Synthesis and Reactions of Five-Membered Heterocycles Using Phase Transfer Catalyst (PTC) Techniques

Ahmed M. El-Sayed,1 Omyma A. Abd Allah,1 Ahmed M. M. El-Saghier,1 and Shaaban K. Mohamed2,3

1 Department of Chemistry, Faculty of Science, Sohag University, Sohag 82524, Egypt
2 Chemistry and Environmental Division, Manchester Metropolitan University, Manchester M1 5GD, UK
3 Chemistry Department, Faculty of Science, Minia University, El-Minia 61519, Egypt

Correspondence should be addressed to Omyma A. Abd Allah; omymatif66@yahoo.com

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1. Introduction

Organic synthesis is an essential way to get chemical products having practical applications such as pharmaceuticals, plant protection agents, dyes, photographic sensitizers, and monomers. Transformations of starting materials into desired final products usually require number of chemical operations in which additional reagents, catalysts, and solvents are employed. Thus, during any synthetic method, besides the desired products, many waste materials are produced because transformations of reactants into products are neither quantitative nor selective processes. This waste could be regenerated, destroyed, or disposed. This will lead to consuming much energy and creating heavy burden on the environment. Therefore it is of a great importance to develop and use synthetic methodologies that minimize or eliminate such problems. One of the most common and efficient methodologies that fulfill this requirement is employing phase-transfer catalysis techniques [1–4]. The most significant advantages of use of PTCs in industrial applications are [5]

(1) elimination of organic solvents,
(2) elimination of dangerous, inconvenient, and expensive reagents such as NaH and NaNH2,
(3) increasing the reactivity and selectivity of the active species,
(4) improving the yield and purity of products to the optimum records,
(5) simplifying the whole synthetic process and making it safer and objective,
(6) reducing industrial wastes and overall costs and saving energy which gives a positive impact on economic and environmental interests,
(7) accelerating and performing mimic reactions in an efficient mode.

1.1. Fundamentals of Phase Transfer Catalysis (PTC). First phase transfer catalysis was discovered by Jarrouse and Hebd in 1951 when they observed that the quaternary ammonium
salt and benzyltriethylammonium chloride accelerated two-phase reaction of benzyl chloride with cyclohexanol (Figure 1; (1)) and the two-phase alkylation reaction of phenylacetonitrile with benzyl chloride or ethyl chloride [6] (Figure 1; (2)).

In addition, numerous publications and patents [7–12] have been reported during the period of 1950–1965. PTCs techniques have been further developed by Makosza et al. for the purpose of obtaining more efficient and pure yield [13–16].

1.2. Mechanism of Phase-Transfer Catalysis. All phase-transfer catalyzed reactions involve at least two steps:

(1) transfer of one reagent from its ground phase into the second phase as an intermediate,

(2) reaction of the transferred reagent with the non-transferred reagent, for example, the alkylation of phenylacetonitrile with alkyl halide using aqueous NaOH as a base and tetrabutylammonium halide.
(QX) as a catalyst can be formulated as shown in Figure 2.

The concept of phase-transfer catalysis is not limited to anion transfer but is much more general, so that, in principle, one could also transfer cations, free radicals, or whole molecule. Phase transfer catalysis is classified as liquid-liquid, liquid-solid, liquid-gas, solid-gas, or solid-solid systems.

2. Application of Phase Transfer Catalysis in Synthesis of Five-Membered Ring of Heterocyclic Compounds

2.1. Synthesis of Five-Membered Ring Heterocycles Containing One Heteroatom. Treatment of anilinomethylene- malononitrile 1 with ethyl chloroacetate, chloroacetamide, phenacyl chloride, or diethyl bromomalonate in 1:1:1 molar ratio (dioxan/K$_2$CO$_3$/tetrabutylammonium bromide (TBAB)) afforded the corresponding substituted pyrroles 2a–c and 3, respectively [17] (Figure 3).

The catalytic cycle which explains the reaction pathway can be simplified as in Scheme 1.

A simple and convenient synthesis of 2-amino-1-aryl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitriles 6 was achieved by reaction of N-aryl-2-chloroacetamide 4 and malononitrile 5 under solid-liquid PTC condition (CH$_3$CN/K$_2$CO$_3$/18-crown-6) at room temperature [18] (Figure 4).

3-Amino-4-ethoxycarbonyl-1-phenyl-5-thioxo-2,5-dihydro-2-pyrrolidene malononitrile 9a was prepared via reaction of malononitrile 5, phenyl isothiocyanate 7, and ethoxymethylenemalononitrile 8a in 1:1:1 molar ratio under the PTC mixture of dioxan/K$_2$CO$_3$/(TBAB). Replacing of ethyl ethoxymethyleneacyanoacetate 8b with 8a gave ethyl[3-amino-4-ethoxy-carbonyl-1-phenyl-5-thixo-2,5-di- hydro-2-pyrrolidene]cyanoacetate 9b and 10 under the same experimental conditions [19] (Figure 5).

Moreover, the reaction of ethyl cyanoacetate 11 with phenyl isothiocyanate 7 and ethoxymethylenemalononitrile 8a or ethyl ethoxymethyleneacyanoacetate 8b in 1:1:1 molar ratio under same PTC experimental conditions afforded the corresponding pyrrole derivatives 12a, b, and 13 [19] (Figure 6).

Reaction of methyl 2,5-dibromopentanoate 14 with trichloroacetamide 15 under solid-liquid technique (CH$_3$CN/K$_2$CO$_3$/TEBACl) yielded methyl N-trichloroacetyl-2-pyrrolidine carboxylate 16 [20] (Figure 7).

Substituted pyrrolidines 19 were synthesized via the 1,3-dipolar cycloaddition reaction between imino esters 17 (derived from alanine and glycine with alkanes) and alkyl acrylate 18 in a mixture of THF or toluene, KOH, and TBACl [21] (Figure 8).

1,4-Di(malononitrilemethyleneamino)benzene 20 was allowed to react with ethyl chloroacetate, chloroacetamide, phenacyl chloride, or diethyl bromomalonate in 1:2 molar ratios under solid-liquid PTC technique to give the corresponding 1,4-bi(1-pyrrolyl) benzene derivatives 21a–c and 22 [17] (Figure 9).

Pyrrolidine derivatives 24 were obtained with thiophenes 25 from the reaction of diethyl cyanomalonate 23 with phenyl isothiocyanate 7 and chloroacetanilide or chloroacetamide using the PTC of (DMF/K$_2$CO$_3$/TBAB) [22] (Figure 10).
One-pot reaction of malononitrile 5, carbon disulphide, and chloroacetamide in 1:1:1 molar ratio under solid-liquid PT catalysis (benzene/K$_2$CO$_3$/TBAB) has furnished 3-amino-2-carboxyamido-4-cyano-5-mercaptothiophene 26 [23] (Figure 11). Also, treatment of malononitrile 5 with CS$_2$ and ethyl chloroacetate under the same experimental conditions gave the corresponding thiophene derivative 27 [23] (Figure 11).

Different thiophene compounds (24 and 28–30) prepared from reaction of diethyl cyanomalonate 23 with carbon...
\[
R \text{CONOR} + R_1 \text{CH(OH)COOR} \xrightarrow{\text{KOH}} \left[ \begin{array}{c} \text{R} \\ \text{R}_1 \\ \text{R}_1 \\ + \\ - \end{array} \right]
\]

**Figure 8**

\[
\text{NC=H-CH=NC} + \text{CICH(CO$_2$Et)$_2$} \xrightarrow{\text{CICH$_2$Cl}} \text{21a–c}
\]

**Figure 9**

\[
\text{EtO}_2\text{C-SH} + \text{EtxNCS} \xrightarrow{\text{PTC}} \left[ \begin{array}{c} \text{Et} \\ \text{O} \\ \text{O} \\ - \end{array} \right] \xrightarrow{\text{PTC}} \left[ \begin{array}{c} \text{PhN} \\ \text{PhN} \\ \text{PhNH} \\ + \end{array} \right]
\]

**Figure 10**

\[
\text{CH$_2$(CN)$_2$ + CS$_2$ + ClCH$_2$CONH$_2$} \xrightarrow{\text{PTC}} \text{26}
\]

**Figure 11**
disulphide or phenyl isothiocyanate 7 along with active halocompounds under solid-liquid phase condition (dioxan/K$_2$CO$_3$/TBAB) have been reported by Abd Allah and El-Sayed [22] (Figure 12).

2-Thiophenylidenes 31–33 were obtained through the reaction of either malononitrile 5 or ethyl cyanoacetate 11 with carbon disulphide along with ethoxymethyleneisonitrile 8a or ethyl ethoxymethyleneacetate 8b using liquid-solid technique (dioxan/K$_2$CO$_3$/TBAB) [19] (Figure 13).

In this reaction, the yield of products was found to be a temperature dependent. Thus, at low temperature (40°C) it affords the aminothiophene derivative 32a in high yield while at high temperature hydroxythiophene 32b or 33b was the sole product but in low yield.

The reaction of pyridosultam 34 with 3-chloropropyl thiocyanate under the experimental condition (toluene/aq. NaOH/TBAB) yielded the corresponding bicyclic derivative 35 [24] (Figure 14).

4-Amino-5-cyano-2-hydroxy-3-furancarboxylic acid 37 and compound 38 were synthesized by treating 1-phenyl-3,5-pyrazolinedione 36 with bromomalononitrile under solid-liquid condition (dioxan/K$_2$CO$_3$/TBAB) (Figure 15) [25].

The reaction pathway for the formation of unexpected compound 37 was assumed to proceed via catalytic hydrolysis of compound 38 into the furan derivative 37 and phenyl hydrazine [25] (Figure 16).

Condensation of salicylaldehyde 39 and its derivatives with various esters of chloroacetic acids 40 in the presence of TBAB led to the synthesis of benzo[b]furans 41 under solventless and microwave irradiation technique [26] (Figure 17).

Liquid-liquid PTC reaction of 4-chlorobutyronitrile 42 with nonenolizable aldehydes 43 via sequence of an addition cyclization reaction gave tetrahydrofuran-3-carbonitrile derivative 44 [27] (Figure 18).

Fused bis-arylbenzodifurans 46 have been synthesized by condensing 2,4-diacyl resorcinol 45 with various p-substituted phenacyl bromides [28] (Figure 19).

Methyl or ethyl 3-amino-4-arylthiophenes-2-carboxylates 48a–f were synthesized by Thorpe reaction through the treatment of 3-hydroxy-2-arylacrylonitriles 47a–f and methyl or ethyl thioglycolates with hydrochloric acid by using different PTC conditions (solid-liquid or liquid-liquid). The solid-liquid PTC conditions using 18-crown-6 along with potassium hydroxide as a catalyst are the method with excellent yields. The reactions were carried out in acetonitrile at RT [29] (Figure 20).

In Japp-Klingemann reaction the indole derivatives 52 have been prepared as indicated in Figure 21. The addition of a suitable PTC catalyst to the reaction could significantly improve the reaction process. Firstly, aryl amines 49 were diazotized and reacted under alkaline conditions ethyl 2-[2-(1,3-dioxo-1,3-dihydro-2H-isoxindol-2-yl)ethyl]-3-oxobutanoate 50 using PTC-promoted Japp-Klingemann reaction for the formation of unexpected compound 37.
reaction to form the ring-opened aryl hydrazones 51. These aryl hydrazones were cyclized and converted into the corresponding indole derivatives 52 by adding hydrochloric acid in ethanol [30] (Figure 21).

Synthesis of dimethyl phosphinyl substituted tetrahydropyrroles 55 via 1,3-cycloaddition reaction of the azomethine 53 to electron deficient alkenes such as α,β-unsaturated ketones (e.g., benzylideneacetophenone 54), esters, and nitriles took place in high yield and low diastereoselectivity in phase-transfer catalysis conditions (solid potassium carbonate, triethylbenzylammonium chloride (TEBA)) in acetonitrile as a solvent [31] (Figure 22).

When Schiff base 53 and ethyl cinnamate 56 reacted under different phase-transfer catalysis conditions (10 equivalents of aqueous NaOH (50%)/TEBA/DMSO), the ester of pyrrolidinecarboxylic acid 57 has not been formed;
instead the acid itself 58 was obtained as a mixture of two diastereoisomers [31] (Figure 23).

2.2. Synthesis of Five-Membered Ring Heterocycles Containing Two Heteroatoms. (4Z)-4-(4-amino-1,3-dithiol-2-ylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one derivative 60 was the product of a reaction of 3-methyl-1-phenyl-2-pyrazoline-5-one 59 with CS₂ and chloroacetonitrile in equimolar ratio under solid-liquid technique (benzene/K₂CO₃/TBAB) [23] (Figure 24).

Similarly, 1-phenyl-3,5-pyrazolidinedione 36 was treated with CS₂ and ethyl chloroacetate under the same condition
\[
\text{Figure 27}
\]

\[
\text{Figure 28}
\]

\[
\text{Figure 29}
\]

\[
\text{Figure 30}
\]

\[
\text{Figure 31}
\]
(benzene/K₂CO₃/TBAB) to give the corresponding (4Z)-4-(4-oxo-1,3-dithiolan-2-ylidene)-1-phenylpyrazolidine-3,5-dione 61 [25] (Figure 25).

The addition reaction of ethyl 3,4-diamino-5-cyanotriothio[2,3-b]thiophene-2-carboxylate 62 to carbon disulfide, followed by cyclization reaction through the treatment with chloroacetonitrile or ethyl chloroacetate under PTC conditions (K₂CO₃, TBAB, dioxane), furnished 3,4-bis(4-amino-2-thioxo-1,3-thiazol-3(2H)-yl)-5-propanoylthieno[2,3-b]thiophene-2-carbonitrile 63 and 3,4-bis(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-5-propanoylthieno[2,3-b]thiophene-2-carbonitrile 64, in satisfactory yields [32] (Figure 26).

Moreover, the addition reaction of compound 62 to carbon disulfide followed by cycloalkylation reaction with 1,2-dibromoethane, at 1:1:1 molar ratio under same PTC conditions, afforded the corresponding bis-1,3-dithiolan-2-ylidene 65 [32] (Figure 27).

Treatment of triazepene compound 66 with dibromides using liquid-liquid condition (benzene/NaOH/TBAB) furnished pyrazole derivatives 67a, b [33] (Figure 28).

1,3-Dipolar cycloaddition of various substituted nitrimines 68 to the appropriate alkenyl dipolarophiles 69 in aqueous media and in presence of a surfactant afforded a number of 1-aryl-5-substituted-4,5-dihydropyrazoles 70 [34] (Figure 29).

Preparation of 5-substituted oxazoles 74 or imidazoles 75 was achieved by reaction of p-tolysulphonylmethyl isocyanide 71 with aldehydes 72 R₁CH=NR₂ or 73 (R₁, R₂ = substituted phenyl, heteroaryl, and alkyl) under liquid-liquid condition [35, 36] (Figure 26). The interaction of 3-chloro-3-methyl-1-butyne 76 with 4,6-dimethyl-5-arylazo-2-thiopyrimidine 77 under liquid-liquid phase (benzene/aq. KOH/BTEAcI) afforded 4,6-dimethyl-5-[2-(2-methylprop-1-enyl)-1H-benzimidazol-1-yl]pyrimidinyl-(5H)-thiones 78 [37] (Figure 31).

Reactions of 5-phenylmethylenedithiohydantoin 79 with 1,2-dibromoethane 80 under liquid-liquid conditions (benzene/aq. NaOH/TBAB) afforded 2,3-dihydro-6-phenylmethylene-5-oxo-imidazo[2,3-b]thiazolines 81 [38] (Figure 32).

A variety of 4-thiazolidinone derivatives 83a–g were successfully synthesized via in situ formation of ketene-N,S-acetals 82a–g which in turn was reacted with ethyl chloroethyl acetate, chloroacetamide, or chloroacetyl chloride followed by ring closure to afford the desired 4-thiazolidinones 83a–g [39] (Figure 33).

One of the medicinal applications for PTC techniques is synthesis of sibenadet hydrochloride 87 which is a potent drug used for treatment of chronic obstructive pulmonary disease. This bioactive molecule was synthesized by O-alkylation of phenylethanol 84 with the alkyl bromide 85 under PTC condition to form the alkylated product 86 in 97% yield. Reaction of 86 with benzothiazole derivative led to formation of the desired product 86 [40] (Figure 34).

Treatment of an equimolar amount of 2-mercaptoquinazolin-4(3H)-one 88 and dihalo compounds such as 1,2-dibromoethane and chloroacetyl chloride underwent S-
\[
\text{OH} + \text{H}_2\text{C} = \text{Br} \xrightarrow{\text{NaOH/H}_2\text{O} \text{TBAHSO}_4} \text{Sibenadet hydrochloride}
\]

Figure 34

\[
\text{84} + \text{H}_2\text{C} = \text{Br} \xrightarrow{\text{NaOH/H}_2\text{O} \text{TBAHSO}_4} \text{Sibenadet hydrochloride}
\]

Figures 35 and 36
Figure 37

Figure 38

Figure 39

Figure 40
R = OMe (a), OEt (b), Me (c), H (d), Br (e)

**Figure 41**

\[
\begin{align*}
\text{NC} - \text{CN} &\quad + \text{CS}_2 + \text{XCH}_2\text{Y} \quad \text{PTC} \\
&\quad \xrightarrow{X = \text{Cl, Br}} \text{107a, b}
\end{align*}
\]

*a, Y = COOEt  
*b, Y = CN

**Figure 42**

\[
\begin{align*}
\text{H}_3\text{CO} - \text{COCH}_3 &\quad + \text{CS}_2 + \text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5 \\
&\quad \xrightarrow{108} \text{109}
\end{align*}
\]

**Figure 43**

\[
\begin{align*}
\text{CH}_2(\text{CN})_2 + \text{PhNCS} + \text{ClCH}_2\text{CO}_2\text{Et} &\quad \xrightarrow{110}
\end{align*}
\]

**Figure 44**

**Figure 45**
N-cyclo-alkylation by using PTC conditions, giving 2,3-dihydro-5H-[1,3]thiazolo[2,3-b]quinazolin-5-one \(89\) and \(5H\)-[1,3]-thiazolo-[2,3-b]quinazoline-3,5(2H)-dione \(90\), respectively [41] (Figure 35).

The PTC reaction of 3-phenyl-2-thiohydantoin \(91\) with dihalo compounds, namely, ethylene dibromide or 1,3-dibromopropane, with \(CS_2\), yielded 1,3-dithioxane derivative \(92a\) or 5-(1,3-dithian-2-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one derivative \(92b\), respectively [42] (Figure 36).

Treatment of the thiourea \(93\) and urea \(94\) derivatives with ethyl bromoacetate under PTC condition using TBAB as a catalyst and benzene/anhydrous \(K_2CO_3\) as liquid-solid phases gave imidazolidinediones \(95a, b\) via ring closure pathway [43] (Figure 37).

2.3. Synthesis of Five-Membered Ring Heterocycles Containing Three Heteroatoms. Alkylation of \((2Z,5Z)-5\)-benzylidene-2-(hydroxyimino)imidazolidin-4-one \(96\) with methylene bromide in benzene/aq. \(NaOH\) in presence of TBAB as a catalyst gave 2-phenyl-2,3-dihydro-6-phenylmethylene-5-oxo-imidazo[2,1-c]-1,2,4-triazole \(97\). On the other hand, alkylation of the oxime derivative of 5-phenylmethylene thiodyantoin \(98\) with methylene bromide gave 3-(IH)-6-phenylmethylene-5-oxo-imidazo[2,1-c]-1,2,4-oxadiazoles \(99a, b\) [38] (Figure 38).

Anastrozole \(101\) which acts as selective aromatase inhibitor and is employed effectively in treatment of advanced breast cancer in postmenopausal women has been synthesized in good yield by methylation reaction of 3,5-bis(cyanomethyl)toluene \(100\), using methyl chloride and 50% aq. \(NaOH\)/TEBA as a PTC condition [40] (Figure 39).

2.4. Synthesis of Five-Membered Ring Heterocycles Containing Four Heteroatoms. 5-Alkyl and 5-aryltetrazoles \(104\) were synthesized in good yield from reaction of alkyl(aryl)thiocyanates \(102\) with azide \(103\) under PTC conditions [44] (Figure 40).

Functionally substituted tetrazoles have been synthesized from the corresponding \(N,N',N''\)-triarylbenzene-1,3,5-tricarboxamides \(105\) via sequential transformation of these compounds into imidoyl chlorides and treatment of the latter with sodium azide under conditions of phase-transfer catalysis. As a result, a number of heterocyclic structures \(106a-106e\) containing three tetrazole rings have been isolated [45] (Figure 41).

3. Synthesis of Fused Five-Membered Ring Heterocycles

Functionally substituted thieno(2,3-b)thiophenes \(107a, b\) were synthesized in a one-pot reaction of malononitrile \(5\), \(CS_2\), and \(\alpha\)-halocarboxylic acid or \(\alpha\)-halonitrile electrophiles in 1:1:2 molar ratios using \((benzene/K_2CO_3/TBAB)\) as a PTC condition [23] (Figure 42).

Another different thienothiophene \(109\) was synthesized via the reaction of acetylacetone \(108\) with \(CS_2\) and ethyl chloroacetate in 1:1:2 molar ratio under the same experimental conditions [46] (Figure 43).

Thieno(2,3-b)pyrrole derivative \(110\) was obtained by treating malononitrile \(5\) with phenyl isothiocyanate \(7\) and ethyl chloroacetate in 1:1:2 molar ratio using \((benzene/K_2CO_3/TBAB)\) as a phase transfer catalyst [23] (Figure 44).

Likewise, under the same conditions, 3-methyl-1-phenyl-2-pyrazoline-5-one \(63\) was subjected to react with \(CS_2\) and chloroacetanilide in 1:1:1 molar ratio where 6-cyano-4,6-dihydro-3-methyl-1-phenylthieno(3,4-c)pyrazol-4-thione \(111\) was obtained in good yield [23] (Figure 45).

1-Phenyl-3,5-pyrazolinedione \(36\) was allowed to react with \(CS_2\) along with chloroacetanilide or ethyl chloroacetate...
under the same conditions to give the corresponding thioxothienopyrazolone derivatives 112 [25] (Figure 46).

Reaction of 4-hydroxydithiocoumarin 113 with allyl bromide 114 under liquid-liquid technique (CH₂Cl₂/aq. NaOH/TBAB or TBACl) gave 2-methyl-2,3-dihydro-4H-thieno[2,3-b]benzothiopyran-4-one 115 [47] (Figure 47).

Treating of pyridazinium ylides 116 with N-phenylmaleimide, maleic and fumaric esters, resulted in the cycloadduct products 117–120 with high stereospecificity in the presence of KF and trioctylmethylammonium chloride or without solvent in the presence of aliquat 336 as phase transfer catalyst [48] (Figure 48).

Under solid-liquid technique (dioxan/K₂CO₃/TBAB), bis-thieno(1,8)naphthyridines 122 were prepared by reaction of 4,5-diamino-3,6-dicyano-(1,8)naphthyridine-2,7-dithiol 121 with ethyl chloroacetate, chloroacetonitrile,
phenacyl bromide, or chloroacetamide in 1:2 molar ratio or from reaction of 4,5-diamino-2,7-dichloro-3,6-dicyano(1,8)naphthyridine 123 with two equivalents of ethyl mercaptoacetate [49] (Figure 49).

Similarly 4-amino-3,5-dicyano-2-mercapto-6-methylthiopyridine 124 was reacted with ethyl chloroacetate, chloroacetanitrile, phenacyl bromide, or chloroacetamide in 1:1 molar ratio using the same PTC condition to give the corresponding thieno(2,3-b)pyridines 125 or pyrrolo(2,3-d)thieno(2,3-b)pyridines 126 [49] (Figure 50).

Using solid-liquid technique (dioxan/K$_2$CO$_3$/TBAB), 2-ylidenemalononitrile and ethyl 2-ylidencyanoacetate of both 2,3-dihydrobenzothiazole 127 and 2,3-dihydrobenzoxazole 128 were allowed to react with chloroacetanitrile, ethyl chloroacetate, or phenacyl bromide in equimolar ratio which afforded the corresponding substituted pyrrolo[2,1-b]benzothiazoles 129 or substituted pyrrolo[2,1-b]benzoxazoles 130, respectively [42]. Similarly, (3-amino-2-(1,3-dihydro-2H-benzimidazol-2-ylidene)propanenitrile malononitrile 131a or ethyl 3-amino-2-(1,3-dihydro-2H-benzimidazol-2-ylidene)propanoate 131b were treated under the same PTC conditions, where the corresponding pyrrolo[2,3-b]pyrrolo[1,2-f]benzimidazoles 132 were obtained [50] (Figure 51).

Reaction of 2,7-dichloro-1,8-naphthyridine derivative 133 with ethyl glycinate hydrochloride in 1:1 molar ratio under solid-liquid technique (dioxan/K$_2$CO$_3$/TBAB) afforded the corresponding bis-pyrrolo(1,8)naphthyridine derivative 134 [49] (Figure 52).
\[ \text{133} \quad \text{+ HCLH}_2\text{NCH}_2\text{COOEt} \rightarrow \text{PTC} \rightarrow \text{134} \]

\[ \text{Z} = \text{CN, CHO, PhCO} \]

\[ \text{135} \]

\[ \text{PTC} \quad 1:1 \rightarrow \text{136} \]
\[ \text{PTC} \quad 1:2 \rightarrow \text{137} \]
\[ Y = \text{NH}_2, \text{H, Ph} \]

\[ \text{138} \]

\[ \text{PTC} \quad \text{ClICH}_2\text{CN} \quad (1:1:1)/\text{PTC} \]
\[ \text{ClICH}_2\text{CO}_2\text{Et} \quad (1:1:1)/\text{PTC} \]
\[ \text{PhCOCH}_2\text{Br} \quad (1:1:1)/\text{PTC} \]

\[ \text{CS}_2 \]

\[ \text{ClICH}_2\text{CN} \quad (1:1:2)/\text{PTC} \]
\[ \text{ClICH}_2\text{CO}_2\text{Et} \quad (1:1:2)/\text{PTC} \]
\[ \text{PhCOCH}_2\text{Br} \quad (1:1:2)/\text{PTC} \]
\[ \text{NC} \quad \text{NH}_2 \quad \text{COOEt} \quad \text{PhCONH} \quad \text{PTC} \quad \text{Br} \]

\[ \text{CN} \quad \text{CN} \quad \text{NH}_2 \quad \text{H} \quad \text{S} \quad \text{S} \quad \text{PTC} \quad \text{EtOOC} \]

Figure 55

\[ \text{X} \quad \text{NH}_2 \quad \text{COOEt} \quad \text{PhCONH} \quad \text{PTC} \quad \text{Br} \]

\[ \text{Y} \quad \text{NH}_2 \quad \text{OH} \quad \text{PTC} \quad \text{Br} \]

a: X = CN, b: X = COOEt

Figure 56

\[ \text{R} = 4\text{-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4 \]

Figure 57

\[ \text{R} = p\text{-ClC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4 \]

Figure 58

\[ \text{R} = p\text{-ClC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4 \]

Figure 59
Thieno(2,3-b) thiopyran derivatives 136 were obtained from reaction of the thiopyran derivative 135 with ethyl chloroacetate in 1:1 molar ratio (dioxan/K$_2$CO$_3$/TBAB), while on carrying out the same reaction under the same conditions but in 1:2 molar ratio gave the corresponding thienopyrrolothiopyran derivatives 137 [51] (Figure 53).

Treatment of 3-amino-1-phenyl-2-pyrazoline-5-one 138 with chloroacetonitrile using solid-liquid condition [52] (Figure 54).

Thieno(2,3-b)pyrrole derivative 148 was obtained by reacting ethyl thiophene-2-ylidenecyanoacetate derivative 3b with phenacyl bromide in a heterogeneous mixture of (dioxan/K$_2$CO$_3$/TBAB) as a PTC [19] (Figure 55).

In the same manner, pyrro-2-ylidenemalononitriles 149a, b were reacted with phenacyl bromide under the same reaction condition and yielded the corresponding thieno(2,3-b)pyrrole derivatives 150a, b [18] (Figure 56).

2,6-Dibenzoyl-5-methyl-3-(substituted styril)benzo[1,2-b:5,4-b]difurans 152 were synthesized from reaction of cinnamoylbenzofurans 151 with phenacyl bromide under liquid-liquid technique (benzene/aq. K$_2$CO$_3$/TBAHSO$_4$) [53] (Figure 57).

Similarly, 2,6-dibenzoyl-3,5-distyrilbenzo[1,2-b:5,4'-b]difurans 154 were prepared by condensing substituted dichalcones 153 with phenacyl bromide under the same preceding PTC conditions [54] (Figure 58).

Also, under the same PTC conditions, dibenzoylbenzofurans 156 were obtained from the reaction of substituted resorcinols 155 with phenacyl bromide [55] (Figure 59).

Moreover, 2,6-diaryl/naphthoyl-3,5-dialkyl/phenylbenzo[1,2-b:5,4-b']difurans 158 were synthesized by condensing 2,4-diacyl/diaroylresorcinols 157 with various p-substituted α-bromo ketones [56] (Figure 60).

Treatment of 3-methyl-1-phenyl-2-pyrazolin-5-one 63 with bromomalononitrile in 1:1 molar ratio yielded 5-amino-4-cyano-3-methyl-1-phenylfuro(2,3-c)pyrazoline 159 [23] (Figure 61).

Furo(1,5)benzodiazepin derivative 161 was obtained by reaction of 1,4-dimethyl-3H-(1,5)benzodiazepin-2-one 160 with chloroacetonitrile under solid-liquid condition (dioxan/K$_2$CO$_3$/TBAB) [57] (Figure 62).

By reaction of 4-methyl-1,3-dihydro-2H-1-benzazepin-2-one 162 with chloroacetonitrile or phenacyl bromide under the solid-liquid phase transfer catalyst (dioxan/K$_2$CO$_3$/TBAB), the corresponding pyrrolo[1,2-a](1,5)benzodiazepine 163 was obtained [58] (Figure 63).

Synthesis of 2,6-di(1-acetyl-2-oxopropylidene)dithioloi[4,5-b:4',5'-e]-4,8-benzoquinone 166 was achieved in one-pot reaction under solid-liquid technique (benzene/K$_2$CO$_3$/TBAB) starting from acrylamide, CS$_2$ to give 165 which in turn reacted with tetrabromo p-benzo-quinone 164 in 2:1 molar ratio [59] (Figure 64).

Treatment of 4-arylidene-1-phenyl-3,5-pyrazoliniones 167 with S,S-acetal derivatives using solid-liquid technique (dioxan/K$_2$CO$_3$/TBAB) yielded the corresponding pyrazolino-(1,3)-dithiolane derivatives 168 [25] (Figure 65).

Some condensed heterocyclic systems 171 were obtained by reacting 3-phenyl-4-amino-s-triazole-5-thiol with bromomalononitrile under solid-liquid condition as a diionic compound containing N and S poles with some dia- and tetralahederivatives 170 as well as α-haloketones and α-halonitrile derivatives under solid-liquid technique [60] (Figure 66).

2-Aminoprop-1-ene-1,1,3-tricarbonitrile 172 was reacted with CS$_2$ or PhNCS along with 3-methyl-1-phenyl-2-pyrazoline-5-one 63 or 2-iminothiazolidin-4-one 173 (dioxan/K$_2$CO$_3$/TBAB) to give the corresponding fused pyrazoles 174 and thiazoles 175, respectively [61] (Figure 67).

The reaction of 1,3-dihydro-4-methyl(1,5)benzodiazepin-2-one 176 with chloroacetonitrile using solid-liquid
Figure 62

\[
\text{160} \quad \text{+ ClCH}_2\text{CN} \quad \rightarrow \quad \text{161}
\]

Figure 63

\[
\text{162} \quad \text{+ ClCH}_2\text{CN} \quad \xrightarrow{\text{PTC/Dioxan}} \quad \text{163}
\]

Figure 64

\[
\text{164} \quad + \quad \text{165} \quad \xrightarrow{\text{PTC}} \quad \text{166}
\]

Figure 65

\[
\text{167} \quad \xrightarrow{\text{CS}_2 + \text{XCH}_2\text{CN} \quad \text{PTC}} \quad \text{168}
\]

\(X = \text{CN, COOEt}\)

\(Ar = p-\text{ClC}_6\text{H}_4, p-\text{NO}_2\text{C}_6\text{H}_4\)

Figure 66

\[
\text{169} \quad + \quad \text{170} \quad \xrightarrow{\text{PTC}} \quad \text{171}
\]
Figure 67

Figure 68

Figure 69

Figure 70
technique (dioxan/K₂CO₃/TBAB) gave the corresponding oxazolo-(1,5)benzodiazepin derivative 177 [57] (Figure 68).

When 7-(methoxyimino)-4-methyl-2H-chromene-2,8-(7H)-dione 178 was treated with crotyltriphenylphosphonium chloride (CTPPCl) 179 (CH₂Cl₂/Li(OH)/CTPPCl), the corresponding chromeno-oxazolone 180 was obtained in which one of the reactants (CTPPCl) acts also as a catalyst [62] (Figure 69).

The triazepine 181 was treated with 1,2-dibromoethane under liquid-liquid technique (benzene/aq. NaOH/BTEACl) to afford the corresponding 6-methyl-8-phenyl-2,3-dihydro[1,3]thiazolo[3,2-d][1,2,4]triazepine-5(6H)-thione 182 [33] (Figure 70).

4. Synthesis of Spiro Five-Membered Ring Heterocycles

Synthesis of spirohodanine heterocycles 184–187 was achieved by treating 5,5-dibromo-3-phenyl-2-thioxo-1,3-thiazolidin-4-one 183 with different bidentates or with mixture of CS₂ and some active methylene compounds under solid-liquid condition (dioxan/K₂CO₃/TBAB) [63] (Figure 71).

Reaction of 4-ethoxymethylene-1-phenyl-3,5-pyrazolidinedione 188 with CS₂ and malononitrile 5 or ethyl cyanoacetate 11 using solid-liquid technique (dioxan/K₂CO₃/TBAB) yielded the corresponding spiro-1,3-dithiolane derivatives 189 [25] (Figure 72).

1-Benzoyl-3,3-dibromo-4-phenyl-(1,5)benzodiazepin-2-one 190 was reacted with different dinucleophiles under PTC condition (dioxan/K₂CO₃/TBAB) to furnish the corresponding spiroheterocycles attached to benzodiazepine moiety 191–193 [64] (Figure 73).

5. Uses of Phase Transfer Catalysis Techniques in Reactions of Five-Membered Heterocycles

5.1. Alkylation and Acylation

5.1.1. N-Alkylation or Acylation. Diez-Barra et al. [65] studied the alkylation of pyrrole 194 by PTC technique in absence of the solvent. The study revealed that the N versus C ratio is not affected by the nature of the catalyst. The nature of the leaving groups have a significant influence where N-alkylation increases in the sequence I < Br < Cl < OTs (Figure 74).

N-alkyl pyrrolidin-2,5-diones 200 [66, 67] were synthesized via reaction of pyrrolidin-2,5-diones with different alkylation reagents under phase transfer catalysis condition (toluene/K₂CO₃/TBAHSO₄) according to (Figure 75).

N-allylindoles 203 were easily carried out via N-allylation of the proper indoles 201 with the suitable allyl halides 202.
\[
\text{HN} \quad \text{OEt} \quad \text{Ph} \quad + \quad \text{CS}_2 \quad + \quad \text{NCCH}_2\text{X} \quad \text{PTC} \\
\xrightarrow{5 \text{ or } 11} \\
\text{HN} \quad \text{Ph} \quad \text{CN} \\
\text{X} = \text{CN, COOEt}
\]

**Figure 72**

\[
\begin{align*}
\text{XH} & \quad \text{YH} \\
\xrightarrow{} & \quad \text{HNNHCNSNH}_2
\end{align*}
\]

**Figure 73**

\[
\frac{\text{NH} + \text{XCH}_2\text{CH} = \text{CHCH}_2\text{OR}}{\text{RX PTC}} \xrightarrow{} \frac{\text{161} \quad 162 \quad 163 \quad 164}{\text{198} \quad 199 \quad 200}
\]

**Figure 74**

\[
\text{R}
\]

**Figure 75**
The reaction was accomplished in diethyl ether via a phase transfer process in which 18-crown-6 was employed as the transfer agent and t-BuOK as the base [68] (Figure 76).

2-Substituted 1-allylpyrroles 206a–c were easily prepared from reaction of 2-formylpyrrole or 2-acetylpyrrole 204 with either 3-chlorobut-1-ene 205a or 3-chloro-2-methylprop-1-ene 205b, respectively, under phase transfer conditions (toluene/NaOH/TBAHSO₄) [69] (Figure 77).

Treatment of pyrroles 204 with 1,2-dichloroethane in presence of 50% NaOH and TBAB as a catalyst yielded the corresponding N-chloroethyl-pyrroles 207 in excellent yield which was transformed into 1,2-divinylpyrroles 208 via its reaction with sodamide using solid-liquid technique (THF/NaNH₂/CH₃PhBr) [70] (Figure 78).

Synthesis of a series of N-alkylpyrroldino[59]fullerenes was achieved via the combination of PTC without solvent and microwave irradiation technique. Thus, 2-phenylpyrroldinofullerene 209 was treated with benzy1, p-nitrobenzyl, p-methoxy-carbonylbenzyl, n-octyl, or allyl bromides in microwave oven in presence of K₂CO₃ and TBAB to yield the corresponding N-alkylpyrroldino[59]fullerenes 210 [71] (Figure 79).

1,3-Bis[2-(aryl)indol-1-yl]propanes 213 and 1,3-bis[3-(aryl)-5-(aryl)pyrazol-1-yl]-propanes 214 were prepared...
from reaction of appropriate 2-arylindoles 211 and 4,5-dihydropyrazoles 212, respectively, with 1,3-dibromopropane, via liquid-liquid technique using TBAHS as a catalyst, benzene as the organic phase, and 50% KOH as an aq. phase [72] (Figure 80).

Indole-2-acetonitrile 215 was treated with (CH$_3$)$_2$CO$_3$ in a mixture of [DMF/TBAB/K$_2$CO$_3$] to afford 1-methylindole-2-acetonitrile 216a and 2-(1-methylindole-3-yl)propionitrile 216b [73] (Figure 81).

Alkylation of indole 217, 2,3-dimethylindole 218 with chlorodifluromethane under liquid-liquid technique (CH$_2$Cl$_2$/aq. NaOH/BzTEACl) afforded the corresponding 1-alkylated derivatives 219 and 220, respectively [74] (Figure 82).

Barraja et al. heated 2-substituted-3-bromoindoles 221 with excess of different nucleophiles, solid KOH, and dibenzo-18-crown as a phase transfer catalyst to afford the corresponding 3-substituted indoles 222 in a satisfactory increase of yield [75] (Figure 83).

Carbazole 223 was alkylated with 1,6-dibromohexane in 1:1 molar ratio to give N-alkyl derivative 224 in a mixture of (benzene/NaOH/TBAB) [76] (Figure 84).

Alkylation of pyrazole 225 with cyclopentyl or cyclohexyl bromides without solvent with PTC system (KOH/
TBAB) afforded the corresponding 1-cyclopentyl or 1-cyclohexylpyrazoles 226a, b, respectively. Likewise treatment of pyrazole with 1,2-dibromoethane in 1:1 or 2:1 molar ratio afforded 1-bromoethylpyrazole or 1,2 bispyrazolyethane 227, 228 [76](Figure 85). Also, alkylation reaction of 1H-pyrazole 225 with linear or branched alkyl halide in liquid-liquid PTC system gave 1-alkyl-1H-pyrazole 229 [77](Figure 85).

The reaction of 3-tert-butylpyrazole 230 with dibromomethane afforded bis(tert-butylpyrazol-1-yl)methane [CH₂(3-t-BuPz)₂] 231. However, the reaction of 3-isopropylpyrazole 232 with dibromomethane under the same condition yielded three isomers, namely, bis(3-isopropylpyrazol-1-yl)methane[CH₂(3-isPrPz)₂] 233, (3-isopropylpyrazol-1-yl-5’-isopropylpyrazol-1’-yl)methane[CH₂(3-iPrPz- 5’-isoPrPz)₂] 234, and bis(3-isopropylpyrazol-1-yl) methane [CH₂(3-iPrPz)₂] 235 [78](Figure 86).

N-Substituted-3,5-diarylpyrazolines 237 and 238 were prepared via liquid-liquid system in (CHCl₃ or benzene/aq. KOH/TBAB) using alkyl and allyl halides, respectively, as alkylating agents for pyrazoles 236 [79](Figure 87).

N-Alkylation reactions of 4,9-dihydro-9-methyl-4,10,10-trioxo-1(2H)-pyrazolo[3,4-c][2,1]-benzothiazepine 239 with dimethyl sulphate, diethyl sulphate, benzyl bromide, benzyl chloride, phenacyl bromide, phenacyl chloride, or cyclohexyl bromide under the liquid-liquid PTC condition of (toluene/NaOH(25%)/BTEACl, TBAB, or TBAHSO₄) produced 1- and 2-alkylated isomers 240a, b. The ratios between these two isomers were calculated [80](Figure 88).

A number of 4-substituted pyrazolo[3,4-d]pyrimidines 241 have been reacted with (2-acetoxyethoxy)methyl bromide using liquid-liquid and solid-liquid techniques. The influences of the solvent and catalyst have been studied [81, 82](Figure 89).
Imidazole 243 was alkylated with different alkyl halides under solid-liquid PTC in absence of solvent where the N-alkyl imidazoles 244a and imidazolium salts 244b were obtained [83] (Figure 90).

1-Alkyl(C₄-C₆)imidazoles 245 were obtained from the alkylation of imidazole 243 with the appropriate n-bromoalkane via PTC technique (benzene/KOH/TBAI) [84] (Figure 91).

1-Alkyl-2-methyl-2-imidazolines 247 were obtained in good to excellent yields by alkylation of 2-methyl-2-imidazoline 246 with organic halides in the absence of solvent [85] (Figure 92).

Using the PTC condition such as (CH₂Cl₂/KOH/TEBA), a mixture (1:1) of N-alkylated 5-nitroimidazoles 250a, b or 6-nitrobenzimidazoles 251a, b was obtained by the reaction of 5-nitroimidazoles 248 or 6-nitrobenzimidazoles 249 with...
Figure 87

Figure 88

Figure 89

Figure 90
Figure 91

\[
\begin{align*}
\text{Scheme 1:} & \quad \text{Imidazole} + RBr \rightarrow \text{Imidazole} \\
243 & \quad R = \text{CH}_3(\text{CH}_2)_n, n = 3-13
\end{align*}
\]

Figure 92

\[
\begin{align*}
\text{Scheme 2:} & \quad \text{Imidazole-CH}_3 + RX \rightarrow \text{Imidazole-CH}_3 \\
246 & \quad \text{H} \\
247 & \quad \text{PTC}
\end{align*}
\]

Figure 93

\[
\begin{align*}
\text{Scheme 3:} & \quad \text{O}_2\text{N}-\text{imidazole} + \text{CH}_3\text{I} \rightarrow \text{O}_2\text{N-Imidazole} + \text{O}_2\text{N-Imidazole} \\
248 & \quad \text{O}_2\text{N-Imidazole} \quad \text{O}_2\text{N-Imidazole} \\
250a & \quad \text{O}_2\text{N-Imidazole} \quad \text{O}_2\text{N-Imidazole}
\end{align*}
\]

Figure 94

\[
\begin{align*}
\text{Scheme 4:} & \quad \text{2,4-Dinitroimidazole} + \text{PhCH}_2\text{Cl} \rightarrow \text{2,4-Dinitroimidazole} + \text{2,4-Dinitroimidazole} \\
249 & \quad \text{2,4-Dinitroimidazole} \quad \text{2,4-Dinitroimidazole} \\
251a & \quad \text{2,4-Dinitroimidazole} \quad \text{2,4-Dinitroimidazole}
\end{align*}
\]

Figure 95

\[
\begin{align*}
\text{Scheme 5:} & \quad \text{2-Imidazolinone} \rightarrow \text{2-Imidazolinone} \\
256 & \quad \text{RX} \\
257 & \quad \text{K}_2\text{CO}_3/\text{TEACl}
\end{align*}
\]
\[
\text{258} \quad \text{N} \quad \text{NH} \\
\quad \text{Ph} \quad \text{PTC} \quad \text{N} \quad \text{Ph} \\
\quad \text{ClCHF}_2 \quad \text{CHF}_2
\]

\text{Figure 96}

\[
\begin{align*}
\text{N} & \quad \text{NH} \\
\quad & \quad \text{R} \\
\text{260} & \quad \text{TBAB, K}_2\text{CO}_3, \text{CH}_3\text{CN} \\
\quad & \quad \text{R} \\
\end{align*} \\
\begin{align*}
\text{N} & \quad \text{NH} \\
\quad & \quad \text{R} \\
\text{261} & \quad \text{N} \quad \text{-(CH}_2)_n\text{CH}_3
\end{align*}
\]

\text{Figure 97}

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{N} \\
\quad & \quad \text{H}_3\text{C} \quad \text{O} \quad \text{N} \\
\text{263} & \quad \text{PhCH}_2\text{Cl} \\
\quad & \quad \text{PhCH}_2\text{Cl} \\
\end{align*} \\
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{N} \\
\quad & \quad \text{H}_3\text{C} \quad \text{O} \quad \text{N} \\
\text{264a} & \quad \text{Ph} \\
\quad & \quad \text{Ph} \\
\text{264b} & \quad \text{Ph}
\end{align*}
\]

\text{Figure 98}

\[
\begin{align*}
\text{N} & \quad \text{H} \\
\quad & \quad \text{N} \\
\text{265} & \quad \text{RX} \\
\quad & \quad \text{RX}
\end{align*} \\
\begin{align*}
\text{N} & \quad \text{H} \\
\quad & \quad \text{N} \\
\text{267} & \quad \text{RX} \\
\quad & \quad \text{RX}
\end{align*}
\]

\text{Figure 99}
methyl iodide or benzyl chloride, respectively, in a satisfactory yield [86] (Figure 93).

Different imidazole compounds such as 2-methylimidazole 252a and 2-methyl-4-nitro imidazole 252b were reacted with different alkyl bromides 253 in an alkaline media, at reflux temperature and in the presence of tetraethylammonium iodide (TEAI) or TBAB as PTC and afforded 1-alkyl imidazole derivatives 254 which exhibited a variety of valuable pharmacological properties [87] (Figure 94).

N-Alkyl-2-acetylbenzimidazoles 257 have been obtained in over 90% yield by alkylating 2-acetylbenzimidazole 256 using the PTC mixture of (CH$_3$CN/K$_2$CO$_3$/TEBACl) at room temperature [88] (Figure 95).

2-Phenylbenzimidazole 258 was alkylated with chlorodifluromethane under liquid-liquid condition (CH$_2$Cl$_2$/aq. NaOH/BzTEACl) to give 1-difluoromethyl-2-phenylbenzimidazole 259 [75] (Figure 96).

The N-alkylated imidazole derivatives 262 were achieved by treating compounds 260 with different alkyl bromide under PTC condition (TBAB/K$_2$CO$_3$/CH$_3$CN) [89] (Figure 97).

Competitive N versus O benzylation of 5,5-dimethyl-3-isoxazolidinone 263 using (CH$_2$Cl$_2$/NaOH) using different PTC catalysts was studied. The ratio of N-/O-alkylations 264a/264b was 2/3 for most cases of catalysts [90] (Figure 98).

Alkylation of 1,2,4-triazole 265 and benzotriazole 267 has been performed either in basic media under solvent free PTC conditions or in absence of base by conventional and microwave heating. Several parameters affecting the selectivity have been studied [91]. Arylation of 1H-1,2,3-benzotriazole 267 with activated aryl halides in a medium of aromatic hydrocarbons under PTC condition using inorganic bases and acetyltrimethylammonium bromide as a phase transfer catalyst was studied. Both N(1)- and N(2)-arylated products 269a and 269b, respectively, have been isolated. Their ratio has depended on the nature of the employed base and the reactivity of arylating agent [92] (Figure 99).
Pyrazole, imidazole, 1, 2, 4-triazole, indazole, benzotriazole

Treatment of benzotriazole 267 with chlorodifluoromethane under liquid-liquid conditions (CH$_2$Cl$_2$/aq. NaOH/BzTEACl) has afforded 1-(difluoromethyl)-1H-benzotriazole 270 [74] (Figure 100).

Reaction of 4-substituted-1,2,3-triazole 271 with alkyl bromide 272 under basic condition using PTC Bu$_4$NBr produced N-substituted 1,2,3-triazole derivatives 273a–c [93] (Figure 101).

The alkylation of 5-benzyl-1H-tetrazole 274 under liquid-liquid technique such as (CH$_2$Cl$_2$/aq. NaOH/BzTEACl) gave a mixture of 5-benzyl-1-difluoromethyl-1,2,3,5-tetrazole 275a in 23% and 4-benzyl-1-difluoromethyl-1,2,3,5-tetrazole 275b in 15% [74] (Figure 102).

A series of 5-alkythio-1-aryltetrazoles 277 were prepared by alkylation reaction of the corresponding 1-aryltetrazole-5-thiols 276 with alkyl bromides under solid-liquid PTC technique [94], whereas without solvent and also under PTC technique several N-p-nitrophenylazoles 279–288 were synthesized by direct arylation of the corresponding azolo compound 278 with p-fluoronitrobenzene [95], while the alkylation reaction of 1-aryltetrazol-5-ones 289 with dibromoalkanes under both liquid-liquid and solid-liquid PTC
Figure 105

![Chemical Reaction](image1)

**Figure 105**

Figure 106

![Chemical Reaction](image2)

**Figure 106**

Figure 107

![Chemical Reaction](image3)

**Figure 107**

Figure 108

![Chemical Reaction](image4)

**Figure 108**

Figure 109

![Chemical Reaction](image5)

**Figure 109**

310 311

HO-Furanc-2-oH + Br(CH2)12Br → Furanc-2-o-(CH2)12-S-CH2-Br

312 313

X(CH2)2X

314

n = 1, 4, 5; X = Br

O

315

Figure II0

Chrolyl O-CH2-CH2-OH + CH3Cl/T.B.A.B. → Chrolyl O-CH2-CH2-OH

316 317

Benzyl bromide/NaOH

Figure III

Ph \( \text{N} \) \( \text{N} \) O

318

Ph \( \text{N} \) \( \text{N} \) O

319a, b

\( \text{Br}(\text{CH2})2\text{Br} \)

PTC

Figure II2

Ar\( ^- \)

322

Ar\( ^- \)

320

RX → R-Ar^- + \( \text{BrCH2CH2Br} \)

321a–h

R = Me, Et, CH3CHO, CH2CO2Et, CH(CO2Et)2, COMe, CO2Et, p-NO2-C6H4-N = N

Figure II3
systems provided a convenient route to prepare bis-tetrazolon derivatives 290 and 4-bromoalkyl derivatives 291 [96] (Figure 103).

N-Acetylated adenosine 292 was alkylated with benzyl bromide, methyl iodide, or allyl bromide in the presence of tetrabutylammonium bromide as a PTC catalyst in CH₂Cl₂/NaOH to give the corresponding N-alkyl-6-N-acetyl adenosines 293a, b [97] (Figure 104).

N-alkylation reaction of adenine 294 took place with different alkyl halides under the phase transfer conditions using microwave irradiation assistance [98] (Figure 105).

5-Aryloxymethyl-2-[(2-chlorophenyl)oxyacetylamido]-1,3,4-thiadiazoles 280 are synthesized from reaction of 2-chlorophenoxycetacetyl chloride 297 with 5-aryloxymethyl-2-amino-1,3,4-thiadiazoles 296 under liquid-liquid condition using PEG-400 as a catalyst [99] (Figure 106).

N-Alkylation of 3-phenyl-2-thiohydantoin-5-arylidene derivative 299 has been carried out by using monohalocompounds such as allyl bromide as an alkylating agent. The reaction was proceeded through nucleophilic displacement under PTC conditions of solid-liquid phases such as a mixture of anhydrous potassium carbonate, dioxane, and TBAB as a heterogeneous catalyst. The corresponding alkylated product 300 was obtained in a good yield [42] (Figure 107).

Alkylation reaction of pyrazoles 301–303 with 2-chloroethylamine under the condition of phase-transfer catalysis was carried out in a liquid-solid system using benzene as an organic solvent and BTEAC as a catalyst. Reaction between equimolar amounts of reactants led to poor yields (20–40%) of the alkylated products 304–306 due to concurrent dehydrochlorination of 2-chloroethylamine. The yield was considerably decreased in going from pyrazole (301) to 3,5 dimethylpyrazole (303) whereas the maximal yield of alkylated products (70–80%) was obtained by using one of the following ratios: pyrazole:NaOH:2-chloroethylamine 1:2:2, 3-(5)methylpyrazole:NaOH:2 chloroethylamine 1:3:3, or 3,5-dimethylpyrazole:NaOH:2-chloroethylamine 1:5:5 [100] (Figure 108).

In the N-alkylation reaction of pyrazole, 3-(5)-methylpyrazole, and 3,5-dimethylpyrazole 301–303 with dichloroethane (DCE), the dehydrochlorination of the obtained 1-(β-chloroethyl)pyrazoles has been carried out to give the corresponding products N-vinylpyrazoles 307–309 (Figure 9) in low yield. Attempts to carry out the reaction under standard conditions (water/benzene/NaOH/TEBAC) did not lead to the desired result. The yield of all products was sharply increased when benzene was replaced with an excess of dichloroethane. The reaction investigation showed that the ease of alkylation depends strongly on the basicity of the pyrazole. The introduction of an electron-donating substituent (e.g., Me) into the molecule of pyrazole 301 increases the electron density at the “pyrazole” nitrogen atoms. As a result, deprotonation was hindered and the base was consumed in elimination of dichloroethane. It must also be mentioned that a 5- to 7-folds excess of dichloroethane was necessary to obtain optimal yields on alkylation of compounds 301–303 [101] (Figure 109).

5.1.2. O-Alkylation or Acylation. 2,5-Didodecyloxymethylfuran 311 was obtained via alkylation of 2,5-dihydroxym-
\[
\text{Figure I16}
\]
\[
\text{Figure I17}
\]
\[
\text{Figure I18}
\]
\[
\text{Figure I19}
\]
\[
\text{Figure I20}
\]
Figure 121

Ar^− + F-Ph-SO₂Cl → Ar^− 340

NΗ 339 N + SO 2ClF 341

Figure 122

F=O-O 344 + NLO CH₃ 345 PTC 346

Figure 123

N≡NH + Cl=O 347

Cl 348 N≡N 349

Figure 124

H 350 + Cl-PO₂-S-sec-Bu 351 352

Figure 125

O-Br 353 O-CH₂ 354
ethylfuran 310 with dodecyl bromide without solvent using (KOH/aliquat) as a catalyst, while alkylation of furfuryl alcohol 312 with 1,12-dibromododecane under the same PTC conditions produced the corresponding furanic diether 313 [102] (Figure 110).

Similarly, 2-furfuryl alcohol 312 was subjected to react with alkyl dihalides 314 using (benzene/KOH/polyethylene glycol (PEG-400)) to yield the corresponding difuranyl diethers 315 [102] (Figure 110).

4-(benzyloxy)-2-[1(2E)-but-2-en-1-yl oxy]-5-methoxytetrahydrofuran-3-ol 317 was obtained from benzylation of 2-O-methyl-5-O-crotyl-α,β-D-ribofuranoside 316 using benzyl bromide in aq. solution of NaOH/CH₂Cl₂ and TBAB as a catalyst [103] (Figure 111).

5.1.3. S-Alkylation. PTC alkylation of arylidene derivative 318 using dihalocompounds such as ethylene dibromide or 1,3-dibromopropane afforded the thioalkylated dimers 319a, b, respectively, via s-alkylation pathway followed by dimerization reaction [42] (Figure 112).

5.1.4. C-Alkylation. Reaction of 2-thiono-N(m-tolyl)thiazolidin-4-one 320 with methyl bromide, ethyl bromide, chloroacetaldehyde, ethyl chloroacetate, diethyl malonate, acetyl chloride, ethyl chloroformate, or p-nitrobenzenediazonium tetrafluoroborate under solid-liquid system and using the heterogeneous mixture of (dioxan/K₂CO₃/TBAB) as a PTC yielded the corresponding 5-substituted thiazolidin-4-ones 321a–h and yielded the corresponding spiro thiazolidin-4-one derivatives 322 when reacted with 1,2-dibromoethane under the same PTC condition [104] (Figure 113).

4-Benzyl-2-phenyl-2-oxazoline-4-carboxylic acid tert-butyl ester 324 was prepared via the alkylation of 2-phenyl-2-oxazoline-4-carboxylic acid tert-butyl ester 323 with benzyl
\[
\begin{align*}
&\text{384} \xrightarrow{\text{ArCHO, PTC}} \text{385} \\
&\text{Ar} = \text{Ph, } p\text{-MeO-C}_6\text{H}_4\text{.} \\
&\text{2'-Thienyl-; 2'-turyl-}
\end{align*}
\]
bromide using (toluene/KOH(s)/Cinchona alkaloids) as a PTC [105] (Figure 114).

2-Thioxo-3,5,7-trisubstituted-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-4(1H)-ones 327 have been prepared via phase transfer ribosylation of 2-thioxo-3,5,7-trisubstituted pyrido[2,3-d]pyrimidin-4(1H)-ones 325 with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide 326 in biphasic solvents such as CH₂Cl₂/50% aq. NaOH using TBAB as a catalyst [106] (Figure 115).

In the presence of dioxane as a solvent under PTC conditions, one-pot reaction of 3-phenyl-2-thiohydantoin 91 with CS₂ and halocompounds such as ethyl bromide or benzyl chloride afforded 5-[bis(ethylsulfanyl)methylidene]-2-(ethylsulfanyl)-3-phenyl-3,5-dihydro-4H-imidazol-4-one 328a and 5-[bis(benzylsulfanyl)methylidene]-2-(benzylsulfanyl)-3-phenyl-3,5-dihydro-4H-imidazol-4-one 328b, respectively [42] (Figure 116).

Acylation of imidazolones 318 using chloroacetyl chloride under PTC conditions yielded the corresponding acylated aryldened derivative 329 [42] (Figure 117).

5.1.5. Miscellaneous Alkylation. 5-Bromorhodanine derivative 330 was effectively used as an alkylating agent for some mono- or dianionic moieties containing S, N, or O under
solid-liquid phase transfer catalysis conditions. Thus, with 4-hydroxy-2-mercaptopyrimidine, where possible S, N, or O sites are available, the reaction afforded the S-substituted product. With 2-aminobenzothiazole or piperazine, the reaction yielded the corresponding N-substituted 331a, b or the disubstituted products 332 [104] (Figure 118).

In a plan to study C- versus O-alkylation of the pyrazoline derivatives, 3-methyl-1-phenyl-2-pyrazolin-5-one 333 was treated under PTC condition with different bromoorganic compounds such as benzyl bromide, 1,3-dibromopropane, methyl bromoacetate, bromoacetaldheyde, or diethylacetal as alkyllating agents either in the absence or the presence of carbon disulphide and afforded numerous of C- or O-alkylated derivatives 334a-e, 335a-e [107] (Figure 119).

Reaction of 6-hydroxy-3,4-dihydroquinoline 337 and 1-cyclohexyl-5-(4-bromo-butyl)-1,2,3,4-tetrazole 336 in a heterogeneous mixture of toluene/H2O, K2CO3 and TBACl as a catalyst gave 6-[4-(1-cyclohexyl-1,2,3,4-tetrazol-5-yl)-butoxy]-3,4-dihydrocarbostyril 338 in 99% purity [108] (Figure 120).

5.2. Sulphonylation. 4,5-Dihydro-3,5-diaryl-1-(4-fluorophenylsulphonyl)pyrazoles 341 and 2-aryl-1-(4-fluorophenylsulphonyl)indoles 343 were prepared from reaction of 4-fluorophenylsulphonyl chloride 339 with the appropriate 4,5-dihydro-3,5-diarylpyrazoles 340 or 2-arylindoles 342, via solid-liquid phase (THF/KOH/TBAB) [107] (Figure 121).

N-Sulphonylation product 346 was prepared through treating 2-chloro-6,6-difluoro-1,3-dioxolano[4,5-f]benzimidazole 344 with 3,5-dimethylsulfoxol-4-sulphonyl chloride 345 via PTC protocol (toluene/aq. K2CO3/TBAB) [109] (Figure 122).

5.3. N-Carbonylation. Carbonyldimidazol 349 was prepared in 87% yield via reaction of imidazol 347 with phosgene 348 under PTC condition (chlorobenzene/NaOH/ tributylhexadecylphosphonium bromide (TBHDPB)) [110] (Figure 123).

5.4. N-Phosphorylation. Reaction of 1,3-thiazolidin-2-one 350 with S-sec-Bu-O-Et chlorophosphorothiolate 351 in the presence of NaOH and N-dodecyl-N-methylethiophosphinimium bromide gave s-sec-Bu O-Et(2-oxo-3-thiazolidinyl) phosphothiolate 352 in 84% yield [111] (Figure 124).

5.5. Elimination Reactions. β-Elimination of bromomethyl cyclic ketyl acetals 353 was carried out under solid-liquid phase (THF/BuOK/Aliquat 336) to prepare the corresponding cyclic ketene acetals 354 [112] (Figure 125).

Reaction of 6-chloro-2-chloromethyl-3-nitroimidazo [1,2-b]pyridazine 355 with 3 equivalents of nitroalkane anion derivative 356 under liquid-liquid PTC protocol (CH2Cl2/H2O/TBAB(OH)) gave 3-nitroimidazo[1,2-b]pyridazines 357 bearing trisubstituted ethylenic double bond derivatives in a good yield [113] (Figure 126).

Vinylolation of indole 358 with ClCH2CH2Br was achieved under PTC condition (toluene/KOH/18-crown-6) and afforded the corresponding N-vinyl derivative 359. Similarly, under the same reaction conditions N,S-divinyl derivatives 362 and 363 were prepared from 3-mercaptopyridine 360 and 2-mercaptopbenzimidazole 361, respectively [109] (Figure 127).

5.6. Condensation Reactions. Arylidene-thiazolidin-4-ones 385 were synthesized from condensation reaction of 2-thiino-N-(m-tolyl)thiazolidin-4-one 384 with aromatic or heteroaldehydes under solid-liquid PTC technique [104] (Figure 128).

5.7. Addition Reactions. Reaction of 2-thiino-N-(m-tolyl) thiazolidin-4-one 386 with formaldehyde or some arylidenemalononitriles via PTC technique (dioxane/K2CO3/TBAB) afforded the corresponding 5-hydroxymethyl derivative 387 or Michael type adduct 388, respectively. While the addition reaction of cyanoacetamide to 5-(p-methoxybenzylidine)-2-thiino-N-(m-tolyl)thiazolidine 4-one 389 followed by condensation reaction under the same technique gave 7-anisyl-6-cyano-2-thiino-3-(m-tolyl)thiazolo [4,5-b]pyridin-5-one 390 [104] (Figure 129).

5.8. Ring Expansion. Treatment of 5-alkyl(aryl)-3H-pyrr- roline-2-ones 391 with dichlorocarbene using (CHCl3/NaOH/BTEAB) at 20–30°C afforded the intermediates 1-alkyl-6,6-dichloro-2-azabicyclo[3.1.0]hexan-3-ones which directly rearranged and dehydrochlorinated to give 6-alkyl(aryl)-1-phenyl-5-oxohydropyridin-2-ones 392 [110] (Figure 130).

Also, ring transformation of indole derivatives 393 has been induced by dichlorocarbene (aq. KOH/TBABSO4H) to produce 3-haloquinoline 394 in a good yield. Also, under similar conditions, reaction of 3-formyl-2-(3-chloro-4-fluorophenyl)indole 395 with dichlorocarbene gave 3-chloro-[2,2-dichloro-3-oxiranyl]-2-(3′-chloro-4′-fluoro)quinoline 396. The evolved HCl gas has been eliminated during the reaction [III] (Figure 131).

5.9. Ring Opening. Treatment of benzosultams 400 with different disulphides under PTC technique (CH3CN/K2CO3/TBAHSO4) gave the corresponding 2-methylamino-benzaldehyde dithioacetals 401 [24] (Figure 132).

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>PTC</td>
<td>Phase transfer catalysis</td>
</tr>
<tr>
<td>TEBACl</td>
<td>Triethylbenzylammonium chloride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>BTEACL</td>
<td>Benzyltriethylammonium chloride</td>
</tr>
<tr>
<td>TBACl</td>
<td>Tetrabenzylammonium chloride</td>
</tr>
<tr>
<td>TBAHSO4</td>
<td>Tetrabutylammonium hydrogen sulphate</td>
</tr>
<tr>
<td>CTTPCl</td>
<td>Crotlytriethylphosphonium chloride</td>
</tr>
<tr>
<td>TBAHS</td>
<td>Tetrabutylammonium hydrogen sulphate</td>
</tr>
<tr>
<td>t-BuPz</td>
<td>Tert-butyl pyrazole</td>
</tr>
<tr>
<td>IPrPz</td>
<td>Isopropylpyrazole</td>
</tr>
</tbody>
</table>
TEAI: Tetraethylammonium iodide
PEG: Polyethylene glycol
DCE: Dichloroethane
TBHDPB: Tributylhexadecylphosphonium bromide
TBA(OH): Tetrabutylammonium hydroxide
BTEAB: Benzyltriethylammonium bromide.

Conflict of Interests
The authors declare that they have no conflict of interests.

References


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