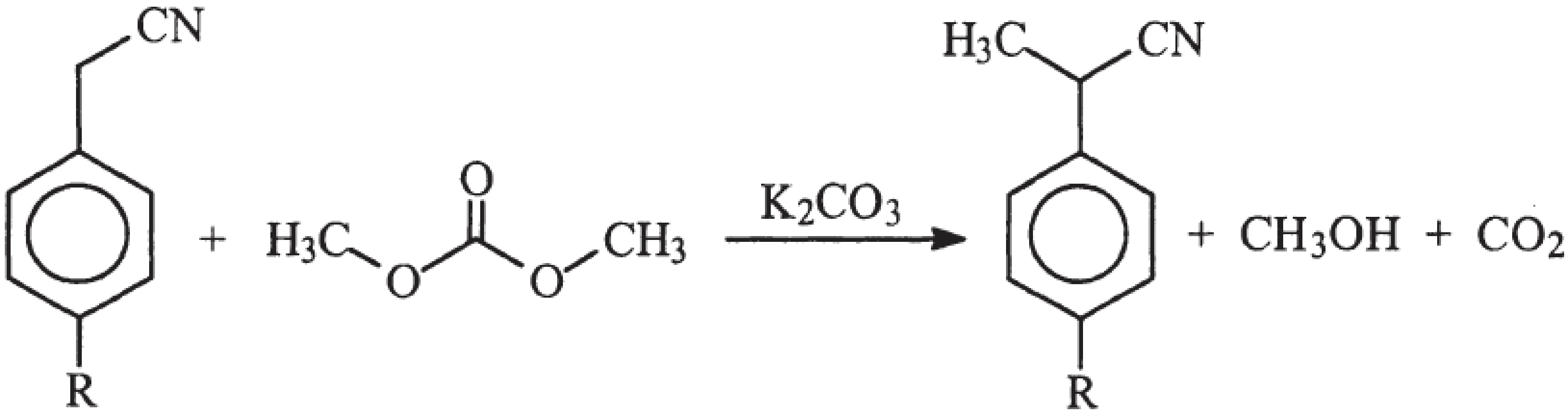
Green Reagent

Dimethylcarbonate (DMC) as methylating agent

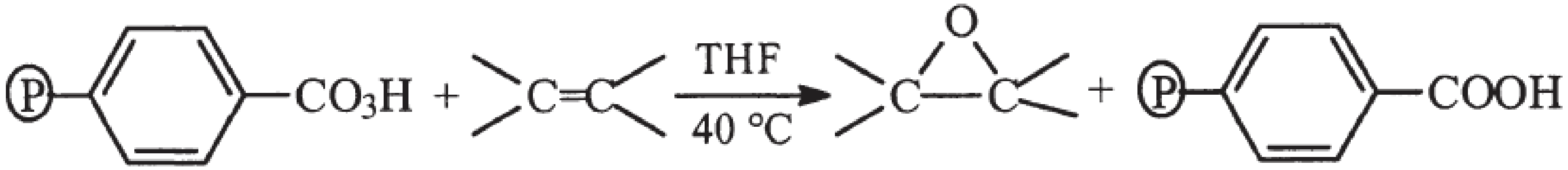


Conventional methylation reactions employ methyl halides or methyl sulfate. The toxicity of these compounds and their environmental consequences render these syntheses somewhat undesirable.

Reference: P. Tundo, F. Trotta and G. Moraglio, J. Org. Chern., 1987,52, 1300.
P. Tundo, F. Trotta and G. Moraglio, J. Chern. Soc., Perkin Trans. 1, 1989, 1070.

Green Reagent

Polymer Supported Reagents

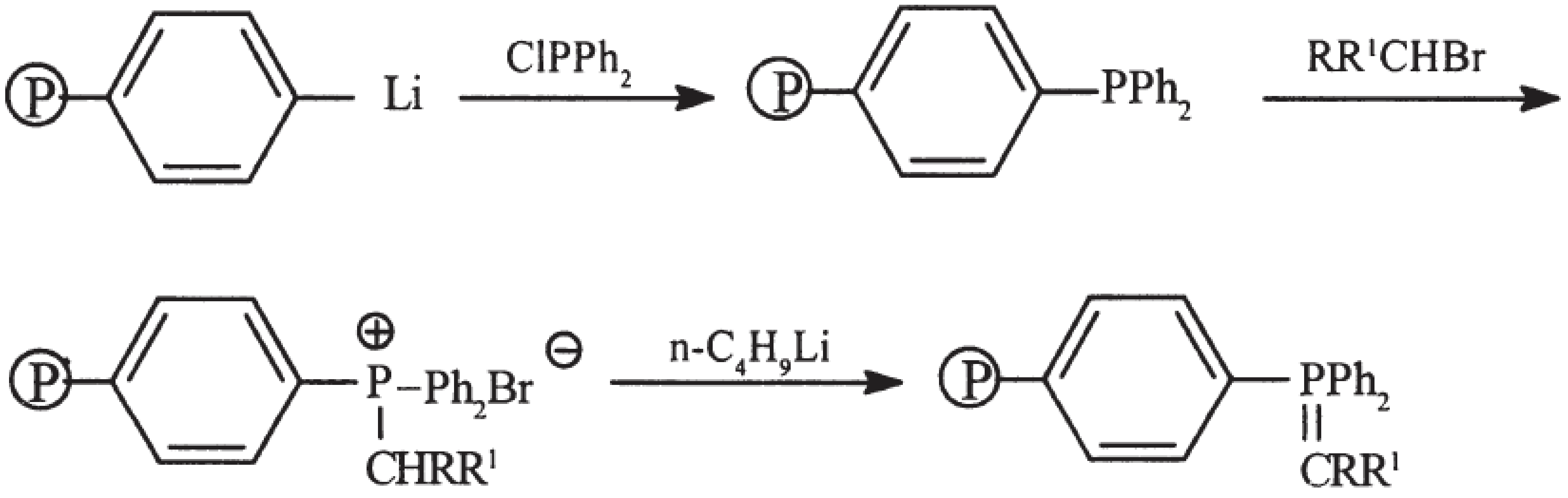


The main advantage of using these reagents is that any excess of the reagent can be recovered by filtration and used again.
Also, the isolation of the product is very easy.

Reference: (a) IMJ. Frehet and K.E. Haque, Macrornolecules, 1975,8, 130.
(b) C.R. Harrison and P. Hodge, J. Chern. Soc., Chern. Cornrnun., 1974, 1009.

Green Reagent

Polymer Supported Reagents: Polystyrene Wittig Reagent



Polystyrene
Wittig reagent

The polymeric Wittig reagent reacts with carbonyl compounds (e.g. $C_6H_5COCH_3$, p-CIC_6H_4CHO, C_6H_5CHO etc.) to give the usual products

Reference: (a) M.I Farrall and J.M.J. Frechet, J Org. Chern., 1976,41,3877.
(b) W Heitz and R. Michels, Angew. Chern. Int. Ed., 1972, 11,298.

Green Catalysts

Acid Catalysts

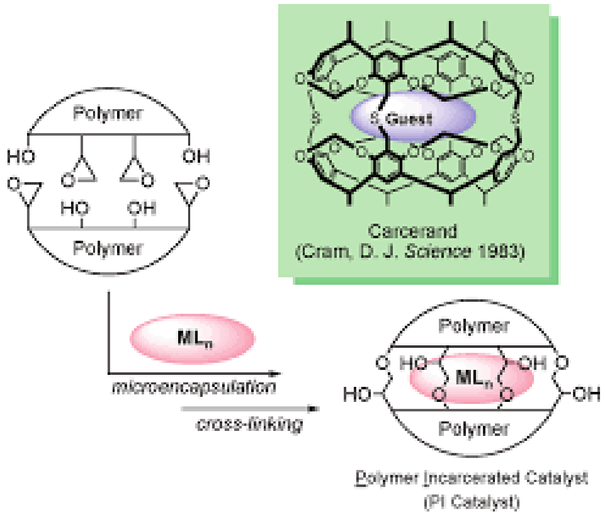
The traditional catalyst hydrogen fluoride, an extremely corrosive, hazardous and toxic chemical used in the production of linear alkylbenzenes (LAB's), has been successfully replaced by a solid acid catalyst, viz. fluorided silica-alumina catalyst, which does not require special material of construction (of the container), involves lower operating costs and obviates the need for an acid scrubbing system and waste disposal of calcium fluoride.

Microencapsulated Lewis acids have replaced traditional corrosive monomeric Lewis acids in the reactions like Michael, Friedel Crafts, Mannich reactions etc.

Green Catalysts

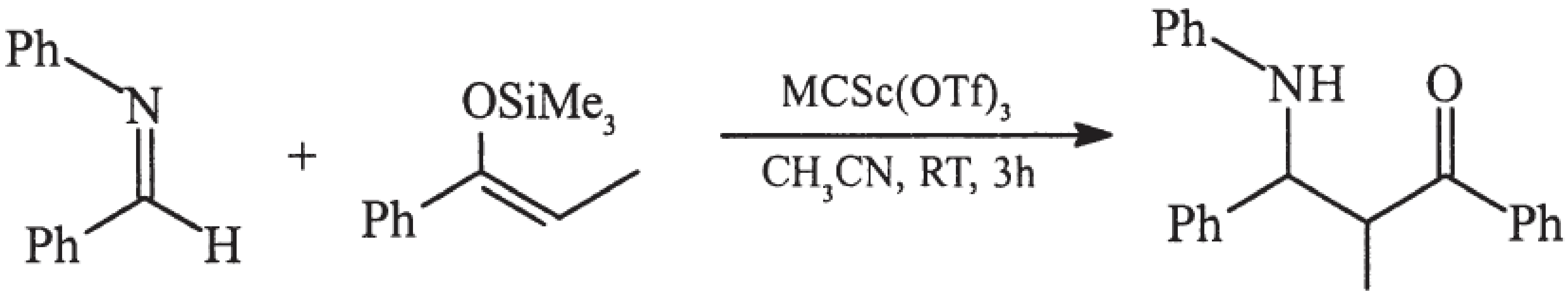
Acid Catalysts

Microencapsulated scandium trifluoro methane sulfonate has been introduced as catalyst in its line of "Green" Chemical Reagents. Scandium Trifluoromethanesulfate [Sc(OTf)$_3$ or Sc(SO$_3$CF$_3$)$_3$] is a water-stable Lewis Acid that is useful in many synthetic reactions. Scientists produced a microencapsulated Sc(OTf)$_3$ that is recoverable and reusable. It demonstrates higher activity than monomeric Lewis Acid in reactions such as Imino Aldol Reactions, Quinoline Synthesis, Friedel-Crafts Acylation, etc.

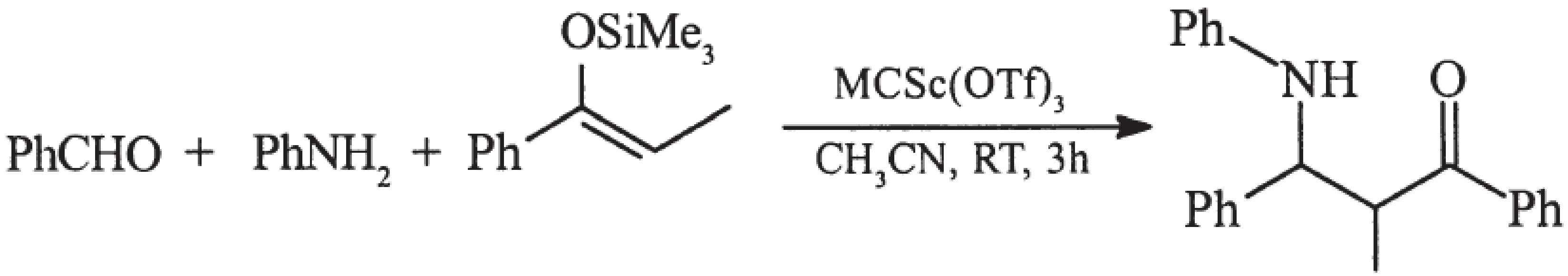


Green Reagent

Acid Catalysts



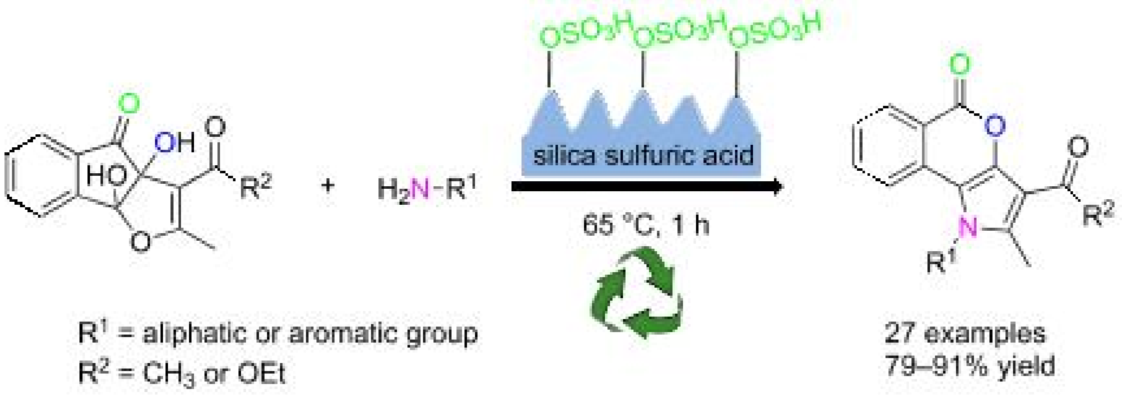
[$MCSc(OTf)_3$] = Microencapsulated scandium trifluoro methane sulfonate



Reference: 1. S. Kobayashi, I. Hachiya, H. Ishitani and M. Araki, Synlett., 1993,472.
2.. A. Kawada, S. Mitamura and S. Kobayashi, Synlett., 1994,545.
3.. S. Kobayashi, M. Araki and M. Yasuda, Tetrahedron Lett., 1995,36,5773.

Green Reagent

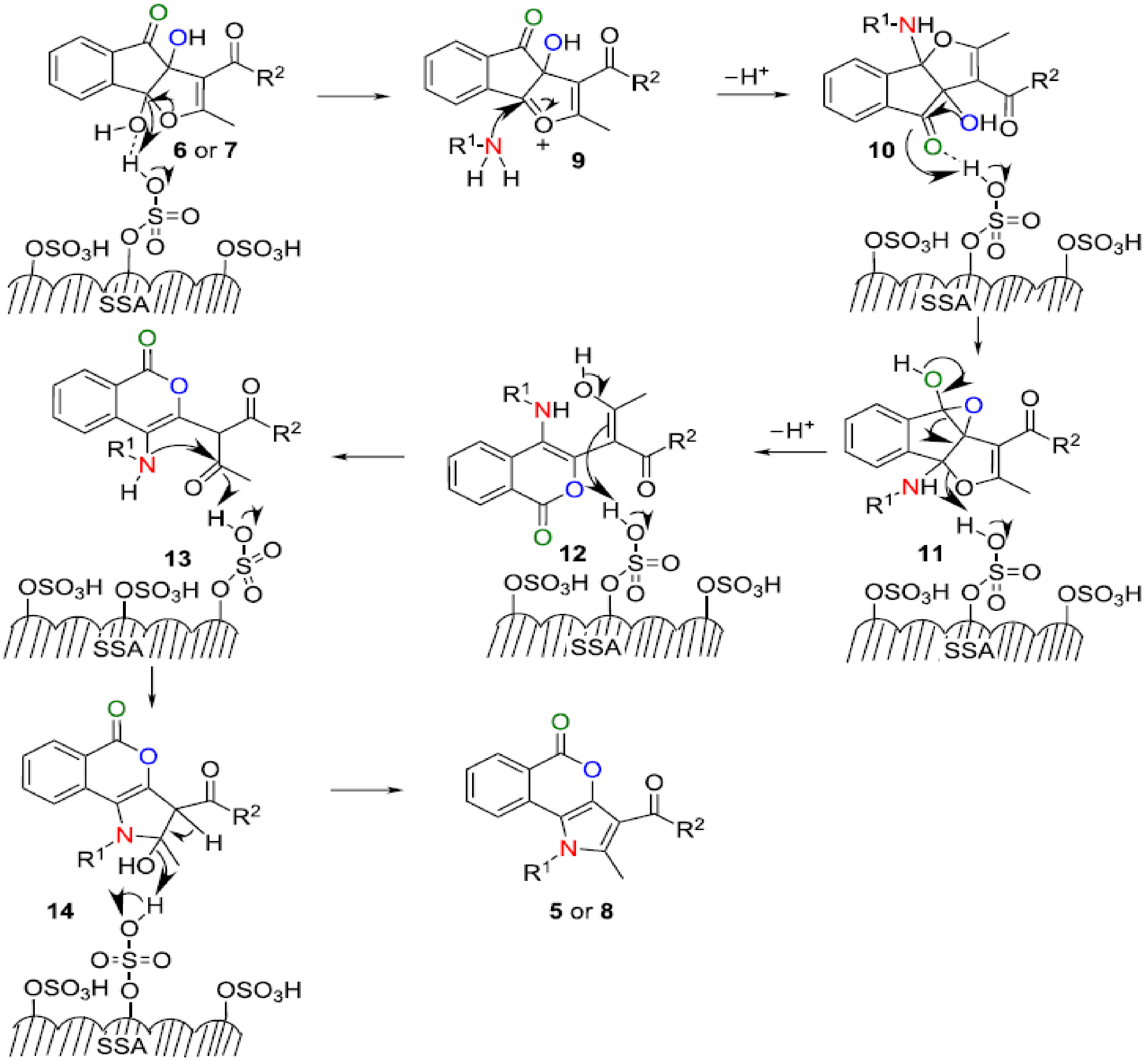
Silica sulfuric acid: a reusable solid catalyst



The methodology has a series of intrinsic advantages such as easy preparation of the solid supported SSA from chlorosulfonic acid and silica gel, less energy and manpower usage, easy product isolation/purification and operational simplicity, which lead to the synthetic route "benign by design". This is the first report, in which a rearrangement reaction has been carried out on the solid surface of SSA.

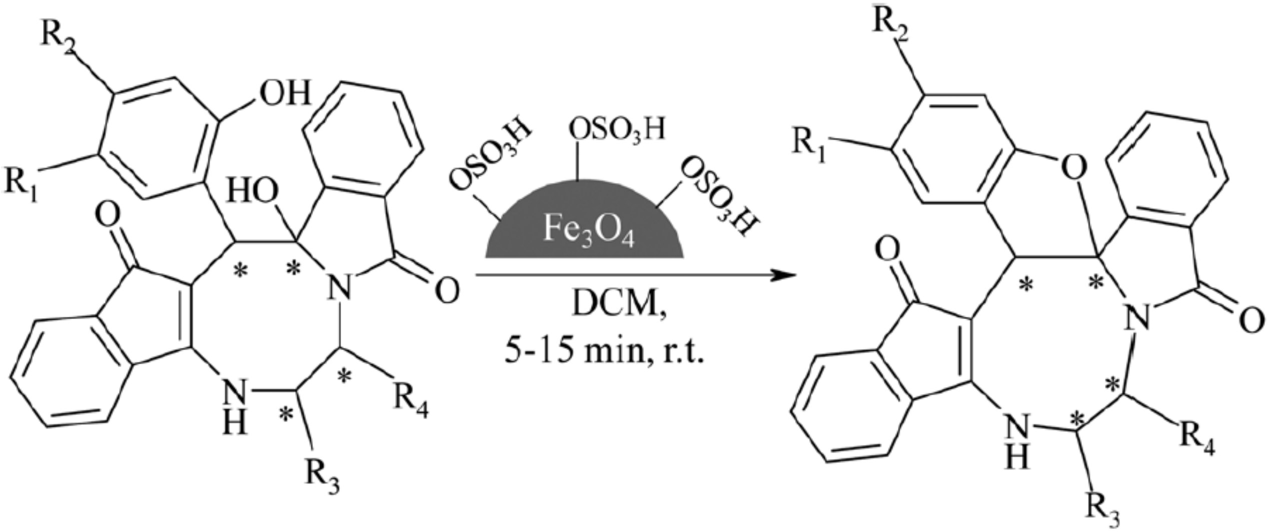
Reference: Beilstein J. Org. Chem. 2013, 9, 2344–2353.

Green Reagent



Green Reagent

Magnetically separable a reusable solid catalyst



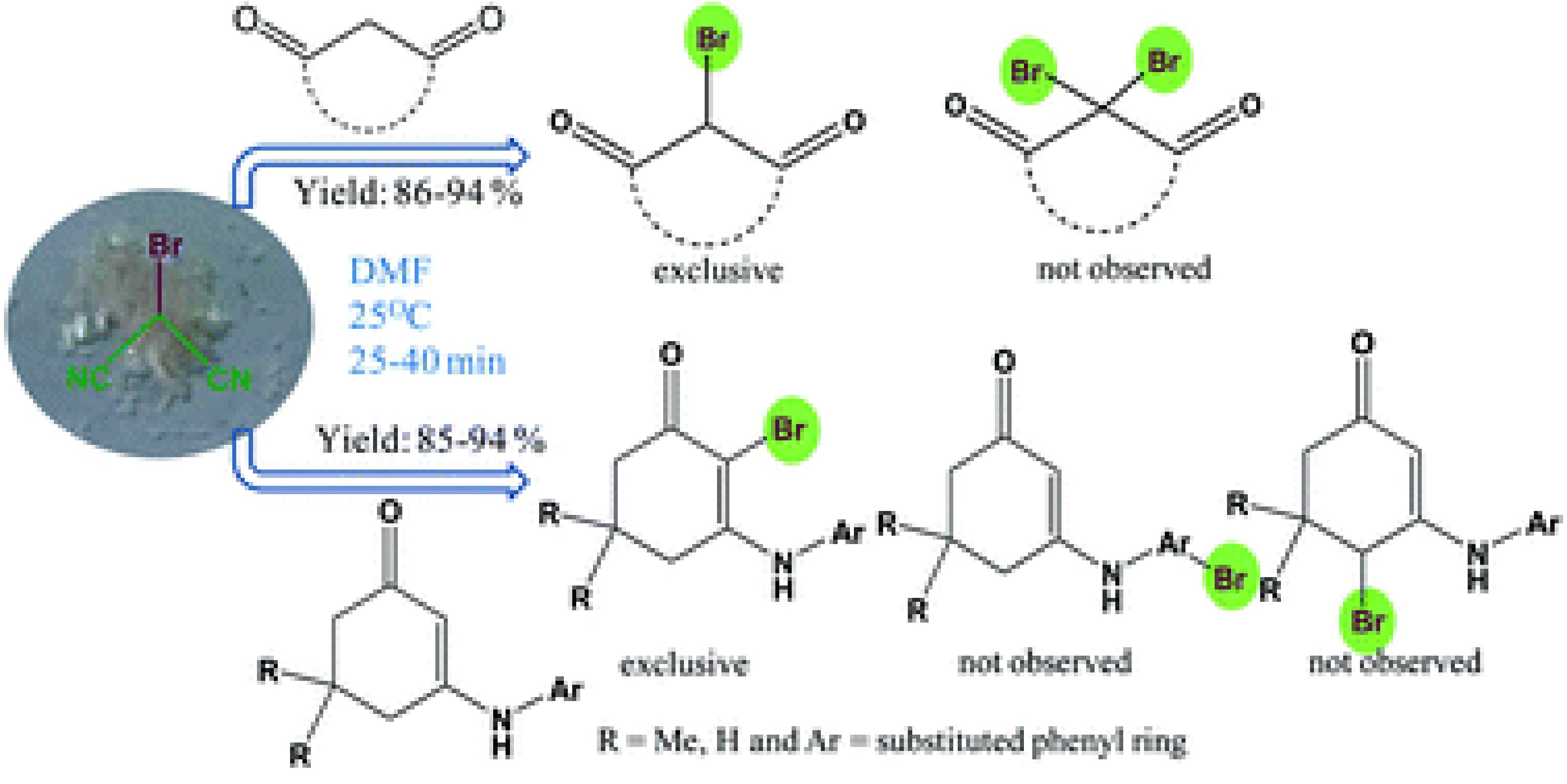
R_1, R_2, are H, Me, F, Cl, Br, OMe
$R_3 = R_4 = H$ in **1a-f** and **1a′-f′**
R_3 =Me, R_4 = H in **1g-l** and **1g′-l′**
R_3, R_4 = -$(CH_2)_4$- in **1m-r** and **1m′-r′**

2a-f and **2a′-f′**
2g-l and **2g′-l′**
2m-r and **2m′-r′**

Reference: Sudipta Pathak, Kamalesh Debnath, Md. Masud Rahaman Mollick and Animesh Pramanik, RSC Adv., 2014, 4, 23779

Green Reagent

Less corrosive Reagents: Monobromomalononitrile (MBM)



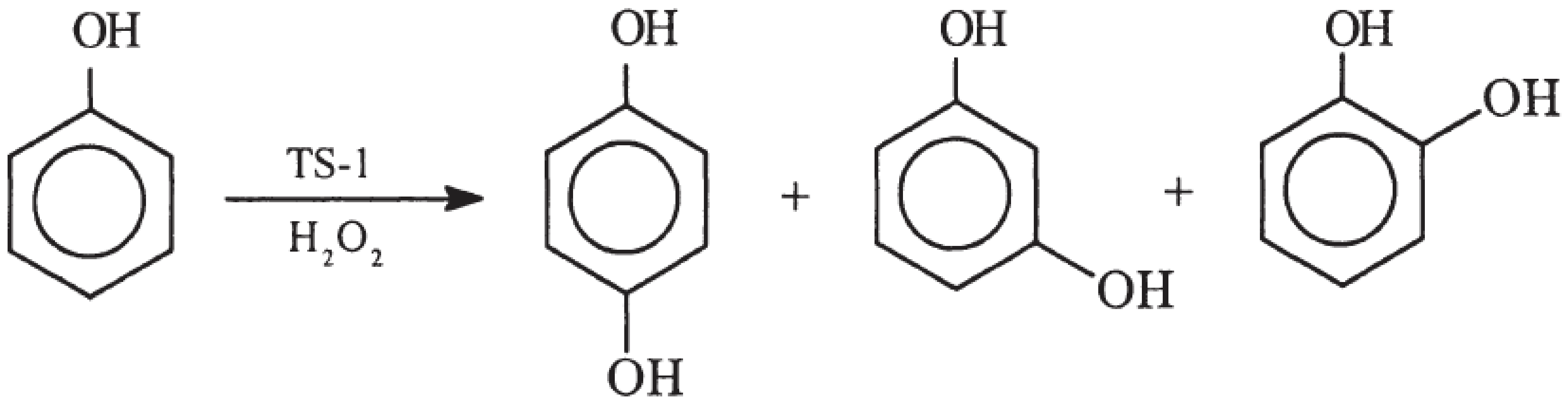
Green Reagent

MBM can act as a selective and efficient mono brominating agent. The efficacy of the methodology lies in the bromination of 1,3-dicarbonyl compounds and enamines containing activated aromatic rings. This methodology has the advantages of easy preparation of MBM, shorter reaction time and high yields of the product formation. The less reactive MBM can be a very good substitute for relatively more reactive NBS in regioselective mono bromination of 1,3-dicarbonyl compounds and enamines. Moreover the application of this metal free organo brominating agent is environmental friendly and can be considered as a green reagent within the domain of Green Chemistry principles.

Reference: Sudipta Pathak, Ashis Kundu and Animesh Pramanik, RSC Adv., 2014, 4, 10180

Green Reagent

Oxidation Catalysts

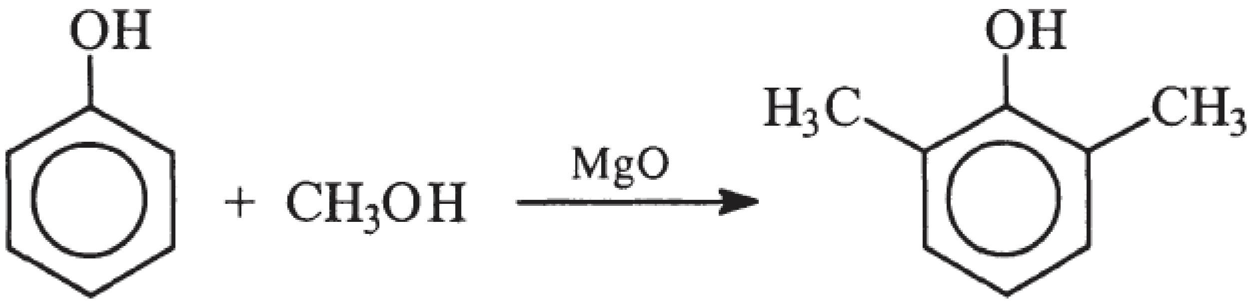


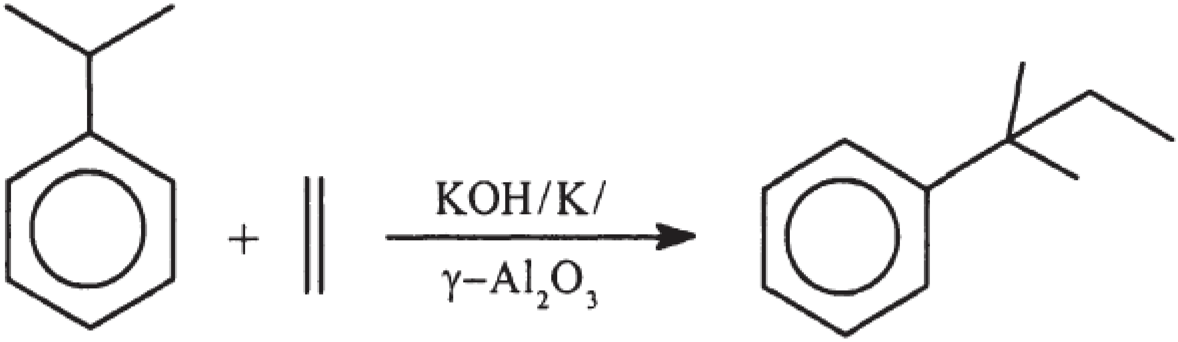
There has been considerable success in the use of molecular sieves (titanium and vanadium) in commercial units. The most important application oftitanium silicates (TS-I) is the hydroxylation of phenol, giving mixtures of hydroquinone and catechol. The process is clean, giving excellent conversion to product with very little waste.

Reference: A.W. Ramaswamy, S. Sivbasanker and P. Ratnasamy, Microporous Mater, 1994,2,451.

Green Reagent

Basic Catalysts





The industrial applications of basic catalysts are in the alkylation of phenol, side chain alkylation and isomerisation reactions

Reference: (a) H. Clark, A.P. Kybett and OJ. Macquarrie, 'Supported Reagents: Preparation, Analysis and Applications', VCH, New York, 1992.
(b) T. Ando, S.1. Brown, I.H. Clark, D.G. Cork, T. Hanatusa, 1. Lehira, I.M. Miller and M.J. Robertson, J Chern. Soc., Perkin Trans., 1986, 2, 1133.

Green Methodology

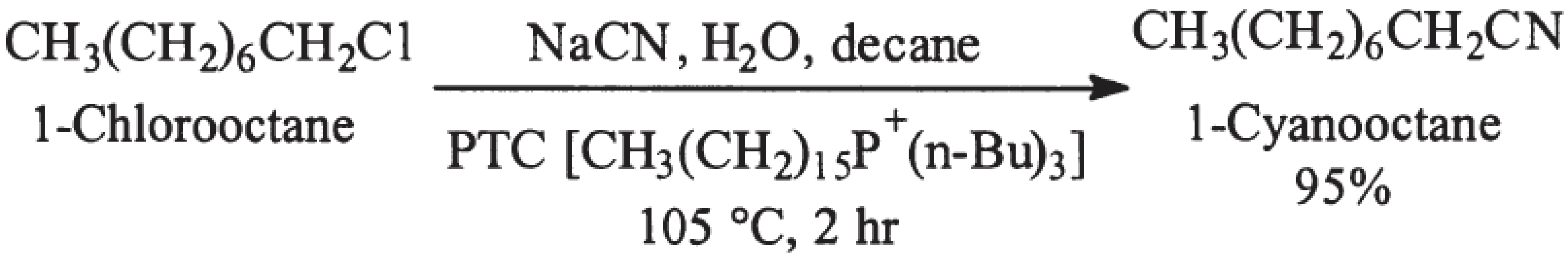
Phase-transfer catalysts (PTC)

Difficulties are often encountered in organic synthesis if the organic compound is soluble in organic solvent and the reagent in water. In such cases, the two reactants will react very slowly and the reaction proceeds only at the interface where these two solutions are in contact. The rate of the reaction can, of course, be slightly increased by stirring the reaction mixture and by using aprotic polar solvents, which solvate the cations so that the anions are free. Such solvents (like dimethylsulfoxide, dimethylformamide) are expensive and their removal is difficult. Also the use of strong bases (which are necessary for the reactions like Wittig etc.) create other problems and many side reactions take place. These problems can be overcome by using a catalyst, which is soluble in water as well as in the organic solvent. Such catalysts are known as phase-transfer catalysts (PTC).

Green Methodology

Phase-transfer catalysts (PTC)

The PTC reaction, in fact, is a methodology for accelerating the reaction between water insoluble organic compounds and water soluble reactants (reagent). The basic function of PTC is to transfer the anion (from the reagent) from the aqueous phase to the organic phase. As a typical example, the reaction of 1-chlorooctane with NaCN in water does not give 1-cyanooctane even if the reaction mixture is stirred for several days. However, if a small quantity of an appropriate PTC is added the product is formed in about 2 hr giving 95% yield



$$\underset{\text{1-Chlorooctane}}{CH_3(CH_2)_6CH_2Cl} \xrightarrow[\text{PTC } [CH_3(CH_2)_{15}P^+(n\text{-}Bu)_3]\ 105\ ^\circ C,\ 2\ hr]{NaCN,\ H_2O,\ decane} \underset{\substack{\text{1-Cyanooctane}\\ 95\%}}{CH_3(CH_2)_6CH_2CN}$$

Green Methodology

Exapmles of Phase-transfer catalysts (PTC)

(i) Aliquat 336: methyl trioctyl ammonium chloride, $N^+CH_3(C_8H_{17})_3Cl^-$

ii) Benzyl trimethyl ammonium chloride or bromide (TMBA), $N^+(CH_3)_3CH_2C_6H_5X^-$ (X = Cl or Br)

(iii) Benzyl triethyl ammonium chloride or bromide (TEBA), $N^+(C_2H_5)_3CH_2C_6H_5X^-$ (X = CI or Br)

(iv) Tetra-n-butyl ammonium chloride, bromide, chlorate or hydroxide, $N^+(n\text{-}Bu)_4X^-$ (X = CI, Br, $Cl0_4$, OH)

(v) Cetyl trimethyl ammonium chloride or bromide (CTMAB for bromide), $N^+(CH_3)_3(CH_2)_{15}CH_3X^-$ (X = CI or Br)

(vi) Benzyl tributyl ammonium chloride, $C6H_5CH_2(n\text{-}C_4H_9)_3N^+CI^-$

vii) Benzyl triphenyl phosphonium iodide, $C_6H_5CH_2(C_6H_5)_3P^+I^-$

Another catalyst, crown ether is also widely used as PTC.

Green Methodology

Advantages of Phase-transfer catalysts (PTC)

(i) Are fast and do not require vigorous conditions.

(ii) Do not require expensive aprotic solvents.

(iii) The reaction usually occurs at low temperature.

(iv) The reaction is conducted in water and hence does not require anhydrous conditions.

(v) With the help of PTC the anion is made available in the organic solvent and so the nUc1eophilicity increases.

(vi) The work-up procedure is simple.

(vii) Use of strong bases (like alkoxide, sodamide, sodium hydride) in the reactions is avoided. The reaction proceeds even with OH- as it becomes strong nuc1eophile in presence of PTC.

(viii)Except the reactions which are sensitive to water, all other reactions can be carried out by PTC.

Advantages of PTC w.r.t. Green Chemistry

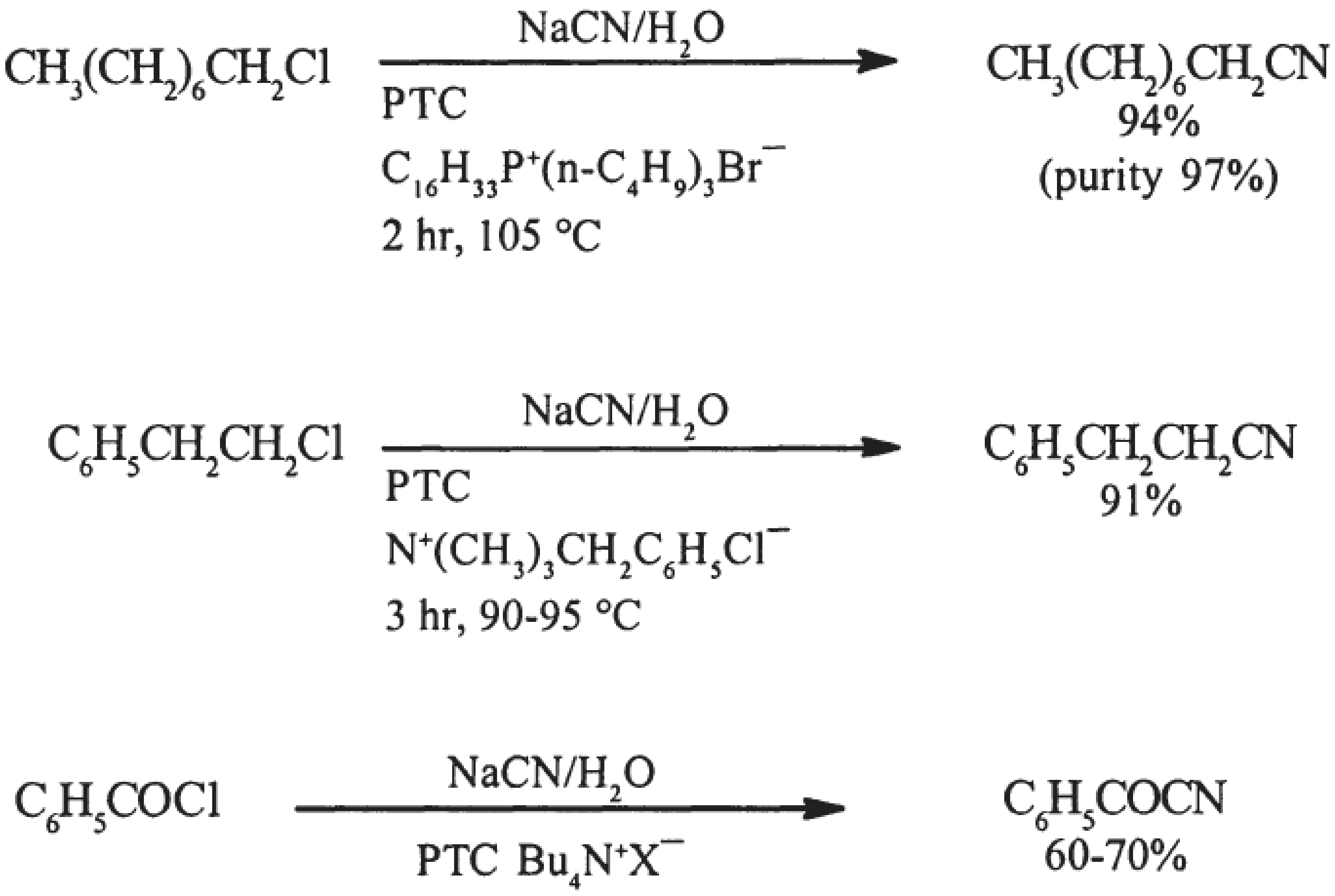
(i) As the reaction is in two phases, a benign solvent may be used since PTC devoids the solubility for all the reactants like dipolar aprotic solvent and dimethylcarbonate. Moreover, in some cases organic solvents may not be required at all, the substrate forming the second phase.

(ii) The procedures of separation are simple resulting in less waste as the organic layer is mainly free from water soluble compounds and can easily be decanted off. It is important to vigil the concentration of anion in organic phase as it should not exceed the concentration of catalyst (unless it is soluble in absence of a catalyst).

(iii) PTC catalysed reactions are very rapid as the anions in the organic phase have very few water molecules associated with them making them highly reactive because of less activation energy which causes higher productivity.

(iv) These reactions can be run at a lower temperature owing to reduced activation energy that causes greater selectivity and lesser by-productformation.

Application of PTC



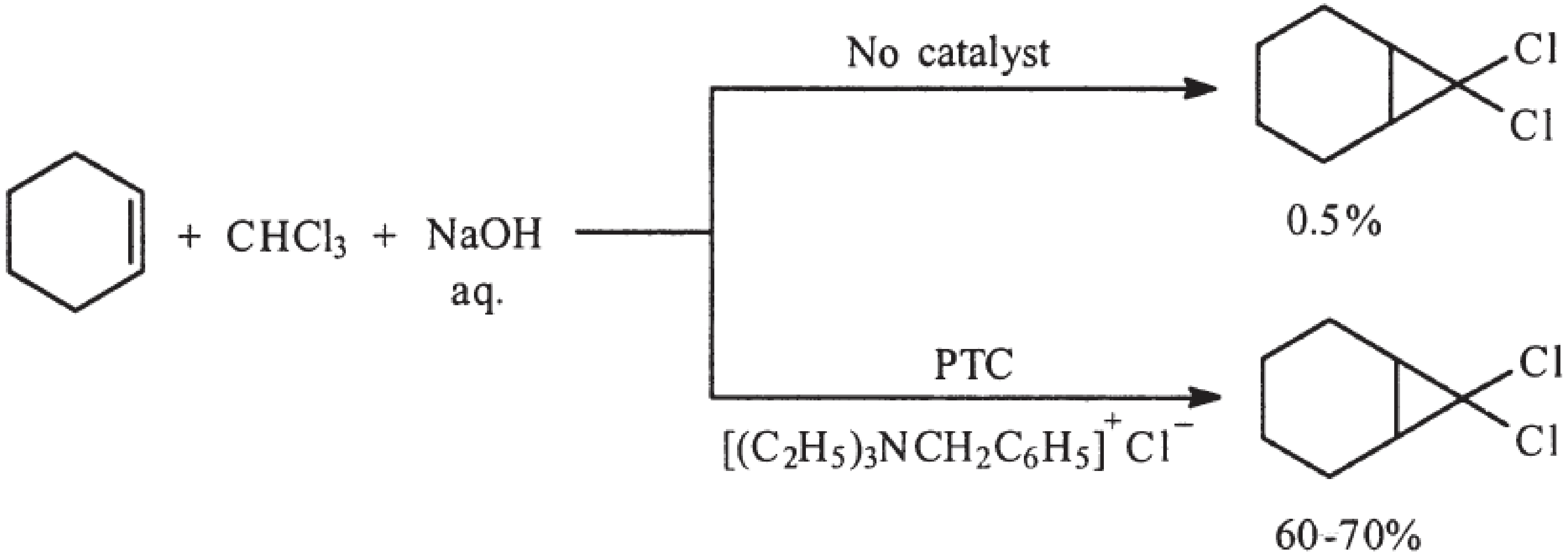
$$CH_3(CH_2)_6CH_2Cl \xrightarrow[\substack{\text{PTC} \\ C_{16}H_{33}P^+(n\text{-}C_4H_9)_3Br^- \\ \text{2 hr, 105 °C}}]{NaCN/H_2O} \underset{\substack{94\% \\ \text{(purity 97\%)}}}{CH_3(CH_2)_6CH_2CN}$$

$$C_6H_5CH_2CH_2Cl \xrightarrow[\substack{\text{PTC} \\ N^+(CH_3)_3CH_2C_6H_5Cl^- \\ \text{3 hr, 90-95 °C}}]{NaCN/H_2O} \underset{91\%}{C_6H_5CH_2CH_2CN}$$

$$C_6H_5COCl \xrightarrow[\text{PTC } Bu_4N^+X^-]{NaCN/H_2O} \underset{60\text{-}70\%}{C_6H_5COCN}$$

Reference: (a) Y.K. Ahluwalia and Renu Aggarwal, Organic Synthesis: Special Techniques, NarosaPublishing House, New Delhi, 200-1. (b) Y.K. Ahluwalia and Renu Aggarwal, Organic Synthesis: Special Techniques, Narosa Publishing House, New Delhi, 2001, pp. 1-58 and the references cited therein. (c) C.M. Starks,J Am. Chern. Soc., 1971,93,195.

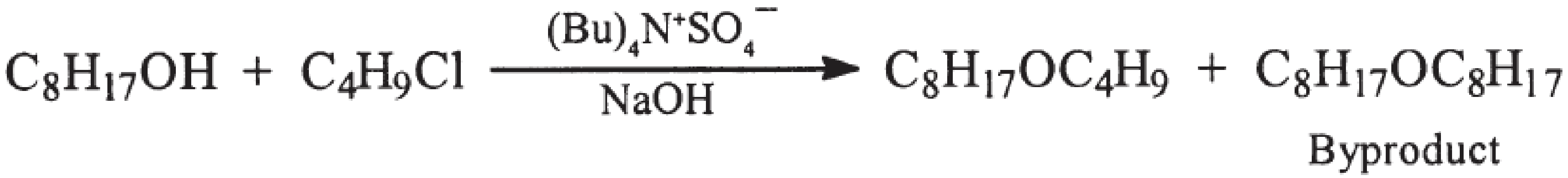
Application of PTC



Reference: A.P. Kreshkov, E.N. Sugushkima and B.A. Krozdov, J Appl. Chern., USSR (English Trans.), 1965,38,2357.

Green Methodology

Williamson's Ether Synthesis



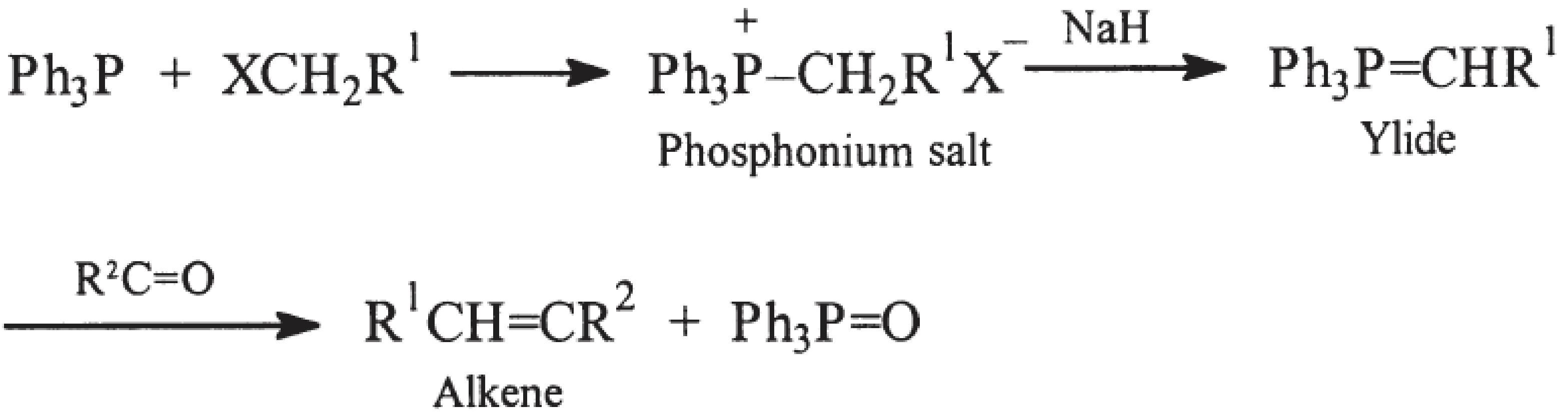
$$C_8H_{17}OH + C_4H_9Cl \xrightarrow[\text{NaOH}]{(Bu)_4N^+SO_4^-} C_8H_{17}OC_4H_9 + \underset{\text{Byproduct}}{C_8H_{17}OC_8H_{17}}$$

The PTC technique provides a simple method for conducting Williamson ether synthesis. Use of excess alcohol or alkyl halide, lower temperature and larger alcohol (e.g. $C_8H_{17}OH$) give higher yields of ethers

Reference: Jorrouse and C.R. Hebd, Scances A cad. Sci. Ser. C, 1951,232, 1424; H.H. Freeman and R.A. Dubois, Tetrahedron Lett., 1975,3251.

Green Methodology

The Wittig Reaction



$$Ph_3P + XCH_2R^1 \longrightarrow \underset{\text{Phosphonium salt}}{Ph_3\overset{+}{P}-CH_2R^1X^-} \xrightarrow{NaH} \underset{\text{Ylide}}{Ph_3P{=}CHR^1}$$

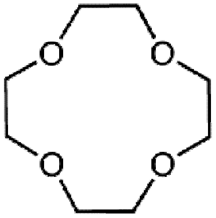
$$\xrightarrow{R^2C{=}O} \underset{\text{Alkene}}{R^1CH{=}CR^2} + Ph_3P{=}O$$

It has been found that the formation of ylide from phosphonium salt can be very conveniently effected by using a PTC in aq. NaOH. In PTC method the yield of the olefin increases. However, this PTC method is applicable only to aldehydes; no olefin is obtained from ketones. Even with this limitation, this method is very convenient for the preparation of a number of olefins of the type $RCH{=}CHR^1$.

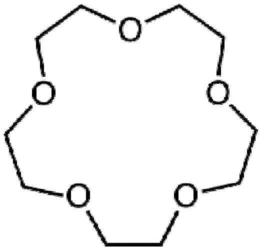
Reference: G. Markl and A. Merz, Synthesis, 1975,245; S. Hung and J. Stemmier, Tetrahedron Lett., 1974,315; W. Tagaki, I. Inouse, Y. Yano and T. Okanogi, Tetrahedron Lett., 1974, 2587.

Crown Ethers

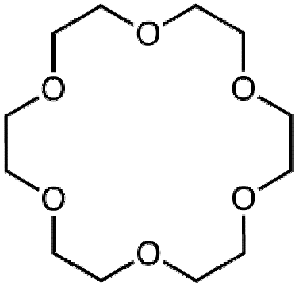
Crowm ether is a group of cyclic polyethers which are used as phase transfer catalysts. These have been used for esterifications, saponifications, anhydride formation, oxidations, aromatic substitution reactions, elimination reactions, displacement reactions, generation of carbenes, alkylations etc.



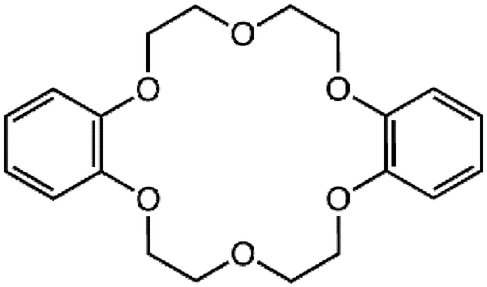
12-crown-4



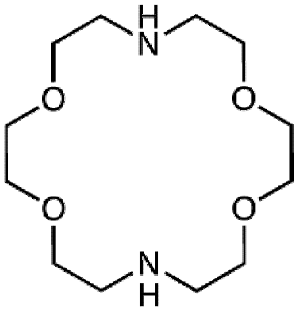
15-crown-5



18-crown-6

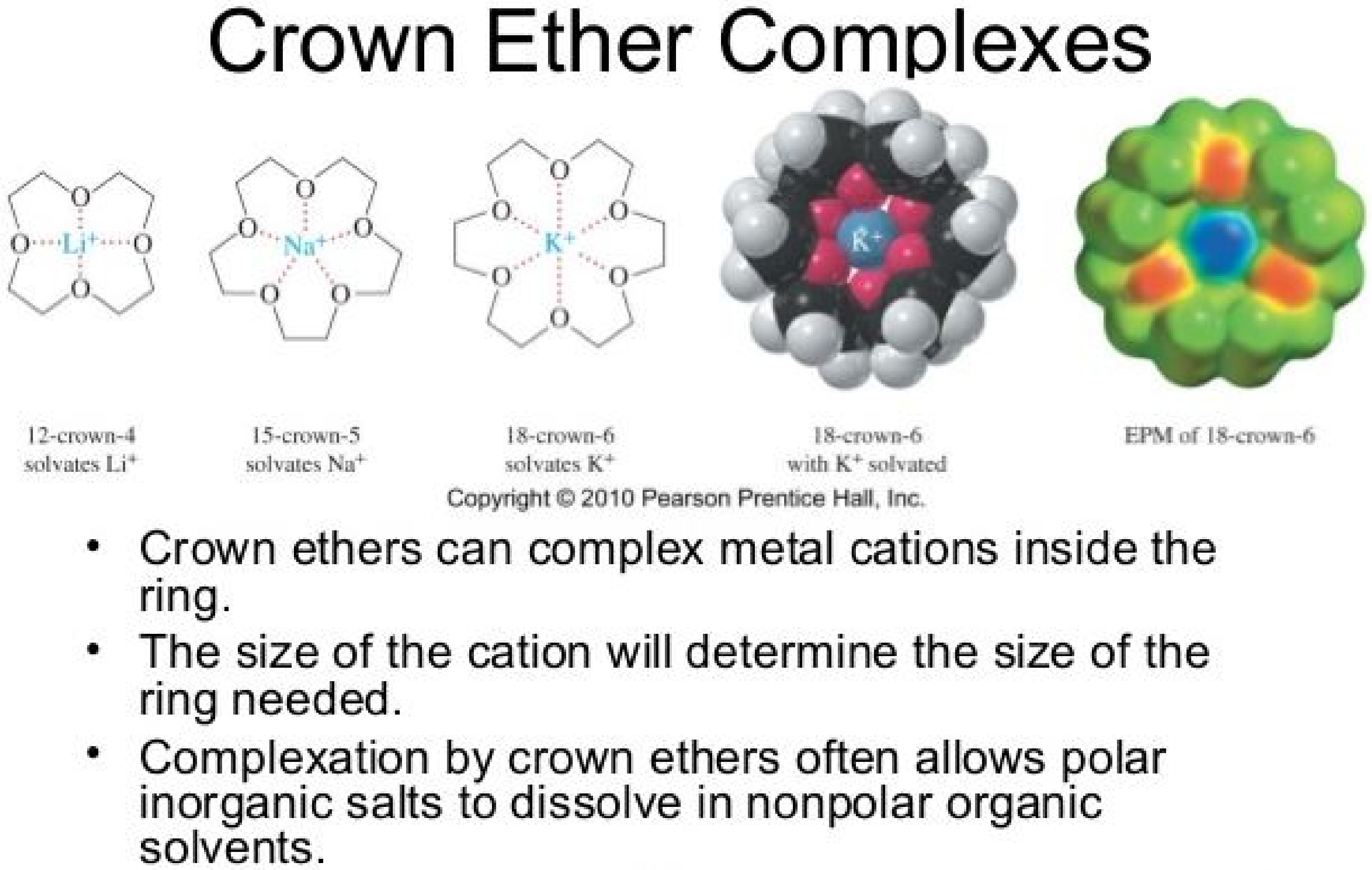


dibenzo-18-crown-6



diaza-18-crown-4

Crown Ethers with metal ion



Crown Ether Complexes

12-crown-4 solvates Li$^+$

15-crown-5 solvates Na$^+$

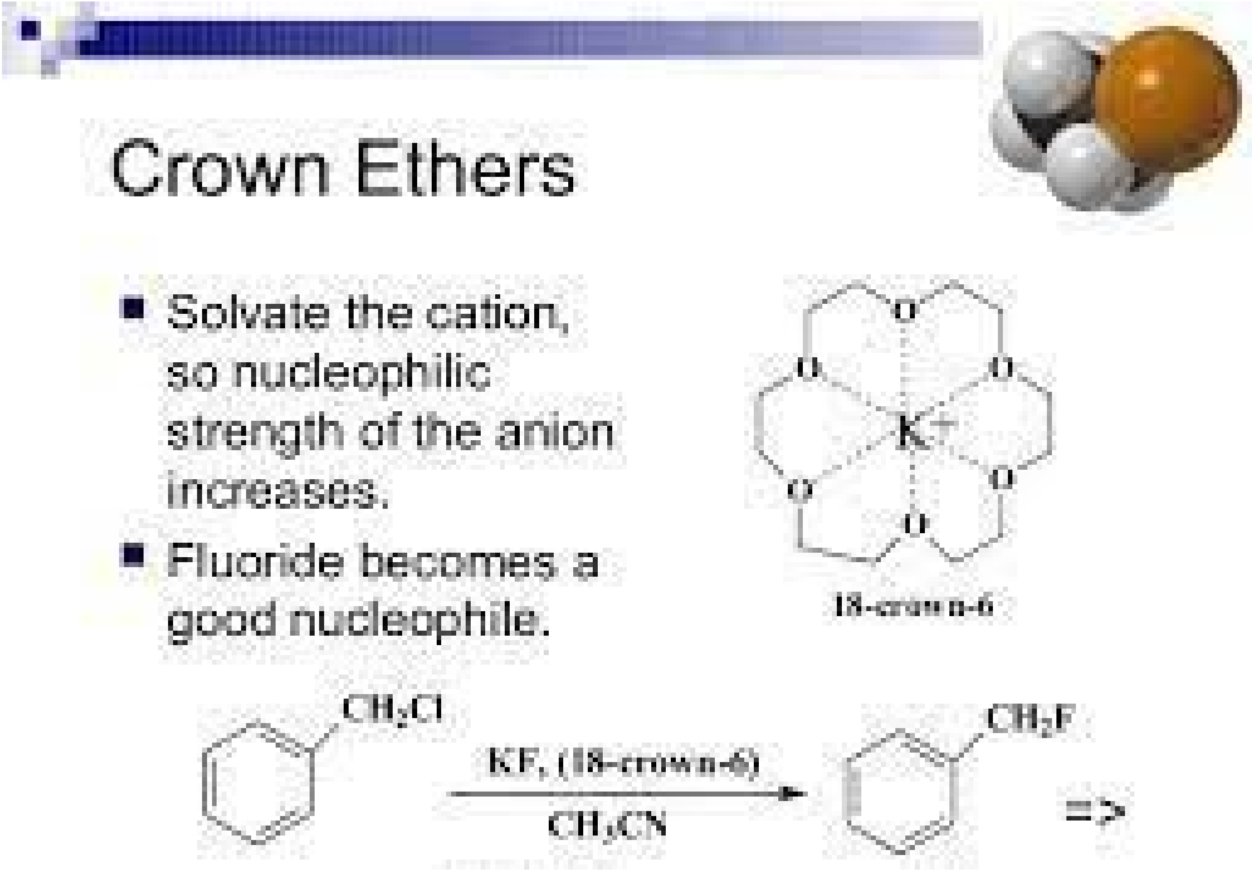
18-crown-6 solvates K$^+$

18-crown-6 with K$^+$ solvated

EPM of 18-crown-6

- Crown ethers can complex metal cations inside the ring.
- The size of the cation will determine the size of the ring needed.
- Complexation by crown ethers often allows polar inorganic salts to dissolve in nonpolar organic solvents.

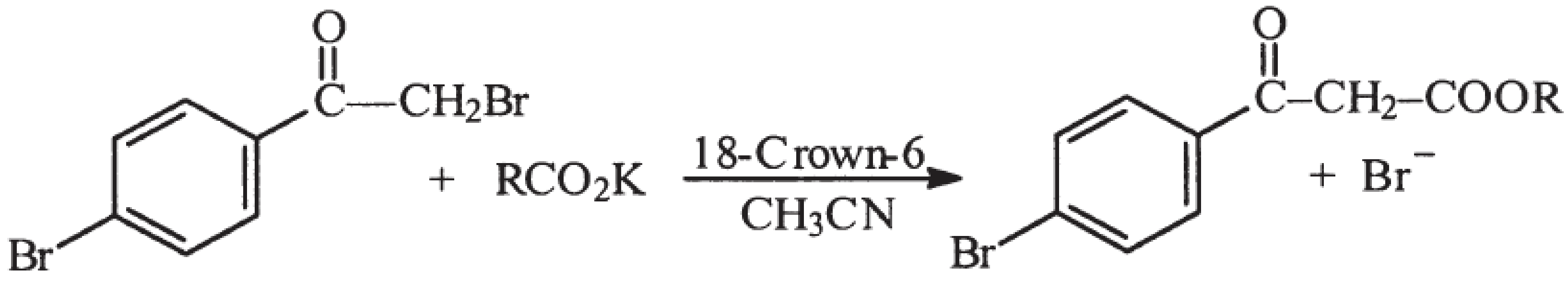
Application of Crown ether



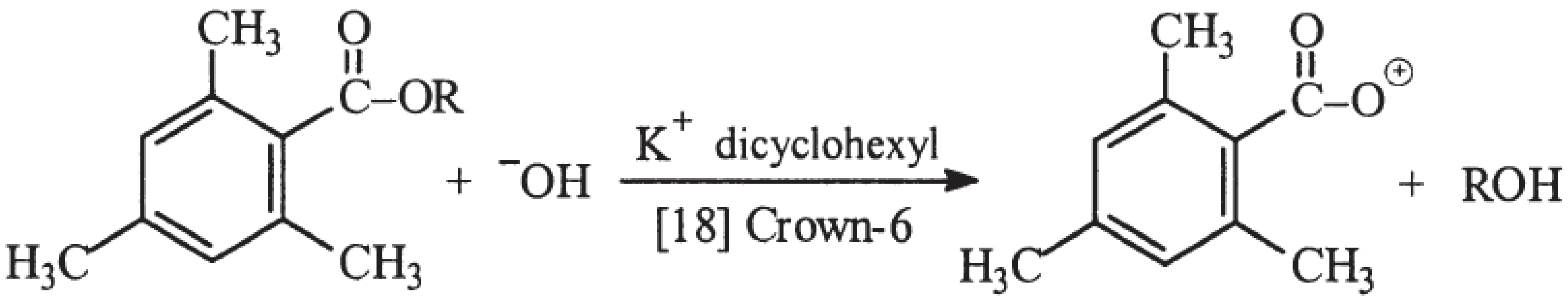
Crown Ethers

- Solvate the cation, so nucleophilic strength of the anion increases.
- Fluoride becomes a good nucleophile.

Phase Transfer Catalyst



R = H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, C_6H_5, 2-$CH_3C_6H_4$,
2,4,6-trimethylbenzoyl, 4-t-butyl C_6H_4

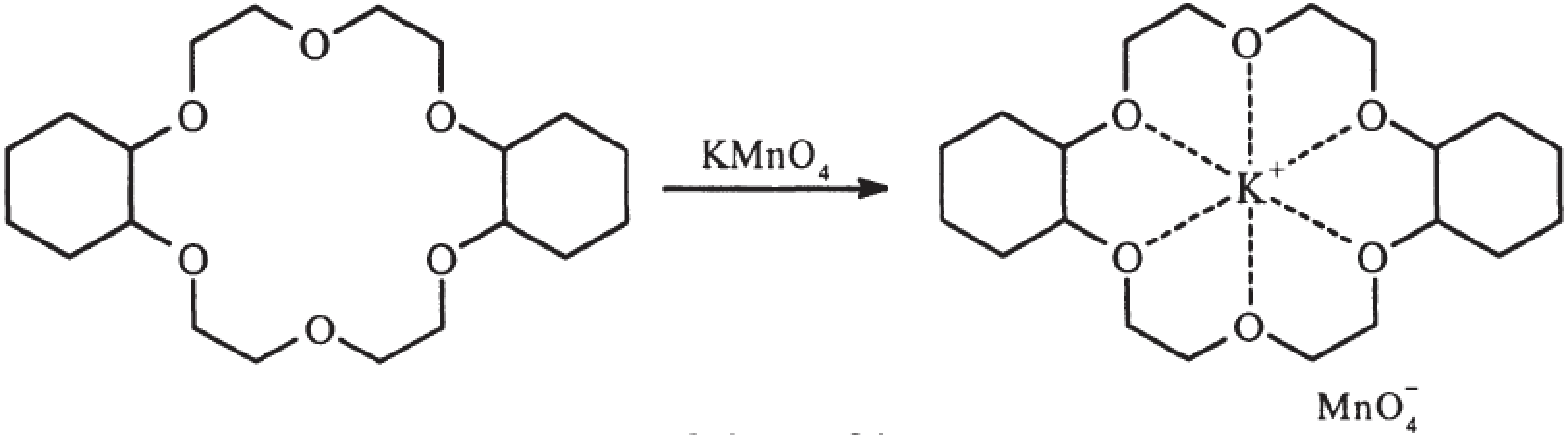


R = CH_3, t-Bu, neopentyl

Reference: C.J. Pedersen, J. Arn. Chern. Soc., 1967,89,2485,7017; 1970,92,386,391; C.J. Pedersen and H.K. Friensdorff, Angew. Chern. Int. Ed. Engl., 1972, 11, 16.

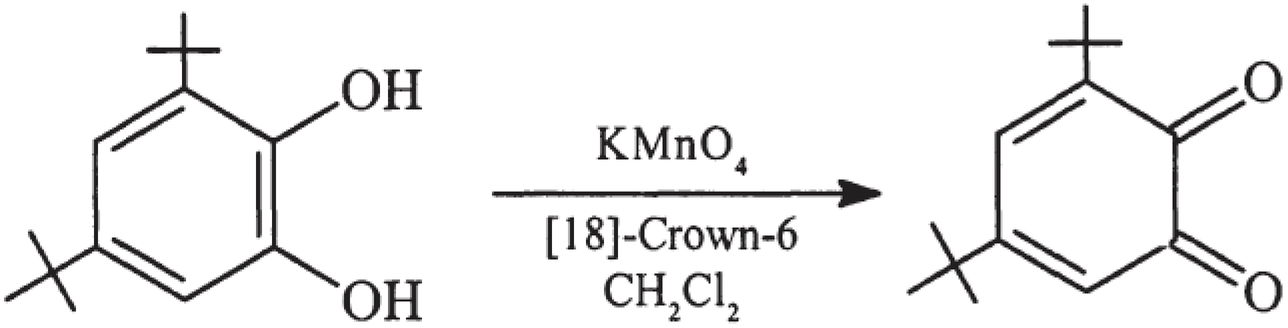
Green Reagent

Potassium permanganate is the most widely used reagent for the oxidation of organic compounds. It is usually used in aqueous solution and this restricts its usefulness since many compounds are not sufficiently soluble in water and only a few organic solvents like acetic acid, t-butanol, dry acetone and pyridine are resistant to the oxidising action of the reagent. Alternatively, oxidation in presence of crown ether, dicyclohexano-18-crown-6 forms a permanganate complex. Under these conditions permanganate becomes soluble in benzene and the resulting solutions are excellent reagents for oxidation of a variety of organic substrate in organic solvents.



Use of Phase Transfer Catalyst

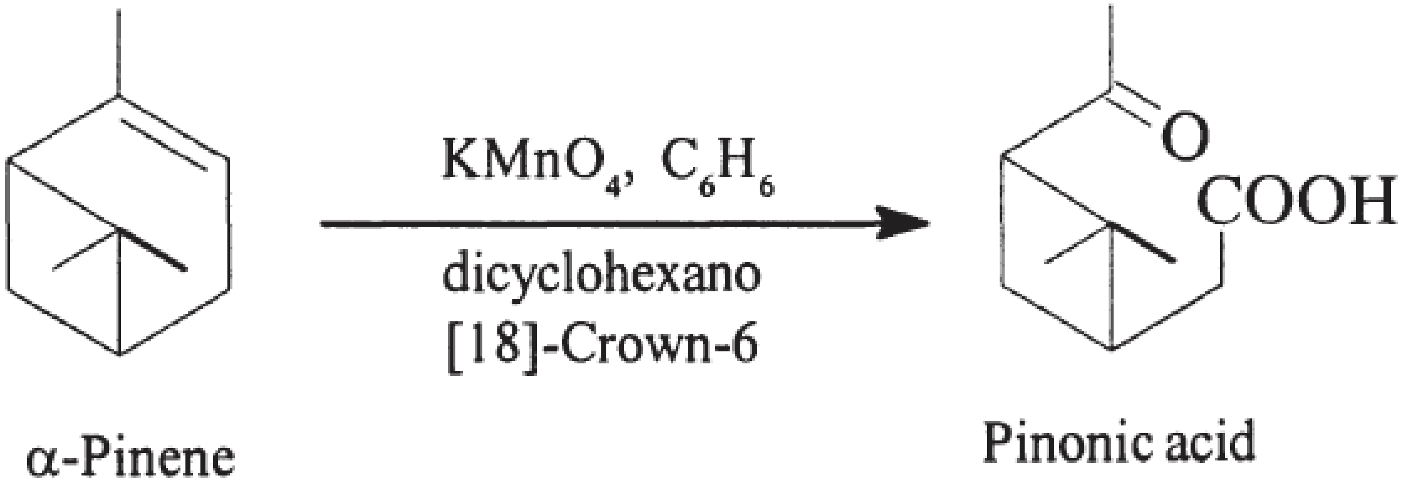
Applying this technique, substituted catechols are converted into corresponding o-quinones in excellent yields wherein only one equivalent of $KMnO_4$ is used.



Reference: Charles M. Starks and Charles Liotta, Phase Transfer Catalysts, Academic Press, N.Y.

Use of Phase Transfer Catalyst

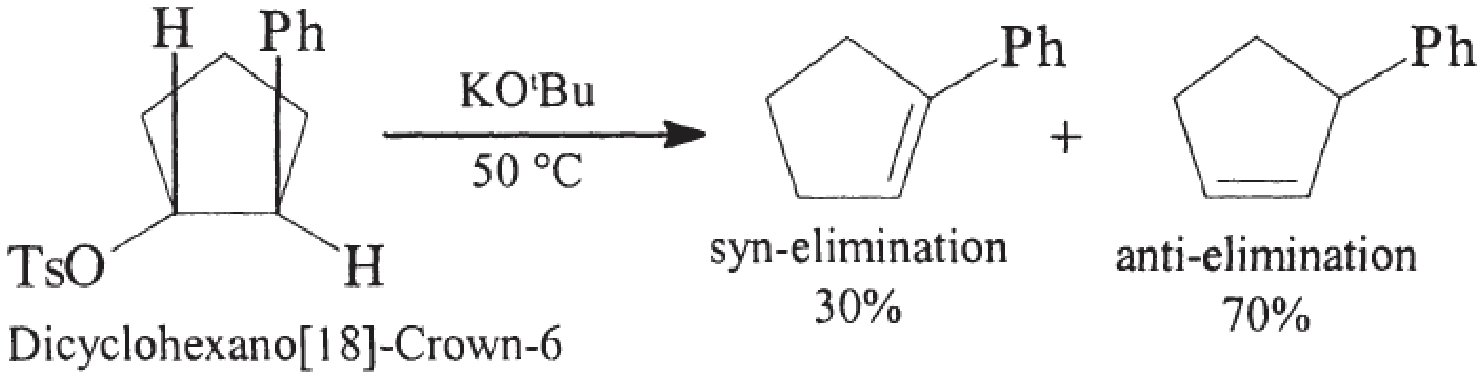
Oxidation of a.-pinene in the presence of crown ethers yield pinonic acid in 90% yield



Reference: D. Sam and H.E. Simmons, J. Arn. Chern. Soc., 1972,94,4024.

Use of Phase Transfer Catalyst

Crown ethers ability to enhance or alter the reaction is significantly important



Reference: G. Gokel, Crown Ethers and Cryptands Monograph, Royal Society of Chemistry, Cambridge, 1991.

Microwave: Green Chemistry

Nonnally microwaves have wavelengths between 1 cm and 1 m (frequencies of 30 GHz to 300 Hz). These are similar to frequencies of radar and telecommunications. In order to avoid any interference with these systems, the frequency of radiation that can be emitted by household and industrial microwave oven is regulated, most of the appliances operate at a fixed frequency of 2.45 GHz.

The microwaves, as we know, are used for heating purposes. The mechanism of how energy is given to a substance which is subjected to microwave irradiation is complex. One view is that microwave reactions involve selective absorption of electromagnetic waves by polar molecules, non-polar molecules being inert to microwaves. When molecules with a pennanent dipole are submitted to an electric field, they become aligned and as the field oscillates their orientation changes, this rapid reorientation produces intense internal heating.

Continuation

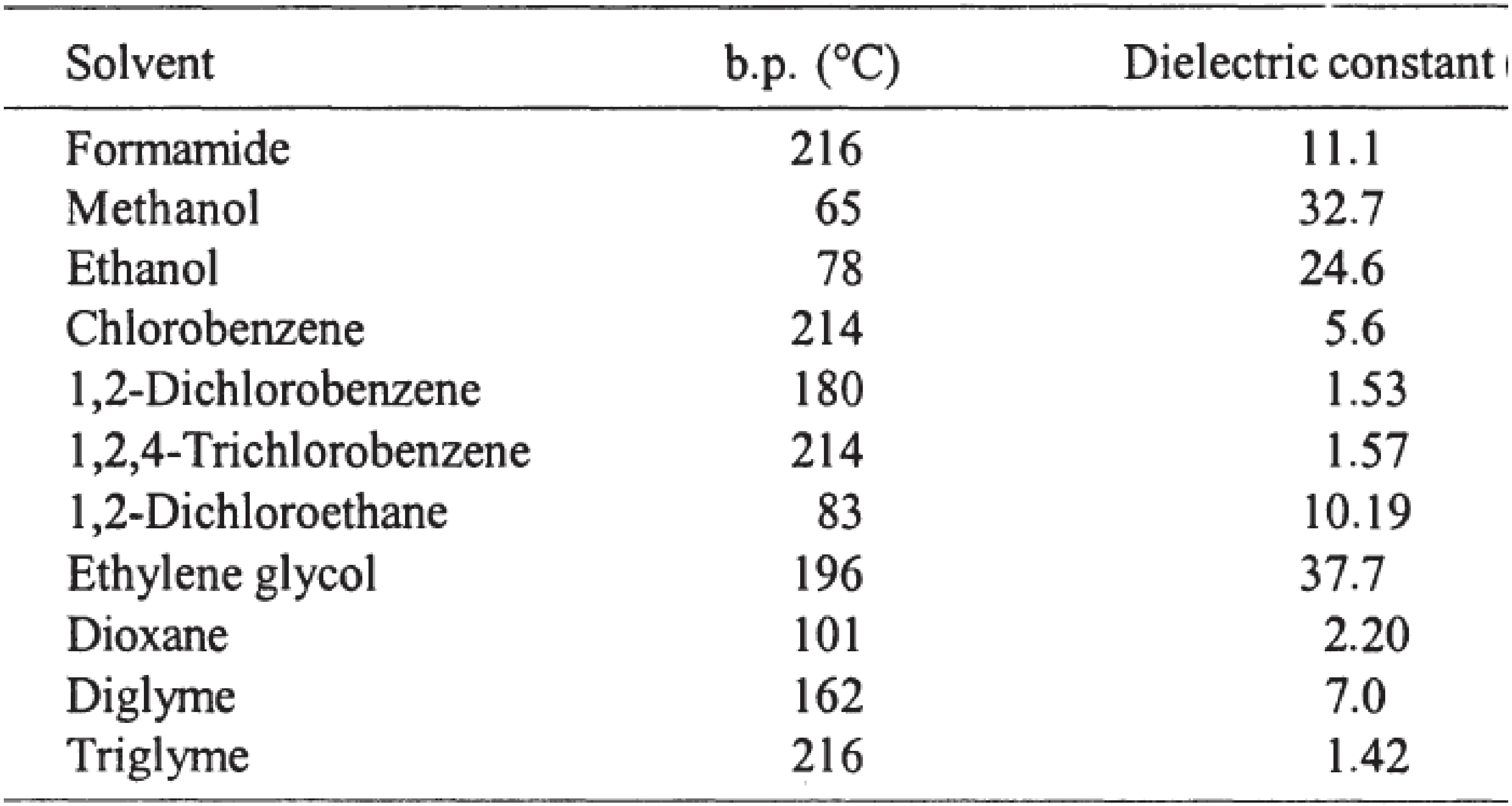
The main difference between classical heating and microwave heating, lies in core and homogenous heating associated with microwaves, whereas classical heating is all about heat transfer by preheated molecules.

The preferred reaction-vessel for microwave induced organic reaction, is a tall beaker (particularly for small scale reactions in the laboratory), looselycovered and the capacity ofthe beaker should be much greater than the volume of the reaction mixture. Alternatively, teflon and polystyrene containers can be used. These materials are transparent to microwaves. Metallic containers should not be used as reaction vessels.

In microwave induced organic reactions, the reactions can be carried out in a solvent medium or on a solid support in which no solvent is used. For reactions in a solvent medium, the choice of the solvent is very important. The solvent to be used must have a dipole moment so as to absorb microwaves and a boiling point at least 20-30 °C higher than the desired reaction temperature.

Continuation

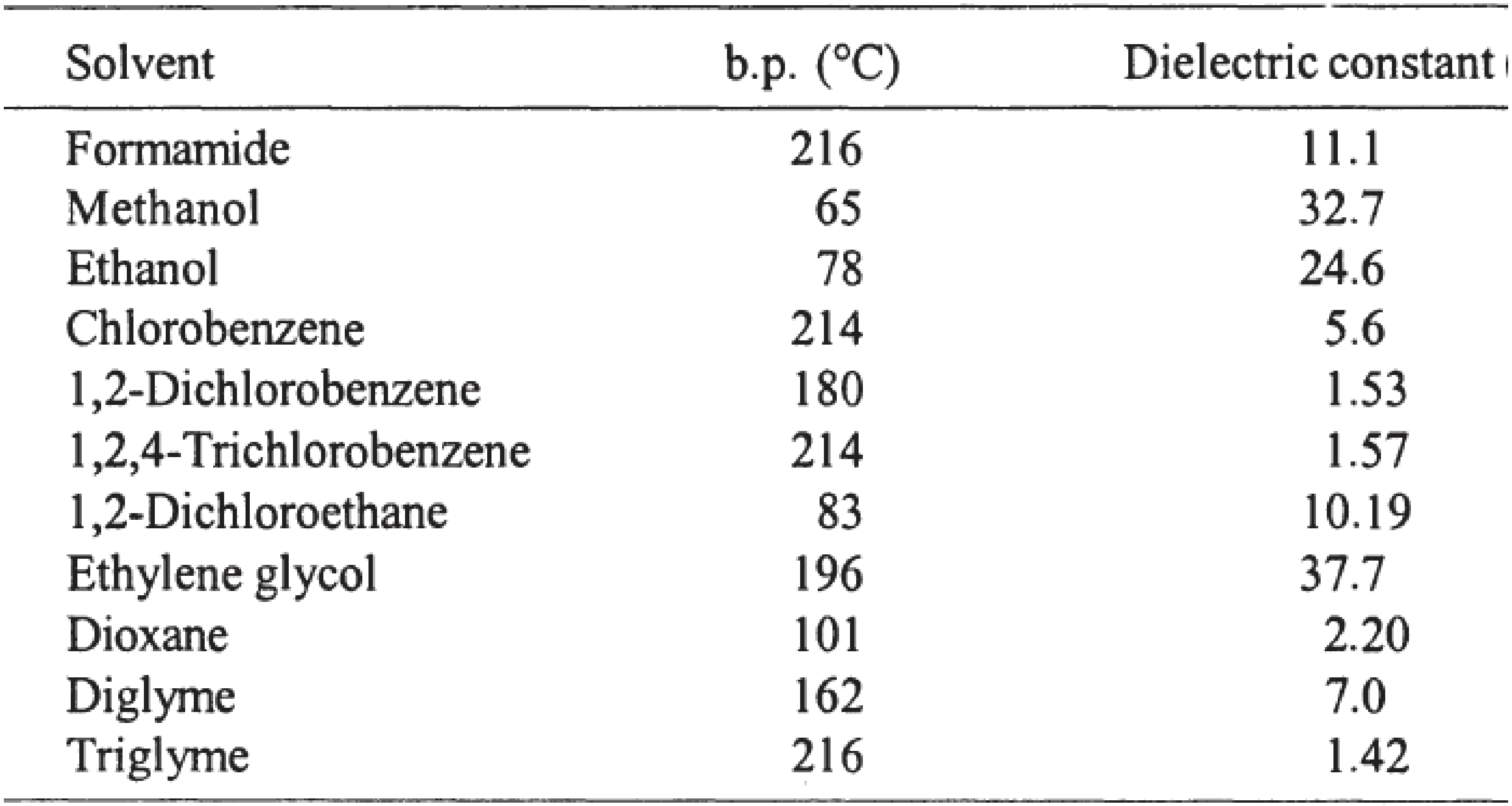
An excellent solvent in a domestic microwave oven is N ,N – dimethylfonnarnide (DMF) (b.p. 160 °C, ε = 36.7). The solvent can retain water fonned in a reaction, thus, obviating the need for water separation. Some other solvents of choice are given as follows:



Solvent	b.p. (°C)	Dielectric constant
Formamide	216	11.1
Methanol	65	32.7
Ethanol	78	24.6
Chlorobenzene	214	5.6
1,2-Dichlorobenzene	180	1.53
1,2,4-Trichlorobenzene	214	1.57
1,2-Dichloroethane	83	10.19
Ethylene glycol	196	37.7
Dioxane	101	2.20
Diglyme	162	7.0
Triglyme	216	1.42

Continuation

An excellent solvent in a domestic microwave oven is N ,N – dimethylfonnarnide (DMF) (b.p. 160 °C, ε = 36.7). The solvent can retain water fonned in a reaction, thus, obviating the need for water separation. Some other solvents of choice are given as follows:



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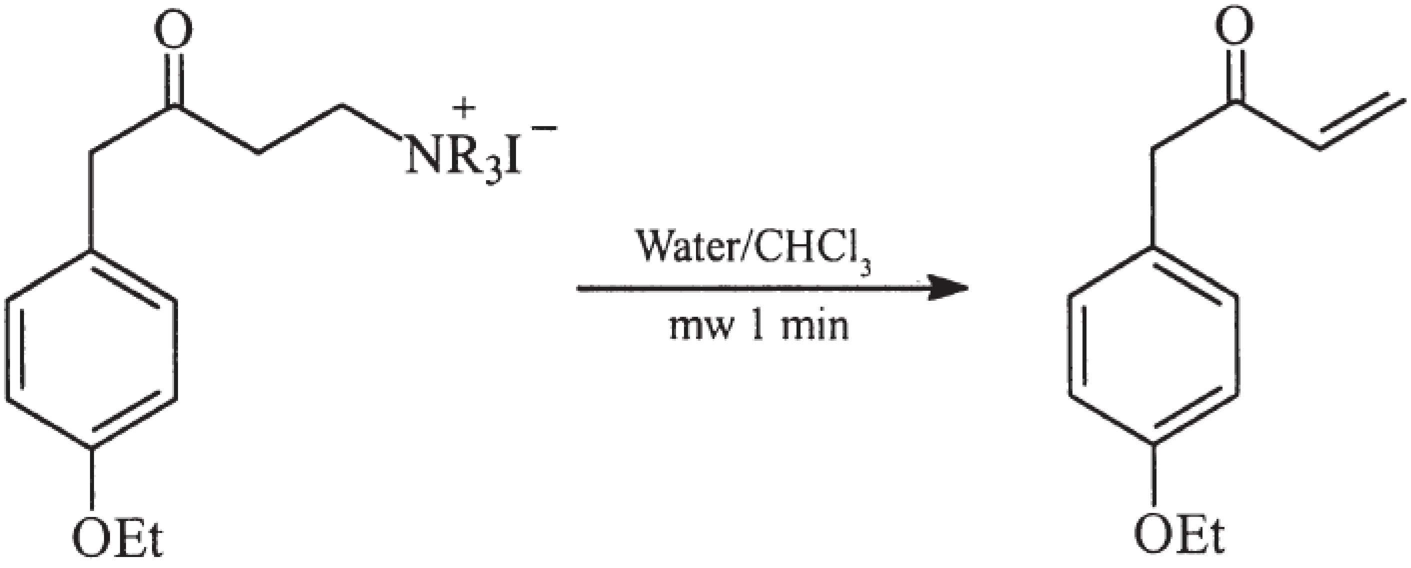
1,2,4-Trichlorobenzene	214	1.57
1,2-Dichloroethane	83	10.19
Ethylene glycol	196	37.7
Dioxane	101	2.20
Diglyme	162	7.0
Triglyme	216	1.42

Continuation

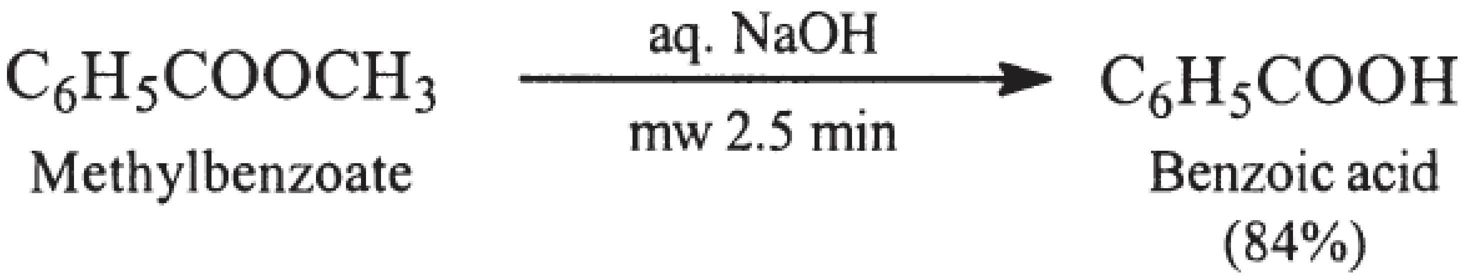
Hydrocarbon solvents, for example, hexane (ε 1.9), benzene (ε 2.3), toluene (ε 2.4) and xylene are unsuitable because of less dipole moment and also because these solvents absorb microwave radiations poorly. However, addition of small amounts of alcohol or water to these solvents can lead to dramatic coupling effects. Liquids which do not have a dipole moment cannot be heated by microwaves. By adding a small amount of a dipolar liquid to a miscible non-dipolar liquid, the mixture will rapidly achieve a uniform temperature under irradiation.

Microwave Assisted Reaction



In this method, normally quaternary ammonium salts are heated at high temperature and the yield of the product is low. Use of microwave irradiation has led to high-yielding synthesis of a thermally unstable Hofmann elimination product. In this water-chloroform system is used.

Microwave Assisted Reaction

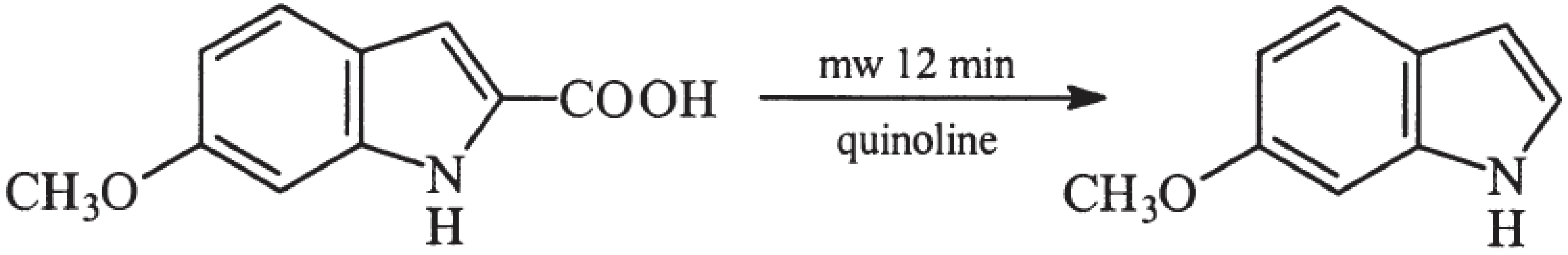


$$\underset{\text{Methylbenzoate}}{C_6H_5COOCH_3} \xrightarrow[\text{mw 2.5 min}]{\text{aq. NaOH}} \underset{\substack{\text{Benzoic acid}\\(84\%)}}{C_6H_5COOH}$$

Saponification of methylbenzoate in aqueous sodium hydroxide under microwave conditions (2.5 min) gives 84% yield of the benzoic acid.

References: M.N. Gedye, F.E. Smith and K.C. Westaway, Can. J. Chern., 1988,66, 17.

Microwave Assisted Reaction:Decarboxylation



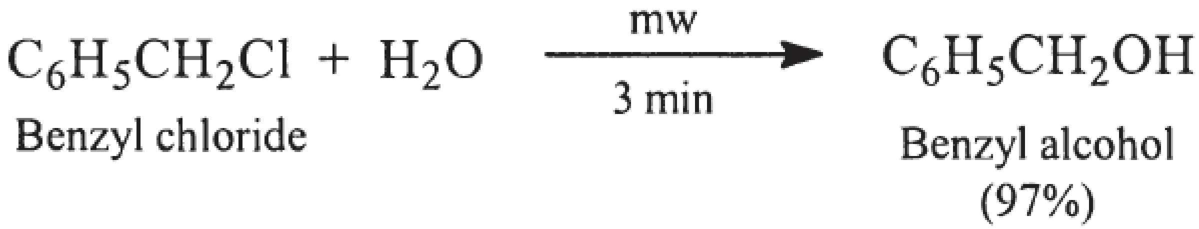
6-Methoxy indole-2-carboxylic acid

6-Methoxyindole
99%

Conventional decarboxylation of carboxylic acids involve refluxing in quinoline in presence of copper chromite and the yields are low. However, in the presence of microwaves, decarboxylation takes place in much shorter time.

References: G.B. Jones and B.I. Chapman, J. Org. Chern., 1993, 58, 5558.

Microwave Assisted Reaction



$$C_6H_5CH_2Cl + H_2O \xrightarrow[3\ \text{min}]{\text{mw}} C_6H_5CH_2OH$$

Benzyl chloride

Benzyl alcohol (97%)

Hydrolysis of benzyl chloride with water in microwave oven gives 97% yield of benzyl alcohol in 3 min. The usual hydrolysis in normal way takes about 35 min.

Reference: R.N. Gedye, W Rank and K.C. Westaway, Can. J. Chern., 1991,69,700.

Microwave Assisted Reaction

$$\mathrm{C_6H_5CH_2Cl + H_2O \xrightarrow[3\ min]{mw} C_6H_5CH_2OH}$$

Benzyl chloride

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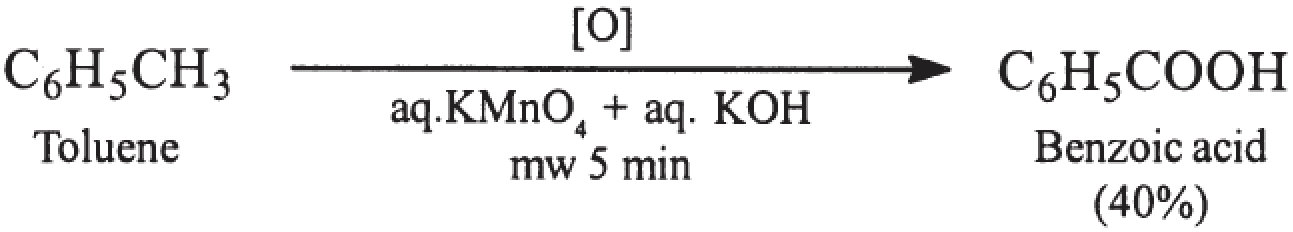
Microwave Assisted Reaction

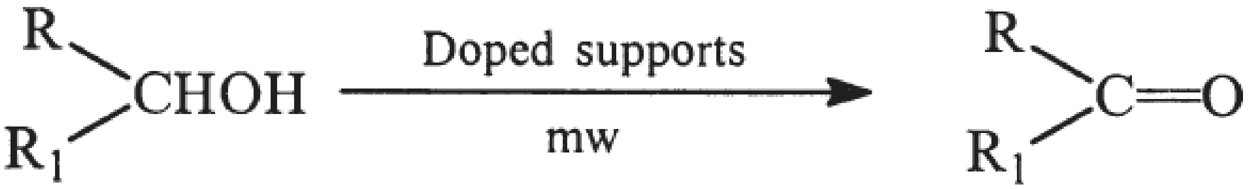


$$C_6H_5CH_3 \xrightarrow[\text{aq.KMnO}_4\text{ + aq. KOH}\ \text{mw 5 min}]{[O]} C_6H_5COOH$$

Oxidation of toluene with $KMnO_4$ under normal conditions of refluxing takes 10-12 hr compared to reaction in microwave conditions, which takes only 5 min and the yield is 40%

Reference: M.N. Gedye, F.E. Smith and K.C. Westaway, Can. J. Chern., 1988,66, 17.

Microwave Assisted Reaction

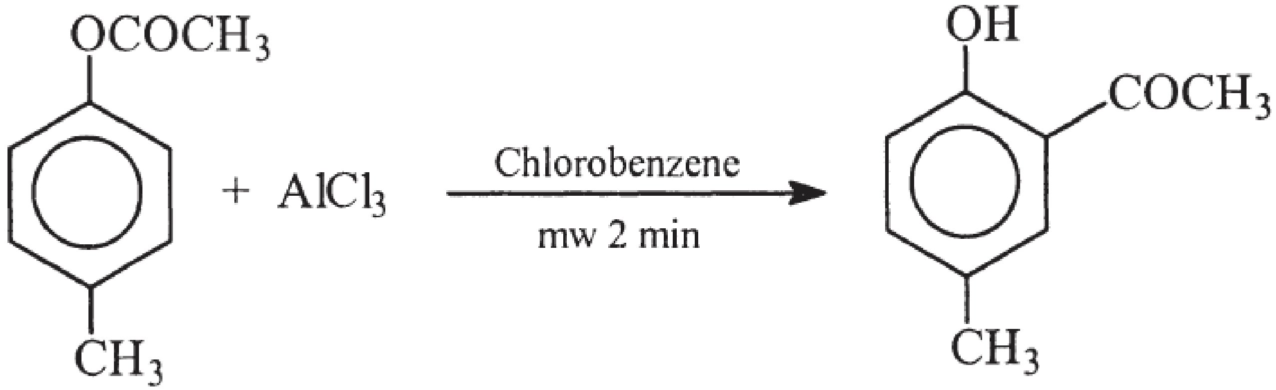


R, R_1 = various aromatic, aliphatic and heterocyclic groups

Similarly, secondary alcohols have been oxidised under microwave irradiation by using doped supports like clayfen (montmorillonite K1O + iron (III) nitrate), silica manganese dioxide, claycop (montmorillonite K1O + copper(II) nitrate)-H_2O_2, CrO_3-wet alumina, iodobenzenediacetate-alumina, $CuSO_4$-alumina, oxone-wet alumina.

Reference: R.S. Verma and R.K. Saini, Tetrahedron Lett., 1997,38,2623; R.S. Verma and D. Kumar, Synth. Cornrnun., 1999,29,1333.

Microwave Assisted Reaction



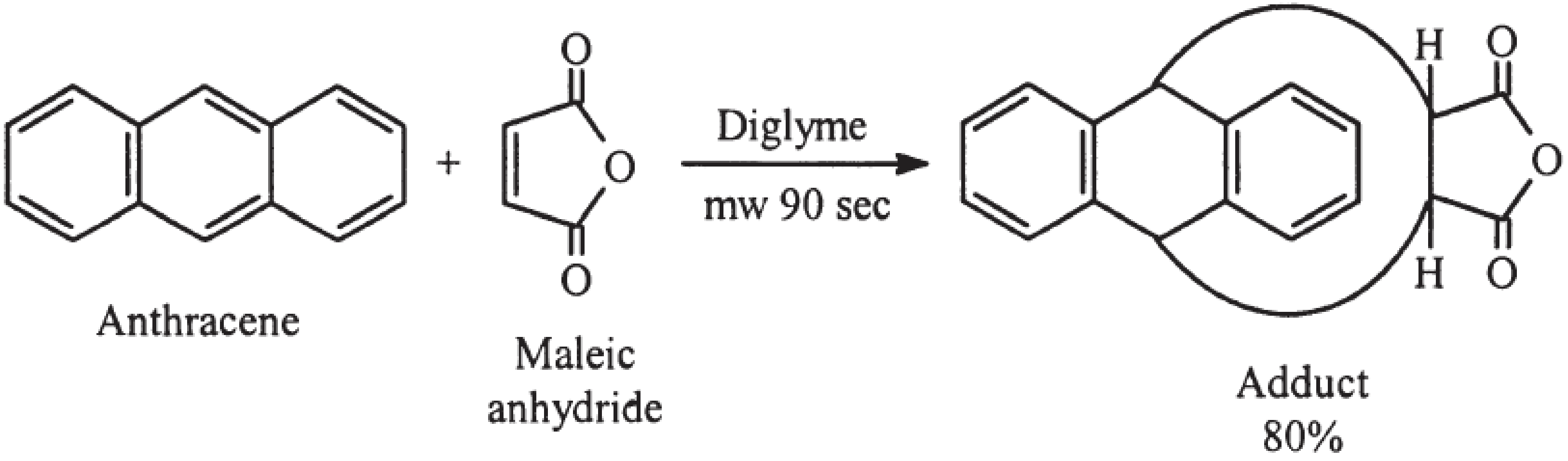
p-Cresyl acetate

2-Hydroxy-4-methyl acetophenone 85%

Fries rearrangement is a useful method for the preparation of phenolic ketones and is usually carried out by heating a mixture of substrate and aluminium chloride. There is considerable rate enhancement of Fries rearrangement by conunercial microwave ovens over conventional methods. Thus, a mixture of p-cresyl acetate and anhydrous aluminium chloride are heated in dry chlorobenzene in a sealed tube in a microwave oven for 2 min to give 85% yield of the product.

Reference: V. Sridar and V.S. Sundara Rao,Indian J. Chern., 1994, 33B, 184.

Microwave Assisted Reaction



The reaction involves 1,4-addition of an alkene (e.g., maleic anhydride) to a conjugated diene (e.g. anthracene) to form an adduct of six membered ring. Under usual conditions, the reaction requires a reflux period of 90 min. However, under microwave conditions diglyme is used as a solvent and 80% yield of the adduct is obtained in 90 sec.

Reference: R.I. Giguene, T.L. Bray and S.M. Duncan, Tetrahedron Lett., 1986,27(41),4945.

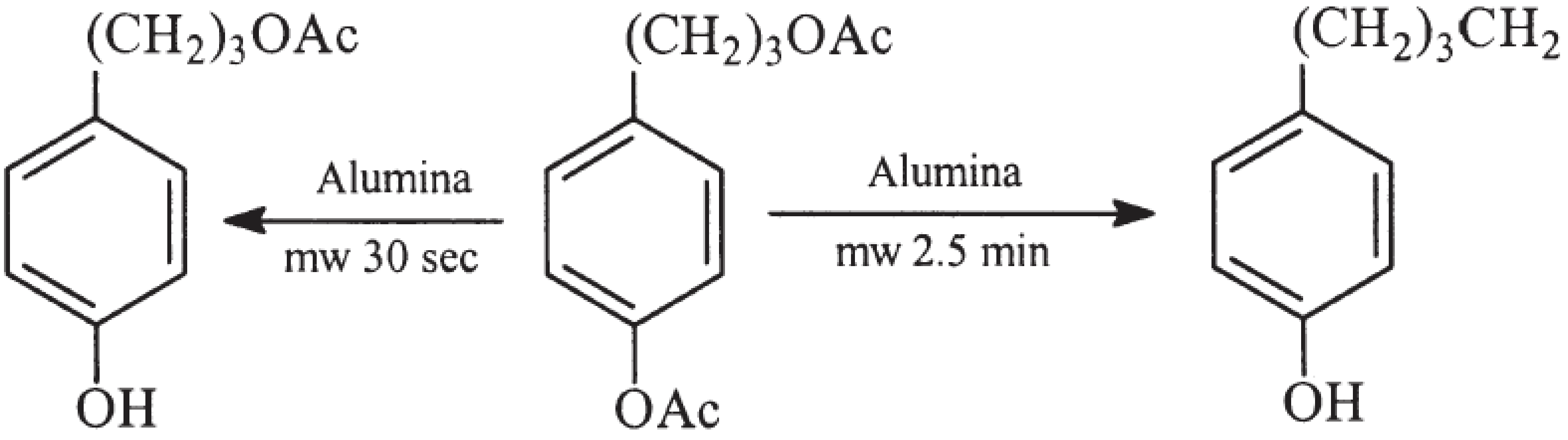
Microwave Assisted Reaction: Solvent Free Reactions

Application of microwave irradiation in organic reactions has added a new dimension to solid phase synthesis. By the use of this technique, it is now possible to carry out reactions without the use of toxic or other solvents, which is one of the main problems associated with green synthesis. In these, the reactants are dissolved in a suitable solvent like water, alcohol, methylene chloride etc. and the solution stirred with a suitable adsorbent or solid support like silica gel, alumina or phyllosilicate (M^{n+} -montomorillonite). After stirring, the solvent is removed in vacuo and the dried solid support on which the reactants have been adsorbed are used for carrying out the reaction under microwave irradiation. Following are some of the important applications of solid support synthesis.

Microwave Assisted Reaction: Solvent Free Reactions

$$C_6H_5CH(OAc)_2 \xrightarrow[\text{mw 40 sec}]{\text{Neutral alumina}} C_6H_5CHO$$

Benzaldehyde diacetate → Benzaldehyde



Reference: (a) R.S. Varma, A.K. Chatterjee and M. Verma, Tet. Lett., 1993, 34(20), 3207.
(b) R.S. Varma, M. Varma and A.K. Chatterjee, J. Chern. Soc. Perkin Trans. I, 1993,999.

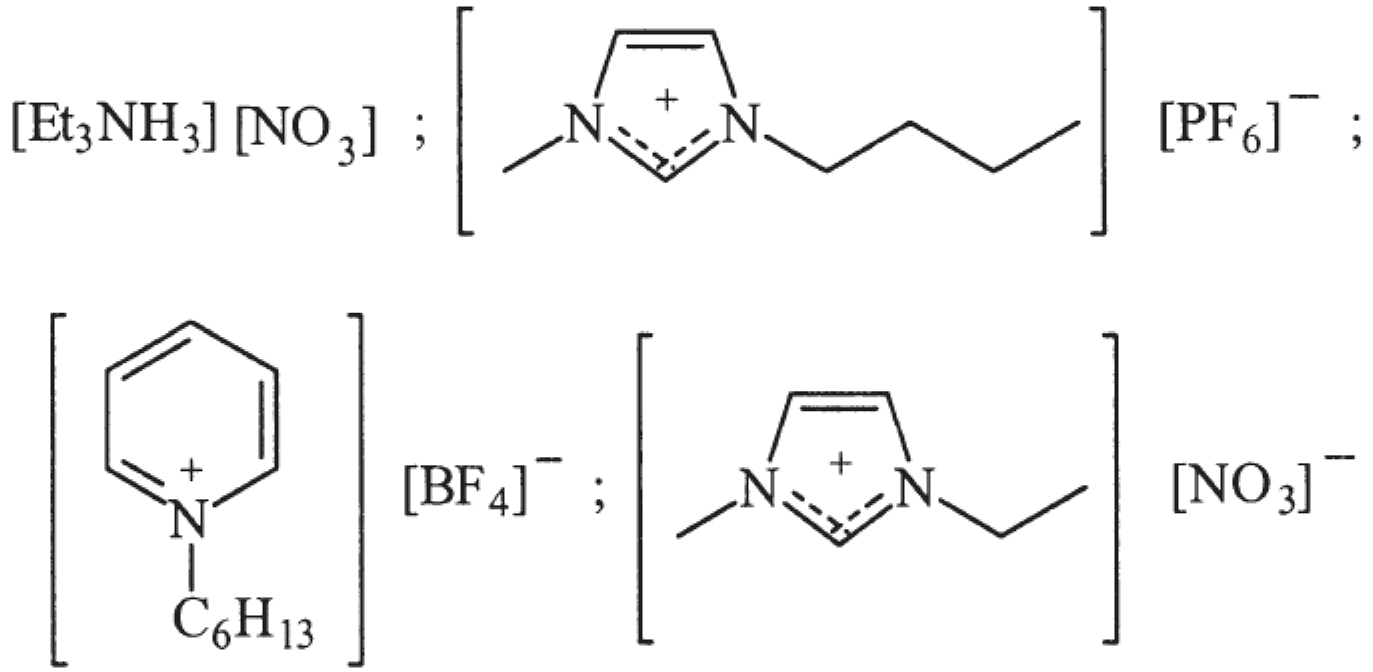
Ionic Liquids as Green Solvents

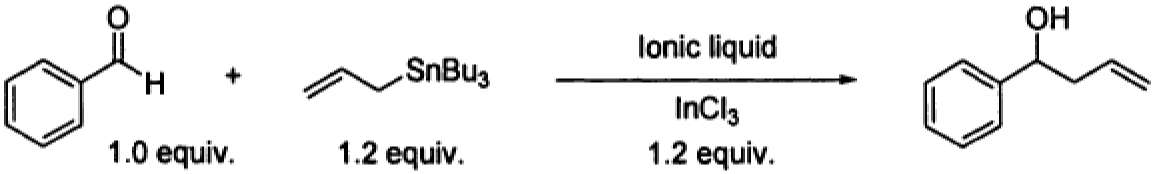
The commonly used solvents like benzene, toluene, methylene chloride etc. for organic synthesis, particularly in industrial production, are known to cause health and environmental problems. In view of this, the search for alternatives to the damaging solvent is of highest priority. This is particularly important as solvents are used.in huge amounts (in industrial production) and these are mostly volatile liquids, which are difficult to contain.

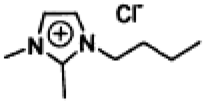
Broadly speaking, ionic liquids are oftwo types: simple salts (made up of a single anion and cation) and binary ionic liquids; the latter are salts where an equilibrium is involved. It is the binary ionic liquids that are used as green solvents.

Ionic Liquids as Green Solvents

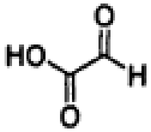
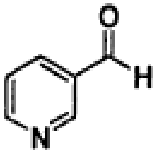
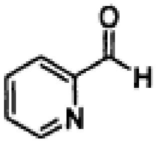
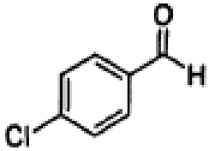
Examples of Ionic Liquids



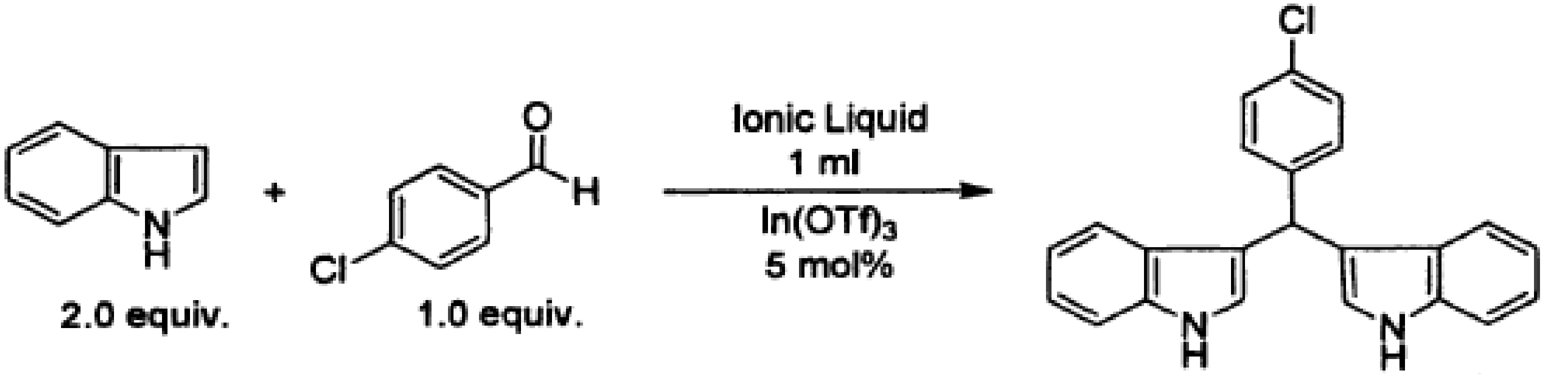


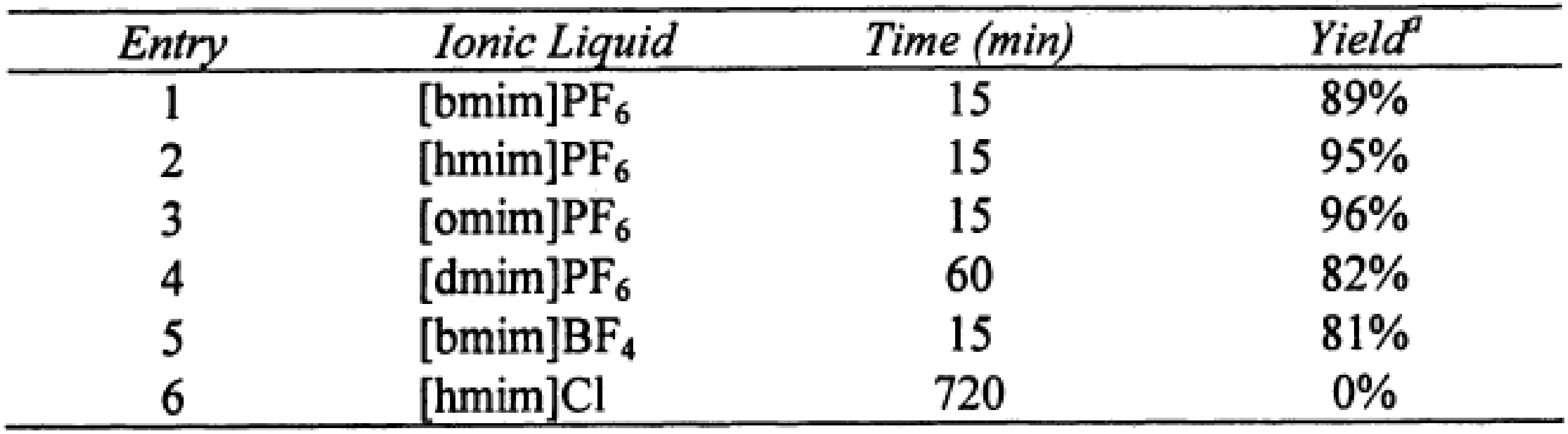
Entry	*Ionic Liquid*	*Temp (°C)*	*Time (hour)*	*Yield*[a]
1	 [bmim]Cl	40	16	70%
2	 [hmim]Cl	25	16	80%
3	 [omim]Cl	25	14	82%
4	 [hmim]BF_4	25	12	75%
5	 [bmmim]Cl	55	16	68%
6	 [epy]Cl	60	16	66%
7	 [bpy]Br	45	14	60%
8	 [hpy]Br	40	14	62%

Ionic Liquids in Organic Synthesis

Entry	Aldehyde	Time (hour)	Yield[a]
1		8	93%
2		14	88%
3		14	86%
4		16	82%

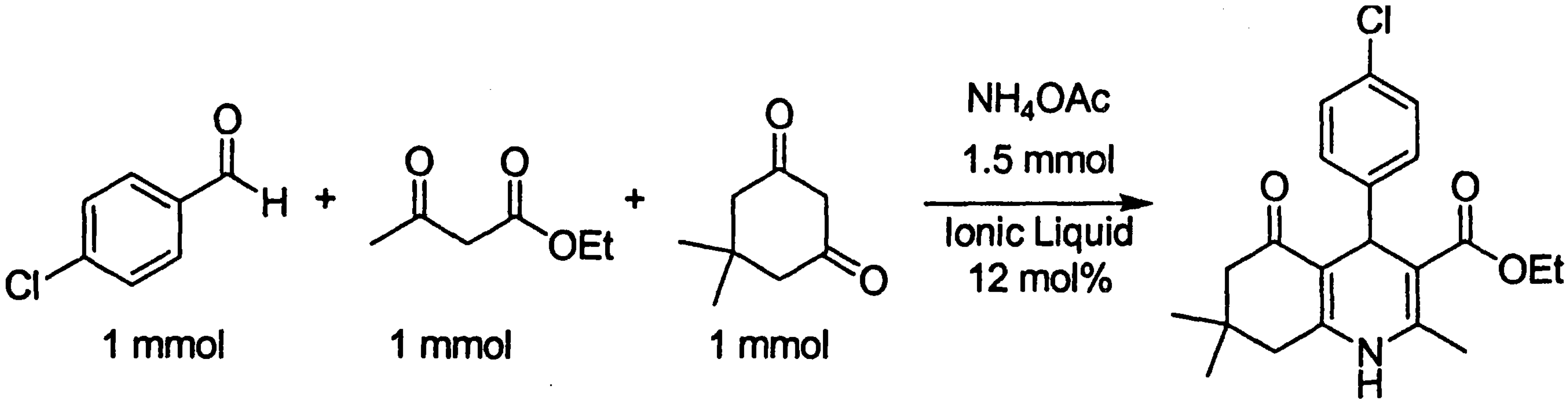
Ionic Liquids in Organic Synthesis





Entry	*Ionic Liquid*	*Time (min)*	*Yield*[a]
1	$[bmim]PF_6$	15	89%
2	$[hmim]PF_6$	15	95%
3	$[omim]PF_6$	15	96%
4	$[dmim]PF_6$	60	82%
5	$[bmim]BF_4$	15	81%
6	[hmim]Cl	720	0%

Ionic liquid-catalyzedfour-component synthesis of polyhydroquinoline derivatives in neat condition.



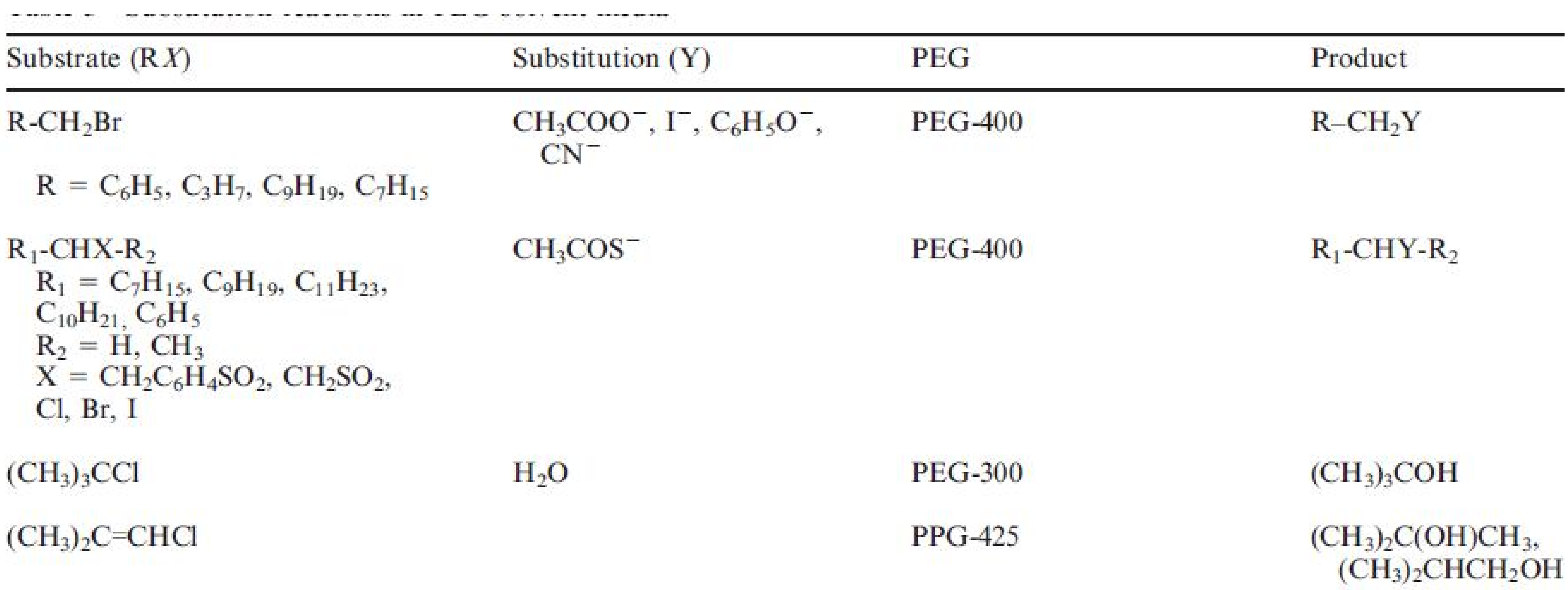
Entry	*Ionic Liquid*	*Time (min)*	*Yield*[a]
1	$[bmim]BF_4$	7	83%
2	$[hmim]BF_4$	8	95%
3	$[omim]BF_4$	15	91%
4	$[nmim]BF_4$	6	86%
5	$[dmim]BF_4$	10	96%
6	$[hmim]PF_6$	10	95%
7	[hmim]Br	12	96%

PEG (Polyethylene glycol)

In recent years PEG aqueous solutions have been widely used in many different kinds of reaction systems. Their low-toxicity, low volatility, and biodegradability represent important environmentally benign characteristics, which are particularly attractive when combined with their relatively low cost as a bulk commodity chemical. In addition, aqueous PEG solutions may often substitute for expensive and often toxic PTCs. The developed state of knowledge with regard to the toxicological properties of PEG is of considerable current advantage compared to the paucity of knowledge for many other potential alternative solvent systems.

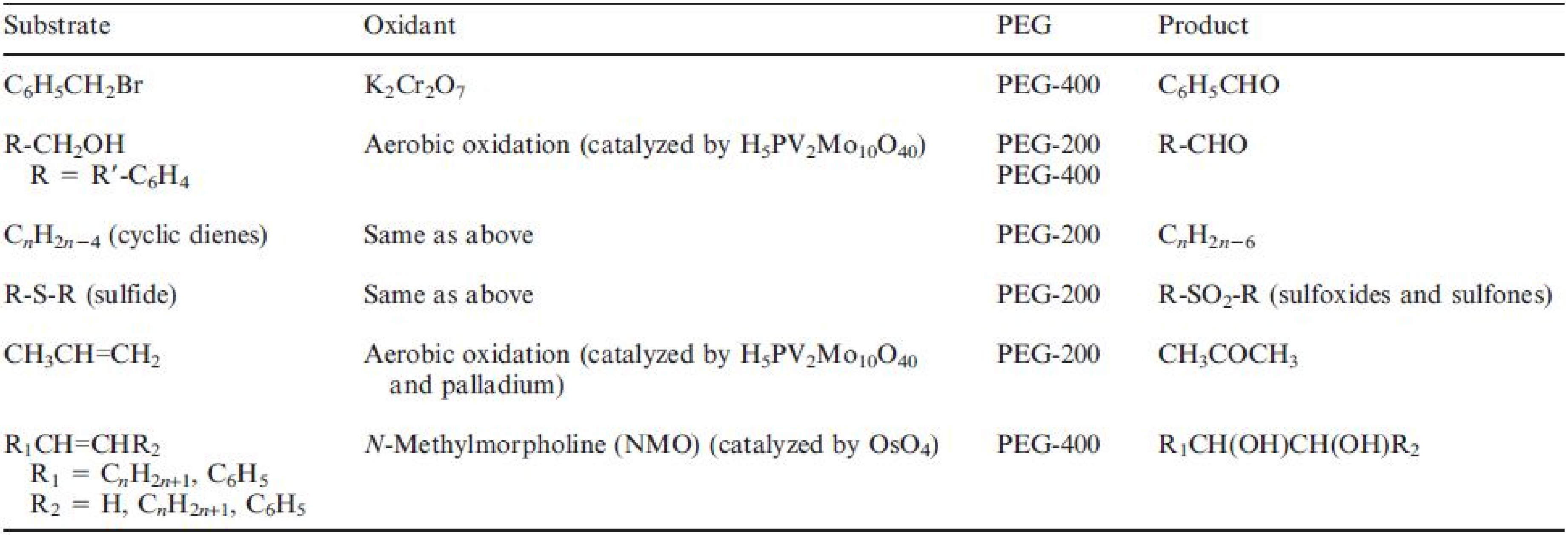
Reference: Green. Chem., 2005, 7, 64–82.

PEG as Solvent in Organic Synthesis



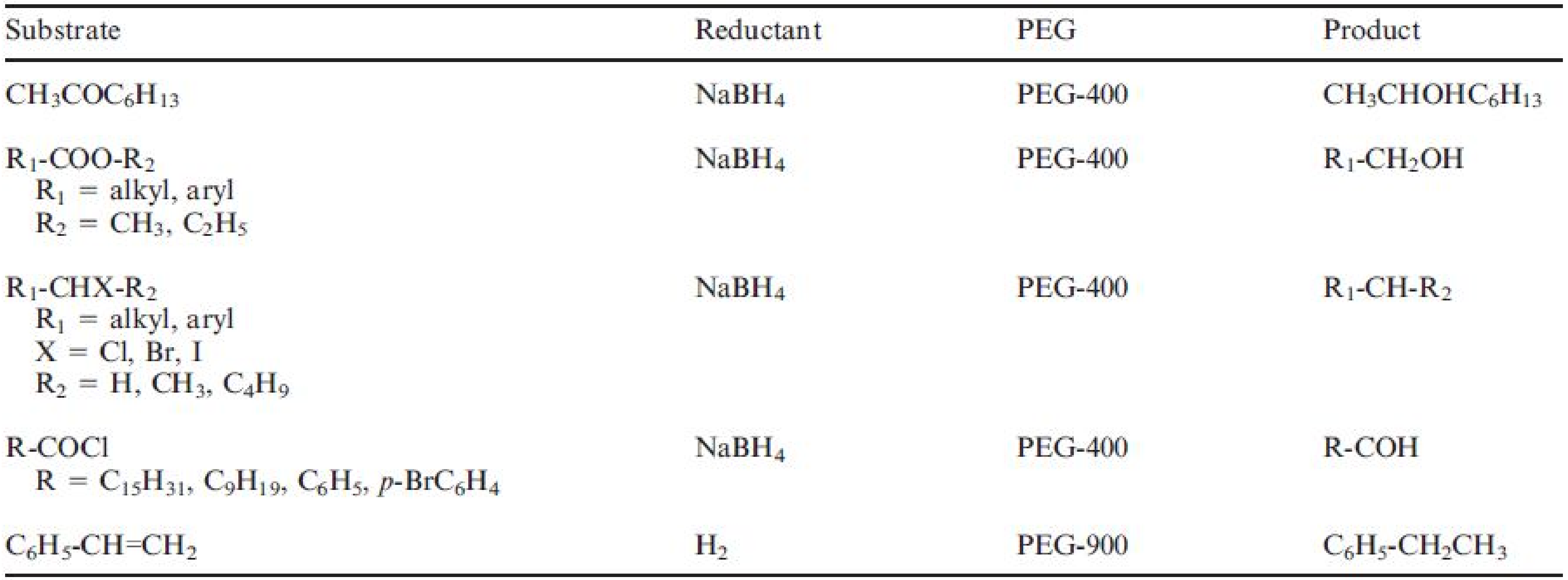
Substrate (RX)	Substitution (Y)	PEG	Product
R-CH_2Br R = C_6H_5, C_3H_7, C_9H_{19}, C_7H_{15}	CH_3COO^-, I^-, $C_6H_5O^-$, CN^-	PEG-400	R–CH_2Y
R_1-CHX-R_2 R_1 = C_7H_{15}, C_9H_{19}, $C_{11}H_{23}$, $C_{10}H_{21}$, C_6H_5 R_2 = H, CH_3 X = $CH_2C_6H_4SO_2$, CH_2SO_2, Cl, Br, I	CH_3COS^-	PEG-400	R_1-CHY-R_2
$(CH_3)_3CCl$	H_2O	PEG-300	$(CH_3)_3COH$
$(CH_3)_2C{=}CHCl$		PPG-425	$(CH_3)_2C(OH)CH_3$, $(CH_3)_2CHCH_2OH$

PEG as Solvent in Organic Synthesis



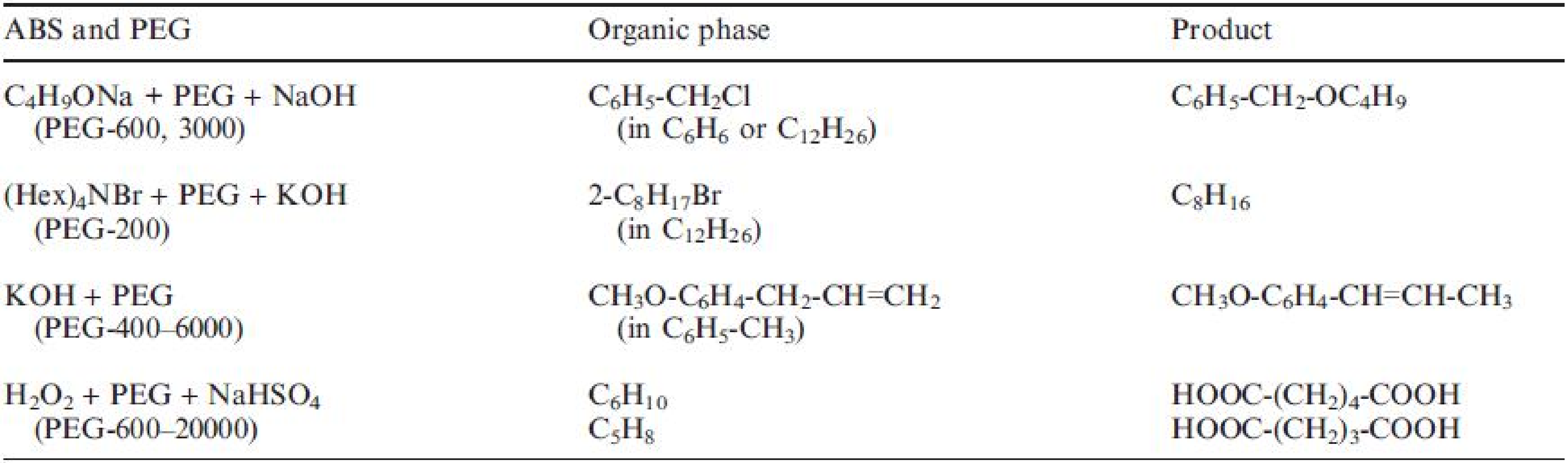
Substrate	Oxidant	PEG	Product
$C_6H_5CH_2Br$	$K_2Cr_2O_7$	PEG-400	C_6H_5CHO
R-CH_2OH R = R′-C_6H_4	Aerobic oxidation (catalyzed by $H_5PV_2Mo_{10}O_{40}$)	PEG-200 PEG-400	R-CHO
C_nH_{2n-4} (cyclic dienes)	Same as above	PEG-200	C_nH_{2n-6}
R-S-R (sulfide)	Same as above	PEG-200	R-SO_2-R (sulfoxides and sulfones)
$CH_3CH=CH_2$	Aerobic oxidation (catalyzed by $H_5PV_2Mo_{10}O_{40}$ and palladium)	PEG-200	CH_3COCH_3
$R_1CH=CHR_2$ $R_1 = C_nH_{2n+1}$, C_6H_5 R_2 = H, C_nH_{2n+1}, C_6H_5	*N*-Methylmorpholine (NMO) (catalyzed by OsO_4)	PEG-400	$R_1CH(OH)CH(OH)R_2$

PEG as Solvent in Organic Synthesis



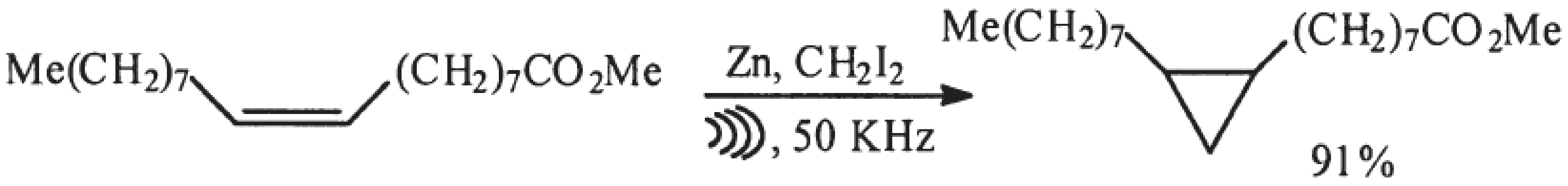
Substrate	Reductant	PEG	Product
$CH_3COC_6H_{13}$	$NaBH_4$	PEG-400	$CH_3CHOHC_6H_{13}$
R_1-COO-R_2 R_1 = alkyl, aryl $R_2 = CH_3, C_2H_5$	$NaBH_4$	PEG-400	R_1-CH_2OH
R_1-CHX-R_2 R_1 = alkyl, aryl X = Cl, Br, I $R_2 = H, CH_3, C_4H_9$	$NaBH_4$	PEG-400	R_1-CH-R_2
R-COCl $R = C_{15}H_{31}, C_9H_{19}, C_6H_5$, *p*-$BrC_6H_4$	$NaBH_4$	PEG-400	R-COH
C_6H_5-$CH{=}CH_2$	H_2	PEG-900	C_6H_5-CH_2CH_3

PEG as Solvent in Organic Synthesis



ABS and PEG	Organic phase	Product
C_4H_9ONa + PEG + NaOH (PEG-600, 3000)	C_6H_5-CH_2Cl (in C_6H_6 or $C_{12}H_{26}$)	C_6H_5-CH_2-OC_4H_9
$(Hex)_4NBr$ + PEG + KOH (PEG-200)	2-$C_8H_{17}Br$ (in $C_{12}H_{26}$)	C_8H_{16}
KOH + PEG (PEG-400–6000)	CH_3O-C_6H_4-CH_2-CH=CH_2 (in C_6H_5-CH_3)	CH_3O-C_6H_4-CH=CH-CH_3
H_2O_2 + PEG + $NaHSO_4$ (PEG-600–20000)	C_6H_{10} C_5H_8	HOOC-$(CH_2)_4$-COOH HOOC-$(CH_2)_3$-COOH

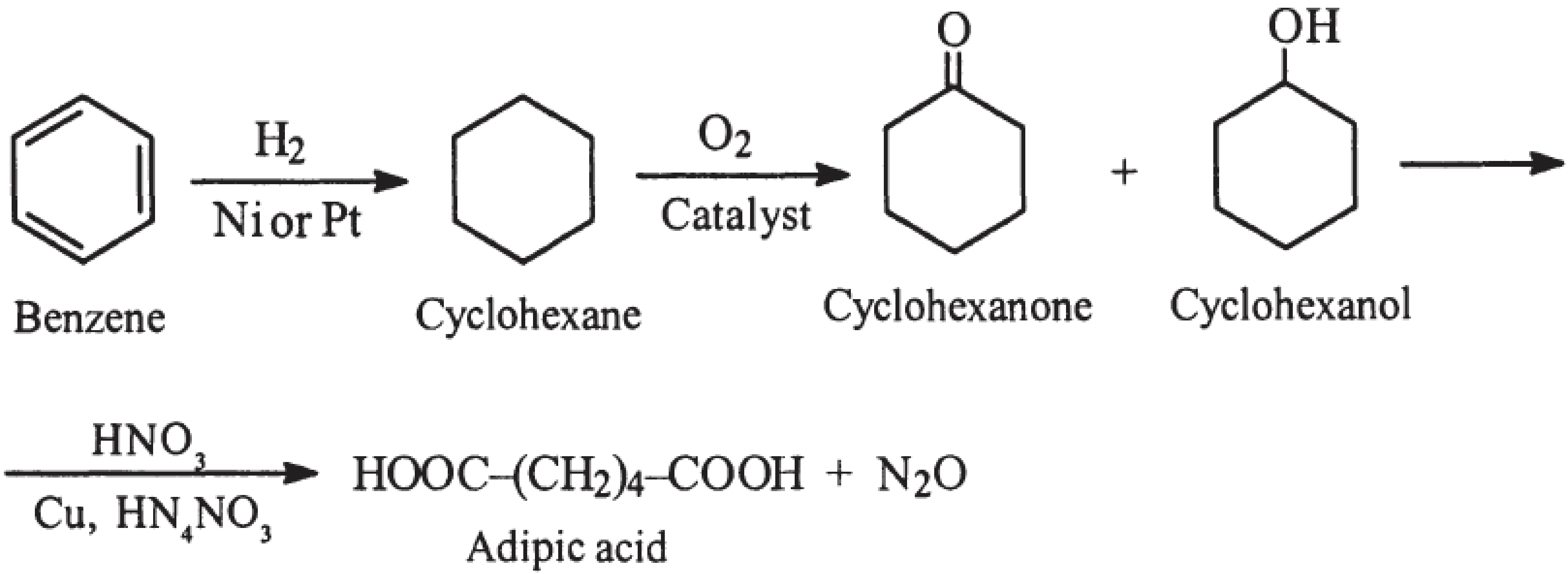
Ultrasound Assisted Green Synthesis



In this reaction, sonochemically activated zinc and methylene iodide are used. The generated carbene adds on to an olefinic bond to give 91 % yield of the cyclopropane derivative compared to 51 % yield by the normal route. The above method can be scaled up and has several advantages. The reagent used, Zn/CH_2I_2 is known as Simmons-Smith reagent.

Reference: H. Tso, T. Chou and H. Hung, J. Chern. Soc. Chern. Cornrnun., 1887, 1552.

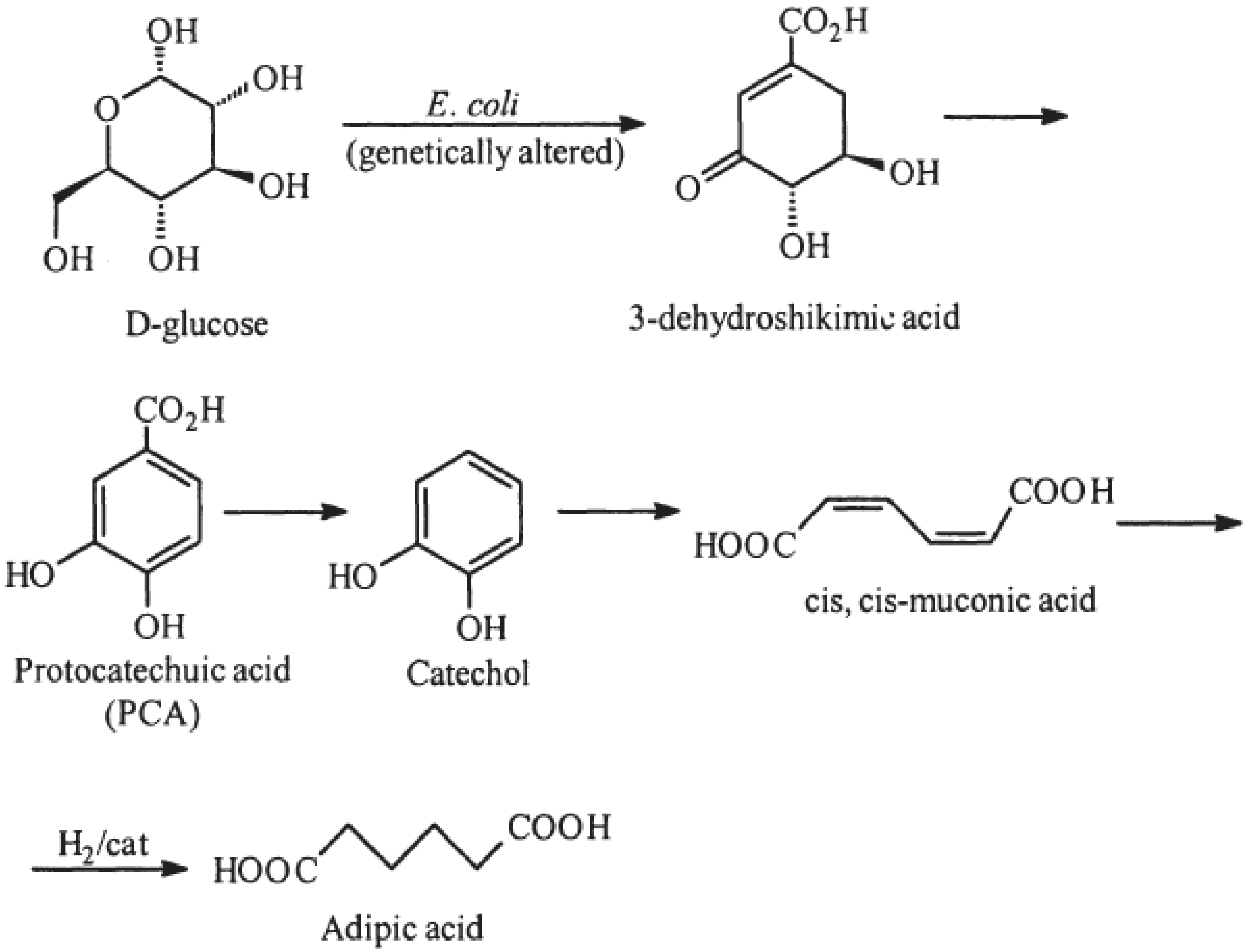
Synthesis of Adipic Acid



Adipic acid is required in large quantities (about 1 billion kg a year) for the synthesis of nylon, plasticizers and lubricants. Conventionally, adipic acid is made from benzene

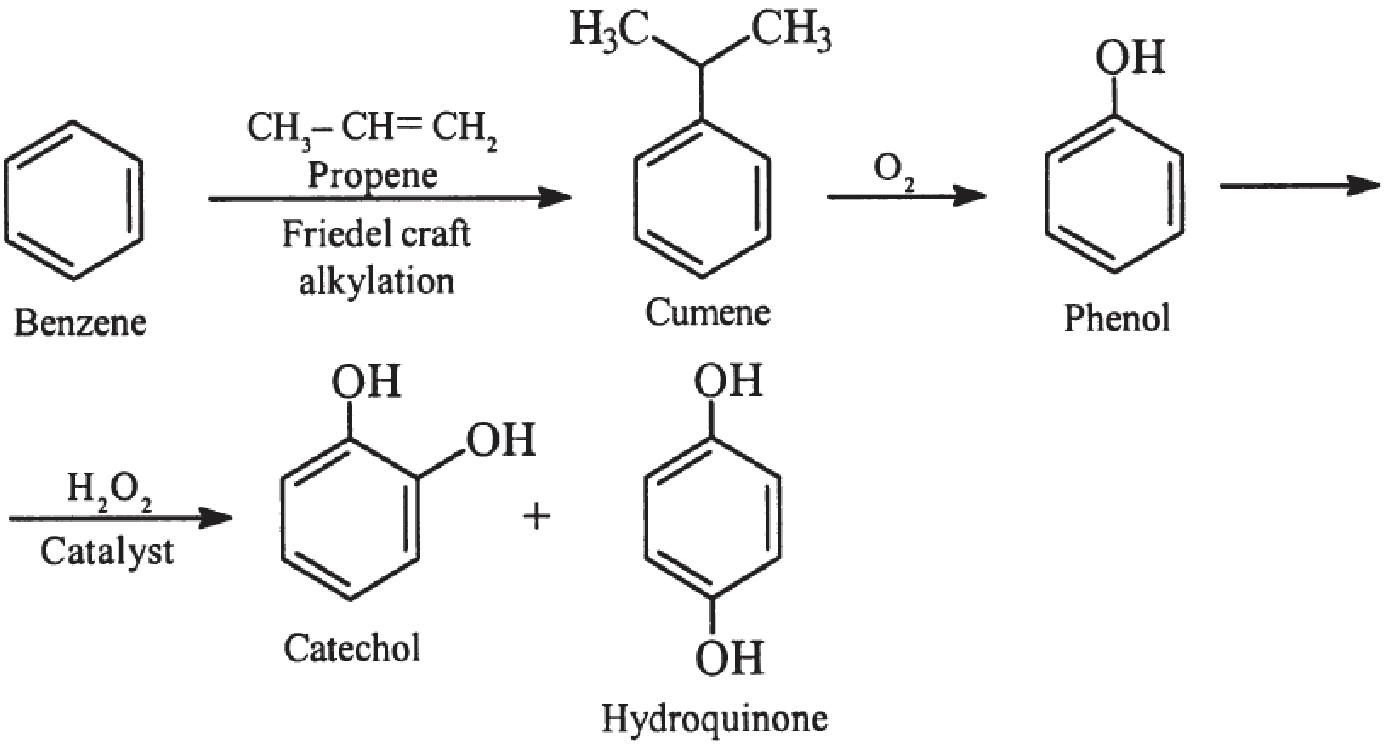
Reference: R.I. Giguene, T.L. Bray and S.M. Duncan, Tetrahedron Lett., 1986,27(41),4945.

Synthesis of Adipic Acid



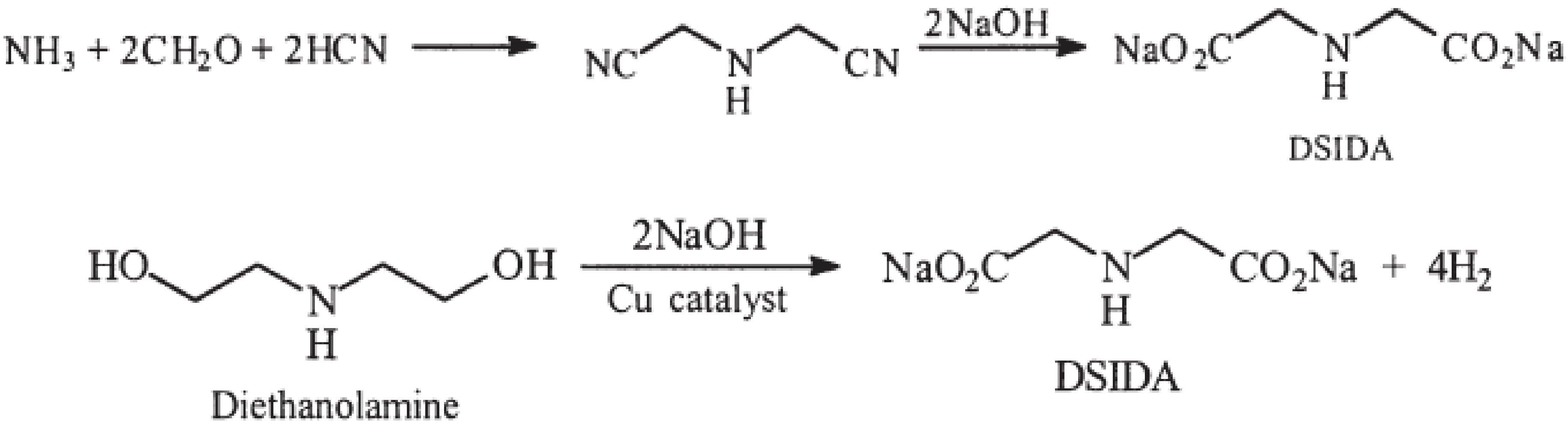
Reference: R.I. Giguene, T.L. Bray and S.M. Duncan, Tetrahedron Lett., 1986,27(41),4945.

Conventional Synthesis of Catechol



Adipic acid is required in large quantities (about 1 billion kg a year) for the synthesis of nylon, plasticizers and lubricants. Conventionally, adipic acid is made from benzene

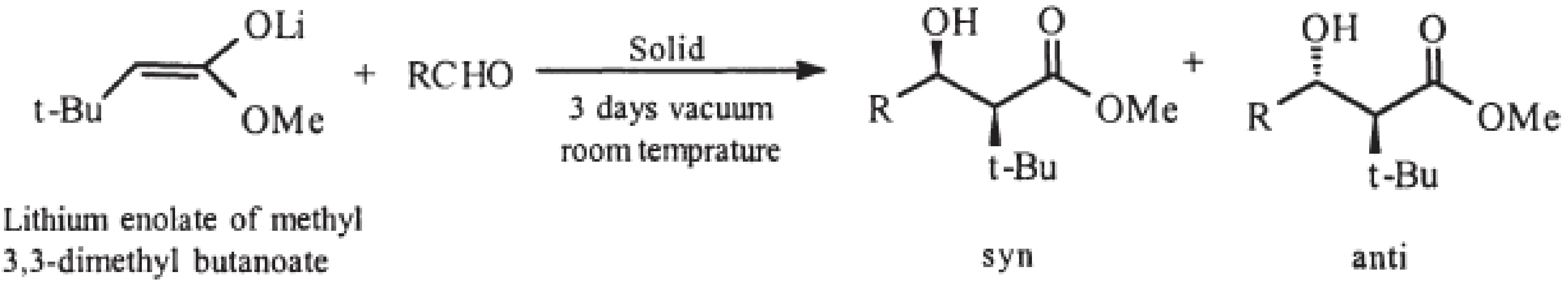
Green synthesis of DSIDA



Using strecker synthesis, disodium iminodiacetate (DSIDA) an intermediate for the manufacture is Monsantos' Roundup (herbicide) was synthesised. In the above synthesis hydrogen cyanide, a hazardous chemical is used and this requires special handling to minimise the risk to workers and the environment. An alternative green synthesis of DSIDA was developed by Monsanto.

Reference: T. Paul Anastas and John C. Warner, Green Chemistry, Theory and Practice, Oxford University Press, 1998, pp. 98-99.

Green Synthesis: Aldol Condensation

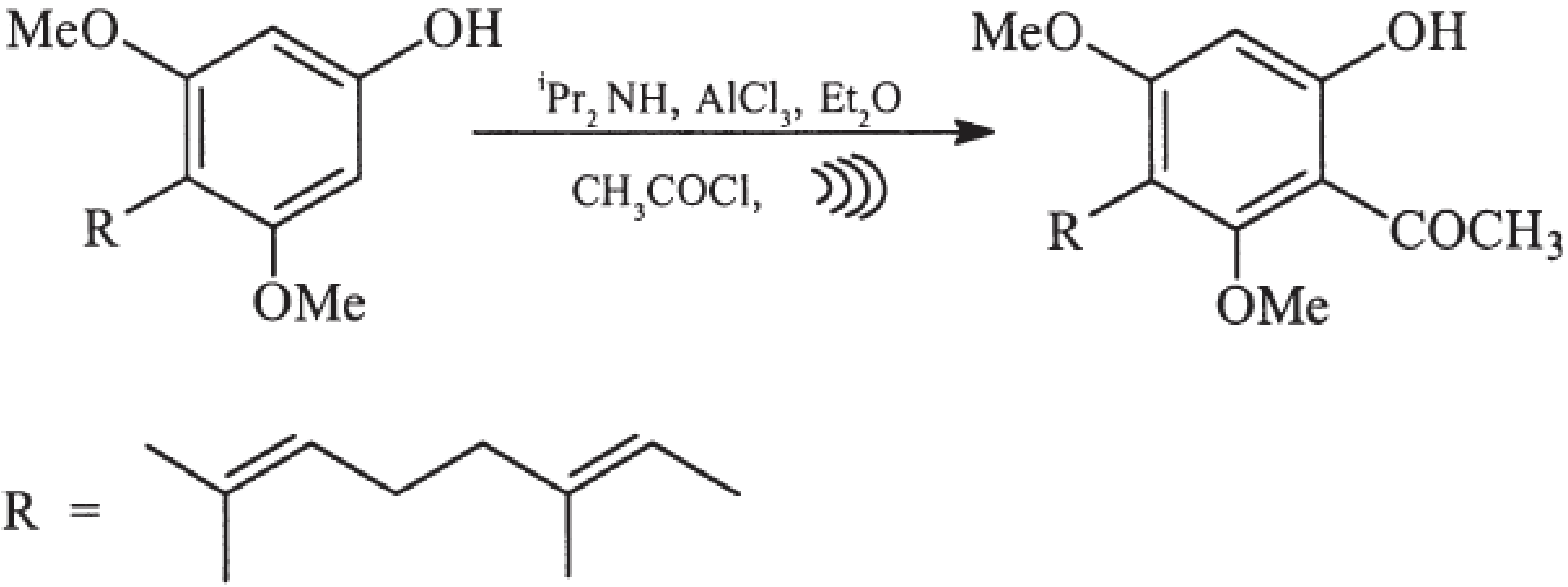


R = 2-$OCH_3C_6H_4$–, 4-Cl-C_6H_4
4-$NO_2C_6H_4$–, 3-$NO_2C_6H_4$–, 2-$NO_2C_6H_4$–
4-NO_2-2-thienyl

The aldol condensation of the lithium enolate of methyl-3,3-dimethylbutanoate with aromatic aldehydes gives (the reaction is carried out by mixing freshly ground mixture of the lithium enolate and powdered aldehyde in vacuum for 3 days at room temperature) a 8:92 mixture of the syn and anti products in 70% yield.

Reference: Y. Wef, R. Bakthavatechalam, Tetrahedron Lett., 1991,32, 1535.

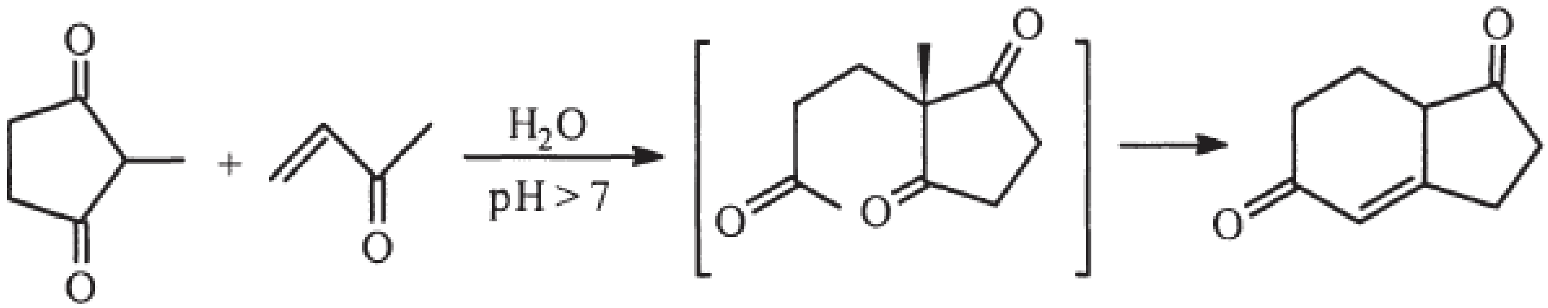
Friedel-Crafts Reaction



The Friedel-Crafts acylation of aromatic compounds is facilitated by ultrasound.

Reference: D.M. Trose and B.P. Coppola, J. Arn. Chern. Soc., 1982,104,6879.

Michael Reaction



It is an addition reaction between an α,β-unsaturated carbonyl compound and a compound with an active methylene group (e.g., malonic ester, acetoacetic ester, cyanoacetic ester, nitroparaffins etc.) in presence of a base, e.g., sodium ethoxide or a secondary amine (usually piperidine).

In this reaction, use of water as solvent gave better yields and pure compound compared to reaction with methanol in presence of a base.

Reference: A. Michael, 1. Prak. Chem., 1887,35(2),349; E.D. Bergmann, D. Ginsburg and R. Pappo, Org. Reactions, 1959, 10, 179.

Knoevenagel Reaction

The condensation of aldehydes or ketones, with active methylene compounds (especially malonic ester) in presence of a weak base like ammonia or amine (primary or secondary) is known as Knoevenagel reaction. However, when condensation is carried out in presence of pyridine as a base, decarboxylation usually occurs during the condensation. This is known as Doebner.

The Knoevenagel reaction has been carried out between aldehydes and acetonitrile in water. Thus, salicylaldehydes react with malononitrile at room temperature in the heterogeneous aqueous alkaline medium to give α-hydroxybenzylidene malononitriles, which are converted directly to 3-cyanocoumarins by acidification and heating

Knoevenagel Reaction

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + \underset{\text{Malonic acid}}{CH_2(COOH)_2} \xrightarrow{\text{Base}} CH_3CH{=}C(COOH)_2$$

$$\downarrow -CO_2$$

$$\underset{\text{Crotonic acid}}{CH_3CH{=}CHCOOH}$$

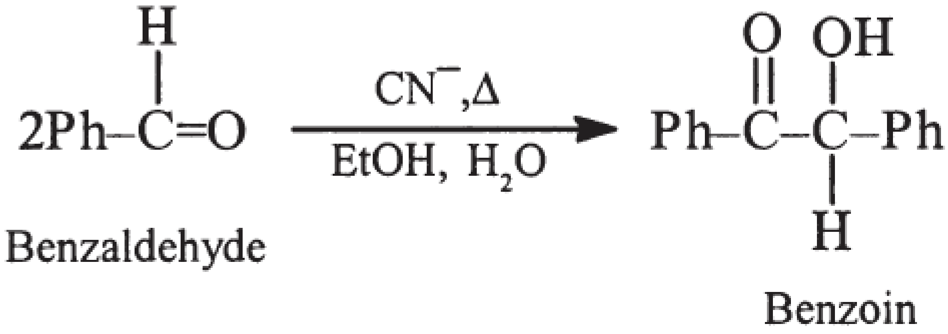
$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow[\text{benzene}]{\text{Pyridine}} C_6H_5CH{=}C\,(COOC_2H_5)_2$$

$$\xrightarrow[\text{2) } H_3O^+]{\text{1) hydrolysis}} C_6H_5CH{=}C(COOH)_2 \xrightarrow[-CO_2]{\Delta} \underset{\text{Cinnamic acid}}{C_6H_5CH{=}CHCOOH}$$

Reference: 1. F. Knoevenagel, Ber., 1898,31,2596.
2.. J.R. Johnson, Org. Reactions, 1942,1,210.
3. O. Doebner, 1900,33,2140.
4. Y. Nakono, S. Nik, S. Kinouchi, H. Miyamae and M. Igarashi, Bull. Chern. Soc. Japan, 1992,65,2934.

Benzoin Condensation

It consists in the treatment of aromatic aldehydes with sodium or potassium cyanide, usually in an aqueous ethanolic solution to give a-hydroxy ketones (benzoins).

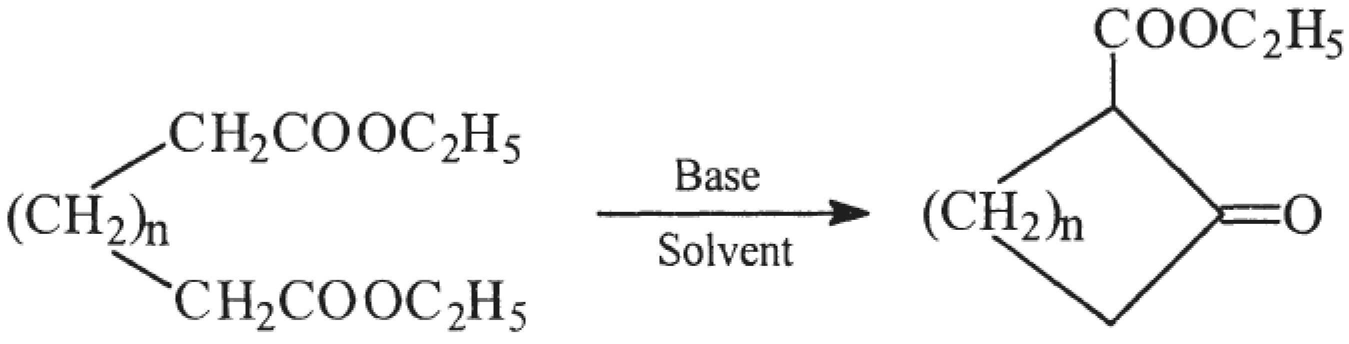


It is found that benzoin condensation of aldehydes are strongly catalysed by a PTC (quaternary ammonium cyanide in a two phase system). In a similar way, acyloin condensations are easily effected by stirring aliphatic or aromatic aldehydes with a quaternary catalyst (PTC), N-laurylthiazolium bromide in aqueous phosphate buffer at room temperature.

Refernces: 1. J. Solodar, Tetrahedron Lett., 1971,287.
2. W. Tagaki and H. Hara, J. Chern. Soc. Chern. Cornrnun., 1973, 891.

Dieckmann Condensation

Dieckman condensation reactions of diesters have been carried out in solid state in presence of a base (like Na or NaOEt) using high-dilution conditions in order to avoid intermolecular reaction. It has been found that the Dieckman condensation of diethyl adipate and pimelate proceed very well in absence of the solvent; the reaction products were obtained by direct distillation of the reaction mixture. In this method the diester and powdered Bu^{t}OK were mixed using a pestle and mortar for 10 min. The solidified reaction mixture was neutralised with p-TsOH.H_2O and distilled to give cyclic compounds.

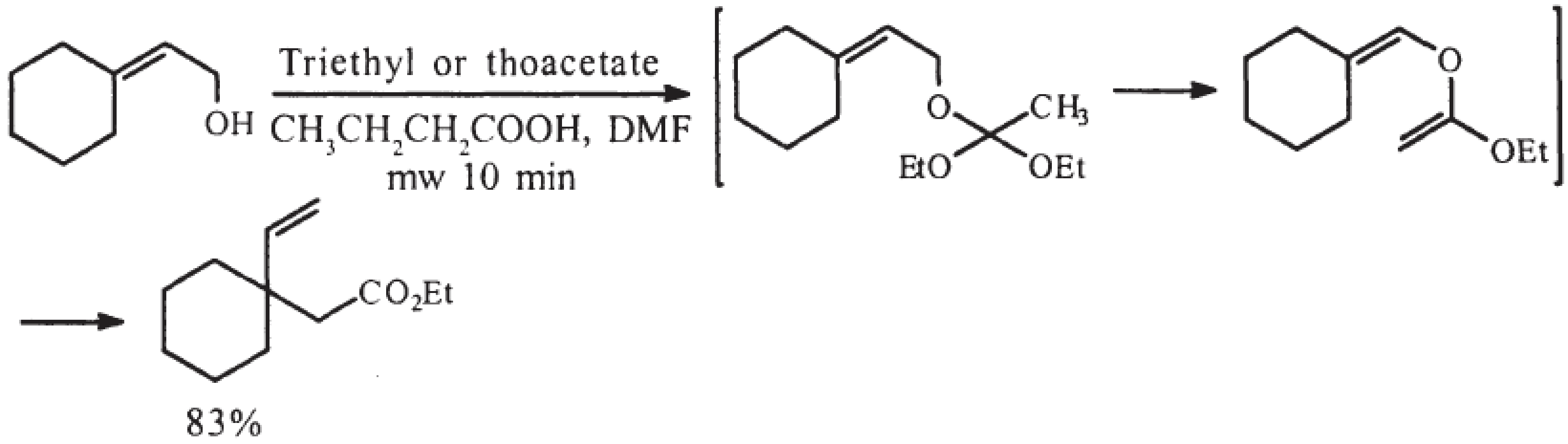


Diethyl adipate (n = 2)
Diethyl pimelate (n = 3)

60-70%

Reference: F. Toda, T. Suzuki and S. Higa, J. Chern. Soc. Perkin Trans. 1, 1998, 3521.

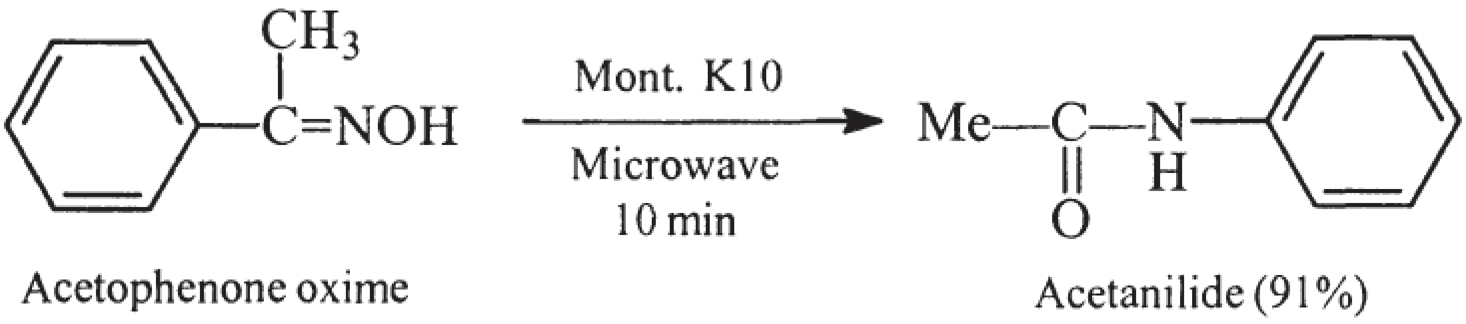
Claisen Rearrangement



In the usual conventional procedure, a mixture of allyl alcohol, triethyl orthoacetate and propanoic acid is heated in a sealed tube for 48 hr. However, under microwave conditions a mixture of allyl alcohol, triethyl orthoacetate and propanoic acid in dry dimethylformamide is heated in microwave oven for 10 min. The product is obtained in 83% yield.

Reference: A. Srikrishna and S. Nagaraju,J. Chern. Soc. Perkin Trans. 1,1992,311.

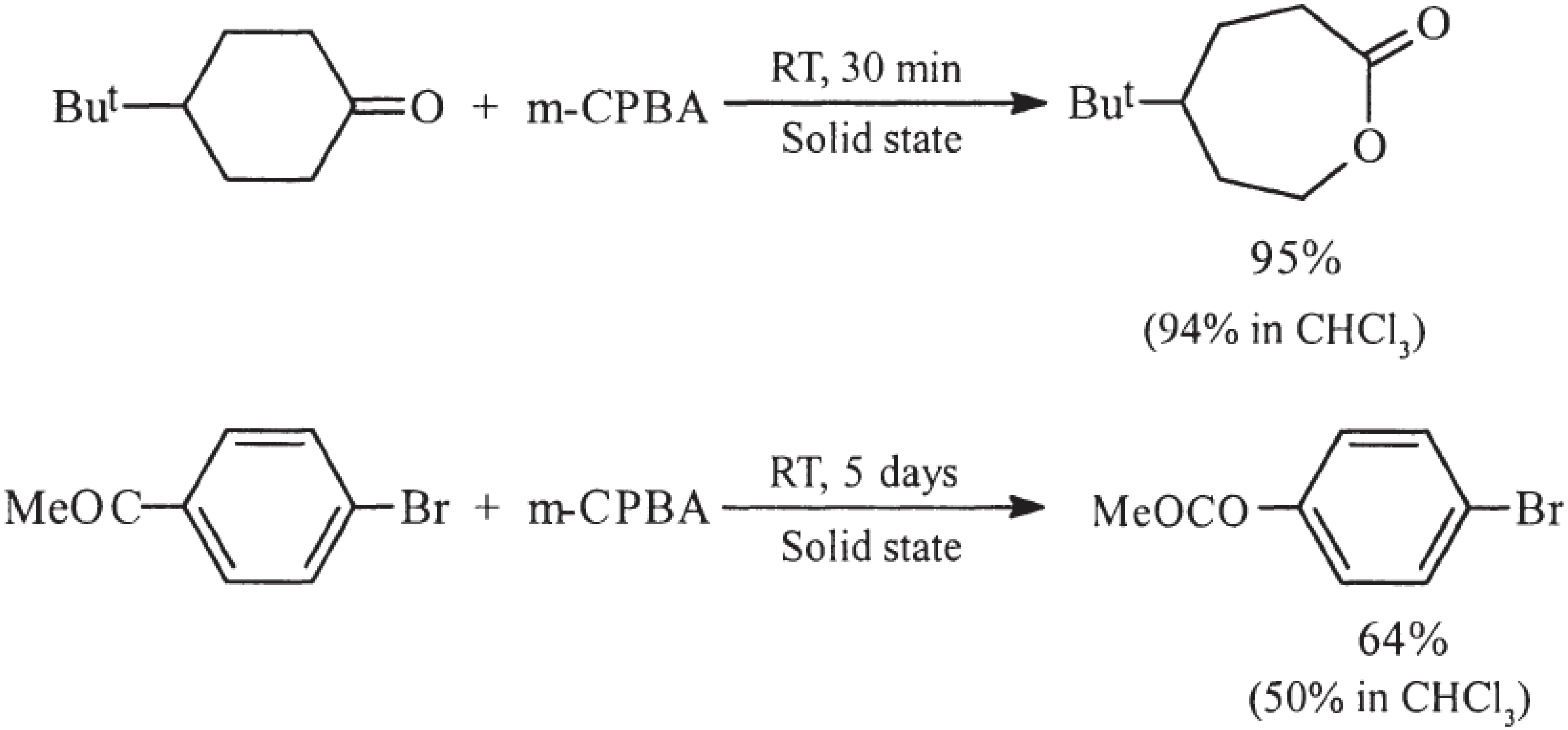
Beckmann Rearrangement



Usually, Beckmann rearrangement of oximes of ketones are converted into anilides by heating with acidic reagents like PCl_5, HCOOH, $SOCl_2$ etc. However, solid-state Beckmann rearrangement has been reported. In this method oxime of a ketone is mixed with montmorillonite and irradiated for 7 min in a microwave oven to give corresponding anilide in 91 % yield

Reference: I. Almena, A. Diaz-Ortiz, E. Diez-Barra, A. Hos and A. Loupy, Chern. Lett., 1990, 333; S. Caddick, Tetrahedron, 1995, 10400.

Baeyer-Villiger oxidation

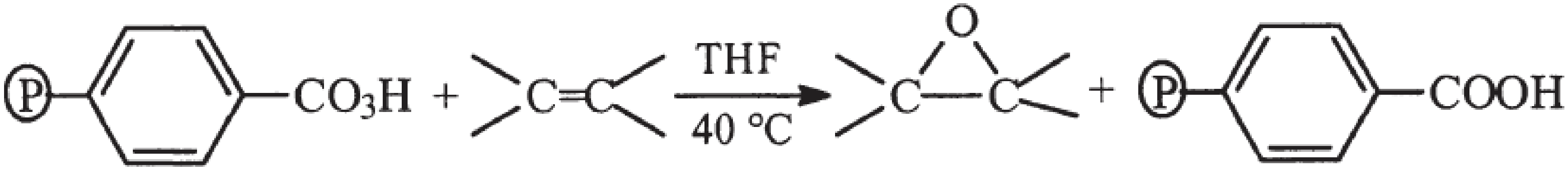


Some Baeyer-Villiger oxidation of ketones with m-chloroperbenzoic acid proceed much faster in the solid state than in solution. In this method, a mixture of powdered ketone and 2-mole equivalent of m-chloroperbenzoic acid is kept at room temperature to give the product. The yields obtained in solid state are much better than in $CHCl_3$.

Reference: K. Tanaka and F. Toda, Chern. Rev., 2000,100,1028-29.

Green Reagent

Polymer Supported Reagents



The main advantage of using these reagents is that any excess of the reagent can be recovered by filtration and used again.
Also, the isolation of the product is very easy.

Reference: (a) IMJ. Frehet and K.E. Haque, Macrornolecules, 1975,8, 130.
(b) C.R. Harrison and P. Hodge, J. Chern. Soc., Chern. Cornrnun., 1974, 1009.

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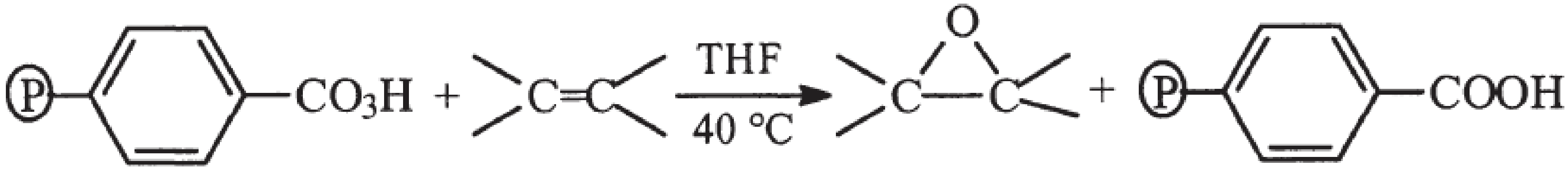

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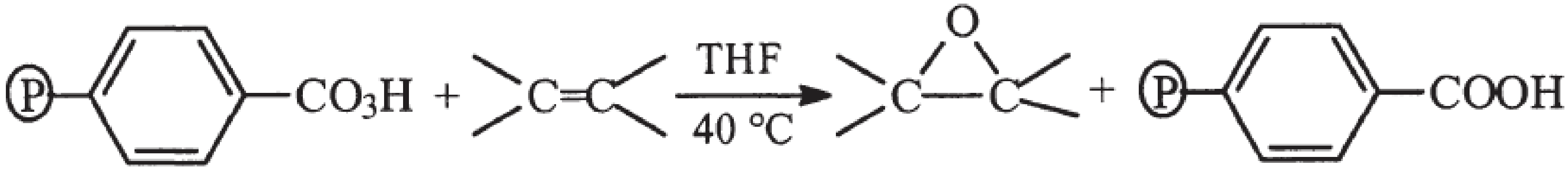

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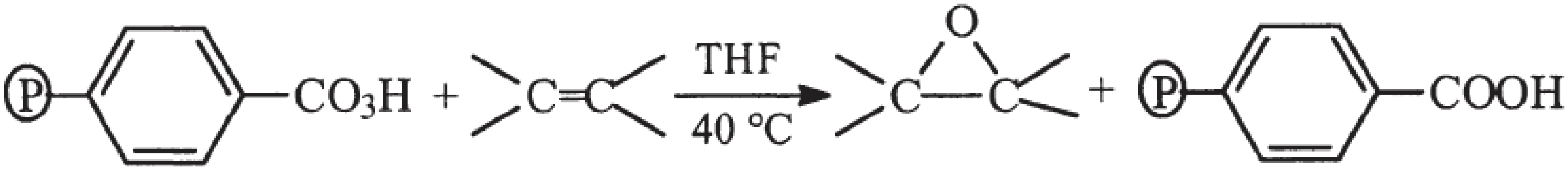

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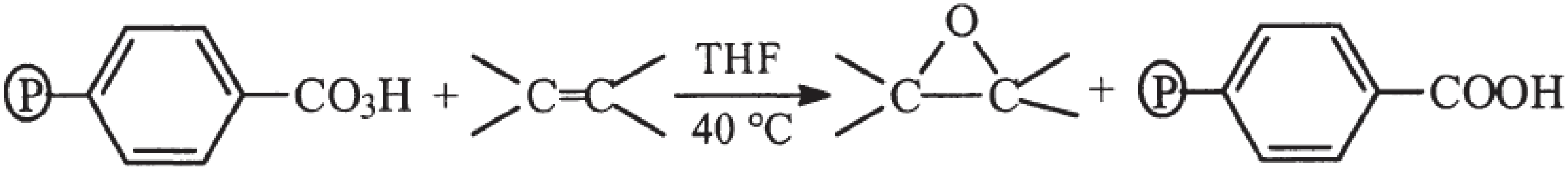

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