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MECHANISMS OF CATALYTIC REACTIONS

Phase-Transfer Catalysis in the Chemistry of Heterocyclic Compounds

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Abstract—Methods for the preparation of heterocyclic systems, the chemical transformations of heterocyclic compounds under conditions of phase-transfer catalysis, and the use of quaternized heterocycles as phase-transfer catalysts are considered.

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INTRODUCTION

Considerable advances in the chemistry of heterocyclic compounds in the last 15–20 years have been closely related to the use of phase-transfer catalysis. Information on this subject matter published to the mid-1990s has been summarized in reviews [1, 2], monographs [3–6], and a handbook of phase-transfer catalysis by Keller [7]. In this article, new data concerning the use of phase-transfer catalysis in the chemistry of heterocyclic compounds are discussed; for the most part, these data have been obtained in the past two decades. The remarkable advantages of this method are exemplified in structurally different heterocyclic substrates.

In a wide variety of heterocyclic compounds from different classes, attention is focused on nitrogen-containing heterocycles. This is due to the fact that these compounds find extensive use as highly effective broad-spectrum drugs [8], high-energy materials [9], analytical reagents [10], the components of ionic liquid [11] or gas-generation compositions [12], etc.

As applied to nitrogen-containing heterocyclic compounds, the method of phase-transfer catalysis was found highly efficient. In a number of cases, important information on reaction mechanisms was obtained by studying phase-transfer catalytic reactions with the participation of nitrogen-containing heterocycles. Phase-transfer catalysts were found among quaternized nitrogen-containing heterocycles; these catalysts are superior to ordinary quaternary ammonium salts in a number of characteristics.

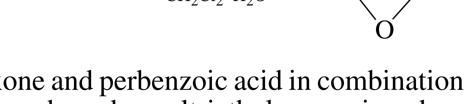
Many examples of the successful application of phase-transfer catalysis to the synthesis of heterocyclic compounds that are difficult or impossible to prepare using other methods are well known. First, this is the synthesis of small heterocycles, which are highly sensitive to the action of acids and bases. The most impressive results were obtained in the development of functionalization methods for such substrates: the alkylation (arylation) of ambident heterocyclic anions, the oxidation (reduction) of polyfunctionally substituted substrates, nucleophilic substitution in a side chain, etc.

Let us consider step by step methods for the preparation of heterocyclic compounds, the chemical transformations of these compounds under conditions of phase-transfer catalysis, and the use of heterocycles as phase-transfer catalysts.

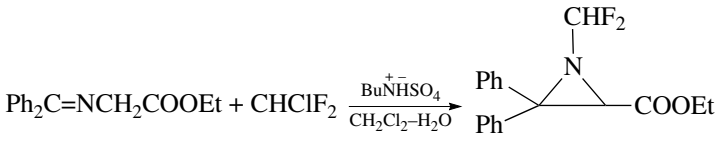
PREPARATION OF HETEROCYCLIC COMPOUNDS UNDER CONDITIONS OF PHASE-TRANSFER CATALYSIS

The most interesting results were obtained with the use of phase-transfer catalysis for the oxidation of structurally different imines by oxidizing agents such as potassium permanganate, Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), ammonium persulfate, sodium perborate, sodium hypochlorite, hydrogen peroxide, *tert*-butyl peroxide, and perbenzoic acid [13].

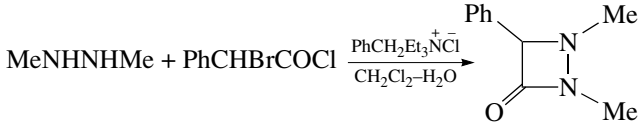
The oxidation is performed in the methylene chloride–water two-phase system. Tetrabutylammonium bromide, decyltriethylammonium bromide, benzyltriethylammonium bromide, and 2,3,5-triphenyltetrazolium chloride are used as phase-transfer catalysts:



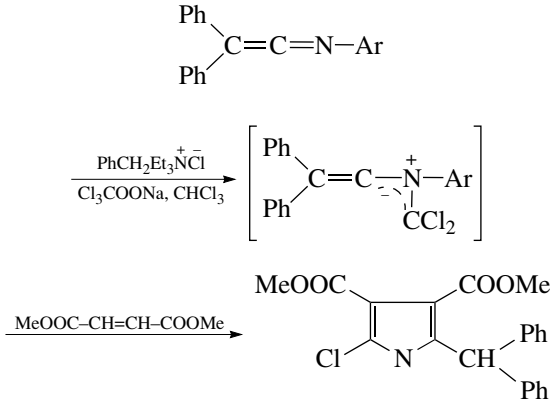
Oxone and perbenzoic acid in combination with catalysts such as benzyltriethylammonium bromide and 2,3,5-triphenyltetrazolium chloride exhibited the highest efficiency. In this case, corresponding oxaziridines were formed in 50–93% yields. Note that corresponding aziridines were formed by the interaction of ketimines with chlorodifluoromethane in the methylene chloride–water two-phase system in the presence of tetrabutylammonium bisulfate [14]:



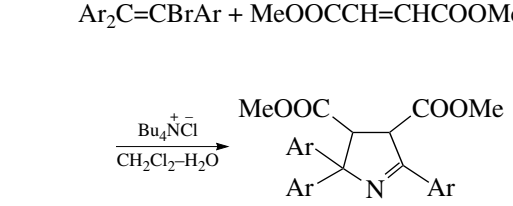
In the series of four-membered heterocycles, phase-transfer catalysis was successfully used for the preparation of diazetidinones [15]:



The use of phase-transfer catalysis in the chemistry of five-membered heterocyclic compounds has been studied much better. A few procedures for the construction of a pyrrole ring, which are used in the preparation of pyrroles under conditions of phase-transfer catalysis, are well known. According to one of these procedures, substituted pyrroles are prepared by the interaction of dimethyl fumarate with keteniminylides, which are formed on the treatment of *N*-(2,2-diphenylvilylidene)anilines with dichlorocarbene generated under conditions of phase-transfer catalysis [16]:

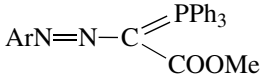


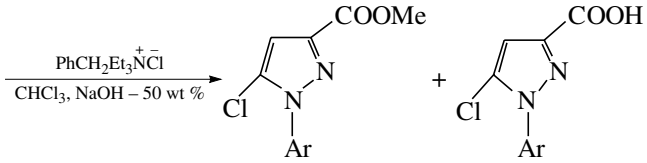
The advantage of phase-transfer catalysis can be clearly exemplified in the synthesis of functionally substituted pyrrolines and pyrrolidones, which cannot be prepared by other procedures [17]:



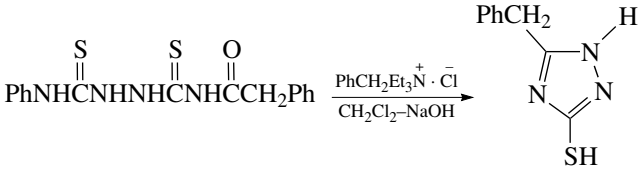
Note that the alkylation of cyanamide with 1,4-dibromobutane in an aqueous solution of sodium hydroxide in the presence of Aliquat 336 is a convenient method for the preparation of *N*-cyanopyrrolidine [18].

Moreover, a few simple and efficient procedures for the synthesis of pyrazoles and pyrazolines under conditions of phase-transfer catalysis were developed. One of them consists in the interaction of arylazomethylenetriphenylphosphoranes with dichlorocarbene generated under conditions of phase-transfer catalysis [19]:

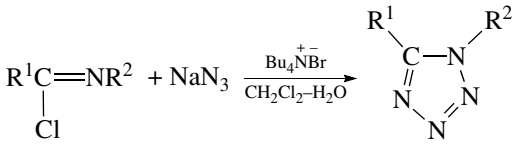




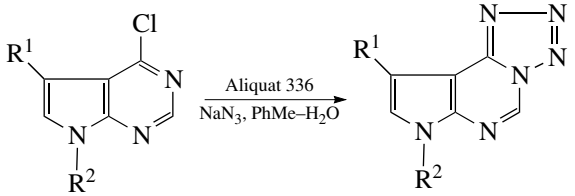
The heterocyclization of corresponding thiohydrazides belongs to preparation methods for other five-membered heterocycles, in particular, triazoles, with the use of phase-transfer catalysis [20]:



Phase-transfer catalysis has received wide acceptance in the production of 1,5-disubstituted tetrazoles. In the interaction of imidoyl chlorides with sodium azide in the methylene chloride–water two-phase system in the presence of tetrabutylammonium bromide or 2,3-diphenyl-5-butyltetrazolyl bromide, 1,5-disubstituted tetrazoles were formed in 85–92% yields. The reaction occurred at room temperature and was complete 2 h after mixing the reagents [21]:



Very good results were also obtained on the treatment of heterocyclic imidoyl chlorides with sodium azide in the toluene–water two-phase system in the presence of Aliquat 336 [22]:

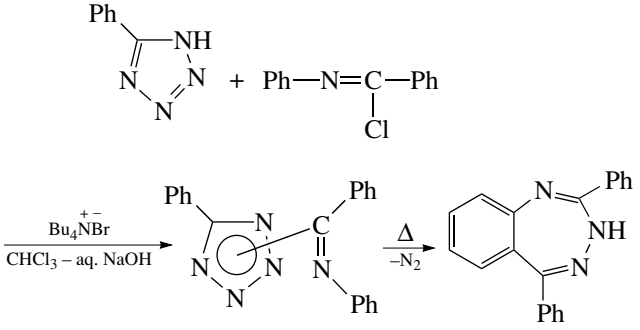


The corresponding tetrazoles were formed in 60–75% yields.

On going from liquid–liquid to solid–liquid systems, tetrazoles were formed in the above high yields; however, the reaction time increased to 12–14 h.

Note that this method for the preparation of 1,5-disubstituted tetrazoles has an undoubted advantage over the ordinary method that consists in the interaction of imidoyl chlorides with hydrazoic acid solutions, which are extremely dangerous in operation.

Finally, the use of phase-transfer catalysis for the preparation of previously inaccessible 1,3,4-triazepines, in which the triazepine ring is annelated to the benzene, naphthalene, or pyridine ring, should be mentioned. On the treatment of 5-aryltetrazoles with *N*-aryl(hetaryl)benzimido chlorides in the chloroform–aqueous sodium hydroxide two-phase system in the presence of tetrabutylammonium bromide, corresponding *N*-imidoyltetrazoles are formed; the thermolysis of these *N*-imidoyltetrazoles results in the formation of 1,3,4-triazepines [23–25]:



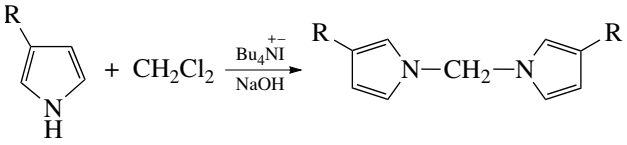
With the use of many examples, this method was demonstrated to be multipurpose and applicable to the design of complex heterocyclic systems containing several triazepine rings [26].

REACTIONS OF HETEROCYCLIC COMPOUNDS UNDER CONDITIONS OF PHASE-TRANSFER CATALYSIS

Studies of the chemical transformations of heterocyclic compounds under conditions of phase-transfer catalysis allowed one to extend considerably the synthetic capabilities of well-known reactions, to develop simple procedures for the preparation of previously inaccessible compounds, and to take a new view of many chemical reactions whose mechanisms were considered well established.

Among many reactions of heterocyclic compounds that occur under conditions of phase-transfer catalysis, alkylation, acylation, sulfonation, and silylation are better understood, whereas reactions with dihalocarbenes, oxidation, and reduction are understood much less well.

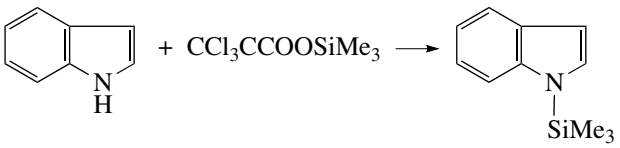
Any heterocyclic compounds that can form sufficiently stable heteroanions under the action of strong bases readily react with alkylating, acylating, sulfonating, and silylating agents. Quaternary ammonium salts and crown ethers are most frequently used as phase-transfer catalysts in these processes. Depending on the properties of reactants, the reactions are performed in liquid–liquid or solid–liquid systems. Pyrrole and indoles are readily alkylated with alkyl halides and alkyl sulfates in the liquid–liquid system [27]. In the alkylation of pyrroles with methylene chloride, corresponding bis derivatives are formed in high yields [28]:



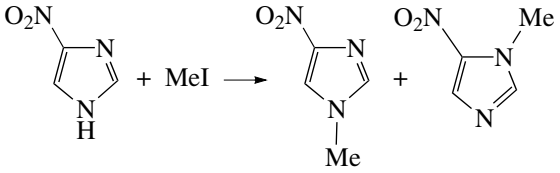
It was noted that the selectivity of alkylation of 2-aminopyrroles with dimethyl sulfate depends on the ratio between the reagents [29]. At a pyrrole/alkylating agent ratio of 1 : 1.1, alkylation occurred only at the nitrogen atom of the heterocyclic ring.

Pyrrole and indole also readily enter acylation, sulfonation, and silylation reactions.

Of studies devoted to these reactions, a work by Golan and Lee [30], who used trimethylsilyl trichloroacetate as an alkylating agent, should be noted. The reaction occurs at 100°C in the presence of potassium carbonate, and 18-crown-6 is a catalyst:

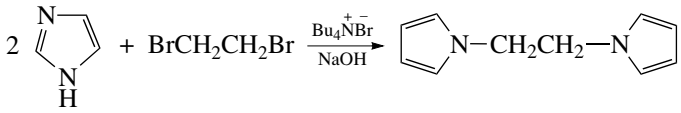


The alkylation of pyrazoles and imidazoles has been studied in considerable detail [31, 32]. It was found that, in the alkylation of 4-nitroimidazole, the ratio between reaction products depends on the nature of the alkylating agent. If this agent is methyl iodide, 1-methyl-4-nitroimidazole is the main reaction product:

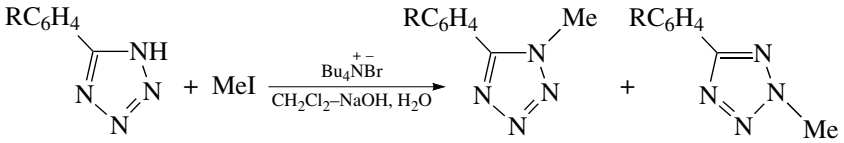


If dimethyl sulfate is used in place of methyl iodide, the fraction of the 3-methyl derivative in the reaction products increases to 32%.

A number of studies were devoted to the alkylation of 1,2,4-triazole and benzotriazole under conditions of phase-transfer catalysis. The alkylation of these compounds with dibromoethane is most interesting from the standpoint of synthesis [32]. Previously inaccessible bis(triazolyl)ethanes can be prepared in good yields by this procedure:



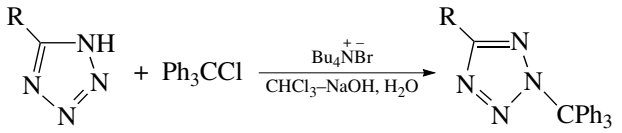
In the past decades, attention has been focused on the use of phase-transfer catalysis in the chemistry of tetrazoles. This is primarily due to the wide use of tetrazoles for the synthesis of highly effective pharmaceuticals, which are common in medical practice. The use of phase-transfer catalysis in the chemistry of tetrazoles can be exemplified in alkylation and oxidation reactions. The alkylation of 5-substituted tetrazoles was studied using a large series of 5-aryl- and 5-alkyl(aryl)sulfatetrazoles as an example. Methyl iodide and dimethyl sulfate were used as alkylating agents, and the reactions were performed in the methylene chloride–aqueous sodium hydroxide two-phase system in the presence of tetrabutylammonium bromide [33]:



It was assumed that the use of phase-transfer catalysis will dramatically affect the process selectivity. However, it was found that the ratios between N_1 and N_2 isomers formed by the alkylation of tetrazoles in an uncatalyzed process and under conditions of phase-transfer catalysis were almost equal. It was found that the reason consisted in the structure peculiarities of tetrazolium salts, in which the tetrabutylammonium cation is arranged above the plane of the tetrazole ring.

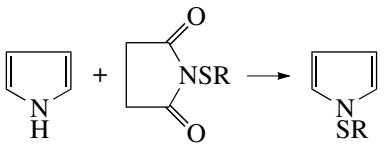
The selectivity of alkylation of 5-substituted tetrazoles changed if methyl chloromethyl ether or triphenylchloromethane was used as an alkylating agent. In the former case, the corresponding N_1- and N_2-substituted tetrazoles were formed in a ratio of 1 : 2 [34].

In the alkylation of 5-alkyl(aryl)tetrazoles with triphenylchloromethane, the reaction occurred regioselectively with the formation of 5-substituted 2-trityltetrazoles [35]:



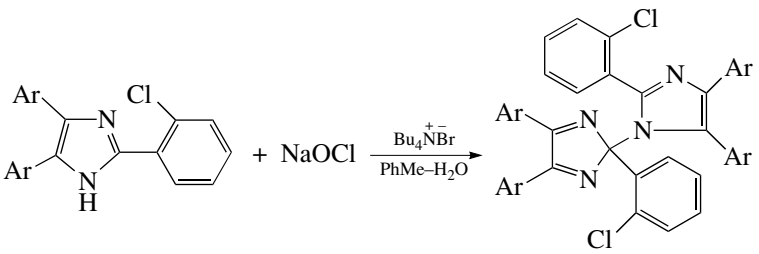
In the alkylation of 1-aryltetrazol-5-ones and 1-aryltetrazol-5-thiones under conditions of phase-transfer catalysis, only corresponding *N*- and *S*-alkyl derivatives were formed [36–38].

Of other reactions of nitrogen-containing heterocycles, the synthesis of corresponding *N*-alkylthio derivatives should be primarily noted. Thus, in the reaction of pyrrole with *N*-(alkylthio)succinimide or *N*-(alkylthio)phthalimide in the methylene chloride–water system in the presence of tetrabutylphosphonium bromide, 1-(alkylthio)pyrroles were formed in 75–95% yields [39]:

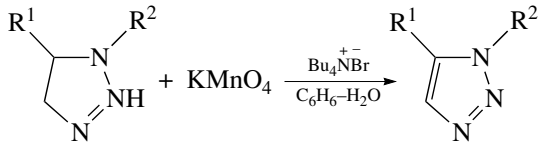


Under the same conditions, corresponding 1-(alkylthio)indoles were prepared from indole. Evidently, the reaction can be extended to other nitrogen-containing heterocycles.

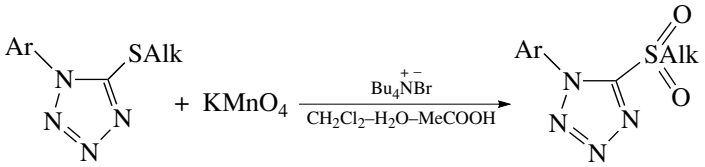
Oxidation occupies a prominent place among the reactions of heterocyclic compounds under conditions of phase-transfer catalysis. Previously [2], an unusual case of oxidative dimerization was found on the treatment of 2,4,5-trisubstituted imidazoles with sodium hypochlorite:



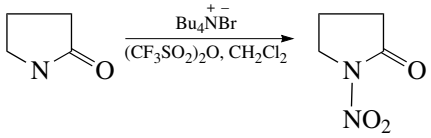
Under conditions of phase-transfer catalysis, 1,2,3-triazolines are readily oxidized by potassium permanganate to corresponding 1,2,3-triazoles [40]:



With the use of many examples, it was demonstrated that, in the oxidation of 5-alkylsulfanyl-1-aryltetrazoles with potassium permanganate in the methylene chloride–aqueous acetic acid two-phase system in the presence of tetrabutylammonium bromide, corresponding 5-sulfonyltetrazoles were formed in high yields [37, 41, 42]:



Finally, the direct nitration of heterocycles under conditions of phase-transfer catalysis should be noted [43]:



It is hoped that this method for the introduction of the nitro group will be highly effective in the nitration of acid-sensitive heterocyclic substrates.

QUATERNIZED HETEROCYCLES AS PHASE-TRANSFER CATALYSTS

Interest in the use of nitrogen-containing heterocycles quaternized at the nitrogen atom as phase-transfer catalysts is due to the fact that quaternary ammonium, arsonium, and phosphonium salts, which are commonly used for this purpose, are highly toxic and insufficiently stable at elevated temperatures; they cannot always be regenerated and are inaccessible in a number of cases. However, only tetrazolium [44] and pyridinium [45] salts have been systematically studied from this standpoint. It was found that 2,3,5-trisubstituted tetrazolium salts are highly competitive with a commonly used phase-transfer catalyst such as tetrabutylammonium bromide in terms of catalytic activity, whereas they are much superior to it in terms of thermal stability.

Finally, note that the use of tetrazolium salts is most effective in reactions that occur in an organic solvent–water two-phase system with a neutral or acidic aqueous phase, as well as in the cases that the catalyst exhibits its high thermal stability. To perform a great number of phase-transfer catalytic reactions, *N*-alkyl-4-(*N*',*N*'-dialkylamino)pyridinium salts were used [46]; these salts are much superior to tetrabutylammonium bromide in terms of thermal stability. The use of pyridinium salts is particularly effective in nucleophilic substitution and dehydrohalogenation reactions. Pyridyl sulfoxides and pyridinium N-oxides also exhibit high catalytic activity in nucleophilic substitution reactions [47, 48]. Among the advantages of these catalysts are their accessibility and the possibility of full regeneration after use in a reaction medium.

Thus, the above discussion of experimental data concerning the use of phase-transfer catalysis in the chemistry of heterocyclic compounds demonstrates the various capabilities of this method. Currently, reactions with the participation of heteroanions that cannot be performed under conditions of phase-transfer catalysis are difficult to imagine. The advances of the above method in this area are undoubted. Unfortunately, the same cannot be said of cationic reactions, although interest in the use of phase-transfer catalysis in these processes is very high.

So-called reverse phase-transfer catalysis, in which a substrate is transferred from an organic phase to an aqueous phase where a reaction occurs, has received practically no attention [48]. Very few publications were devoted to the mechanistic studies of phase-transfer catalytic reactions.

At the same time, note that the use of phase-transfer catalysis in the chemistry of heterocyclic compounds goes far beyond pure laboratory studies; phase-transfer catalysis is implemented in industrial processes in increasing frequency [46, 49].

ACKNOWLEDGMENTS

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