Review Article

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

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Phase transfer catalysts (PTCs) have been widely used for the synthesis of organic compounds particularly in both liquid-liquid and solid-liquid heterogeneous reaction mixtures. They are known to accelerate reaction rates by facilitating formation of interphase transfer of species and making reactions between reagents in two immiscible phases possible. Application of PTC instead of traditional technologies for industrial processes of organic synthesis provides substantial benefits for the environment. On the basis of numerous reports it is evident that phase-transfer catalysis is the most efficient way for generation and reactions of many active intermediates. In this review we report various uses of PTC in syntheses and reactions of five-membered heterocycles compounds and their multifused rings.

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 catalyses 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

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

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

SCHEME 1

(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_2CO_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-1*H*-pyrrole-3-carbonitriles **6** was achieved by reaction of *N*-aryl-2-chloroacetamide **4** and malononitrile **5** under solid-liquid PTC condition ($CH_3CN/K_2CO_3/18$ -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_2CO_3 /(TBAB). Replacing of ethyl ethoxymethylenecyanoacetate **8b** with **8a** gave ethyl[3-amino-4-ethoxy-carbonyl-1-phenyl-5-thioxo-2,5-dihydro-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 ethoxymethylenecyanoacetate **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_3CN/K_2CO_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-bis(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 chloroacetonitrile or chloroacetamide using the PTC of (DMF/ K_2CO_3 /TBAB) [22] (Figure 10).

Different thiophene compounds (**24** and **28–30**) prepared from reaction of diethyl cyanomalonate **23** with carbon

FIGURE 8

FIGURE 9

FIGURE 10

FIGURE 11

FIGURE 12

disulphide or phenyl isothiocyanate **7** along with different active halocompounds under solid-liquid phase condition (dioxan/ K_2CO_3 /TBAB) have been reported by Abd Allah and El-Sayed [22] (Figure 12).

2-Thiophenyldienes **31–33** were obtained through the reaction of either malononitrile **5** or ethyl cyanoacetate **11** with carbon disulphide along with ethoxymethylenemalononitrile **8a** or ethyl ethoxymethylenecyanoacetate **8b** using liquid-solid technique (dioxan/ K_2CO_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 solely 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 dihydrothiophene 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_2CO_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-diacetyl 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-isoindol-2-yl)ethyl]-3-oxobutanoate **50** using PTC-promoted Japp-Klingemann

FIGURE 13

FIGURE 14

FIGURE 15

FIGURE 16

FIGURE 17

FIGURE 18

FIGURE 19

FIGURE 20

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;

FIGURE 21

FIGURE 22

FIGURE 23

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. (4*Z*)-4-(4-amino-1,3-dithiol-2-ylidene)-5-methyl-2-phenyl-2,4-dihydro-3*H*-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

FIGURE 24

FIGURE 25

FIGURE 26

FIGURE 27

FIGURE 28

FIGURE 29

FIGURE 30

FIGURE 31

FIGURE 32

FIGURE 33

(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-cyanothieno[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(2*H*)-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 nitrilimines **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*-tolylsulphonylmethyl isocyanide **71** with aldehydes **72** R₁CH=NR₂ or **73** (R₁, R₂ =

substituted phenyl, heteroaryl, and alkyl) under liquid-liquid condition [35, 36] (Figure 30).

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/BTEACl) afforded 4,6-dimethyl-5-[2-(2-methylprop-1-enyl)-1*H*-benzimidazol-1-yl]pyrimidinyl-(5*H*)-thiones **78** [37] (Figure 31).

Reaction of 5-phenylmethylenethiohydantoin **79** with 1,2-dibromoethane **80** under liquid-liquid conditions (benzene/aq. NaOH/TBAB) afforded 2,3-dihydro-6-phenylmethylen-5-oxo-imidazo[2,3-*b*]thiazole **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(3*H*)-one **88** and dihalocompounds such as 1,2-dibromoethane and chloroacetyl chloride underwent S- and

FIGURE 34

FIGURE 35

FIGURE 36

FIGURE 37

FIGURE 38

FIGURE 39

FIGURE 40

FIGURE 41

FIGURE 42

FIGURE 43

FIGURE 44

FIGURE 45

FIGURE 46

FIGURE 47

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 dihalocompounds, namely, ethylene dibromide or 1,3-dibromopropane, with CS₂, 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 K₂CO₃ 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 thiohydantoin **98** with methylene bromide gave 3-(1H)-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-arylthiotetrazoles **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**, CS₂, and α-halocarbethoxy or α-halonitrile electrophiles in 1:1:2 molar ratios using (benzene/K₂CO₃/TBAB) as a PTC condition [23] (Figure 42).

Another different thienothiophene **109** was synthesized via the reaction of acetylacetone **108** with CS₂ 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/K₂CO₃/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 CS₂ and chloroacetonitrile 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 CS₂ along with chloroacetonitrile or ethyl chloroacetate

FIGURE 48

FIGURE 49

under the same conditions to give the corresponding thioxo-thienopyrazolone derivatives **112** [25] (Figure 46).

Reaction of 4-hydroxydithiocoumarin **113** with allyl bromide **114** under liquid-liquid technique ($\text{CH}_2\text{Cl}_2/\text{aq. NaOH/TBAB}$ or TBACl) gave 2-methyl-2,3-dihydro-4*H*-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/ $\text{K}_2\text{CO}_3/\text{TBAB}$), 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,

FIGURE 50

FIGURE 51

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, chloroacetonitrile, 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_2CO_3 /TBAB), 2-ylidenemalononitrile and ethyl 2-ylidenecyanoacetate of both 2,3-dihydrobenzothiazole **127** and 2,3-dihydrobenzoxazole **128** were allowed to react with chloroacetonitrile, 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-2*H*-benzimidazol-2-ylidene)propanenitrile malononitrile **131a** or ethyl 3-amino-2-(1,3-dihydro-2*H*-benzimidazol-2-ylidene)propanoate **131b** were treated under the same PTC conditions, where the corresponding pyrrolo[2,3-b]pyrrolo[1,2-f]benzoimidazoles **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_2CO_3 /TBAB) afforded the corresponding bis-pyrrolo(1,8)naphthyridine derivative **134** [49] (Figure 52).

FIGURE 52

FIGURE 53

FIGURE 54

FIGURE 55

FIGURE 56

FIGURE 57

FIGURE 58

FIGURE 59

FIGURE 60

FIGURE 61

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/K₂CO₃/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 CS₂ along with chloroacetonitrile, ethyl chloroacetate, or phenacyl bromide in 1:1:1 and 1:1:2 molar ratios using [dioxan/K₂CO₃/TBAB] as a PTC gave the corresponding thienopyrazoles **139–143**, **145** and respectively, **144**, **146** and **147**, fused thiazines [52] (Figure 54).

Thieno(3,4-b)pyrrole derivative **148** was obtained by reacting ethyl thiophene-2-ylidenecyanoacetate derivative **31b** with phenacyl bromide in a heterogeneous mixture of (dioxan/K₂CO₃/TBAB) as a PTC [19] (Figure 55).

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

2,6-Dibenzoyl-5-methyl-3-(substituted styryl)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. K₂CO₃/TBAHSO₄) [53] (Figure 57).

Similarly, 2,6-dibenzoyl-3,5-distyrylbenzo[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, dibenzoylbenzodifurans **156** were obtained from the reaction of substituted resorcinols **155** with phenacyl bromide [55] (Figure 59).

Moreover, 2,6-diaroyl/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-3*H*-(1,5)benzodiazepin-2-one **160** with chloroacetonitrile under solid-liquid condition (dioxan/K₂CO₃/TBAB) [57] (Figure 62).

By reaction of 4-methyl-1,3-dihydro-2*H*-1-benzazepin-2-one **162** with chloroacetonitrile or phenacyl bromide under the solid-liquid phase transfer catalyst (dioxan/K₂CO₃/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)dithiolo [4,5-b:4',5'-e]-4,8-benzoquinone **166** was achieved in one-pot reaction under solid-liquid technique (benzene/K₂CO₃/TBAB) starting from acetylacetone, CS₂ 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-pyrazolinediones **167** with S,S-acetal derivatives using solid-liquid technique (dioxan/K₂CO₃/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 **169** as a dianionic compound containing N and S poles with some di- and tetrahaloderivatives **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 CS₂ or PhNCS along with 3-methyl-1-phenyl-2-pyrazoline-5-one **63** or 2-iminothiazolidin-4-one **173** (dioxan/K₂CO₃/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

FIGURE 63

FIGURE 64

FIGURE 65

FIGURE 66

FIGURE 67

FIGURE 68

FIGURE 69

FIGURE 70

FIGURE 71

technique (dioxan/ K_2CO_3 /TBAB) gave the corresponding oxazolo-(1,5)benzodiazepin derivative **177** [57] (Figure 68).

When 7-(methoxyimino)-4-methyl-2*H*-chromene-2,8-(7*H*)-dione **178** was treated with crotyltriphenylphosphonium chloride (CTPPCl) **179** (CH_2Cl_2 /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(6*H*)-thione **182** [33] (Figure 70).

4. Synthesis of Spiro Five-Membered Ring Heterocycles

Synthesis of spirorhodanine 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 CS_2 and some active methylene compounds under solid-liquid condition (dioxan/ K_2CO_3 /TBAB) [63] (Figure 71).

Reaction of 4-ethoxymethylene-1-phenyl-3,5-pyrazolidinedione **188** with CS_2 and malononitrile **5** or ethyl cyanoacetate **11** using solid-liquid technique (dioxan/ K_2CO_3 /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/ K_2CO_3 /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 $\text{I} < \text{Br} < \text{Cl} < \text{OTs}$ (Figure 74).

N-alkyl pyrroliden-2,5-diones **200** [66, 67] were synthesized via reaction of pyrroliden-2,5-diones with different alkylating reagents under phase transfer catalysis condition (toluene/ K_2CO_3 /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**.

FIGURE 72

FIGURE 73

FIGURE 74

FIGURE 75

FIGURE 76

FIGURE 77

FIGURE 78

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/CH₃Ph₃Br) [70] (Figure 78).

Synthesis of a series of N-alkylpyrrolidino[59]fullerenes was achieved via the combination of PTC without solvent and microwave irradiation technique. Thus, 2-phenylpyrrolidinofullerene **209** was treated with benzyl, *p*-nitrobenzyl, *p*-methoxy-carbonylbenzyl, *n*-octyl, or allyl bromides in microwave oven in presence of K₂CO₃ and TBAB to yield the corresponding N-alkylpyrrolidino[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

FIGURE 79

FIGURE 80

FIGURE 81

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 $(\text{CH}_3)_2\text{CO}_3$ in a mixture of $[\text{DMF}/\text{TBAB}/\text{K}_2\text{CO}_3]$ 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 chlorodifluoromethane under liquid-liquid technique ($\text{CH}_2\text{Cl}_2/\text{aq. NaOH}/\text{BzTEACl}$) 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/

FIGURE 82

FIGURE 83

FIGURE 84

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 [$\text{CH}_2(3\text{-t-BuPz})_2$] **231**. However, the reaction of 3-isopropylpyrazole **232** with dibromomethane under the same condition yielded three isomers, namely, bis(5-isopropylpyrazol-1-yl)methane [$\text{CH}_2(5\text{-isoPrPz})_2$] **233**, (3-isopropylpyrazol-1-yl-5'-isopropylpyrazol-1'-yl)methane [$\text{CH}_2(3\text{-iPrPz}-5'\text{-isoPrPz})_2$] **234**, and bis(3-isopropylpyrazol-1-yl) methane [$\text{CH}_2(3\text{-iPrPz})_2$] **235** [78] (Figure 86).

N-Substituted-3,5-diarylpyrazolines **237** and **238** were prepared via liquid-liquid system in (CHCl_3 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).

FIGURE 85

FIGURE 86

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–C₁₄)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

FIGURE 92

FIGURE 93

FIGURE 94

FIGURE 95

FIGURE 96

FIGURE 97

FIGURE 98

FIGURE 99

FIGURE 100

FIGURE 101

FIGURE 102

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-nitroimidazole **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 ($\text{CH}_3\text{CN}/\text{K}_2\text{CO}_3/\text{TEBACl}$) at room temperature [88] (Figure 95).

2-Phenylbenzimidazole **258** was alkylated with chlorodifluoromethane under liquid-liquid condition ($\text{CH}_2\text{Cl}_2/\text{aq. NaOH}/\text{BzTEACl}$) 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

261 under PTC condition ($\text{TBAB}/\text{K}_2\text{CO}_3/\text{CH}_3\text{CN}$) [89] (Figure 97).

Competitive N versus O benzylation of 5,5-dimethyl-3-isoxazolidinone **263** using ($\text{CH}_2\text{Cl}_2/\text{NaOH}$) 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

FIGURE 103

FIGURE 104

Treatment of benzotriazole **267** with chlorodifluoromethane under liquid-liquid conditions ($CH_2Cl_2/aq. NaOH/BzTEACl$) has afforded 1-(difluoromethyl)-1*H*-benzotriazole **270** [74] (Figure 100).

Reaction of 4-substituted-1,2,3-triazole **271** with alkyl bromide **272** under basic condition using PTC Bu_4NBr produced *N*-substituted 1,2,3-triazole derivatives **273a–c** [93] (Figure 101).

The alkylation of 5-benzyl-1*H*-tetrazole **274** under liquid-liquid technique such as ($CH_2Cl_2/aq. NaOH/BzTEACl$) 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-alkylthio-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

FIGURE 106

FIGURE 107

301, 304 R = R' = H; 302, 305 R = CH₃, R' = H; (a), R' = CH₃, R = H; (b) 303, 306 R = R' = CH₃

FIGURE 108

301, 304, 307 R = R₁ = H; 302, 305, 308 R = H, R₁ = Me, R = Me, R₁ = H; 303, 306, 309. R, R₁ = Me

FIGURE 109

FIGURE 110

FIGURE 111

FIGURE 112

$R = \text{Me, Et, CH}_2\text{CHO, CH}_2\text{CO}_2\text{Et, CH(CO}_2\text{Et)}_2,$
 $\text{COMe, CO}_2\text{Et, } p\text{-NO}_2\text{-C}_6\text{H}_4\text{-N} = \text{N}$

FIGURE 113

FIGURE 114

FIGURE 115

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 $\text{CH}_2\text{Cl}_2/\text{NaOH}$ 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)oxyacetyl-amido]-1,3,4-thiadiazoles **280** are synthesized from reaction of 2-chlorophenyl oxyacetyl 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-Didodecyloxymethyl-furan **311** was obtained via alkylation of 2,5-dihydroxym-

FIGURE 116

FIGURE 117

FIGURE 118

FIGURE 119

FIGURE 120

FIGURE 121

FIGURE 122

FIGURE 123

FIGURE 124

FIGURE 125

FIGURE 126

FIGURE 127

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 difurfuryl diethers **315** [102] (Figure 110).

4-(benzyloxy)-2-[(2*E*)-but-2-en-1-yloxy]-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

FIGURE 128

FIGURE 129

FIGURE 130

FIGURE 131

FIGURE 132

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 CH_2Cl_2 /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 CS_2 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 arylidene 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, bromoacetaldehyde, or diethylacetal as alkylating 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) butoxyl]-3,4-dihydrocarbostyryl **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-dioxolo[4,5-f]benzimidazole **344** with 3,5-dimethylisoxazole-4-sulphonyl chloride **345** via PTC protocol (toluene/aq. K₂CO₃/TBAB) [109] (Figure 122).

5.3. N-Carbonylation. Carbonyldiimidazole **349** was prepared in 87% yield via reaction of imidazole **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-methylephedrinium 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/Bu^tOK/Aliaquat **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/TBA(OH)) gave 3-nitroimidazo[1,2-b]pyridazines **357** bearing trisubstituted ethylenic double bond derivatives in a good yield [113] (Figure 126).

Vinylation 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-mercaptoindole **360** and 2-mercaptobenzimidazole **361**, respectively [109] (Figure 127).

5.6. Condensation Reactions. Arylidenethiazolidin-4-ones **385** were synthesized from condensation reaction of 2-thiono-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-thioxo-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*-methoxybenzylidene)-2-thioxo-N-(*m*-tolyl)thiazolidin-4-one **389** followed by condensation reaction under the same technique gave 7-anisyl-6-cyano-2-thioxo-3-(*m*-tolyl)thiazolo [4,5-*b*]pyridin-5-one **390** [104] (Figure 129).

5.8. Ring Expansion. Treatment of 5-alkyl(aryl)-3*H*-pyrrolin-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-4-[2,2-dichloro-3-oxiranyl]-2-(3'-chloro-4'-fluorophenyl)quinoline **396**. The evolved HCl gas has been eliminated during the reaction [111] (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

PTC:	Phase transfer catalysis
TEBACl:	Triethylbenzylammonium chloride
THF:	Tetrahydrofuran
TBAB:	Tetrabutylammonium bromide
DMF:	Dimethylformamide
RT:	Room temperature
DMSO:	Dimethyl sulfoxide
BTEACl:	Benzyltriethylammonium chloride
TBACl:	Tetrabutylammonium chloride
TBAHSO ₄ :	Tetrabutylammonium hydrogen sulphate
CTPPCl:	Crotyltriphenylphosphonium chloride
TBAHS:	Tetrabutylammonium hydrogen sulphate
<i>t</i> -BuPz:	Tert-butyl pyrazole
IPrPz:	Isopropylpyrazole

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.

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