New Synthetic Methods Vol. 1

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About this book

The quest for new compounds has always been and will always remain one of the major objectives of chemistry. Hitherto unknown dimensions are thus brought to light and materials with new or improved properties are discovered. Knowledge and selection of the most suitable method is perhaps the most important step in any attempt to solve a synthetic problem.

It is therefore the aim of the papers collected in this series to describe modern methods of synthetic chemistry in such a way that their advantages, ranges of application, reaction conditions and requirements as well as their limitations become obvious, without however relating every little detail that would be of importance only in specific cases. All papers have previously appeared in "Angewandte Chemie", and it was the unusual interest which they aroused among the readers of this journal that led to their presentation in the form of this book. Divested, as it were, of all the other material which had to accompany them in the pages of the journal, the articles should prove more handy and of even greater value to the synthetic chemist.

Contents

Phase-Transfer Catalyzed Two-Phase Reactions in Preparative Organic Chemistry

By Eckehard V. Dehmlow[*]

Quaternary ammonium and phosphonium salts catalyze reactions between substances located partly in an aqueous and partly in an organic phase. Use of such phase-transfer catalysts simplifies and accelerates numerous reactions traditionally conducted in nonaqueous media. These reactions include carbene reactions, nucleophilic substitutions, alkylations of ketones and nitriles, Wittig and Darzens reactions, formation of ethers and esters. Other reactions such as hydrolysis and oxidation can be accelerated.

1. Introduction

1.1. Principles and Terminology

Reactions between substances located partly in an organic phase and partly in an aqueous phase are frequently slow and ineffective. Attempts are therefore generally made to obtain all the components, for example in nucleophilic substitutions, in a homogeneous medium. If a hydroxylic solvent is selected many reactions still proceed relatively slowly owing to extensive solvation of the anions; solvolytic side reactions may also interfere. While polar aprotic solvents are often more suitable for such reactions, they are usually more expensive and more difficult to recover; traces of water may sometimes also interfere. Moreover, increased formation of undesirable *O*-alkyl products usually occurs in alkylations of mesoionic anions.

The past few years have witnessed the ascendance of a new technique in which reactions are conducted in aqueous-organic

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two-phase systems in the presence of an ammonium or phosphonium salt. Typical examples are:

1) Generation of dichlorocarbene from chloroform, concentrated sodium hydroxide, and a few mol-% of triethyl(benzyl)-ammonium chloride.

2) Alkylation of benzyl cyanide in the presence of aqueous sodium hydroxide and a small amount of the above ammonium salt.

3) Reaction of 1-chlorooctane with aqueous sodium cyanide. This can be accomplished in 1.8 hours in 99% yield if 1.3 mol-% of tributyl(hexadecyl)phosphonium bromide is present. Without the catalyst no 1-cyanooctane is formed, even after two weeks' boiling.

Other variants of such reactions are carried out with molar quantities of the ammonium or phosphonium salt.

The new method has no need of the anhydrous solvents otherwise required and will therefore attract increasing industrial interest. As will be demonstrated in this report, most experience has so far been gained in the fields of carbene generation and alkylation. Nevertheless other reactions (hydrolyses, condensations, oxidations, *etc.*) have also been executed in two-phase systems with catalysts.

No uniform terminology has yet been adopted for the new method. *Brändström*[1] has proposed the term "extractive alkylation" for the specific case of alkylation in the presence of molar amounts of catalyst, and otherwise speaks of applications of ion-pair extraction in preparative organic chemistry. *Makosza* employs expressions such as "catalytic alkylation"[2, 3] and "catalytic development of dihalocarbenes"[4]. The most illustrative term seems to be that of "phase-transfer catalysis"[5, 6] introduced by *C. M. Starks* which will therefore be adopted here.

1.2. Ion-Pair Extraction

This topic leads up to phase-transfer catalysis proper, from both a preparative and a mechanistic viewpoint, and will therefore be considered first.

In analytical and inorganic chemistry, typical ionic compounds are frequently extracted from aqueous solution into organic solvents in the form of ion pairs (for reviews, see refs.[7,8]). The idea that salts might have a significant solubility in organic phases is relatively strange to the preparative organic chemist. However, *Brändström* and *Gustavii*[9] showed that with suitable solvents it is possible to extract the salts of most amines in almost quantitative yield. Tertiary amines are more readily extracted than their secondary or primary counterparts. A high molecular weight and absence of hydrophilic groups favor extraction. The salts of hydrohalic acids, nitric acid, perchloric acid, tetrafluoroboric acid, and also hydrogen sulfates, azides, cyanides, and nitrites can be transferred to the organic phase without difficulty. Of crucial importance are the following factors:

1) Working concentrations should be as high as possible. Since the ion pairs associate in organic media, unfavorable extraction constants (in dilute solution) can thus be overcome.

2) Choice of solvent is important. *Brändström* and *Gustavii*[9] used an amine bearing hydrophilic side groups as model compound, *viz.* 1-(2-allylphenoxy)-3-isopropylamino-2-propanol, and after a single run under defined conditions were able to extract the following quantities: with chloroform 100%, with 1,2-dichloroethane 93%, with methylene chloride 88%, with ether or carbon tetrachloride 0.6%, with ethyl acetate 16%. Chloroform and methylene chloride will therefore be the extractants of choice.

3) The presence of an excess of anion (as acid or inorganic salt) strongly enhances the extractability of the organic salt.

Given a rough knowledge of their extraction behavior the application of these principles even permits the separation of amines having different structures and properties (*e.g.* primary/secondary; strongly lipophilic/strongly hydrophilic) by simple extraction into chloroform (for details and procedures see ref.[10]).

In the same way as alkylammonium salts of inorganic acids, the salts of weak organic acids can also be extracted and obtained in crystalline form. *Brändström*[11,12] uses commercially available tetrabutylammonium hydrogen sulfate as standard starting material. It is converted into the ammonium hydroxide by aqueous caustic soda and immediately extracted into a chloroform or methylene chloride solution of the organic compound. Concentration of the organic phase furnishes the pure ammonium salt which is soluble in most organic solvents and can subsequently undergo reaction in anhydrous solvent. The following types of compounds could be extracted as tetrabutylammonium salts[11, 12]: carboxylic acids, phenols, β-diketones, β-cyanoacetic esters, β-keto esters and sulfones, acylmalonic esters, and benzamide. On the other hand, quantitative ion-pair extraction is unsuccessful with still weaker acids such as alcohols, benzyl cyanide, benzyl ketones, aliphatic carbonyl compounds, and malonic esters. However, these compounds can be alkylated by the phase-transfer technique (see Section 2.3).

The isolated tetrabutylammonium salts possess preparative interest on two counts: firstly, they can be alkylated within seconds or minutes; secondly, choice of a suitable solvent

Table 1. Isopropylation of tetrabutylammonium pentanedionate [13].

Solvent	*C*-/*O*-Alkylation
DMSO	0.72 : 1
Acetone	0.72 : 1
Acetonitrile	0.92 : 1
Chloroform	1.04 : 1
Dioxane	1.91 : 1
Toluene	13.8 : 1

Table 2. Alkylation of tetrabutylammonium pentanedionate in chloroform [14].

Alkylating agent	Rel. yield [%] mono- + bis-*C*-alkyl	*O*-alkyl	Reaction time [min]
CH_3I	98.5	1.5	10
C_2H_5I	88	12	15
$(CH_3)_2CHI$	50.5	49.5	30
n-C_4H_9I	87	13	15

can promote *C*-alkylation as against *O*-alkylation compared to the conventional procedure[13–17] (cf. Tables 1 and 2). The pronounced reactivity of the ion pairs in alkylation is explained by the fact that they are only slightly solvated in chloroform and methylene chloride.

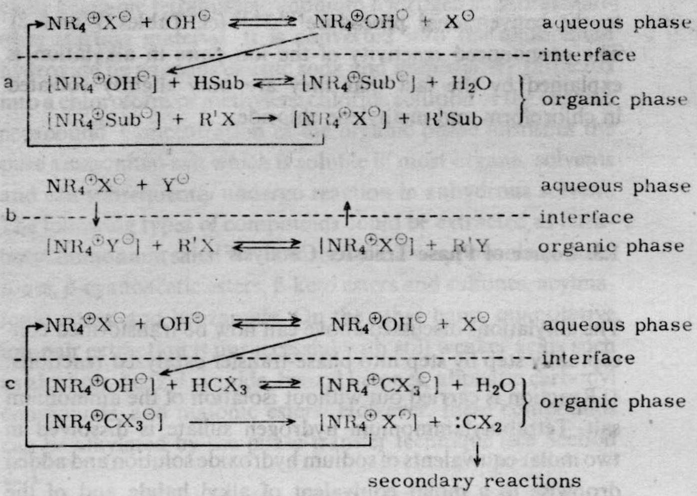
1.3. Course of Phase-Transfer Catalysis

The alkylations discussed above can now be transformed conceptually step by step into phase-transfer catalyzed reactions:

1) Reaction is carried out without isolation of the ammonium salt. Tetrabutylammonium hydrogen sulfate is dissolved in two molar equivalents of sodium hydroxide solution and added dropwise to a molar equivalent of alkyl halide and of the compound to be alkylated. The reaction is often exothermic; the mixture becomes neutral within a few minutes.—This constitutes "extractive alkylation" according to *Brändström*[16].

2) In the next step the procedure is extended to compounds whose low acidity precludes their quantitative extraction as ion pairs (*e.g.* benzyl cyanide, see Section 1.2). The organic phase will then contain both ion pairs and unchanged substrate. Although the local concentration of ion pairs is low, the reactivity of the anion is so high that it is always rapidly removed from the partition equilibrium. Consequently, alkylation takes *ca.* 30 minutes and is sometimes exothermic and sometimes requires heating[1].

3) Reduction of the amount of ammonium ion present to a few mol-% will not cause any fundamental change. A certain concentration of the ion pair will still be present in the organic phase and rapidly be consumed. The ammonium salt migrates back and forth between the phases. It transfers the hydroxide ions as an ammonium hydroxide ion pair from the aqueous phase to the organic medium, where it is converted into an ion pair with the substrate as anion. This is then alkylated. The ammonium salt returns again to the aqueous medium where the hydroxide is regenerated (Scheme 1a).



Scheme 1. Course of phase-transfer catalysis. For details see text. Ion pairs are enclosed in square brackets.

The simpler Scheme 1 b applies to other nucleophilic displacements, such as the reaction between cyanide and chlorooctane mentioned in the introduction.

Generation of dihalocarbenes from aqueous sodium hydroxide, ammonium salt, and haloform can likewise be interpreted as in Scheme 1 c.

All these reactions can, of course, only proceed quantitatively if the aqueous/organic partition equilibrium permits preferential transfer of $X^{\ominus}$ into the aqueous phase. This is not necessarily always the case. For instance, reaction between cyanide and iodooctane comes to a halt after 5—30% conversion. Replacement of the aqueous phase by fresh cyanide starts the reaction off again until the concentration of iodide once more reaches the equilibrium value. Before attempting an unknown reaction it may be necessary to first examine the partitioning behavior of the anions involved.

That the course of phase-transfer catalysis described above appears reasonable does not constitute proof of its validity. Several authors have considered other possibilities. The catalysts employed are all more or less typical detergents, and hence it was suspected that reaction occurs at the interface[4, 18, 100a] or in a micellar phase[19-23]. Much interest is in fact currently being focused upon the micellar catalysis of a wide range of organic reactions[24].

More detailed mechanistic studies afforded the following evidence which is all in favor of the concepts described: small ions (*e.g.* tetramethylammonium) are not suitable as catalysts. In contrast, large ions (*e.g.* tetrabutylammonium and tetradodecylammonium which are not surfactants) are very effective, regardless of their molecular shape[6, 25, 100b]. In anhydrous nonpolar solvents the salts used undergo only slight association[6]. The mixing speed has no influence on the reaction kinetics once a limiting value for thorough mixing has been reached[6, 28, 100b]. The rate constant of the alkyl halide/-cyanide reaction is proportional to the amount of catalyst and of first order in alkyl halide[5, 6]. The same applies to the reaction of thiophene oxide with 1-bromooctane in benzene/water in the presence of various catalysts[100b]. On solvolysis of 2-bromooctane with aqueous sodium hydroxide/ammonium salt catalyst, an elimination-substitution ratio was found that is typical of reaction in anhydrous media[25, 26]. Finally, the anion transfer equilibrium aqueous phase/organic phase can be determined. It depends upon the relative concentrations, the amount of water present, and the polarity of the organic medium[6].

Selectivity data for dichlorocarbene generation are available[5] which show that the same kind of free dichlorocarbene species is formed as in other methods[27]. However, the actual phase-transfer process has not yet been subjected to kinetic analysis. Nevertheless, the only question open to conjecture is whether the reaction with solvent chloroform already occurs at the interface[100a] or, at least in part, after penetration into the organic phase. Formerly dihalocarbenes were generally assumed to be exceptionally sensitive to moisture, since chloroform is known to undergo hydrolysis to formate. It was found, however, that the carbene formed by the phase-transfer technique undergoes further reaction so rapidly that it is hardly hydrolyzed. This would contraindicate formation of the major portion of the carbene at the interface.

2. Preparative Applications

2.1. α-Elimination

2.1.1. Dichlorocarbene Additions (Mąkosza Reaction)

The preferred catalyst for generation of dihalocarbenes from haloform with 50% sodium hydroxide is triethyl(benzyl)ammonium chloride[4]. However, trihexyl(methyl)-[5] and cetyltrimethylammonium chloride[19] are also recommended. The inexpensive reagents chloroform and caustic soda are best employed in large excess[28].

Selectivity comparisons of addition of $\dot{C}Cl_2$ to normal olefins were mentioned in Section 1.3. If relatively unreactive substances are presented to the carbene a complicated situation will arise: the highly reactive CCl_2 can react with the substrate, the solvent, itself, or its precursor. Dihalocarbene will therefore display various "net reactivities" towards "poor" substrates. It is found that the CCl_2 generated by phase-transfer reaction is exceptionally reactive towards substrates which hardly react, if at all, with conventionally generated dichlorocarbene (*e.g.* from potassium *tert*-butoxide and chloroform). This is because the carbene is formed close to its site of further reaction and a large excess is easily generated.

Apart from normal alkenes and enol ethers[4,5,19], the Mąkosza reaction can also be used to dichlorocyclopropanate sterically hindered olefins (*e.g.* triphenylethylene) and electron-deficient olefins (*e.g.* methacrylonitrile), as well as acetylenes[*][28,29]. However, addition is no longer observed with tetraphenylethylene and the di-, tri-, and tetrachloroethylenes.—Conventional dihalocarbene reagents usually add only once to conjugated olefins; electron withdrawal by the chlorine atoms deactivates the molecule towards a second attack. Single and multiple additions can easily be accomplished with "phase-transfer dichlorocarbene" depending upon the reaction conditions[28,30,31]. Schemes 2 and 3 show typical examples.

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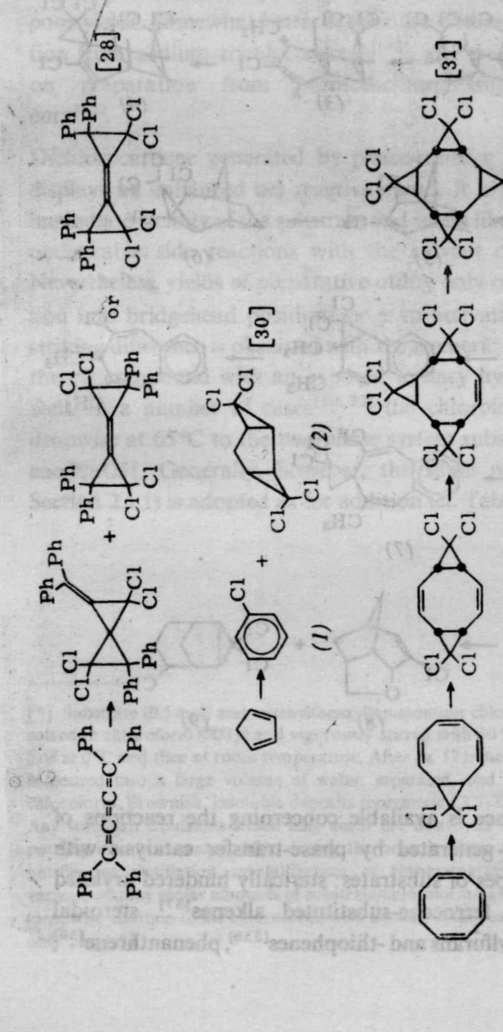
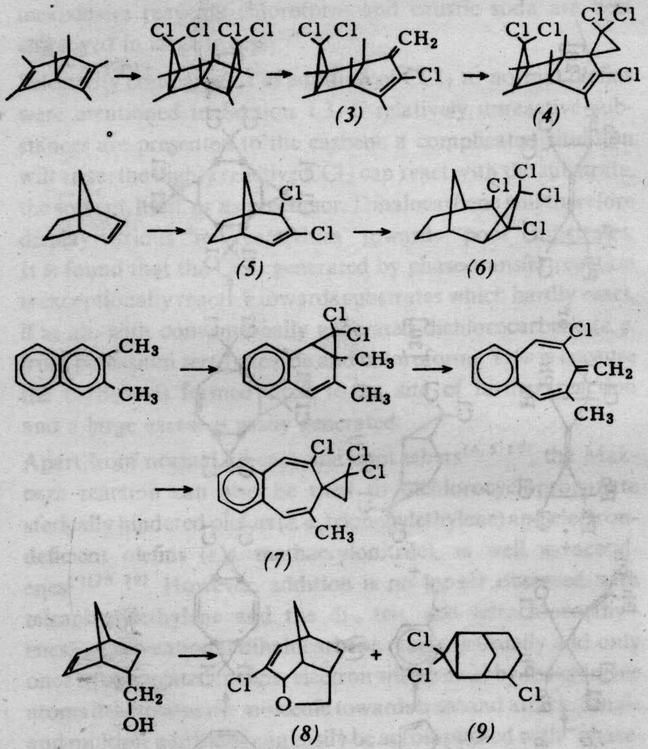
[*] Hydrolysis to secondary products occurs here: cyclopropenones and conjugated acetylenic ketones are formed [28, 57].

The isolation of tricycloheptane *(2)* deserves particular attention. The corresponding monoadduct is transformed into *(1)* extremely readily by base. In other cases multiple adducts are final products of a series of reactions [*(4)*, *(6)*, *(7)*]. The intermediate *(3)* can be obtained with dichlorocarbene from potassium *tert*-butoxide/chloroform[30a]. Depending on the conditions the major product from norbornene can be chosen as *(5)* or *(6)*[32]. *Weyerstahl et al.* observed conversion of



Scheme 2.

alkylaromatic compounds into spirononatrienes by CCl$_2$. Formation of *(7)* is typical; alkylbenzenes usually afford several isomers[33]. In other cases side groups participate in the reaction, *e.g.* with *(8)* and *(9)*[34]. Ring enlargements occur with 1,4,5,8-tetramethoxynaphthalene and tetramethylpurpurogallin to yield substituted benzocyclooctatrienones and 2,3-benzohomotropones[101].



Scheme 3.

Further experience is available concerning the reactions of dichlorocarbene generated by phase-transfer catalysis with the following types of substrates: sterically hindered arylated olefins[28,35,36], ferrocene-substituted alkenes[37], steroidal olefins[38], methylfurans and -thiophenes[33b], phenanthrene[39];

indenes[52], bicyclo[2.2.1]heptenes[32, 40] and -heptadienes[30], enolacetates of bicyclo[3.2.1]octanones[41], Schiff bases[53], and enamines[54] (for general procedure see footnote[*]).

2.1.2. Insertions of Dichlorocarbene

C—H insertion reactions of dichlorocarbene generated conventionally from potassium *tert*-butoxide and chloroform or with sodium methoxide/trichloroacetic ester are rare and give poor yields. Somewhat better results are obtained on generation from sodium trichloroacetate[42], and even better ones on preparation from bromodichloromethyl(phenyl)mercury[43].

Dichlorocarbene generated by phase-transfer catalysis also displays an enhanced net reactivity since it is formed in the immediate vicinity of the substrate and is less likely to undergo undesirable side reactions with the solvent or with itself. Nevertheless, yields of preparative utility only occur on insertion into bridgehead positions or α to activating groups. A striking difference is observed with the isomeric decalins: only the *cis* compound with an exposed tertiary hydrogen reacts well. In a number of cases[20, 22] the chloroform is added dropwise at 65 °C to the two-phase system substrate-in-benzene/NaOH. Generally, however, the same procédure (see Section 2.1.1) is adopted as for addition (cf. Table 3).

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[*] Substrate (0.5 mol) and triethyl(benzyl)ammonium chloride (1 g) are dissolved in chloroform (500 g) and vigorously stirred with 50 % NaOH (500 g), first at 0 °C and then at room temperature. After *ca.* 12 h the reaction mixture is poured into a large volume of water, separated, and reextracted with chloroform. Brownish, insoluble deposits (polymeric CCl_2?) are disregarded. Any stubborn emulsions which may occur are destroyed by repeated slow pouring into fresh water. After drying the organic phase is drawn off and purified by distillation, crystallization, or chromatography [28].—Other variants employ molar amounts of substrate/chloroform/caustic soda at 45 °C (dropwise addition of the chloroform) with stirring of the reaction mixture for only 1 h [4, 5].