THE PRESENT USE AND THE POSSIBILITIES OF PHASE TRANSFER CATALYSIS IN DRUG SYNTHESIS

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Abstract: After a short introduction, the actual possibilities and the prospective use of phase transfer catalysis in drug preparation are reviewed (198 ref.)

CONTENTS

Glossary.- In reaction schemes the following terms are used:

PTC = Phase Transfer Catalysis

Y^- = A nucleophilic anion, e.g. CN^-, R_3C^-, RO^-, RCO_2^-, F^-,....

L = A leaving group, e.g. Cl, Br, OSO_2Me,....

Z = An electron withdrawing group: NO_2, CN, CF_3,....

M^+ = An alkaline or alkaline-earth cation: Na^+, K^+, Ca^{2+},....

Q^+X^- = A quaternary ammonium or phosphonium halide.

Other substituents or atoms follow the IUPAC rules and their meaning is self evident.

The following *abbreviations* are frequently used:

TEBA = Triethyl benzyl ammonium chloride.

TEAB = Tetrabutyl ammonium bromide.

$TBAHSO_4$ = Tetrabutyl ammonium hydrogen sulfate.

TBACl = Tetrabutyl ammonium chloride.

18c6 = 18 crown 6.

Adogen or aliquat = A mixture containing mainly trioctyl methyl ammonium chloride.

I. INTRODUCTION

Phase Transfer Catalysis is one of the most attractive new techniques in organic synthesis. The method has a very broad scope of application. Chemically, the possibilities include the preparation of compounds from starting materials unreactive or decomposed under other conditions, and more generally the increase of the yields or of the selectivities in a large number of syntheses. Moreover from a practical point of view the method is simple, the work up is easy, and the reagents and solvents are of low cost.

Several references have been published on the theory and practical uses of Phase Transfer Catalysis (books[1-5]; reviews[6-12]); they can be consulted for a listing of the reactions already reported. However, if general papers have appeared on the application of Phase Transfer Catalysis to several fields of chemistry, e.g. heterocyclic chemistry[13], macromolecular chemistry[14], industrial chemistry[15], dye chemistry[16],.. no reviews exist, to the best of our knowledge[17], on the applications of phase transfer catalysis in Medicinal Chemistry, or more specifically to the synthesis of drugs or pharmaceutical intermediates. This is the purpose of the present paper.

Basically Phase Transfer Catalysis is a method which allows to carry out a reaction between a substrate soluble in an organic solvent and an ionic reagent insoluble in this solvent. Ionic reagents (saline compounds) are used in synthesis for two reasons:

- they exist as such and are not used under their neutral form, e.g. nitriles are prepared from a halide and NaCN not HCN[18]; aromatic fluorides are obtained by halogen exchange with KF not HF[19].

- when the same reaction, e.g. a nucleophilic substitution, can be carried out either with a neutral or with an ionic nucleophile, the ionic species is always more reactive (by 10^4 to 10^6)[20], e.g. Na^+RO^->ROH, $Na^+R_2N^-$>R_2NH, Na^+RS^->RSH.

However, the heterogeneous conditions corresponding to the use of high concentrations of anionic nucleophiles in organic solvents lead to a poor contact between reagents and to low reaction rates.

A well documented method used to increase the mutual solubility of hydrophilic and lipophilic reagents is to carry out the reactions in protic solvents (in fact mostly hydroxylic) such as alcohols. However, when a nucleophilic anion is dissolved in a protic solvent it is always hydrogen bonded to the solvent and therefore its reactivity is greatly decreased.

Another class of compounds has attracted much interest: dipolar aprotic solvents[21]. The most commonly used are DMF, DMSO, HMPA, acetonitrile and nitromethane; they have the property to dissolve in part (if not completely) saline reagents without hydrogen bonding with them. Therefore they have the advantage to increase the rate of a large number of reactions[22].

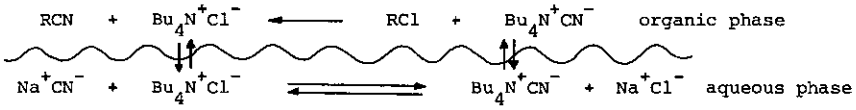
Unfortunatly polar aprotic solvents have several inconveniences: they are expensive; they must be used under anhydrous conditions; they are difficult to remove from the reaction medium because of their high boiling points; they are miscible with water, which means that purification using aqueous solution must be avoided when upscaling chemical processes.

A method was really needed that would allow to dissolve ionic reagents in common apolar solvents, give easy and safe reaction conditions and afford increased yields of reaction and improved purity of compounds. Phase Transfer Catalysis meets all these conditions.

1. Liquid-Liquid Phase Transfer Catalysis

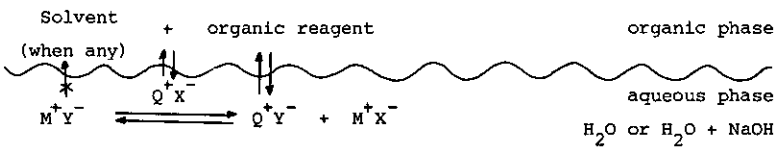
The following example, first reported by Starks, shows the possibilities of PTC[23]: if octyl chloride diluted in decane is reacted with sodium cyanide dissolved in water, at 105°C with a strong agitation, no reaction occurs after 3 hours. If 1.5% of hexadecyl tributyl phosphonium bromide is added, a 99% yield of octyl nitrile is obtained within 2 hours[24].

The following scheme shows how the reaction proceeds when a tetrabutyl ammonium chloride is used as catalyst.



The sodium cyanide which is soluble in water does not migrate into the organic phase. Upon addition of a quaternary ammonium chloride, an exchange occurs in the aqueous phase between the cations Na^+ and Bu_4N^+, and the ion pair $Bu_4N^+CN^-$, lipophilic enough because of the 16 carbons of the quaternary ammonium, transfers in the organic phase where the reactions take place.

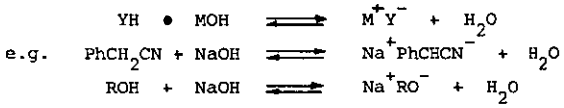
Experimentally, liquid-liquid PTC corresponds to a system made of two phases: an organic phase containing a liquid reagent with (or without) an organic solvent non miscible in water and an aqueous phase containing in most cases a nucleophilic reagent Y^-M^+. Moreover a quaternary ammonium or phosphonium catalyst is partitionned between the two phases.



Depending upon the nature of the nucleophile two possibilities exist:

a) M^+Y^- is dissolved directly in water, e.g. Na^+CN^-, K^+F^-,...

b) or M^+Y^- is obtained by exchange between a neutral reagent and a base,



In the last case the aqueous phase contains water and a concentrated base (usually $NaOH/H_2O$, 50/50 by weight).

The scheme reported above for synthesis of nitriles is a good representation of phase transfer mechanism when no additional base is necessary and when the quaternary ammonium salt is soluble in part in water. When an additional base is necessary in the aqueous phase or when the quaternary ammonium salt is not soluble in the aqueous phase, the mechanistic scheme may involve in addition an interfacial proton abstraction or an interfacial cation exchange[1,9,23-30]. These modifications of the basic PT mechanistic scheme may have practical consequences in the importance of agitation to obtain good yields of reaction.

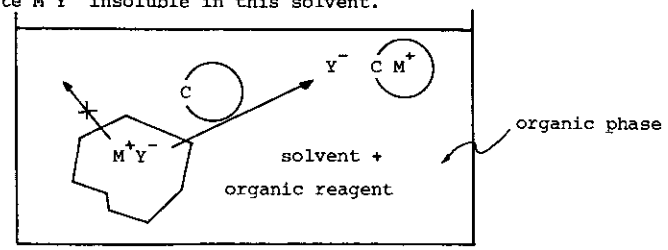
Whatever the intimate mechanistic scheme, the activation of the anion is due to the exchange

of the paired counter cation and to the consequent solubilisation of a more reactive loose ion pair in a solvent of low polarity.

2. Solid-Liquid Phase Transfer Catalysis

Solid-liquid PTC corresponds experimentally to reactions occurring with an organic reagent soluble in a solvent and a solid substrate M^+Y^- insoluble in this solvent.

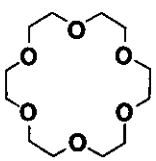
: complexant: crown ether, cryptant, chelatant.



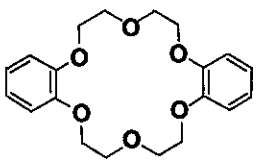
If a complexant  is added, the solid M^+Y^- is solubilized in the solvent and reacts under mild conditions.

In a specific example, potassium permanganate is added to a solution of benzene containing an olefin. Under these conditions the crystals of $KMnO_4$ stand at the bottom of the flask, the solvent is colorless and no reaction occurs. If a small amount of 18 crown 6 is added, the solvent immediately turns purple (the permanganate dissolves) and the olefin is smoothly oxidized.

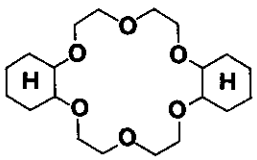
The complexants first used were the crown ethers, prepared by Pedersen[31], which showed high complexing abilities of alkaline and alkaline earth cations[32] with the following properties:



18 crown 6



dibenzo 18 crown 6



dicyclohexyl 18 crown 6

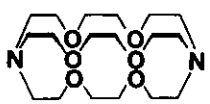
a.- extraction of cations owing to the selective complexation which depends upon the size and the substitution of the macrocyclic ether[33].

b.- activation of the anion paired to the complexed cation; the anion is said to be "naked"[35].

Following the first series of crown ethers made by Pedersen[31] a tremendous amount of macrocyclic complexants have been synthesized in which structural parameters have been changed to obtain increased complexing abilities[36-40].

Among all the new compounds prepared two series deserve a special mention:

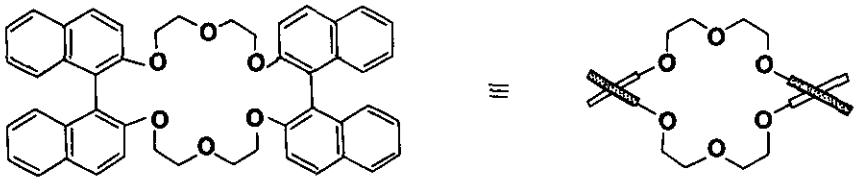
- the *cryptates* made by Lehn et al have given an extra dimension (conceptually and practically) to the high complexing power of crown ethers[11,41-44].



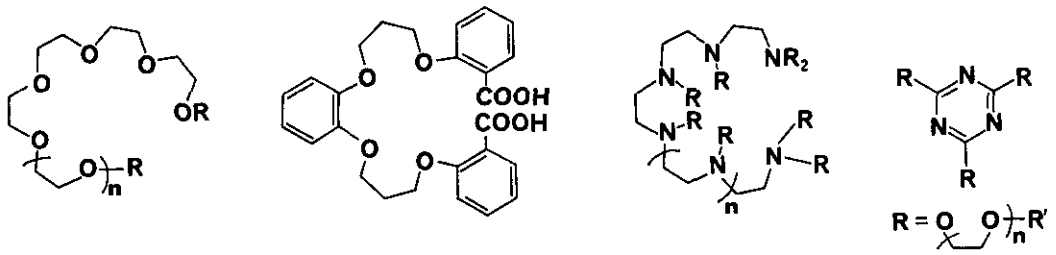
2,2,2-cryptate

1,1,1-cryptate

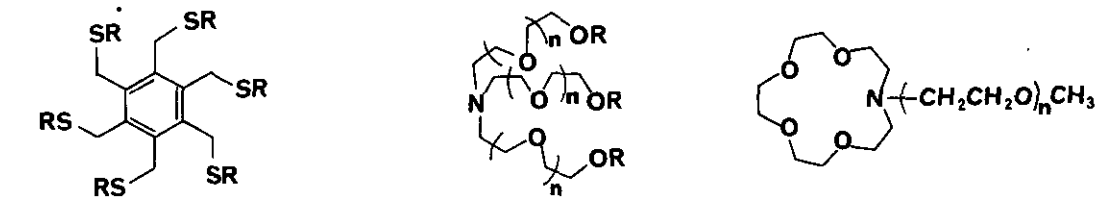
- the chiral host molecules designed by Cram et al have achieved splendid results in the separation of enantiomers and open new promises in asymmetric induction[45,46].



On the other side open chain equivalents of crown ethers and cryptates have been prepared. They show a lower complexing activity than their closed ring equivalents, but they are efficient enough and far more easily prepared and consequently cheaper. Typical structures are glymes[47-48], noncyclic polyether compounds[49], polyethylene amines[50,51], "polypodes"[52,53], "octopus"[54], "tridents"[55,56], "lariat-ethers"[57,58], etc.



glymes noncyclic polyethers polyethylene amines "polypodes"



"octopus" "tridents" "lariat ethers"

Presently the majority of current syntheses is more likely to be carried out with liquid-liquid transfer conditions, with quaternary ammonium and phosphonium catalysts. Solid-liquid catalysis using complexants is still hampered by the high price of catalysts like crown-ethers or cryptants. In some cases, when water needs to be strictly avoided, reactions are conducted under solid-liquid conditions, with a quaternary ammonium or phosphonium catalyst (not a complexant). Moreover in order to solve the problem of catalyst recovery a new technique has been proposed: Triphase Catalysis.

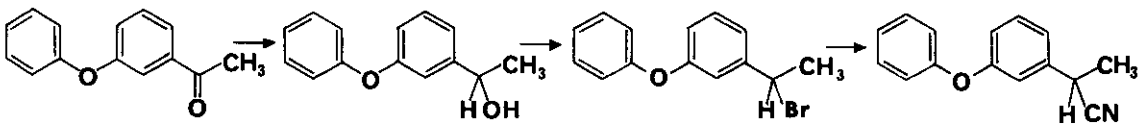
3. Triphase Catalysis

This technique developped by Regen[59-63] is an extension of both liquid-liquid PTC and solid-liquid PTC. It makes use of biphasic organic-aqueous system and of a catalyst (quaternary salt, crown ether or glyme) supported on a polymeric backbone. The technique has the advantages of homo-

geneous catalysis, owing to the selection of a catalyst having an appropriate molecular structure, and of heterogeneous catalysis since the catalyst is easily filtered off and recovered after the reaction. In principle the syntheses already reported under liquid-liquid or solid-liquid conditions may be extended to triphase conditions; in practice further kinetic and experimental data are needed to test the possibilities of all reactions[63].

II. PTC CLASSIFIED ACCORDING TO THE REACTION TYPE

Drugs being complex molecules synthesized in several steps, it is quite common that at least one step can be carried out by PTC. An example of the multiple possibilities offered by PTC is provided by the synthesis of the antiinflammatory *fenoprofen*[65]. Reduction of the acetophenone derivative 1 by means of sodium borohydride leads to the corresponding alcohol 2; reaction with phosphorous tribromide gives 3; displacement of the halide with cyanide gives a substituted propionitrile 4, whose saponification affords *fenoprofen*.



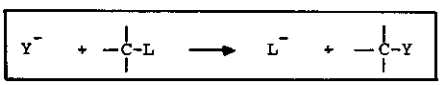
1 2 3 4

All the steps of the preceding scheme have been carried out by PTC on equivalent or similar compounds: reduction of the aryl ketone 1 to the secondary alcohol 2[66]; preparation of the bromo (or chloro) derivative 3 from the secondary alcohol 2[67,68], and transformation into the nitrile 4[24].

In order to give a comprehensive presentation of the applications of PTC to the preparation of pharmaceutical intermediates, we have arranged the syntheses reported in the literature according to the general scheme of the reaction mechanisms. To show the possibilities of the method we have selected further examples from "The Organic Chemistry of Drug Synthesis"[64] by Lednicer and Mitscher and from "Précis de Pharmacie Chimique usuelle" of Lespagnol[69]. Moreover, from the knowledge of the practical uses of PTC we have also tried to indicate what could be the possible limits of the technique.

1. Nucleophilic Substitutions at Saturated Carbon (NSCsp^3)

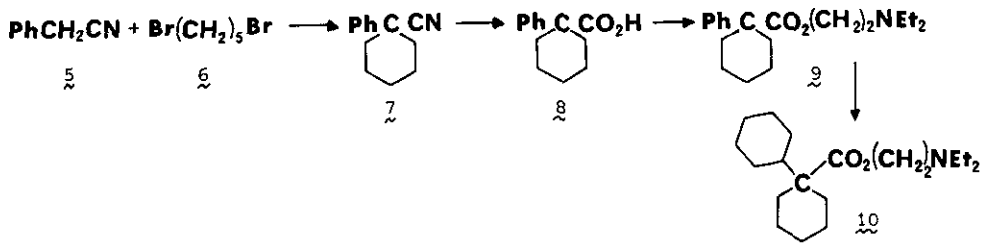
Phase Transfer will catalyse the following reactions where Y is a negatively charged nucleophile and L a leaving group.



1a. C-alkylations by NSCsp^3

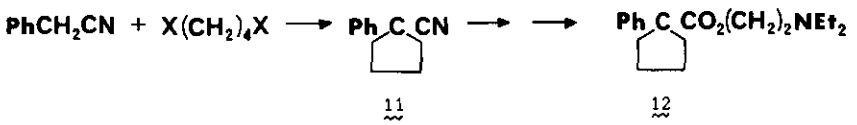
□ First step in the synthesis of *dicyclonine*, a spasmolytic agent.

Phenylacetonitrile (5) is alkylated with 1,5-dibromopentane (6) and the intermediate obtained 7 is saponified, the resulting acid 8 is esterified with N,N-diethylethanolamine (9) and the catalytic reduction of the aromatic ring affords *dicyclonine* (10)[70].



The first step has been carried out by Makosza using liq.-liq. PTC[71].

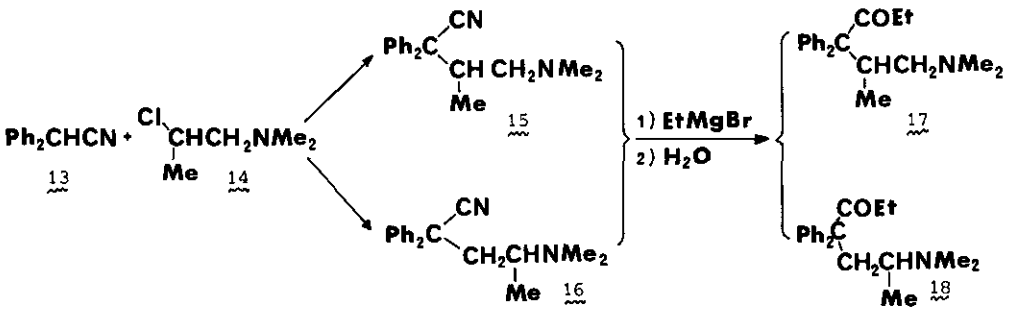
□ First step in the synthesis of *caramiphene* (12), an antiparkinsonian[72].



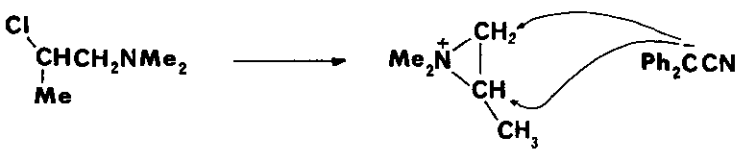
The preparation of the intermediate 11 has been made by PTC[71].

□ First step in the preparation of *methadone*, an analgesis agent.

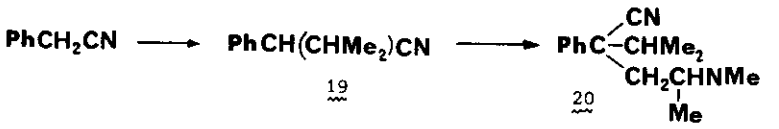
Alkylation of diphenylacetonitrile (13) by 14 using sodium amide affords two isomeric compounds which subsequently are converted to *methadone* (18) and *isomethadone* (17)[73,74] by treatment with ethylmagnesium bromide followed by hydrolysis.



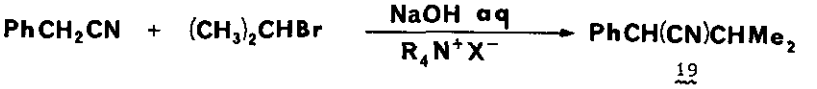
When the first step is carried out under phase transfer conditions using quaternary ammonium salts[75,76] or dicyclohexyl 18-crown-6[76], the ratio 16/15 is increased and the overall yield improved. This is an interesting example of the change of selectivity that PTC brings when an anchimeric assistance[77] occurs during a substitution reaction.



⊡ First step in the preparation of *isoaminile* 20, an antitusive.

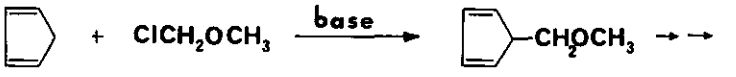


The alkylation of phenylacetonitrile with isopropyl bromide was made using sodamide in an early Patent[78]; but PTC using liq.-liq. conditions and a quaternary ammonium salt affords 19 in higher yield[71].



⊡ First step of the synthesis of prostaglandins.

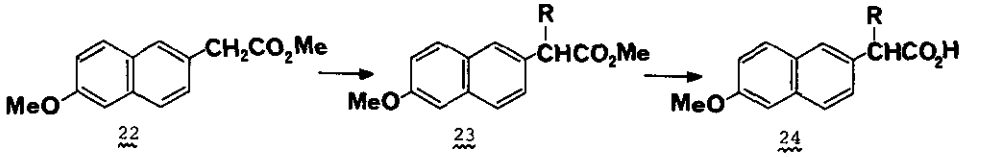
Alkylation of the anion of cyclopentadiene with chloromethyl ether affords the diene 21, which is converted after several steps into a prostaglandin precursor[79].



Makosza[80] has described a PT method of alkylation of cyclopentadiene using aqueous NaOH and a quaternary ammonium salt.

⊡ An intermediate step in the synthesis of the antiinflammatory, *naproxen*.

Alkylation of the anion of the compound 22, using $NaNH_2$ and methyl iodide affords 23 whose subsequent saponification gives *naproxen* (24)[81].

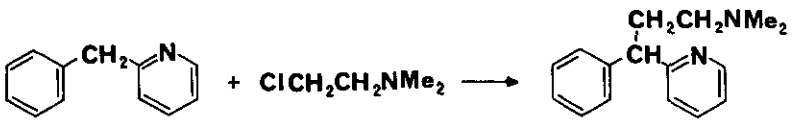


The Phase Transfer α-alkylation of tert-butylarylacetic esters[82]

has been reported; but the same reaction with methyl esters, corresponding to the step 22 → 23, is hampered by hydrolysis when liquid-liquid PTC is used.

⊡ Last step of the synthesis of *pheniramine*, an antihistaminic agent.

The protons on the methylene group of compound 25 are removed by strong bases such as sodium amides or butyl lithium. Alkylation of the resulting carbanion with N-(2-chloroethyl)dimethylamine affords *pheniramine* (26)[83].

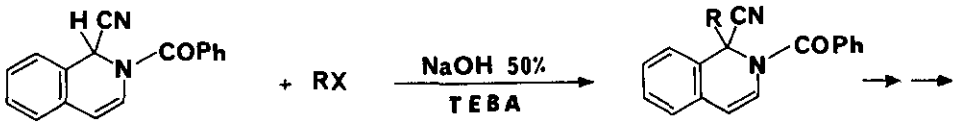


25 26

However, the pK_a associated with the dissociation of the CH_2 protons of 25 is too high ($pK_a \simeq 30$) to allow the formation of an anion[84] and conversion of 25 to 26 under liq.-liq. PT conditions.

⊡ A starting material for the synthesis of alkaloids (Reissert compounds).

Alkylation of the Reissert compound 27a[85] followed by an alkaline hydrolysis affords an isoquinoline 27b used in the synthesis of alkaloids[86].



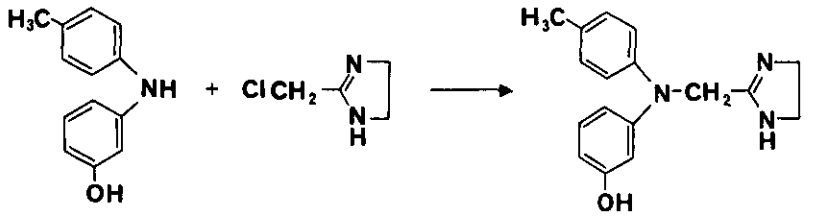
27a 27b

1b. N-alkylations by NSCsp[3]

The reactions described in this section are carried out with amines of low basicity where the nitrogen atom is bonded to electron withdrawing substituents or linked to (or included in) aromatic rings.

⊡ Last step in the synthesis of *phentolamine*, an α-adrenergic blocking agent.

Phentolamine (30) can be prepared by alkylation of the aminophenol 28 with the halide 29[87].



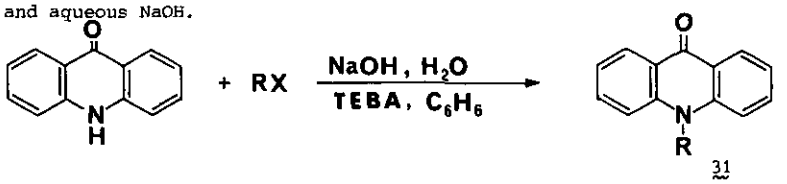
28 29 30

Similar alkylation reactions have been described with Ph_2NH using TEBA and NaOH with DMSO or HMPT, H_2O[88].

$$Ph_2NH + PhCH_2Cl \longrightarrow Ph_2NCH_2Ph$$

⊡ Synthesis of substituted acridanones with antiallergic and antiviral activities.

Acridanone derivatives 31 have been prepared[89,90] by alkylation reaction under PT conditions with TEBA and aqueous NaOH.



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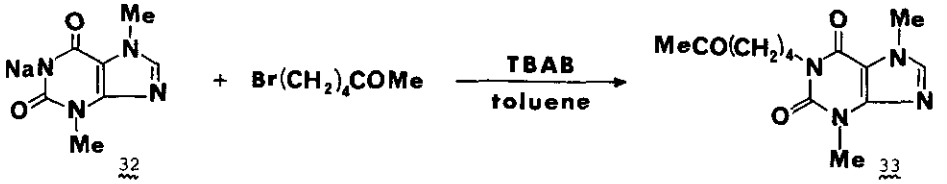
⊡ Last step in the synthesis of 1-(5-oxohexyl)theobromine, a vasodilatator.

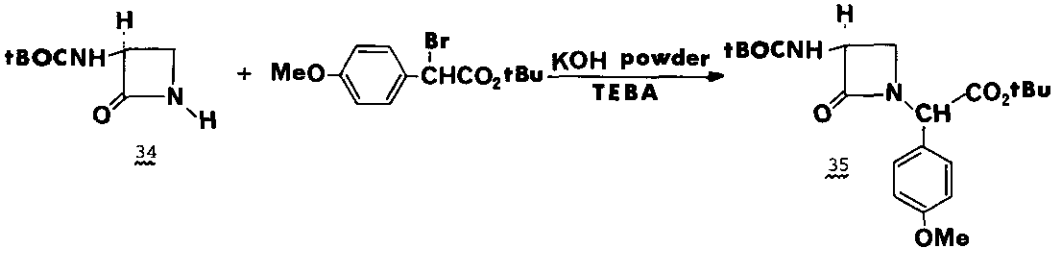
Reaction of sodium theobromine (32) with $Br(CH_2)_4COCH_3$ in toluene and TBAB as catalyst affords the theobromine derivative 33[91].



32 33

⊡ Key intermediate in the synthesis of *nocardicin A*, a β-lactam antiobiotic.

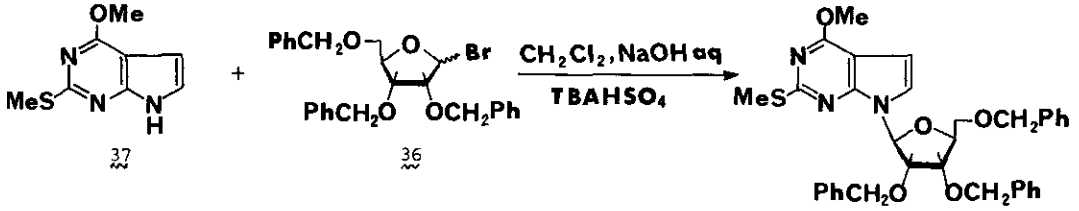
Alkylation of the β-lactam 34 with tert-butyl-α-bromo-(p-methoxyphenyl)acetate with powdered KOH and TEBA gives *nocardicin A* (35). The optimum amount of catalyst is 2-10%, but K_2CO_3 or Et_3N are not efficient[92].



34 35

⊡ Potential interferon-inductor intermediate from glycosidation of a pyrimidine derivative[93].

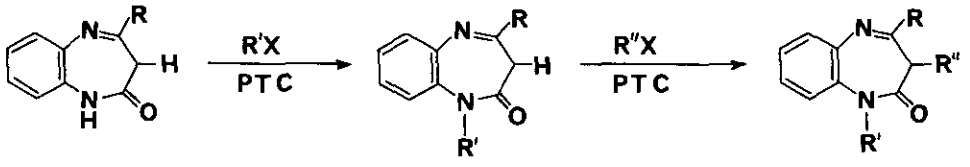
A regioselective N-7-glycosylation has been made when reacting a tri-O-benzyl-bromo-ribose (36) with a pyrimidine derivative 37 under PT conditions[94].



37 36

⊡ Alkylation of benzodiazepine derivatives 38, potential anxiolytics.

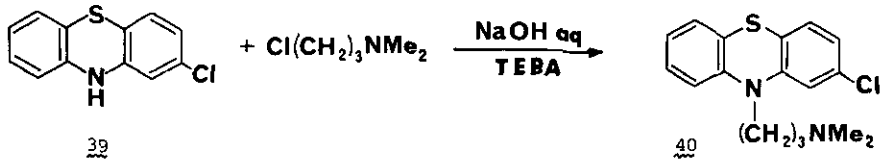
The alkylation reaction is carried out in two steps; the first occurs at nitrogen and the second at carbon. Both substitutions are made under Phase Transfer conditions[95].



38

⊡ Last step in the synthesis of *chlorpromazine*[96], an antipsychotic.

Chlorophenothiazine 39 can be alkylated with $Cl(CH_2)_3NMe_2$, using sodium amide to give *chlorpromazine* (40)[96]. The same reaction has been carried out using aqueous NaOH and TEBA, affording *chlorpromazine* in good yields[97].

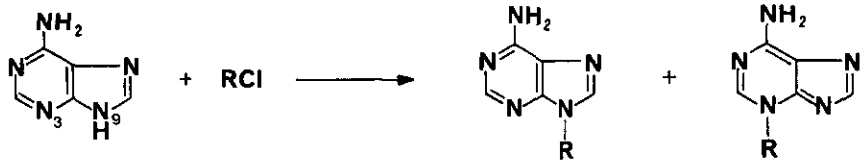


39 40

⊡ Selective alkylation of adenine derivatives.

In most pharmaceutical applications, the compound substituted in position 9 is the most active isomer (41). However, alkylation under neutral conditions affords the 3-isomer (42). When the reaction is carried out under basic conditions (Na, EtOH) the 3-isomer is formed but the 9-isomer is the major component.

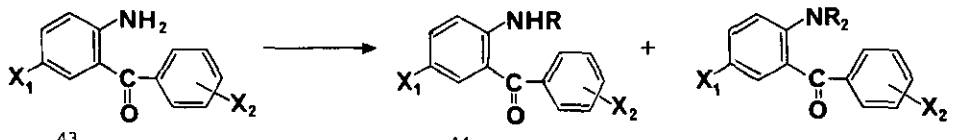
When the sodium or potassium salt of adenine is alkylated in a polar aprotic solvent: DMSO, DMF or HMPA, the 9-isomer is formed with 80-90% selectivity[98]. Using a method of alkylation of nucleosides and nucleotides, adenine has been methylated chiefly in position 9 by CH_3Br with TBAF (tetrabutylammonium fluoride in equimolar amount) in THF[99]. More recently a biphasic liq.-liq. method of alkylation of adenine has been described[98]; using aqueous NaOH and 5% of an ammonium salt (TEBA or Adogen), the 9-isomer was obtained as the major component. These studies indicate that beside providing simple and efficient synthetic procedures, PTC can modify completely the selectivity of alkylation reactions.



41 42

⊡ Synthesis of 2-alkylaminobenzophenones 44, synthetic intermediates in the manufacture of anxiolytics.

This is another interesting example of selective PT synthesis. The conventional methods of alkylation of 2-aminobenzophenones 43 are selective (mono versus dialkylation) only if a three-step process is used with formation of an intermediate sulfonamide[100] or secondary amide[100]. Otherwise direct alkylation with alkyl sulfate in acetic acid[101] or with polyphosphate esters[102] affords a mixture of mono- and di-alkylated derivatives. A PTC method[103] using powdered hydroxide and TBAB in THF, overcomes this difficulty and gives in one step a high yield of mono-alkylated derivative 44 (purity > 99%).



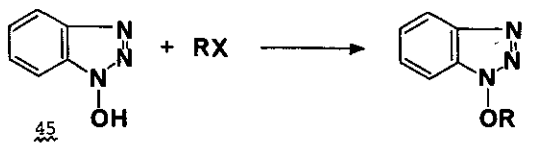
43 44

1c. O-alkylation by NSCsp[3]

O-alkylation of alcohols[26,104] and phenols[105,106] has been carried out by PTC. The results have been and will be extended to hydroxyl functionnality on saturated, aromatic and heteroaromatic molecules.

⊡ Alkylation of hydroxybenzotriazoles, important in peptide synthesis.

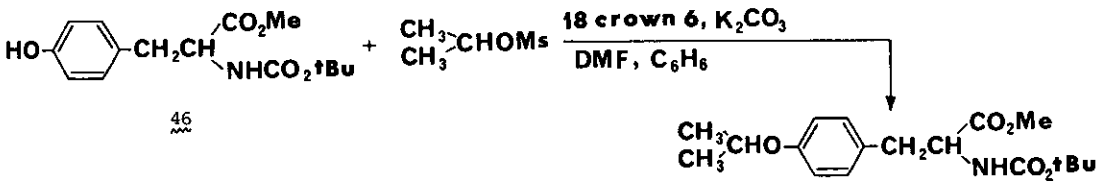
1-Hydroxybenzotriazoles (45) are alkylated in good yields, at the oxygen atom, under PT conditions using TBACl as catalyst[107].



45

⊡ Intermediate step in the synthesis of tyrosine derivatives, antidiuretic antagonists.

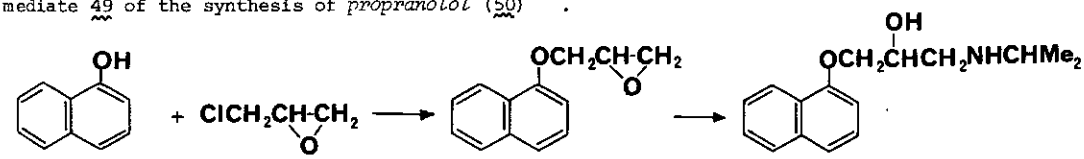
A synthesis of phenol ethers[108] has been adapted to the O-alkylation of protected (BOC) tyrosine methyl ester (46)[109] with isopropyl mesylate using PT the yield is 61%, whereas with other conventional methods it is very poor (4%).



46

⊡ Intermediate step in the synthesis of *propranolol* (β-adrenergic antagonist).

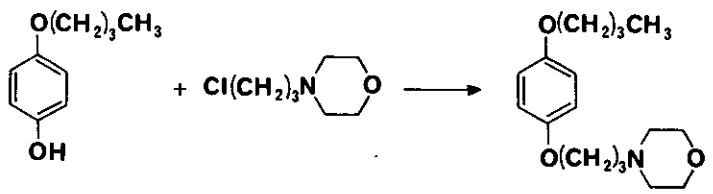
The O-alkylation of β-naphthol (47) by epichlorhydrin (48) under PT conditions affords an intermediate 49 of the synthesis of *propranolol* (50)[110].



47 48 49 50

⊡ Last step in the synthesis of *pramoxine*, a local anesthetic[111].

The previous PT etherifications may be extended to the alkylation of the ether 51 with N-(3-chloropropyl)morpholine to afford *pramoxine* (52).

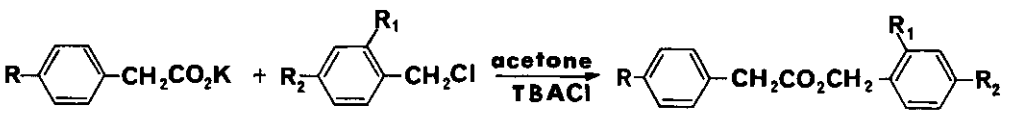


51 52

On the other hand the direct synthesis of esters from alkali metal carboxylate and halides, under PT conditions[112] has been extended to the following reaction :

⊡ Intermediate step in the preparation of cephalosporins[113].

When the alkali metal salts of benzyl carboxylate derivatives 53 are reacted with substituted benzyl halides 54, in an organic solvent containing a phase transfer catalyst, e.g. $Bu_4N^+Cl^-$, benzyl esters 55 are obtained which are useful as acylating agents for the preparation of antibiotics.

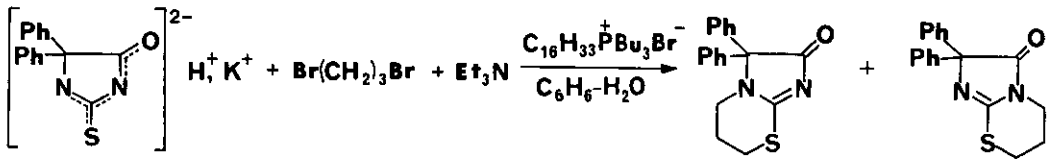


53 54 55

1d. N,S-alkylations

⊡ Synthesis of hydantoin derivatives, having anticonvulsant activities.

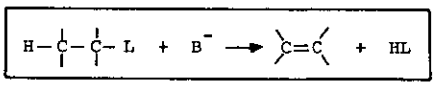
The potassium salt of 5,5-diphenyl-2-thiohydantoin (56) has been alkylated with almost quantitative yields, under PT conditions giving a ratio 64/36 of isomers 58/57[114].



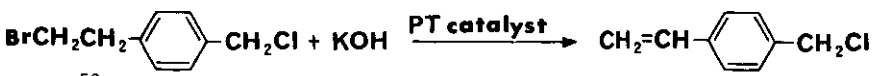
56 57 58

Under conventional conditions using DME, the yield is moderate and the ratio 58/57 is reversed.

2. β-Eliminations



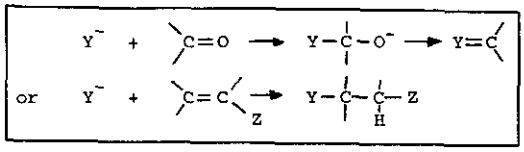
β-Eliminations under phase transfer conditions, have been described using "hard" bases such as KOH, tBuOK or KF, with quaternary ammonium or phosphonium and crown ether catalysts[115]. Very little has appeared in Medicinal Chemistry but an interesting example is an intermediate step in the synthesis of polymeric support for biologically active polymers[116]: the preparation of p-chloromethylated styrene (60), by reaction of p-(2-bromoethyl)benzyl chloride (59) with potassium hydroxide is greatly improved using PT catalysts e.g. TBAB or 18 crown 6[117].



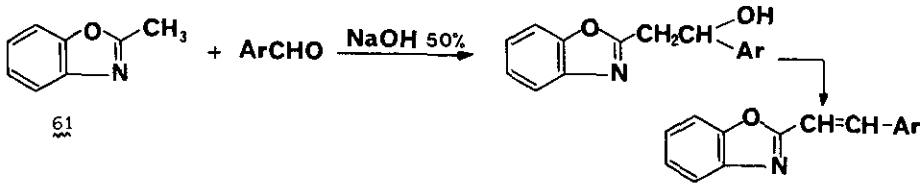
59 60

3. Nucleophilic Additions at Unsaturated Carbon (NACsp^2)

They correspond mostly to addition of nucleophiles to carbonyl compounds or polarized double bonds, followed in some cases by elimination :



The nucleophiles added under PT conditions are of several types: carbanionic species reacting with aldehydes[118,119,120], e.g. 61[118],



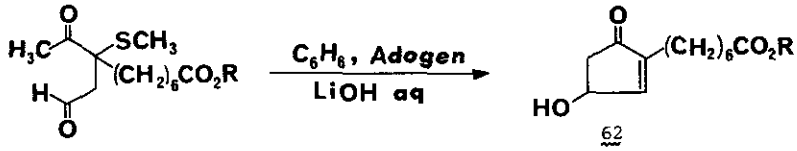
61

carbanions as starting materials in Darzens reaction[121,122]; nitrogen nucleophiles in Michael type additions[123].

The following examples of inter or intra nucleophilic additions have been described in the field of drug synthesis.

▣ Intermediate step in the synthesis of a prostaglandin precursor 62.

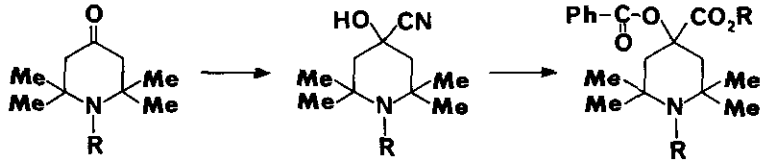
This reaction under PT conditions corresponds to an internal aldol condensation followed by elimination of SCH_3, a better leaving group than OH[124].



62

▣ Intermediate step in the synthesis of α-*eucaine*, a local anesthetic.

The cyanohydrin 63 is a key intermediate in the synthesis of α-*eucaine* (64).

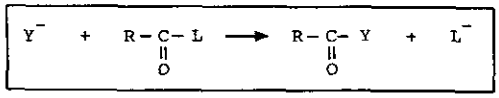


63 64

Cyanohydrins and esters of cyanohydrins have been obtained respectively, using TEBA as catalyst, with a ketosugar derivative and KCN[125]; or with an aldehyde, KCN and a saturated halide[126]. The same reaction conditions could be extended to the synthesis of 63 or 64[127].

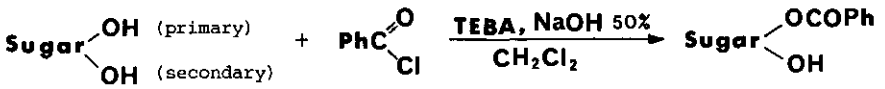
4. Nucleophilic Substitutions at Unsaturated Carbon (NS at Csp^2)

They correspond chiefly to the following reaction scheme :



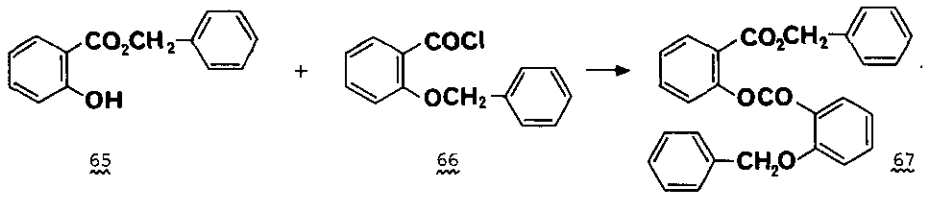
4a. Synthesis of esters by acylation of alcohols.

These reactions have been reported under PT conditions, in the acylation of carbohydrates[128]; the method is selective and a primary OH group of a sugar reacts preferably to a secondary OH[129].



□ First step in the synthesis of *salsalate*, a latentiated form of salicyclic acid.

By analogy, the PT technique may be used in the condensation of benzyl salicylate (65) with the acid chloride of salicylate benzyl ether (66) to produce a protected dimer 67, the direct precursor of *salsalate*[130].

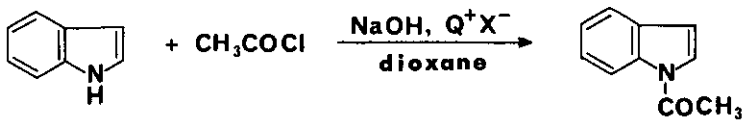


65 66 67

However, if the ester group of 65 were hydrolysed under aqueous liq.-liq. conditions, a solid-liq. technique, using powdered KOH[131], may overcome this inconvenience.

4b. Synthesis of amides by acylation of amines.

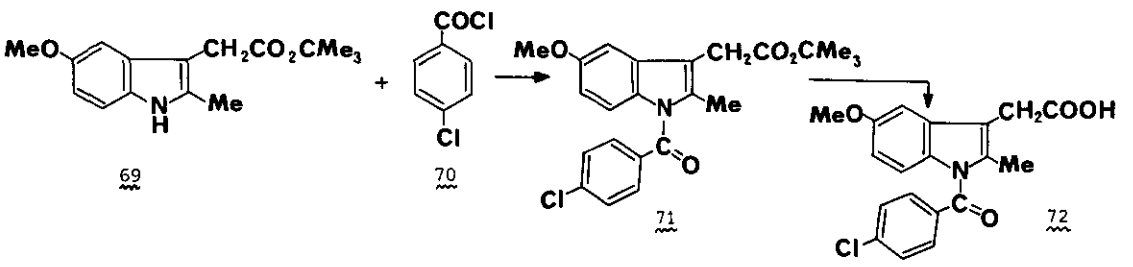
Several indole derivatives have biological activities which are much dependent on the nature of substituents. In most cases the active molecules are substituted at the nitrogen atom by alkyl or acyl substituents. Therefore the PT acylation of indole (68), using powdered NaOH and quaternary ammonium salts, is of interest[131].



68

□ Intermediate step in the synthesis of *indomethacin*, an antiinflammatory agent.

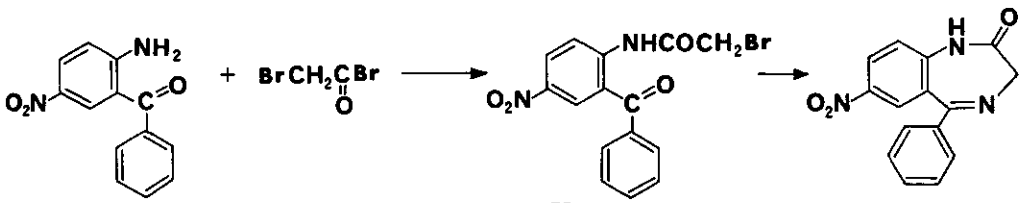
The tert-butyl ester of 2-methyl-5-methoxyindoleacetic acid (69) could be acylated under similar conditions with p-chlorobenzoyl chloride (70) to afford an intermediate 71 of *indomethacin* (72).



69 70 71 72

⊡ Intermediate step in the synthesis of *nitrazepam*, a sleep-inducing agent.

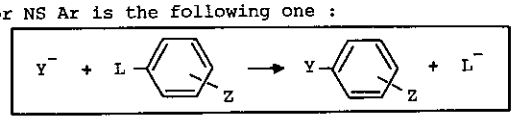
The reaction of 2-amino-5-nitrobenzophenone (73) with bromoacetyl bromide (74) affords the amide 75[132]. Selective monoalkylation of the primary amine in 73 could possibly be made with PT catalysis (cf. reference[103]).



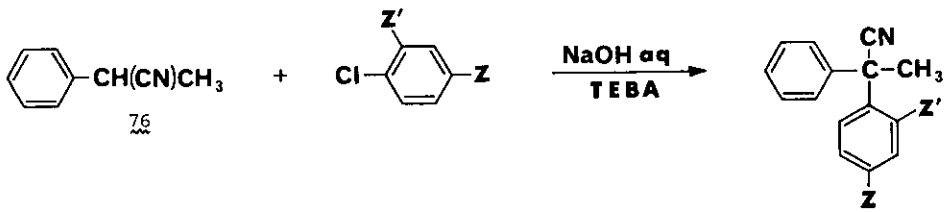
73 74 75

5. Nucleophilic Substitution at Aromatic Molecules (NS Ar)

The reaction scheme for NS Ar is the following one :



The first reaction in these series where PTC has been used was described by Makosza et al.[133, 134,135]; mostly phenylacetonitrile derivatives 76 have displaced leaving groups such as Cl and NO_2 on activated aromatics.

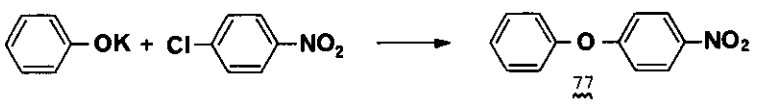


76

Besides phenylacetonitrile derivatives, other nucleophilic reagents have been used: phenols[136, 137], alcohols[138], sulfite[139] and fluoride[140].

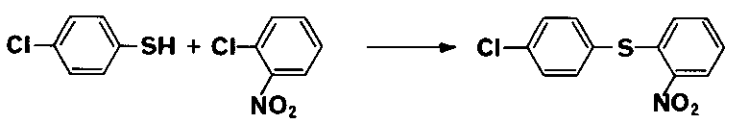
⊡ Synthesis of diphenyl ether derivatives.

The conditions of reference[136] are directly applicable to the preparation of a 4-nitrophenyl-phenyl ether (77)[141]



77

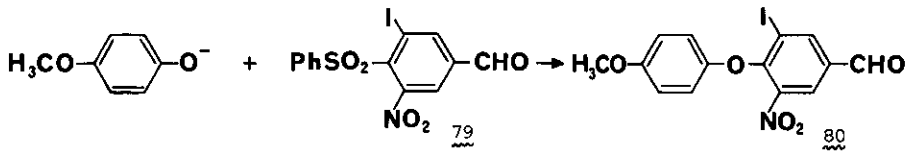
as well as to the synthesis of 2-nitrophenyl-4 —chlorophenyl thioether (78)



78

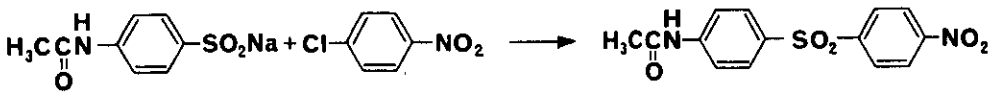
⊡ Intermediate step in the synthesis of thyroxine, a thyroid hormone[142].

The benzenesulfonate 79 is also suited for nucleophilic aromatic substitutions under PT conditions, since the SO_2Ph leaving group is activated by the ortho nitro as well as the para carbonyl group. Treatment of 79 with the anion of the monophenyl ether of hydroquinone gives the substituted diphenyl ether 80, precursor of thyroxine.



⊡ First step of the synthesis of *dapsone*, an antileprosy drug[143].

The synthesis of *dapsone*, starting with aromatic nucleophilic substitution of the sodium salt of the sulfinic acid 81 on p-chloronitrobenzene affords the sulfone 82. This reaction may be carried out using PTC, provided appropriate conditions are found.



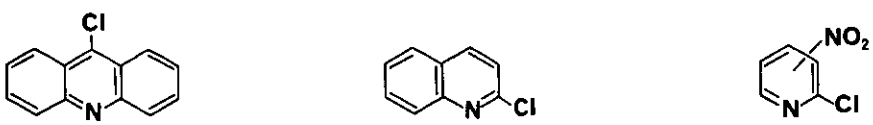
81 82

One should remember that all the studies on Phase Transfer Catalysis applied to aromatic substitutions show a chemical limit : the leaving groups on benzene derivatives need to be activated by at least one electron-withdrawing substituent on the ring.

6. Nucleophilic Substitutions at Heteroaromatic Molecules (NS Het)

An earlier example of halide exchange with KF on pentachloropyridine was reported using a 2,2,2-cryptate catalyst[144].

Analogous reactions have been carried out with derivatives of phenylacetonitrile and 9-chloroacridine (83)[145], 2-chloroquinoline (84)[146] and 2-chloro-3-(or 5)nitropyridine (85)[147,148].



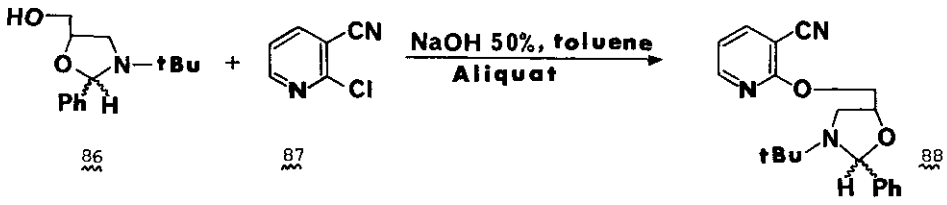
83 84 85

Besides carbanions, other nucleophiles have been used : alcohols[149], phenols[150], phthalamide[151] and cyanide[152].

⊡ Intermediate step in the synthesis of antihypertensive agents.

The introduction of a β-adrenergic blocking moiety 86 on 2-chloro-3-cyanopyridine (87) has been carried out under PT conditions, which proved superior to the conventional procedure using NaH/DMF,

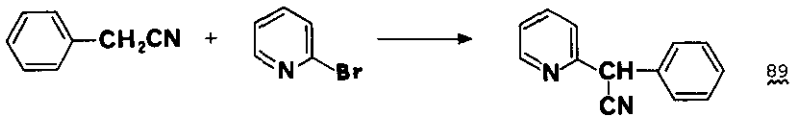
to afford an intermediate 88 in the preparation of antihypertensive agents[149].



86 87 88

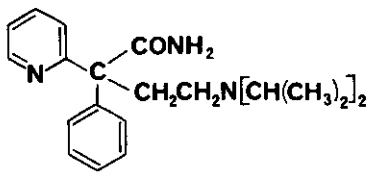
□ Intermediate step in the synthesis of phenyl-(2-pyridyl)-acetonitrile derivatives.

The addition of phenylacetonitrile to 2-bromopyridine using hard bases, such as $NaNH_2$[153], affords a molecule 89 which is the intermediate in the preparation of several active agents,

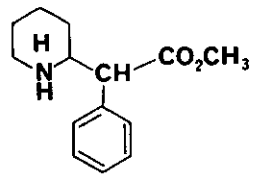


89

e.g. *disopyramide* (90, an antiarrhytmic)[154] and *methylphenidate* (91, an analeptic)[155].



90

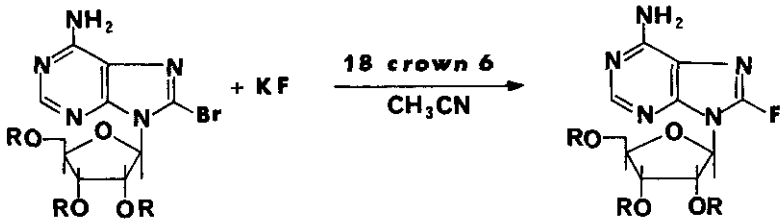


91

The preparation of the intermediate 89 could be carried out under PT conditions, unfortunately the method fails when using liq.-liq. conditions[150].

□ Synthesis of pyrimidine derivatives with antitumor properties.

The halogen exchange using KF and a bromo derivative of pyrimidine 92 has been carried out with 18 crown 6 in acetonitrile and affords the derivative 93[156], 2',3',5'-tris-O-acetyl-8-fluoro-adenosine.



92 93

7. Oxidations

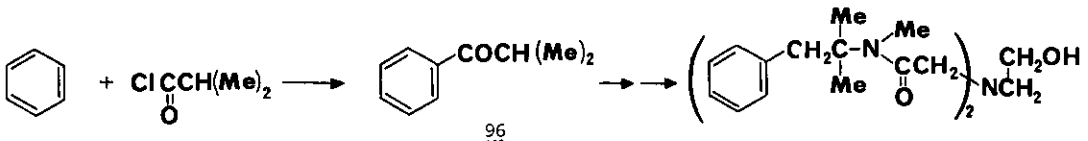
Phase Transfer Catalysis is a convenient and efficient technique for oxidation of organic compounds under mild conditions. The following is a sample of references corresponding to oxidizing systems working under PT conditions : permanganate with quaternary ammonium salt (TCMA or TBAB)[157] or dicyclohexyl 18 crown 6[158]; chromate, mainly with the $HCrO_4^-$ form of a resin-bound quaternary cation [159]; hypochlorite[160]; osmium tetroxide and ruthenium tetroxide as cocatalysts with other oxidizing systems[161]; superoxide[162], and peroxides[163]. The molecules oxidized include terminal olefins (into carboxylic acids), internal olefins (into diols), primary alcohols (into carboxylic acids), secondary alcohols (into ketones), benzyl alcohols (into benzaldehydes),...

An interesting application of PTC to the oxidation of organic molecules is the conversion of substituted phenylacetonitriles 94 to phenylketones 95[164,165].

$$\underset{94}{PhCH(R)CN} \xrightarrow[C_6H_6,\ TEBA]{NaOH\ 50\%,\ O_2\ or\ air} \underset{95}{Ph\text{-}\overset{\overset{O}{\|}}{C}\text{-}R}$$

□ First step in the synthesis of *oxoethazine*, a local anesthetic.

The synthesis reported[166] starts with the Friedel-Crafts acylation of benzene with isobutyryl chloride to give the ketone 96.



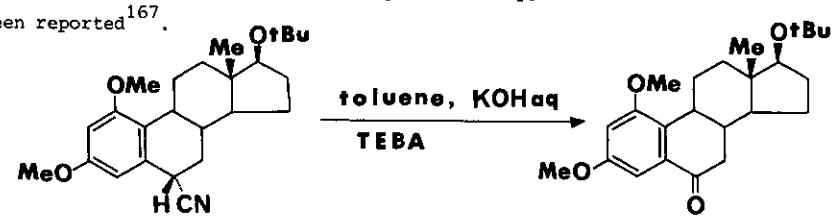
96

An alternative method could involve alkylation of phenylacetonitrile (94, R = H to R = iPr) followed by oxidation; both steps can be run under PT conditions.

$$PhCH_2CN \longrightarrow PhCH(CN)CH(Me)_2 \longrightarrow \underset{96}{PhCOCH(Me)_2}$$

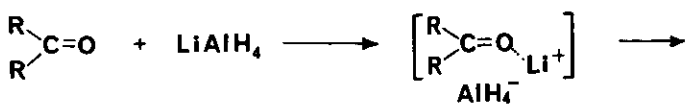
□ Intermediate step in the synthesis of a highly potent estrogen.

During a recent synthesis of an estrogen, a PT oxygenation of the intermediate cyanoestratriene has been reported[167].



8. Reductions

The use of Phase Transfer Catalysis in reductions with common complex hydrides such as $LiAlH_4$ or $NaBH_4$ seems very promising. However, the study of the mechanism of reduction using $LiAlH_4$ shows the importance of the electrophilic catalysis of the cation Li^+ [168,169].

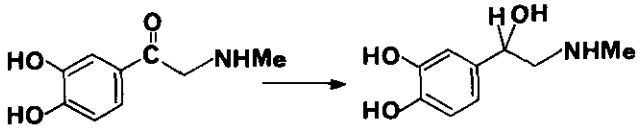


Therefore the introduction of a cryptate in the course of the reduction of cyclohexanone by $LiAlH_4$ completely suppresses the reaction.

On the other hand, the presence of Aliquat increases the rate of reduction of ketones when using $NaBH_4$ in aqueous NaOH[24]. Tetraalkylammonium borohydrides are also reported as reducing agents in apolar solvents[170,171]. The best results in the reduction of ketones to alcohols, using tetraalkylammonium ions to transfer BH_4^- from aqueous to organic phase, have been obtained with salts containing a hydroxylic group on the carbon β to the nitrogen atom[66,172,173].

⊡ Last step in the synthesis of *epinephrine*.

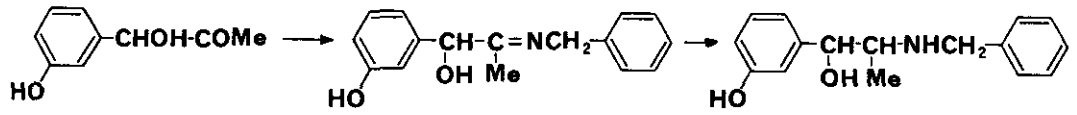
The reduction with borohydride using PT conditions may be extended to the ketone 97 in order to obtain the amino alcohol 98 which is resolved as the tartrate salt to afford the (-)isomer of *epinephrine*.



97 98

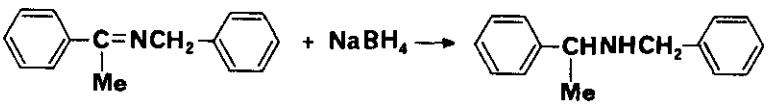
⊡ Last step in the synthesis of *metaraminol*, used to raise blood pressure.

Formation of the Schiff base of compound 99 gives an intermediate 100 which is reduced to the corresponding amine 101; the drug is the (-)isomer[175].



99 100 101

The reduction step 100→101 is very similar to the following reaction carried out under PT conditions with $NaBH_4$[176].



9. Carbenes

The preparation of dichlorocarbene under biphasic conditions was published by Makosza in 1969[177]. Using a reservoir of 50% aqueous NaOH and chloroform he was able to obtain a high yield of dichlorocyclopropanation of an olefin.

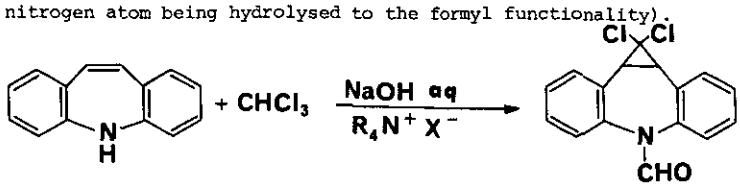
This method is clearly superior to previous procedures which involved sodium ethoxide or potassium tert-butoxide in anhydrous solvents[178].

Besides the liq.-liq. two phase method described by Makosza and Starks[179], a solid-liquid method may be prefered to prevent the hydrolysis of the carbene, when compounds of low reactivity are used[180].

Dichlorocarbenes prepared under PT conditions have been involved in the following reactions:

⊡ Preparation of an azepine derivative, intermediate in the synthesis of psychotropic drugs.

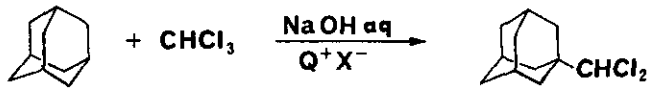
The synthesis of the intermediate 103 has been achieved[181] by addition to the double bond of 102 and insertion in the NH bond of two molecules of dichlorocarbene prepared under PT conditions (the $CHCl_2$ on the nitrogen atom being hydrolysed to the formyl functionality).



102 103

⊡ Preparation of adamantane derivatives.

Adamantane derivatives are found in several families of substances recognized as drugs[182]. The adamantane moiety has been used to increase the lipophilic character of these compounds. Therefore, the easy introduction of a functionality in the adamantane molecule may help to build up a more complex structure. This is the case with the reaction of adamantane with chloroform under PT conditions which gives an insertion of dichlorocarbene into a tertiary CH bond[183].

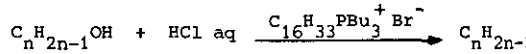


10. Biphasic Catalysis under Acidic Conditions

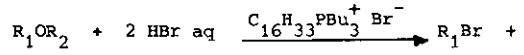
All the syntheses reported up to this point involve the transfer of nucleophilic reagents under basic or neutral conditions. A few references correspond to reactions run under acidic conditions. More fundamentally it would be of interest to extent biphasic catalysis to the transfer of protons or positively charged electrophiles from an aqueous solution to an apolar solvent. For this purpose two main types of systems have been described in the literature.

a- Systems using a standard quaternary ammonium or phosphonium catalyst which transports a proton from an aqueous acidic solution to an organic phase and catalyses the following reactions:

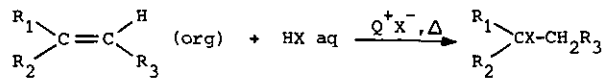
▲ Conversion of primary alcohols to alkyl bromides[184].



▲ Cleavage of ethers[185].



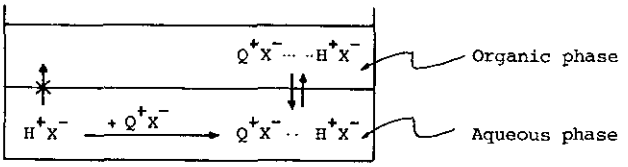
▲ Addition of hydracids to alkenes[186].



▲ Acid hydrolysis of carboxylic esters[187].

$$RCO_2R' + HBr\ aq \xrightarrow[110^{\circ}C]{Q^+X^-} RCO_2H$$

The origin of the catalytic effect is probably due to an extraction of HX, associated to a quaternary salt, from water to the organic solvent[188].



b- Systems using a phase transfer catalyst with a lipophilic anion (not cation). The process being a "negative picture" of the classical PT catalysis with exchange of anions and transfer of the proton or of the electrophile. Under that heading have been described:

▲ Hydrolysis of esters using tetraphenyl borate, $Na^{+-}BPh_4$[189].

▲ Azo coupling with transfer of a diazonium ion associated to a dodecylbenzenesulfonate obtained from : $Na^{+-}O_3SC_6H_4C_{12}H_{23}$[191].

▲ Azo coupling or Friedel-Crafts alkylations with stable tetrakis[3,5-di(Fmethyl)phenyl borate] (TFPB)[192,193].

Very little has been specifically applied to the synthesis of pharmaceutical intermediates but the potentiality of the method is real.

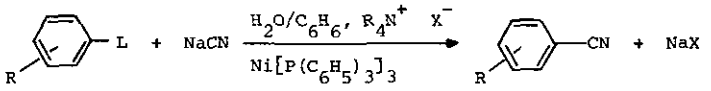
11. Reactions with Organometallic Catalysts

A new very promising area, where PTC will undoubtedly find important applications, is transition metal chemistry. Two recent reviews have been published on the subject[194,195] and the following are typical reactions related to that topic.

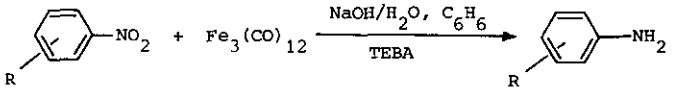
▲ Carbonylation of organic halides[196,197].

$$RX + CO + NaOH \xrightarrow[NaOH/H_2O,\ Q^+X^-]{\text{transition metal catalyst}} RCO_2Na$$

▲ Substitution of aromatic halides[194].



▲ Reduction of nitro compounds[198].



Almost certainly several reactions combining transition metal and Phase Transfer Catalysis will find new applications in drug synthesis.

III. CONCLUSION

In conclusion, the possibilities of Phase Transfer Catalysis in the synthesis of drugs are enormous. Owing to its high chemical versatility and economical advantages the technique will find applications in both academic and industrial laboratories. Presently the interest in the method is extremely high and in the coming years a vast amount of patent and journals literature will be published. We hope that the presentation of this review, which follows a mechanistic guideline will help to rationalize the results already reported, to better design new synthesis, and to open new promises in the use of PTC in drug synthesis.

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