# PHASE TRANSFER CATALYSIS IN THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS. A REVIEW

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This review covers new data on the use of phase transfer catalysis in the chemistry of heterocyclic compounds. The following reactions are considered: alkylation, acylation, reactions with dihalocarbenes, preparations of ethers and esters, the formation of halo derivatives, oxidation and reduction, and isotope exchange. The advantages of phase transfer catalysis are examined and the prospects for its further development in heterocyclic chemistry are discussed.

Phase transfer catalysis is a new method in synthetic organic chemistry which has achieved general recognition over the past decade. Universality, convenience, availability and low cost of the solvents used, and high product yields are the major advantages of this method.

Phase transfer catalysis has been the subject of an extensive literature including monographs [1-3] and reviews of specific aspects [4-14] such as the industrial application of this method [14]. These sources partially relate to questions concerning the transformations of heterocyclic compounds under phase transfer catalysis conditions. However, a general review of this subject, except for the review of Gallo et al. [13], who examined earlier work, is lacking.

In the present review, a summary is given of the literature data on the use of phase transfer catalysis in heterocyclic chemistry published within the past five years, including the first half of 1982.

The fundamentals of phase transfer catalysis were examined in detail in previous studies [1-3].

The application of phase transfer catalysis in heterocyclic chemistry gives good results in most cases.

The structure and reactivity of the heterocyclic substrates should be taken into account in selecting the conditions for carrying out these reactions, including the possibility of rearrangement in reactions with halocarbenes, the ambident nature of many heterocyclic anions, and the high sensitivity of many small rings to the action of bases.

The major factors which determine the rate and selectivity of reactions of heterocyclic compounds proceeding under phase transfer catalysis conditions are the nature of the phase transfer catalyst and the properties of the reaction medium. The information available indicates that tetrabutylammonium salts and organic solvents such as hydrocarbons, methylene chloride, and chloroform are the most effective catalysts for liquid–liquid systems. The best results for liquid–solid systems are obtained with crown ethers in acetonitrile.

Most two-phase reactions of heterocyclic compounds occur at room temperature, which is a significant advantage of this method. The most common reactions of heterocyclic compounds proceeding under phase transfer catalysis conditions are considered below.

## ALKYLATION AND ACYLATION

Alkylation reactions have been most studied of the numerous transformations of heterocyclic compounds which proceed under phase transfer catalysis conditions. This is not surprising since alkylation is the most convenient method for the formation of C–C, C–N, C–O,

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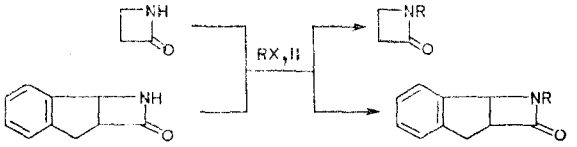
and other bonds in heterocycles. In some cases, carrying out alkylation under phase transfer catalysis conditions permits us to obtain heterocyclic compounds whose preparation would be difficult or completely impossible by other methods.

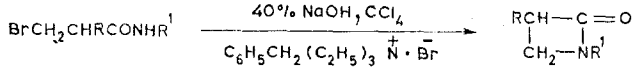
Any heterocyclic compounds which are capable of forming stable heteroanions by the action of strong bases are smoothly alkylated under phase transfer catalysis conditions. Alkylation in a heterophase system usually occurs under mild conditions, which is especially important for thermally unstable heterocycles. We should note that heterocyclic compounds may enter phase transfer reactions not only as substrates but also as alkylating agents.

On the basis of the available information, the alkylation of aziridine and its derivatives under heterophase conditions has not been studied sufficiently. The alkylation of aziridine by simple alkyl halides in the presence of benzyltriethylammonium chloride (I) has been described [15]. The reaction of aziridine with benzyl chloride in the presence of catalyst I gives a quantitative yield of N-benzylaziridine [16]. These results have fundamental significance since the alkylation of aziridines proceeds with difficulty and ring opening under usual conditions.

Azetidone and annelated azetidones are alkylated by alkyl and alkylaryl halides in the presence of tetrabutylammonium bromide (II) [17]:

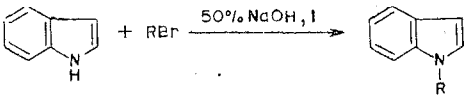



Several examples of the preparation of azetidone under heterophase conditions have been described. Substituted azetidones are formed as a result of intramolecular alkylation of N-substituted amides of β-bromopropionic acid [18-20]:

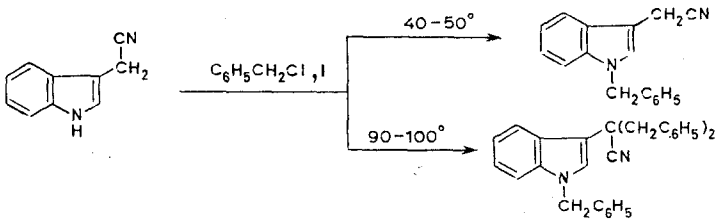



The alkylation of pyrrole under phase transfer conditions has hardly been studied. It has only been reported that crown ethers are efficient catalysts for the alkylation of the potassium salt of pyrrole by alkyl halides [21]. On the other hand, phase transfer catalysis has become a common method for the alkylation of various pyrrole derivatives, in particular, of indoles.

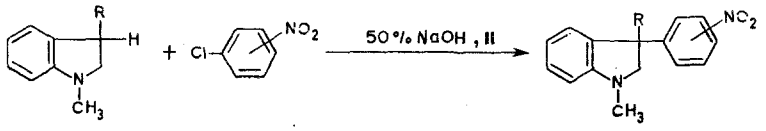
Thus, the reaction of indole with alkyl bromides in the presence of catalyst I gives a good yield of the corresponding 1-alkyl derivatives [22]:




Analogous results were obtained when methyl iodide, dimethyl sulfate and diethyl sulfate are the alkylating agents and tetrabutylammonium sulfate (III) is the catalyst [23]. In addition to quaternary ammonium salts, crown ethers have been used as catalysts in the alkylation of indole [21]. The reaction direction and product composition in the alkylation of indoles depend on the reaction conditions. The alkylation of 3-cyanomethylindole by benzyl chloride at 40-50°C leads to the N-benzyl derivative. The alkylation at elevated temperature occurs both at the heterocyclic nitrogen atom and at the methylene group carbon [24]:

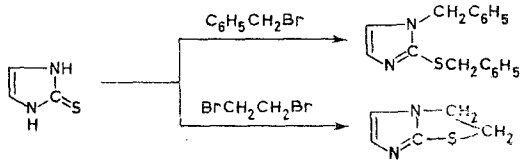



The alkylation of indoles under phase transfer catalysis conditions has been studied in the case of the reaction of 1-methyl-, 1,3-dimethyl-, and 1-methyl-3-phenylindolines with 2- and 4-nitrochlorobenzenes [25]:

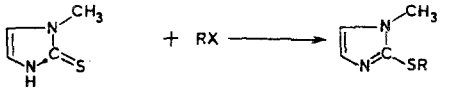


Of the other pyrrole derivatives, we should note butyrolactam, phthalimide, and carbazole, whose alkylation under phase transfer catalysis conditions has been studied by several workers [21, 22, 26-29]. The advantages of phase transfer catalysis in the alkylation of phthalimide are especially evident [27-29]. Completion of this reaction usually requires heating the reagents to 100-150°C. The use of a two-phase system in the presence of hexadecyltributylphosphonium bromide permits a lowering of the temperature to 25-50°C. Carbazole is alkylated just as readily under heterophase conditions with benzyltriethylammonium chloride [22] and 18-crown-6 macrocyclic polyether as catalysts [21]. Finally, the alkylation of 4-methoxy-2-(methylthio)-7H-pyrrole[2,3-d]pyrimidine by 2,3,4-tri(O-benzyl)-d-arabinofuranosyl bromide in the presence of benzyltrimethylammonium bromide (IV) has been described [30].

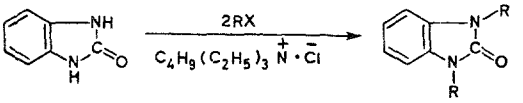
Five-membered rings containing two nitrogen atoms in the ring, namely, imidazole and pyrazole, are smoothly alkylated under phase transfer catalysis conditions. Quaternary ammonium salts [31] or crown ethers [21] serve as the catalysts. The use of crown ethers is preferable from the preparative viewpoint since the alkylation products are formed in higher yield. The alkylation of several imidazole derivatives has also been described. Thus, the rection of 2,3-dihydro-2-imidazolethione with a twofold amount of benzyl bromide in the presence of catalyst II gives a good yield of the corresponding N,S-dialkyl derivatives [32]. The alkylation of imidazolethione by dibromoethane proceeds analogously [33]:



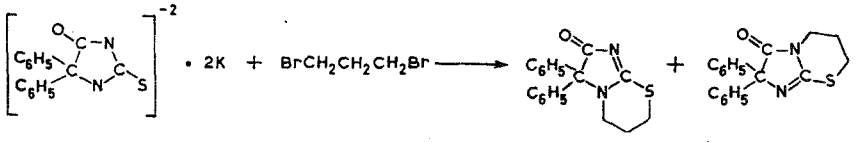
Under the same conditions, the alkylation of 3-methyl-2,3-dihydro-2-imidazolethione yields only S-alkylimidazoles:



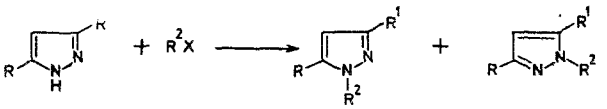
On the other hand, by going to benzimidazolone, the alkylation proceeds at the heterocyclic nitrogen atoms [34]:



It is interesting that when there are three potential reaction sites in the substrate (N, O, and S atoms), the alkylation proceeds only at the nitrogen or sulfur atoms. An example of this tendency is found in the alkylation of 5,5-diphenyl-4-imidazolone-2-thione by dibromopropane in the presence of phosphonium salts [35]:



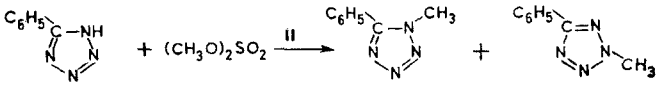
In the alkylation of 3,5-disubstituted pyrazoles containing simple substituents by benzyl bromide in dimethylformamide and under phase transfer catalysis conditions, the ratio of the $N_{(1)}$ and $N_{(2)}$ isomers formed is virtually identical [36]:



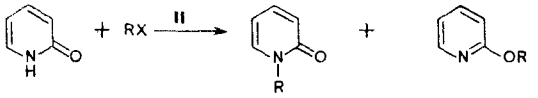
However, if there is a bulky substituent at [5] the fraction of the $N_{(1)}$ isomer is enhanced in heterophase alkylation [36].

Of the other five-membered rings containing two heteroatoms, the alkylation of thiazole-2-thione and benzothiazole-2-thione in the presence of catalysts I and II has been reported [37]. Phase transfer catalysis has been used in the alkylation of triazoles and tetrazoles. Benzotriazole is alkylated by methyl iodide in the presence of potassium tert-butylate and 18-crown-6 polyether to give a 70% yield of 1-methylbenzotriazole [21].

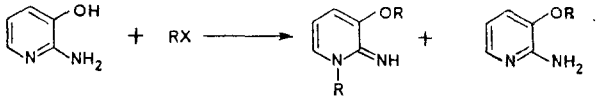
The present authors report that the alkylation of 5-phenyltetrazole by dimethyl sulfate under ordinary conditions gives 70% of the $N_{(2)}$ isomer, while, in a two-phase system in the presence of catalyst II, the yield of this isomer is increased to 85%:



The alkylation of several pyridine derivatives under phase transfer catalysis conditions has been reported. The alkylation of 2- and 3-pyridine derivatives by alkyl halides in the presence of phase transfer catalysts gives the N-isomer as the predominant product [38]:

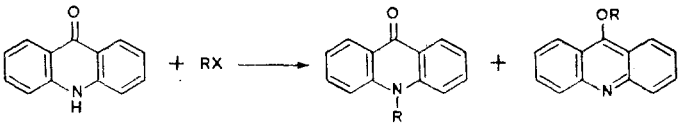


The alkylation of 2-amino-3-hydroxypyridine under ordinary conditions gives a mixture of N- and O-isomers while in a two-phase system in the presence of quaternary ammonium salts, the major reaction product is the O-isomer [39]:



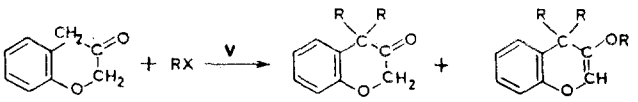
Such a reaction direction is clearly related to tautomeric transformations of the substrate under the alkylation conditions.

The alkylation of 1,4-dihydropyridines by methyl bromide and benzyl bromide proceeds in good yield with quaternary ammonium salts as the phase transfer catalysts [40]. Contradictory results were obtained in a study of the alkylation of acridone under phase transfer catalysis conditions. It was initially reported that the alkylation of acridone by dimethyl sulfate in the presence of catalyst I gives a quantitative yield of the O-methyl derivative [41]. However, a later study of the reaction showed that the ratio of the isomeric alkylation products depends significantly on the nature of the alkylating agent and may vary widely [42]:



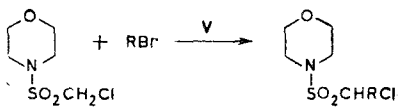
On the other hand Galy et al. [42] noted that the N-alkylation product was apparently incorrectly assigned the structure of the O-isomer by Willner and Halpern [41].

Phase transfer catalysis has been used in the alkylation of 3-chromanone with tetrabutylammonium chloride (V) as the catalyst. The C- and O-derivatives are obtained depending on the nature of the alkylating agent [43]:

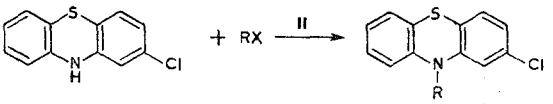


Six-membered rings with two heteroatoms in the ring such as pyrimidines, 1,4-oxazines, and 1,4-triazines are also alkylated under phase transfer catalysis conditions. The alkylation of 5-substituted uracils by dimethyl sulfate and simple alkyl halides in the presence of tetrabutylammonium bromide gives 80-100% yields of the $N_{(1)}$, $N_{(2)}$-dialkyl derivatives [44].

An interesting case of alkylation at the carbon atom of a methylene group was reported in the case of chloromethylsulfomorpholide [45]:

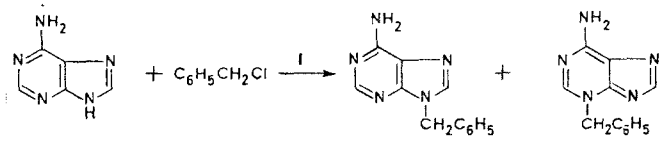


Finally, the alkylation of 2-chlorophenothiazine by ethyl bromide and benzyl chloride yields the corresponding N-derivatives in 42% and 70% yield, respectively [46]:

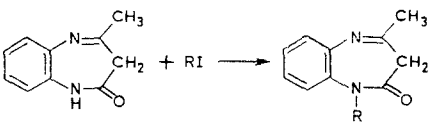


Heterophase alkylation may be used to obtain six-membered rings with two ring heteroatoms. Thus, the intermolecular alkylation of N-substituted amides of haloacetic acids yields 2,5-diketopiperazines [19].

Several examples of the alkylation of more complex heterocyclic systems using phase transfer catalysis have been described. Thus, the reaction of adenine with benzyl chloride yields a mixture of isomers in 75:25 ratio [47]:

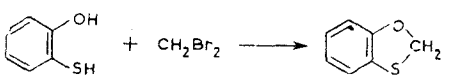


Dihydrobenzo[b]-1,4-diazepine is smoothly alkylated under heterophase conditions [48]:

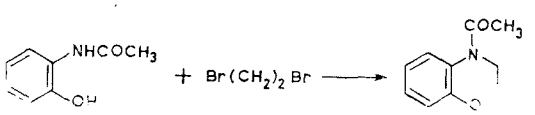


As already noted, heterocyclic compounds may enter interphase reactions not only as substrates but also as alkylating agents. Several typical examples of such reactions may be given: the alkylation of 2-amino-3-hydroxypyridine by 2-chloromethylthiophene [39], of 2-thionethiazole by 2-bromothiazole [37], of 1-naphthylacetonitrile by N-chloroethylpiperidine [49], and of phenylacetonitrile by 4-chloro- and 4-nitropyridine N-oxides [50] and 9-chloroacridine [51].

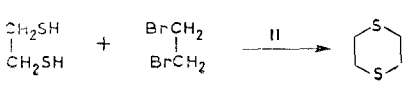
In some cases, alkylation under phase transfer conditions is a convenient method for the preparation of heterocyclic compounds. Thus, the alkylation of 2-mercaptophenol by methylene bromide gives an 80% yield of 1,3-benzoxathiole [52]:



2,3-Dihydro-1,4-benzoxazine may be obtained analogously [53]:

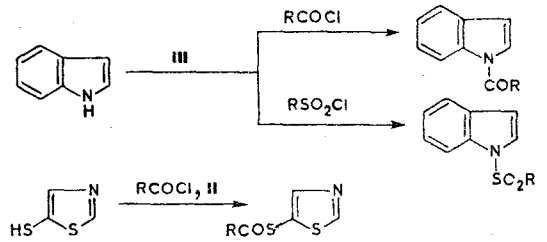


A simple method for the preparation of 1,4-dithiane involves the alkylation of ethylenedimercaptane by dibromoethane [33]:

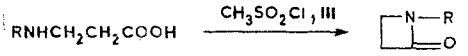


1,4-Dithiane was obtained previously by the pyrolysis of thiirane over aluminum oxide.

Acylation and sulfonation of heterocyclic compounds under phase transfer catalyst conditions have been studied to a much less extent than alkylation. Nevertheless, the use of heterophase systems for such purposes may be considered to give significant advantages. The acylation and sulfonation of heterocycles under phase transfer catalysis conditions proceed at room temperature. The reaction products are formed in virtually quantitative yields. Several examples of such reactions have been described including the acylation and sulfonation of indole [54, 55] and the acylation of thiazoles [56]:




We should also note a simple and efficient method for the preparation of substituted azetidones involving the reaction of derivatives of β-aminopropionic acid with methylsulfonyl chloride [57]:

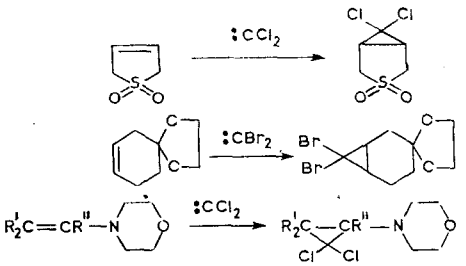



## REACTIONS WITH DIHALOCARBENES

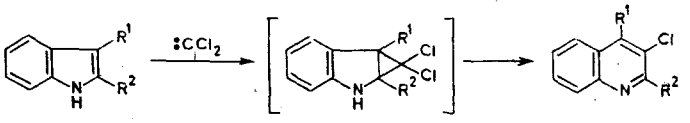
The development of carbene chemistry in recent years has been directly related to the development of phase transfer catalysis.

The generation of carbenes in two-phase systems differs from previously known methods and is extremely convenient. This has permitted an extensive study of the reactions of heterocyclic compounds with halocarbenes generated under phase transfer conditions.

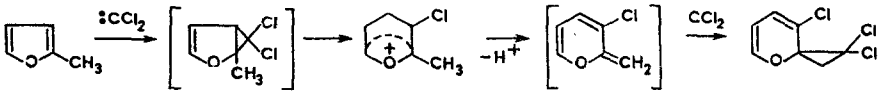
The cyclopropanation of heterocyclic compounds by dihalocarbenes under phase transfer catalysis conditions has been described for 3-thiolene dioxide [58], 2-cyclohexene-1,3-dioxalane [59], and 4-vinylmorpholine [60]:




The reactions of carbenes with simple five-membered heterocycles such as pyrroles, furans, and thiophenes are especially interesting. In all cases, the reaction of dihalocarbenes with these compounds gives new heterocyclic systems. Thus, the addition of dichlorocarbene to indole leads to a quinoline [61, 62]:

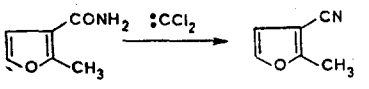



The reaction of dichlorocarbene with 2-methylfuran gives 2-dichlorocyclopropyl-3-chloro-α-pyran as the result of consecutive cyclopropanation, ring opening, and repeated cyclopropanation [63]:

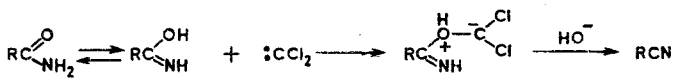



The reaction of dichlorocarbene with 2-methylthiophene proceeds analogously [63].

Primary amides of heterocyclic carboxylic acids react with dihalocarbenes and are converted in high yield to nitriles [64, 65]:

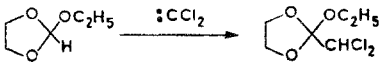


This reaction presumably proceeds with the formation of an intermediate zwitter ion, whose subsequent deprotonation leads to the corresponding nitrile:

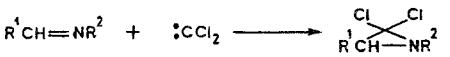


In light of the very facile generation of dihalocarbenes under phase transfer catalysis conditions and the high yields of the final products, this reaction may be recommended as a convenient method for the preparation of nitriles of heterocyclic carboxylic acids.

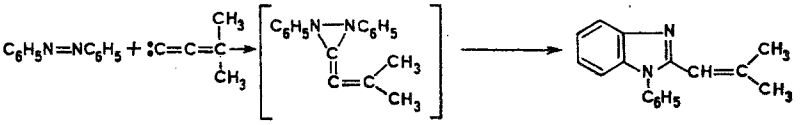
The reaction of dihalocarbenes with heterocyclic compounds involving insertion at a C–H bond is an interesting but, unfortunately, only slightly studied reaction. Thus, the reaction of 2-ethoxy-1,3-dioxalane with dihalocarbene gives 2-ethoxy-2-dichloromethyl-1,3-dioxalane [66]:



The reactions of carbenes may be used to prepare several heterocyclic compounds. Thus, for example, the corresponding 2,2-dichloroaziridines are formed in high yield in the reaction of dichlorocarbene with imines [67, 68]:



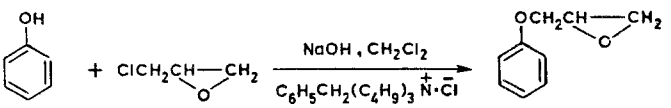
It is interesting that the addition of dimethylvinylidenecarbene generated under phase transfer catalysis conditions to azobenzene leads to 1-phenyl-2-isobutenylbenzylimidazole, whose formation apparently proceeds as a result of rearrangement of the initially obtained, unstable diazidine [69]:



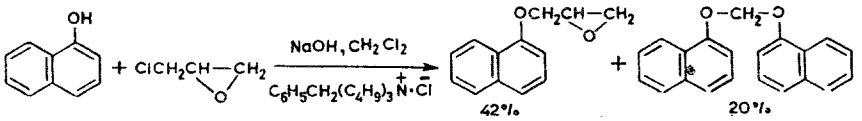
## PREPARATION OF ETHERS AND ESTERS

In comparison with the traditional methods for the preparation of ethers and esters, the heterophase method has a number of advantages. The use of this method permits us to avoid the preliminary preparation of alcoholates of alcohols and acyl halides, which significantly simplifies the reaction procedure. Phase transfer catalysis is especially effective when the carboxylic acids used to prepare esters are sensitive to the action of acid catalysts which are used in the esterification of alcohols.

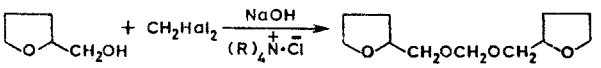
McKillop et al. [70] used phase transfer catalysis to prepare ethers from phenol, 1- and 2-naphthols, and epichlorohydrin. The reaction with phenol proceeds with high selectivity and the yield of the corresponding ether is 77%:



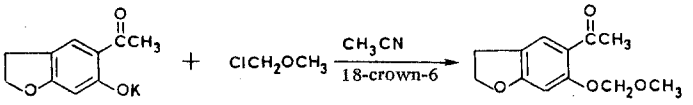
In the case of 1- and 2-naphthols, the corresponding dinaphthoxymethanes are formed in addition to glycidol ethers as a result of a side reaction with methylene chloride used as the solvent:



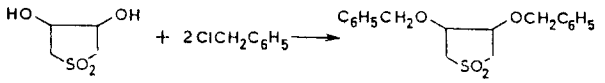
Ethers may also be obtained by the alkylation of heterocyclic alcohols. Thus, symmetrical formals are obtained from 2-hydroxymethyltetrahydrofuran and dihalomethanes [71]:



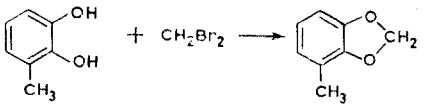
The reaction of 5-acetyl-6-hydroxybenzo-2,3-dihydrofuran with monochloromethyl ether in acetonitrile gives a 79% yield of the corresponding ether [72]:



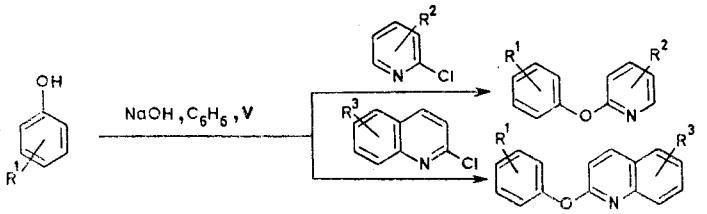
Good results were obtained in the alkylation of 3,4-dihydroxytetrahydrothiophene-1,1-dioxide by methyl iodide and benzyl chloride in the presence of trioctylbenzylammonium hydroxide [73]:



Ethers are formed in good yield in the reaction of substitued 1,2-dihydroxybenzenes with dibromomethane. The catalyst in this case is trioctylmethylammonium chloride [74]:



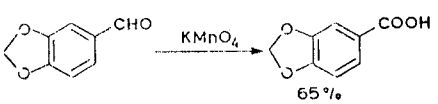
Phase transfer catalysis is extremely effective in the preparation of ethers from phenols and substituted 2-chloropyridines and 2- and 4-chloroquinolines [75]. The reactions proceeds under mild conditions and the corresponding ethers are formed in good yield in most cases:



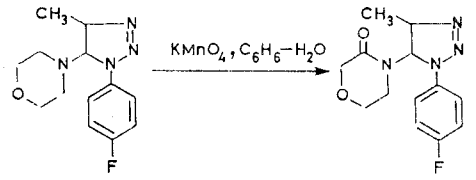
Although the advantages of phase transfer catalysis as a general method for the preparation of esters are obvious, this method has not been commonly employed in heterocyclic chemistry. This failure is even more remarkable since the preparation of the glycidyl ester of stearic acid was described in one of the first studies on phase transfer catalysis [2]. Unfortunately, these studies were not expanded and only a few examples of the use of phase transfer catalysis for the preparation of esters have been described: the synthesis of the methyl esters of epoxyacids [76] and of 2-substituted spiro-orthoesters [77].

## OXIDATION AND REDUCTION

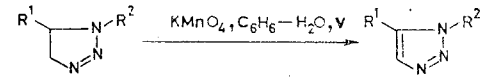
In a number of cases, the oxidation of heterocyclic compounds is impossible due to the limited solubility of these compounds in water. Such difficulties may be readily overcome by carrying out the oxidation under phase transfer catalysis conditions. In a heterophase medium containing an organic substrate, oxidizing agent and quaternary salt catalyst, the lyophilic cation and anion of the oxidizing agent form an ion pair which is extracted into the organic phase, in which the oxidation occurs. It is important to note that the heterocyclic system is not disturbed in oxidation under phase transfer conditions. Evidence for this is found in the oxidation of piperonal by potassium permanganate in the presence of cetyltrimethylammonium bromide (VI) [78]:



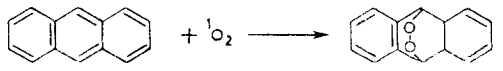
The effect of temperature on the oxidation selectivity has been studied for such heterocycles as substituted triazoles. In the oxidation of 1-(4-fluorophenyl)-4-methyl-5-morpholinotriazoline at room temperature in the presence of catalyst VI, the oxidation affects the morpholine fragment [79]:



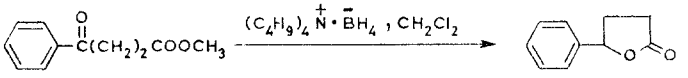
1,5-Disubstituted triazolines are converted to the corresponding triazoles under analogous conditions but heating at reflux [80]:



Finally, we should note the oxidation of anthracene by singlet oxygen generated under phase transfer catalysis conditions using photosensitized eosin [81]:



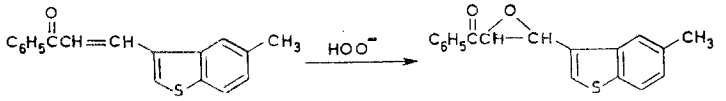
The use of phase transfer catalysis in reduction reactions does not give perceptible advantages relative to the traditional methods. On the other hand, aldehydes, ketones, and acid chlorides of carboxylic acids are smoothly reduced by tetrabutylammonium borohydride in methylene chloride. The reduction of esters proceeds at a lower rate. The reduction of methyl 4-benzolypropionate gives 4-phenylbutyrolacetone [82]:



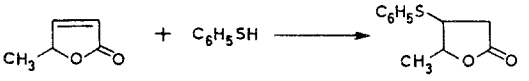
## THE MICHAEL REACTION

The use of quaternary ammonium salts as catalysts for the Michael reaction in heterocyclic chemistry has been known for more than two decades. On the other hand, information on carrying out this reaction under phase transfer catalysis conditions is extremely limited.

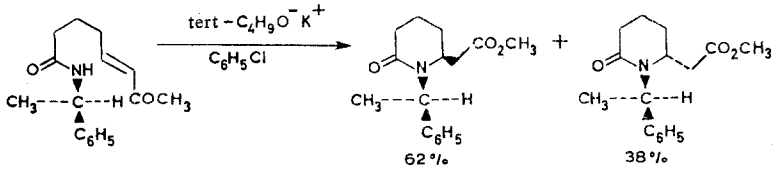
The addition of the peroxide and tert-butylperoxide ions generated under phase transfer catalysis conditions to α,β-unsaturated ketones has been described recently [83]:



In the presence of tetrabutylammonium fluoride, phenylmercaptan adds to 5-methyl-2-furanone in virtually quantitative yield [84]:

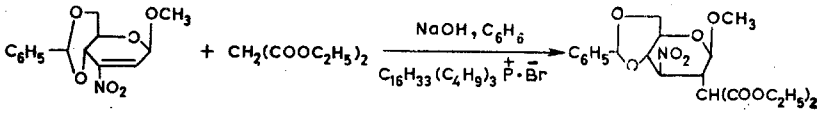


In intramolecular Michael cyclization of the ethyl ester of 6-(1-phenylethyl)carbamoyl-2-hexenoic acid proceeds under ordinary conditions to give a mixture of stereoisomeric esters [85]:



On the other hand, an inversed ratio of isomeric esters is obtained when the reaction is carried out in the presence of 18-crown-6 polyether as catalyst.

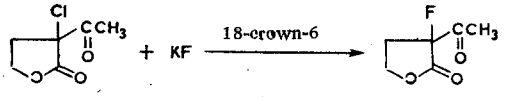
High selectivity is noted in the reactions of compounds containing activated methylene groups with 3-nitro-β-hexopyranosides [86, 87]:



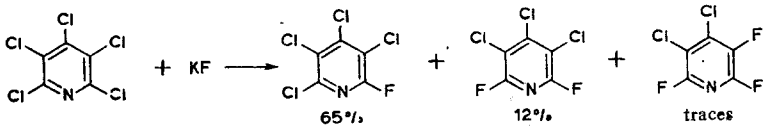
FINKELSTEIN REACTION

The use of phase transfer catalysis for the preparation of halo derivatives using the Finkelstein reaction does not yield significant advantages in comparison with the usual methods of halogenation in acetone. However, phase transfer catalysis gives good results in the preparation of fluorides. The synthesis of these derivatives is usually difficult.

Several examples of the successful use of phase transfer catalysis for the preparation of heterocyclic fluoro derivatives have been described. The chlorine atom in 3-chloro-3-acetyltetrahydro-2-furanone is replaced by fluorine by heating the reagents in acetonitrile at reflux in the presence of 18-crown-6-polyether [88]:



Heating of pentachloropyridine with potassium fluoride in the presence of cryptate gives a mixture of fluoropyridines. The major reaction product is 2-fluorotetrachloropyridine. 2,6-Difluorotrichloro- and 2,3,6-trifluorodichloropyridines are formed with considerably greater difficulty [89]:



ISOTOPE EXCHANGE

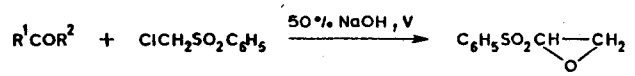
An interesting example which illustrates the scope of phase transfer catalysis in heterocyclic chemistry is isotope exchange [90, 91]. Isotope exchange in such heterocycles as thiophenes, imidazoles, thiazoles, and pyridines occurs at higher rates in the organic solvent—NaOD—$D_2O$ heterophase system than under ordinary conditions. The extent of exchange is greater than 90%. The nature of the catalyst and solvent affects the rate of H—D exchange. The catalysts form the following series relative to their efficiency: $(R)_4\overset{+}{N}\cdot Hal^-$ > $(R)_4\overset{+}{P}\cdot Hal^-$ > $(R)_4\overset{+}{As}\cdot Hal^-$. Of the quaternary ammonium salts, $[CH_3(CH_2)_4]_4\overset{+}{N}\cdot Br^-$ is the best catalyst. Isotope exchange proceeds at maximum rate when octane or benzene is used as the organic phase.

The information available indicates that heterophase isotope exchange may be recommended as a convenient preparative method for obtaining deuterated heterocyclic compounds.

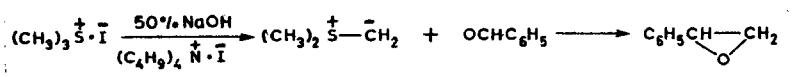
OTHER REACTIONS

In this section, we consider little studied reactions of heterocyclic compounds carried out under phase transfer catalysis conditions. This, however, does not imply that these reactions do not hold theoretical interest or lack promise for practical application. The opposite is more likely. The examples given below indicate the inexhaustible possibilities of the phase transfer catalysis method.

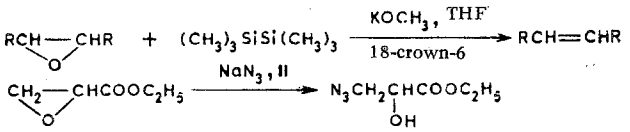
The reaction of ketones with chloromethylarylsulfones under phase transfer catalysis conditions may be seen as a general method for the preparation of substituted oxiranes [92]:



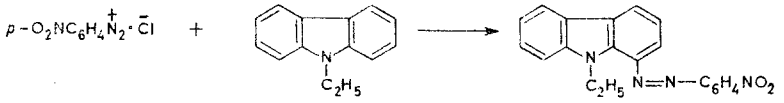
Oxiranes are formed in high yield in the reaction of aldehydes or ketones with sulfur ylides generated under phase transfer catalysis conditions [93, 94]:



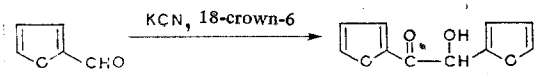
Oxiranes react smoothly under heterophase conditions with potassium trimethylsilane [95] and sodium azide [96] to form olefins and azides, respectively:



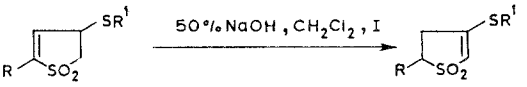
The reaction of p-nitrophenyldiazonium salts with N-ethylcarbazole under phase transfer catalysis conditions deserves attention. In this case, the aryldiazonium cation forms an ion pair with the lipophilic anion of 4-dodecylphenylsulfonate and is transferred to the organic phase, in which the following coupling reaction occurs rapidly [97]:



Crown ethers are effective catalysts for the benzoin condensation of furfural [98]:

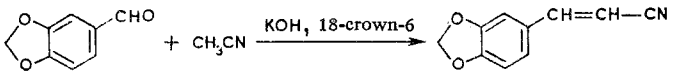


3-Alkylthio-2,3-dihydrothiophene-1,1-dioxide and 3-alkylthio-2,5-dihydrothiophene-1,1-dioxide isomerize under phase transfer catalysis conditions to give 3-aklylthio-4,5-dihydrothiophene-1,1-dioxides [99]:



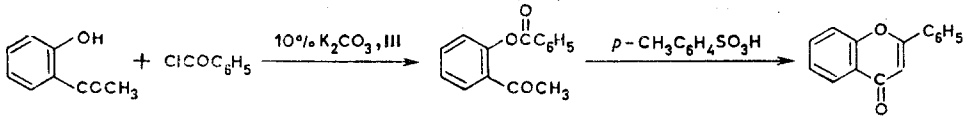
The chlorination of cis-2,5-diphenyltetrahydrothiophene-1,1-dioxide by carbon tetrachloride in the presence of catalyst I proceeds with inversion of configuration and leads to trans-2,5-dichloro-2,5-diphenyltetrahydrothiophene-1,1-dioxide [100].

2-Methylbenzoxazole and 2-methylbenzothiazole react smoothly under heterophase conditions with aromatic aldehydes [101]. In turn, heterocyclic aldehydes condense with acetonitrile in the presence of crown ethers [102]:

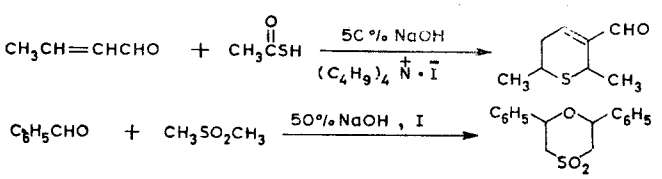


Furfural, 2-, 3-, and 4-formylpyridines undergo the Horner reaction with phosphonates under phase transfer catalysis conditions and the corresponding alkenes are formed in good yield [103].

The use of phase transfer catalysis in the preparation of chromones permits a significant simplification of the step involving acetylation of 2-hydroxyphenyl alkyl ketones which, under ordinary conditions, requires heating of the reagents at high temperature [104]:



Six-membered heterocycles containing a sulfur atom in the ring whose synthetic methods have not been sufficiently elaborated are obtained under phase transfer catalysis conditions by the reaction of aldehydes with thiolacetic acid [105] and dimethyl sulfate [106]:



Finally, we should note that heterocyclic compounds such as N-methylimidazole [107], quinuclidinium salts [83], and 1-azotricyclo[4.4.4.$0^{1,6}$]tetradecyl bromide [108] are used as phase transfer catalysts.

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# SYNTHESIS AND TRANSFORMATIONS OF 2-BROMOMETHYL DERIVATIVES OF 4,5-DIHYDROXYBENZOFURAN

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4,5-Diacetoxy- and 4-acetoxy-5-methoxy derivatives were obtained by the acylation of 2-methyl-3-carboethoxy-4,5-dihydroxy-6-chlorobenzofurans and 2-methyl-3-carboethoxy-4-hydroxy-5-methoxy-6-chlorobenzofurans (and their 6-bromo analogs). The bromination of these derivatives by N-bromosuccinimide gave the corresponding 2-bromomethyl derivatives. The reaction of these 2-bromomethyl derivatives with primary and secondary amines, sodium acetoacetic and sodium malonic esters gave 2-aminomethyl derivatives and derivatives of acetoaetic and malonic esters.

The present work is a continuation of a study of 4,5-dihydroxybenzofurans [1] and is devoted to the synthesis and transformation of their 2-bromomethyl derivatives. 4- and 5-Acetoxy derivatives of benzofuran, in contrast to the corresponding hydroxy- and methoxy derivatives, are brominated not in the benzene ring but rather in the furan ring or in the furan ring methyl group [2-4]. Thus, we initially carried out the acetylation of 2-methyl-3-carboethoxy-4,5-dihydroxy-6-chlorobenzofuran and 2-methyl-3-carboethoxy-4-hydroxy-5-methoxy-6-chlorobenzofuran and their 6-bromo analogs in order to obtain the 2-bromomethyl derivatives. The subsequent bromination of acetoxy derivatives Ia-d with N-bromosuccinimide in the presence of benzoyl peroxide gave high yields of 2-bromomethyl-3-carboethoxy-4,5-diacetoxy-6-chlorobenzoburan (IIa), its 6-bromo anlog (IIb), 2-bromomethyl-3-carboethoxy-4-acetoxy-5-methoxy-6-chlorobenzofuran (IIc) and its 6-bromo analog (IId).

TABLE 1. Chemical Shifts of Ia-d, Ia, b, d, and VI in $CD_3COCD_3$ (σ, ppm)[a]

| Compound[b] | 7-H (s) | 4(5)-OCOCH₃ | 5-OCH₃ | 2-CH₃, 2-CH₂Br (s) |
|---|---|---|---|---|
| Ia | 7,65 | 2,32<br>2,36 | — | 2,70 |
| Ib | 7,77 | 2,30<br>2,35 | — | 2,70 |
| Ic | 7,52 | 2,36 | 3,83 | 2,70 |
| Id | 7,63 | 2,36 | 2,82 | 2,67 |
| IIa | 8,10 | 2,33<br>2,40 | — | 5,00 |
| IIb | 8,20 | 2,34<br>2,40 | — | 5,00 |
| IId | 7,82 | 2,38 | 3,84 | 5,00 |
| VI[c] | 7,47 | | 3,86 | — |

[a]The spectra of IIa and IIb were taken in $(CD_3)_2SO$. [b]The signals of the protons of $3\text{-}CO_2C_2H_5$ groups are seen and a triplet and quartet at 1.36-1.42 and 4.33-4.65 ppm, respectively. [c]The signals of the 4-OH and 2-CHO protons are present as singlets at 10.8 and 10.4 ppm, respectively.

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