PHASE TRANSFER CATALYSIS IN PHARMACEUTICAL INDUSTRY – WHERE ARE WE?

MICHAŁ FEDORYŃSKI[1,2]*, MAGDALENA JEZIERSKA-ZIĘBA[1] and BARBARA KĄKOL[1]

[1]Industrial Chemistry Research Institute, 8 Rydygiera St., 01-793 Warsaw, Poland
[2]Warsaw University of Technology, Faculty of Chemistry, 75 Koszykowa St., 00-662 Warsaw, Poland

Abstract: Basic concept of phase transfer catalysis, its specific features and applications in pharmaceutical industry are described.

Keywords: phase transfer catalysis, carbanions, dihalocarbenes, alkylation, asymmetric synthesis, chiral quaternary ammonium salts, drug synthesis

Organic synthesis is still the main way to produce pharmaceuticals. Among the reactions used for transformations of substrates into final products, especially important are those in which the abstraction of a proton from C, O, N, S, etc. acids, under the action of bases, results in the formation of the corresponding anions. These anions, being nucleophilic agents, enter a variety of reactions with electrophilic partners. It is obvious that proper selection of the base-solvent system used for reactions induced by bases is of crucial importance. Phase Transfer Catalysis (PTC) seems to be most general, efficient and environment-friendly methodology of performing reactions in which organic and inorganic anions react with organic substrates. According to this methodology reactions are performed in immiscible two-phase systems.

One phase (inorganic) is a source of inorganic anions (if they are available as salts) or base for generation of organic anions. The salts or base are most often used as aqueous solutions, or less frequently in the form of powdered solids. The second (organic) phase contains organic reactants, usually neat or sometimes in appropriate solvents. Upon the introduction of a catalyst – tetraalkylammonium (TAA) salt – continuous transfer of reacting anions, present or produced in the interfacial region, into the organic phase in the form of lipophilic ion pairs with the catalyst cation takes place. All the further reactions occur in the organic phase.

In this paper we describe the basic concept, special features, numerous and important advantages of PTC, its applications in pharmaceutical industry (taken mostly from recent literature) and perspectives for the future.

Basic concept of phase transfer catalysis

Further discussion will be limited to the reactions in which reacting anions are generated *in situ* from the corresponding precursors under the action of base located in the inorganic phase. Most often it is an aqueous solution of sodium or potassium hydroxide – so called liquid-liquid system, or powdered alkali metal carbonates, hydroxides etc. – so called liquid-solid system. This methodology was discovered and introduced into laboratory practice in 1965 by Mąkosza.

Organic anions in PTC systems are generated via deprotonation of the appropriate precursors in the interfacial region between two immiscible phases – organic (containing CH, OH, NH, SH, etc. acid, electrophilic reagent and a catalyst) and inorganic. Anions thus formed cannot migrate to the organic phase as the sodium or potassium salts, since inorganic counterions are strongly solvated in the aqueous phase. They can exist in the interfacial region – less precisely at the phase boundary – in an adsorbed like state. In this state organic anions are very unreactive, being able to react only with very strong electrophiles.
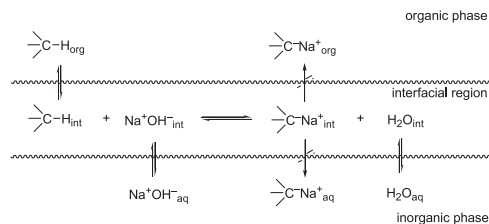

In the presence of a catalyst – TAA salt or another source of organic cations, for instance alkali metal cations complexed with crown ether or ethers of poly-

ethylene glycols – these anions enter in the interfacial region fast and diffusion controlled ion exchange results in the formation of lipophilic ion pairs TAA cation/organic anion, which are then transferred from the phase boundary into organic phase.
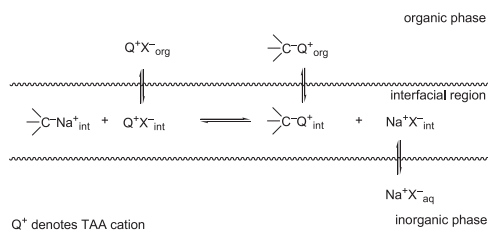
Further reactions, for instance alkylations occur in the organic phase.
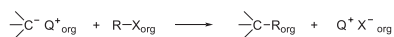
The catalyst cation probably plays an important role also in the deprotonation step decreasing the energy of transition state by influence of the positive charge from the opposite site of the reaction centre. The degree of deprotonation of anion precursor at the phase boundary – the acid-base equilibrium


is a function of its acidity. Since the lipophilic ion pairs formed via ion exchange

depart from the phase boundary, a component of the equilibrium leaves the equilibrium site, thus the equilibrium is shifted to the right. Due to this effect organic compounds of low acidity (of pK_a value up to ~ 24) can be efficiently converted into the corresponding anions which subsequently enter desired reactions. Taking into account the value of pK_a of water ~ 15.7, a significant hiperbasic effect is observed in these systems expanding applicability of sodium hydroxide as the base in PTC catalyzed, base-promoted reactions. Thanks to this hyperbasic effect aqueous sodium hydroxide can be used for generation and reactions of a large range of carbanions and other organic anions instead of commonly used strong bases such as sodium amide, sodium hydride, potassium t-butoxide etc.

The major advantages of PTC in both laboratory and especially industrial applications are: elimination of organic solvents; elimination of dangerous, inconvenient and expensive bases such as alkali metal amides, hydrides, alcoholates etc., and use of alkali metal hydroxides or carbonates; high reactivity of the active species; high yields and purity of products, low investment cost, minimization of industrial wastes etc.

Examples of PTC reactions carried out in the presence of bases can be found in numerous reviews and monographs (1). It is worth mentioning that the first industrial application of this methodology was in a Polish pharmaceutical factory in the early 1960s for ethylation of phenylacetonitrile:
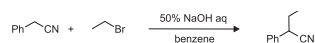

and later it was used in many other companies.

Special features of phase transfer catalysis and its applications in pharmaceutical industry

Presently PTC is a common methodology for alkylation of a large variety of organic anions derived from OH, NH, SH etc. acids, and particularly of carbanions of nitriles, esters, ketones, sulfones, acidic hydrocarbons and many others. For hydrolyzable compounds of higher CH acidity such as alkyl cyanoacetates, malonates, acetoacetates etc. liquid-solid PTC system, in which anhydrous potassium carbonate is used as a base, is particularly advantageous. Carbanions reactions other than alkylation are also efficiently carried out in PTC system: nucleophilic substitution of halogen or other leaving groups located in *para* or *ortho* position in nitroarenes by methinic carbanions; addition of carbanions to carbonyl groups – especially important are syntheses of oxiranes in the Darzens reaction of aldehydes and ketones with carbanions of chloronitriles, sulfones etc.; addition of carbanions to polar carbon-carbon double bonds, particularly useful when followed by further reactions, such as formation of cyclopropane derivatives, and many others.

Below we present selected examples of the applications of PTC for syntheses of biologically active compounds, taken mostly from recent literature. Synthesis of Sibenadet hydrochloride – a potent drug used for treatment of chronic obstructive pulmonary disease, includes *O*-alkylation process carried out on about one hundred kilogram scale in PTC system (2).
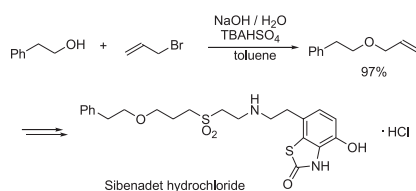
3-Cyclopentyloxy-4-methoxybenzaldehyde – an intermediate in the synthesis of phosphodiesterase IV isoenzyme inhibitor PDA-641, used for the treatment of asthma, inflammatory disorders and depression – was prepared on a multikilogram scale by *O*-alkylation of isovanillin with cyclopentyl bromide in liquid-solid PTC system (3).
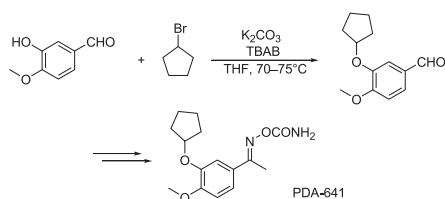
Aryl *S*-β-glycosides of 1-thio-*N*-acetylglucosamine were obtained by glycosylation of appropriate arylthiols with α-glucosaminyl chloride under PTC conditions. They are the starting materials for the synthesis of some muramyl dipeptide glycosides, which stimulate an antibacterial resistance toward *Staphylococcus aureus* in mice (4).
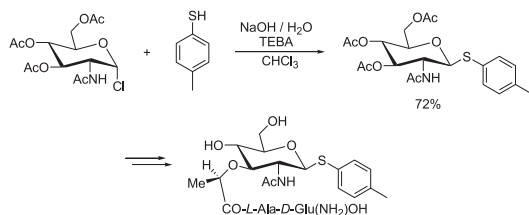
Regioselective *N*-alkylation of some urea derivatives with benzyl chloride has been performed using liquid-solid PTC conditions. Many compounds with depicted skeleton fragments are biologically active, possessing antiarrhythmic and anticarcinogenic properties (5).
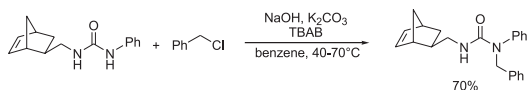
Many acridone derivatives are antitumoral, antiparasitic, and antiviral agents. *N*-Alkylation of acridones proceeds efficiently under PTC conditions (6).
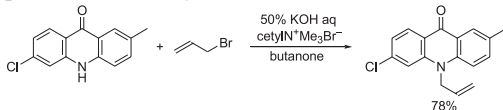
Significantly improved and efficient process for the production of Donepezil hydrochloride – acetylcholinesterase inhibitor used for the threatment of Alzheimer's type diseases – was reported recently on kilogram scale (7). The crucial step – condensation of 1-benzylpiperidine-4-carboxaldehyde with 5,6-dimethoxyindan-1-one was optimized using different bases. The best result – 88% yield, 99% purity without column purification – was obtained in PTC system with 10% NaOH aq solution in the presence of tetrabutylammonium bromide (TBAB) (7).
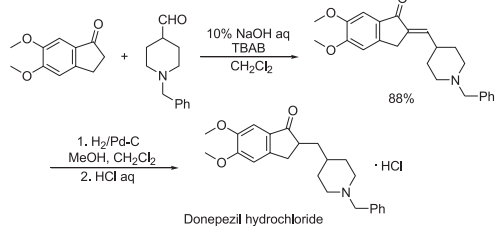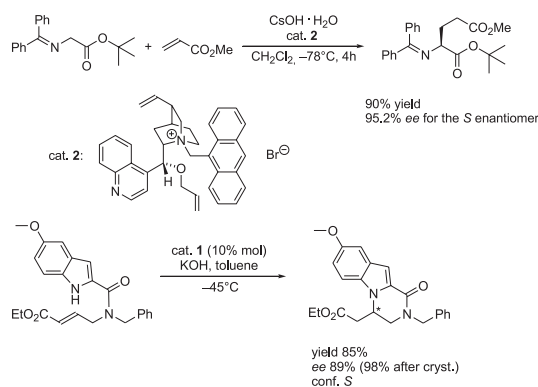
The most important event for the development of PTC applications during the last 15–20 years was undoubtedly the demonstration by the chemists from Merck Co. the possibility to conduct an asymmetric synthesis with the use of this methodology. They showed that TAA salt produced via benzylation of cinchona alkaloid is an efficient PT catalyst for enantioselective methylation of substituted indanone derivative (8).
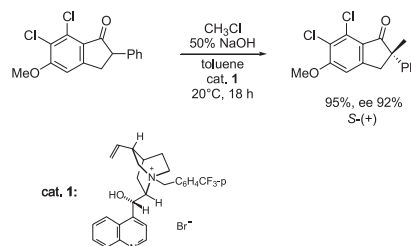
The possibility of asymmetric synthesis in PTC system, induced by chiral TAA salts was not obvious. The chiral catalyst, according to commonly accepted mechanistic picture of its action, exerts only ionic and hydrophobic interaction with reacting substrate. Thus its effect, differentiating energies of the two diastereomeric transition states leading to two new chiral chiral centers should be rather minor.

In the last years this problem was successfully solved by chemists from O'Donnell, Lygo, Corey and Maruoka groups, who developed proper, structurally well-defined, chiral TAA salts, which display not only ionic interactions with reacting species. Presently asymmetric PTC is an extremely important and general tool in organic synthesis, routinely used for alkylation of Schiff bases derived from glycine – which constitutes a general method of asymmetric synthesis of α-aminoacids and their derivatives, Michael addition, aldol reaction, epoxidation, aziridination etc. Hundreds of papers on this subject appeared in the last fifteen years, they are exhaustively discussed in a monograph edited by K. Maruoka, published in 2008 (9). A review concerning practical aspects of asymmetric PTC will be also published this year (10). Some illustrative examples are given below, [references (11–16), respectively].

The last example represents multikilogram scale practical asymmetric synthesis of estrogen receptor β selective antagonist, the key step of which is asymmetric Michael addition of indanone derivative to methyl vinyl ketone. Although the ee value obtained is not impressive, simple crystallization of the product from isopropyl acetate upgraded optical purity to 97% ee.

A lot of data, reported in recent literature, leads to the conclusion that the originally proposed by Mąkosza (17) mechanistic picture of PTC processes, carried out in the presence of a base, adequately illustrates the general mechanism of the catalytic process. However, some phenomena, which have been discovered over the past years show that we are still far from a full understanding of the processes which take place in the PTC reactions. Fortunately, these observations generally increase and not decrease the applicability of PTC.

For instance, it is well established that the monoalkylation of arylacetonitrile carbanions with primary alkyl bromides carried out in the presence of 50% aqueous sodium hydroxide and a lipophilic quaternary

ammonium salt catalyst, results in high yields. However, under these conditions the yields of reactions with *sec*-alkyl bromides seldom exceed 60%, introduction of the second alkyl group to the 2-arylalkanenitriles proceeds with difficulty, yields of 1-aryl-1-cyanocyclobutanes in reactions with 1,3-dibromopropane are low, and finally, cyclopropanation of phenylacetonitrile with 1,2-dichloro- or 1,2-dibromoethanes does not proceed – dehydrohalogenation of the dihaloalkane is the only observed process.

In all the cases mentioned a simple replacement of 50% sodium hydroxide solution for $60 – 75\%$ potassium hydroxide results in a significant increase of the yields and purity of products or allows the reaction to proceed (18).

It is worthy to note that the above reaction, carried out in the presence of 50% NaOH, resulted in dehydrobromination of cyclohexyl bromide.

Isopropylation of 3,4-dimethoxyphenylacetonitrile is an important step in the synthesis of Verapamil, used in the treatment of hypertension, angina pectoris, cardiac arrhytmia and cluster headaches.

A product of cycloalkylation of 4-chlorophenylacetonitrile with 1,3-dibromopropane – a precursor of Sibutramine, antiobesity and antidepressant drug – is obtained in good yield and without inseparable allylated side products, from the competitive β-elimination process with 1,3-dibromopropane (18).

A possible explanation of the facts presented above involves a kinetic effect, since for more concentrated solutions of hydroxides alkylation proceeds much faster and dominates over side reactions.

A crucial step of the synthesis of Anastrozole – selective aromatase inhibitor, effective for the treatment of advanced breast cancer in postmenopausal women – consists on exhaustive methylation of 3,5-

bis(cyanomethyl)-toluene. This process was performed using methyl iodide and NaH/DMF (yield 88%) (19), or methyl chloride and 50% NaOH aq/benzyltriethyl-ammonium chloride (TEBA) (yield 70%) (20).

Anastrozole

However, in the last case the quality of the product obtained prohibited its application to the synthesis of drug – probably it was contaminated by mono-, di- and trimethylated compounds. Undoubtedly the application of 60% or more concentrated KOH solutions should overcome all these problems.

Probably the most spectacular example of application of PTC for reactions of organic anions is generation and reactions of dihalocarbenes (and many other carbenes) in α-elimination reaction. We will limit ourselves to the reactions of dichlorocarbene (DCC).

Generation of this active electrophilic specie from chloroform in PTC system (concentrated aqueous sodium hydroxide as a base in the presence of a catalytic amount of TEBA), carried out in the presence of alkenes leads to the addition products of DCC – 1,1-dichlorocyclopropane derivatives, which are formed in high yields (Mąkosza reaction) (21).
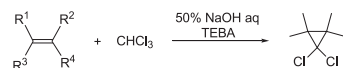

The utility of *gem*-dihalogenocyclopropanes as starting materials in organic synthesis is well documented (22).

Of special interest are Banwell and coworkers works on the synthesis of natural products (or their analogs) and other compounds possessing biological activity, in which readily available *gem*-dihalogenocyclopropanes were used as building blocks (23). Synthesis of an alkaloid (–)-erythramine, isolated from a variety of plant sources, which displays cardiovascular activity and molluscicidal properties is an illustration (24).

(–)-Erythramine
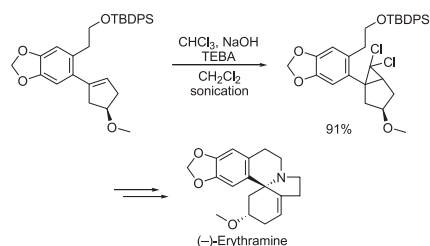
It is worthy to note that apart from dihalocyclopropanation of alkenes PTC was successfully applied

to a variety of other carbenic reactions, such as insertion into CH bonds, reactions with primary and secondary amines (giving isonitriles and N-formylated amines, respectively), Schiff bases (to form dihalogenoaziridine derivatives), some aromatic heterocycles (which usually lead to products of rearrangement of initial adducts) and with many other electrophiles. Some recent examples are given below [references (25–28), respectively].
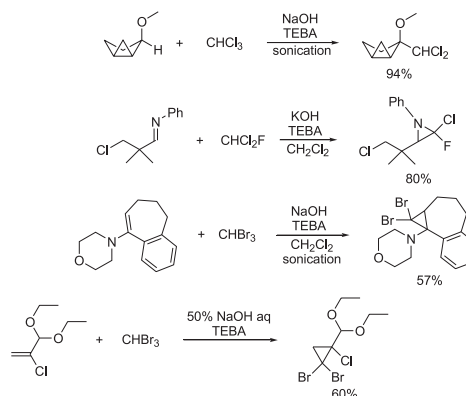
In many cases these reactions have gained practical value thanks to the PTC methodology. For instance, the reaction of chloroform with primary amines leading to isonitriles was previously used only as an analytical method.

The now commonly accepted mechanistic picture for the generation and reactions of trihalomethyl anions and dihalocarbenes is as follows: on the phase boundary between the organic phase containing haloform, an alkene (or other compound reacting with dihalocarbene), and inorganic phase (concentrated aqueous sodium hydroxide), deprotonation of haloform produces trihalomethyl anions which are adsorbed at the interface. The ion exchange between TAA catalyst, present in the system, and trihalomethyl anions at the interface produces lipophilic ion pairs TAA cation/trihalomethyl anion, which migrate into the organic phase where the trihalomethyl anions undergo reversible dissociation to dihalocarbene and TAA salt. The former reacts with alkene to produce dihalocyclopropane derivative, whereas TAA salt migrates to the interfacial region where it enters again the ion exchange, so another TAA cation/trihalomethyl anion ion pair is formed and the process proceeds continuously. Under these conditions there is a real equilibrium between carbenes and trihalomethyl anions in the organic phase, because all the components are soluble in this phase.

$$\bar{C}Cl_3Q^+ \quad \rightleftharpoons \quad CCl_2 \; + \; Q^+Cl^-$$

It is worthy to note that there is no base or its conjugated acid in the organic phase. Because of that

the desired reactions proceed in high yield and selectivity.

From this picture, it is obvious that the main function of the catalyst in PTC reactions is to provide soluble in the organic phase lipophilic ion pair TAA cation/trihalomethyl anion. Thus the structure of the catalyst should not exert any strong specific effect on the reaction course, providing it is lipophilic enough. However, there are many observations that the rates of PTC carbene reactions and the structure of the products depend on the structure of TAA cations and also on the kind of the solvent used. Probably the most spectacular example is the reaction of chloroform with *t*-butyl acrylate. When TEBA chloride is used as a catalyst, a mixture of *t*-butyl 4,4,4-trichlorobutyrate, 1-*t*-butoxycarbonyl-2,2-dichlorocyclopropane and a product of further transformation of the latter (1-*t*-butoxycarbonyl-4,4,5,5-tetrachlorospiropentane) are formed (29).
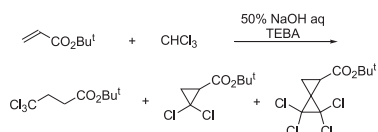
The same reaction carried out in the presence of tetramethylammonium halide (TMAX) (instead of TEBA) as a catalyst produces almost exclusively a cyclopropane derivative. Reaction with TEBA, carried out in heptane as a solvent leads to Michael addition product in good yield (30).

A possible explanation of the results presented above can be as follows: It is obvious that the TMA/trichloromethyl anion ion pairs, formed at the interphase cannot penetrate the whole bulk of the organic phase (in the 50% NaOH/benzene/cat. TMABr system, after vigorous stirring and phase separation, the ammonium salt was found in the aqueous phase!). Due to the small size of TMA cations, these ion pairs are rather tight and inactive, thus as a result the trichloromethyl anion does not react with Michael acceptor. However, the TMA/trichloromethyl anion ion pair may find itself much further from the boundaries of the interfacial region compared to the case of the sodium cation/trichloromethyl anion ion pair and can therefore dissociate there to DCC, which slowly adds to elactrophilic alkene.

The presence of nonpolar heptane solvent probably shifts the equilibrium

$$\bar{C}Cl_3Q^+ \; \rightleftharpoons \; CCl_2 \; + \; Q^+Cl^-$$

to the left. One can expect that in such a system, the nonpolar solvent decreases the solubility of TEBA cation/trichloromethyl anion in the organic phase, but the solubility of this ion pair is still better compared with TEBA. On the other hand, the presence of a nonpolar solvent should not exert a strong effect on the tightness of this ion pair. As ion pairs with TEBA cation are less tight than these with TMA cation, therefore the trichloromethyl anion is reactive enough to add to Michael acceptor. An alternative explanation is that the TMA cation/trichloromethyl anion ion pairs are less stable than other TAA/trichloromethyl anion species and decompose to the hard-hard ion combination TMACl and dichlorocarbene before a Michael reaction can occur.

Another example of catalyst influence on reaction course are reactions of chloroform with aldehyde enol esters. These substrates form products of formal addition of trichloromethyl anion to the vinyl group in the α position to the acyloxy substituent, when the reaction is carried out in the presence of TEBA (31).
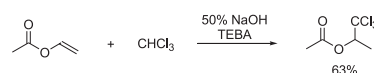
The mechanism involves the hydrolytic generation of an acetaldehyde, addition of the trichloromethyl anion to its carbonyl group and finally fast *O*-acylation of the adduct by vinyl acetate (32).
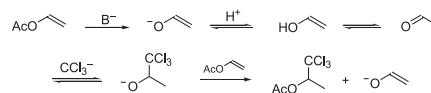

In the presence of TMABr and a large excess of chloroform, a mixture of both chain and cyclopropane product is formed, in which carbene addition product prevails (33).
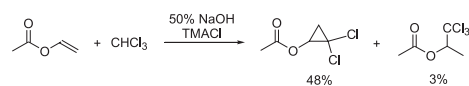

These results can be explained similarly, as in the case of dichlorocyclopropanation of electrophilic alkenes, carried out in the presence of TMA salts. Furthermore, formation of cyclopropane derivatives may result from the use of a large quantity of chloroform, conditions which disfavor the cleavage of enol esters by means of hydroxide anion.

It was shown recently that reactive aldehydes (especially formaldehyde) can be generated *in situ* in PTC systems from acylals – esters of geminal diols – and introduced into reactions with various nucleophiles (34). Formaldehyde was generated from easy available methylene diacetate in the presence of 60% aqueous potassium hydroxide or solid potassium carbonate as a base and TBAB as a catalyst. With 2-phenylalkanenitriles, chloroform, bromoform, alkyl malonic esters, 2-nitropropane, some NH acids etc. products of hydroxymethylation or acetoxymethylation of appropriate organic anions were formed, depending on the kind of substrate and reaction conditions, usually in good yields.
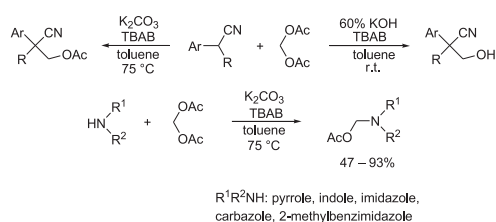
Of special interest is the reaction of methylene diacetate with 5-chloro-2-phenylpentane nitrile, carried out in the presence of 60% KOH aq and TBAB, in which 3-phenyltetrahydro-2H-pyran-3-carbonitrile was obtained in high yield.
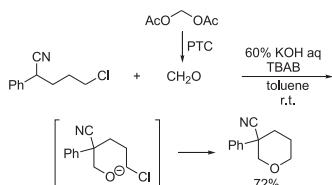
This process consists of the addition of nitrile anion to a carbonyl group of formaldehyde formed *in situ*, with subsequent intramolecular cyclization of aldol oxoanion thus formed.

All these reactions offer an interesting alternative to known hydroxymethylation reactions, described in the literature (*N*-hydroxymethylphthalimide or benzotriazolylmethanol as a formaldehyde source, organolithium bases; paraformaldehyde in acetonitrile, sodium hydride). 2-Aryl-2-hydroxymethylalkane nitriles (especially in enantiopure form) are useful substrates in syntheses of many biologically active compounds.

CONCLUSION

It should be emphasised that the possible applications of PTC are much wider than discussed in this article – including applications in the metaloorganic chemistry, the polymer industry, oxidation processes, β-elimination reactions, co-catalyzed processes etc. There are hundreds of industrial applications of PTC presently known. Of course, PTC is not limited to pharmaceutical industry and using this methodology one can also produce plant protection agents, dyes, monomers, photographic chemicals etc. It wouldn't be an exaggeration to say that when designing a new process or a method of synthesis, which include reactions involving anions, one should consider PTC as the first choice.

REFERENCES

1. Dehmlow E.V., Dehmlow S.S.: Phase Transfer Catalysis, 3rd ed., VCH, Weinheim 1993. Starks C.M., Liotta C.L., Halpern M.: Phase Transfer Catalysis, Fundamentals, Applications and Industrial Perspectives, Chapman & Hall, New York 1994. Mąkosza M., Fedoryński M.: Pol. J. Chem. 70, 1093 (1996). Handbook of Phase Transfer Catalysis, Sasson Y., Neumann R., Eds., Blackie Academic and Professional, London, 1997. Mąkosza M., Fedoryński M.: in Interfacial Catalysis, Volkov A.G., Ed., p. 159, Marcel Dekker, New York 2003 (reprinted in: Catal. Rev. 45, 321, 2003). Jones R. A.: Quaternary Ammonium Salts: Their Use in Phase Transfer Catalysis, Academic Press, San Diego 2001.

2. Giles M.E., Thomson C., Eyley S.C. et al.: Org. Proc. Res. Dev. 8, 628 (2004).

3. Wilk B.K., Mwisiya N., Helom J.L.: Org. Proc. Res. Dev. 10.1021/op800058n.

4. Zemlyakov A.E., Tsikalova V.N., Arizova L.R. et al.: Rus. J. Bioorg. Chem. 34, 223 (2008).

5. Kasyan L.I., Kasyan A.O., Tarabara I.N. et al.: Cent. Eur. J. Chem. 6, 161 (2008).

6. Xuarez L., Pellon R.F., Fascio M., Montesano V., D'Accorso N.: Heterocycles 63, 23 (2004).

7. Niphade N., Mali A., Jagtap K. et al.: Org. Proc. Res. Dev.: 10.1021/op800066m.

8. Dolling U.-H., Davis P., Grabowski E.J.J.: J. Am. Chem. Soc. 106, 446 (1984). Hughes D.L., Dolling U.-H., Ryan. K.M., Schoenewaldt E.F., Grabowski E.J.J.: J. Org. Chem. 52, 4745 (1987).

9. Asymmetric Phase Transfer Catalysis, Maruoka K., Ed., Wiley-VCH, Weinheim 2008.

10. Maruoka K.: Org. Proc. Res. Dev. 10.1021/op 7002979.

11. Corey E.J., Noe M.C.: Org. Synth. 80, 38 (2003).

12. Bandini M., Eichholzer A., Tragni M., Umani-Ronchi A.: Angew Chem. Int. Ed. 47, 3238 (2008).

13. Kitamura M., Arimura Y., Shirakawa S., Maruoka K.: Tetrahedron Lett. 49, 2026 (2008)

14. Patterson D.E., Xie S., Jones L.A. et al.: Org. Proc. Res. Dev. 11, 624 (2007).

15. Kano T., Lan Q., Wang X., Maruoka K.: Adv. Synth. Catal. 349, 556 (2007).

16. Scott J.P., Ashwood M.S., Brands K.M. J. et al.: Org. Proc. Res. Dev. 10.1021/op700178q.

17. Mąkosza M.: Pure Appl. Chem. 43, 439 (1975).

18. Barbasiewicz M., Marciniak K., Fedoryński M.: Tetrahedron Lett. 47, 3871 (2006).

19. Jackson T., Woo L.W.L., Trusselle M.N. et al.: Org. Biomol. Chem. 5, 2940 (2007).

20. Chojecka-Koryn E., Zagrodzki B.: Przem. Chem. 85, 338 (2006). Achmatowicz O., Pucko W., Chojecka-Koryn E. et al.: Pat. PL 197935 (2008).

21. Mąkosza M., Wawrzyniewicz M.: Tetrahedron Lett. 4659 (1969).

22. Fedoryński M.: Chem. Rev. 103, 1099 (2003).

23. Banwell M.G., Beck D.A. S., Stanislawski P.C., Sydnes M.O., Taylor R.M.: Current Org. Chem. 9, 1589 (2005). Banwell M. G.: Pure Appl. Chem. 80, 669 (2008).

24. Stanislawski P.C., Willis A.C., Banwell M.G.: Org. Lett. 9, 3503 (2007). Stanislawski P. C., Willis A. C., Banwell M.G.: Chem. Asian J. 2, 1127 (2007).

25. Brinker U.H., Lin G., Xu L., Smith W.B., Mieusset J.-L.: J. Org. Chem. 72, 8434 (2007).

26. Shinkevich E.Yu., Tehrani K.A., Khlebnikov A.F., Novikov M.S.: Tetrahedron 64, 7524 (2008).

27. Bissember A.C., Phillis A.T., Banwell M.G., Willis A.C.: Org. Lett. 9, 5421 (2007).

28. Sydnes L.K., Holmelid B., Kvernenes O.H. et al.: Tetrahedron 63, 4144 (2007).

29. Fedoryński M., Ziółkowska W., Jończyk A.: J. Org. Chem. 58, 6120 (1993).

30. Fedoryński M.: Tetrahedron 55, 6329 (1999).

31. Mąkosza M., Fedoryński M.: Roczniki Chem. 46, 533 (1972).

32. Martz J.T., Gokel G.W., Olofson R.A.: Tetrahedron Lett. 1473 (1979).

33. Fedoryński M., Kubicka-Prusik M., Kursa M., Jończyk A.: Tetrahedron 53, 1053 (1997).

34. Stefaniak F., Fedoryński M.: in On the borderland between chemistry and biology (Polish) Koroniak H., Barciszewski J. Eds., Vol. 16, p. 216, Scientific Publisher UAM, Poznań 2006.