. L. Kad, J. Kaur, S. Nayyar and J. Singh, *Indian J. Chem.*, 2001, **40B**, 715.

Solventless synthesis of thiohydantoins over K_2CO_3

M. Kidwai, R. Venkataramanan and B. Dave

Department of Chemistry, University of Delhi, Delhi-110007, India.
E-mail: mkidwai@mantraonline.com

Received 9th July 2001
First published as an Advance Article on the web 5th October 2001

Potassium carbonate supported solventless synthesis of thiohydantoins under microwave irradiation is described. The use of K_2CO_3 not only eliminates the need for external base to neutralize HCl evolved but enables aqueous work up, thus rendering the reaction procedure free of organic solvents in both the reaction step and work-up, procedure.

Introduction

Environmentally friendly synthesis of organic compounds without using organic solvents has come several steps closer in recent years.[1–3] Strict environmental legislations have forced scientists all over the world to develop alternative syntheses of biologically and synthetically important compounds. Solvent-free synthesis generally refers to absence of solvents in the synthetic step itself, however, a considerable amount of solvent is used in adsorption of reagents and elution of the product which lessens the environmentally benign approach. Neat reactions on the other hand have their own practical problems such as overheating and charring of compounds due to ineffective dissipation of energy *etc*. However, coupling of solventless synthesis with microwaves[1–4] shows benefits of shorter reaction times, uniform heating and higher yields.

Thiohydantoins have proved to be interesting owing to their associated diverse biological activities.[5,6] Various synthetic procedures for their synthesis has been reported[6,7] in the literature. The common route for the synthesis of thiohydantoin derivatives is the reaction of isothiocyanates with appropriate nitrogen compounds. Apart from this route, reactions of thioureas with chloroacetyl chloride or chloroacetic acid have also been reported.

In order to minimize solvent usage potassium carbonate was used as reaction medium in the synthesis of thiohydantoins, as the work-up requires only water. Further K_2CO_3 serves as a base, eliminating the need of external base to neutralize the HCl evolved during reaction.

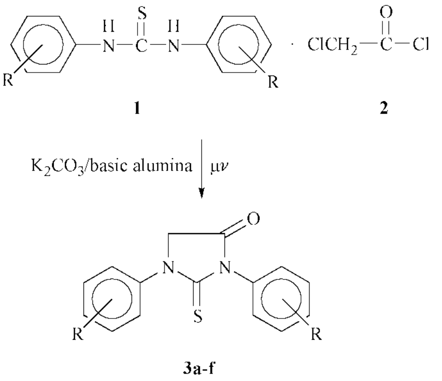
Results and discussion

N,*N*-Diarylthoiurea **1** and chloroacetylchloride **2** were deposited over K_2CO_3[8a] and irradiated in a microwave oven (approximate temperature 95–105 °C) for *ca*. 2 min (Table 1) to yield the thiohydantoins **3a–f**. For a comparative study the reactants were adsorbed over basic alumina[8b] and irradiated (approximate temperature 110–115 °C) for 2–3 min (Table 1). The elution of product from a 1 gram reaction batch, in the case of basic alumina requires *ca*. 25–30 ml of ethanol, whereas with K_2CO_3 only water is required thus eliminating the usage of organic solvent in the work-up stage. On the other hand, with neat reactants, reaction completion was not observed even after 3 min of irradiation and further irradiation led to charring of the compounds. On a low power setting of 560 W, after 5 min *ca*. 80% completion with two spots were observed. Further irradiation again resulted in onset of charring.

To study the microwave effect on K_2CO_3 with respect to basic alumina, 15 g of both were separately irradiated for 2 min. It was observed that for K_2CO_3 only a temperature of 45–50 °C was attained, whereas with basic alumina a temperature of

Table 1 Reaction times and yields for thiohydantoins **3a–f**

			K_2CO_3		Basic alumina	
Compound	R	mp/°C	*t*/s	Yield (%)	*t*/s	Yield (%)
3a	H	96–97	110	80	140	82
3b	*o*-Me	91–93	120	84	140	82
3c	*o*-MeO	86–88	130	84	160	81
3d	*p*-MeO	118–120	140	86	160	84
3e	*p*-Cl	135–136	160	86	180	85
3f	*p*-Br	140–142	160	88	180	84



Scheme 1 R = H, *o*-Me, *o*-MeO, *p*-MeO, *p*-Cl, *p*-Br.

Green Context

Carrying out organic reactions in the absence of solvents is one of the more important goals in clean synthesis. However, the green chemistry credentials of such processes can be rather questionable when large quantities of polluting solvents are used in the pre-process (adsorption/mixing) and post-process (desorption/purification) steps. Here a quite simple solventless synthetic process is described which involves only methanol and ethanol in the pre- and post-process steps. The procedure involves the synthesis of thiohydantoins which have interesting and useful biological activities. High product yields are obtained for a variety of products. *JHC*

DOI: 10.1039/b106034c

85–90 °C was reached. Thus K_2CO_3 is less microwave active and allows a larger fraction of irradiation to be available for the reactants as compared to basic alumina. This also helps in more absorption of excess thermal energy from the reactants by K_2CO_3 so preventing charring.

The above observations, support the fact that K_2CO_3 not only acts as base, but also helps in the dissipation of excess energy. Replacement of K_2CO_3 with Na_2CO_3 led to no significant change in reaction time or yield. Under conventional heating at similar temperature (105–110 °C), the reaction took 3–4 h and gave only 50–60% yield. Moreover, the reaction required constant stirring to prevent charring.

In conclusion, we have developed an environmentally benign technique for the synthesis of thiohydantoins, which requires no organic solvent for elution. Further, this can be applied for the synthesis of many other heterocyclic compounds.

Experimental

^{1}H NMR spectra were recorded on Perkin-Elmer R-32 (90 MHz, $CDCl_3$) instrument using TMS as internal standard. IR spectra were recorded on a 1710 Perkin-Elmer FTIR spectrophotometer using KBr discs (IR and NMR data not cited herein). The reaction was carried out in an unmodified domestic microwave oven (KENSTAR, OM 9925E) at 2450 MHz. Melting points were taken on an electrothermal apparatus and were uncorrected. The purity of the compounds was checked on silica gel coated Al plates (Merck).

General procedure

To a methanolic solution of 0.01 mol of *N*,*N*-diarylthiourea **1** and 0.01 mol of chloroacetylchloride **2**, was added 15 gr of K_2CO_3/basic alumina. The reaction mixture was air dried and irradiated in domestic microwave oven (800 W) for 2–3 min. On completion of reaction, as monitored by TLC (every 30 s) the reaction mixture was treated with cold water/ethanol. The product obtained from filtration/evaporation was dried and recrystallized from methanol.

Acknowledgement

The author R. V. is thankful to the Council of Scientific and Industrial Research, New Delhi for the financial assistance.

References

1 D. C. Dittmer, *Chem. Ind.*, 1997, 779; R. S. Varma, *Green Chem.*, 1999, **1**, 43.

2 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacqualt and D. Mathe, *Synthesis*, 1998, 1213; S. Deshayes, L. Marion, A. Loupy, J. L. Luche and A. Petit, *Tetrahedron*, 1999, **55**, 10851.

3 M. Kidwai, *Pure Appl. Chem.*, 2001, **73**, 147.

4 M. Kidwai, R. Venkataramanan, R. K. Garg and K. R. Bhushan, *J. Chem. Res. (S)*, 2000, 586; M. Kidwai, B. Dave, P. Misra, R. K. Saxena and M. Singh, *Inorg. Chem. Commun.*, 2000, **3**, 465.

5 H. Arnold, E. Kuehas and N. Brock, *Ger. Pat.*, 1135915, 1962; *Chem. Abstr.*, 1963, **61**, 9504; R. Sarger, *U.S. Pat.*, 4130714, 1978; *Chem. Abstr.*, 1980, **92**, 94401.

6 M. H. Khan, K. Begum and Nizamuddin, *Pest. Res. J.*, 1997, **9**, 86 and references therein; V. Chazeau, M. Cussac and A. Boucherle, *Eur. J. Med. Chem.*, 1992, **27**, 615; V. Chazeau, M. Cussac and A. Boucherle, *Eur. J. Med. Chem.*, 1992, **27**, 839.

7 J. Matthews and R. A. Rivero, *J. Org. Chem.*, 1997, **62**, 6090; J. H. V. Maarseveen, *Comb. Chem. High Throughput Screening*, 1998, **1**, 185; Y. Durust and F. Nohut, *Synth. Commun.*, 1999, **29**, 1997; S. Wua and J. M. Janusz, *Tetrahedron Lett.*, 2000, **41**, 1165; C. A. Lopez and G. G. Trigo, *Adv. Heterocycl. Chem.*, 1985, **38**, 177.

8 (*a*) Potassium Carbonate, 99% : Aldrich Catalogue no. 31.026-3 (used as supplied); (*b*) Aluminium Oxide, activated, basic, Brockmann I : Aldrich Catalogue no. 19, 944-3; ~150 mesh, 58 Å, surface area; 155 m^2 g^{-1}.

Solvent-free synthesis of calix[4]resorcinarenes

Brett A. Roberts,[a] Gareth W. V. Cave,[a] Colin L. Raston[b] and Janet L. Scott*[a]

[a] *Centre for Green Chemistry, P.O. Box 23, Monash University, 3800, Victoria, Australia. E-mail: janet.scott@sci.monash.edu.au*
[b] *School of Chemistry, University of Leeds, Leeds, UK LS2 9JT*

Received 21st May 2001
First published as an Advance Article on the web 9th October 2001

Calix[4]resorcinarenes may be prepared in high yield and purity by direct reaction of resorcinol and benzaldehyde derivatives in the presence of a catalytic amount of solid acid and at ambient temperature under solvent-free conditions. This represents a viable alternative to traditional solution phase methodology. The solvent-free method measures up well with respect to energy usage, solvent wastes and associated hazards, reaction time and yield. In addition, the relevant benzaldehyde derivatives are prepared in polypropylene glycol, which is readily recycled.

Introduction

Calix[4]resorcinarenes are large cyclic tetramers which have found application as supramolecular tectons[1] and host molecules,[2] as components in liquid crystals,[3] photoresists,[4] selective membranes,[5] surface reforming agents,[6] HPLC stationary phases,[7] and as ion channel mimics[8] and metal ion extraction agents.[9]

The synthesis of calix[4]resorcinarenes was first reported in the in the late 19th century by Baeyer[10] and the most commonly used synthetic methodology is still that of a Brönsted acid-catalysed cyclocondensation between an aldehyde **1** and resorcinol **2** to yield the cyclic tetramer calix[4]resorcinarene **3** achieved by heating the constituents to reflux in a mixture of mineral acid and alcohol. (The Lewis acid catalysed condensation of resorcinol and benzaldehyde has been reported,[11] but not widely applied, and other methods utilizing Lewis acids rely on the use of starting materials such as 2,4-dimethoxycinnamates[12] requiring deprotection to yield resorcinarenes with free hydroxy groups.)

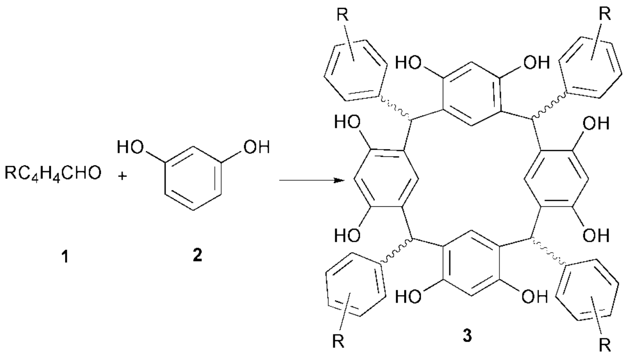
The duration of the reaction has been shown to vary from a few hours[13,14] to several days[15–18] although Weinelt and Schneider have reported shorter reaction times utilizing dry HCl dissolved in methanol.[19] Large-scale synthesis involves large volumes of solvent and the use of large quantities of acid (usually a 2:2:1 ratio of ethanol, water and concentrated HCl).[20] In a previous study on the synthesis of cyclotriveratrylene (CTV) derivatives[21] we have shown that the use of ionic liquids or solvent-free methods provide efficient 'greener' protocols for the acid catalysed cyclocondensation reactions used to prepare these large supramolecular tectons. Such processes alleviate the need for large volumes of solvent and acid, are energy efficient and high yielding and are potentially applicable to starting materials containing acid labile groups.

We now report the synthesis of a number of calix[4]resorcinarenes (including three novel compounds) achieved under solvent-free conditions by the direct reaction of aldehyde and resorcinol in the presence of catalytic quantities of a solid acid. The methodology is simple, high-yielding, energy-efficient and applicable to a variety of aldehyde starting materials. A 'greener' route to the aldehyde starting materials using polypropylene glycol (PPG) as solvent, is also described.

Results and discussion

Reaction of **1** and **2** is achieved by simply grinding together equimolar quantities of starting material in the presence of a catalytic amount of *p*-toluenesulfonic acid. As noted previously,[21,22] the reaction mixtures are viscous liquids or pastes even where all reagents are solids. The melt phase stiffens within minutes to yield a sticky solid that hardens further on standing. ^{1}H NMR analysis of this material reveals almost quantitative conversion to product and crude **3** is isolated by simply washing the ground product with water to effect removal of the catalyst. Recrystallisation from hot methanol affords pure material in high yield.

The synthesis of the most widely used of the resorcinarenes, *C*-methylcalix[4]resorcinarene, may also be readily achieved by direct reaction of solid resorcinol and liquid acetaldehyde.[23] Unfortunately, this methodology does not give access to resorcinarenes, such as **3f**, that have previously proven difficult to synthesise,[18] indicating that the mechanism of reaction is likely to be no different from that suggested in methods



Scheme 1

Green Context

Calix[4]resorcinarenes have found application in a number of areas including liquid crystals, HPLC stationary phases, metal ion extraction agents and as host molecules. Traditional synthesis involves often very slow reactions and large volumes of solvents. In this paper, a much improved and simplified synthetic procedure is described which is solvent-free, employs a solid acid, and is relatively quick. The high-yielding synthesis of three new, highly functionalised calix[4]resorcinarenes is described. *JHC*

involving dissolution of reagents in a solvent prior to reaction. We would suggest that this is the reaction of two mutually dissolved reagents and thus while 'solvent-free' is still occurring in 'solution'. The only difference being that dissolution is not achieved by addition of an extra (solvent) component but is instead due to mutual miscibility of the reagents.

In comparison to the time scale for most conventional syntheses (several hours to days),[13–20] the solvent-free reactions described here reach a substantial degree of conversion within minutes. No external heating is required and the grinding method is used to achieve particle size reduction and efficient mixing. High intensity grinding, which is an energy expensive process, is not required as the reaction mixture does not remain dry and powdery but becomes a viscous liquid melt or solution.[22] Yields are also often substantially higher using the solvent-free methodology as is indicated in Table 1. Compounds **3c–e** have not, to our knowledge, been previously reported and have been characterised by mass spectrometry, ^{1}H and ^{13}C NMR, microanalysis and X-ray structure elucidation (**3c**).

The aldehydes **1c–e** used in the synthesis of **3c–e** are, in keeping with the environmentally friendly theme, synthesised under conditions that are 'greener' than those conventionally used. Traditional solvents are replaced with polypropylene glycol (PPG), which is a viscous solvent with negligible vapour pressure. 4-Hydroxybenzaldehyde, potassium carbonate and the corresponding bromo- or dibromo-alkane are heated to 60 °C in PPG for 2 h, the aldehyde isolated by distillation and the PPG recycled, obviating the need for lengthy reaction times, extractive work-up and chromatographic purification.[24]

Calix[4]resorcinarenes commonly occur in two isomeric forms, namely the *cis-cis-cis* (*rccc*) and the *cis-trans-trans* (*rctt*) isomers,[19] which are distinguishable by comparison of ^{1}H NMR spectra as described by Cram and coworkers.[18] Solution studies indicate the presence of **3d** in the form of the *rccc* isomeric product with C_{4v} symmetry, or 'crown' isomer ($>95\%$),[25] as illustrated schematically in Fig. 1(a). The single broad resonance for the aromatic OH, coupled with single resonances for the asymmetric H_a and H_b protons on the resorcinol ring indicate a single environment for the calix[4]resorcinarene in solution. In contrast, compounds **3c** and **3e** indicate a mixture of isomers in solution. These were established as *rccc* (33%) and *rctt* or 'chair' isomer which exhibits C_{2h} symmetry[25] (66%), based on ^{1}H NMR integration. The *rctt* isomer [illustrated schematically in Fig. 1(b)] was identified by two sets of peaks for the OH, H_a and H_b resonances, characteristic of C_{2h} symmetry.

Table 1 Yields and isomeric distribution for compounds **3a–f**

Compound	**1** (R)	Yield **3** (%)[a]	*rccc*:*rctt*
a	H[19]	90(90,[19] 83[18])	1:2 (lit. 1:2)[19]
b	*o*-OH[18]	81(78)[18]	1:2 (lit. 1:2)[18]
c	*p*-O(CH$_2$)$_3$CH$_3$	96	1:2
d	*p*-O(CH$_2$)$_7$CH$_3$	80	95:5
e	*p*-O(CH$_2$)$_4$Br	92	1:2 → 0:100[b]
f	*p*-NO$_2$	0	—

[a] Mixture of isomers. Yield determined post reaction and washing but prior to recrystallisation. Product losses are largely due to difficulties in transferring small quantities of glassy products from a mortar and pestle, thus, yields of larger scale reactions would be expected to be significantly improved. [b] Dependent on extent of reaction time.

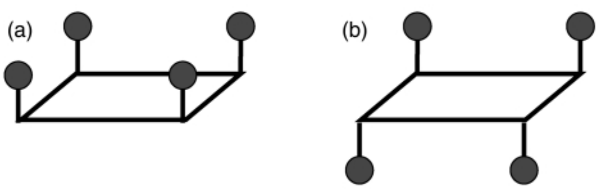


Fig. 1 Schematic of *rccc* and *rctt* isomers.

Interestingly, compound **3d** alone occurs almost exclusively as the *rccc* isomer, while **3a** and **3b** exhibit the expected mixture of isomers[18,19] which is reflected in the isomeric distribution of **3c** and **3e**. The predominance of the *rctt* isomer contrasts with molecular modeling calculations,[26] which indicate that the *rccc* isomer in the crown conformer is favoured over the *rctt* isomer in the chair conformer (in the absence of solvent effects) by 6.3, 8.5 and 14.4 kcal mol^{-1} for compounds **3c**, **d** and **e** respectively. Hydrogen bonds between adjacent hydroxy groups on the resorcinol and staggering of the phenyl groups help to stabilise the *rccc* crown conformers, while the *rccc* boat conformer is of similar energy to the *rctt* chair conformer. The distribution of isomers has been attributed to differential solubilities[18] which may also play a role in the solvent-free reactions where differential crystallisation from the melt or liquid phase may occur.

Altering the reaction time did not lead to an increase in the formation of the C_{4v} isomer for compounds **3c** and **3e**. Despite heating the starting materials to 85 °C for 5 h, the ratio of the C_{4v} isomer never exceeded 33%. However, when the reaction mixture containing compound **3e** was left to stand for an extended period of time, before work-up, solution studies indicate the presence of only the *rctt* isomer. This conversion can be compared to a study by Cram and coworkers[18] on the reaction of resorcinol with 4-methoxybenzaldehyde, that revealed that an increase in reaction time led to an increase in the formation of the C_{2h} isomer.

Single crystal diffraction studies on compound **3c**,† indicates that the *rctt* calix[4]resorcinarene crystallises in the form of the chair isomer with C_{2h} symmetry. This confirms assignment of isomers from NMR data. Compared with the more common crown isomer, there are only a few examples of structurally characterised chair isomers.[15,18,27,28] Compound **3c** crystallises in the space group $P\bar{1}$ with one molecule of the calix[4]resorcinarene and two molecules each of DMF and acetone in the unit cell. The asymmetric unit comprises one half of the resorcinarene with associated, hydrogen-bonded solvent molecules, illustrated in Fig. 2, and the remainder of the resorcinarene is generated through a crystallographic inversion centre. The axial position of the phenyl groups deriving from the benzaldehyde, which are bonded in a *cis-trans-trans* fashion (*rctt* configuration), and chair conformation of the macrocycle is illustrated in Fig. 3. All resorcinol hydroxy groups form hydrogen bonds. These include OH···O H-bonds with acceptor carbonyl oxygen atoms of the included solvent molecules, a long OH···O H-bond with a resorcinarene molecule translated 1 unit cell along *a* and an OH···Ar interaction directed towards the aromatic ring of the aldehyde moiety of a neighbouring resorcinarene, as indicated in Fig. 3. Individual 'tapes' of H-

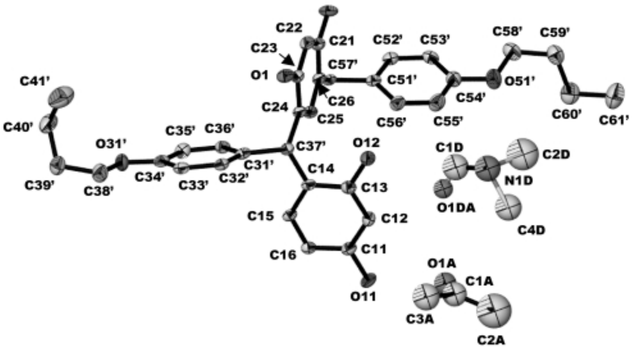


Fig. 2 ORTEP diagram of **3c** with thermal ellipsoids plotted at the 50% probability level. Alternative positions for the disordered solvent molecules are omitted for clarity.

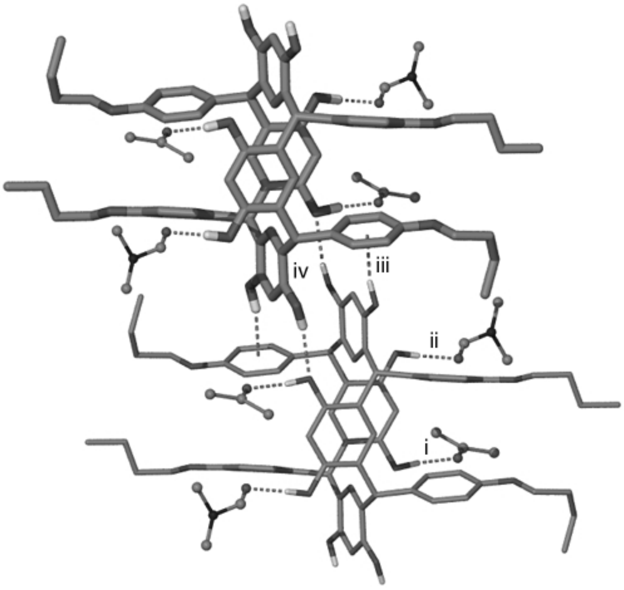


Fig. 3 Molecular structure of **3c** derived from single crystal structure data. Two molecules of **3c** are shown with four DMF and four acetone molecules (disordered positions omitted for clarity). Hydrogen bonds are shown as dotted lines.

Unique H-bond geometries

	O···O/Å	H···O/Å	OHO/°
(i) O11–H11O···O1A	2.752(6)	1.79(2)	171(5)
(ii) O12–H12O···O1D	2.868(4)	1.72(3)	166(6)
(iii) O11–H11O···centroid(Ar)^b	3.177(3)	2.23(3)	165(6)
(iv) O1–H1O···O11^a	3.032(5)	2.22(5)	142(6)

a = $x + 1, y, z$. b = $2 - x, 2 - y, 1 - z$.

bonded **3c** and solvent molecules propagate in the [100] direction as illustrated in Fig. 4.

In conclusion, we have shown a simple, solvent-free, energy efficient, clean pathway for the synthesis of three new, highly functionalised calix[4]resorcinarenes. This method also demonstrates a cost-effective alternative to commercially available products. The extended alkyl chain in the *para* position, offers enormous potential for further binding through both covalent and non-covalent interactions and is an area of further study.

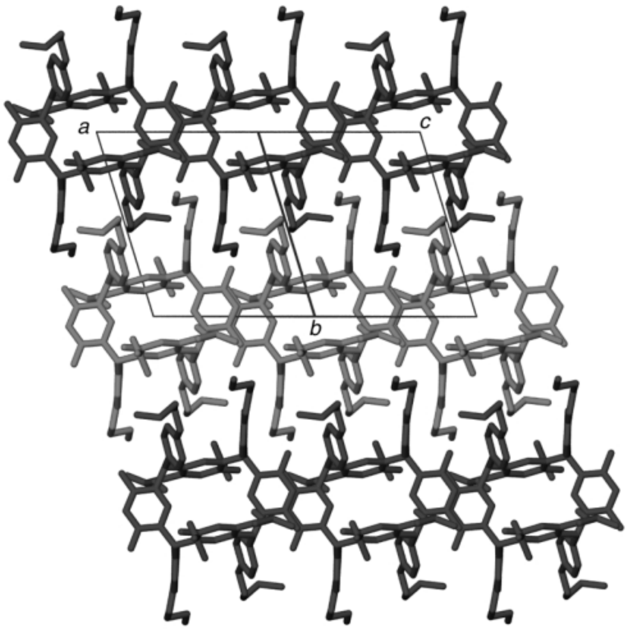


Fig. 4 Packing diagram of **3c** viewed perpendicular to (101) showing 'tapes' of hydrogen bonded calix[4]resorcinarene molecules and H-bonded occluded solvent.

Experimental

^{1}H (300 MHz) and ^{13}C (75 MHz) were recorded on a Bruker DPX 300 instrument in ppm (δ) and referenced to TMS. Melting points were recorded on an Electrothermal digital melting point apparatus and are uncorrected. Molecular modeling calculations were carried out using the Discover minimisation package of the MSI Insight II molecular modeling program[26] with standard CVFF forcefields and the structure minimised using the conjugate gradients algorithm with a convergence criterion of the average derivative being < 0.001 kcal mol^{-1}. Single crystal diffraction data were collected on an Enraf-Nonius Kappa CCD at 123 K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, 1° φ and ω scans). The structure was solved by direct methods using the program SHELXS-97[29] and refined by full matrix least-squares refinement on F^2 using the programs SHELXL-97[30] and Xseed.[31] Non-hydrogen atoms of the calix[4]resorcinarene were refined anisotropically whilst those of the DMF and acetone solvent molecules were refined isotropically. The solvent molecules show evidence of disorder and three positions for the DMF methyl groups, each with 66% occupancy, are modeled (sof = 0.667). The DMF carbonyl oxygen is also disordered over two positions (70 and 30% occupancy). All hydrogen atoms, except those of the hydroxy groups, were inserted at geometrically determined positions. Hydroxy hydrogen atoms (all of which are involved in hydrogen bonds) were identified in electron density difference maps and refined with simple bond length restraints.

Synthesis

All commercially available reagents were purchased from Aldrich and used as supplied, unless stated otherwise. Aldehydes **1c–e** could also be prepared by reaction in polypropylene glycol and the synthesis of **1d**, the only benzaldehyde derivative not readily available from commercial sources, is described below.

1d: 1-Bromooctane (1.58 g, 8.20 mmol) was added to a stirred slurry of 4-hydroxybenzaldehyde (1 g, 8.20 mmol) and anhydrous potassium carbonate (1.13 g, 8.20 mmol) in polypropylene glycol (average M_n *ca.* 425, 5 cm^3). The reaction mixture was heated (60 °C, 2 h) in a round-bottomed flask equipped with an air condenser. The pure product was isolated by vacuum distillation (125 °C, 0.5 mmHg).Yield 98% (1.88 g, 8.02 mmol). δ_H (300 MHz, 298 K, CDCl$_3$) 0.83 (3H, t, ^3J 7.0 Hz, CH$_3$), 1.25 (10H, m, chain), 1.73 (2H, m, OCH$_2$CH$_2$), 3.95 (2H, t, ^3J 6.5 Hz, OCH$_2$), 6.89 (2H, AA′XX′, Ar), 7.72 (2H, AA′XX′, Ar), 9.80 (1H, s, aldehyde).

The PPG was recycled by filtering it through a sintered funnel (porosity 1) under reduced pressure and the experiment was repeated three times using the original sample of PPG (yields 98, 97 and 97% consecutively). The PPG was observed to gradually change from colourless to yellow during the four batch processes.

3a–e: In a typical synthesis a 1 : 1 mixture of the starting aldehyde and resorcinol (0.5 to 1.0 g scale), along with a catalytic amount of *p*-toluenesulfonic acid (*ca.* 5%) were added together in a mortar and pestle and ground vigorously. Within seconds a viscous paste forms which hardens on further grinding. The paste was left to stand for up to 1 h, during which time it solidified to yield a red solid. The solid was reground, washed with water to remove any acid, filtered and the pure product recrystallised with hot methanol.

Characterisation

3c: Yield 96%, mp > 250 °C (decomp.) ESI-MS (70 eV) $[M]^+$ (calc: *m*/*z* 1081.3, found 1081.5). Microanalysis: some of the resorcinarene products have a propensity to form solvates which (due to variable desorption of occluded solvent molecules) renders microanalysis results irreproducible and these are therefore not included.

δ_H (300 MHz, 298 K, acetone-d$_6$) C_{2h} isomer: 0.98 (12H, t, ^3J 5.3 Hz, CH_3), 1.50 (8H, m, CH_2), 1.75 (8H, m, CH_2), 3.97 (8H, t, ^3J 6.4 Hz, OCH_2), 5.67 (4H, s, CH), 5.93 (2H, s, ArH *meta* to OH, equatorial), 6.26 (2H, s, ArH *ortho* to OH, axial), 6.41 (2H, s, ArH *ortho* to OH, equatorial), 6.51 (10H, s, ArH, *meta* to OH, axial and AA′XX′ ArH *ortho* to O–alkyl), 6.67 (8H, AA′XX′ ArH *meta* to O–alkyl), 7.11 (4H, s, ArOH), 7.55 (4H, s, ArOH).

C_{4v} isomer : 0.98 (12H, t, ^3J 5.3 Hz, CH_3), 1.50 (8H, m, CH_2), 1.75 (8H, m, ^3J 6.4 Hz, CH_2), 4.00 (8H, t, OCH_2), 5.73 (4H, s, CH), 6.30 (4H, s, ArH *ortho* to OH), 6.43 (4H, s, ArH, *meta* to OH), 6.62 (8H, m, AA′XX′ ArH *ortho* to O–alkyl), 6.75 (8H, m, AA′XX′ ArH *meta* to O–alkyl), 7.32 (8H, s, ArOH). δ_C (75.0 MHz, 298 K, acetone-d$_6$} 14.2, 18.8, 20.0, 29.1, 32.4, 42.9, 57.7, 68.1, 103.2, 114.2, 114.4, 122.7, 122.9, 131.0, 132.3, 136.3, 137.5, 154.0, 154.2, 157.7, 158.9 (signals for both isomers combined due to overlap of signals).

Crystals of **3c** suitable for X-ray analysis were grown by slow diffusion of hexane into a solution of the calix[4]resorcinarene in acetone–DMF (95:5). The crystals produced in this manner were small but all attempts to achieve good quality single crystals by other methods of crystallization such as slow evaporation of solvent or slow cooling proved fruitless, yielding only microcrystalline powders or oils. The small crystals obtained did not diffract strongly and long exposure times were required leading to higher than desirable levels of diffuse scattering.

3d: Yield 80%, mp > 260 °C (decomp.), ESI-MS (125 eV) $[M]^+$ (calc: *m*/*z* 1305.7, found: 1305.8). Microanalysis: calc. (found): C, 77.27 (76.31); H, 8.03 (8.19)%.

δ_H (300 MHz, 298 K, acetone-d$_6$) C_{4v} isomer: 0.88 (12H, m, CH_3), 1.25 (32H, m, CH_2), 1.53 (8H, m, CH_2), 1.81 (8H, m, CH_2), 3.98 (8H, m OCH_2), 5.74 (4H, s, CH), 6.25 (4H, s, ArH *ortho* to OH), 6.39 (4H, s, ArH, *meta* to OH), 6.61 (8H, AA′XX′ ArH *ortho* to O–alkyl), 6.77 (8H, AA′XX′ ArH *meta* to O–alkyl), 7.31 (8H, s, ArOH). δ_C (75.0 MHz, 298 K, acetone-d$_6$) 14.7, 23.7, 27.4, 29.4–31.3, 68.87, 103.8, 114.7, 122.8, 131.1, 132.7, 146.2, 154.5, 158.2.

3e: Yield 92%, mp > 200 °C (decomp.), ESI-MS (100 eV) $[M + Na]^+$ (calc: *m*/*z* 1419.8, found: 1419.1). Microanalysis: calc. (found) C, 58.65 (58.39); H, 5.13 (5.13)%.

δ_H (300 MHz, 298 K, acetone-d$_6$) C_{2h} isomer: 1.95 (8H, m, CH_2), 2.13 (8H, m, CH_2), 3.65 (8H, m, CH_2Br), 3.96 (8H, m OCH_2), 5.68 (4H, s, CH), 5.91 (4H, s, ArH *meta* to OH, equatorial), 6.33 (4H, s, ArH *ortho* to OH, axial), 6.44 (4H, s, ArH, *ortho* to OH, equatorial), 6.52 (12H, s, ArH *meta* to OH, axial and AA′XX′ ArH *ortho* to O–alkyl), 6.77 (8H, AA′XX′ ArH *meta* to O–alkyl), 7.15 (4H, s, ArOH),7.53 (4H, s, ArOH).

C_{4v} isomer: 1.95 (8H, m, CH_2), 2.13 (8H, m, CH_2), 3.67 (8H, m, CH_2Br), 4.00 (8H, m OCH_2), 5.77 (4H, s, CH), 6.25 (4H, s, ArH *ortho* to OH), 6.39 (4H, s, ArH, *meta* to OH), 6.67 (8H, AA′XX′ ArH *ortho* to O–alkyl), 6.70 (8H, AA′XX′ ArH *meta* to O–alkyl), 7.34 (8H, s, ArOH). δ_C (75.0 MHz, 298 K, acetone-d$_6$) 29.4, 35.1, 42.7, 43.3, 68.0, 103.6, 103.8, 114.7, 114.825, 122.9, 123.2, 131.2, 131.5, 132.6, 133.3, 137.0, 138.2, 154.4, 154.5, 157.9, 158.0 (signals for both isomers combined due to overlap of signals).

References

† *Crystal data* for **3c**: $C_{80}H_{98}N_2O_{16}$ ($C_{68}H_{70}O_{12}\cdot 2C_3H_8NO\cdot 2C_3H_6O$), M_r = 1343.60, triclinic, space group $P\bar{1}$, a = 11.2391(2), b = 12.8890(2), c = 14.4780(4) Å, α = 90.734(1), β = 110.956(1), γ = 112.210(1) °, V = 1786.48(6) Å^3, Z = 1, μ(Mo-Kα) = 0.086 mm^{-1}. Of 30522 reflections measured, 8752 were unique (R_{int} = 0.0984) with 3850 with $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$]: R_1 = 0.0979, wR_2 = 0.2273, GOF on F^2 = 0.938 for 428 refined parameters and 6 restraints (bond lengths associated with OH groups and disordered solvent).

CCDC reference number 168122. See http://www.rsc.org/suppdata/gc/b1/b104430n/ for crystallographic data in CIF or other electronic format.

1 L. R. MacGillivray and J. L. Atwood, *J. Solid State Chem.*, 2000, **152**, 199; L. R. MacGillivray, P. R. Diamente, J. L. Reid and J. A. Ripmeester, *Chem. Commun.*, 2000, 359; R. G. Harrison, N. K. Dalley and A. Y. Nazarenko, *Chem. Commun.*, 2000, 1387.

2 G. M. Martinez, C. R. Teran, O. A. Tlapanco, A. Toscano and R. Cruz-Almanza, *Fullerene Sci. Technol.*, 2000, **8**, 475; F. C. Tucci, A. R. Renslo, D. M. Rudkevich and J. Rebek, *Angew. Chem., Int. Ed.*, 2000, **39**, 1076.

3 K. Yonetake, T. Nakayama and M. Ueda, *J. Mater. Chem.*, 2001, **11**, 761.

4 H. Ito, T. Nakayama and M. Ueda, *US Pat.*, US 6093517, 2000; O. Haba, K. Haga, M. Ueda, O. Morikawa and H. Konishi, *Chem. Mater.*, 1999, **11**, 427; T. Nakayama, D. Takhashi, K. Takeshi and M. Ueda, *J. Photopolym. Sci. Technol.*, 1999, **12**, 347.

5 N. Tbeur, T. Rhlalou, M. Hlaibi, D. Langevin, M. Metayer and J.-F. Verchere, *Carbohydr. Res.*, 2000, **329**, 409; O. Pietraszkiewicz, M. Kozbial and M. Pietraszkiewicz, *Pol. J. Chem.*, 1998, **72**, 886.

6 K. Ichimura, E. Kurita and M. Ueda, *Eur. Pat.*, EP 671220, 1995.

7 O. Pietraszkiewicz and M. Pietraszkiewicz, *J. Inclusion Phenom. Macrocycl. Chem.*, 1999, **35**, 261.

8 N. Yoshino, A. Satake and Y. Kobuke, *Angew. Chem., Int. Ed.*, 2001, **40**, 457.

9 E. Gaunert, H. Barnier, L. Nicod, A. Favre-Reguillon, J. Foos, A. Guy, C. Bardot and M. Lemaire, *Sep. Sci. Technol.*, 1997, **32**, 2309; L. S. Kuznetsova, A. R. Mustafina, A. Y. Ziganshina and E. K. Kazakova, *J. Inclusion. Phenom. Macrocycl. Chem.*, 2001, 65.

10 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1872, **5**, 25; A. Baeyer, *Ber. Dtsche. Chem. Ges.*, 1872, **5**, 280.

11 O. I. Pieroni, N. M. Rodriguez, B. M. Vuano and M. C. Cabaleiro, *J. Chem. Res. (S)*, 1994, 188.

12 B. Botta, M. C. Di Giovanni, G. D. Monache, M. C. De Rosa, E. Gacs-Baitz, M. Botta, F. Corelli, A. Tafi, A. Santini, E. Benedetti, C. Pedone and D. Misiti, *J. Org. Chem.*, 1994, **59**, 1532; B. Botta, P. Iacomacci, C. Di Giovanni, G. D. Monache, E. Gacs-Baitz, M. Botta, A. Tafi, F. Corelli and D. Misiti, *J. Org. Chem.*, 1992, **57**, 3259.

13 A. G. S. Högberg, *J. Org. Chem.*, 1980, **45**, 4498.

14 T. Haino, D. M. Rudkevich, A. Shivanyuk, K. Rissanen and J. Rebek, Jr., *Chem.-Eur. J.*, 2000, **6**, 3797.

15 K. N. Rose, M. J. Hardie, J. L. Atwood and C. L. Raston, *J. Supramol. Chem.*, 2001, **1**, 35.

16 T. Gerkensmeier, W. Iwanek, C. Agena, R. Fröhlich, S. Kotila, C. Näther and J. Mattay, *Eur. J. Org. Chem.*, 1999, 2257.

17 J. B. Niederl and H. J. Vogel, *J. Am. Chem. Soc.*, 1940, **62**, 2512.

18 L. M. Tunstad, J. A. Tucker, E. Dalcanale, J. Weiser, J. A. Bryant, J. C. Sherman, R. C. Helgeson, C. B. Knobler and D. J. Cram, *J. Org. Chem.*, 1989, **54**, 1305.

19 F. Weinelt and H.-J. Schneider, *J. Org. Chem.*, 1991, **56**, 5527.

20 D. J. Cram and J. M. Cram, *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, 1994, p. 89.

21 J. L. Scott, D. R. MacFarlane, C. L. Raston and C. M. Teoh, *Green Chem.*, 2000, 123.

22 G. Rothenberg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am Chem. Soc.*, 2001, **123**, 8701.

23 G. W. V. Cave, M. J. Hardie, B. A. Roberts and C. L. Raston, *Eur. J. Org. Chem.*, 2001, 3227.

24 M.-A. Guillevic, M. E. Light, S. J. Coles, T. Gelbrich, M. B. Hursthouse and D. W. Bruce, *J. Chem. Soc., Dalton Trans.*, 2000, 1437.

25 Nomenclature used by P. Timmerman, W. Verboom and D. N. Reinhoudt, *Tetrahedron*, 1996, **52**, 2663 and references therein.

26 BIOSYM MSI, San Diego, CA, USA, 2000.

27 A. Shivanyuk, E. F. Paulus, V. Böhmer and W. Vogt, *Angew. Chem., Int. Ed.*, 1997, **36**, 1301.

28 K. J. Palmer, R. Y. Wong, L. Jurd and K. Stevens, *Acta. Crystallogr., Sect. B*, 1976, **32**, 847; G. Zahn, K. Müller and G. Mann, *Z. Kristallogr.*, 1994, **209**, 473; O. Middel, W. Verboom, R. Hulst, H. Kooijman, A. L. Spek and D. N. Reinhoudt, *J. Org. Chem.*, 1998, **63**, 8259; G. Rumboldt, V. Böhmer, B. Botta and E. F. Paulus, *J. Org. Chem.*, 1998, **63**, 9618.

29 G. M. Sheldrick, SHELXS-97, University of Gottingen, 1990.

30 G. M. Sheldrick, SHELXL-97, University of Gottingen, 1997.

31 L. J. Barbour, X-Seed—a graphical interface to the SHELX program suite, University of Missouri, 1999.

Liquid phase oxidation of amines to azoxy compounds over ETS-10 molecular sieves

Suresh B. Waghmode, Smita M. Sabne and S. Sivasanker*

Catalysis Division, National Chemical Laboratory, Pune 411 008.
E-mail: siva@cata.ncl.res.in

Received 18th June 2001
First published as an Advance Article on the web 23rd October 2001

A convenient method for the oxidation of aryl amines to azoxybenzenes with H_2O_2 or tertiary butyl hydroperoxide over the titanosilicate ETS-10 is reported. Over ETS-10, aniline is transformed into azoxybenzene in greater than 97% yield with H_2O_2 as the oxidant. Substituted anilines are also transformed in good yields. Yield and H_2O_2 efficiency depend largely on experimental parameters such as catalyst concentration, H_2O_2: substrate mole ratio and the nature of the solvent.

Introduction

The oxidation of arylamines is an important reaction in the synthesis of oxygenated derivatives such as hydroxylamine, nitroso, nitro, oxime, azo and azoxy compounds. Azoxybenzenes (AZY) have been utilized as dyes, analytical reagents, reducing agents, stabilizers and polymerization inhibitors. Azobenzene (AZO) and mixed (especially) AZY compounds with both aryl and alkyl groups are also of interest because of their physiological activity and their applications in liquid crystals.[1–3] A variety of oxidation methods (stoichiometric and catalytic routes) have been reported for the preparation of these compounds. For example, aromatic amines can be oxidized with stoichiometric oxidants such as peracetic acid,[4] MnO_2,[5] $Pb(OAc)_4$,[5] $Hg(OAc)_2$[6,7] barium manganate,[8] Ru–H_2O_2,[9] $H_3PW_{12}O_{40}$,[10] 2,4,6-tri-*tert*-butylphenol/$K_3Fe(CN)_6$/KOH,[11] galvinoxyl/$K_3Fe(CN)_6$/KOH[11] and Bi–KOH.[11]

Many of the catalytic processes reported for the oxidation of amines use soluble salts of transition metal cations, such as Ti(IV), V (IV)[12] and Mo (VI)[13,14] or Fe(III) and -(VI).[15] In view of the current interest in environmental protection, we have been working on the development of heterogeneous catalysts for the oxidation of amines. A solid titanosilicate catalyst (TS-1) has been reported to be useful in the oxidation of amines to azobenzene (AZO) and azoxybenzene (AZY) compounds with H_2O_2.[16–18] TS-1 is a medium pore zeolite with pore diameter of ~ 5.5 Å and useful only for oxidation of small molecules.

In the present paper we report the oxidation of aniline over ETS-10 molecular sieves possessing large pores (~8 Å). We have also compared the activity of ETS-10 with other catalysts such as TiO_2, Ti-MCM-41 and TS-1. The influence of the catalyst amount, H_2O_2 concentration, recycle of catalyst and the use of different oxidants and solvents are also reported. The oxidation of different aniline derivatives has also been investigated in this study.

Experimental

Preparation of catalysts

ETS-10, TS-1 and Ti-MCM-41 molecular sieves were prepared according earlier reported procedures.[19–21]

(a) Synthesis of ETS-10. The hydrothermal synthesis of ETS-10 using $TiCl_4$ was carried out with a gel of following molar composition: 3.70 Na_2O : 0.95 K_2O : TiO_2 : 5.70 SiO_2 : 171.0 H_2O.[19] In a typical synthesis, a solution of 9.3 g NaOH in 40 g distilled water was added to a vigorously stirred solution of 52.5 g sodium silicate (28.6% SiO_2, 8.82% Na_2O, 62.58% H_2O) and 40 g distilled water. This was followed by the dropwise addition of 32.75 g $TiCl_4$ solution (25.4 mass% $TiCl_4$, 25.9 mass% HCl and 48.6 mass% H_2O) to this mixture with rapid stirring. 7.8 g $KF{\cdot}2H_2O$ was then added to the above gel ($pH = 11.2 \pm 0.1$) and the mixture stirred well. The mixture was then transferred to a stirred stainless steel autoclave (300 ml, Parr Instrument, USA) and crystallization was carried out at 200 °C with stirrer speed of 300 rpm for 16 h. After crystallization, the product was filtered off and washed with deionised water until the pH of the filtrate was 10.7–10.8. It was dried at 100 °C for 10 h and calcined at 450 °C in dry air for 6 h.

(b) Synthesis of TS-1. The gel composition (after removing alcohol) was 0.36 TPAOH : 0.03 TiO_2 : SiO_2 : 20 H_2O.[20]To 26.0 g tetraethyl orthosilicate (TEOS), 45 g of aqueous tetrapropyl ammonium hydroxide (20% TPAOH Aldrich) was added to hydrolyze the TEOS. To this resultant liquid mixture, a solution of 1.29 g titanium tetrabutoxide, $Ti(OBu)_4$, in 3.0 g dry isopropyl alcohol was added dropwise under vigorous stirring. The clear liquid was stirred for 1 h in order to complete the hydrolysis of TEOS and $Ti(OBu)_4$. The mixture was further stirred at 70 °C for about 3 h to remove the alcohol. The crystallization was done in a stirred autoclave (300 ml, Parr, Instrument, USA) at 180 °C for 24 h. The stirrer speed was about 200 rpm. The crystalline solid thus obtained was filtered

Green Context

The oxidative coupling of anilines to azo- and azoxybenzenes is a reaction of fundamental importance in the synthesis of many products especially dyestuffs. Stoichiometric oxidants which have traditionally been used have resulted in the production of large quantities of toxic waste, with little prospect of effective recycling. The use of cleaner oxidants such as hydrogen peroxide or air is thus desirable. This paper demonstrates that using a Ti-containing large pore molecular sieve, such a transformation can be carried out in high yield and, importantly, with excellent selectivity towards both anilines and hydrogen peroxide. ***DJM***

DOI: 10.1039/b105316g

off, washed with deionised water, dried at 100 °C and calcined at 550 °C in dry air for 6 h.

(c) Synthesis of Ti-MCM-41. Ti-MCM-41 was prepared based on the procedure of Beck *et al.*[21] The molar composition of the gel and the synthesis procedure are given below: $SiO_2:0.02\ TiO_2:0.089\ (cTMA)_2O:0.16\ (TMA)_2O:18\ H_2O$. In a typical synthesis 2.08 g of TMAOH (tetramethylammonium hydroxide) dissolved in 10 g water and added to 16.7 g of (cTMACl/OH) (cetyltrimethylammonium chloride/hydroxide; 17.9 mass% Cl, 6.7 mass% OH) with stirring. Fumed silica (3.1 g) was then added slowly in about 10 min to the above solution under stirring. The stirring was continued for 1 h after completion of addition. To this mixture under stirring 13.6 g TMA (tetramethylammonium) silicate was added. The thick gel formed was stirred further for 15 min. Finally 1.04 g titanium tetrabutoxide in 5.0 g isopropyl alcohol was added slowly to the above gel. The mixture was then transferred to a stainless steel autoclave and heated at 110 °C for 5 days. The solid material was filtered off, washed with deionised water, dried at 100 °C and calcined at 550 °C in dry air for 6 h.

The Si/Ti ratio was 5.7, 35 and 50, in the three catalysts, ETS-10, TS-1 and Ti-MCM-41, respectively. Powder X-ray diffraction data of the calcined samples (collected on Rigaku Model D-MAX II VC) revealed the samples to be highly crystalline. Elemental analysis was done by Atomic Adsorption Spectroscopy (AAS). The chemical composition and surface areas of the samples are given in Table 1.

Reaction procedure

All the reactions were carried out in the liquid phase in a 50 ml round-bottomed flask equipped with a magnetic stirrer and a cold water condenser. Substrate (3.0 mmol), hydrogen peroxide (3.0 mmol), solvent (10 ml) and 60 mg catalyst were taken in a flask and refluxed over an oil bath kept at 70 °C. Conversions have been calculated on substrate basis. The progress of the reaction was monitored by a gas chromatograph (Varian CX) using a capillary column CP Sil 5CB, (diameter 0.5 mm and 30 m long).

Results and discussion

ETS-10 molecular sieve has been used as a basic catalyst for Aldol-type condensation,[22] alcohol dehydrogenation[23] and acylation reactions.[24] ETS-10 is a large pore titanosilicate molecular sieve. The framework structure of ETS-10 consists of corner shared oxygen ions of $[TiO_6]^{2-}$ octahedra and $[SiO_4]$ tetrahedra. The $[TiO_6]^{2-}$ octahedra are linked as chains in perpendicular directions in the framework. Owing to the octahedral arrangement of Ti^{4+} ions, two negative charges are associated with each Ti ion. These charges are compensated by extra framework alkali (Na^+/K^+) ions. As a result of the large amount of alkali ions present, ETS-10 behaves as a basic material. The projection of ETS-10 framework along the *a* axis is shown in Fig. 1. ETS-10 molecular sieve possesses three-dimensional 12 membered-ring (12-MR) channels with a pore diameter of 7.6 Å. The Ti - atoms are accessible through 12-MR pore openings, some of which are blocked by the extra-framework alkali metal ions.[24]

Table 1 Composition and BET surface area of molecular sieves

No.	Sample	Si/Ti ratio	BET surface area/$m^2\ g^{-1}$
1	Na/K-ETS-10	5.7	460
2	Cs-ETS-10	5.7	381
3	TS-1	35	372
4	Ti-MCM-41	50	950
5	TiO_2	—	60

The framework structure of TS-1 consists of corner shared oxygen ions of $[TiO_4]$ and $[SiO_4]$ tetrahedra. As Ti^{4+} ions substitute isomorphously the Si^{4+} ions, TS-1 is electrically neutral and does not possess ion exchange property. TS-1 is member of the pentasil family isomorphous with ZSM-5 and silicalite-1. Its pore system consists of 10-MR openings. TS-1 has elliptical straight channels having a diameter of 5.1 × 5.6 Å intersected perpendicularly by circular sinusoidal channels having a diameter of 5.4 Å. The framework structure of TS-1 as viewed from the *b* direction is shown in Fig. 1(b).

The Ti-MCM-41 used is a mesoporous material (TiO_2–SiO_2) with unidimensional pores of diameter about 40 Å. The coordination of the Ti^{4+} ions is expected to be both tetrahedral and octahedral.

The Si/Ti ratios and BET surface areas of the catalysts used in this study are presented in Table 1. Aniline oxidation reactions were carried out over different catalysts (Fig 2A). Among these catalysts, ETS-10 possesses higher activity and selectivity followed by Ti-MCM-41 and TS-1. TiO_2 also shows some catalytic activity, but AZY selectivity is low. ETS-10 exhibits the highest selectivity for AZY followed by Ti-MCM-41, TS-1 and TiO_2.

In aniline oxidation, initially nitrosobenzene (NSB) and AZY were formed over ETS-10 catalyst. Nitrobenzene (NO) and traces of AZO were also observed under the reaction conditions. Nitrosobenzene (NSB), which was formed at an early stage of the reaction, disappeared with time while the concentration of AZY (Fig 2B) increased.

In reactions carried out in the liquid phase, the catalyst performance is greatly influenced by the nature of the solvent. We have carried out the reaction of aniline using different solvents. The results are presented in Fig. 3A. Selvam and Ramaswamy[18] have reported that NSB was the major product over TS-1 when acetonitrile was used as the solvent. The present catalyst (ETS-10) shows high activity (~79.2% in 4 h.)

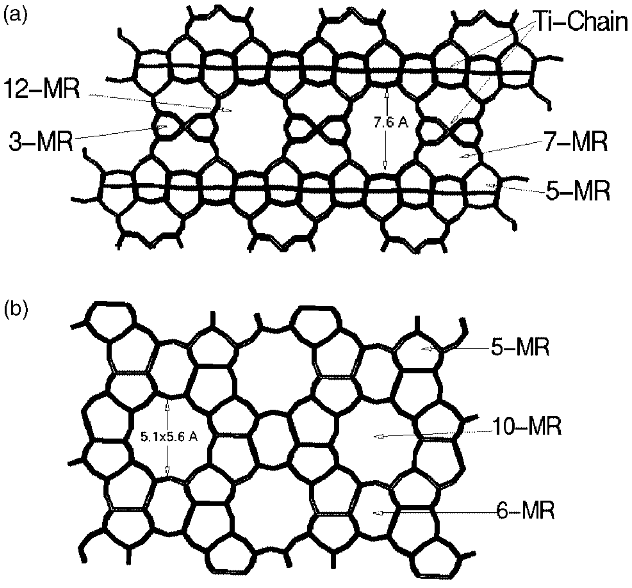


Fig. 1 (a) The framework structure of ETS-10 viewed along either the *a* or *b* directions showing the 12-MR pores and the other rings associated with them. The $[TiO_6]^{2-}$ octahedra are linked in chains running in perpendicular direction. (b) The framework structure of TS-1 viewed from the *b* direction showing the cross-sectional view of the 10-MR straight channels. TiO_4 tetrahedra are isomorphously substituted in silicalite (MFI) framework.

Table 2 Oxidation of various arylamines with H_2O_2 over ETS-10[a]

No.	Substrate	Conversion	NSB	NO_2	AZO	Other	AZY	Selectivity
1	Aniline	79.2	1.0	0.4	0.6	—	77.2	97.5
2	Aniline[a]	57.9	—	0.6	26.1	1.3	30.0	51.8
3	*o*-Toluidine	60.9	5.8	0.7	0.9	6.9	46.6	76.5
4	*m*-Toluidine	78.6	1.2	1.0	0.4	4.9	70.3	89.5
5	*p*-Toluidine	61.3	1.1	0.5	2.1	5.0	51.8	84.5
6	*m*-Anisidine	60.3	1.5	2.9	1.0	4.5	50.4	83.6
7	*p*-Anisidine	38.9	0.9	1.2	2.5	8.2	26.1	67.1
8	Cyclohexylamine	20.7	8.6[b]	—	—	12.1	—	—
9	*n*-Hexylamine	13.6	0.3	0.8	—	5.9	6.6	48.4
10	4-Chloroaniline	38.6	3.6	1.1	13.0	2.3	18.6	48.2
11	2-Aminophenol	2.1	—	0.2	—	1.9	—	—
12	3-Aminophenol	33.0	0.1	2.6	1.7	18.3	10.2	30.9
13	4-Aminophenol	6.6	—	2.1	—	1.1	3.3	50.0
14	4-Amino-2-chlorophenol	31.2	0.9	0.3	1.3	1.8	26.9	86.1
15	2-Nitroaniline	16.1	—	2.7	—	—	3.4	55.7
16	3-Nitroaniline	6.3	—	3.6	—	2.7	—	—
17	4-Nitroaniline	14.7	—	2.1	—	—	2.6	55.3

Reaction conditions: catalyst = 60 mg; temperature = 70 °C; substrate = 3.0 mmol; H_2O_2 = 3.0 mmol; solvent = methanol (10 ml); duration of reaction 6 h. [a] Oxidant, 3.0 mmol t-BHP. [b] Cyclohexanone oxime.

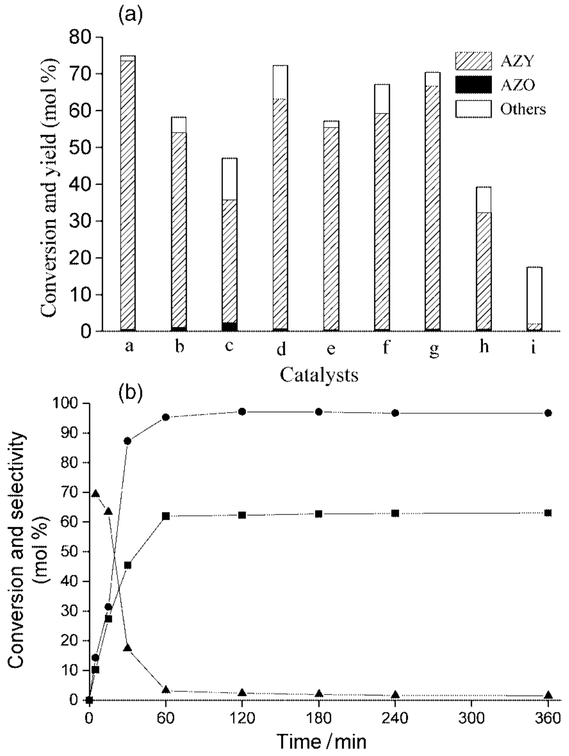


Fig. 2 (A) Activity of different catalysts in aniline oxidation: (a) as prepared ETS-10, (b) ETS-10 after one cycle; (c) ETS-10 after two cycles; (d) activity after calcination at 450 °C; (e) Cs-ETS-10; (f) TS-1; (g) Ti-MCM-41; (h) TiO_2 and (i) without catalyst; AZO = azobenzene; AZY = azoxybenzene and others = nitrobenzene and nitrosobenzene. *Reaction conditions*: catalyst = 60 mg; temperature = 70 °C; substrate = 3.0 mmol; H_2O_2 = 3.0 mmol; solvent = methanol (10 ml) and duration of reaction = 4 h. (B) Influence of the reaction time on conversion and product selectivities for aniline oxidation over ETS-10. *Reaction conditions*: catalyst = 90 mg; temperature = 70 °C; substrate = 3.0 mmol; H_2O_2 = 3.0 mmol; solvent = methanol (10 ml); duration of reaction = 6 h; (■) conversion, (▲) selectivity for NSB and (●) selectivity for AZY.

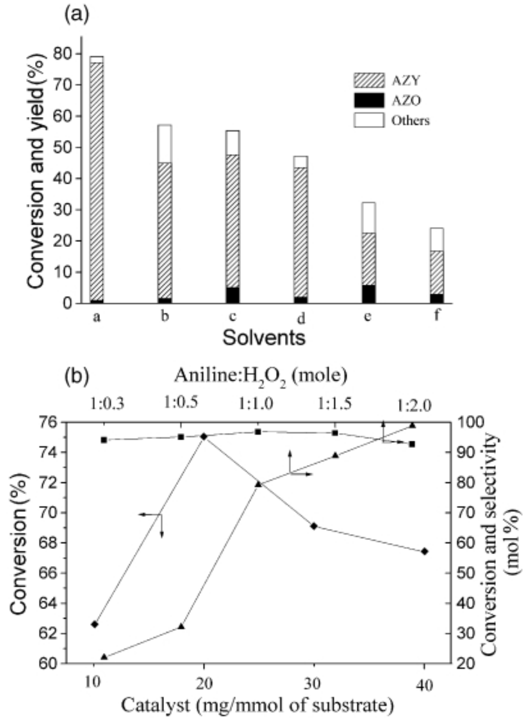


Fig. 3 (A) Influence of the solvents in aniline oxidation over ETS-10: (a) methanol; (b) acetone; (c) acetonitrile; (d) tetrahydrofuran; (e) benzene; (f) methanol–water (1 : 1 mass%). *Reaction conditions*: catalyst = 60 mg; temperature = 70 °C; substrate = 3.0 mmol; H_2O_2 = 3.0 mmol, duration of reaction 6 h and solvent = 10 ml. (B) Influence of the amount of catalyst (ETS-10) and aniline: H_2O_2 (mol) ratio on conversion and azoxybenzene selectivity in aniline oxidation: *Reaction conditions* for catalyst quantity studies: catalyst = 30, 60, 90 or 120 mg; temperature = 70 °C; substrate = 3.0 mmol; H_2O_2 = 3.0 mmol; solvent = methanol (10 ml) and duration of reaction = 4 h. *Reaction conditions* for H_2O_2 quantity studies: catalyst = 60 mg; temperature = 70 °C; substrate = 3.0 mmol; H_2O_2 = 1, 1.5, 3, 4.5 and 6 mmol; solvent = methanol (10 ml) and duration of reaction = 6 h; (▲) conversion; (■) selectivity for AZY and (◆) conversion.

and selectivity (97.1%) for AZY in methanol as solvent. AZY was also the major product in acetonitrile solvent. The activity of ETS-10 in different solvents for aniline oxidation is in the order: methanol > acetone > acetonitrile > tertrahydofuran > benzene > methanol + water (1 : 1 mass%) (Fig. 3A). Selectivity for AZY is in the order: methanol > tetrahydofuran > acetonitrile > acetone > methanol–water (1 : 1) > benzene. Water is not a good solvent partly due to the low solubility of aniline even at the reaction temperature.

Oxidation reactions in the liquid phase are usually performed with low oxidant/substrate ratios in order to maximize peroxide selectivity and to decrease the yield of over-oxidized products. It has been reported in the literature that it is necessary to use

H_2O_2/aniline molar ratios > 3 to obtain the selective formation of NSB with homogeneous catalysts.[1] The influence of the aniline: H_2O_2 molar ratio on conversion and selectivity (AZY) are presented in Fig. 3B. Over ETS-10, aniline conversion increases with molar ratio of H_2O_2/aniline. Aniline conversion is ~99% in 6 h when H_2O_2/aniline (molar ratio) = 2 (Fig. 3B). Our results indicate that product distribution is not affected much with increase in H_2O_2/aniline molar ratio from 0.3 to 2.0.

As the ETS-10 catalyst amount is increased, the conversion of aniline goes through a maximum at 20 mg catalyst per mmol of substrate (Fig. 3B). This surprising result is due to the decomposition of H_2O_2 by the catalyst becoming more important when more catalyst is used.

Recycle of the catalyst shows a decrease in activity and selectivity for AZY over ETS-10 [Fig 2B: (a), (b) and (c)]. This is due to the adsorption of amino compounds over the active sites of the catalytic material. After calcination at 450 °C for 4 h, the activity and selectivity are retained [Fig 2B: (d)]. The ETS-10 molecular sieve retained its structure before and after reaction as confirmed by X-ray diffraction patterns.

In order to study the scope and limitation of this reaction, various substituted aromatic aryl amines and some aliphatic amines were subjected to oxidation under the influence of ETS-10 and the reaction was found to be quite a general one (Table 2). When aniline was reacted over ETS-10 with t-BHP (*tert*-butyl hydroperoxide) as oxidant, a conversion of only 17% was obtained with the major product being AZO (entry 2, Table 2). *Ortho*- and *para*-toluidine were converted less than *meta*-toluidine (entries 3, 4 and 5). *meta*-Anisidine showed higher conversion than para-anisidine (entries 6 and 7). In the case of cyclohexylamine, the product was mainly the oxime (entry 8). *n*-Hexylamine was less reactive than the aromatic amines (entry 9). All the substituted anilines studied (Table 2) were less reactive and selective than aniline. In general, substituted anilines with electron donating groups in the *meta* position were more reactive than when these substituents were in the *ortho* or *para* positions.

Acknowledgements

S. B. W. thanks CSIR, New Delhi, for a senior research fellowship.

References

1 T. Ikeda and O. Tsutumi, *Science*, 1995, **268**, 1873.
2 D. Campbell, L. R. Dix and P. Rostron, *Dyes Pigm.*, 1995, **29**, 77.
3 T. L. Gilchrist, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 7, p. 735; D. H. Rosenblatt and E. P. Burrows, in *the Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*, ed. S. Patai, Wiley, Chichester, 1982, p. 1085.
4 O. D. Wheeler and D. Gonzales, *Tetrahedron*, 1964, **20**, 189.
5 H. E. Baumgarten, A. Staklis and E. M. Miller, *J. Org. Chem.*, 1965, **30**, 1203.
6 K. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, 1962, **84**, 4914.
7 E. Werkurt and E. C. Angell, *Synth. Commun.*, 1988, **18**, 1331.
8 R. G. Srivastav, R. L. Pandey and P. S. Venkatramani, *J. Indian Chem., Sect. B*, 1981, **20**, 995.
9 G. Barak and Y. Sasson, *J. Org. Chem.*, 1989, **54**, 3484.
10 E. Y. Belyaev, E. B. Melnikov, V. E. Zadov and G. A. Suboch, *Russ. J. Org. Chem.*, 2000, **36**, 1003.
11 X.-Y. Wang, Y.-L. Wang, Z.-Y. Zhang, C.-L. Wang, J.-P. Li, L. Shi and Z.-F. Duan, *Synth. Commun.*, 1999, **29**, 481; X.-Y. Wang, Y.-L. Wang, J.-P. Li, Z.-F. Duan and Z.-Y. Zhang, *Synth. Commun.*, 1999, **29**, 2271; D. Laskar D. Prajapati and J. S. Sandhu, *J. Chem. Soc., Perkin Trans. 1*, 2000, **1**, 67.
12 R. A. Sheldon and J. Dakka, *Catal., Today*, 1994, **19**, 215.
13 S. Tollari, M. Cuscela and F. Porta, *J. Chem. Soc. Chem. Commun.*, 1993, 1510.
14 S. Tollari, D. Vergani, S. Banfi and F. Porta, *J. Chem. Soc. Chem. Commun.*, 1993, 442.
15 S. Satoru, M. Miura and M. Nomura, *J. Org. Chem.*, 1989, **54**, 4700; H. Huang, D. Sommerfeld, B. C. Dunn, C. R. Lloyd and E. M. Eyring, *J. Chem. Soc., Dalton Trans.*, 2001, 1301.
16 S. Suresh, R. Joseph, B. Jayachandran, A. V. Pol, M. P. Vinod, A. Sudalai, H. R. Sonawane and T. R. Ravindranathan, *Tetrahedron*, 1995, **51**, 11305.
17 S. Gontier and A. Tuel, *Appl. Catal. A: General*, 1994, **118**, 178; *J. Catal.*, 1995, **157**, 124.
18 T. Selvam and A. V. Ramaswamy, *Chem. Commun.*, 1996, 1215.
19 T. Das, A. J. Chandwadkar and S. Sivasanker, *Chem. Commun.*, 1996, 1105.
20 A. Thangaraj, R. Kumar, S. P. Mirajkar and P. Ratnaswamy, *J. Catal.*, 1991, **130**, 1.
21 J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T-W. Chu, D. H. Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins and J. L. Schlenker, *J. Am. Chem. Soc.*, 1992, **114**, 10834; T. Blasco, A. Corma, M. Navarro and J. Perez Pariente, *J. Catal.*, 1995, **156**, 65.
22 A. Philippou and M. W. Anderson, *J. Catal.*, 2000, **189**, 395.
23 A. Philippou, M. Naderi, J. Rocha and M. W. Anderson, *Catal. Lett.*, 1998, **53**, 221.
24 S. B. Waghmode, V. V. Thakur, A. Sudalai and S. Sivasanker, *Tetrahedron Lett.*, 2001, **42**, 3145.

Copper supported on mixed alumina/gallium oxide pillared α-tin phosphate for De-NO$_x$ applications

P. Braos-García, J. Santamaría-González, P. Maireles-Torres, E. Rodríguez-Castellón and A. Jiménez-López*

Departamento de Química Inorgánica, Cristalografía y Mineralogía, Facultad de Ciencias,
Universidad de Málaga, Campus de Teatinos, 29071 Málaga, Spain.
E-mail: ajimenezl@uma.es

Received 18th July 2001
First published as an Advance Article on the web 8th November 2001

Alumina- and mixed alumina/gallium oxide-pillared α-tin phosphate have been impregnated with different amounts of copper *via* the incipient wetness method. Their characterization by X-ray photoelectron spectroscopy, H_2 temperature-programmed reduction and NO temperature-programmed desorption has allowed to gain insight into the nature of the copper species. These are present as small CuO clusters (not detectable by XRD) as well as forming part of spinel-like structures. NO-TPD studies show that only NO is desorbed from all the catalysts. Ga_3Al_{11}-SnP with 4.9 wt% Cu interacts most strongly with NO and this catalyst exhibits the highest degree of reduction of Cu^{2+} to Cu^+ after the catalytic reaction. The catalysts are active for the selective catalytic reduction (SCR) of nitric oxide with propane in the presence of excess oxygen.

Introduction

Currently, nitrogen oxides (NO$_x$) constitute an important environmental problem which is facing more restrictive regulation. NO$_x$ gases are mainly emitted in high temperature combustion processes, both from stationary and automotive sources. Selective catalytic reduction (SCR) is a very interesting alternative for the abatement of NO from combustion sources.

Cu-ZSM-5 is very active for SCR of NO by hydrocarbons, in the presence of oxygen,[1] but lacks durability because it suffers from high deactivation in engine tests. This deactivation process has been attributed either to the presence of water and SO_2 in the gas effluents,[2,3] or to zeolite dealumination, taking place at high temperatures and favouring the concomitant migration of active species to sites not accessible to the reactant molecules.[4] A solution could be the use of more thermally stable supports. Alumina and modified aluminas, used as carriers, are shown to facilitate the dispersion of the active metal, and exhibit good performances for the SCR of NO.[5–7]

On the other hand, pillared layered solids can also be employed as carriers, since the presence of nanoparticles of alumina might increase the dispersion of the active phase. This family of porous materials can be considered as two-dimensional zeolite-like structures, and are obtained from layered hosts (clays, metal(IV) phosphates, *etc*.) by cationic exchange with inorganic polyhydroxo-cations, and subsequent thermal treatment which gives rise to the corresponding oxide nanoparticles, which permanently prop apart the layers creating zeolite-like interlayer and interpillar spaces. Solids with high surface areas and acidity can thus be prepared.[8,9] Pillared materials prepared from lamellar α-metal(IV) phosphates have already been demonstrated to be active in several catalytic reactions,[10–14] exhibiting, for instance, a high thermal stability in oxidative catalysis performed at temperatures as high as 500 °C.

The present work is focused on the use of copper supported on alumina and mixed alumina/gallium oxide-pillared tin phosphates as catalysts in the SCR of NO with propane as reducing agent in an excess of oxygen, and the evaluation of the effect of the nature of copper species, degree of dispersion and reducibility on the catalytic performance.

Results and discussion

Characterization of catalysts

XRD studies indicate that the alumina- and mixed alumina/gallium oxide-pillared tin phosphates, used as supports, are amorphous solids after calcination at 500 °C, reflecting the absence of long-range order. Only the Ga_3Al_{11}-SnP material shows a diffraction signal corresponding to a basal spacing of *ca.* 20 Å. The supports possess S_{BET} values between 87 and 178 $m^2\ g^{-1}$, being mesoporous solids with a certain contribution of micropores (Table 1). The mesoporous nature of these materials might be attributed to platelet stacking or end–end particle interactions, while the microporosity arises from the interlayer cavities induced by pillaring. Furthermore, these supports are acid solids, with total acidity per surface area unit measured by NH_3-TPD, ranging from 3.0 to 5.9 μmol NH_3 m^{-2} and increasing, as expected, with the gallium content, owing to the higher acidity of this element relative to Al(III).

In Table 1, it can be seen that upon the incorporation of copper oxide, in all cases, the specific surface area values decrease. Thus, catalysts prepared using Ga_3Al_{11}-SnP as support, show a reduction in surface area of between 45 and

Green Context

While the treatment of emissions is not part of green chemistry *per se* we must recognise that the effective treatment of inevitable process emissions is important. This should involve minimal inputs in terms of materials and energy as well as being highly efficient and not creating secondary pollutants. Here we can read about a new material for the selective catalytic reduction of nitric oxide and propane. The paper also reports important data on the preparation and characterisation of these useful materials. Knowledge about the redox properties of the active phase should prove to be especially useful potentially in synthetic as well as destructive applications. *JHC*

DOI: 10.1039/b106392h

58%, increasing with the amount of copper supported. This reduction in area can be mainly attributed to the blockage of micro- and meso-pores by CuO particles resulting from the impregnation process. The Ga_6Al_7-SnP-Cu4.9 catalyst shows the minimum decrease in its S_{BET} value, probably due to its mesoporous nature.

Considering the acid characteristics of catalysts, they have a total acidity higher than those of the supports, indicating that copper oxide particles can act as Lewis acid sites. However, there is no clear relationship between the acidity and the amount of copper added, thus suggesting that the aggregation state of the supported CuO will affect the resulting acidity.

X-Ray photoelectron spectroscopy allows detection of the existence of a fraction of Cu^{2+} ions forming part of a spinel-like structure. The XPS spectrum in the region of Cu 2p (Fig. 1) exhibits a large and asymmetric peak with a maximum at 932.0–932.5 eV, assigned to CuO,[15] accompanied by a shoulder at 934.5–935.0 eV, attributed to Cu^{2+} in spinel-like structure occupying octahedral sites.[16,17] This latter coordination contrasts with that in bulk spinel where copper is predominantly in a tetrahedral environment.[18] Table 2 details the percentage of Cu^{2+} in each environment. The amount of spinel-like copper increases with copper loading, as can be seen for catalysts on Ga_3Al_{11}-SnP with variable copper contents. In the same way, the percentage of copper in the spinel-like structure of catalysts with 4.9 wt% Cu slightly decreases with gallium content, ranging from 21.3 to 19.2% for catalysts containing gallium, whereas a value of 32.7% is reached for the Al-SnP-Cu4.9 catalyst. These results suggest that diffusion of Cu^{2+} ions into the mixed Ga/Al oxide nanostructures is more difficult; perhaps the higher ionic potential of gallium ions hinders the diffusion of Cu^{2+} ions in such oxide nanoparticles.

The surface Sn/Cu atomic ratios, calculated from XPS, decrease with copper content, and in all cases they are lower than the corresponding bulk values (Table 2). This behaviour is typical of supported catalysts with a low degree of coverage, and reflects dispersion of the active phase on the supports. This latter assumption is supported by the absence in the corresponding XRD patterns of peaks at 2.52 and 2.32 Å, typical of CuO crystallites, or a peak at 2.44 Å, attributable to $CuAl_2O_4$.[5] The H_2-TPR curves of the family of copper supported Ga_3Al_{11}-SnP catalysts (Fig. 2) show that the catalyst with the lowest copper loading, 2.5 wt%, has a reduction profile consisting of a very broad band, extended from 180 to 425 °C. This large reduction interval indicates that Cu(II) species are located in many different chemical environments, while the high reduction temperatures probably reveals a strong interaction with the support surface. With increasing copper content, a peak the maximum of which shifts to lower temperatures, is observed, indicating that the reduction process of Cu^{2+} to Cu^0 becomes easier.[6] Taking into account that the H_2-TPR curve of bulk CuO displays a single reduction peak at lower temperature (220 °C), and, on the other hand, that the reduction temperature decreases as the particle size of CuO increases,[18] it seems that a good dispersion is achieved on the Ga_3Al_{11}-SnP support, even for high copper loading. Concerning the shoulder appearing in all catalysts between 300 and 400 °C, this could be attributed to the reduction of Cu^{2+} forming spinel-like structures, already detected by XPS, which, according to literature reports, are more difficult to reduce.[5]

For catalysts with 4.9 wt% of copper supported on the different supports (Fig. 3), a peak is observed, the temperature of maximum intensity of which varies from 241 °C for Ga_3Al_{11}-SnP-Cu4.9 to 285 °C for $GaAl_{13}$-SnP-Cu4.9. Furthermore, a large shoulder is more pronounced upon increasing the percentage of Cu^{2+} in spinel-like structure, in accord with the XPS data. Among catalysts with 4.9 wt% of copper, that supported on Ga_3Al_{11}-SnP is the most easily reducible.

An NO temperature-programmed desorption study of catalysts with 4.9 wt% of copper (Fig. 4) indicates that, in all cases, only NO is desorbed. Similar results have already been reported for copper catalysts supported on mordenite, but, in this latter case, NO and O_2 were detected at high temperatures due to the

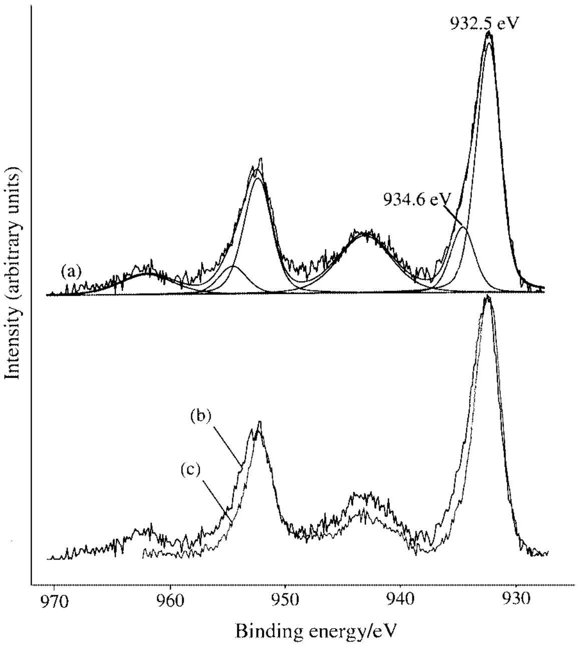


Fig. 1 Cu 2p core level X-ray photoelectron spectra for Ga_3Al_{11}-SnP-Cu4.9: (a) fresh (deconvoluted), (b) fresh and (c) spent catalyst.

Table 1 Chemical composition, textural and acidic properties of alumina and mixed alumina/gallium oxide pillared tin phosphate supports and the corresponding copper containing catalysts

Sample	Chemical composition (wt%)				
	Al_2O_3	Ga_2O_3	S_{BET}/m² g⁻¹	$V_\mu{}^a$/cm³ g⁻¹	Total acidity/ μmol NH_3 m⁻²
Al-SnP	18.9	—	164	0.075	3.0
Al-SnP-Cu2.5			76	0.027	5.2
Al-SnP-Cu4.9			71	0.024	5.8
$GaAl_{13}$-SnP	16.7	3.4	178	0.068	3.2
$GaAl_{13}$-SnP-Cu4.9			86	0.028	10.1
Ga_3Al_{11}-SnP	13.7	11.9	174	0.134	4.9
Ga_3Al_{11}-SnP-Cu2.5			95	0.034	8.3
Ga_3Al_{11}-SnP-Cu4.9			86	0.032	7.9
Ga_3Al_{11}-SnP-Cu7.1			74	0.029	11.5
Ga_3Al_{11}-SnP-Cu9.2			73	0.029	9.3
Ga_6Al_7-SnP	3.7	26.5	87	0.036	5.9
Ga_6Al_7-SnP-Cu4.9			70	0.024	9.6

[a] Micropore volume obtained using the Dubinin–Radushkevich equation.

Table 2 XPS data of copper supported catalysts

Sample	Cu $2p_{3/2}$ E_b/eV[a]		%Cu in spinel-like structure	Sn/Cu Atomic ratio Surface[a]	Bulk	Cu $2p_{3/2}$/satellite area ratio (%) Fresh	Spent
Al-SnP-Cu2.5	932.5	934.8	23.0	1.62	5.02	1.75	1.95
Al-SnP-Cu4.9	932.4	934.8	32.7	1.14	2.51	1.27	3.21
$GaAl_{13}$-SnP-Cu4.9	932.5	935.0	21.3	1.79	2.53	1.73	2.87
Ga_3Al_{11}-SnP-Cu2.5	932.0	934.6	18.0	2.56	4.30	1.54	2.24
Ga_3Al_{11}-SnP-Cu4.9	932.5	934.6	20.4	1.60	2.15	1.93	3.23
Ga_3Al_{11}-SnP-Cu7.1	932.4	934.5	26.8	1.02	1.45	1.57	2.91
Ga_3Al_{11}-SnP-Cu9.2	932.3	934.5	37.5	0.98	1.10	1.33	2.34
Ga_6Al_7-SnP-Cu4.9	932.5	935.0	19.2	2.24	2.21	1.39	2.26

[a] From XPS analysis.

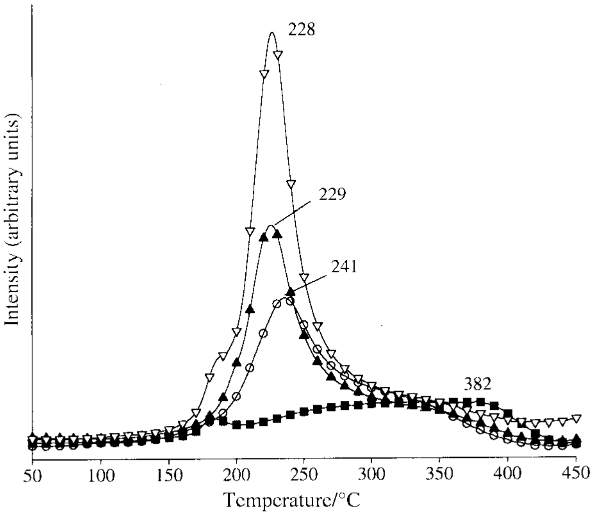


Fig. 2 H_2-TPR curves of copper supported catalysts on Ga_3Al_{11}-SnP: (■) 2.5, (○) 4.9, (▲) 7.1 and (▽) 9.2 wt% of copper.

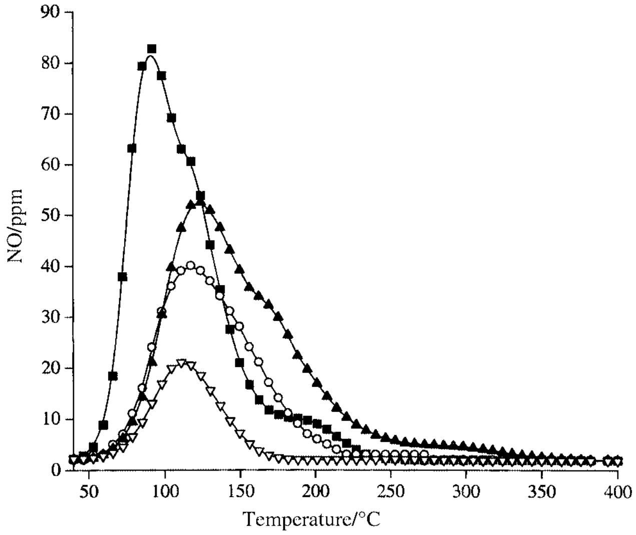


Fig. 4 NO-TPD curves of copper supported catalysts with 4.9 wt% of copper on: (■) Al-SnP, (○) $GaAl_{13}$-SnP, (▲) Ga_3Al_{11}-SnP and (▽) Ga_6Al_7-SnP.

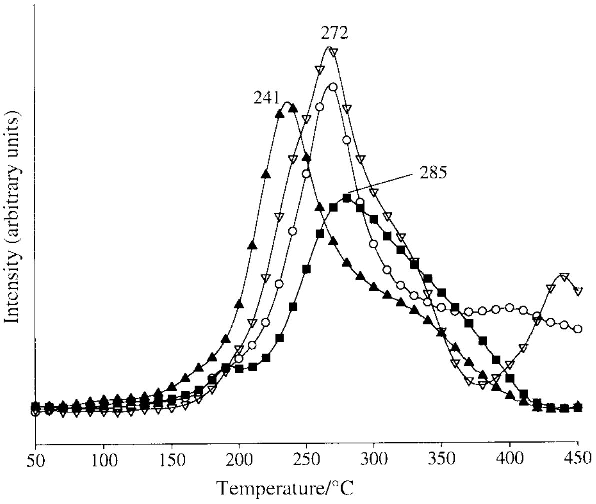


Fig. 3 H_2-TPR curves of copper supported catalysts with 4.9 wt% of copper on: (○) Al-SnP, (■) $GaAl_{13}$-SnP, (▲) Ga_3Al_{11}-SnP and (▽) Ga_6Al_7-SnP.

decomposition of NO_3^- and NO_2^- adsorbed species.[19] However, this behaviour differs from that found for copper-exchanged ZSM-5 zeolite, where N_2O was also observed at low temperatures.[20] Regarding the amount of NO and its desorption temperature range, they seem to depend on the type of support. Thus, the highest amount of NO desorbed is found for the Al-SnP-Cu4.9 catalyst, which exhibits the lowest surface Sn/Cu atomic ratio, 1.14 (Table 2), and hence the maximum amount of surface copper. However, its interaction with NO molecules is very weak, since desorption occurs at low temperatures, as demonstrated by the maxima at 92 and 117 °C. Among gallium containing catalysts, Ga_3Al_{11}-SnP-Cu4.9 retains the highest amount of NO, and its desorption occurs at higher temperatures (123 and 169 °C), which can be explained by a good metal oxide dispersion and, furthermore, its special interaction with the substrate could favour the establishment of a strong linkage with NO molecules.

Catalytic results

It has previously been reported that for a given feed (oxygen, hydrocarbon and NO), the catalytic performance in the selective catalytic reduction of NO depends on both the type of hydrocarbon and the active species.[21] In order to evaluate the catalytic behavior of this family of copper-based catalysts we have chosen propane as the reducing agent. Furthermore, the presence of oxygen in excess is required since there are two chemical reactions competing for this molecule [eqn. (1) and (2)]:

$$C_3H_8 + 2\,NO + 4\,O_2 \rightarrow N_2 + 3\,CO_2 + 4\,H_2O \qquad (1)$$

$$C_3H_8 + 5\,O_2 \rightarrow 3\,CO_2 + 4\,H_2O \qquad (2)$$

Under our experimental conditions, the reaction products were N_2, NO_2 and CO_2, whereas neither N_2O nor CO were detected. The study of the NO conversion as a function of the reaction temperature for catalysts obtained from the Ga_3Al_{11}-SnP support (Fig. 5), shows that conversion always increases

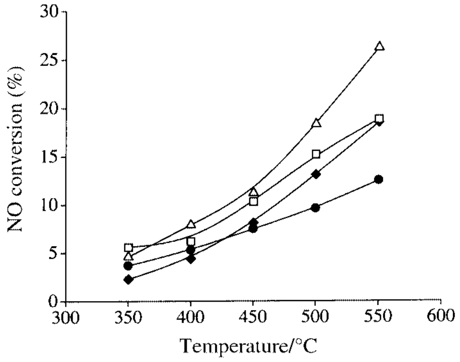


Fig. 5 NO conversion as a function of the reaction temperature of copper supported on Ga_3Al_{11}-SnP: (●) 2.5, (△) 4.9, (◆) 7.1 and (□) 9.2 wt% of copper. Experimental conditions: NO = 1000 ppm, C_3H_8 = 1000 ppm, 2.5 vol% O_2, flow rate = 150 cm^3 min^{-1}, space velocity = 60000 cm^3 g^{-1} h^{-1}.

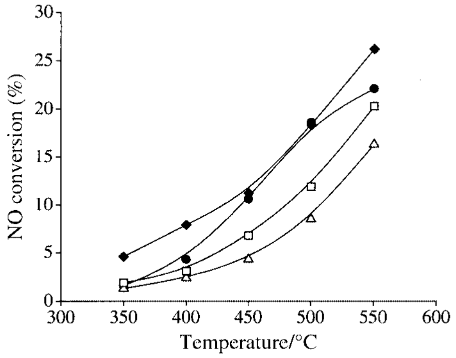


Fig. 6 NO conversion as a function of the reaction temperature of copper supported catalysts with 4.9 wt% of copper on: (●) Al-SnP, (△) $GaAl_{13}$-SnP (◆) Ga_3Al_{11}-SnP and (□) Ga_6Al_7-SnP.

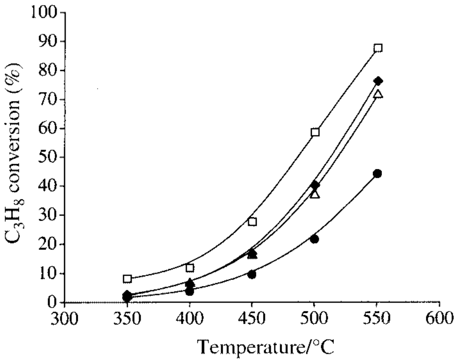


Fig. 7 Propane conversion as a function of the reaction temperature of copper supported on Ga_3Al_{11}-SnP: (●) 2.5, (△) 4.9, (◆) 7.1 and (□) 9.2 wt% of copper.

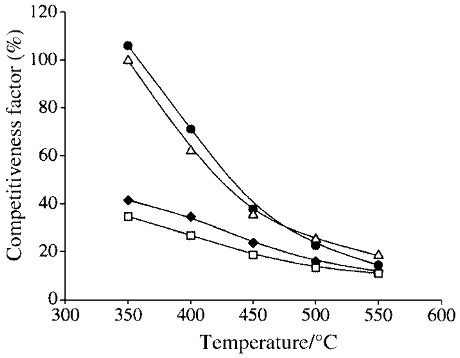


Fig. 8 Competitiveness factor of propane conversion as a function of the reaction temperature of copper supported on Ga_3Al_{11}-SnP: (●) 2.5, (△) 4.9, (◆) 7.1 and (□) 9.2 wt% of copper.

with temperature. It also depends on the copper content, the catalyst with 4.9 wt% of copper being the more active at 550 °C, with a conversion of 26.2%. The catalyst with 2.5 wt% Cu presents the lowest catalytic activity, which can be rationalized by its H_2-TPR data which point to the presence of less reducible copper species, and therefore the formation of the active species Cu^+ in this catalytic reaction is more difficult. Among the other catalysts derived from Ga_3Al_{11}-SnP, with a similar temperature for the maximum of reduction, that with 4.9 wt% of copper shows the highest amount of exposed copper oxide. Moreover, taking into account that increasing the copper loading leads both to an increase in the spinel percentage (difficult to reduce) and an increase in CuO particle size, the highest activity of catalyst Ga_3Al_{11}-SnP-Cu4.9 in the temperautre range 400–550 °C can be explained on the basis of a higher presence of surface Cu^{2+} species. Analogous results have been described in the literature; thus, Park and Ledford[22] found a decrease in catalytic activity when increasing the amount of copper supported on alumina, that is, as isolated copper species increasingly are replaced by discrete CuO particles.

Considering the influence of the support in the SCR of NO for a fixed Cu loading, 4.9 wt% (Fig. 6), it can be appreciated that the most active catalyst, in all range of temperatures studied, again is Ga_3Al_{11}-SnP-Cu4.9. These results agree well with both the NO-TPD data, which evidenced the strongest interaction of this catalyst with the NO molecules, and its lower H_2 reduction temperature. Although peaks in H_2-TPR curves are assigned to total Cu^{2+} to Cu^0 reduction process, it is possible, under our experimental conditions, that only a partial reduction process takes place, leading to Cu^+ ions, which are thought to be the active species in this catalytic reaction, due to their capacity to generate dinitrosyl complexes.[23,24]

Regarding the propane conversion, in Fig. 7 it can be observed that, for catalysts derived from Ga_3Al_{11}-SnP, this also increases as the reaction temperature is increased, ranging, at 550 °C, between 43 and 85%. Therefore, it can be argued that upon increasing the temperature the combustion reaction of propane is favoured relative to the selective reduction of NO. Similar conversion percentages have been obtained on catalysts with 4.9 wt% of copper.

In all cases, a decay in the competitiveness factor with temperature can be observed, the values ranging between 11 and 18% for catalysts derived from Ga_3Al_{11}-SnP with variable copper loadings (Fig. 8), and between 10 and 22% for catalysts on different supports with the same copper content (4.9 wt%). The most active catalyst, Ga_3Al_{11}-SnP-Cu4.9, shows a competitiveness value of 18.2% at 550 °C..

The catalytic activity of these copper oxide impregnated materials are similar to those described for alumina pillared zirconium phosphate impregnated with copper oxide.[25] However, the catalysts studied in the present work are more active than those based on copper oxide supported over alumina pillared montmorillonite.[26] They are also more active than copper oxide supported on alumina catalysts[27] which indicates that the dispersion of alumina, as nanoparticles in the interlayer region of layered tetravalent metal phosphates, favours the formation of small CuO particles, *i.e.* it leads to a better dispersion of the active phase.

Nevertheless, a copper containing ZSM-5 catalyst (2.8 wt% of copper), under the same reaction conditions, exhibits a NO conversion close to 100% with a TOF value of 15.62 × 10^{-4} molecules of NO per Cu atom and also is almost seven times higher than the most active of our catalysts, 2.30 × 10^{-4} molecules of NO per Cu atom (Table 3). The low TOF values can be explained taking into account that, according to the proposed mechanism for the NO SCR with propane, not only a presence of Cu^{2+} ions easily reducible to Cu^+ is required, but also the activation of the reducing agent molecule (propane) on

Table 3 Catalytic properties of copper supported catalysts in the SCR of NO

Catalyst	NO conversion (%)	C_3H_8 conversion (%)	Activity/ µmol g_{cat}^{-1} s^{-1}	10^4 TOF/molec$_{NO}$ at$_{Cu}^{-1}$ s^{-1}
Al-SnP-Cu2.5	7.9	44.4	0.05	1.35
Al-SnP-Cu4.9	22.1	90.2	0.15	1.94
$GaAl_{13}$-SnP-Cu4.9	16.3	51.1	0.11	1.43
Ga_3Al_{11}-SnP-Cu2.5	12.5	44.1	0.09	2.13
Ga_3Al_{11}-SnP-Cu4.9	26.2	71.4	0.18	2.30
Ga_3Al_{11}-SnP-Cu7.1	18.5	76.2	0.13	1.12
Ga_3Al_{11}-SnP-Cu9.2	18.8	87.6	0.13	0.89
Ga_6Al_7-SnP-Cu4.9	20.3	42.5	0.14	1.78
Cu-ZSM5-Cu2.8	86.6	98.9	0.59	15.62

the acidic Brönsted sites of support.[26] These acid sites are scarce in these materials the most abundant being of Lewis type.

The spent catalysts after the NO SCR were studied by XPS in order to determine the nature of the copper species after catalysis. Cu 2p spectra corresponding to Cu(II) species are characterised by a doublet, Cu $2p_{3/2}$ at *ca.* 932.4 eV and Cu $2p_{1/2}$ at *ca.* 952.4 eV signals, both accompanied by weak and wider satellite peaks at *ca.* 943.1 and 962.0 eV, respectively. From Fig. 1, significant differences between the spectra before and after the catalytic reaction are observed (Table 2). Thus, in spent catalysts, the satellite peak corresponding to Cu $2p_{3/2}$ diminishes, while that of Cu $2p_{1/2}$ almost disappears. By comparing the integrated area ratios of the Cu $2p_{3/2}$ and satellite bands, an increase is observed after the catalytic reaction. Since copper species with lower oxidation state (0 or 1+) only show the main peaks, it can be deduced that these increments of integrated area ratios are caused by the disappearance of Cu^{2+} ions due to its partial reduction to generate Cu^+ during SCR of NO. It is noteworthy that the most active catalyst, Ga_3Al_{11}-SnP-Cu4.9, shows the highest area ratio, indicating that it easily forms the Cu^{2+}/Cu^+ pair, required in this catalytic reaction.

The most active catalyst, Ga_3Al_{11}-SnP-Cu4.9, has been chosen to evaluate the influence of parameters such as the partial oxygen pressure, and the NO and propane concentrations in the feed on the catalytic performance. Fig. 9 shows the effect of oxygen addition; in the absence of oxygen, the NO conversion is 11%, increasing to 24% as the oxygen concentration is raised to 0.5 vol%. However, further increase does not affect the NO conversion, which remains almost constant and near to 21% and hence the reaction is zero order with respect to oxygen. These results are in agreement with those reported in the literature for copper catalysts based on alumina pillared zirconium phosphate[25] and Co-ZSM-5.[25]

Concerning propane conversion, an enhancement is observed for oxygen partial pressures above 1.5 vol%, the oxidation reaction of propane being considerably favoured with the conversion value stabilized around 71%. Although an excess of oxygen implies a higher degree of oxidation of propane, and thus, a lower competitiveness factor, this is necessary, since, in addition to preventing the formation of carbonaceous deposits, which would deactivate the catalyst, it favours the reoxidation of Cu(I) to Cu(II), and the formation of NO_2 and oxygenated products with propane.[28]

Fig. 10, shows NO and propane conversions as a function of the propane concentration in the feed. It can be observed that the NO conversion is enhanced up to 44%. From a plot of log (rate of reduction) *vs.* log (partial pressure propane in feed) a reaction order of this reactant of 0.51 is found.

The evolution of NO and propane conversions as a function of the NO composition in the feed (Fig. 11) shows a decay in the NO conversion, although as the propane conversion remains almost constant, the competitiveness factor increases. The order of reaction with respect to NO is 0.44, which is also near to those found using other catalytic systems.

Finally, the influence of the space velocity (*F*/*W*) on NO and propane conversions has been studied. From Fig. 12, it can be observed that NO conversion decreases from 30 to 14% upon increasing this parameter from 20000 to 120000 cm^3 h^{-1} g^{-1}. However, although the propane conversion is much more affected, diminishing from 89 to 40%, this decrease is almost parallel to that of NO conversion, and so the competitiveness factor scarcely changes with space velocity.

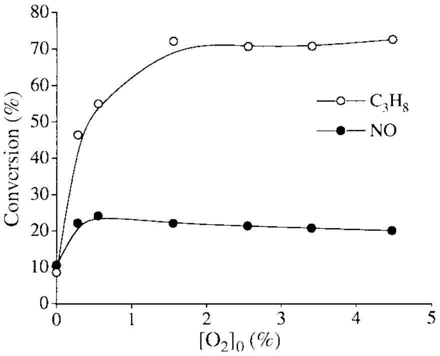


Fig. 9 Effect of the oxygen concentration on the propane and NO conversions for Ga_3Al_{11}-SnP-Cu4.9 catalyst at 550 °C.

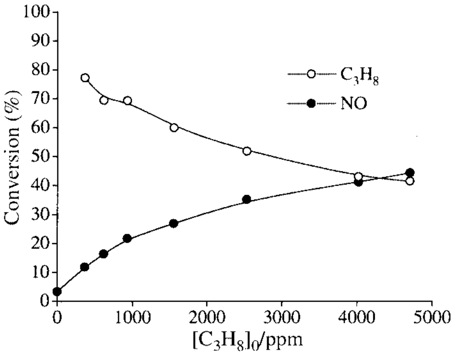


Fig. 10 Variation of the propane and NO conversions with the propane concentration in the feed for Ga_3Al_{11}-SnP-Cu4.9 catalyst at 550 °C.

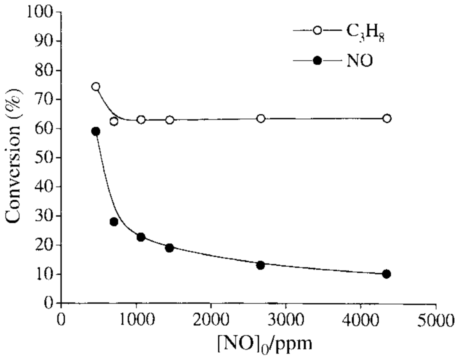


Fig. 11 Dependence of the propane and NO conversions with the NO concentration in the feed for Ga_3Al_{11}-SnP-Cu4.9 catalyst at 550 °C.

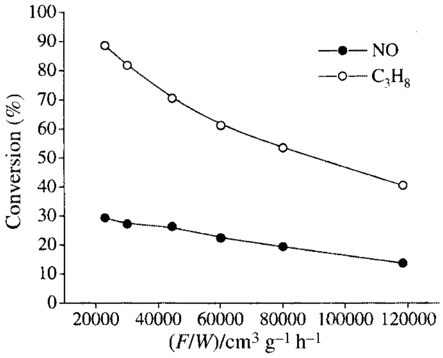


Fig. 12 Variation of the propane and NO conversions as a function of the space velocity for Ga_3Al_{11}-SnP-Cu4.9 catalyst at 550 °C.

In conclusion, copper oxide supported on alumina and mixed alumina/gallium oxide pillared tin phosphate catalysts exhibit a moderate activity in the selective catalytic reduction of NO with propane. Among them, catalyst Ga_3Al_{11}-SnP-Cu4.9 is the most active because it combines suitable conditions, such as high dispersion of the active phase and good reducibility. The full characterisation of the catalysts obtained in this work, especially relating to the redox properties of the active phase is of great interest when considering the use of these catalysts for the SCR of NO with other reducing agents such as ammonia.

Experimental

Preparation of catalysts

A series of porous materials based on alumina and mixed alumina/gallium oxide (with Al/Ga molar ratios of 1/13, 3/11, and 6/7) pillared α-tin phosphates have been synthesised as described elsewhere,[29] and calcined in air at 500 °C for 8 h. These supports are designated as Al-SnP, $GaAl_{13}$-SnP, Ga_3Al_{11}-SnP and Ga_6Al_7-SnP.

These solids were then impregnated with copper species by using the incipient wetness method with aqueous copper acetate solutions followed by solvent evaporation in air at 60 °C, and calcination at 500 °C for 4 h. In this manner, catalysts with different copper loading have been prepared. The weight percentage of copper present on each catalyst is indicated after the name of the support (for instance AlSnP-Cu4.9 corresponds to 4.9 wt% of Cu on the AlSnP support).

A Cu-ZSM-5 sample, prepared by ion-exchange with copper acetate at room temperature of a synthesized ZSM-5 (Si/Al molar ratio of 13.5, copper content of 2.8 wt% corresponding to an exchange level of 79%), was used as a reference.

Characterization methods

XRD patterns were obtained with a Siemens D501 diffractometer using Cu-Kα radiation and a graphite monochromator. N_2 adsorption–desorption isotherms at 77 K were measured in a conventional volumetric apparatus after outgassing of samples at 200 °C and 10^{-4} Torr overnight. The total acidity of catalysts was elucidated by temperature-programmed desorption of ammonia (NH_3-TPD), between 100 and 500 °C, as previously described.[29]

XPS analyses were carried out with a Physical Electronics 5700 instrument with an Mg-Kα X-ray excitation source ($h\nu$ = 1253.6 eV) and a hemispherical electron analyser. Accurate ± 0.1 eV binding energies were determined with respect to the position of the adventitious C 1s peak at 284.8 eV. The residual pressure in the analysis chamber was maintained below 10^{-9} Torr during data acquisition.

Hydrogen temperature-programmed reduction (H_2-TPR) curves were obtained between 40 and 450 °C, using a H_2/Ar flow (48 cm^3 min^{-1}, 10 vol% of H_2) and a heating rate of 10 °C min^{-1}. The water produced in this reaction was eliminated by passing the gas flow through a cold finger (−80 °C). The hydrogen consumption was monitored by an on-line gas chromatograph (Shimadzu 6C-14A) equipped with a TCD. Previously, samples (50 mg) were treated at 500 °C under a O_2/He flow (50 cm^3 min^{-1}, 5 vol% of O_2) for 30 min, and then under a helium flow (100 cm^3 min^{-1}) for 30 min.

The study of the temperature-programmed desorption of NO (NO-TPD) was carried out using *ca.* 150 mg of catalyst, previously treated at 550 °C under a flow of 70 cm^3 min^{-1} of O_2/He (5 vol% of O_2) for 30 min, and then under a flow of 100 cm^3 min^{-1} of He for 30 min. Once at room temperature, NO adsorption was carried out by passing a flow of 100 cm^3 min^{-1} of 0.05 vol% NO in helium for 30 min. Then, a helium flow of 100 cm^3 min^{-1} was passed until a stable signal of NO was obtained (baseline). Desorption of NO was performed between 40 and 550 °C, with a heating rate of 10 °C min^{-1}, under a helium flow of 100 cm^3 min^{-1}. During this process eluted gas was monitored and quantified using an on-line quadrupole mass spectrometer Pfeiffer Balzers OmniStar, equipped with a ChannelTron detector.

The catalytic activities in the SCR of NO were measured using a micro-reactor in a steady-state flow mode. 150 mg of samples (0.3–0.4 mm particle diameter) were packed into a tubular quartz reactor (6 mm i.d.) and plugged with quartz wool. Catalysts were activated at 500 °C (10 °C min^{-1} heating rate) under a helium flow of 70 cm^3 min^{-1} for 1 h. The reaction mixture was prepared by using four mass-flow controllers and consisted of 1000 ppm NO, 1000 ppm propane and 2.5% O_2 (balanced with helium) with a total flow rate of 150 cm^3 min^{-1}. Under these experimental conditions, the space velocity (*F*/*W*) was 60000 cm^3 h^{-1} g^{-1}. The reaction temperature was varied between 350 and 550 °C. An on-line quadrupole mass spectrometer Pfeiffer Balzers OmniStar was used to monitor the gas effluent at each temperature and thus to measure the NO and propane concentration. The activity was obtained on the basis of disappearance of NO fed. The competitiveness factor was calculated as the ratio of mol propane reacted with NO to the total mol propane consumed in the reaction.

Acknowledgements

This research was performed under the contract No. BRPR CT97 0545 of the European Union. We also wish to thank the CICYT (Spain) (Project MAT97-906) for financial support. P.B.G. thanks Junta de Andalucía (Spain) for a fellowship.

References

1 M. Iwamoto and N. Mizuno, *J. Auto Eng.*, 1993, **207**, 23.
2 M. J. Heimrich and M. L. Deviney, *SAE Pap.*, 930736, 1994.
3 J. N. Armor, *Appl. Catal. B*, 1994, **4**, N18.
4 T. Tanabe, T. Iijima, A. Koinai, J. Mizuno, K. Yokota and A. Isoga, *Appl. Catal. B*, 1996, **6**, 145.
5 J. A. Anderson, C. Márquez Álvarez, M. J. López Muñoz, I. Rodríguez Ramos and A. Guerrero Ruiz, *Appl. Catal. B*, 1997, **14**, 189.
6 K. W. Yao, S. Jaenicke, J. Y. Lin and K. L. Tan, *Appl. Catal. B*, 1998, **16**, 291.
7 H. Praliaud, S. Mikhailemko, Z. Chajar and M. Primet, *Appl. Catal. B*, 1998, **16**, 359.
8 *Pillared Layered Structures: Current Trends and Applications*, ed. I. V. Mitchell, Elsevier, London, 1990, pp. 137.
9 P. Olivera-Pastor, P. Maireles-Torres, E. Rodríguez-Castellón, A. Jiménez-López, T. Cassagneau, D. J. Jones and J. Rozière, *Chem. Mater.*, 1996, **8**, 1758.

10 A. Jiménez-López, J. Maza-Rodríguez, E. Rodríguez-Castellón and P. Olivera-Pastor, *J. Mol. Catal. A*, 1996, **108**, 175.

11 F. J. Pérez-Reina, E. Rodríguez-Castellón and A. Jiménez-López, *Langmuir*, 1999, **15**, 8421.

12 J. Mérida-Robles, P. Olivera-Pastor, E. Rodríguez-Castellón and A. Jiménez-López, *J. Catal.*, 1997, **169**, 317.

13 J. Mérida-Robles, E. Rodríguez-Castellón and A. Jiménez-López, *J. Mol. Catal. A*, 1999, **145**, 169.

14 B. Solsona, J. M. López-Nieto, M. Alcántara-Rodriguez, E. Rodríguez-Castellón and A. Jiménez-López, *J. Mol. Catal. A*, 2000, **153**, 199.

15 G. Ertl, R. Hierl, H. Knözinger, N. Thiele and H. P. Urbach, *Appl. Surf. Sci.*, 1980, **5**, 49.

16 E. C. Marques, M. R. Friedman and D. J. Dahm, *Appl. Catal.*, 1985, **19**, 387.

17 P. A. Berger and J. F. Roth, *J. Phys. Chem.*, 1967, **71**, 4307.

18 R. M. Friedman, J. J. Freeman and F. W. Lytle, *J. Catal.*, 1978, **55**, 10.

19 C. Torre-Abreu, M. F. Ribeiro and G. Delahay, *Appl. Catal. B*, 1997, **14**, 261.

20 Y. Li and J. N. Armor, *Appl. Catal.*, 1991, **76**, L1.

21 M. Iwamoto and H. Hamada, *Catal. Today*, 1991, **10**, 57.

22 W. Park and J. S. Ledford, *Appl. Catal. B: Environ.*, 1998, **15**, 221.

23 Y. Li and J. N. Armor, *Appl. Catal. B*, 1993, **2**, 239.

24 J. O. Petunchi, G. Stilly and W. K. Hall, *Appl. Catal. B*, 1993, **2**, 303.

25 R. Hernández-Huesca, J. Santamaría-González, P. Braos-García, P. Maireles-Torres, E. Rodríguez-Castellón and A. Jiménez-López, *Appl. Catal. B: Environ.*, 2000, **732**, 1.

26 S. Perathoner and A. Vaccari, *Clay Miner.*, 1997, **32**, 123.

27 Z. Chajar, M. Primet, H. Praliaud, M. Chevrier, C. Gauthier and L. Mathis, *Appl. Catal. B*, 1994, **4**, 199.

28 J. O. Petunchi and W. K. Hall, *Appl. Catal. B*, 1993, **2**, L17.

29 P. Braos-García, E. Rodríguez-Castellón, P. Maireles-Torres, P. Olivera-Pastor and A. Jiménez-López, *J. Phys. Chem B*, 1998, **102**, 1672.

Solvent-free, two-step synthesis of some unsymmetrical 4-aryl-1,4-dihydropyridines

Waldo H. Correa and Janet L. Scott*

Centre for Green Chemistry, P.O. Box 23, Monash University 3800, Victoria, Australia.
E-mail: janet.scott@sci.monash.edu.au

Received 18th July 2001
First published as an Advance Article on the web 30th October 2001

4-Aryl-1,4-dihydropyridines are efficiently synthesised under solvent-free conditions in high yield. The use of volatile solvents is restricted to recrystallisation of the product, which, due to the high degree of conversion, is kept to a minimum. Optimisation of reaction conditions by careful consideration of the reaction rate and extent of conversion is demonstrated. This is yet another example of how readily solvent-free reactions may be implemented in the highly reproducible and efficient preparation of pure therapeutic agents with minimal production of waste and optimised use of energy.

Introduction

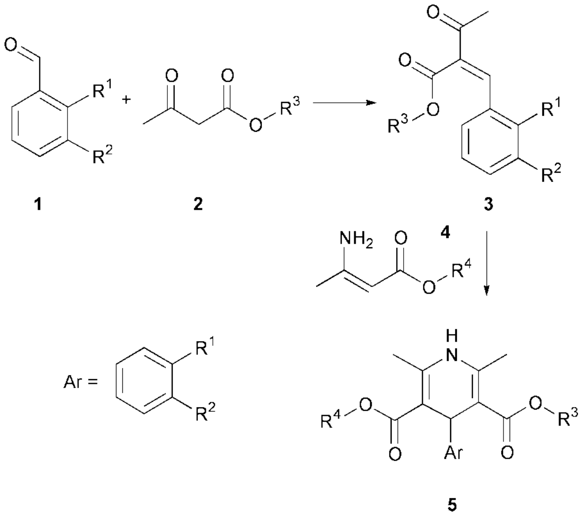
4-Aryl-1,4-dihydropyridines **5** are potent blockers and activators of L-type calcium channels[1] and are extensively used in the treatment of cardiovascular disease (CVD) which is a leading cause of death the world over (41.4% of deaths in the USA in 1996 were a result of CVD).[2] Second generation calcium channel blockers such as Amlodipine,† the world's best selling drug for the treatment of hypertension (marketed as Norvasc by Pfizer with sales of $2.6 billion in 1998),[2] sustained release calcium antagonists such as Nisoldipine‡ and older products such as Felodipine§ and Nifedipine¶ are all members of the 1,4-dihydropyridine class and, together with other calcium antagonists accounted for 3.1% of the total world pharmaceutical market of $297.6 billion at the end of the 3rd quarter 2000.[3]

The Hantzsch pyridine synthesis[4] described in 1882 provides a convenient route to the preparation of all symmetrical dihydropyridines. This reaction consists in essence in the condensation of an aromatic aldehyde with an excess of an acetoacetate ester and ammonia.[5,6] Unsymmetrically 3,5- (or 2,6-) substituted dihydropyridines are usually synthesised by a two-step process such as that illustrated in the Scheme 1.

While this has been described as a one-pot procedure,[7] it is more common to react the aromatic aldehyde **1** with an appropriate acetoacetate ester **2** to produce the benzylidene intermediate **3** which is further reacted with 3-aminocrotonic acid ester **4** yielding the unsymmetrical 1,4-dihydropyridine **5**.[8,9–15]

Various strategies have been employed to maximise conversion and minimise reaction time and these include azeotropic removal of water,[9–11] catalyst optimisation,[9,12] use of microwave heating,[13] and selective de-esterifaction of diesters using acid catalysts.[14] With the exception of the methodology employing microwave heating, reaction times are of the order of 2–40 h and overall yields for the two-step synthesis are significantly lower than quantitative (30–65%). Extractive work-ups[15] and the need to separate symmetrical diester byproducts from the desired product[9] serve to increase the usage of volatile organic compounds (VOCs) and decrease efficiency with respect to yield and number of process steps.

Recently, it has been reported that many reactions proceed efficiently, rapidly and with a high degree of selectivity under



Scheme 1

Green Context

4-Aryl-1,4-dihydropyridines are used in the treatment of cardiovascular disease, one of the world's leading causes of disease. Its synthesis is typical of those in organic chemistry that usually involve more than one step, auxiliaries such as reagents and solvents, and low overall atom efficiencies. Here we see how solventless reactions can significantly improve the economic and environmental efficiency of the synthesis is of these pyridines. Optimisation of the reaction conditions has been achieved by studying reaction rate and the extent of conversion. The simple but effective synthesis of valuable products is achieved in a single pot, with minimal auxiliaries, easy product recovery and low levels of work.

JHC

---

† 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate.

‡ Methyl,2-methylpropyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate.

§ Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

¶ Dimethyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate.

DOI: 10.1039/b106397a

solvent-free conditions.[16] We now report the solvent-free synthesis of 4-aryl-1,4-dihydropyridines and the application of measurement of rate and extent of conversion to the optimisation of such reactions. This methodology provides an exceptionally high-yielding and simple route to some common drug products and is demonstrated to be a significant improvement on the solution phase methodology with respect to energy efficiency, reaction time, extent of conversion and isolated yield. In addition, the hazards associated with the use of volatile organic solvents are obviated and the resultant quantity of waste significantly reduced.

Results and discussion

The solvent-free, two-step synthesis of a number of 4-aryl substituted 1,4-dihydropyridine-3,5-dicarboxylic acid derivatives **5** proceeds rapidly at moderate temperatures to produce pure product in high yield (almost quantitative in most cases) with very small amounts of attendant waste. The results of the synthesis of a number of compounds, with varying aryl, and ester substituents, are presented in Table 1.

In common with the previously published procedures this is a two-step process that initially requires contact between a benzaldehyde derivative **1** and acetoacetate ester **2,** as a solventless reaction, in the presence of a catalytic amount of a 1:1 mixture of piperidine and glacial acetic acid. The resultant benzylidene **3** is then reacted, without further purification, with methyl-3-aminocrotonate **4** and a small additional quantity of glacial acetic acid to generate the corresponding dihydropyridines **5** in quantitative or near-quantitative conversion in almost all cases.

As the reaction may be shown to proceed at reasonable rate even at ambient temperature (25 °C), an analysis of the rate of conversion of **1** and **2** to **3** at different temperatures was undertaken with a view to optimisation of reaction time and temperature.

The system under study is not a closed system (H_2O is allowed to escape) and thus this does not represent a reaction rate but rather an effective rate of conversion to product **3** under the specific circumstances. It should also be noted that a transient intermediate corresponding to the non-dehydrated adduct occurs and the reaction may be represented as **1** + **2** → [alcohol intermediate]→ **3** + H_2O. No attempt is made to relate rate and mechanism or 'molecularity' of reaction yet the effective rate measured allows determination of an effective overall rate constant and therefore analysis of the effect of changing temperature on the rate of conversion.

Measured extents of conversion α, where α = [**3**]/([**1**]+[**3**]),[17] at temperatures ranging from 25 to 80 °C are plotted in Fig. 1. An effective first order rate expression $f(\alpha) = kt$ where $f(\alpha) = -\ln(1-\alpha)$ is found to provide the best fit over the largest range of α values (typically α = 0–0.9) and an effective rate constant k is derived from the gradient of the line derived from application of the integrated rate law function at each temperature and used to model continuous rate curves. Values of the effective overall rate constant k derived at each temperature are detailed in Table 2.

A plot of ln k *vs.* reciprocal temperature, Fig. 2, reveals an interesting phenomenon. At 25, 40 and 60 °C the system exhibits isokinetic behaviour and a straight line may be fitted to yield estimates of E_a and pre-exponential factor A. However ln k at 80 °C does not fall on this line, in other words the measured k_{eff} is lower, by a factor of 2.4, than would be predicted from an Arrhenius plot (2.6×10^{-3} s^{-1} *vs.* 6.3×10^{-3} s^{-1}). While it is possible that this represents a large experimental error at this rapid rate of conversion, it may be true that a different overall 'mechanism' is implied at this temperature and that elevation of

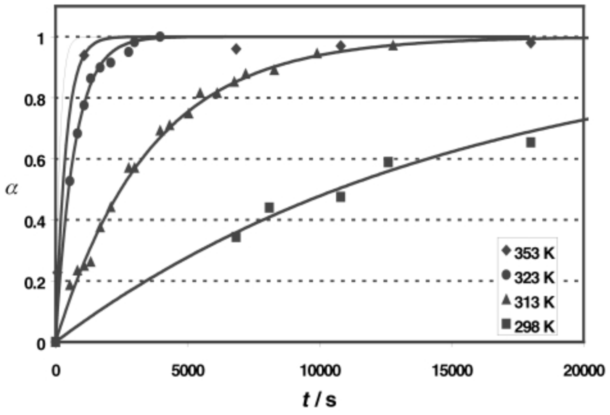


Fig. 1 α *vs.* time (t) curves for the formation of **3b** from **1b** and ethyl acetoacetate at 25, 40, 60 and 80 °C. Continuous modeled rate curves are derived as follows: the integrated form $f(\alpha)$ of various possible rate law expressions are plotted *vs.* t and examined for linearity. An effective first order rate expression $f(\alpha) = kt$ where $f(\alpha) = -\ln(1-\alpha)$ is found to provide the best fit over the widest range of α values (typically α = 0–0.9) and k estimated from the gradient of this line is used to generate the solid curves ($\alpha = 1 - e^{-kt}$) depicted here. The fine line represents the curve predicted for conversion at 80 °C from an examination of the Arrhenius plot depicted in Fig. 2.

Table 1 Comparison of yields and duration of reaction for conversion to **3** and **5**

				3		**5**		
	R^1	R^2	R^3	Conv.[a] (%)	t/h	Conv.[a] (%)	t/h	Yield (%)
a	H	H	Et	98	0.3	>99	2.4	96
b	NO_2	H		>99	0.4	61	3.0	—[c]
						73	22[b]	—[c]
c	H	NO_2		90	0.2	>99	2	95
d	H	Cl		>99	0.7	>99	1.0	94
e	Cl	Cl		96	1.0	>99	1.8	96
f	H	H	Bu^t	97	0.3	94	3.0	
						>99	5.0	92
g	NO_2	H		>99	0.4	5	0.2	—[c]
						27	20	—[c]
h	H	NO_2		90	1.0	91	1.5	87
i	H	Cl		95	1.0	95	2.0	
						>99	4.0	91
j	H	Cl	$PhCH_2$	>99	1.0	>99	1.5	99

[a] Compound **3** was not isolated; extent of conversion determined from ^{1}H NMR analysis. [b] After a further 19 h at ambient temperature the reaction was found to have proceeded, but even lengthy reaction times at elevated temperature did not lead to substantially improved conversion to **5b**. [c] Product not isolated due to poor conversion.

Table 2 Values of k derived from a consideration of the gradient of plots of $f(\alpha) = -\ln(1-\alpha)$ for the conversion of **2b** and ethylacetoacetate to **3b**

T/K	k/s^{-1}	α Range of fit
298	6.5×10^{-5}	0–0.93
313	2.8×10^{-4}	0–0.97
333	1.4×10^{-3}	0–0.90
353	2.6×10^{-5}	0–0.94

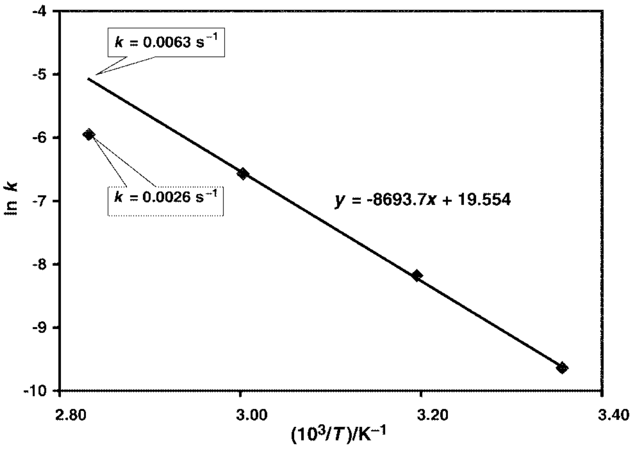


Fig. 2 Arrhenius plot, ln k *vs.* t, for k values derived from fit of an F1 rate law. Extrapolation of the line fitted to temperatures ranging from 25 to 60 °C indicates an expected value of k of 6.3×10^{-3} s^{-1} while the measured value is found to be only 2.6×10^{-3} s^{-1}.

temperature does not lead to the expected rate increase. The reaction mixture is an oil which was observed to become steadily more viscous as the reaction proceeds. Thus it is not unreasonable to postulate that diffusion (or mixing) of **1** + **2** becomes the rate limiting factor in the conversion to **3** at elevated temperatures. Above 60 °C diminishing returns are achieved with respect to increase in rate of conversion and an analysis of quantity of product produced *vs* energy input would be expected to exhibit a maximum at some temperature between 60 and 80 °C. While this optimum temperature may vary for each **3** it is worthy of note that this provides an adequate method for optimisation of temperature to achieve maximum rate of formation of **3**.

The fact that the reaction proceeds at an acceptable rate at room temperature provides an opportunity for reaction in systems containing heat labile species. No large excess of acetoacetate is required to drive the reaction to completion and no disubstituted impurities are detected by NMR analysis.

^{1}H NMR analysis of the benzylidene intermediates **3** reveal a mixture of E and Z isomers and recrystallisation from ethanol was used to preferentially crystallise the Z isomer of **3g** for purposes of identification. In all cases the Z isomer predominates. ^{1}H NMR analysis of this crystalline material reveals a single set of signals and the single crystal structure[18] of **3g** confirms the assignment of NMR data. The molecular structure of **3g** is presented in Fig. 3 and analysis of the angles of the planes indicated on the diagram reveal that the aromatic ring is twisted out of the plane of the newly formed double bond system by 53.8(1)°. Similarly the atoms associated with C11 are twisted out of the plane by 70.2(1)° while sp^2 centre C9 and bonded atoms is almost coplanar with the newly formed double bond. The oily nature of unrecrystallised compounds **3** is almost certainly due to the occurrence of a mixture of E and Z isomers and the presence of small amounts of the catalyst system, as solid Z isomer may be isolated quite readily by recrystallisation from solvents such as ethanol. In fact, the oils obtained will often crystallise upon prolonged standing post reaction.

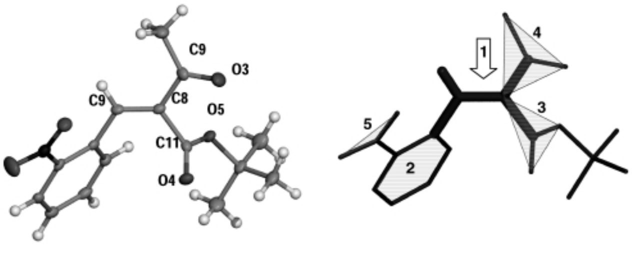


Fig. 3 Molecular diagram of **3g** from single crystal structure data. Ellipsoids are plotted at the 50% probability level. Planes referred to in the text are labelled and all except '1' (the plane of the vinylic bond and substituents) are represented as shaded polygons. The angles (°) between the planes indicated are: 1 and 2, 53.8(1); 5 and 2, 7.4(4); 1 and 4, 14.4(2); 1 and 6, 70.2(1).

The intermediate is not isolated, nor is the catalyst removed prior to reaction with *ca.* 1 mol equivalent of methyl aminocrotonate. A small quantity of glacial acetic acid is added and the reaction **3** + **4** to produce **5** again proceeds with alacrity as evidenced by the extent of conversion *vs.* time data for the conversion of **3e** to **5e** presented in Fig. 4.

Close inspection of the early part of the conversion curve reveals an apparently sigmoidal shaped curve. This might well be indicative of an induction period or a change in dominant process leading to two superimposed curves. This induction period is also reflected in preliminary data obtained from calorimetry experiments and is the subject of a significant further investigation. It proved impossible to model this accurately using an F1 expression and instead a deceleratory curve described by the expression $kt = [1-(1-\alpha)^{1/3}]^2$ (the so-called D3 rate equation[19]) and offset to the coincide with the inflection point, provides the best model. There appears to be a continual increase in the rate of conversion of reagents to products with increased temperature (Table 3, Fig. 5), and it is clear that a minimum temperature exists below which poor conversion of reagents to products is achieved. In fact, at 30 °C

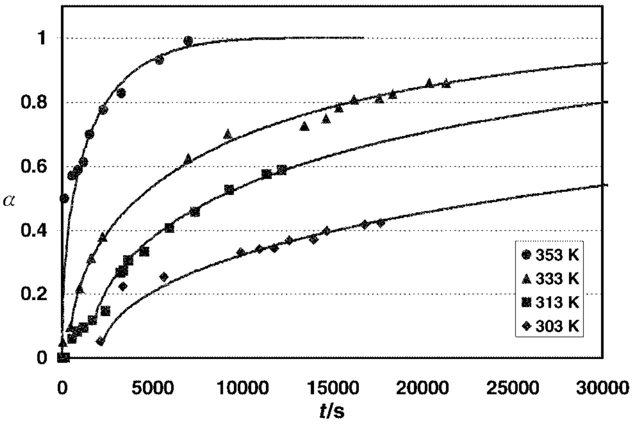


Fig. 4 α *vs.* t curves for the formation of **5e** from **3e** and ethyl acetoacetate at 30, 40, 60 and 80 °C. Continuous modeled rate curves are generated by the expression $\alpha = 1-(1-(kt)^{1/2})^3$ derived from $kt = [1-(1-\alpha)^{1/3}]^2$.

Table 3 Values of k derived from a consideration of the gradient of plots of $f(\alpha) = [1-(1-\alpha)^{1/3}]^2$ for the conversion of **3e** and methyl aminocrotonate to **5e**

T/K	k/s^{-1}	α Range of fit
303	1.90×10^{-6}	0–0.40[a]
313	6.00×10^{-6}	0–0.60
333	1.10×10^{-5}	0–0.86
353	7.00×10^{-5}	0–0.93

[a] Reaction is arrested at 42% conversion.

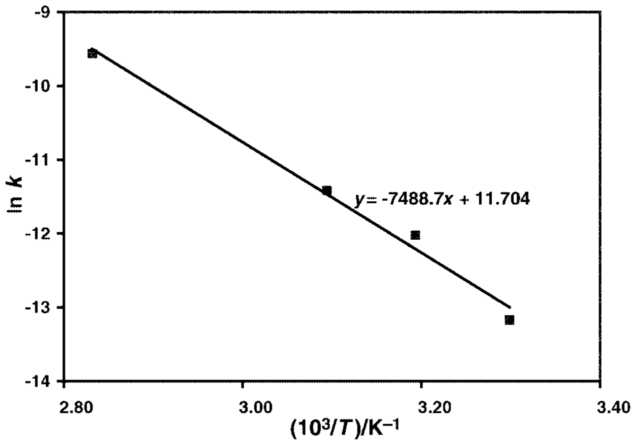


Fig. 5 Arrhenius plot, ln *k* *vs.* *t* for *k* values derived from fit of a D3 rate law to the overall process of addition and ring closure.

the reaction is arrested at approximately 42% conversion. An increase of only 10 °C to 40 °C is sufficient to drive the reaction substantially to completion under the conditions of the experiment (99% conversion after *ca.* 28 h) and this indicates the wide temperature range over which this conversion may be effected.

Of all the benzylidene derivatives tested only the 2-nitro derivatives **3b** or **3g** proved recalcitrant in conversion to the corresponding dihydropyridines. Conversions remained poor even after lengthy reaction times and the product did not solidify. Analysis of the resultant oils indicated the presence of unreacted starting materials and product. Attempts to improve the extent of conversion by altering the catalyst quantities utilised were ineffective, and an optimum catalyst concentration of 0.2 mol% was identified. Further increase in catalyst quantity *reduces* the rate of formation of the product and has no effect on the extent of conversion. Similar optimum catalyst concentrations may be identified in each case. The failure of this methodology when applied to *o*-nitro derivatives (although not *p*-nitro) is unfortunate as these constitute an important group of dihydropyridine drugs. This effect has been noted previously and ascribed to a combination of steric and electronic effects.[20]

In conclusion, an efficient, optimised solvent-free method for the synthesis of 4-aryl-1,4-dihydropyridine compounds has been developed. Efficient conversion to products and resultant reduction in purification, results in minimisation of waste and maximisation of resource use.

Experimental

Molecular characterisation

All melting points were determined on an Electrochemical digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz Spectrometer in $CDCl_3$ solution with TMS as reference. Electrospray mass spectrometry (ESI) was carried out on a Micromass Platform II API QMS Electrospray mass spectrometer with cone voltage at 35 V, using acetone as the mobile phase. Analyses were always conducted in positive (ESI$^+$) mode. Single crystal diffraction data were collected on an Enraf-Nonius Kappa CCD at 123 K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, 1° φ and ω scans). The structure was solved by direct methods using the program SHELXS-97[21] and refined by full matrix least-squares refinement on F^2 using the programs SHELXL-97[22] and Xseed.[23] Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted at geometrically calculated positions with temperature factors constrained to 1.5 times the isotropic equivalents of the parent atoms.

Rates of conversion

Samples were taken from the reaction mixture at measured time intervals, dissolved in $CDCl_3$ and refrigerated until NMR data could be acquired. (It was ascertained by comparative experiments that dissolution in $CDCl_3$ followed by refrigeration slowed the rate of reaction to an undetectable level). Estimates of extent of conversion α, where α is the ratio **3**/(**3** + **1**), or **5**/(**5** + **3**) were derived from ^{1}H NMR integrated peak areas for suitable well resolved signals, and tested against a variety of integrated rate law expressions. The best expression to describe the data was determined from the degree of linearity of the fitted expression over the range α = 0–0.9 and the value of k (the effective rate constant) estimated from the gradient of the fitted line.

Synthetic procedures

All reagents were of 98% purity or greater and used as purchased from the supplier unless noted otherwise. Solvent free experiments were performed in round bottom flasks of appropriate capacity, immersed in an oil bath preheated to the desired reaction temperature, with stirring accomplished using a magnetic stirrer. Both were thoroughly cleaned and acetone rinsed prior to use. All catalyst volumes were delivered using a well-calibrated micro-syringe. Extent of conversion for the formation of **3** and **5** were calculated by comparison of integrated values of well-defined product and reagent peaks using suitable ^{1}H NMR data.

General procedure for the preparation of benzylidene intermediates (3a–e)

In a typical synthesis a 1:1.1 mixture of an appropriate benzaldehyde **1** and an acetoacetate ester **2** were stirred for approximately 1 min at the requisite temperature until the respective reagents had amalgamated to form a homogeneous viscous liquid. 0.018 mol equivalents each of piperidine and glacial acetic acid were added to the stirred mixture and the reaction allowed to proceed until near quantitative conversion was detected by ^{1}H NMR analysis of samples. The products, which were a mixture of *E* and *Z* isomers, were yellow or orange oils. In some cases the *Z*-isomer could be isolated as a solid by recrystallisation from ethanol, although this was only done for purposes of identification.

3a. Conversion 98% (oil). ESI-MS, *m*/*z* 241.0 (calc. 241.1) [M+Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 2:1 (*Z*:*E*); *Z*-isomer, δ 1.24 (3H, t, J = 6 Hz, CH_3), 2.38 (3H, s, CH_3), 4.30 (2H, q, J = 6 Hz, OCH_2), 7.34–7.56 (Ar-H), 7.55 (1H, s, vinylic CH). *E*-isomer, δ 1.30 (3H, t, J = 6 Hz, CH_3), 2.33 (3H, s, CH_3), 4.27 (2H, q, J = 6 Hz, OCH_2), 7.32–7.66 (Ar-H), 7.64 (1H, s, vinylic CH).

3b. Conversion >99% (oil). ESI-MS, *m*/*z* 286.0 (calc. 286.1) [M+Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 2:1 (*Z*:*E*): *Z*-isomer, δ 0.99 (3H, t, J = 7.2 Hz, CH_3), 2.49 (3H, s, CH_3), 4.06 (2H, q, J = 7.2 Hz, OCH_2), 7.35–8.25 (Ar-H), 8.10 (1H, s, vinylic CH). *E*-isomer, δ 1.36 (3H, t, J = 6.9 Hz, CH_3), 2.17 (3H, s, CH_3), 4.34 (2H, q, J = 6.9 Hz, OCH_2), 7.35–8.25 (Ar-H), 8.05 (1H, s, vinylic CH).

3c. Conversion 90% (oil). ESI-MS, *m*/*z* 286.0 (calc. 286.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 2 : 1 (*Z*:*E*); *Z*-isomer, δ 1.30 (3H, t, *J* = 7.2 Hz, CH_3), 2.45 (3H, s, CH_3), 4.33 (2H, q, *J* = 7.2 Hz, OCH_2), 7.56–8.33 (Ar-H), 8.25 (1H, s, vinylic CH). *E*-isomer, δ 1.35 (3H, t, *J* = 7.2 Hz, CH_2), 2.39 (3H, s, CH_3), 4.36 (2H, q, *J* = 7.2 Hz, OCH_2), 7.56–8.33 (Ar-H), 8.33 (1H, s, vinylic CH).

3d. Conversion > 99% (oil). ESI-MS, *m*/*z* 275.0 (calc. 275.0) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 2.5 : 1 (*Z*:*E*); *Z*-isomer, δ 1.27 (3H, t, *J* = 7.2 Hz, CH_3), 2.41 (3H, s, CH_3), 4.29 (2H, q, *J* = 7.2 Hz, OCH_2), 7.30–7.57 (Ar-H), 7.49 (1H, s, vinylic CH). *E*-isomer, δ 1.32 (3H, t, *J* = 7.2 Hz, CH_3), 2.34 (3H, s, CH_3), 4.32 (2H, q, *J* = 7.2 Hz, OCH_2), 7.30–7.57 (Ar-H), 7.57 (1H, s, vinylic CH).

3e. Conversion 96% (oil). ESI-MS, *m*/*z* 309.0 (calc. 309.0) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$) 2 : 1 (*Z*:*E*); *Z*-isomer, δ 1.15 (3H, t, *J* = 7.2 Hz, CH_3), 2.46 (3H, s, CH_3), 4.21 (2H, q, *J* = 7.2 Hz, OCH_2), 7.30–7.57 (Ar-H), 7.82 (1H, s, vinylic CH). *E*-isomer, δ 1.35 (3H, t, *J* = 7.2 Hz, CH_3), 2.46 (3H, s, CH_3), 4.32 (2H, q, *J* = 7.2 Hz, OCH_2), 7.30–7.57 (Ar-H), 7.89 (1H, s, vinylic CH).

3f. Conversion 97% (oil). ESI-MS, *m*/*z* 269.1 (calc. 269.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$) 2 : 1 (*Z*:*E*); *Z*-isomer, δ 1.52 (9H, s, $OC(CH_3)_3$), 2.41 (3H, s, CH_3) 7.37–7.58 (Ar-H), 7.37 (1H, s, vinylic CH). *E*-isomer, δ 1.53 (9H, s, $OC(CH_3)_3$), 2.33 (3H, s, CH_3), 7.37–7.58 (Ar-H), 7.48 (1H, s, vinylic CH).

3g. Conversion > 99% (oil). ESI-MS, *m*/*z* 314.1 (calc. 314.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 3 : 1 (*Z*:*E*), *Z*-isomer, δ1.23 (9H, s, $OC(CH_3)_3$), 2.46 (3H, s, CH_3) 7.31–8.23 (Ar-H), 7.98 (1H, s, vinylic CH). *E*-isomer, δ 1.55 (9H, s, $OC(CH_3)_3$), 2.46 (3H, s, CH_3) 7.31–8.23 (Ar-H), 7.92 (1H, s, vinylic CH).

3h. Conversion 90% (oil). ESI-MS, *m*/*z* 314.1 (calc. 314.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 3 : 1 (*Z*:*E*); *Z*-isomer, δ 1.54 (9H, s, $OC(CH_3)_3$), 2.37 (3H, s, CH_3) 7.28–8.77 (Ar-H), 8.00 (1H, s, vinylic CH). *E*-isomer, δ 1.54 (9H, s, $OC(CH_3)_3$), 2.37 (3H, s, CH_3), 7.28–8.77 (Ar-H), 7.92 (1H, s, vinylic CH).

3i. Conversion 95% (oil). ESI-MS, *m*/*z* 303.0 (calc. 303.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$) 2 : 1 (*Z*:*E*); *Z*-isomer, δ 1.53 (9H, s, $OC(CH_3)_3$), 2.41 (3H, s, CH_3) 7.30–7.54 (Ar-H), 7.41 (1H, s, vinylic CH). *E*-isomer, δ 1.47 (9H, s, $OC(CH_3)_3$), 2.33 (3H, s, CH_3), 7.30–7.54 (Ar-H), 7.48 (1H, s, vinylic CH).

3j. Conversion > 99% (oil). ESI-MS *m*/*z* 337.0 (calc. 337.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): 2 : 1 (*Z*:*E*), *Z*-isomer, δ 2.39 (3H, s, CH_3), 5.29 (2H, s, OCH_2) 7.18–7.50 (Ar-H), 7.50 (1H, s, vinylic CH). *E*-isomer, δ 2.34 (3H, s, CH_3), 5.28 (2H, s, CH_2), 7.18–7.50 (Ar-H), 7.62 (1H, s, vinylic CH).

General procedure for the preparation of 4-aryl-substituted-1,4-dihydropyridinedicarboxylic esters 5a–j

A 1 : 1.1 mixture of an appropriate benzylidene intermediate **3** and methyl-3-aminocrotonate **4** were stirred for 1 min at the requisite temperature until the respective reagents had amalgamated to form a homogeneous viscous oil. To this was added 0.15 mol equivalent of glacial acetic acid and the reaction mixture stirred at the elevated temperature under N_2 flow to remove water produced. Quantitative or near quantitative conversions were generally achieved within 1 to 4 h. Where further purification was required, the resultant products **5** were recrystallised from a minimum amount of isopropyl alcohol.

5a. > 99%, yield 96% (pale-yellow solid), m.p. 136–137 °C (lit. 135–136 °C [24]). ESI-MS, *m*/*z* 316.2 (calc. 316.2) [M + H]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ 1.22 (3H, t, CH_3), 2.32 (6H, s, CH_3), 3.64 (3H, s, *J* = 7.2 Hz, CH_3), 4.10 (2H, q, *J* = 7.2 Hz, OCH_2), 4.98 (1H, s, CH), 5.68 (1H, br s, NH) 7.09–7.29 (Ar-H).

5b. Conversion 61% (dark orange oil) (the product was not isolated due to the poor conversion measured; no recrystallisation was carried out).

5c. > 99%, yield 95% (pale-yellow solid), mp 159 °C (lit. 159 °C[14]).

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ 1.22 (3H, t, *J* = 7.2 Hz, CH_3), 2.36 (6H, s, CH_3), 3.63 (3H, s, CH_3), 4.18 (2H, q, *J* = 7.2 Hz, OCH_2), 5.08 (1H, s, CH), 5.91 (1H, br s, NH), 7.32—8.4 (Ar-H).

5d. Conversion > 99%, yield 94% (pale-yellow solid), mp 120–121 °C. ESI-MS, *m*/*z* 372.2 (calc. 372.1) [M + Na]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz, CH_3), 2.31 (3H, s, CH_3), 2.32 (3H, s, CH_3), 3.61 (3H, s, CH_3), 4.07 (2H, q, *J* = 7.2 Hz, OCH_3), 5.46 (1H, s, CH), 5.62 (1H, br s, NH), 7.04–7.33 (Ar-H).

5e. Conversion > 99%, yield 96% (white solid), mp 144–146 °C (lit. 145 °C[25]). ESI-MS, *m*/*z* 384.2 (calc. 384.1) [M + H]$^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ 1.18 (3H, t, *J* = 7.2 Hz, CH_3), 2.31 (6H, s, CH_3), 3.61 (3H, s, CH_3), 4.06 (2H, q, *J* = 7.2 Hz, OCH_2), 5.45 (1H, s, CH), 5.63 (1H, br s, NH), 7.04–7.33 (Ar-H).

5f. Conversion > 99%, yield 92% (pale yellow solid), mp 157–159 °C. ESI-MS, *m*/*z* 366.2 (calc. 366.2) [M + Na]$^+$.

^{1}H NMR, (300 MHz, 298 K, $CDCl_3$): δ 1.35 (9H, s, $OC(CH_3)_3$), 2.27 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.56 (3H, s, CH_3), 5.57 (1H, br s, NH), 5.74 (1H, s, CH),7.21–7.76 (Ar-H).

5g. Conversion 57% (orange oil) (the product was not isolated due to the poor conversion measured; no recrystallisation was carried out).

5h. Conversion 91%, yield 87% (pale yellow solid), mp 112–114 °C.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ 1.39 (9H, s, $OC(CH_3)_3$), 2.33 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.64 (3H, s, CH_3), 5.03 (1H, s, CH), 5.68 (1H, br s, NH), 7.38–8.18 (Ar-H).

5i. Conversion >99%, yield 91% (pale yellow solid). ESI-MS, *m*/*z* 400.2 (calc. 400.1) $[M + Na]^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ 1.40 (9H, s, $OC(CH_3)_3$), 2.31 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.64 (3H, s, CH_3), 4.96 (1H, s, CH), 5.74 (1H, br s, NH), 7.10–7.25 (Ar-H).

5j. Conversion >99% yield 99% (orange oil). This product was not recrystallised from isopropyl alcohol. Instead, the oil was washed with hexane at slightly elevated temperature (30 °C) for 20 minutes and the hexane decanted. The resultant oil was then washed three times with slightly alkaline Na_2CO_3 solution before drying and weighing. ESI-MS, *m*/*z* 412.2 (calc. 412.1) $[M + H]^+$.

^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ 2.33 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.64 (3H, s, CH_3), 5.29 (2H, s, OCH_3), 5.64 (1H, br s), 7.10--7.38 (Ar-H).

Acknowledgements

This work was supported by an Australian Research Council (ARC), Special Research Centre grant for the formation of the Centre for Green Chemistry, Monash University.

References

1 J. G. Gerber and A. S. Nies, in *The pharmacological basis of therapeutics*, ed. A. G. Gilman, T. W. Rall, A. S. Nies and P. Taylor, Pergamon Press, 8th edn., 1990, 784–813.
2 G. B. Zavoico, *Drug Market Dev. Newslett.*, 2000, http://www.pharmalicensing.com/features/disp/961691288_39523e988df12
3 *IMS Health report 'The Changing Face of Medicine'*, 2000, http://www.inpharm.com/intelligence/ims011200.html
4 A. Hantzsch, *Justus Liebigs Ann Chem.*, 1882, **1**, 215.
5 B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th edn., 1996, pp. 1166–1169.
6 F. Bossert, W. Elberfeld and W. Vater, *US Pat.*, 3644627, 1972.
7 P. B. Berntsson, S. A. I. Carlsson, J. O. Gaardner and B. R. Ljung, *US Pat.*, 4264611, 1981.
8 P. Naab, *Eur. Pat.*, 0319814, 1989; W. Teller, W. Koebernick, A. Haff, P. Naab and M. Press, *US Pat.*, 4600778, 1986.
9 R. Desai, D. A. Aguilar and M. Aslam, *World Pat.*, 9724326, 1997.
10 P. Naab, W. Lange and W. Teller, *US Pat.*, 4904789, 1990.
11 S. Hiroaki and H. Shizuo, *Eur. Pat.*, 0371492, 1990.
12 J. Auerbach, *US Pat.*, 5310917, 1994.
13 R. Alajarin, J. Jordan, J. Vaquero and J. Alvarez-Builla, *Synthesis*, 1995, 389.
14 A. Kakuiri and H. Ikawa, *Jpn. Pat.*, 07196612, 1995.
15 A. Gustavsson, A. Kallstrom and S. Palmer, *World Pat.*, 9725313, 1997; D. Pieraccioli, *Eur. Pat.*, 0370974, 1990.
16 K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; F. Toda, *Acc. Chem. Res.*, 1995, **28**, 480; G. Rothenberg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am. Chem. Soc.*, 2001, **123**, 8701.
17 The 'concentration' of components **1** and **3** is, in fact, inferred from inspection of the integrated areas of well resolved signals in the ^{1}H NMR spectra of the reaction mixtures.
18 *Crystal data* for **3g**: $C_{15}H_{17}NO_5$, $M_r = 291.30$, orthorhombic, space group $Pna2_1$, $a = 9.1435(2)$, $b = 27.8109(3)$, $c = 5.8488(10)$ Å, $V = 1487.3(3)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.098 mm^{-1}. Of 5454 reflections measured, 1978 were unique with 1450 $I > 2\sigma(I)$, R indices $[I > 2\sigma(I)]$, $R_1 = 0.0490$, $wR_2 = 0.0869$, GOF on $F^2 = 1.039$ for 194 refined parameters. CCDC reference number 167675. See http://www.rsc.org/suppdata/gc/b1/b106397a/ for crystallographic data in CIF or other electronic format.
19 M. E. Brown, in *Introduction to Thermal Analysis – Techniques and Applications*, Chapman and Hall, London and New York, 1988.
20 L. E. Hinkel, E. E. Ayling and W. H. Morgan, *J. Chem. Soc.*, 1931, **133**, 1835.
21 G. M. Sheldrick, SHELXS-97, University of Gottingen, 1990.
22 G. M. Sheldrick, SHELXL-97, University of Gottingen, 1997.
23 L. J. Barbour, X-Seed—a graphical interface to the SHELX program suite, University of Missouri, 1999.
24 A. M. Van Rhee, J. Jiang, N. Melman, M. E. Olah, G. L. Stiles and K. A. Jacobson, *J. Med. Chem.*, 1996, **39**, 2980.
25 P. B. Berntsson, S. A. I. Carlsson, J. O. Gaarder and B. R. Ljung, *Eur. Pat.*, 031801, 1981.

Simultaneous microwave and ultrasound irradiation: a rapid synthesis of hydrazides

Yanqing Peng and Gonghua Song*

Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai, 200237, China. E-mail: ghsong@ecust.edu.cn

Received 1st October 2001
First published as an Advance Article on the web 6th November 2001

Hydrazinolysis of esters is dramatically promoted by simultaneous microwave and ultrasound irradiation using an innovative and efficient reaction apparatus.

Introduction

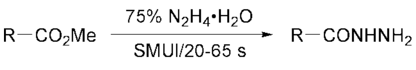
Enhancing the efficiency and maneuverability of organic synthesis constitutes one of the most exciting challenges to synthetic chemists. Much attention has been given to the applications of sonochemistry[1] and microwave dielectic heating[2] in organic synthesis because of the enhanced reaction rates, simplified manipulation and work-up, and higher purity of final products. Up to now, however, there are only a few reports in the literature that mentioned the acceleration of chemical processes by simultaneous microwave and ultrasound irradiation. These processes included esterification of propanol with acetic acid, condensation of urea,[3] esterification of stearic acid with butanol,[4] and sample preparation in chemical analysis.[5] It is inexplicable to us that the potential of this challenging, yet very promising technique has not yet been more systematacially investigated.

Hydrazides are important intermediates in organic synthesis, especially in the preparation of pharmaceuticals and agrochemicals. To date, a variety of procedures have been developed to prepare hydrazides. Acyl anhydrides and acid chlorides[6] both react rapidly with hydrazine to give hydrazides. However, acid chlorides and anhydrides are so reactive that it is difficult to stop the reaction short of diacylation. The most widely used method to prepare hydrazides is hydrazinolysis of the corresponding esters with hydrazine monohydrate.[7] Recently, Toda *et al.* reported the use of inclusion complexes of hydroquinone and hydrazine as an alternative of hydrazine monohydrate in solid state hydrazinolysis of esters.[8] Esters seldom produce significant amounts of diacylhydrazine, but less reactive esters may require inconveniently long reaction times and/or severe reaction conditions.

We report herein a dramatically improved method for the hydrazinolysis of esters under simultaneous microwave and ultrasound irradiation in the absence of organic solvents and other auxiliary agents such as surfactants (Scheme 1).

Results and discussion

The linchpin of this strategy is the construction of a practical apparatus. Chemat *et al.* employed decalin as an energy-transfer medium for ultrasound irradiation in their apparatus.[3,5] However, this design required the penetration of sonic energy through the media and walls of reaction vessel, resulting in inevitable losses of energy. Recently, we have developed a novel and efficient apparatus that is schematically illustrated in Fig. 1. Using proper protective techniques, our design enables the horn to be immersed directly in the reaction mixture. This minimizes the energy loss resulting from the transfer medium.



(SMUI: simultaneous microwave and ultrasond irradiation)

Scheme 1

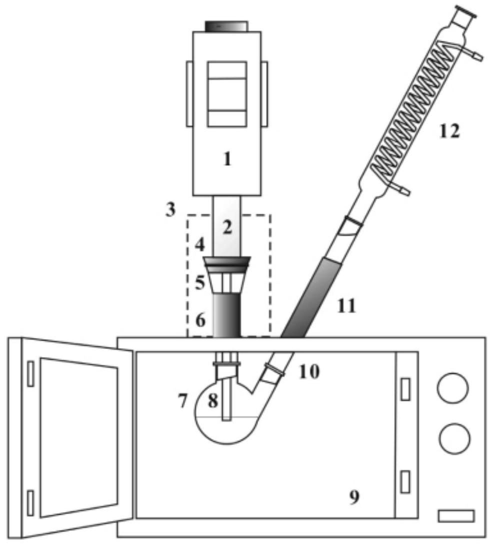


Fig. 1 Apparatus for microwave–ultrasound combined reactions: 1, transducer housing; 2, upper horn; 3, copper mesh screen; 4, rubber stopper; 5, adaptor; 6, port; 7, two-necked Pyrex flask; 8, detachable horn; 9, multimode cavity; 10, adaptor; 11, chock; 12, condenser.

Green Context

It is likely that the solution of many of the problems facing Green Chemistry will require an integration of techniques. In this paper we see a rare example of the repeated use of simultaneous microwave and ultrasound irradiation. This is applied to the hydrozinolysis of esters to prepare the widely used hydrazides. The method avoids organic solvents and other auxiliary agents. The enhancement in reaction rates through the use of the integrated technologies is remarkable and the authors attempt to explain this on the basis of enhanced heat and mass transfer. ***JHC***

DOI: 10.1039/b108878p

As a result, higher power utilization and acoustic intensity is realized.

Using the hydrazinolysis of methyl salicylate as a model system, we studied the reaction under different reaction conditions (Table 1). We first carried out the reaction without irradiation in a two-phase heterogeneous system under refluxing conditions. 73% yield of the desired product was obtained after 9 hours. We then studied the reaction time and product yields under ultrasound, microwave, and simultaneous microwave and ultrasound irradiation, respectively (Table 1). The results clearly show that simultaneous microwave and ultrasound irradiation achieved the best results both in terms of reaction time and yield.

Table 1 Hydrazinolysis of methyl salicylate using different methods

Run	Method	Time	Yield (%)[a]
1	Conventional reflux	9 h	73
2	Ultrasound (50 W) + reflux	1.5 h	79
3	Microwave (200 W)	18 min	80
4	SMUI (mw 200 W + us 50 W)	40 s	84

[a] Isolated yields.

Having completed the initial study described above, we then applied the microwave–ultrasound combination protocol to a variety of substrates. The results, summarized in Table 2, indicated the generality of the reaction for various esters. In all cases the reactions went to completion in very short times and gave good to excellent yields.

This dramatic acceleration effect may be attributed to a combination of enforced heat transfer due to microwave irradiation and intensive mass transfer at phase interfaces caused by sonication.

In many heterogeneous reactions, the rate-determining step is the mass transfer at the interface between two (or more) phases. With sonication, the liquid jet caused by cavitation propagates across the bubble towards the phase boundary at a velocity estimated at several hundreds of m s^{-1}, and violently hits the surface. The intense agitate leads to the mutual injection of droplets of one liquid into the other, resulting in the formation of fine emulsions.[9] These ultrasonically produced emulsions are smaller in size and more stable than those obtained conventionally and require little or no surfactant to maintain stability.

The principles of green chemistry dictate that chemical transformations should be designed to (a) minimize required energy input, either mechanical or thermal, thus minimizing the unavoidable and associated environmental impact of excessive energy consumption,[10] and (b) minimize the use of harmful organic solvents.[11] Simultaneous microwave and ultrasound irradiation achieved these goals by enhanced heat and mass transfer over conventional methods and by using aqueous media, thus eliminating any organic solvents or other auxiliary agents. In all respects, reactions performed under microwave–ultrasound irradiation can be regarded as environmentally friendly chemical processes.

Table 2 Microwave–ultrasound combined hydrazinolysis of various methyl esters

Entry	R	Time/s	Yield (%)[a]
1	Ph	30	81
2	4-ClC_6H_4	25	91
3	4-HOC_6H_4	65	83
4	4-MeC_6H_4	30	82
5	4-$MeOC_6H_4$	40	90
6	4-BrC_6H_4	25	84
7	2-FC_6H_4	20	85
8	2,4-$Cl_2C_6H_3$	20	94
9	Furyl	40	86
10	1-Naphthyl	40	79
11	$PhCH_2$	35	82
12	$C_{11}H_{23}$	20	86
13	$C_{17}H_{35}$	20	81

[a] All yields refer to isolated products which were characterized by mp data and IR spectral analysis.

In summary, an innovative and efficient protocol using simultaneous microwave and ultrasound irradiation has been developed for the first time for the synthesis of hydrazides from esters and hydrazine monohydrate. This method is simple, fast and environmentally friendly. The development of this combination technique opens an extremely promising new area in the field of organic synthesis. The extension of this technique to other reaction systems is currently under investigation in our laboratory.

Experimental

The microwave unit consists of microwave source, waveguide, circulator, water load, power detector and multimode cavity. Microwave power generated with magnetron (operating frequency: 2450 MHz) is regulated from 0–1000 W by an fully variable power supply. The ultrasound unit consists of an energy source (stepless regulation, 0–100 W), transducer, and probe (0–100 W, 20 ± 1 kHz, type JHN-M-1). It is essential that great precautions are taken when fixing the copper mesh screen. The screen must be fastened tightly on the detachable horn and port with a fastener and checked for radiation leakage with a microwave leakage detector, otherwise the microwaves could leak from the gap between the screen and multimode cavity and cause physiological injury.

The reaction products were all known compounds and identified by comparison of their melting point (uncorrected) and IR spectra (recorded on a Nicolet Nexus 470 spectrophotometer in KBr) with those described in the literature.

Typical procedure

A mixture of ester (20 mmol) and 75% hydrazine monohydrate (10 mL) was introduced into a 25 mL two-necked Pyrex flask. The tip of detachable horn should be immersed just under the liquid surface in order to obtain optimal sonication. The ultrasound and microwave source are switched on successively (power level: ultrasound 50 W, microwave 150 W). The mixture was irradiated simultaneously by microwaves and ultrasound for a specified period. On completion of the reaction (monitored by TLC), the mixture was concentrated under reduced pressure and then cooled to room temperature. The resulting crude product was collected and recrystallized from aqueous ethanol.

References

1 For selected reviews, see: J. P. Lorimer and T. J. Mason, *Chem. Soc. Rev.*, 1987, **16**, 239; J. Lindley and T. J. Mason, *Chem. Soc. Rev.*, 1987, **16**, 275; K. S. Suslick, *Sci. Am.*, 1989, **260**, 80; C. Einhorn, J. Einhorn and J. Luche, *Synthesis*, 1989, 787; R. L. Hunicke, *Ultrasonics*, 1990, **28**, 291; K. S. Suslick, *Science*, 1990, **247**, 1439; J. Berlan and T. J. Mason, *Ultrasonics*, 1992, **30**, 203; P. D. Martin, *Chem. Ind. (London)*, 1993, 233; N. Serpone and P. Colarusso, *Res. Chem. Intermed.*, 1994, **20**, 635; T. J. Mason, *Chem. Soc. Rev.*, 1997, **26**, 443; P. Cintas and J.-L. Luche, *Green Chem.*, 1999, **1**, 115.

2 For selected reviews, see: D. M. P. Mingos and D. R. Baghurst, *Chem. Soc. Rev.*, 1991, **20**, 1; R. A. Abramovitch, *Org. Prep. Proc. Int.*, 1991, **23**, 683; A. Loupy, B. Gram and J. Sansoulet, *New J. Chem.*, 1992, **16**, 233; G. Majetich and R. Hicks, *Res. Chem. Intermed.*, 1994, **20**, 61; D. M. P. Mingos, *Chem. Ind. (London)*, 1994, 596; S. Caddick, *Tetrahedron*, 1995, **51**, 10403; C. T. Ponne and P. V. Bartels, *Radiat. Phys. Chem.*, 1995, **45**, 591; C. R. Strauss and R. W.

Trainor, *Aust. J. Chem.*, 1995, **48**, 1665; K. C. Westway and R. N. Gedye, *J. Microwave Power Electromag. Energy*, 1995, **30**, 219; D. A. C. Stuerga and P. Gaillard, *J. Microwave Power Electromag. Energy*, 1996, **31**, 87; A. K. Bose, B. K. Banic, N. Lavlinskaia, M. Jayaraman and M. S. Manhas, *CHEMTECH*, 1997, **9**, 18; S. A. Galema, *Chem. Soc. Rev.*, 1997, **26**, 233; A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathé, *Synthesis*, 1998, 1213; R. S. Varma, *Green Chem.*, 1999, **1**, 43; C. R. Strauss, *Aust. J. Chem.*, 1999, **52**, 83; R. S. Varma, *Pure Appl. Chem.*, 2001, **73**, 193.

3 F. Chemat, M. Poux, J.-L. Di Martino and J. Berlan, *J. Microwave Power Electromag. Energy*, 1996, **31**, 19.

4 F. Chemat, M. Poux and S. A. Galema, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2371.

5 A. Lagha, S. Chemat, P. V. Bartels and F. Chemat, *Analusis*, 1999, **27**, 452.

6 C. Naegeli and G. Stefanovich, *Helv. Chim. Acta*, 1928, **11**, 609.

7 (*a*) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, *J. Am. Chem. Soc.*, 1953, **75**, 1933; (*b*) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 1964, **86**, 418.

8 F. Toda, S. Hyoda, K. Okada and K. Hirotsu, *J. Chem. Soc., Chem. Commun.*, 1995, 1531.

9 J.-L. Luche, *Synthetic Organic Sonochemistry*, Plenum Press, New York, 1998, p. 109.

10 P. Tundo, P. Anastas, D. S. Black, J. Breen, T. Collins, S. Memoil, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem.*, 2000, **72**, 1207.

11 J. H. Clark, *Green Chem.*, 1999, **1**, 1.

Zeolite-catalyzed cyclocondensation reaction for the selective synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones†

V. Radha Rani, N. Srinivas, M. Radha Kishan, S. J. Kulkarni* and K. V. Raghavan

Catalysis Division, Indian Institute of Chemical Technology, Hyderabad-7, India.
E-mail: sjkulkarni@iict.ap.nic.in

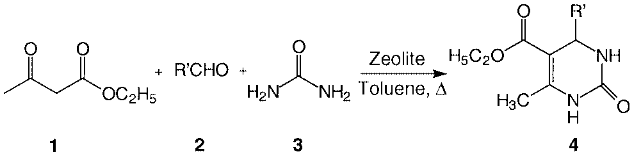
Received 22nd August 2001
First published as an Advance Article on the web 9th November 2001

A zeolite catalyzed, single step and environmentally friendly process for the synthesis of dihydropyrimidinones, a pharmacologically important class of compounds, is reported. Reusability of the catalyst and the ease of separation of pure product, selectively and in high yields in comparison to the classical Biginelli reaction, are a few of the unique features of this process.

Introduction

The growing concern for the environment demands the development of eco-friendly and economic processes wherein even hazardous byproducts are not desirable. Zeolites, due to their acidic and shape-selective nature, have been found to be a suitable replacement for various homogeneous acid catalysts.

The dihydropyrimidinone core and its derivatives form an important class of compounds, as it is present in a large family of natural products with broad biological activities. They generally possess intriguing therapeutic and pharmacological properties.[1] Several of their functionalised derivatives are used as calcium channel modulators and antihypertensive α_{1a}-antagonists.[2] Attempts to synthesize these moieties by the Biginelli reaction over various homogeneous catalysts such as $BF_3 \cdot OEt_2$,[3] polyphosphate esters[4] or lanthanum chloride heptahydrate,[5] have been reported. Heterogeneous catalysts such as KSF (montmorillonite)[6] have also been employed but their reusability is limited to a few runs only. Here, we report a clean and single-step liquid phase cyclocondensation reaction of aromatic aldehydes, β-ketoesters and urea in toluene (Scheme 1) over zeolites with high yields and selectivity.



Scheme 1

Results and discussion

The choice of aldehyde was dictated by the ability to promote its condensation with **3** to form an intermediate which is stabilized by the framework Al in zeolites, which in turn cyclizes with **1** to form **4** over zeolites (Scheme 2). The synthesis of these moieties is detailed in Table 1, using 0.5 g of various zeolites with varying acidity and surface area. The catalysts were recycled for five runs without significant loss of activity. The maximum yield of the product was obtained over HY catalyst showing that high acidity is required to facilitate the cyclocondensation reaction. The XRD patterns before and after the reaction revealed that the zeolite retained its crystallinity throughout. Thus, the catalyst can be reused. In addition to its

Table 1 Synthesis of 5-alkoxy carbonyl-4-phenyl-3,4-dihydropyrimidinones

Entry	Catalyst	Yield (%)	Ammonia uptake/mmol g^{-1}	BET surface area/m^2 g^{-1}
1	HZSM-5	21	1.73	310.0
2	HY	80	2.82	490.0
3	MCM-41	38	1.20	901.0

Reagents and conditions: benzaldehyde–ethyl acetoacetate–urea (molar ratio = 1 : 0.8 : 1); catalyst wt. = 0.5 g; solvent: toluene (20 ml); reflux.

Table 2 Dihydropyrimidinones synthesized using HY catalyst

Entry	R′	Yield (%)
1	H	64
2	CH_3	42
3	C_6H_5	80
4	$4\text{-}CH_3OC_6H_4$	71
5	$4\text{-}HOC_6H_4$	76
6	$2,4\text{-}Cl_2C_6H_3$	74
7	$4\text{-}Me_2NC_6H_4$	63
8	$2,4,6\text{-}(CH_3O)_3C_6H_2$	59
9	$4\text{-}O_2NC_6H_4$	68

Reagents and conditions: aldehyde–ethyl acetoacetate–urea (molar ratio = 1 : 0.8 : 1); catalyst wt. = 0.5 g; solvent: toluene (20 ml); reflux.

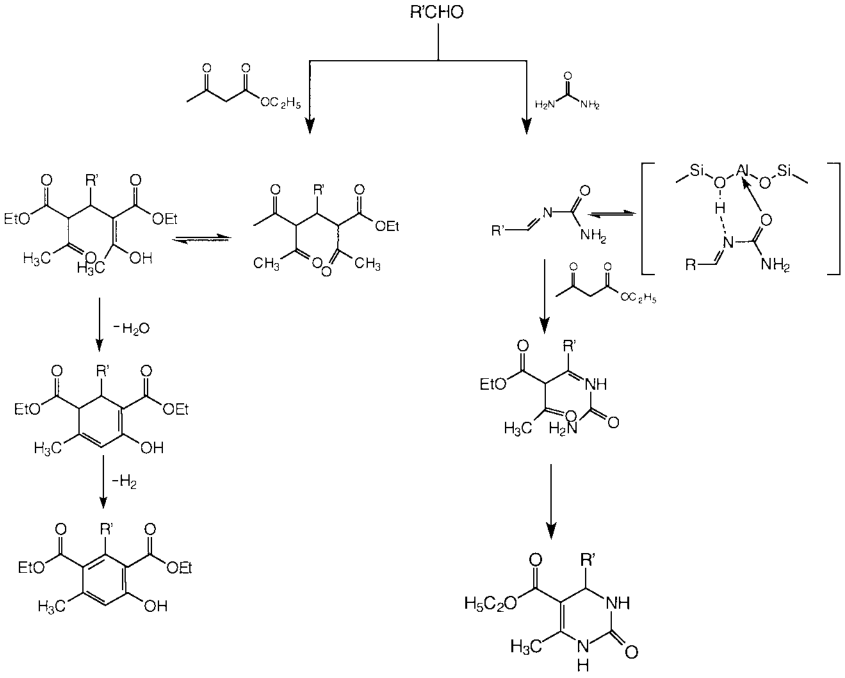
Green Context

Catalysis is one of the most important technologies for improving the environmental performance of chemical reactions. Heterogeneous catalysis, while commonly used in vapour phase reactions, has been under-utilised in liquid phase organic synthesis although it offers the very important green chemistry advantage of simplifying the separation stage and removing the need for an aqueous quench to remove the catalyst. Zeolites are the most established of heterogeneous catalysts and here we see their successful application in an important organic reaction. The synthesis of dihydropyrimidinones has been achieved in a single-step liquid phase cyclocondensation reaction of aromatic aldehydes, β-ketoesters and urea in toluene using zeolite catalysts. Product yields are generally good and the catalyst can be reused several times. *JHC*

---

† IICT Communication No. 4737.

DOI: 10.1039/b107612b



Scheme 2 Possible mechanism for the synthesis of dihydropyrimidinones.

simplicity, this catalyst resulted in higher yields for aliphatic aldehydes (Table 2, entries 1 and 2) which normally show extremely poor yields in the Biginelli reaction.[7] The efficiency of the Biginelli reaction is substrate dependent with the use of more highly functionalized or sterically encumbered groups leading to severely reduced yields. While a small amount of catalyst was sufficient for to obtain high yields, the amount of β-ketoesters used was lower than required according to the stoichometry, in order to reduce the possibility of itself undergoing intracondensation.

Conclusion

We have developed an eco-friendly method for the direct synthesis of pyrimidinones over zeolite catalysts with good yields and selectivity where the catalyst can be re-used several times.

Experimental

The composition of anhydrous HY (Si/Al = 2.43) zeolite used is $H_{56}(SiO_2)_{136}(AlO_2)_{56}$ and was obtained from PQ Corporation, USA. The composition of anhydrous HZSM-5 (Si/Al = 15) is $H_6(SiO_2)_{90}(AlO_2)_6$ and was obtained from Conteka, Sweden. The composition of MCM-41 is $Al_2O_3 : 31.01\ SiO_2 : 2.2\ (surfactant)_2O : 3.16\ (TEA)_2O : 1.89\ Na_2O : 615\ H_2O$ and was synthesized according to the procedure given in ref. 8 to an aqueous solution of aluminium isopropoxide (0.38 g) was added an aqueous solution of sodium hydroxide (0.3 g) in a 50 ml beaker and the solution allowed to stir at 80 °C until a clear solution was formed. Then 9.4 ml of tetraethylammonium hydroxide (TEAOH) and Ludox colloidal silica (9.26 g) were added dropwise while stirring at room temperature. Then hexadecyltrimethylammonium bromide (10.55 g) was added slowly to the above solution. The pH of the mixture was maintained at 11.0–11.5. Finally, the gel mixture was transferred into an autoclave and heated at 100 °C for 24 h. The solid product was recovered by filtration, washed with deionized water and dried in air. The as-synthesized samples were calcined at 500 °C in air.

The synthesis of 4-phenyl dihydropyrimidinone is described as a representative example: 10 mmol (1.51 g) of benzaldehyde, 8 mmol (1.30 g) of ethyl acetoacetate and 10 mmol (0.6 g) of urea were dissolved in 20 ml of toluene, to which 0.5 g of calcined and dried zeolite catalyst was added. Reaction was performed at reflux for 12 h with monitoring by TLC. Then the reaction mixture was filtered and washed repeatedly with hot methanol and the pure zeolite catalyst recovered. The filtrate was concentrated *in vacuo* and the pure yellow crystalline solid product recovered. Its identity was confirmed by mass spectrometry, NMR and its melting point.

Acknowledgements

V. R. R., N. S. and M. R. K. thank the CSIR, New Delhi for the award of fellowships.

References

1 G. C. Rovnyak, S. D. Kimall, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang and S. Moreland, *J. Med. Chem.*, 1995, **38**, 119; K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougouta, J. Schwartz, K. M. Smillie and M. F. Malley, *J. Med. Chem.*, 1990, **33**, 262; H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda, T. Ishihara, K. Funahashi, F. Satah, M. Morita and T. Noguchi, *J. Med. Chem.*, 1989, **32**, 2399.

2 J. J. Baldwin, D. A. Claremon and D. E. McClure, *US Pat.* 4 609 494, 1986; J. J. Baldwin, S. M. Ptizenberger and D. E. McClure, *US Pat.* 4 675 321, 1987; K. S. Atwal, *US Pat.* 4 684 655, 1987; K. S. Atwal, *US Pat.* 4 684 656, 1987.

3 E. H. Hu, D. R. Sidler and U. H. Dolling, *J. Org. Chem.*, 1998, **63**, 3454.

4 C. O. Kappe and S. F. Falsone, *Synlett*, 1998, 718.

5 J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.*, 2000, **41**, 9075.

6 F. Bigi, S. Carloni, B. Fraullanti, R. Maggi and G. Sarton, *Tetrahedron Lett.*,1999, **40**, 3465.

7 P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360; D. J. Brown, *The Pyrimidines*, Wiley, New York, 1962, ch. 12, p. 440; for a review of the Biginelli reaction, see: C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937.

8 C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli and J. S. Beck, *Nature*, 1992, **359**, 710.

In situ infrared spectroscopic studies of the Friedel–Crafts acetylation of benzene in ionic liquids using $AlCl_3$ and $FeCl_3$

Szilárd Csihony, Hasan Mehdi and István T. Horváth*

Department of Chemical Technology and Environmental Chemistry, Eötvös University,
Pázmány Péter sétány 1/A, H-1117 Budapest, Hungary. E-mail: istvan.t.horvath@hit-team.net

Received 20th August 2001
First published as an Advance Article on the web 19th November 2001

In situ infrared spectroscopic studies have revealed that the mechanism of the Friedel–Crafts acetylation of benzene is exactly the same in ionic liquids as in 1,2-dichloroethane. The reaction of acetyl chloride with benzene in the presence of MCl_3 (M = Al or Fe) in the ionic liquid 1-butyl-3-methylimidazolium chloride, ([bmim]Cl), leads to the formation of several key intermediates including the MCl_3 adducts of the acetyl chloride, the acetylium ion $[CH_3CO]^+[MCl_4]^-$, and the final product, the MCl_3 adduct of acetophenone.

Introduction

One of the key objectives of green chemistry is the elimination or replacement of hazardous and volatile organic solvents in industrial processes.[1] Since the development of a solvent free process could be limited by the intrinsic nature of the chemistry under consideration, a wide range of alternative solvents with significantly different solvent properties have been utilized including water,[2] alcohols,[3] ionic[4] and fluorous[5] media as well as supercritical liquids.[6]

Friedel–Crafts acylation of aromatic compounds has been an important reaction in the production of pharmaceuticals and fine chemicals for more than a century.[7] Various methods have been used to study the possible mechanisms[8] including *in situ* IR[9] and NMR.[10] Some of the key intermediates have been prepared[9c,d] and structurally characterized.[11] Since most of the conventional industrial processes are performed in volatile and hazardous halogenated solvents, their replacement with ionic liquids could considerably lower the environmental risks involved. Although various Friedel–Crafts reactions have already been performed using ionic liquids,[12,13] no detailed mechanistic study has, as yet, been reported. We have now established that the mechanism of the Friedel–Crafts acetylation of benzene in the presence of MCl_3 (M = Al or Fe) is exactly the same in 1-butyl-3-methylimidazolium chloride, ([bmim]Cl), as in 1,2-dichloroethane.

Results and discussion

In order to compare the mechanism of the Friedel–Crafts acetylation of benzene with acetyl chloride in the presence of MCl_3 (M = Al or Fe) in ionic liquids to that in 1,2-dichloroethane, we have used two different ionic liquids prepared from [bmim]Cl and $AlCl_3$ or $FeCl_3$, respectively. It has been established that the addition of 2 equivalents of $AlCl_3$ to [bmim]Cl leads to an equilibrium mixture shown in eqn. (1).[14]

$$[\mathrm{bmim}]\mathrm{Cl} + 2\ \mathrm{AlCl_3} \rightleftharpoons [\mathrm{bmim}]^+[\mathrm{AlCl_4}]^- + \mathrm{AlCl_3} \rightleftharpoons [\mathrm{bmim}]^+[\mathrm{Al_2Cl_7}]^- \qquad (1)$$

Preliminary Mössbauer measurements indicate that the addition of $FeCl_3$ to [bmim]Cl leads to an equilibrium mixture that could contain solid $FeCl_3$, Fe_2Cl_6, [bmim][$FeCl_4$] and [bmim]-[Fe_2Cl_7], depending on the molar ratio of [bmim]Cl and $FeCl_3$.[15]

When the reaction of acetyl chloride (8.4 mmol) with benzene (9.2 mmol) in the presence of $AlCl_3$ (16.8 mmol) in [bmim]Cl (8.4 mmol) was followed by *in situ* IR at room temperature, only the rapid disappearance of the acetyl chloride and the proportional appearance of the $AlCl_3$ adduct of acetophenone could be observed. Similar results were obtained when [bmim]Cl was replaced with 1,2-dichloroethane (5 mL) as solvent using the same molar ratio of acetyl chloride and $AlCl_3$. It should be emphasized, that the addition of acetyl chloride to the heterogeneous mixture of $AlCl_3$ and 1,2-dichloroethane resulted in the dissolution of all solid $AlCl_3$ within 1 min at room temperature to form a clear pale yellow solution. The absence of any intermediates suggests that after the activation of acetyl chloride all the following reactions have lower activation energies. In order to observe key intermediates, we first added acetyl chloride (39.7 mmol) to a solution of $AlCl_3$ (39.7 mmol) and [bmim]Cl (19.8 mmol) in the next experiment, and only after 2 h was benzene (43.6 mmol) introduced. A similar experiment was also performed by replacing [bmim]Cl with 1,2-dichloroethane (10 mL) as solvent. The *in situ* IR spectra in [bmim]Cl (Fig. 1) and in 1,2-dichloroethane (Fig. 2) show strikingly similar spectral features in the carbonyl region.

Green Context

The substitution of environmentally threatening volatile organic solvents is at the heart of green chemistry. The alternative reaction media that are currently attracting most scientific interest include ionic and fluorous liquids, supercritical CO_2 and water. These solvents are however, very different to traditional organic solvents and it is an enormous and risky assumption to think of such solvents simply as substitutes. It is very important that where possible we study the intermediates produced in such solvents during important organic reactions. Friedel–Crafts reactions remain a great challenge for green chemistry—but can we replace a system such as $AlCl_3$–CH_2Cl_2 with say, an aluminium-rich ionic liquid without dramatically changing the key intermediates and hence the reaction pathway? Here we see the use of the powerful technique *in situ* IR spectroscopy, to determine the identity of the intermediates during a typical Friedel–Crafts acetylation reaction. Remarkably the same substrate–catalyst and product–catalyst complexes are produced, and it does seem as though the mechanism of this vital reaction is preserved even through such a fundamental change to the auxilaries. *JHC*

DOI: 10.1039/b107515m

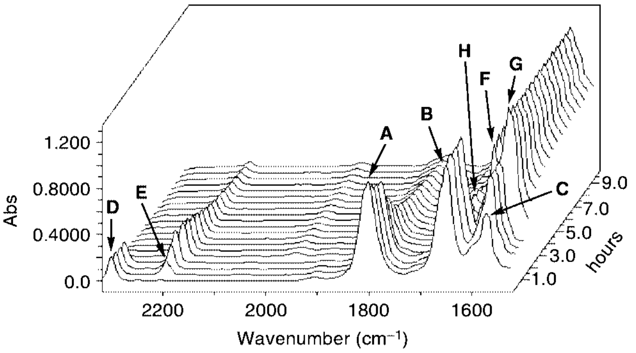


Fig. 1 *In situ* IR spectra of the Friedel–Crafts acetylation of benzene with acetyl chloride in the presence of $AlCl_3$ in [bmim]Cl. Benzene was added after the fourth spectrum was collected.

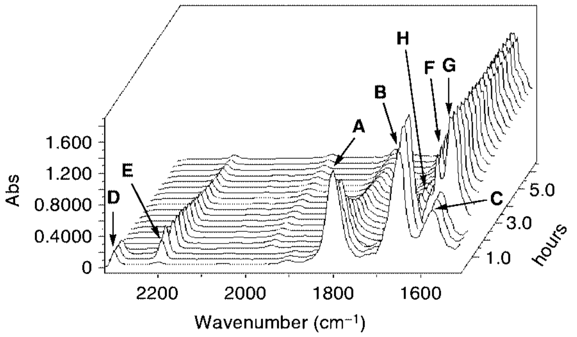


Fig. 2 *In situ* IR spectra of the Friedel–Crafts acetylation of benzene with acetyl chloride in the presence of $AlCl_3$ in 1,2-dichloroethane. Benzene was added after the third spectrum was collected.

Careful analysis of these spectra reveals that immediately after the addition of acetyl chloride, indicated by the strong band at 1800 cm^{-1} (A), three new bands appeared at 2300 cm^{-1} (D), 1644 cm^{-1} (B) and 1571 cm^{-1} (C). While band D is due to the acetylium ion $[CH_3CO]^+[AlCl_4]^-$,[9a,11a,16] bands B and C are assigned to $CH_3CClO \rightarrow AlCl_3$[9a,b,17] and the 1:2 complex of acetyl chloride and $AlCl_3$, respectively. The structure of the latter could either be $CH_3CClO \rightarrow 2AlCl_3$[17] or $CH_3CClO \rightarrow Al_2Cl_6$.[18] In the next 2 h another new band appeared at 2200 cm^{-1} (E) at a much slower rate. This band has been observed before in similar systems and was assigned to $[(CH_3CO)_2CHCO]^+[AlCl_4]^-$ formed *via* the trimerization of the acetylium ion.[9d,e] After the addition of benzene, bands B, C and D disappeared immediately, the bands A and E decreased slowly, and the bands assigned[19] to the $AlCl_3$ adduct of acetophenone at 1586 cm^{-1} (F) and 1559 cm^{-1} (G) appeared proportionally to the disappearance of band A. It should be noted, that after the disappearance of band B, another band was observable at 1636 cm^{-1} (H), which showed a similar time dependence to that of band E. This was confirmed by monitoring the reaction using a five-fold excess of acetyl chloride (200 mmol) in the absence of benzene in 1,2-dichloroethane (Fig. 3). The intensity of these two bands increased proportionally and remained constant after 14 h. Therefore, bands E and H are assigned to $[(CH_3CO)_2CHCO]^+[AlCl_4]^-$.[9d,e] It should be also noted, that in the presence of excess acetyl chloride, the band at 1571 cm^{-1} (C), assigned to the complex of acetyl chloride and two $AlCl_3$, appeared at a much slower rate than the band of $CH_3CClO \rightarrow AlCl_3$ at 1644 cm^{-1} (B), as expected.

The reaction of acetyl chloride and benzene in the presence of $FeCl_3$ in [bmim]Cl proceeds through similar intermediates to that of $AlCl_3$ and the spectral features in [bmim]Cl are exactly the same as that of in 1,2-dichloroethane. Thus, when acetyl chloride (24 mmol) was added to a solution of $FeCl_3$ (25 mmol) and [bmim]Cl (12 mmol) at room temperature, three new peaks appeared immediately at 2292 cm^{-1} (D), 1890 cm^{-1} (B) and 1675 cm^{-1} (C) (Fig. 4). Bands D and C are assigned to the acetylium ion $[CH_3CO]^+[FeCl_4]^-$ and the $FeCl_3$ adduct of acetyl chloride, respectively. In the next 30 min two new bands appeared at 2196 cm^{-1} (E) and 1660 cm^{-1} (H) at a much slower rate, assigned to $[(CH_3CO)_2CHCO]^+[FeCl_4]^-$. After the addition of benzene, bands A, B, C, D and E disappeared and the bands assigned to the $FeCl_3$ adduct of acetophenone at 1598 cm^{-1} (F) and 1521 cm^{-1} (G) appeared immediately, indicating a very fast acetylation reaction. The origin of band B is not clear at this time. Since its position at 1890 cm^{-1} is 90 cm^{-1} higher than that of free acetyl chloride, it certainly cannot be assigned to an $FeCl_3$ adduct of acetyl chloride.

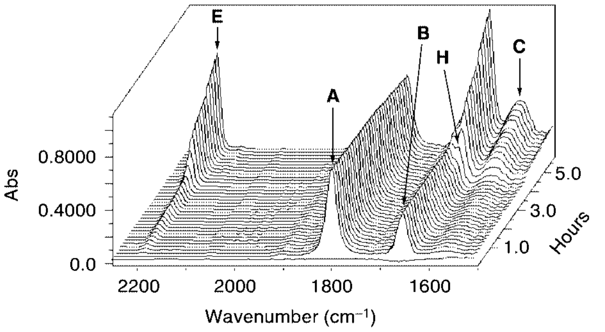


Fig. 3 *In situ* IR spectra of the reaction of acetyl chloride with $AlCl_3$ in 1,2-dichloroethane.

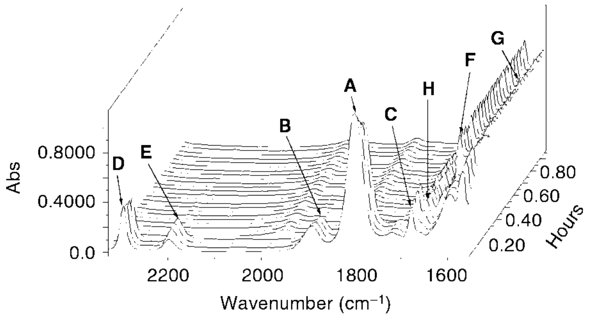
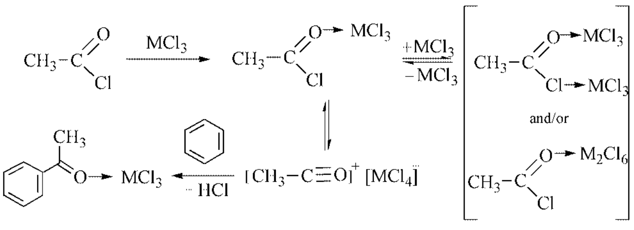


Fig. 4 *In situ* IR spectra of the Friedel-Crafts acetylation of benzene with acetyl chloride in the presence of $FeCl_3$ in [bmim]Cl. Benzene was added after the fourth spectrum was collected.

Concerning the overall reaction mechanism, our results indicate that the reaction starts with the activation of the acetyl chloride by the Lewis acids MCl_3 (M = Al or Fe) to form various adducts of acetyl chloride with MCl_3 (Scheme 1). These complexes are in rapid equilibrium with the acetylium ion $[CH_3CO]^+[MCl_4]^-$, which is in turn, attacks benzene leading to the MCl_3 adduct of acetophenone, the final product of the reaction, and HCl. It should be noted that in the absence of benzene the trimerization of the acetylium ion could result in formation of $[(CH_3CO)_2CHCO]^+[MCl_4]^-$ in a multi-step reaction.



Scheme 1 Proposed mechanism of the Friedel–Crafts acetylation of benzene with acetyl chloride in the presence of MCl_3 (M = Al, Fe).

In conclusion, we have confirmed that the acetylium cation $[CH_3CO]^+[MCl_4]^-$ (M = Al or Fe) is the key intermediate in the Friedel–Crafts acetylation reactions of benzene in ionic liquids. The most important result of our study is the fact that the replacement of a traditional halogenated solvent with ionic liquids did not alter the mechanism of the Friedel–Crafts acetylation reaction. This information will certainly help to design green catalysts operating in ionic liquids or other alternative media.

Experimental

All *in situ* infrared spectroscopic experiments were performed in standard glassware under N_2 using a ReactIR 1000 spectrometer (Applied Systems Inc, a Mettler–Toledo Company: www.asirxn.com). All chemicals were obtained from commercial sources: $AlCl_3$ (Carlo Erba Reagenti), $FeCl_3$ (Merck), acetyl chloride (Aldrich), 1-cholorobutane (Aldrich), 1,2-dichloroethane (Aldrich), 1-methylimidazole (Aldrich), and benzene (Reanal). The ionic liquid 1-butyl-3-methylimidazolium chloride was prepared by the method of Seddon (The Queen's University of Belfast, Northern Ireland): a 100 ml three necked round-bottomed flask was charged with 1-methylimidazole (22 ml, 276 mmol freshly distilled from CaH_2) and 1-cholorobutane (33 ml, 287 mmol) and heated to 75 °C for 48 h under N_2. The excess of 1-chlorobutane was removed *in vacuo* at 80 °C. The pale yellow ionic liquid solidified at room temperature forming a white solid (99% isolated yield). The ionic liquids were prared *in situ* from MCl_3 (M = Al, Fe) and [bmim]Cl under N_2.

Acknowledgement

This work was partially supported by the Hungarian National Scientific Research Fund (OTKA-T032850) and Exxon Mobil Research and Engineering Company, Annandale, NJ, USA. The donation of the ReactIR 1000 instrument by Applied Systems Inc, a Mettler–Toledo Company is greatly appreciated. We also thank Professor K. Seddon and Dr J. Holbrey, The Queen's University of Belfast, Northern Ireland, for providing the synthetic procedure for 1-butyl-3-methyl-imidazolium chloride.

References

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

2 B. Cornils and W. A. Herrmann, *Aqueous-phase Organometallic catalysis*, Wiley-VCH, Weinheim, Germany, 1998.

3 W. Keim, *Chem. Ing. Technal.*, 1984, **56**, 850.

4 T. Welton, *Chem. Rev.*, 1999, **99**, 2071; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772.

5 I. T. Horváth, *Acc. Chem. Res.*, 1998, **31**, 641.

6 P. G. Jessop and W. Leitner, *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH, Weinheim, Germany, 1999.

7 C. Friedel and J. M. Crafts, *Bull. Soc. Chim. Fr.*, 1877, **27**, 482; C. Friedel and J. M. Crafts, *Bull. Soc. Chim. Fr.*, 1877, **27**, 530.

8 G. A. Olah, *Friedel–Crafts and Related Reactions, Vol. III–IV*, Wiley-Interscience, New York, USA, 1964; G. A. Olah, *Friedel–Crafts Chemistry*, Wiley-Interscience, New York, USA, 1973.

9 (*a*) B. P. Susz and J. J. Wuhrmann, *Helv. Chim. Acta*, 1957, **40**, 971; (*b*) D. Cook, *Can. J. Chem.*, 1959, **37**, 48; (*c*) D. Cassimatis, J. P. Bonnin and T. Thephanides, *Can. J. Chem.*, 1970, **48**, 3860; (*d*) A. Germain, A. Commeyras and A. Casadevall, *Chem. Commun.*, 1971, 633; (*e*) A. Germain, A. Commeyras and A. Casadevall, *Bull. Soc. Chim. Fr.*, 1972, **8**, 3177.

10 G. A. Olah, S. J. Kuhn, S. H. Flood and B. A. Hardie, *J. Am. Chem. Soc.*, 1964, **86**, 2203; G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, 1969, **91**, 5801; L. K. Tan and S. Brownstein, *J. Org. Chem.*, 1983, **48**, 302; F. Bigi, G. Casnati, G. Sartori and G. Predieri, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1319.

11 (*a*) F. P. Boer, *J. Am. Chem. Soc.*, 1968, **94**, 6706; (*b*) B. von Bernard and R. Weiss, *Angew. Chem.*, 1974, **86**, 12.

12 J. A. Boon, J. A. Levisky, J. L. Pflug and J. S. Wilkes, *J. Org. Chem.*, 1986, **51**, 480.

13 C. J. Adams, M. J. Earle, G. Roberts and K. R. Seddon, *J. Chem. Soc., Chem. Commun.*, 1998, 2097; A. Stark, B. L. MacLean and R. D. Singer, *J. Chem. Soc., Dalton Trans.*, 1999, 63; M. H. Valkenberg, C. DeCastro and W. F. Hölderich, *Appl. Catal. A: General*, 2001, **215**, 185.

14 S. Tait and R. A. Osteryoung, *Inorg. Chem.*, 1984, 23, 4352; K. M. Dieter, C. J. Dymek, Jr., N. E. Heimer, J. W. Rovang and J. S. Wilkes, *J. Am. Chem. Soc.*, 1988, **110**, 2722.

15 H. Mehdi, Z. Homonnay and I. T. Horváth, unpublished results.

16 (*a*) G. A. Olah, S. J. Kuhn, W. S. Tölgyesi and E. B. Baker, *J. Am. Chem. Soc.*, 1962, **84**, 2733; (*b*) G. A. Olah, A. Germain and A. M. White, in *Carbonium Ions*, ed. G. A. Olah and P. v. R. Schleyer, Wiley-Interscience, New York, USA, 1976, pp. 2049–2133.

17 (*a*) R. Corriu, M. Dore and R. Thomassin, *Tetrahedron*, 1971, **27**, 5601; (*b*) R. Corriu, M. Dore and R. Thomassin, *Tetrahedron*, 1971, **27**, 5819; (*c*) B. Glavincevski and S. Brownstein, *J. Org. Chem.*, 1982, **47**, 1005; (*d*) J.-M. Le Carpentier and R. Weiss, *Acta Crystallogr., Sect. B*, 1972, **28**, 1437.

18 I. S. Akhrem, A. V. Orlinkov, V. I. Bakhmutov, P. V. Petrovskii, T. I. Pekhk, E. T. Lippmaa and M. E. Vol'pin, *Dokl. Akad. Nauk. Ser. Khim.*, 1985, **284**, 627; M. E. Vol'pin, I. Akhrem and A. Orlinkov, *New J. Chem.*, 1989, **13**, 771.

19 B. P. Susz and I. Cooke, *Helv. Chim. Acta*, 1954, **37**, 1273.

Water mediated uncatalyzed facile synthesis of ylidenenitriles of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde

Rajkumar V. Hangarge,[a] Sanjay A. Sonwane,[a] Dilip V. Jarikote[b] and Murlidhar S. Shingare*[a]

[a] *Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431 004 India. E-mail: msshingare11@rediffmail.com*
[b] *OCT Division, National Chemical Laboratory, Pune-8, India*

Received 30th July 2001
First published as an Advance Article on the web 13th November 2001

A simple, efficient and environment ecofriendly route has been developed for the synthesis of ylidenenitriles of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde by the condensation of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde with active methylene compounds *viz.* malononitrile, cyanoacetic acid and cyanoacetamide in distilled water without catalyst at 90 °C for 1–2 h with quantitative yields and higher selectivity.

Introduction

The Knoevenagel condensation is one of the most important, useful and widely employed methods for carbon–carbon bond formation in organic reactions.[1] Treating carbonyl compounds with active methylene compounds in the presence of acids or bases in organic solvents effects Knoevenagel condensation. Ylidenenitriles have increasing applications[2] in industry, medicine, agriculture and biological sciences, and are precursors to heterocycles.[3] The condensation[4–10] reactions of 4-oxo-(4H)-1-benzopyran-3-carbaldehyde with compounds containing active methylene groups are known. These condensation reactions in organic solvents require acid or base catalyst and prolonged heating. With present growing concern about controlling important, and protecting future resources, design of routes having environmentally benign characteristics have attracted considerable interest in organic synthesis.

Results and discussion

In continuation of our work on 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde,[11–14] we were prompted to investigate a recent route of organic synthesis using water as solvent in lieu of organic solvents. Here we report an uncatalyzed Knoevenagel condensation reaction of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde with malononitrile, cyanoacetic acid and cyanoacetamide in distilled water. The earlier reports reveal that the condensation of aldehydes with cyanoacetic acid gave the decarboxylated product,[15] but in our proposed method decarboxylation does not occur, as the reactions were carried out in neutral medium. The use of water as a solvent in organic synthesis is often surprisingly effective even for reactions which are traditionally carried out under anhydrous conditions, despite the fact that the reaction involves a dehydration step. The ylidenenitriles are important in various applications. They are prepared in high yields (Table 1) from 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde and active methylene compounds such as malononitrile, cyanoacetic acid and cyanoacetamide (Scheme 1). In addition, water is an excellent solvent in terms of cost, availability and environmental impact.

The Knoevenagel condensation reactions of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde with malononitrile, cyanoacetic acid and cyanoacetamide were carried out in various solvents such as water, DMF, DMSO, methanol, ethanol and toluene (Table 2). Among these solvents, water was found to be the best solvent for the reaction. In toluene, only 8–13% yield of ylidenenitriles was observed, while in methanol and ethanol nearly equal yields of ylidenenitriles were found ranging from 86 to 89%. The yield of ylidenenitriles in DMF and DMSO ranges from 86 to 91% and 87 to 91% respectively. In short, the yield of ylidenenitriles in water of 91 to 94%, is higher compared to other solvent media.

The substrate, 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde has three active sites: an α,β-unsaturated carbonyl group *i.e.* the pyrone ring, a carbon–carbon double bond and a formyl group of these, the formyl group has the highest reactivity towards active methylene compounds in a completely aqueous medium under catalyst free conditions. In this methodology, the ylidenenitriles are isolated by simple filtration and as a result of which yield losses are avoided. The literature reveals that acids or bases facilitate the Knoevenagel condensation but that prolonged heating is required for completion. In the present methodology, the reactions were completed in a shorter time and under milder reaction conditions. By considering these aspects, our method shows the following advantages: (i) cleaner synthesis, (ii) shorter time, (iii) higher selectivity, (iv) catalyst free, (v) high yields, (vi) ecofriendly and (vii) economical. Thus, this is an excellent method for the preparation of ylidenenitriles.

Conclusion

We have developed an environmental friendly, economically viable and cleaner methodology for the rapid and simple condensation of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde **1** with active methylene compounds **2**, such as malononitrile,

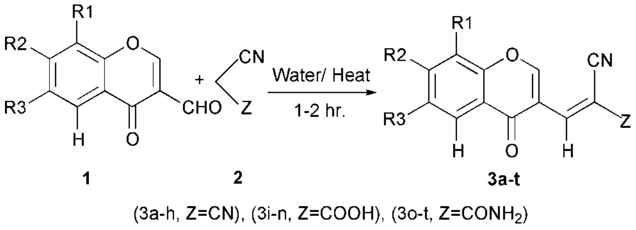
Green Context

The important C–C bond forming Knoevenagel reaction is widely used in organic synthesis and numerous procedures have been developed to ensure efficient reaction. These commonly involve organic solvents and homogeneous or heterogeneous catalysts to give reasonable reaction rates. Here we see a rare example of an efficient Knoevenagel reaction system that avoids both an organic solvent and the need for a catalyst. This very simple procedure is a good illustration of green chemistry reductions at work. *JHC*

DOI: 10.1039/b106871g

Table 1 Water mediated uncatalyzed facile synthesis of ylidenenitriles of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde

					Analysis (%)				
Entry	R^1	R^2	R^3	Z	C	H	N	Yield (%)	Mp/ °C
3a	H	H	H	CN	70.26	2.69	12.60	93	212
3b	H	H	Me	CN	71.15	3.37	11.86	94	210
3c	Me	H	Me	CN	72.03	3.98	11.21	93	232
3d	H	H	Cl	CN	60.94	1.96	10.93	94	252
3e	H	H	Br	CN	51.84	1.66	9.33	94	218
3f	H	Me	Cl	CN	53.33	2.20	8.89	93	226
3g	H	Me	H	CN	71.19	3.31	11.87	92	185
3h	H	Me	Me	CN	70.33	4.00	11.22	91	196
3i	H	H	Me	COOH	65.87	3.54	05.47	93	195
3j	H	H	Cl	COOH	56.64	2.18	5.08	92	244
3k	H	H	Br	COOH	48.74	1.88	4.37	94	186
3l	H	Me	Cl	COOH	58.02	2.75	4.84	92	242
3m	H	Me	H	COOH	65.87	3.53	5.48	94	202
3n	H	Cl	Cl	COOH	50.48	1.61	4.53	91	228
3o	H	H	Me	$CONH_2$	66.17	3.93	11.00	93	218
3p	H	H	Cl	$CONH_2$	56.83	2.54	10.21	92	260
3q	H	H	Br	$CONH_2$	48.91	2.20	8.73	91	226
3r	H	Me	Cl	$CONH_2$	58.23	3.11	9.74	93	262
3s	H	Me	H	$CONH_2$	66.14	3.91	11.04	93	218
3t	H	Cl	Cl	$CONH_2$	50.47	1.94	9.72	94	238



Scheme 1

Table 2 Yield ranges of ylidenenitriles of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde in different solvents

Solvent	Yield (%)
Water	90–94
DMF	86–91
DMSO	87–91
MeOH	86–89
EtOH	86–89
Toluene	8–13

cyanoacetic acid and cyanoacetamide which gave respective ylidenenitriles **3**. The ylidenenitriles are important building blocks for the preparation of various heterocycles.

Experimental

Melting points were measured in open capillaries in a paraffin bath and are uncorrected. The reactions were monitored by TLC [silica, toluene–EtOAc (9:1)]. IR spectra were recorded in Nujol on an FTIR instrument. ^1H NMR spectra were recorded on a 300 MHz instrument with $CDCl_3$–$(CD_3)_2SO$ as a solvent and TMS as an internal standard. Elemental analyses were consistent with the structures.

Spectral data of principal compounds

IR of 3a. ν/cm^{-1}: 3050–2900 (C–H of Ar–H), 2232 (CN), 1590 (C=C), 1659 (C=O of chromone), 1461 (γ-pyrone), 1090 and 1050 (C–O–C).

^{1}H NMR of 3a. δ 8.70 (s, 1H), 7.3 (m, 4H), 6.7 (s, 1H).

IR of 3i. ν/cm^{-1}: 3300–2500 (OH of CO_2H), 2228.86 (CN), 1709 (C=O of CO_2H), 1588 (C=C), 1660 (C=O of chromone), 1460 (γ-pyrone), 1088 and 1050 (C–O–C).

^{1}H NMR of 3i. δ 8.65 (s, 1H), 8.12 (m, 1H), 7.62 (dd, 1H), 7.49 (d, 1H), 6.67 (s, 1H), 2.00 (s, 3H), 10.48 (br s, 1H).

IR of 3o. ν/cm^{-1}: 3350 (N–H asymmetric stretch), 3170 (N–H symmetric stretch) 3010–2980 (C–H of Ar–H), 2238.21 (CN), 1649 (C=O of amide), 1592 (C=C), 1659 (C=O group of chromone), 1460 (γ-pyrone), 1089 and 1060 (C–O–C), 700–600 (broad NH out of plane bend).

^{1}H NMR of 3o. δ 8.66 (s, 1H), 8.13 (m, 1H), 7.62 (dd, 1H), 7.47 (d, 1H), 6.67 (s, 1H), 6.51 (br s, 2H), 2.01 (s, 3H).

Typical experimental procedure

A mixture of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde (10 mmol) and active methylene compound (10 mmol) in 20 ml of distilled water were heated for 1–2 h on a heating mantle at 90 °C. The progress of the reaction was monitored on TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered leading to an orange to red coloured solid. The product was recrystallized from an appropriate solvent and confirmed by spectral data.[16]

Acknowledgements

R. V. H. is thankful to the CSIR, New Delhi, for the award of a Senior Research Fellowship and also thankful to Dr B. M. Bhawal, National Chemical Laboratory, Pune for providing spectral data and reference work.

References

1 L. F. Tietze and U. Beifuss, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon Press, Oxford, 1991, vol. 2, ch. 1.11, p. 341; G. Jones, *Org. React. (New York)*, 1967, **15**, 204.

2 A. J. Fatiadi, *Synthesis*, 1978, 165; A. J. Fatiadi, *Synthesis*, 1978, 241 and references cited therein; F. Freeman, *Chem. Rev.*, 1980, **80**, 329.

3 F. F. Abdel-Latif, R. M. Shaker and N. S. Abdel-Aziz, *Heterocycl. Commun.*, 1997, **3**, 245; M. H. Elnagdi, R. M. Abdel-Motaleb and Mustafa, *J. Heterocycl. Chem.*, 1987, **24**, 1677; F. F. Abdel-Latif and R. M. Shaker, *Indian J. Chem., Sect. B*, 1990, **29**, 322; J. M. Quintela, C. Peinador and M. J. Moreira, *Tetrahedron*, 1995, **51**, 5901; F. F. Abdul-Latif, *Bull Soc. Chim. Fr.*, 1990, **127**, 129.

4 V. K. Polyakov and R. G. Shevtsova, *Ukr. Khim. Zh. (Russ. Ed.)*, 1981, **47**, 85.

5 M. S. Shingare, B. K. Karale, C. H. Gill, K. N. Ganage and M. T. Bachute, *Indian J. Heterocycl. Chem.*, 1999, **9**, 153.

6 A. Treibs, R. William and D. Grimm, *Liebigs Ann. Chem.*, 1981, **3**, 306.

7 G. Hass, J. L. Stanton, A. Vonsprecher and W. Paul, *J. Heterocycl. Chem.*, 1981, **18**, 607.

8 A. P. Shukmat, Y. P. Babbich, N. S. Piveneko and V. K. Polyakov, *Zh. Obshch, Khim.*, 1989, **59**, 1116.

9 J. Prousek, *Collect. Czech. Chem. Commun.*,1993, **58**, 3014.

10 G. V. S. Rama Sarma and V. M. Reddy, *Indian J. Heterocycl. Chem.*, 1993, **3**, 111.

11 B. K. Karale, V. P. Chavan, A. S. Mane, R. V. Hangarge, C. H. Gill and M. S. Shingare, *Synth. Commun.*, 2001, **32**, in press.

12 B. K. Karale, V. P. Chavan, R. V. Hangarge, A. S. Mane, C. H. Gill and M. S. Shingare, *Indian J. Heterocycl. Chem.*, 2001, **10**, 233.

13 R. V. Hangarge, B. K. Karale, A. S. Mane, V. P. Chavan and M. S. Shingare, *Indian J. Heterocycl. Chem.*, 2001, **10**, in press.

14 B. K. Karale, V. P. Chavan, A. S. Mane, R. V. Hangarge, C. H. Gill and M. S. Shingare, *Korean J. Med. Chem.*, 2000, **10**, 84.

15 A. Nohara, H. Kurki, T. Saijo, H. Sugihara, M. Kanno and Y. Sanno, *Korean J. Med. Chem.*, 1977, **20**, 141.

16 R. V. Hangarge, B. K. Karale, A. S. Mane, V. P. Chavan and M. S. Shingare, *Indian J. Chem.*, submitted.

Metal mediated solvent free synthesis of homoallylic alcohols

Philip C. Andrews,*[a] Anna C. Peatt[a] and Colin L. Raston*[b]

[a] *Centre for Green Chemistry/School of Chemistry, Monash University, Clayton, Victoria 3800, Australia. E-mail: p.andrews@sci.monash.edu.au*
[b] *School of Chemistry, University of Leeds, Leeds, UK LS2 9JT. E-mail: c.l.raston@chem.leeds.ac.uk*

Received 10th September 2001
First published as an Advance Article on the web 23rd November 2001

In, Bi, Cu and Zn metals mediate the allylation of various carbonyl compounds under solvent free conditions. Controlling the exothermic nature of these reactions, to prevent decomposition of starting materials, results in good to excellent yields of the corresponding homoallylic alcohols.

Introduction

Developing more benign synthetic procedures in chemical synthesis is important in moving towards sustainable technologies, as part of the rapidly emerging field of green chemistry.[1] In reducing the amount of waste, energy usage, and the use of volatile, toxic and flammable solvents, several approaches are available including avoiding the use of organic solvents for the reaction media.[1] Replacement media include non-volatile and recyclable ionic liquids,[2] H_2O,[3] supercritical CO_2,[4] polyethylene and polypropylene glycol.[5] An alternative approach avoids the use of a reaction medium as the so-called ‘solvent free’ or ‘solventless’ reaction.[6,7]

There are several advantages associated with the use of a solvent free system over the use of organic solvent. These include; (i) there is no reaction media to collect, dispose of or purify and recycle, (ii) on a laboratory, preparative scale, there is often no need for specialised equipment, (iii) extensive and expensive purification procedures such as chromatography can often be avoided due to the formation of sufficiently pure compounds, (iv) greater selectivity is often observed, (v) reaction times can be rapid, often with increased yields and lower energy usage,[6,7] and (vi) economic considerations, since cost savings can be associated with the lack of solvents requiring disposal or recycling. Not surprisingly solvent free synthesis has recently drawn attention from the wider synthetic community. Reactions epitomizing the simplicity, versatility, high yielding and selective nature of solvent free systems include: aldol condensations,[8] sequential aldol and Michael additions,[9] Stobbe condensations,[10] *O*-silylation of alcohols with silyl chlorides[11] and clay catalysed syntheses of trans-chalcones.[12]

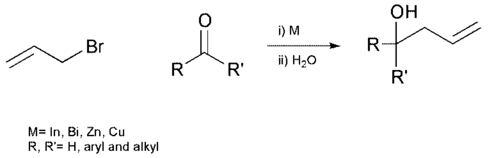
A potential criticism of the solvent free approach, which are inhibiting its widespread introduction into routine synthesis, is the possibility of producing ‘hot spots’, which can lead to run away reactions and consequently the increased likelihood of unwanted side reactions.[5] Thus, measurement of heat of reaction in solvent free systems is important, as is effective heat dissipation. If highly exothermic reactions are identified, which are otherwise suited to solventless conditions, the problem could be addressed through advanced reactor design.[6]

Recently, considerable attention has been given to the development of Barbier–Grignard type reactions in aqueous media using In, Zn and Sn.[3,13,14] Although these reactions can be classed as environmentally benign, the utilisation of aqueous media places several limitations on synthesis including; (i) the inability to carry out moisture sensitive processes such as the allylation of imines and commonly used reagents which are inherently moisture sensitive,[15] such as lithium amides and Grignard reagents, and (ii) the requirement of acidic or ultrasonic activators to produce significant yields when using mediators having a high disposition to form oxides on their surface such as Mg.[16]

Herein, we explore Barbier–Grignard type reactions under solvent free conditions, monitoring their exothermic behaviour and seeking controlling factors, which can alleviate the generation of excessive heat and the consequent decomposition of starting materials. Our studies involved a solventless, one-pot system employing In, Bi, Zn, and Cu as mediators in the allylation of various carbonyl compounds to give the corresponding homoallylic alcohols, Scheme 1. Traditionally, volatile organic solvents have been used as ‘heat sinks’.[6] Furthermore, we find in these systems the lack of unwanted side products, such as the pinacol and Wurtz coupled compounds.

Experimental

A typical experiment involved the addition of the carbonyl compound (5 mmol) to a suspension of the allyl bromide (7.25



Scheme 1

Green Context

The simplification of reaction protocols, minimising the use of auxiliaries, is an important paradigm in green chemistry. Working without solvent gives the potential for a simpler process, smaller plants, and reduces a major source of VOCs, eliminates the energy costs of removal, recycling and eventual disposal of waste solvent. However, the role of the solvent must be taken into account, and thus it is important to control mixing and exotherms if an acceptable process is to be achieved. The work here demonstrates that this is indeed possible for coupling reactions using a series of metals. Thus, the formation of homoallylic alcohols can be achieved under solventless conditions. ***DJM***

DOI: 10.1039/b108188h

mmol) and the commercially available metal powder (5 mmol) in a sealed, 50 ml, round-bottomed flask. The mixture was allowed to react *via* rapid stirring or sonication, at or below room temperature, before quenching with water (*ca.* 0.5 ml). Specific conditions and yields are given in Tables 1 and 2.

Results and discussion

A major consideration in choosing a reactive metal as a mediator in allylation reactions has been its first ionization potential (1st IP), more specifically their similarity to the most reactive alkali metals (Li = 5.39, Na = 5.14) and Mg (= 7.65). The assumption is that greater reactivity can arise from low electron transfer energies and thus higher yields will result from metals with low 1st IPs.[17] Metal mediators investigated herein all have relatively low 1st IPs, (Table 1)[18] in principle favouring single electron transfer (SET) processes in these reactions, (Scheme 2) and it was expected that the reactivity and subsequent yields of the various mediators would closely adhere to trends in the 1st IPs. Surprisingly this was not the case. Those with the highest 1st IPs, notably Zn, required the reaction to be performed at 0 °C to prevent the decomposition of the starting materials, whereas In, with its relatively low 1st IP, produced no such decomposition when reactions were carried out at room temperature, so long as quenching was performed within 3 h of initiation. By varying reaction conditions, (Table 1) for all the metals, decomposition of starting materials previously observed in solvent free systems in the cases of In and Zn was prevented.[19]

Table 1 First ionization potentials (1st IP) and reactions conditions for In, Bi, Cu and Zn[18]

Metal	1st IP/eV	Reaction conditions
In	5.70	Required quenching within 3 h
Bi	5.28	Kept at or below room temperature for 3 h before quenching
Cu	7.73	Sonicated for 24 h before quenching
Zn	9.39	Kept on ice for 3 h before quenching

Table 2 Isolated yields for allylation reactions of various carbonyl compounds in the presence of In, Bi, Cu or Zn

Carbonyl compound	Metal	Allylbromide : aldehyde/ketone : metal ratio	Yield[a] (%)
PhCHO	In	1.5 : 1 : 1	97
PhCHO	Bi	1.5 : 1 : 1	94
PhCHO	Cu	1.5 : 1 : 1	0
PhCHO	Zn	1.5 : 1 : 1	80
2-HOC_6H_4CHO	In	1.5 : 1 : 1	92
2-HOC_6H_4CHO	Bi	1.5 : 1 : 1	81
2-HOC_6H_4CHO	Zn	1.5 : 1 : 1	68
2-$MeOC_6H_4CHO$	In	1.5 : 1 : 1	78
2-$MeOC_6H_4CHO$	Bi	1.5 : 1 : 1	0
4-$MeOC_6H_4CHO$	Bi	1.5 : 1 : 1	0
4-$MeOC_6H_4CHO$	Bi	1.5 : 1 : 1	Decomposition[b]
2-$MeOC_6H_4CHO$	Zn	1.5 : 1 : 1	56
PhCH=CHCHO	In	1.5 : 1 : 1	86
PhCH=CHCHO	Bi	1.5 : 1 : 1	15
PhCH=CHCHO	Zn	1.5 : 1 : 1	51
MeCHO	In	1.5 : 1 : 1	33
Ph(Me)C=O	In	1.5 : 1 : 1	67[c]
Ph(Me)C=O	In	2 : 1 : 1.5	85
$MeCOCH_2COMe$	In	2 : 1 : 1.5	28[d]
Ph_2C=O	In	2 : 1 : 1.5	0
Me_2C=O	In	2 : 1 : 1.5	0
Ph(Me)C=O	Bi	2 : 1 : 1.5	0
Ph(Me)C=O	Bi/In (95/5)	2 : 1 : 1	< 10[c]
Ph(Me)C=O	Zn	1.5 : 1 : 1	17
Ph(Me)C=O	Cu	1.5 : 1 : 1	0

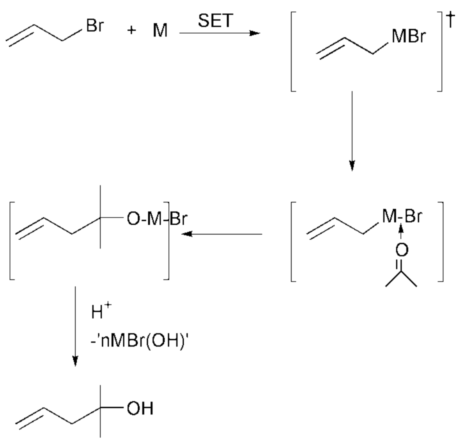
[a] All products gave satisfactory IR, ^1H NMR and GC. [b] Reaction performed at room temperature [c] Estimated by ^1H NMR and GC. [d] $MeCOCH_2C$-$Me(OH)CH_2$ $CH=CH_2$ only; estimated by ^1H NMR and GC/MS.

These findings suggest that the ability of a metal to mediate the allylation of carbonyl species is not solely governed by the ability of the metal to participate in SET processes, as previously postulated.[9] Rather the success of the mediators (judged by the reaction time and subsequent yield) may be also determined by; (i) the ease with which the metal inserts into a C–X bond and its predisposition, or lack thereof, to form a C–M bond in generating the intermediate **1**, (ii) the formation of the alkoxide species **2** and bond energy considerations of the transition from M–C to M–O bonds, and (iii) the dependency of the rate of quenching of the enolate M–O bond strength.

Careful control of the exothermic allylations of the carbonyl compounds studied resulted in good to excellent yields of the target allylic alcohol, (Table 2). Bi metal gave good yields for aromatic aldehydes (80–94%), which are comparable to those produced in equivalent reactions performed in a solvent.[20] However, in the case of –OMe substituted aromatic and aliphatic aldehydes little to no homoallylic alcohol was obtained. These observations can be rationalized by the nature of the R groups of the aldehydes. The aliphatic and *para*-OMe groups are known electron-donating groups, whilst the relatively weak electronegative nature of the *ortho*-OMe prevents attack because of its inability to stabilize the carbonyl group *via* hydrogen bonding and also steric hindrance. Another important observation was that when the allylation of the –OMe substituted aromatic aldehydes was repeated at room temperature, the decomposition of starting materials still occurred, indicating that the exothermic nature of these systems is largely attributed to the insertion of the metal into the C–X bond. In the case of acetophenone little or no homoallylic alcohol was produced even in the presence of a catalytic amount of In (5%), as has been observed for *in situ* reactions performed in DMF.[20] This can be related to the reduced reactivity of the carbonyl groups of ketones.

With its relatively low 1st IP, Cu was expected to result in the formation of allylic alcohols with relative ease. However, the allylic copper intermediate was not observed in these reactions, even with sonication. Thus more forcing conditions are necessary, such as generating an allylic copper species *via* allyl Grignard reagent and CuI,[21] to counteract the relatively noble character of metallic copper, with a full sub-shell of d orbitals involved in metallic bonding.[22] Nevertheless, our observation further supports the formation of an M–C organometallic intermediate as an important factor in such reactions.

With Zn acting as the mediator, no acidic, ultrasonic or Zn/Cu couple system was required to activate the metal powder. This contrasts with previous allylations utilising Zn, which were performed in organic solvents other than THF.[23] Once the



Scheme 2 † Variable/unknown oxidation states.

decomposition of starting materials was alleviated, by carrying out the reaction at *ca.* 0 °C, high yields were obtained. Indeed, yields in the range from 50–80% were achieved for both aliphatic and aromatic aldehydes, whilst evidence of the allylic alcohol, generated from acetophenone was also noted.

With In metal, excellent yields were obtained for both aliphatic and aromatic aldehydes (85–97%). In the case of acetophenone yields were improved, by *ca.* 20%, by increasing the ratio of allyl bromide and In to the ketone. Decreased yields were observed for the diketone, acetylacetone, with the monoallylation product resulting. This indicates the presence of a larger excess of allyl bromide and In may be required to produce the di-substituted ketone, with only 1.5 equivalents of the allylic In species being generated *in situ*. Reactions involving ketones with bulky substituents, such as benzophenone and di-isopropyl ketones did not produce the corresponding homoallylic alcohols, indicating steric hindrance prevents attack of the carbonyl group. A noteworthy observation is that there was no evidence of the possible side products such as the pinacol or Wurtz coupling.

Successfully controlling the exothermic nature of the allylation of carbonyl compounds makes the solvent free approach to the synthesis of homoallylic alcohols a viable synthetic procedure. Although, the nature of the allylic metallic species is not clear at this stage, we assume its ability to be generated is a crucial factor in determining the suitability for metals in such reactions. Investigations into the characteristics of such intermediates and the development of solvent free protocol for air- and moisture-sensitive procedures are currently in progress.

Acknowledgments

We thank the Centre for Green Chemistry at Monash University, the Australian Research Council and the University of Leeds for their financial support.

References

1 P. T. Anastas and J. C. Warner, *Green chemistry: Theory and practice*, Oxford Science Publications, 1998; M. Yochida and P. S. Mariano, *J. Org. Chem.*, 1996, **61**, 4439.

2 J. D. Holbrey and K. R. Seddon, *J. Chem. Soc., Dalton Trans.*, 1999, **99**, 2701.

3 T. H. Chan and Y. Yang, *J. Am. Chem. Soc.*, 1999, **121**, 3228; C. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997.

4 R. S. Oakes, T. J. Heppenstall, N. Shezad, A. A. Clifford and C. M. Rayner, *Chem. Commun.*, 1999, 1459; N. Shezad, A. A. Clifford and C. M. Rayner, *Tetrahedron Lett.*, 2001, **42**, 323; J. A. Darr and M. Poliakoff, *Chem. Rev.*, 1999, **99**, 495.

5 B. A. Roberts, G. W. V. Cave, C. L. Raston and J. L. Scott, *Green Chem.*, 2000, **3**, 280.

6 G. W. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2001, 2159.

7 K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025.

8 C. L. Raston and J. L. Scott, *Green Chem.*, 2000, **2**, 49.

9 G. W. V. Cave and C. L. Raston, *Chem. Commun.*, 2000, 2199.

10 K. Tanaka, T. Sugino and F. Toda, *Green Chem.*, 2000, **2**, 303.

11 B. Hatano, S. Toyota and F. Toda, *Green Chem.*, 2001, 140.

12 R. Ballini, G. Bosica, R. Maggi, M. Ricciutelli, P. Righi, G. Sartori and R. Sartori, *Green Chem.*, 2001, **3**, 178.

13 T. H. Chan, C. Li, M. C. Lee and Z. Y. Wei, *Can. J. Chem.*, 1994, **72**, 1181.

14 T. H. Chan, Y. Yang and C. J. Li, *J. Org. Chem.*, 1999, **64**, 4452.

15 T. H. Chan and W. Lu, *Tetrahedron Lett.*, 1998, **39**, 8605.

16 W. Zhang and C. Li, *J. Org. Chem.*, 1999, **64**, 3230.

17 C. J. Li and T. Chan, *Tetrahedron*, 1999, **55**, 11149.

18 C. E. Moore, *Ionization Potentials and Ionization Limits Derived from the Analysis of Optical Spectra*,, Natl. Stand. Ref. Data Ser., Natl. Bur. Stand., USA, 1970, 34.

19 X. H. Yi, J. X. Haberman and C. J. Li, *Synth. Commun.*, 1998, **28**, 2999.

20 M. Wada and K. Akiba, *Tetrahedron Lett.*, 1985, **26**, 4211.

21 Y. Yamamoto and N. Asao, *Chem Rev.*, 1993, 2207.

22 F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, John Wiley & Sons, New York Inc. 4th edn., 1988.

23 B. C. Ranu, A. Majee and A. R. Das, *Tetrahedron. Lett.*, 1995, **36**, 4885 and references therein.

Enzymatic coupling using a mixture of side chain donors affords a greener process for ampicillin

Luuk M. van Langen,[a] Erik de Vroom,[b] Fred van Rantwijk[a] and Roger A. Sheldon*[a]

[a] *Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands. E-mail: r.a.sheldon@tnw.tudelft.nl*
[b] *DSM Life Sciences, P.O. Box 1, 2600 MA Delft, The Netherlands*

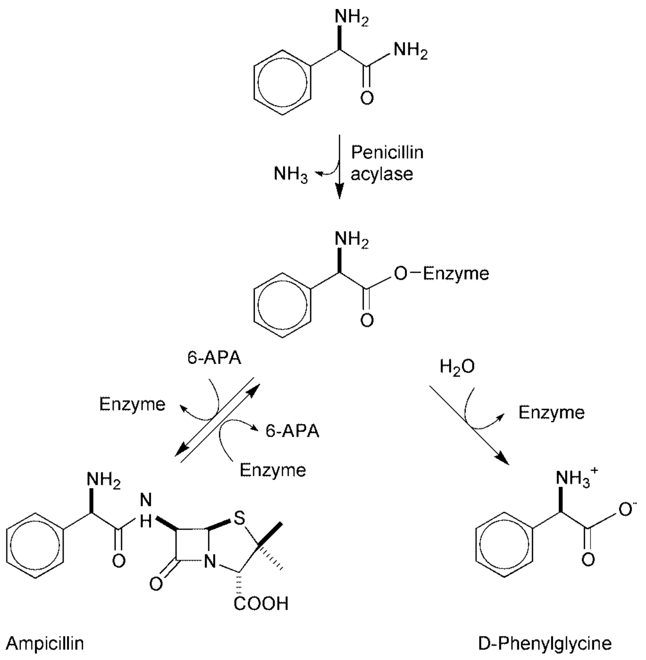
Received 17th May 2001
First published as an Advance Article on the web 27th November 2001

The penicillin acylase catalyzed synthesis of ampicillin, *via* acylation of 6-aminopenicillanic acid with D-phenylglycine amide, is accompanied by the formation of the hydrolysis product D-phenylglycine. The recycling of D-phenylglycine in the process *via* D-phenylglycine methyl ester hydrochloric acid salt was investigated. The efficiency of a resulting innovative process, using both the amide and ester as donors, was compared with the process without recycling and that with recycling *via* the amide. Recycling *via* the ester, in a mixed donor coupling, resulted in the most economic process with respect to the use of chemicals and the production of waste.

Introduction

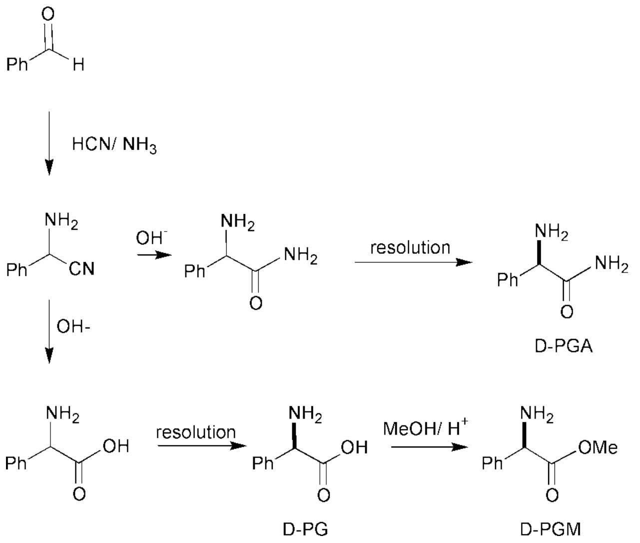
The use of hydrolytic enzymes, such as lipases, proteases and acylases, as catalysts in the synthesis of amides is a valuable addition to the synthetic repertoire. The manufacture of semi-synthetic β-lactam antibiotics such as ampicillin involves the synthesis of amide bonds on a scale of several thousand tonnes annually. Currently, chemical processes are used for the synthesis of semi-synthetic penicillins and cephalosporins. These involve the use of activating and protecting groups and generate copious amounts of non-recyclable waste. The potential advantages of an enzymatic process have been recognized for some time, *e.g.* it has been estimated that in such a green process the waste stream could be reduced by a factor of 3.[1]

Penicillin acylase (penicillin amidohydrolase EC 3.5.1.11) catalyzes the synthesis of ampicillin as shown in Scheme 1.



Scheme 1 Ampicillin synthesis using penicillin acylase. The reaction proceeds *via* an acyl-enzyme intermediate, which can either be aminolyzed by 6-APA, yielding the synthesis product ampicillin or be hydrolyzed resulting in D-(−)-phenylglycine.

Both the amide and ester of D-phenylglycine can be used as the activated donor in this enzymatic process. D-Phenylglycine amide (D-PGA), however, has the advantage over the ester that it can be obtained directly from phenylglycine nitrile, which is



Scheme 2 Synthesis of D-phenylglycine and its derivatives *via* phenylglycine nitrile.

Green Context

The synthesis of amides *via* acylase enzymes is utilised in the synthesis of ampicillin, an antibiotic produced in kilotonne quantities annually by wasteful chemical methods. Enzymatic routes run into difficulties caused by a competing hydrolysis. This paper evaluates different routes whereby the hydrolysis product can be recycled back into the synthetic loop in different ways. Overall it was found that a system whereby the hydrolysis product is esterified and the ester fed into the system along with the amide starting material as a mixed feed provided the optimal option in terms of waste minimisation. *DJM*

the intermediate in the industrial synthesis of D-phenylglycine (D-PG) as shown in Scheme 2. The resolution of the racemic amide can be performed using an L-selective amino-peptidase[2] or by asymmetric transformation of its salt with L-mandelic acid.[3] D-Phenylglycine methyl ester (D-PGM), however, would have to be produced *via* D-PG and its *de novo* synthesis comprises therefore one extra step compared with D-PGA. Hence, D-PGA is the starting material of choice for economic reasons.

The competing hydrolysis of the donor (primary hydrolysis), as well as of the product (secondary hydrolysis) is regarded as the major problem in enzymatic ampicillin synthesis.[4] Economics dictate that the byproduct from the coupling reaction (D-PG) has to be converted into an effective acylating agent to be reused in the process. In this context the choice of the nature of recycling should be considered. Recycling to the original donor, D-PGA, is not the most cost efficient solution as the transformation of D-PG to D-PGA proceeds *via* D-PGM, which is itself an effective donor in the enzymatic reaction.

It is known that D-PG can be transformed into D-PGM by reaction with methanol in the presence of more than one equivalent of a strong acid. The first equivalent of acid is required to protonate the carboxylate function of D-PG, prior to esterification. The transformation of D-PGM into D-PGA can be accomplished *via* ammonolysis, requiring at least two equivalents of ammonia.[5] Recycling of D-PG into D-PGA will therefore generate at least one extra equivalent of salt (Scheme 3).

Consequently we reasoned that the most cost- and waste-efficient enzymatic process for ampicillin would be based on recycling of the hydrolysis product D-PG *via* D-PGM. This results in a quite unusual process, in which the enzymatic acylation of 6-APA is performed with a mixture of D-PGA and D-PGM as donors (Scheme 4). In this paper we present the characteristics and feasibility of this ‘mixed donor’ process.

Results and discussion

6-Aminopenicillanic acid was converted, in a near-quantitative yield, into ampicillin *via* acylation with a 1.6 fold excess of D-phenylglycine amide (D-PGA) in the presence of an immobilized *E. coli* penicillin acylase (Table 1). The ammonia that was liberated in the course of the acylation and hydrolysis reactions was neutralized by titration with 1.5 equivalent (relative to ampicillin) of acid. The excess of D-PGA was nearly completely converted into D-PG at the end of the reaction. Its reactivation and recycle as D-phenylglycine methyl ester hydrochloric acid salt (D-PGM·HCl) would economize on the use of D-PGA, but the acylation would be performed with a mixture of D-PGA and D-PGM·HCl as donors (Scheme 4).

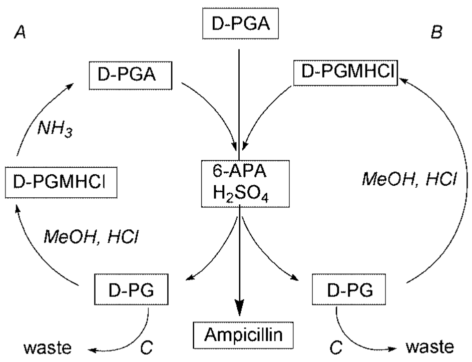
$$\mathrm{R(NH_3{+})\text{-}COO^-} \xrightarrow{\text{MeOH/ 1 eq. HCl}} \mathrm{R(NH_3Cl)\text{-}COOMe + H_2O}$$

$$\mathrm{R(NH_3Cl)\text{-}COOMe} \xrightarrow{\text{2 eq. } \mathrm{NH_3}} \mathrm{R(NH_2)\text{-}CONH_2 + MeOH + 1\ eq.\ NH_4Cl}$$

Scheme 3 Formation of an amide from a free amino acid. In step 1 the free amino acid is transformed to its methyl ester using one equivalent of a strong acid; in step 2 the amide is obtained by ammonolysis of the methyl ester.

We note that phenylglycine esters are preferably isolated as salts because these are more stable and can be isolated in a straightforward manner from the esterification mixture (Scheme 3). To validate the performance of such a ‘mixed donor’ process, the synthesis of ampicillin was studied by applying synthetic mixtures of 60% D-PGA and 40% D-PG ester (Table 1). The yield of ampicillin from such a mixed donor process was comparable with that from a procedure that used only D-PGA. Surprisingly, the reaction rate was markedly enhanced by the use of D-PGM·HCl. The fact that the same rate enhancement was observed with D-PGA/NH_4Cl and that it was substantially lower when D-PGM·$0.5H_2SO_4$ was used suggests that the effect is, at least partly, owing to the presence of chloride ion (see Table 1). The use of the ethyl ester (D-PGE·HCl) also increased the reaction rate, but its effect was less than that of the methyl ester.

We have analyzed, on the basis of these results, three optional enzymatic processes for ampicillin: no recycling of D-PG, recycling *via* D-PGM·HCl and *via* D-PGA (see Table 2). The consumption of starting materials and titrants, as well as the



Scheme 4 Enzymatic ampicillin synthesis in which hydrolyzed acyl donor D-PG is recycled (A) *via* D-PGA, (B) *via* D-PGM and (C) without any recycle.

Table 1 Synthesis of ampicillin using *E. coli* penicillin acylase from mixtures of acyl donors[a]

Acyl donor	Yield[b] (%)	t_{50}[c]/min	Acid consumption[d]
D-PGA	97	380	1.53
D-PGA/D-PGM·HCl (3:2)	96	190	0.42
D-PGA/D-PGE·HCl (3:2)	93	300	0.50
D-PGA/D-PGM·$0.5H_2SO_4$ (3:2)	91	250	0.47
D-PGA/NH_4Cl (5:2)	95	190	1.67

[a] Assemblase® (15 g, 240 U g^{-1}) was used as catalyst. [b] Yield based on 6-APA. [c] Time to 50% conversion of 6-APA to ampicillin. [d] In mol acid consumed per mol produced ampicillin at the end of the conversion.

Table 2 Required chemicals and produced waste per kg ampicillin in the enzymatic synthesis process, comparing D-phenylglycine recycling *via* its amide and ester[a]

	Chemicals/g				Waste/g			
Recycling *via*	D-PGA	HCl	NH_3	H_2SO_4	D-PG	NH_4Cl	$(NH_4)_2SO_4$	Total
No recycle	620	0	0	186	260	0	250	510
Amide	370	64	60	186	0	93	250	343
Ester	370	64	0	51	0	93	70	163

[a] The calculations are based on 96% conversion of 6-APA and 60% conversion of the acyl donor into ampicillin; the surplus of acyl donor is hydrolyzed during the process to D-PG and assumed to be quantitatively isolated and transformed to its amide or ester respectively. The acid consumption in the enzymatic acylation was obtained from Table 1.

production of waste, were calculated on the basis of the results in Table 1, assuming that in the course of the reaction 40% of the donor reagent is hydrolyzed to D-PG, which is isolated and esterified quantitatively. Our calculations predicted that recycling of D-PG would economize on the consumption of D-PGA and would reduce the total waste stream. Moreover, recycling *via* D-PGM·HCl would produce half the waste of the recycle *via* D-PGA, mainly because recycling *via* the ester would consume less acid and, hence, produce less salt.

In a validation experiment, the formed D-PG was isolated and transformed into D-PGM (Table 3) on a laboratory scale and using non-optimized laboratory techniques. This resulted in a process for ampicillin using a mixture of D-PGA and D-PGM·HCl in a 3:1 ratio. In total, three cycles were performed with good results, demonstrating the commercial potential of enzymatic synthesis of ampicillin with mixed acyl donor.

Conclusions

The enzymatic production of ampicillin *via* acylation of 6-APA by D-phenylglycine amide (D-PGA) was optimized by recycling the hydrolytic side product D-phenylglycine (D-PG) into D-phenylglycine methyl ester hydrochloric acid salt (D-PGM·HCl). In the resulting process, using a mixture of D-PGA and D-PGM·HCl as donors, the consumption of acid was considerably lower than when only D-PGA was used. Considering the fact that transformation of D-PG to D-PGM·HCl requires less chemicals and produces therefore less waste salts than recycling to D-PGA, we conclude that the ‘mixed donor’ process constitutes a greener route to ampicillin.

Experimental

General

Immobilized *E. coli* penicillin acylase, Assemblase® (240 U g^{-1} or 315 U g^{-1}), 6-aminopenicillanic acid, D-(−)-phenylglycine amide and D-(−)-phenylglycine methyl ester hydrochloric salt were from DSM, The Netherlands. One penicillin acylase unit is defined as the amount of enzyme that hydrolyzes one µmol of penicillin G per minute at pH 8.0 and 34 °C.

D-Phenylglycine ethyl ester was prepared by heating a solution of D-phenylglycine with 5 equivalents of sulfuric acid in ethanol under reflux conditions for 20 h. After evaporation of the ethanol, water and ethyl acetate were added, the pH was adjusted to pH 8.5 using 25% ammonia and the product was extracted to the organic layer. The separated organic layer was extracted with aqueous hydrochloric acid pH 4; the water was evaporated and the product was recrystallized as its hydrochloric salt from ethanol/propan-2-ol. The sulfuric acid salt of D-phenylglycine methyl ester (D-PG·0.5H_2SO_4) was prepared by extracting a solution of D-phenylglycine methyl ester hydrochloride in water to ethyl acetate at pH 8.5 using 25% ammonia. The organic layer was extracted with dilute sulfuric acid at pH 4. The water was evaporated and methanol added to the remaining syrup, after which the sulfuric acid salt of the ester crystallized.

HPLC analyses

Samples from the reaction mixture were dissolved in water–ethanol (3:2) and acidified with a few drops of phosphoric acid. Resorcinol dimethylether (1,3-dimethoxybenzene) was added as an internal standard. The solution was analyzed by HPLC using a Chrompack Nucleosil C18 column, 5 µ, 150 × 3 mm. The eluent consisted of a solution of 0.68 g KH_2PO_4 and 0.68 g sodium dodecyl sulfate in 700 ml water and 270 ml acetonitrile adjusted to pH 3.0 with phosphoric acid.

Chiral analysis of PG and PGM was performed with a Daicel Chemical Industries Ltd. 4.6 × 150 mm 5 µm Crownpak (+) column using a waters 635 LC pump and a Waters 486 UV detector at 215 nm. The eluent was aqueous $HClO_4$, pH 1.5 at a flow of 0.6 ml min^{-1}; the column temperature was 18 °C.

Enzymatic reaction

6-Aminopenicillanic acid (6.5 g, 30 mmol) and immobilized penicillin acylase were suspended in water (40 g, 10 °C) in a thermostated glass reaction vessel equipped with a stirrer, a pH-electrode, a temperature sensor and a dropping funnel, charged with 3 M sulfuric acid. The reaction was started by adding 10 mmol of acyl donor (for the appropriate mixture of D-PGA and D-PGM, see Tables 1 and 3); the pH of the reaction mixture was maintained at pH 6.3 by automated titration and the temperature was kept constant at 10 °C. At t = 60 min extra acyl donor (10 mmol) was added to the reaction mixture; this procedure was repeated at t = 120, 180 and 240 min. During the course of reaction samples were taken and analyzed by HPLC. At maximum conversion the reaction was stopped by lowering the pH to 4.5 using 3 M sulfuric acid.

Isolation and esterification of D-(−)-phenylglycine

The enzyme was separated from the reaction mixture using a 150 µ sieve. During this process extra water was added to the mixture on the sieve, resulting in 250 ml of the crystal suspension. The suspension was cooled to 5 °C and acidified with 37% hydrochloric acid to pH 1.6. Trace amounts of biocatalyst debris were removed by filtration and at 5 °C the filtrate was adjusted to pH 6 using 25% ammonia. After 30 min the formed ampicillin trihydrate crystals were filtered off. The pH of the remaining solution, containing mainly D-PG and ampicillin (10:3 molar ratio), was lowered to 5.0 with 37% hydrochloric acid and the solution was passed through a 30 mm diameter column containing 100 g XAD-16 resin. The column was eluted with water until 1 l had passed the column. This solution was concentrated to 20 ml under reduced pressure at 60 °C. After cooling on ice the D-PG crystals were filtered off and dried *in vacuo* at 40 °C.

The isolated D-PG was suspended in 150 ml methanol; dry hydrochloric gas was bubbled through until all D-PG had passed into solution and the solution was refluxed for 20 hours using a Soxhlet containing molecular sieves 3A to dry the refluxing

Table 3 Recycling of D-PG into D-PGM·HCl in enzymatic ampicillin synthesis[a]

Cycle	Donor	Conversion of 6-APA (%)	$t_{1/2}$[b]/min	D-PG/ isolated[c] (%)	D-PGM/ isolated[d] (%)	Acid consumption[e]
1	PGA	96	145	72	89	1.57
2	PGA/PGM HCl 3:1	98	130	76	93	0.88
3	PGA/PGM HCl 3:1	98	130	71	n.d.	0.91

[a] Assemblase® (10 g, 315 U g^{-1}) was used as catalyst. [b] Time to 50% conversion of 6-APA into ampicillin. [c] Yield of isolation on the produced amount in the acylation reaction (HPLC). [d] Yield on isolated phenylglycine. [e] In mol acid consumed per mol produced ampicillin at the end of the conversion.

methanol. The methanol was evaporated and the product was dissolved in 5 ml ethanol and under stirring 200 ml diethyl ether was added to precipitate D-PGM hydrochloride. The yields of both the isolation and esterification of D-PG in subsequent cycles are listed in Table 3.

Acknowledgement

Financial support by DSM Life Sciences products and The Netherlands Ministry of Economic Affairs is gratefully acknowledged.

References

1 E. de Vroom, *Chim. Oggi*, 1999, **17**, 65.
2 W. H. J. Boesten, *Ger. Offen.*, 2526594 (DSM/ Stamicarbon), 1976 (*Chem. Abstr.*, 1976, **84**, 149254c); E. M. Meijer, W. H. J. Boesten, H. E. Schoemaker and J. A. M. van Balken, *Biocatalysis in organic synthesis*, ed. J. Tramper, H. C. van der Plas and P. Linko, Elsevier Science Publishers, Amsterdam, 1985, p. 135.
3 W. H. J. Boesten, *Eur. Pat.*, EP 442584 (DSM), 1991 (*Chem. Abstr.*, 1992, **116**, 42062r); W. H. J. Boesten, *Eur. Pat.*, EP 442585 (DSM), 1991 (*Chem. Abstr.*, 1992, **116**, 42063s).
4 A. Bruggink, E. C. Roos and E. de Vroom, *Org. Process Res. Dev*, 1998, **2**, 128.
5 W. H. J. Boesten, *Eur. Pat.*, EP 0002297 (Stamicarbon), 1978.

Catalytic acetylation of alcohols, phenols, thiols and amines with zeolite H-FER under solventless conditions

Subhash. P. Chavan,*[a] R. Anand,[b] K. Pasupathy[a] and B. S. Rao[b]

[a] *Organic Chemistry: Technology Division, National Chemical Laboratory, Pune - 411008, India. E-mail: spchavan@dalton.ncl.res.in*
[b] *Catalysis Division, National Chemical Laboratory, Pune - 411008, India*

Received 8th October 2001
First published as an Advance Article on the web 29th November 2001

Zeolite H-FER catalyzes the acetylation of alcohols, phenols and thiols using acetic anhydride under solventless conditions in excellent yields. The catalyst can be reused without any loss of activity.

Introduction

Acetylation of alcohols and phenols, thiols and amino groups is a fundamental reaction in organic synthesis.[1] This reaction is generally carried out in the presence of bases such as triethylamine or pyridine along with 4-(dimethylamino)pyridine (DMAP) as co-catalyst.[2] Later, Vedejs *et al*[3] reported tributylphosphine (Bu_3P) as a less basic catalyst for acetylation of alcohols. In addition to the above catalysts, protic acids such as *p*-toluenesulfonic acid[4] and Nafion-H,[5] Lewis acids such as $ZnCl_2$,[6] $CoCl_2$,[7] $Sc(OTf)_3$,[8] $Bi(OTf)_3$,[9] and $MgBr_2$[10] are also known to catalyze the acetylation of alcohols and phenols. Montmorillonite K-10 and KSF clay[11] as heterogeneous catalysts have also been reported. Recently yttria–zirconia[12] based Lewis acid and NBS[13] have been reported as acylating catalysts. Most of these reported acid catalysts use Ac_2O as the acetylating agent. They also suffer from certain drawbacks. The catalysts are rather expensive or moisture sensitive. Nevertheless, there is still a great demand for acid catalysts to generate esters under mild conditions.

The application of inorganic solid acids, especially zeolites, as effective heterogeneous catalysts for organic synthesis has received considerable attention in the recent decades due to their unique physical and chemical properties such as shape, selectivity, acidic and basic nature and their thermal stability.[14] The advantages of these catalyst systems over homogeneous systems are well known, such as stability, ease of handling, lack of corrosion and other environmental hazards, ease of recovery and regeneration. Zeolites HSZ-360[15] and H-ZSM-5[16] have been reported for the acetylation of alcohols and phenols under solventless conditions.

Herein we report the acetylation of alcohols, phenols, thiols and amines using acetic anhydride in the presence of a catalytic amount of zeolite H-FER under solventless conditions in high yields, which can be reused without any loss of activity.

Results and discussions

As shown in Table 1, several alcohols, phenols and thiols underwent acetylation very smoothly in excellent yields. Under our reaction conditions chiral alcohols can be easily acetylated with complete retention of optical activity (entry 7) in high yields. The mildness of the present protocol is the key feature, which is evident in acetylation of alcohols containing acid sensitive groups such as acetal (entry 8) and tetrahydropyranyl ether (entry 5), which survived under the reaction conditions. It was observed that primary allylic alcohol (entry 1) underwent smooth acetylation under the applied reaction conditions. An additional feature of the present reaction system is that it tolerates other acid sensitive functionalities such as C–C double and triple bonds (entries 1, 2 and 5, 6). Attempted acetylation of a tertiary alcohol (entry 9) however, gave the acetylated product in only 45% yield based on the recovery of the starting material. A minor amount (15%) of eliminated product was also obtained. This zeolite can be reused several times without any loss of activity, simply by filtering the catalyst, washing with acetone, drying and reusing immediately.

Conclusions

In conclusion, this protocol offers an efficient catalyst for acetylation of alcohols, phenols, thiols and amines with acetic anhydride under solventless conditions. All acetates were obtained in excellent yields under operationally simple experimental conditions. The catalyst can be reused without any loss of activity.

Experimental

The zeolite H-FER catalyst was synthesized according to the reported procedure.[17] In a typical batch, 52.5 g of sodium

Green Context

The acetylation of alcohols (and thiols) is an often used synthetic transformation, and can result in the generation of waste from the catalyst used to prepare the acetate. Aqueous washing not only precludes efficient recovery of the catalyst, but also allows the possibility of partial hydrolysis. This novel protocol relates to the use of a simple stable solid catalyst which can be easily recovered and reused, and which gives excellent conversions in a range of reactions.

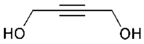
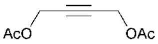
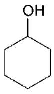
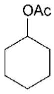
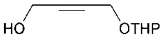
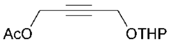
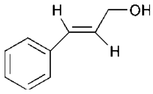
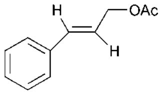
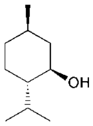
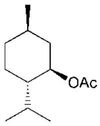
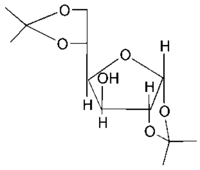
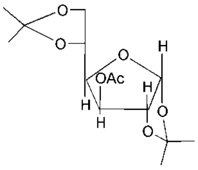
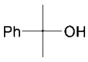
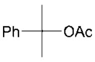
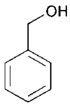
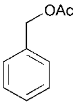
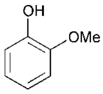
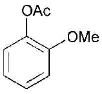
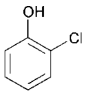
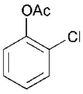
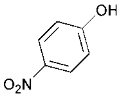
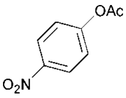
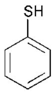
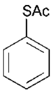
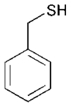
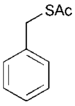
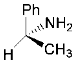
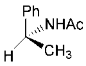
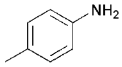
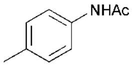
DJM

DOI: 10.1039/b109093c

Table 1 Direct acetylation of alcohols, phenols, thiols and amines with acetic anhydride over Zeolite H-FER

$$\text{R-XH} \xrightarrow[\text{H-FER}]{\text{Ac}_2\text{O}} \text{R-XAc}$$

X = O or S or NH

Entry number	Reactant	Product	Reaction time/h	Isolated yield[d] (%)
1			2[a]	98
2			2[a]	98
3			2[a]	98
4			2.5	97
5			2	91
6			2	94
7			2.5[b]	94
8			2.5	85
9			6	45[e]
10			1.5	99
11			2	95
12			5	94
13			5	99
14			5	91
15			5	94
16			2[c]	99
17			2[c]	99

[a] 3 equivalents of acetic anhydride was used. [b] $[\alpha]_D$ −78.12° (c = 2, C_6H_6). [c] Reaction carried out at room temperature. Other reactions were carried out at 75 °C. [d] All products were identified by their IR, ^{1}H NMR, and mass spectra. [e] Based on recovery of the starting material.

silicate (in 25 ml of distilled water) was stirred with 10 ml pyrrolidine. To this solution, 2.4 g of aluminum sulfate hexadecahydrate (in 25 ml distilled water) and 1.8 g of sulfuric acid (in 10 ml distilled water) was added. Finally, 30 ml of distilled water was added and the gel (pH 11.5 ± 0.2) was stirred vigorously for 2 h and autoclaved in a 300 ml stainless steel Parr autoclave (4842, 300 ml) and heated at 160 °C for 60 h. The initial gel composition was: 20 $Na_2O:Al_2O_3:37$ pyrrolidine$:66.5$ $SiO_2:6.3$ $H_2SO_4:1460$ H_2O. The autoclave was quenched and the product filtered off, washed and dried at 100 °C for 6–8 h. The resulting material was calcined in air at 550 °C for 18–20 h and then exchanged with 1 M NH_4NO_3 solution three times, followed by calcination at 550 °C for 10 h to yield H-FER zeolite.

The catalyst was characterized by X-ray powder diffraction (Rigaku, D-Max III VC diffractometer with Cu-Kα radiation, $\lambda = 1.5404$ Å) for its phase purity. The chemical composition of silica and alumina was established by a wavelength dispersive XRF (3070 Rigaku) spectrophotometer. Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) were carried out in flowing air (3 $dm^3\ h^{-1}$) at a heating rate of 10 °C min^{-1} on an autonomic TG/DTA (SETRAM 92). An Omnisorp 100 CX (COULTIER Corporation, USA) analyzer was used for the measurement of low-pressure nitrogen adsorption to determine the surface area. The Lewis and Bronsted acidity of the H-FER catalyst sample was determined by adsorbing CD_3CN on the catalyst wafer and then characterized by FTIR spectrometry (Nicolet Magne-550 FTIR).

To a mixture of acetic anhydride (15 mmol) and alcohol/thiol/amine (10 mmol), the catalyst (0.15 g) was added and the reaction mixture stirred at 75 °C for the length of time indicated in Table 1. After the completion of the reaction (monitored by TLC and GC), the reaction mixture was extracted with Et_2O and the catalyst filtered off. The filtrate was washed with water. The organic layer was then dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure followed by chromatography over silica gel using light petroleum–ethyl acetate as eluent furnished the corresponding acetate.

Acknowledgements

The authors R.A. and K.P. thank CSIR, New Delhi, India for financial assistantship. Funding by CSIR, New Delhi under the YSA scheme is great fully acknowledge.

References

1 S. S. Rana, J. J. Barlow and K. L. Matta, *Tetrahedron Lett.*, 1981, **22**, 5007; T. S. Li, Y. L. Li and X. T. Liang, *Steroids*, 1990, **55**, 263; T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley Interscience, New York, 2nd edn., 1991; A. A. Mourabit, H. Poujol, C. Poupat, A. Ahond and P. Potier, *Tetrahedron Lett.*, 1996, **37**, 9189.

2 V. Steglich and G. Hotfle, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 981.

3 E. Vedejs, N. S. Bennelt, L. M. Conn, S. T. Diver, M. Gingras, S. Lin, P. A. Oliver and M. J. Peterson, *J. Org. Chem.*, 1993, **58**, 7286.

4 A. C. Cope and E. C. Herrich, *Org. Synth.*, 1963, **Coll. Vol. 4**, 304.

5 R. Kumareswaran, K. Pachamuthu and Y. D. Vankar, *Synlett*, 2000, 1652.

6 R. H. Baker and F. G. Bordwell, *Org Synth.*, 1955, **Coll. Vol. 3**, 141.

7 J. Iqbal and R. R. Srivastava, *J. Org. Chem.*, 1992, **57**, 2001.

8 K. Ishihara, M. Kubota, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4560.

9 A. Orita, C. Tanashi, A. Kakuda and J. Otera, *Angew. Chem., Int. Ed.*, 2000, **39**, 2877.

10 S. V. Pansare, M. G. Malusare and A. N. Rai, *Synth. Commun.*, 2000, **30**, 2587.

11 X. A. Li, T. S. Li and T. H. Ding, *Chem. Commun.*, 1997, 1389.

12 P. Kumar, K. R. Pandey, S. M. Bodas and K. M. Dongare, *Synlett*, 2001, 206.

13 B. Karimi and H. Seradji, *Synlett*, 2001, 519.

14 W. F. Holderich, M. Hesse and F. Naumann, *Angew. Chem., Int. Ed.*, 1998, **27**, 226; Y. Izumi and M. Onaka, *Adv. Catal.*, 1992, **38**, 245; V. Ramamurthy, D. R. Corbin and L. J. Johnson, *J. Am. Chem. Soc.*, 1992, **114**, 3870; K. Pitchumani, M. Warrier and V. Ramamurthy, *J. Am. Chem. Soc.*, 1996, **118**, 9428.

15 R. Ballini, G. Bosica, S. Carloni, L. Ciaralli, R. Maggi and G. Sartori, *Tetrahedron Lett.*, 1998, **39**, 6049.

16 M. M. Heravi, M. Tajbakhsh, B. Mohanjerani and M. Ghassemzadesh, *Ind. J. Chem.*, 1999, **38**, 859.

17 R. K. Ahedi and A. N. Kotasthane, *J. Porous Mater*, 1997, **4**, 171.