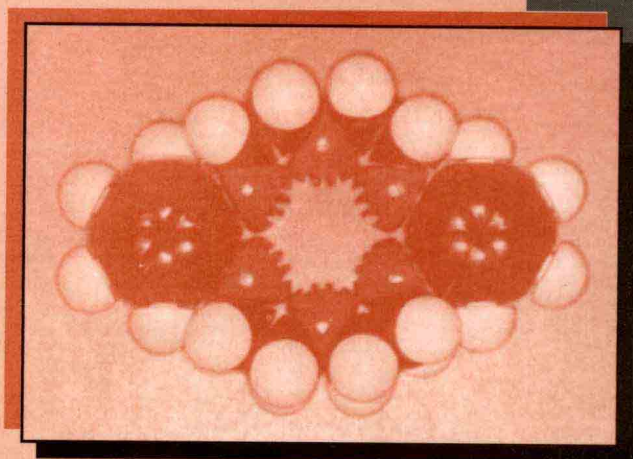


# ORGANIC SYNTHESIS

## Special Techniques



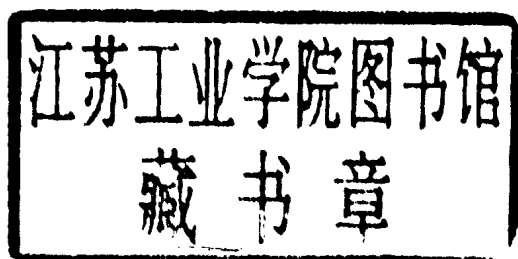
V.K. Ahluwalia  
Renu Aggarwal

# ORGANIC SYNTHESIS

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## Special Techniques

V.K. Ahluwalia □ Renu Aggarwal



Alpha Science International Ltd.  
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## Foreword

In the development of practical sciences, such as organic chemistry, novel techniques have played an important role. Various innovative methods and techniques were devised for speeding up reactions, for carrying out reactions in a continuous fashion, for separation of complex mixtures, and so on. All these have contributed in a big way in the practice of organic chemistry. The last two decades or so have seen the induction of several useful innovations aimed at executing organic compound preparations. These methods have been described in special monographs, review articles and, of course, in the primary literature. However, apparently, no single-volume book covering some of these advances, is available at present. Such a book would be of immense help to students as well as research workers, as it has become almost impossible to keep track of new advances, because of almost explosive growth of new knowledge and information. Professor V.K. Ahluwalia and Dr. Renu Aggarwal deserve congratulations for bringing out such a book.

The topics selected by the authors are of much practical value. The first two chapters deal with *phase transfer catalysis*, a practical strategy which has greatly simplified the execution of several types of base-catalysed reactions and nucleophilic displacement reactions in general, several types of oxidation reactions, and so on. Phase transfer catalysis is now widely practised, using a variety of catalysts, both in research and industrial production. It is essential that students of organic chemistry get an early exposure to this practical method. The next two chapters deal with novel strategies to greatly accelerate the speed of reactions. Energising organic reaction thermally or photochemically is the normal practice. These two chapters describe the use of *microwaves* and *sound waves* with outstanding, and often amazing results. These techniques have great practical value, and already efforts are being made to translate some of these findings into commercial advantage. The last topic concerns *polymer supported reagents and reactions*. Again, this is a very topical subject, as a refined and more sophisticated version of this has acquired much importance in generating molecular diversity.

Thus, the selection of topics has been done very carefully, and the book will serve a very useful purpose of introducing students to these valuable methods.

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# Preface

An organic chemist is primarily concerned with the synthesis of organic molecules, which have diverse uses such as in medicines, agrochemicals, biomolecules (like proteins and peptides) etc. The conventional methods used for various synthesis involve a number of steps and the yields are low. Over the years various special techniques have been devised for speeding up reactions.

This book describes following five special techniques for organic synthesis: (i) use of phase transfer catalysts in organic synthesis, (ii) use of crown ethers in organic synthesis, (iii) microwaves induced organic synthesis, (iv) use of ultrasound in organic synthesis and (v) the use of polymer supported reagents in organic synthesis.

The methods of preparation of typical phase transfer catalysis, the mechanism of PTC reaction, their advantages and applications have been discussed in chapter one. Some typical applications of PTC catalysis are oxidation of toluene into benzoic acid using potassium permanganate in 90% yield and conversion of benzyl chloride into benzyl cyanide in more than 90% yield.

The second chapter deals with the use of crown ethers (a family of cyclic polyethers) in organic synthesis. Special features of crown ethers, their synthesis and applications have been discussed. Laboratory procedures for some synthesis involving the use of PTC and crown ethers have also been given.

Chapter three discusses the use of microwaves in organic synthesis. In microwave induced organic reactions, the reactions are carried out either in solvent medium or on solid support in which no solvent is used. The microwave induced organic reactions can be carried out in much shorter time compared to the time required for reactions under normal conditions. As an illustration esterification reactions which normally take 6–8 hrs can be completed in few minutes in much better yields. A number of procedures have been described.

Use of ultrasound in organic synthesis is described in fourth chapter. A brief account of the generation of ultrasound, the instrumentation and typical application with experimental details have been given.

The last chapter gives the use of polymer supported reagents in organic synthesis. The properties of various polymer support, their advantages and applications are described. The most important use is the synthesis of peptides. Some of the typical reactions, for example, oxime formation, Wittig reaction, crossed aldol condensation, benzoin condensation, the Grignard reaction etc. have been carried out using polymer supported reagents.

All these techniques are described in a number of monographs, review articles, which is the primary literature. However, present book provides considerable details for basic understanding of these techniques. The subject matter is sufficiently comprehensive to permit the teacher to cover any reasonable course of instruction.

The present book, intended to meet the requirements of a chemist throughout his

life, will also cater to the needs of postgraduate students and researchers both in institutes and industries. In fact, understanding of these techniques is a *MUST* for all researchers.

We are thankful to Prof. Sukh Dev, Prof. R.N. Khanna, Prof. M.R. Parthasarathy, Dr. J.M. Khurana, Dr. Suman Dudeja, Dr. Madhu Chopra, Dr. Pooja Bhagat and a large number of other researchers for their help and advice. We express our gratitude to various journals which have accorded permission to reproduce some of the experimental details given in this book.

Finally, we are grateful to Prof. Ramesh Chandra, Director, Dr. B.R. Ambedkar Center for Biomedical Research, University of Delhi, for the help and facilities rendered.

V.K. AHLUWALIA

RENU AGGARWAL

ORGANIC SYNTHESIS  
Special Techniques

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# PHASE TRANSFER CATALYSTS

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## 1. INTRODUCTION

In organic reactions difficulties are often encountered if the organic compound is soluble in an organic solvent and the reagent in water, then the two will react very slowly and the reaction proceeds only at the interface where these two solutions are in contact. The result is very slow or negligible reaction. The rate of reaction, however, can be increased by stirring the solution which depends upon the rate of stirring. Generally due to the low solubility of the organic compound in water and the low solubility of the reagent in organic solvent, the rate of the reaction is very slow. This problem can, however, be overcome by using aprotic polar solvent, which solvate the cation—the result is that the anions are free. But such solvents are expensive and their removal is difficult. Examples of such solvents are, dimethyl sulfoxide (DMSO), dimethylformamide (HCONMe<sub>2</sub>), *etc.* In many reactions, *e.g.* Wittig, very strong bases are required, and the use of strong bases creates many other problems and side reactions take place. These problems can be overcome by using a catalyst, which is soluble in water as well as the organic solvents. Such catalysts are known as Phase Transfer Catalysts.

### 1.1 Definition of Phase Transfer Catalysts (PTC)

The Phase Transfer Catalysts are ionic substances, usually quaternary ammonium salts, where the size of the hydrocarbon group in the cation is large enough to confer good solubility of the salt in organic solvents; in other words, the cation must be highly lipophilic.

In general, the PTC reaction describes a methodology for accelerating reaction between water insoluble organic compounds and water soluble reactants, *e.g.*, the reaction of an organic halide with sodium cyanide. The basic function of the catalyst is to transfer the anion and the reacting salt from the aqueous phase to the organic one. The power of the phase transfer catalysts lies in the fact that it minimises the two important deactivating forces, *viz.*, solvation and ion pairing.

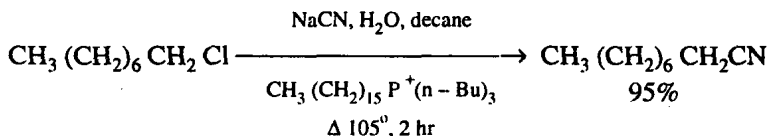
Following three factors play important role in the successful use of phase transfer catalyst reaction:

- i) *Influence of solvent:* Solvent should be aprotic and immiscible with water to avoid strong interactions with the ion pairs. Protic solvents will solvate the anions strongly and will lead to poor reactivity.
- ii) *Influence of cation:* The larger the number of carbon atoms around the central N atom in the PTC, the better is the lipophilicity of the catalyst. For example,  $\text{N}(\text{CH}_3)_4^+ \text{Cl}^-$  is a poor catalyst as compared to  $\text{N}(\text{Bu})_4^+ \text{Cl}^-$ .
- iii) *Salt effects:* Addition of sodium hydroxide and potassium carbonate increases the extraction coefficient many times and thus increases the rate of reaction.

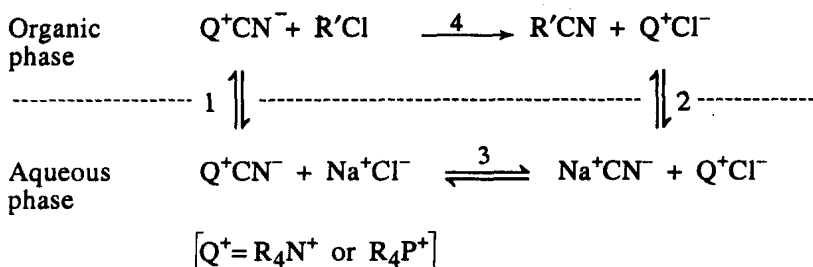
## 2. MECHANISM OF PTC REACTION

The mechanism by which nucleophilic reactivity is enhanced by PTC depends on the solvent effect. The conditions for phase transfer involve the use of two-phase system. The organic substance is dissolved in a water-insoluble organic solvent, such as a hydrocarbon or a halogenated hydrocarbon. The ionic nucleophiles even with vigorous stirring and mixing will show little tendency to react since the nucleophile and the substrate remain separated in the aqueous and organic phase respectively. The situation changes when a PTC is added. The alkyl groups of PTC are sufficiently large enough to confer solubility in the organic phase, the PTC carries nucleophile from the aqueous phase into the organic phase (to maintain electro-neutrality) and the result is that the reaction proceeds satisfactorily in good yield. The general principle of this technique and the concepts behind it are better understood by the following example.

Heating and stirring a mixture of 1-chlorooctane for several days with sodium cyanide give practically no yield of 1-cyanooctane. But if a small quantity of an appropriate salt (PTC) is added, the product is formed in about 2 hrs. Thus,



The above reaction does not take place in the absence of catalyst because the  $\text{CN}^-$  ions cannot cross the interface between the two phases, except in very low concentration. The reason is that  $\text{Na}^+$  ions are solvated by water, and this solvation energy would not be present in organic phase. Thus,  $\text{CN}^-$  ions cannot cross without the  $\text{Na}^+$  ions because that would destroy the electrical neutrality of each phase. In contrast to  $\text{Na}^+$  ions, the quaternary ammonium and phosphonium ions with sufficiently large R groups are poorly solvated in water, and prefer organic solvents. If a small quantity of such a salt is added, three equilibria set up. These are represented as:



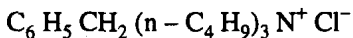
The  $\text{Na}^+$  ions remain in aqueous phase since they cannot pass into organic phase. The  $\text{Q}^+$  ions do cross the interface and carry the anion with them. At the beginning of the reaction, the chief anion present in aqueous phase is  $\text{CN}^-$ . This gets carried to the organic phase (equilibrium 1) where it reacts with  $\text{R}'\text{Cl}$  to produce  $\text{R}'\text{CN}$  and  $\text{Cl}^-$ . The  $\text{Cl}^-$  then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3 takes place entirely in the aqueous phase; it allows  $\text{Q}^+\text{CN}^-$  to be regenerated. The equilibria are normally reached much faster than the actual reaction 4 and so the latter is the rate determining step.

### 3. TYPES OF PHASE TRANSFER CATALYSTS

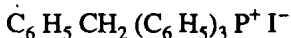
Phase transfer catalysts used are quaternary 'onium' salts such as ammonium, phosphonium, antimonium and tertiary sulphonium salts. However, in practice, only a limited number of ammonium and phosphonium salts are widely used. The more common phase transfer catalysts are commercially available. Some of the PTC's normally used are:

- i) Aliquat 336 :  $\text{N}^+\text{CH}_3 (\text{C}_8\text{H}_{17})_3 \text{Cl}^-$   
Methyl trioctylammonium chloride
- ii) Benzyl trimethylammonium chloride or bromide (TMBA)  
 $\text{N}^+(\text{CH}_3)_3 \text{CH}_2 \text{C}_6\text{H}_5 \text{X}^- (\text{X} = \text{Cl or Br})$
- iii) Benzyl triethylammonium chloride or bromide (TEBA)  
 $\text{N}^+(\text{C}_2\text{H}_5)_3 \text{CH}_2 \text{C}_6\text{H}_5 \text{X}^- (\text{X} = \text{Cl or Br})$
- iv) Tetra-n-butylammonium chloride, bromide, chlorate or hydroxide  
 $\text{N}^+(\text{n-Bu})_4 \text{X}^- (\text{X} = \text{Cl, Br, ClO}_4, \text{OH})$
- v) Cetyl trimethylammonium chloride or bromide (CTMAB for bromide)  
 $\text{N}^+(\text{CH}_3)_3 (\text{CH}_2)_{15} \text{CH}_3 \text{X}^- (\text{X} = \text{Cl or Br})$
- vi) Tetra n-pentyl, tetra n-hexyl and trioctyl propyl ammonium chloride or bromide  
 $(\text{C}_5\text{H}_{11})_4 \text{N}^+ \text{X}^-, (\text{C}_6\text{H}_{13})_4 \text{N}^+ \text{X}^-, (\text{C}_8\text{H}_{17})_3 \text{C}_3\text{H}_7 \text{N}^+ \text{X}^-$   
( $\text{X} = \text{Cl or Br}$ )

vii) Benzyl tributylammonium chloride



viii) Benzyl triphenyl phosphonium iodide



Quaternary phosphonium salts are more expensive than the quaternary ammonium salts, but they do have an advantage of being more thermally stable than the corresponding ammonium salts.

Alternatively, it is some times advantageous to use an agent which can complex an alkali metal cation, solvate it and provide a lipophilic anions which can be solvated by the organic medium. Two such catalysts most widely used are the crown ethers and cryptates. These are discussed in detail in Chapter-2.

Phase transfer catalyst bonded to polymeric matrix are also known. These are discussed in Chapter-5.

#### 4. ADVANTAGES OF PHASE TRANSFER CATALYSTS

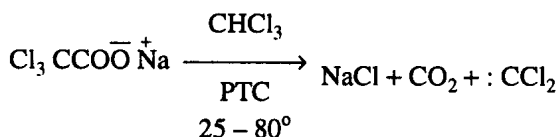
It is now well established that the PTC reactions have considerable advantages over the conventional procedures. The PTC reactions

- i) Do not require vigorous conditions and the reactions are fast.
- ii) Do not require expensive aprotic solvents.
- iii) Do not require high temperatures; the reactions usually occur at low temperature.
- iv) There is no need for anhydrous conditions since water is used as one of the phases.
- v) With the help of PTC, the anion is available in organic solvent and so its nucleophilicity increases.
- vi) In many cases the work up procedure is easier
- vii) Many reactions which require strong base like alkoxide, sodamide, sodium hydride etc. can proceed by even  $\text{OH}^-$  as it becomes strongly nucleophilic in the presence of PTC.
- viii) Almost all reactions can be carried out by PTC except those which are sensitive to water.
- ix) Some special advantages in the use of PTC are: The reactions that do not otherwise proceed can be made to proceed in good yields. Modification of selectivity and modification of product ratio, *e.g.*, O vs C alkylations are also possible. Higher yields through the suppression of side reactions is possible by the use of PTC.

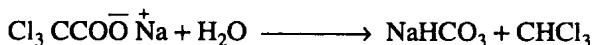
#### 5. TYPES OF PHASE TRANSFER CATALYSED REACTIONS

- i) *Liquid-Liquid phase transfer reaction:* Originally, the PTC reactions were performed using an aqueous phase and an organic phase. This technique is called liquid-liquid phase transfer catalytic reaction.
- ii) *Solid-Liquid phase transfer reaction:* In the above liquid-liquid phase transfer reaction using an aqueous and an organic phase, problems sometimes

arise when coextraction of water of hydration occurs. This may interfere with the desired reaction through suppression or diversion. Therefore, in such cases water should be avoided. This is achieved by working with a solid anionic reagent suspended in an anhydrous organic solution of the substrate. The PTC catalyst transfers the anion from the surface of the crystal lattice to the organic phase. For example, generation of dichlorocarbene by thermal decomposition of sodio trichloroacetate suspended in anhydrous chloroform in the presence of catalytic amount of a quaternary salt.

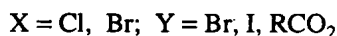
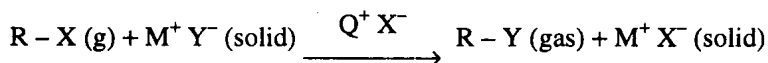


However, if water is used in the above reaction, sodium trichloroacetate is decomposed with water according to the following reaction:



This version of the reaction is generally called solid-liquid phase transfer reaction. Crown ethers are most suitable catalyst for this purpose. Since crown ethers behave as two dimensional system with multiple polar sites, which can approach a crystal lattice so closely that the required movement of the cation from the lattice to ligand is small. In contrast, the onium cations have a sterically shielded cation, so they cannot approach the lattice closely. A major advantage of solid-liquid phase transfer catalysis is "anion activation", possible in more polar solvents (*e.g.*, acetonitrile) which cannot be used with water. Hence, due to less solubilized salt and non solvated anion, reactions are fast with solid-liquid phase transfer catalysts.

- iii) *Solid-gas phase transfer reaction:* In this process the two phases are solid and a gaseous phase. The gaseous substrate is continuously passed through a fixed bed of the reacting salt and a thermally stable PTC (usually  $\text{Q}_4^+\text{P}$ ) absorbed in silica gel. This technique is used in simple nucleophilic displacements such as synthesis of halides, alkyl esters or the halogen exchange.



This reaction has the advantage of giving pure products directly due to the absence of aqueous and organic solvents.

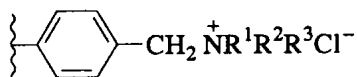
- iv) *Triphase catalyst:* Triphase catalyst is also a phase transfer process in which three phases, *viz.*, organic, aqueous and a solid catalyst are present. The solid catalyst is generally on a polymer support and is insoluble in water or organic



solvent. The triphase catalysis are divided into different categories based on the nature of the activation site.

a) *Insolubilized ammonium and phosphonium salts*

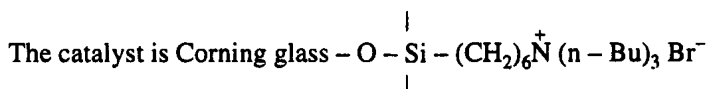
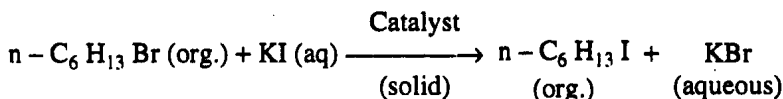
This type of catalyst consists of a cross linked polystyrene resin bearing quaternary ammonium or phosphonium groups as the catalyst (as shown below). Such catalysts are insoluble in the medium.



Based on the results of various experiments following generalisations have been made.

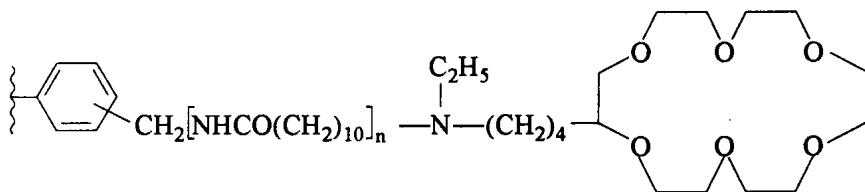
- i) Polymer anchored phosphonium salts exhibit greater activity than analogues of ammonium based resins.
- ii) More extensive cross linking of the support leads to lower activity.
- iii) Lengthening of the alkyl chain between the support and the onium groups significantly improves the yield of the O-alkylated product.

Quaternary ammonium and phosphonium salts covalently attached to glass surface can also be used. For example,



b) *Insolubilized crown ethers and cryptands*

Polymer anchored crown ethers and cryptands, like the polymer supported phosphonium salts, are more useful than the supported ammonium salts owing to their higher-activity and thermal stability. An example of such catalyst is given below:



c) *Insolubilized cosolvents*

Catalysts having cosolvents like properties have been developed. a graft polymer is derived from polyethyleneglycol monomethyl ether and microporous cross linked polystyrene matrix. An illustration is given below.