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Polyphosphoric Acid in Organic Synthesis

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Abstract

Polyphosphoric acid (PPA), a powerful dehydrating agent, has been widely used to perform several important organic reactions and thus has played an important role in the synthesis of organic compounds and natural products. The present micro review describes briefly the use of PPA (i) in the cyclization of acids on the aromatic ring (ii) in acetylation and isopropylation on the aromatic ring, (iii)hydrolysis of esters, (iv) cleavage of epoxides and (v) synthesis of heterocyclic compounds.

Keywords: polyphosphoric acid (PPA), cyclization, acylation, isopropylation, heterocyclic compounds

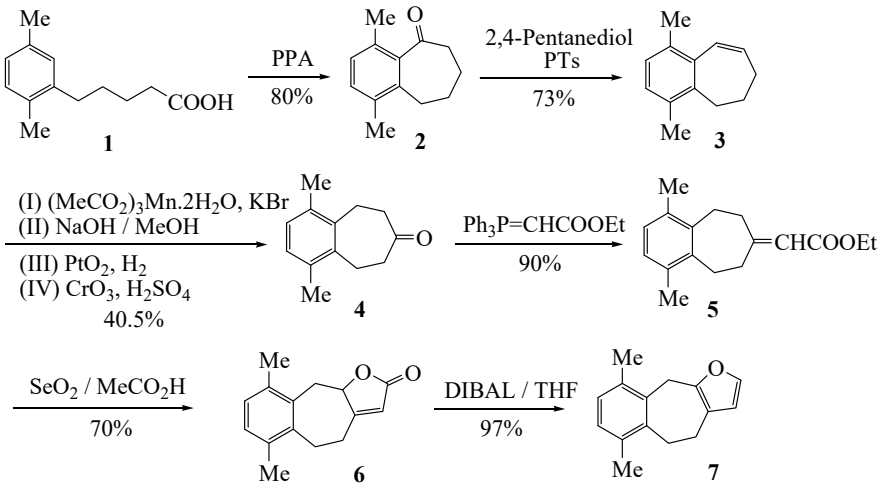
1. Introduction

The commercially available PPA is hygroscopic, highly viscous, clear, colorless, or light amber liquid. The acid is neither soluble nor reacts with nonpolar organic solvents such as toluene or hexane. PPA is prepared by mixing phosphoric acid (85% , d 1.7 g mL-1) with phosphorous pentoxide (P_2O_5) followed by heating at 200 ^oC for 30 min. Due to high viscosity PPA is difficult to pour and stir at room temperature but is much easier to work with a temperature above 60 ^oC. The addition of solvents, such as xylene, simplifies the difficult workup usually associated with PPA. Ice is normally used during the work-up to moderate the exothermic reaction that occurs with water. The commercially available PPA contains 82-85 % P_2O_5. The powerful dehydrating properties, low nucleophilicity and moderate acidity explain the reasons for the wide applications of PPA in organic synthesis.

2. Cyclization of Acids

Several acids on the aromatic ring have been cyclized with PPA to obtain cyclic ketones and some of these ketones have been utilized for the synthesis of natural products. Some examples are given below.

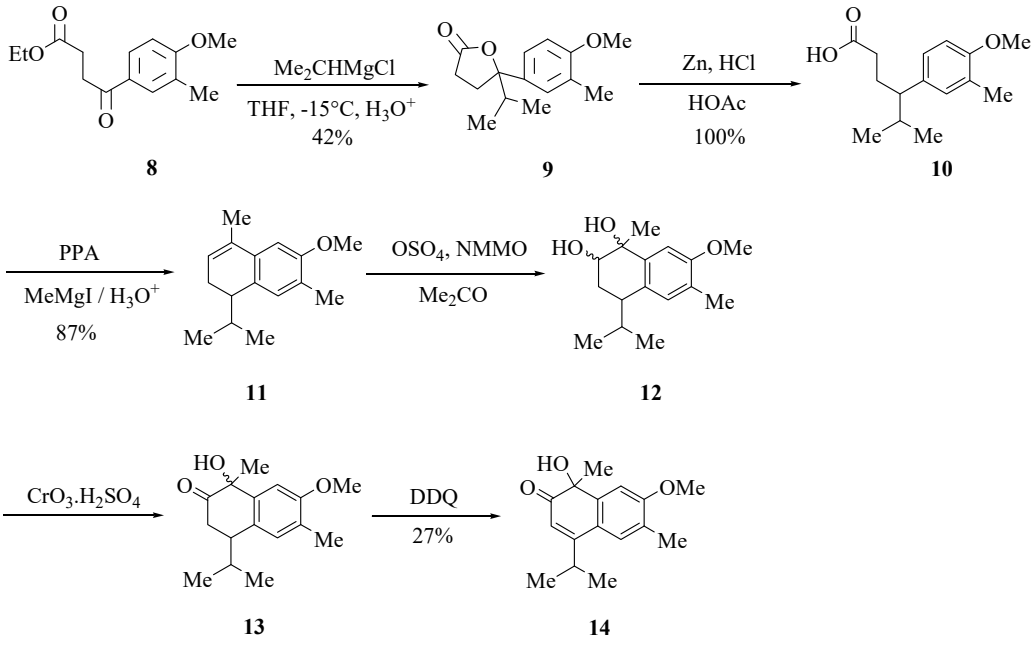
The acid **1** in **Scheme 1**, obtained by Friedel-Crafts alkylation of *p*-xylene with 5-chlorovaleric acid in presence of aluminum chloride, on cyclization with PPA yields the cyclic ketone **2** (Banerjee *etal*. 2002) which on heating with 2,4-pentanediol and *p*-toluenesulfonic acid (Vuligonda *eta*l.1996) yields the alkene **3.** The transformation of the alkene **3** to the reported benzsuberone **4** (Ho & Lin, 1999) is achieved in four steps respectively: acetylation [manganese (III) acetate dihydrate], alkaline hydrolysis (NaOH, MeOH), catalytic hydrogenation (H_2, PtO_2) and oxidation with Jones reagent (Bowers *etal*., 1953).The Wittig reaction of **4** with ethoxy carbonyl methylenetriphenylphosphorene in the presence of a catalytic quantity of benzoic acid in toluene gives the ester **5**. The ester is not obtained in good yield with cinnamic acid.



Scheme 1. Synthesis of tavacpallescenicine by cyclization of aromatic acid 1

Oxidative cyclization of the ester **5** with selenium dioxide in acetic acid furnishes butenolide **6** whose transformation to tavacpallescencine **7** has already been accomplished by heating with DIBAL in THF (Ho & Lin, 1999).

PPA cyclization of the acid has also been used for the synthesis of sesquiterpene lacinilene C methyl ether **14** (McCormick *etal*., 1978). The synthetic route is depicted in **Scheme 2**.



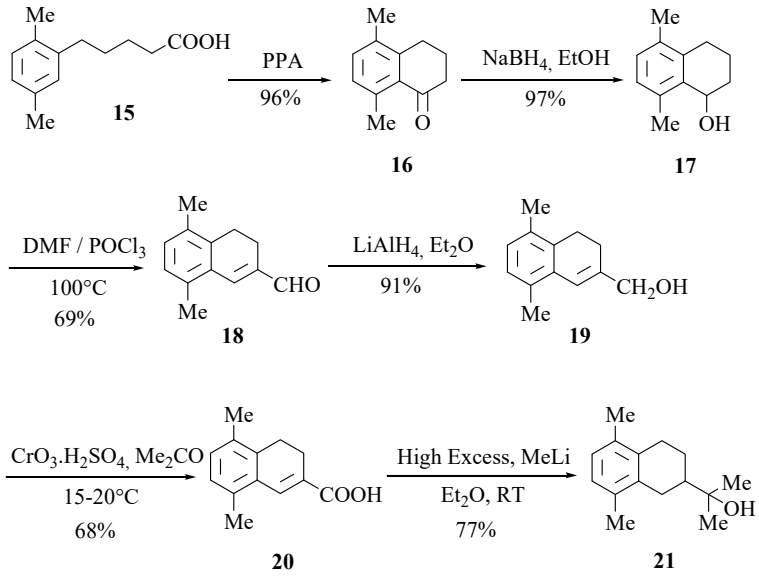
Scheme 2. Synthesis of sesquiterpene lacinilene C methyl ether

Alkylation of the ketoester **8** with isopropylmagnesium chloride in THF at -15°C affords pure lactone **9** whose conversion to the acid **10** is achieved by reduction with zinc and acetic acid.

The transformation of the acid **10** to dihydronaphthalene **11** is accomplished in two steps: (i) cyclization with PPA and (ii) treatment of the resulting tetralone with methylmagnesium iodide. Oxidation of **11** with OsO_4/NMMO.H_2O in acetone gives a mixture of diols **12** (Cocker & Sainsbury, 1965) which is oxidized (Bowers etal., 1953) to yield a mixture of ketone **13** and lacinilene C methyl ether **14**. Treatment of the mixture with dicyanodichlorobenzquinone (DDQ) provides the natural product **14** in 27% yield.

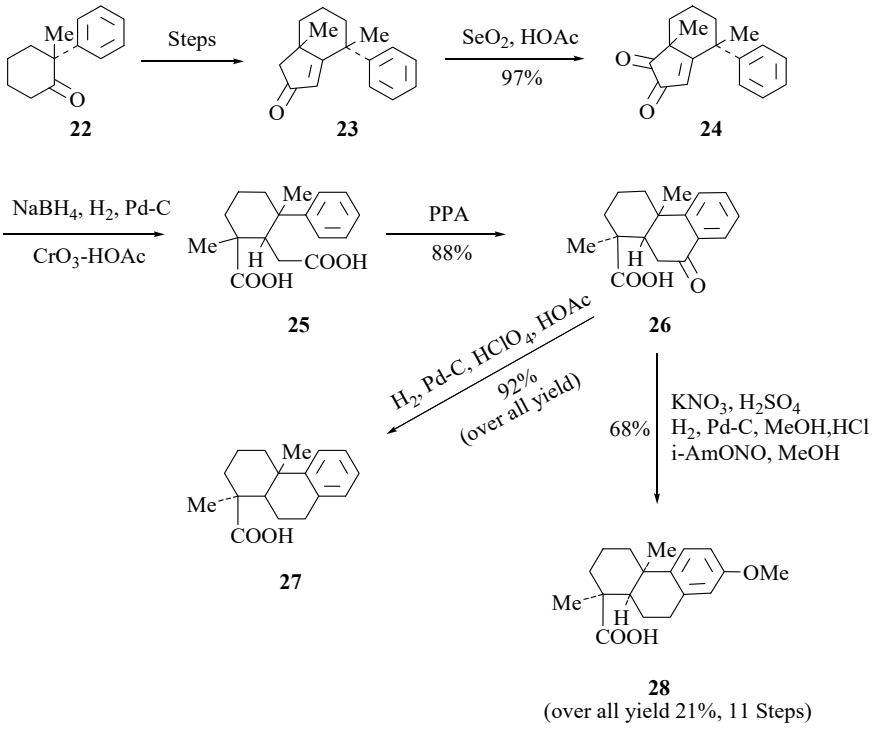
The PPA cyclization has been utilized in the development of a two-step synthesis of 1,2,3,4-tetrahydro-5,8-dimethyl-1-tetralone **16** in high yield (Banerje*e etal.,*2004) whose transformation to sesquiterpene occidol **21** (Mane & Kadam, 1998) has been accomplished without any difficulty and the synthetic route is presented in **Scheme 3**.

Friedel-Crafts alkylation of xylene with chlorobutyric yields acid **15**which on cyclization with PPA affords the tetralone **16** in high yield. An alternative approach of the tetralone **16** has also been published (Mane & Kadam, 1998) but the yield is not high compared with the published procedure (Banerjee *etal*,.2004).The alcohol**17**, obtained by the metal hydride reduction of tetralone**16**, is converted to the aldehyde**18**by Vilsmeier-Hack reagent (Smith, 1954). Metal hydride reduction produces the alcohol **19** which on oxidation with Jones reagent (Bowers *etal.,* 1953) furnishes the acid **20** whose conversion to occidol **21** is achieved in one step by reaction with an excess of methyllithium.



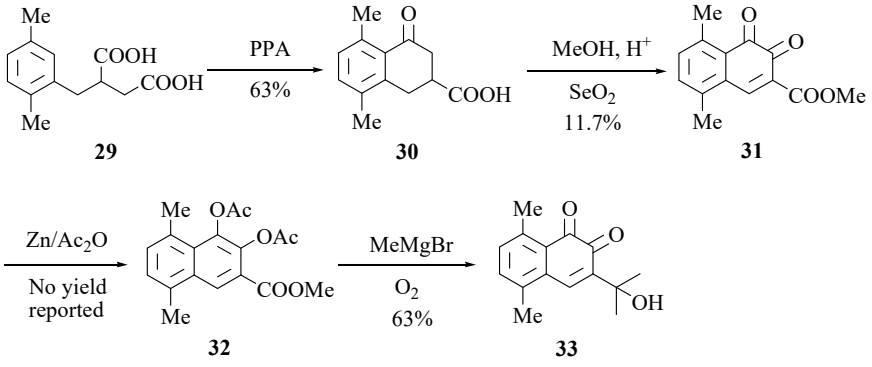
Scheme 3. Synthesis of occidol **21**

PPA cyclization of acid has been sought (Giarruso & Ireland, 1968) to achieve the synthesis of (±)-desoxypodocarpic acid **27** and (±)13-methoxydesoxypodocarpic acid **28**. The synthetic route is depicted in **Scheme 4**. The hydrindenone **23**, prepared from 2-methyl-2-phenylcyclohexanone **22**,on oxidation with selenium dioxide yields dione **24** which is convertedto acid **25** in three steps (reduction, hydrogenation, oxidation respectively). The cyclization of the acid **25** with PPA yields 7-keto-desoxy- podocarpic acid **26** which on hydrogenolyis yield desoxypodocarpic acid **27**. Nitration of **26** followed by hydrogenation and addition of isoamyl nitrate affords 13-methoxydesoxypodocarpic acid **28**.



Scheme 4. Synthesis of (±)-Desoxypodocarpic acid 27 and (±)-13-Methoxydesoxypodocarpic acid 28

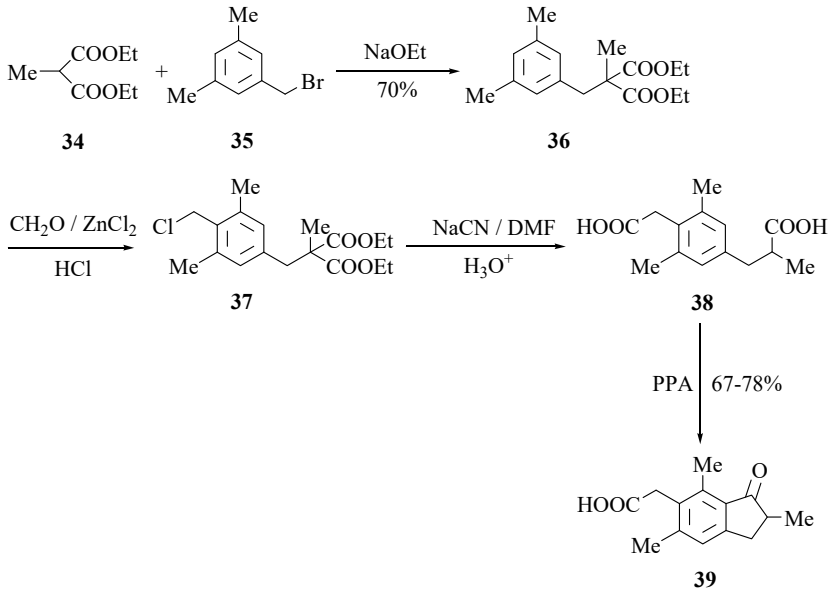
The use of PPA for the cyclization of acids has also been recorded during synthesis of bicarbocyclic sesquiterpene (±)-Emmotin-H **33** (Reddy & Krishna Rao, 1979) as has been described in **Scheme 5**. The cyclization of the acid **29** with PPA affords ketone **30** in 63% yield. Esterification followed by oxidation with selenium dioxide give the O-quinone **31** which is reduced and acetylated respectively to obtainthe diacetate **32**. No yield is reported of this compound. Treatment of the diacetate with excess methylmagnesium bromide followed by air oxidation leads the formation of Emmotin-H **33**.



Scheme 5. Synthesis of Emmotin H

The use of PPA cyclization can be observed in the synthesis (Nambudiry & Krishna Rao, 1974) of Pterosin E, a nor-sesquiterpene isolated by Yoshihara and others (Yoshihara *etal*., 1971). The synthetic route is exhibited in **Scheme 6**.

Alkylation of diethylmethylmalonate **34** with 3,5-dimethylbenzyl bromide **35** affords **36** which on chloromethylation yields **37**. The crude product is converted to the diacid **38** by hydrolysis with sodium cyanide in dimethylformamide. The cyclization of the acid **38** with polyphosphoric acid (PPA) leads the formation of sesquiterpene Pterosin E **39**. It is worthwhile to go through the published works (Mason, 2008, Mason etal., 2008, Edwards etal., 2007, Dodd, 2001, Dodd, 1999, Popp & McEwen, 1958) for more examples.

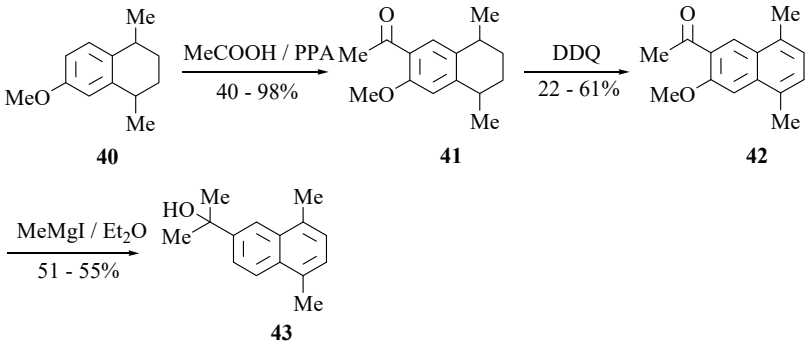


Scheme 6. Alkylation of diethylmethylmalonate **34** with 3,5-dimethylbenzyl bromide **35**

We believe that the cyclization of the above mentioned acids can also be attempted with other acids like sulfuric acid. (Banerjee & Cabrera, 2010).

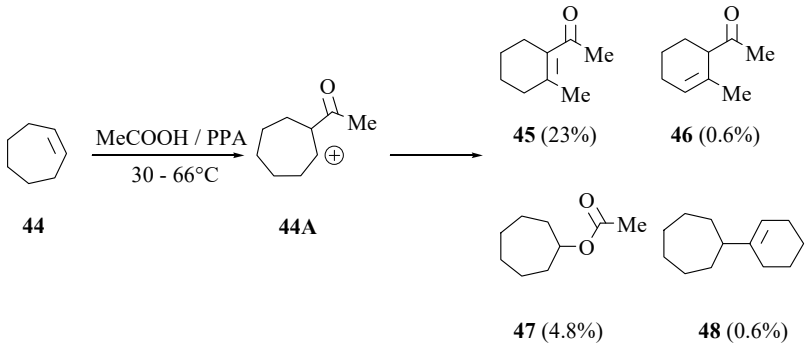
3. Acylation and Isopropylation on Aromatic Ring with PPA

Acylation reaction is one of the most important reactions which has been frequently used for the synthesis of organic compounds. Several intermolecular acylation reactions carried out with PPA have been reported (Popp & McEwen, 1958; Snyder & Werber, 1950). Acylation of 1,4-dimethyl-6-methoxytetralin **40** (Bachute & Mane, 1991) with acetic acid and PPA leads the formation of 7-acetyl-6-methoxy-1,4-dimethyltetralin **41**. Dehydrogenation with DDQ furnishes the naphthalene **42** which is converted to the sesquiterpene Emmotin-G methyl ether **43** (**Scheme7**) with the Grignard reagent.



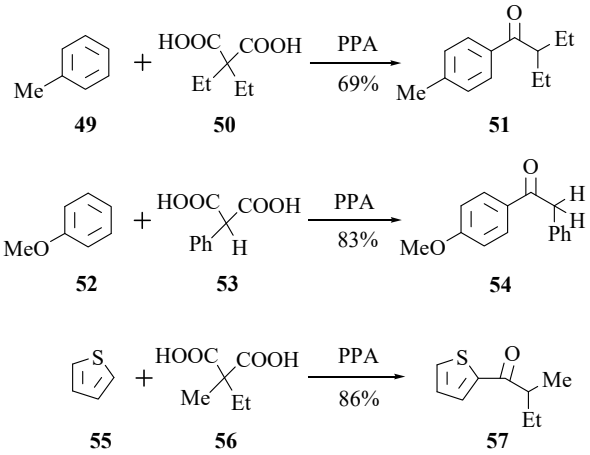
Scheme 7. Synthesis of the sesquiterpene emmotin-G methyl ether 43

The acylation of cycloheptene **44** with acetic acid (Rand & Dollinski, 1966) and PPA produces a mixture of acetylated **45** (23%), **46** (0.6%), ester **47** (4.8%) and the hydrocarbon (0.6%) respectively as shown in **Scheme 8**. The formations of these products can be explained by assuming the generation of the carbocation **44A** which undergoes several intramolecular transformations leading the formation of products **45**, **46**, **47** and **48**.



Scheme 8. Acylation of cycloheptene 44 with acetic acid and PPA

The Friedel-Crafts acylation (Renault *etal*., 1999) ofaromatic compounds for example, toluene **49** with diethylmalonic acid in presence of PPA produces the acylated product **5**1. Similar acylation of anisole **52** and thiophene **55** with phenylmalonic acid **53** and methylethylmalonic acid **56** respectively with polyphosphoric acid (84% minimum) provides the acylated products **54** and **57** respectively (**Scheme 9**).



Scheme 9. Friedel-Crafts acylation

In the phenyl substituent series, the rings carrying an electron-donating group (methyl, methoxy) afford the acylated product at *p*-position in very good yield (82-92%). The absence of *o*-product may be explained as a steric effect of the electrophilic agent. The selective acylation occurs at the α-position of thiophene, 2-bromo-thiophene, thiophene-2-carboxylic acid, and furan whereas pyrrole gives only degradation products and N-phenylprole affords only 5% of the acylated product. The acylation reaction fails if H_3PO_4 or P_2O_5 is used instead of polyphosphoric acid. No acylation occurs with malonic acid ester derivatives and cyanoacetic acid. The acylation reaction under this condition also fails with other diacids such as succinic, glutaric, and adipic acids.

The isopropylation of ketone has been achieved with isopropanol in presence of PPA (Wollinsky *etal.,* 1972). The tricyclic ketone **58** on isopropylation with isopropyl alcohol and PPA furnishes a mixture of the ketones **59** and **60**in 75% yield. Wolff-Kishner reduction of the ketone **59** followed by demethylation with HBr produce ferruginol **61**. (yield not specified). The ketone **60** on demethylation and aerialoxidatin respectively affords xanthoperol **62** (yield not reported**)** which is characterized as its acetate (**Scheme 10**).

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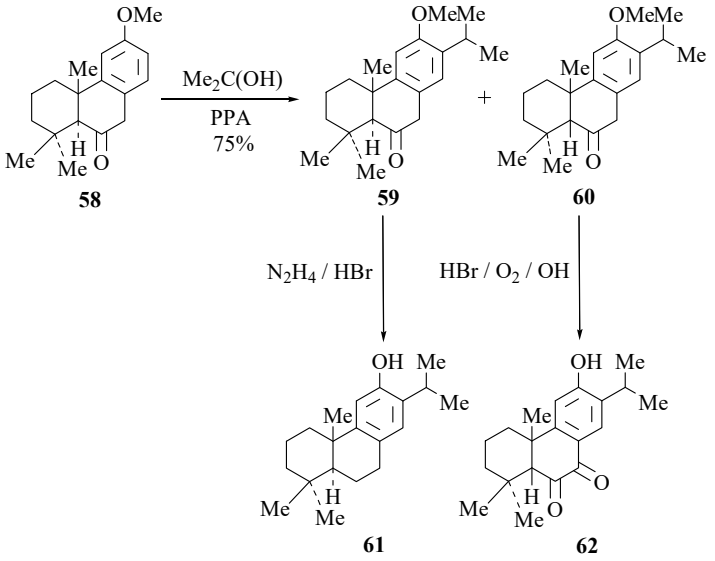
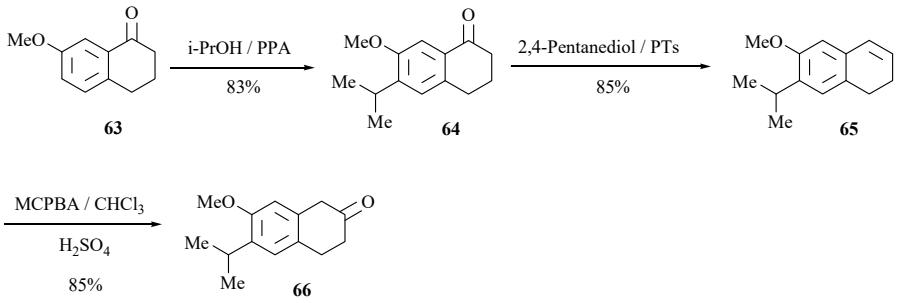


Scheme 10. Isopropylation of ketone 40 with isopropanol

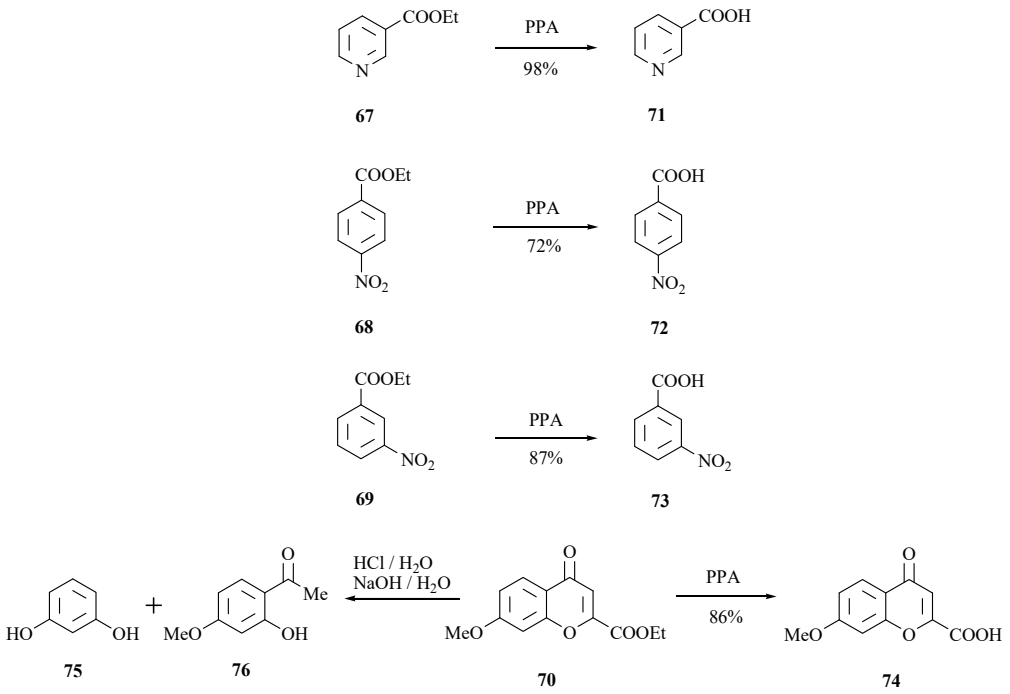
PPA in isopropanol has been utilized for the isopropylation of 7-methoxy-1-tetralone **63** (Cabrera etal., 2014) .The resulting tetralone **64** (**Scheme 11**) obtained in 85% yield, is converted to the tetraline **65** by heating with 2,4-pentanediol and a catalytic amount of *p*-toluenesulfonic acid. Epoxidation of **65** followed by heating with sulfuric acid affords the tetralone **66**. The tetralones **64** and **66** are the potential intermediates for the diterpenes miltirone and carnosic acid respectively.



Scheme 11. Isopropylation of ketone 63 with isopropanol

4. Hydrolysis of Esters into Acids

PPA has been used for the hydrolysis of esters (**67**-**70**) into the acids (**71**-**74**) respectively (**Scheme12) (**He etal., 2002). The use of PPA is particularly useful for the hydrolysis of chromone ester **70** to prevent the formation of the products **75** and **76**.

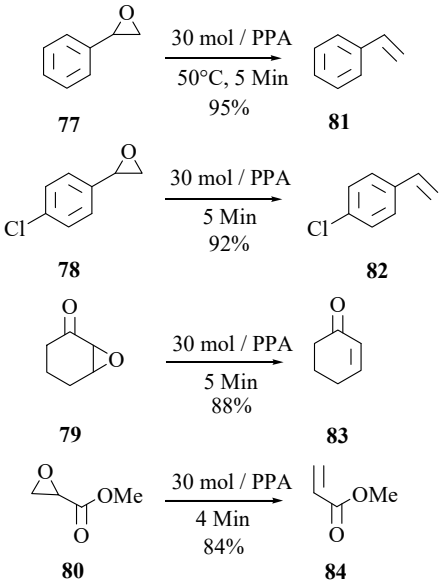


Scheme 12. Hydrolysis of esters into acids

It is worthwhile to mention that exist many reagents that can be utilized for the hydrolysis of esters into acids in mild condition. The use of PPA for the hydrolysis of esters into acid is hardly observed.

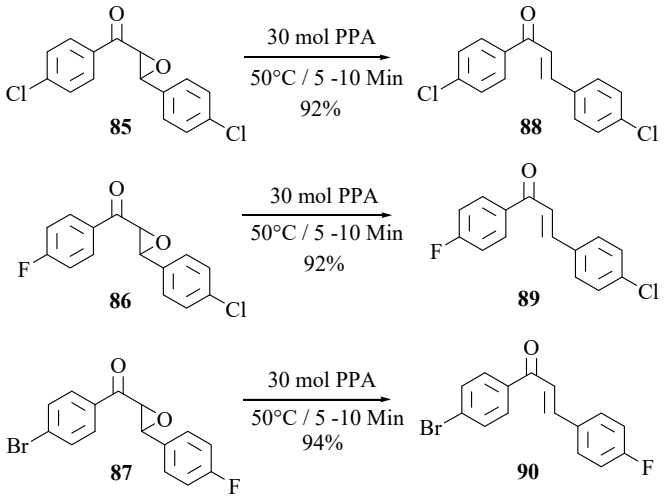
5. Cleavage of Aliphatic and Aromatic Epoxides

PPA in 30mol % is used as promoter for the cleavage of aliphatic and aromatic epoxides to alkenes in excellent yield under neat condition (Pathe & Ahmed, 2015) at 50°C. The present method has several advantages such as use of inexpensive reagent, acquisition of the desired product in high yield and the formation of stereoselective product in short reaction time under ecofriendly reaction conditions. The yield of the alkene gets reduced if the solvent is used to perform the reaction. The following epoxides (**77-80**) have been cleaved to olefins (**81-84)**in high yield (**Scheme 13**) by the present method.

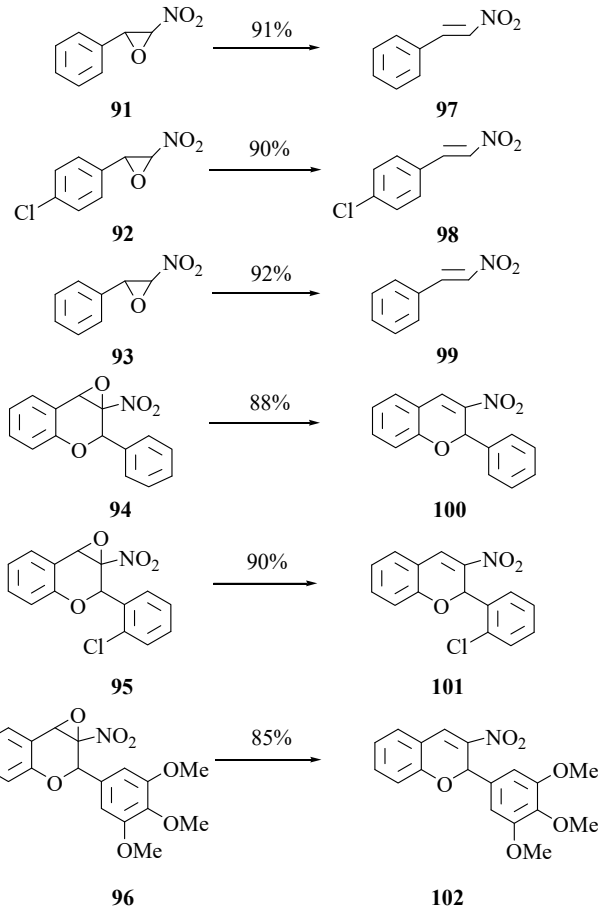


Scheme 13. Cleavage of aliphatic and aromatic epoxides

The above mentioned procedure has also been utilized for the cleavage of several chalcones epoxides to obtain chalcones. The method has proved useful for the transformation of the following chalcones epoxides, e.g. **85-87** to chalcones **88-90** respectively in excellent yield. (**Scheme 14**) Several nitrostyrene oxides, e.g **91-93** and nitrochromeepoxides e.g. **94-96** suffer cleavage to alkenes **97-102** respectively when heated with PPA at 15°C under neat condition (**Scheme 15).**



Scheme 14. Cleavage of several chalcones epoxides to obtain chalcones



Scheme 15. Deoxygenation of various nitrostyrene epoxides, and nitrochromene epoxides chalcones

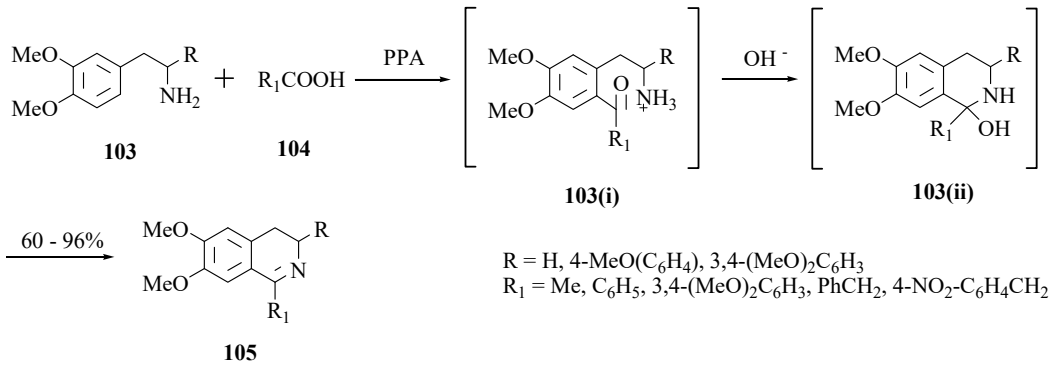
Besides PPA, other acids like sulfuric acid has been used frequently to perform the cleavage of epoxides to obtain olefine (Banerjee etal., 2022).

6. Synthesis of Heterocyclic Compounds with PPA

6(i). Synthesis of isoquinoline and xylopinine

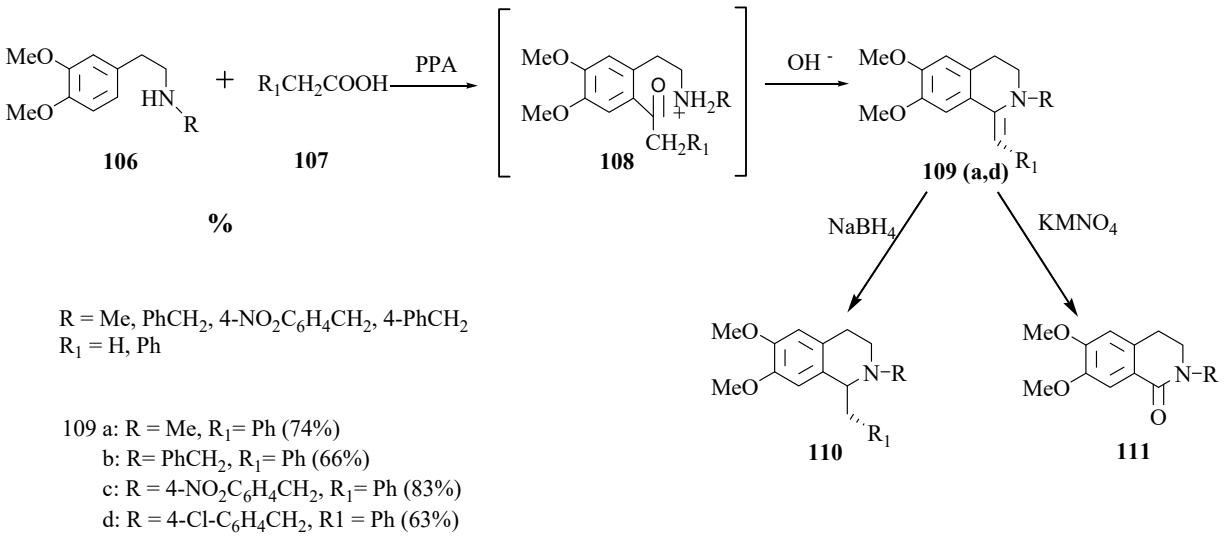
The use of PPA has been observed during the synthesis of heterocyclic compounds. The Bischler-Napieralski (BN) reaction is one of the most effective methods (Whaley & Govindachari, 1951) for the preparation of 3,4-dihydroisoquinoline derivative and in the synthesis of a variety of isoquinoline derivatives and analogs of pharmacological interest. Venkov and Ivanov (Venkov& Ivanov, 1996) have reported a new method for the synthesis of a variety of isoquinolines which involves the reactions of carboxylic acids or their anhydrides and esters with a variety of amines such as homoveratryamine, 1, 2-diphenylethylamines, N-acyl-2-phenylethylamines in non-aqueous acidic media as polyphosphoric acid (PPA). The reaction with anhydrides proceeds faster than the corresponding carboxylic acids or their ester. It has been observed that the homoveratrylamine **103** reacts with the acid **104** in PPA to yield the isoquinoline **105**.

The reaction probably proceeds first with acylation of the activated aromatic ring of the ammonium salt of **103** to **103(i)** and then occurs spontaneous cyclization between the carbonyl group and the amine group to form the isoquinoline **105** via the intermediate **103(ii)** (**Scheme 16**).



Scheme16. Preparation of isoquinoline by the Bischler-Napieralski (BN) reaction in presence of PPA

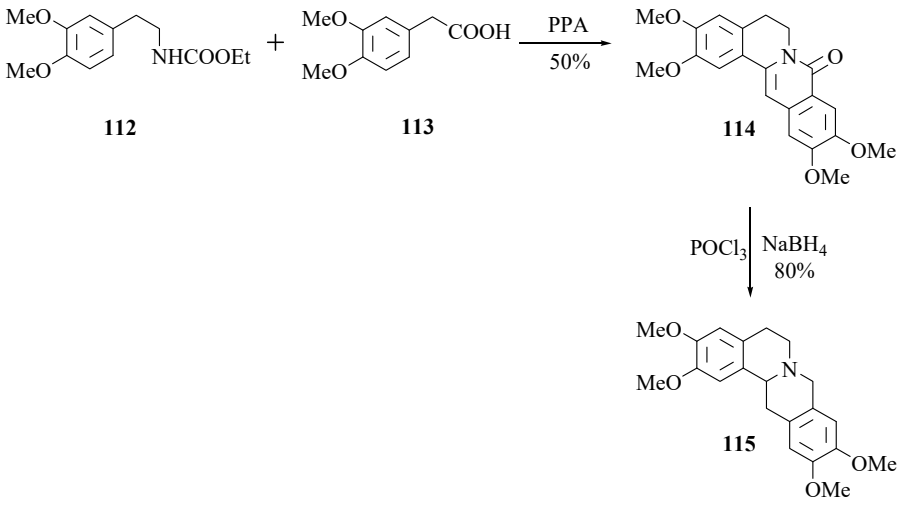
The acylation of the aromatic ring of homoveratrylamine **106** with carboxylic acid **107** in PPA leads to the formation of enamines of isoquinoline **109** (a-d) via the adduct **108** (**Scheme 17**). The ^{1}H NMR spectra clearly shows that **109** is obtained as a mixture of E and Z isomers. Reduction with $NaBH_4$ in MeOH affords the corresponding tetrahydroisoquinolines **110**(unspecific yield) while the oxidation with $KMnO_4$ in $CHCl_3$ in the presence of 18-crown-6 gives dihydroisoquinolones **111**(unreprted yield).



Scheme17. Acylation of the aromatic ring of homoveratrylamine 106 with carboxylic acid 107

These results have provided a convenient procedure for the synthesis of isoquioline enamides as important intermediates in alkaloid synthesis. This method has been applied for the synthesis of the alkaloid xylopinine **115** in two steps (**Scheme 18**). The amine **112** is made to react with homoveratric acid **113** in PPA at 80^{o}C for 5 h to obtain 2,3,10,11-tetramethoxy-

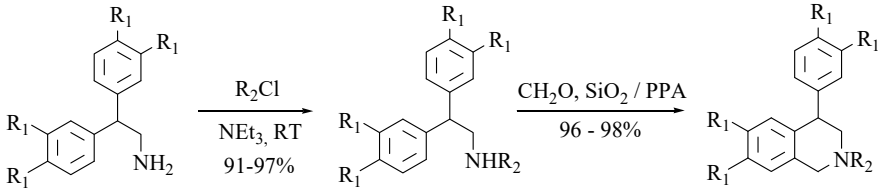
8-oxoprotoberberine **114** which on treatment with $POCl_3$ followed by reduction with $NaBH_4$ in methanol affords the alkaloid xylopinine (2,3,10,11-tetramethoxyberberine) **115**.



112 **113** **114** **115**

Scheme 18. Synthesis of the alkaloid xylopinine 115

PPA suffers from several drawbacks. As 10 to 50 fold excess of acid is generally employed, it is difficult to pour and stir at room temperature, it is necessary to neutralize the reaction mixture very before the product extraction. PPA/SiO_2 has been used as an efficient heterogeneous catalyst for many organic transformations. Recently it has been shown (Manolov *etal*.,2013) the use of silica-supported polyphosphoric acid in the synthesis of tetrahydroisoquinoline derivatives as depicted in **Scheme 19**. The amine **116**, obtained from the aminoacetaldehyde dimethylacetal and 1,2-dimethoxybenzene, on acetylation with acid chlorides or sulfochlorides affords the amides **117** which on cyclization with PPA/SiO_2 yield substituted isoquinolines **118**. The catalyst is recovered quantitativelywithout significant loss of activity The .cyclization is also obtained with MeCOOH:CF_3COOH (4:1) but the yields are lower, and the reaction times are larger. The catalyst is recovered quantitatively without significant loss of activity.

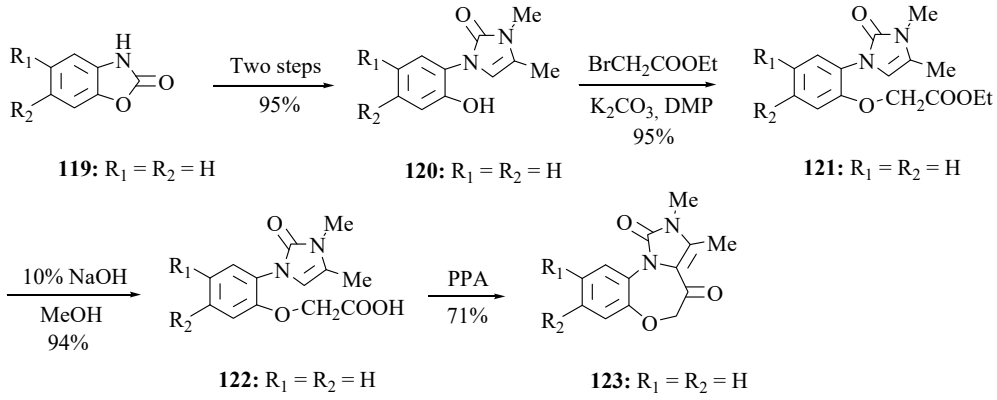


116 **117** **118**

R_1 = OMe; R_2 = COMe, SO_2Me, COPhPh

Scheme 19. Synthesis of tetrahydroisoquinoline

PPA has been utilized for the construction of a new tricyclic ring system containing 1,5-benzooxazepine fused with an imidazolone ring (Stainisheva *etal.,* 2017). The synthetic details are given below (**Scheme 20**). The transformation of benzoxazolone derivative **119** to the imidazolone derivative **120** is achieved two steps (alkylation with chloroacetate and treatment with methylamine in *n*-propanol). Alkylation of **120** with ethylbromoacetate affords **121** which on alkaline hydrolysis yields acid **122** in quantitative yield. The intramolecular cyclization of **122** with PPA furnishes oxazepinedione **123**. Many oxazepinediones have been prepared by changing the substituents eg: R_2 = Cl, R_1=Cl, N-Bz etc.



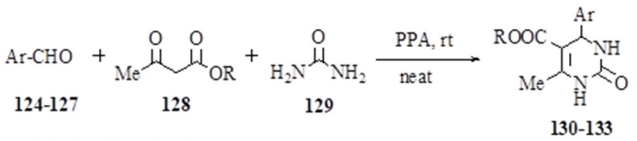
119: $R_1 = R_2 = H$ **120:** $R_1 = R_2 = H$ **121:** $R_1 = R_2 = H$

122: $R_1 = R_2 = H$ **123:** $R_1 = R_2 = H$

Scheme20. The intramolecular cyclization of 122 to obtain the oxazepinedione 123

6 (ii). One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones

Polyphosphoric acid as a catalyst has proved useful for a one-pot synthesis (Zhao *etal.,*2015) of 3,4-dihydropyrimidin-2(1H)-one (DHPMS) **130-133** in good yield by grinding a mixture of aromatic aldehydes **124-127**, ethylacetoacetate **128** (R= Et, Me) and urea **129** under solvent-free condition (**Scheme 21**). The reactions are carried out at room temperature. Many DHPMS have been prepared by using different aldehydes. **Scheme 21** shows the synthesis of some DHPMS by using different aldehydes and different esters. Many important procedures are known for the synthesis of DHPMs(Whaley & Govindachari, 1951). The present method is a simple, time saving, and high yielding process. It has been observed that the different moles ratio of the substrate have some effect on the reaction system. When the mole ratio of aldehyde, β-ketoester, and urea is 1:1:1.5 the yield of DHPMs is highest. The influence of the amount of catalyst on the reaction yield has also been studied. The presence of 0.1 mmol of PPA as a reaction mediator per mmol of reactions provides a higher yield; a higher amount of PPA does not improve the result to a great extent. DHPMS and their derivatives exhibit a wide range of therapeutical and pharmacological properties such as calcium channel blockers, anti-tumor, anti-bacterial and anti-inflammatory behavior (Yang *el a*l., 2021; Yang*etal.*, 2020).



124-127 **128** **129** **130-133**

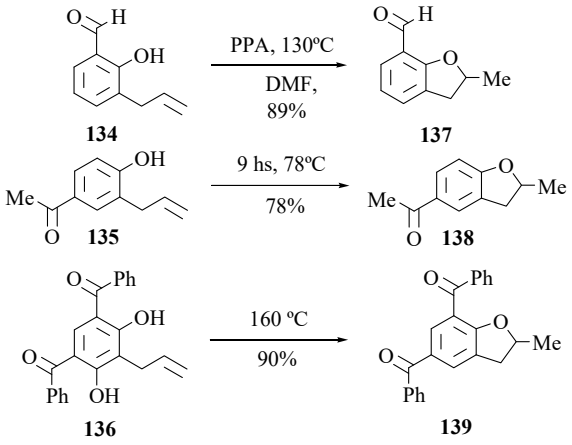
124: Ar = Ph, I; R = Et
125: Ar = 4-$OMeC_6H_4$; R = Et
126 Ar = 4-OHC_6H_4; R = Me
127 Ar = 3-$NO_2C_6H_4$; R = Me

130: Ar = Ph; R = Et (84%)
131: Ar = 4-$OMeC_6H_4$; R = Et (88%)
132: Ar = 4-OHC_6H_4; R = Me (91%)
133: Ar = 3-$NO_2C_6H_4$; R = Me (85%)

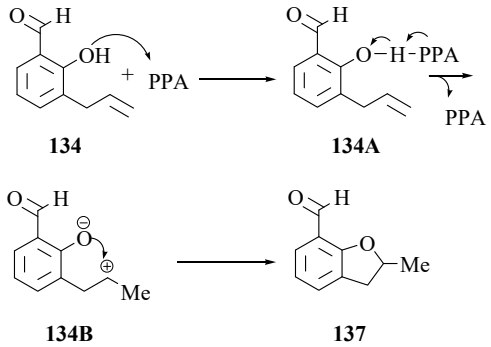
Scheme 21. One pot synthesis of 3,4-dihydropyrimidin-2(1H)-one (DHPMs)

6(iii). Synthesis of Carbonyl Containing Dihydrobenzofurans and Dihydrobenzopyrans

The carbonyl containing O-allyl phenols and O-prenyl phenols undergo cyclization activated by PPA to yield dihydrobenzofurans and dihydrobenzopyrans respectively (Yang et al., 2021). Dihydrobenzofuran and dihydrobenzopyran systems are found in a variety of biologically active compounds and exhibit significant biological activities such as antigen toxic, antiproliferative, anticancer etc. The optimized reaction condition consists in heating the O-allyland O-prenyl phenols (1 equivalent), and PPA (5 equivalent) in DMF at 130ºC for 10 hr under a normal atmosphere. In some cases the reaction conditions are changed. The allyl phenols **134-136** undergo cyclization with PPA providing dihydrobenzofurans **137-139** respectively (**Scheme 22**). The possible mechanism of the cyclization is depicted in **Scheme 23**.



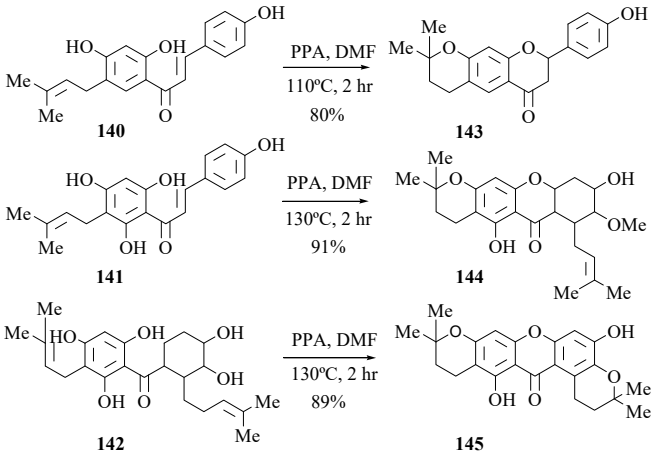
Scheme 22. Cyclization of O-allyl phenols **134-136** to dihydrobenzofurans **137-139** respectively



Scheme 23. Mechanism of the cyclization of O-allyl phenol **134** to dihydrobenzofuran **137**

Firstly phosphorylate adduct **134A** is formed from the allyl phenol **134** on heating with PPA. Electron delocalization within π-π conjugated **134A** due to more polarized the O-H and better stabilization of the negative charge on the oxygen atom form the intermediate **134 B**. Finally the nucleophilic attack leads to the desired product dihydro furane **137**.

Similarly the prenyl phenols **140-142** undergo cyclization with PPA to yield dihydrobenzopyrans **143-145** respectively (**Scheme 24**).



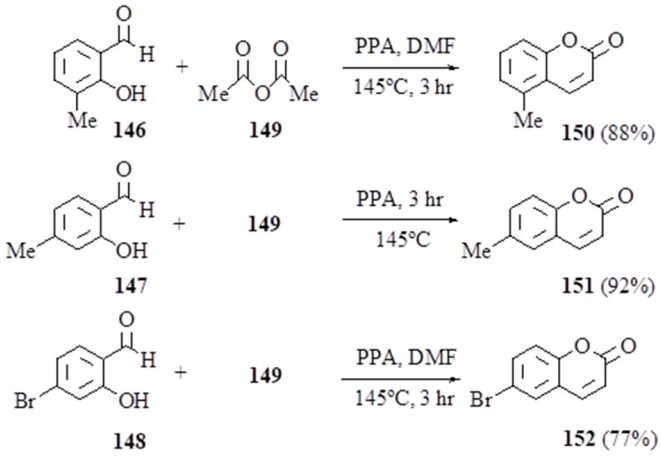
Scheme 24. Cyclization of prenyl phenols **140-142** to dihydrobenzopyrans **143-145** respectively

Exist methods for the cyclization of carbonyl-containing ortho-allyl and ortho-prenyl phenols with sulfuric acid, hydrochloric acid, *p*-toluenesulfonic acid, trifluoroacetic acid, aluminium chloride and zirconium tetrachloride (Yang *eta*l.,2020). However these reported methods suffer several disadvantages such as the formation of unsatisfactory products,

require long reaction time. The optimized condition exists in the use of carbonyl product (1 equivalent), PPA (5 equivalent) in dimethylformamide at 130ºC for 10 hr under a normal atmosphere.

6 (iv) Synthesis of Coumarins

The formations of 3,4-disubstituted coumarins **151-152** have been reported (yang etal., 2021) on heating the substituted salicylaldehydes **146-148** and acetic anhydrides 1**49** respectively with PPA

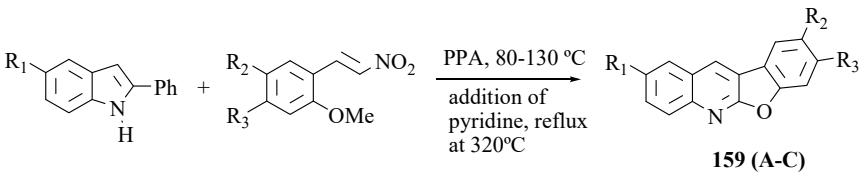


Scheme 25. Synthesis of substitued coumarins

These coumarins have also been formed by employing well-known reactions eg. Peachman reaction, Knoevenegal condensation, Wittig reaction etc. (Yang *etal*., 2020). Most of these methods suffer from some drawbacks including limited substrate scope and sometimes necessity of multistep reactions. The method(Yang *etal*., 2021) promoted by PPA is convenient than the published procedures for the synthesis of coumarins. The reaction performed in EtOH, THF, 1,4-dioxane or DMSO does not give the desiredproduct. The optimized reaction condition consists in the use of substituted salicylaldehydes (1 equiv.), acetic anhydride (2 equiv. in DMF) at 145 ºC for 3 hr under nitrogen atmosphere. The natural and synthetic products which contain coumarin ring system exhibit diversos bioactivities such asanti-oxidant, anti-inflamatory, anti-cancer, anti-tuberculosis, anti-coagulant etc.

6 (v). Synthesis of Benzofuro [2,3-b] and 6H-Indolo [2,3-b]Quinoline Cores

Several indoles (**153-155**)can be made to react with 1-methoxy-2-(2-nitrovinyl)-benzene (**156-158**) using PPA at 80-110ºC (Aksenov *eta*l., 2021) to yield benzofuro[2,3-b]quinolines. In **Scheme 26**, the reaction of indoles (**153-155**) with only nitrovinyl benzene **156** has been discussed. To the resulting complex is added pyridine and heated at 320ºC to yield benzofuro [2,3-b] quinolines **159A-159C** (**Scheme 26**). Although the method does not provide good yield, it allows all synthetic operations to be carried out in a single operation instead of multiple step sequence. Similarly many other benzofuro quinolines have been obtained by the reaction of the indoles (**153- 155**) with nitrovinyl benzene **(154** and **156**).



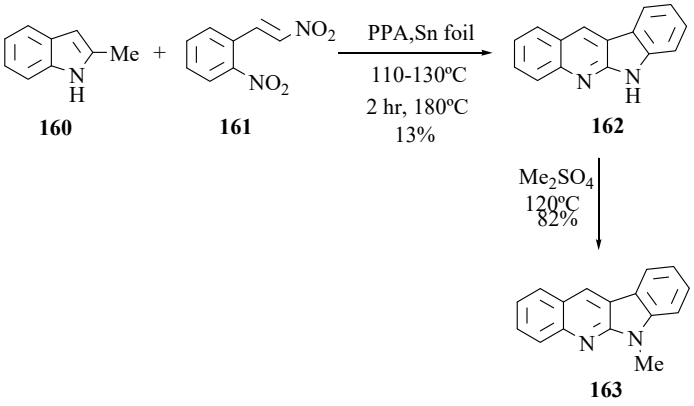
153: R_1 = H
154: R_1 = Cl
155: R_1 = Br

156: R_2 = R_3 = H
157: R_2 = Me, R_3 = H
158: R_2 = Me, R_3 = Cl

159 (A-C)

159-A R_1=R_2=R_3=H (48%)
159-B R_1=Cl, R_2= Me, R_3=H (29%)
159-C R_1=Br, R_2= R_3=H (26%)

Scheme26. Synthesis of benzofuro [2,3-b] quinolones



Scheme 27. Synthesis of norcryptolepine and neocryptolepine

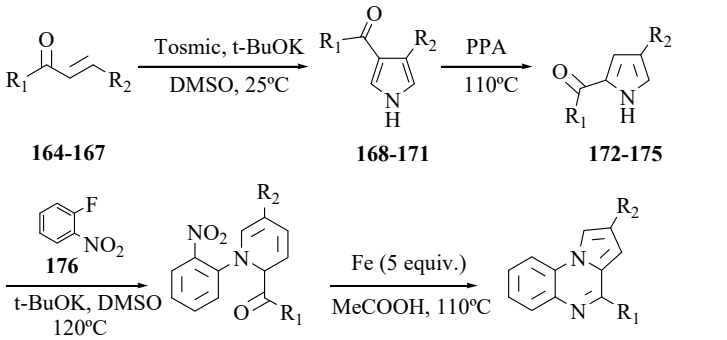
The mentioned method has also been applied for the synthesis of the indolealkaloid neocryptolepine **163**. The synthetic route is described in **Scheme 27**. A mixture of the indole **160** and the nitrostyrene **161,** if heated with PPA at 110-130ºC and Sn foil (3 equiv) followed by further heating for 2 hr at 180ºC, yields norcryptolepine **162** which on methylation affords neocryptolepine **163**.

In conclusion a novel approach has been developed for the synthesis of benzofuro [2,3-b]quinolines and 6H-indole [2,3-b]quinolines by PPA assisted cyclization. This unusual process involves the alkylation of indoles with nitroalkenes, subsequent rearrangement into 3-aryl-2-quinolines and annulation of five-membered ring (furan or pyrrole) to give the teracyclic core. The transformation is quite efficient if one considers the number of steps performed in a single step. In addition it offers an alternative to the known multi-step process.

6(vi). Synthesis of Pyrrolo[1,2-a] Quinoxalines from Chalcones

PPA has been extensively used for the synthesis of several pyrrolo [1,2-a]quinoxalines (Togiti etal., 2021). These compounds exhibitanti-leishmanial and antitumor properties as well as central dopamine antagonists.

The method consists in the treatment of chalcones eg **164-167** with Tosmic (*p*-toluenesulfonyl methyl isocyanide) and potassium *t*-butoxide in DMSO at 25ºC to obtain 2,3'disubstituted pyrroles **168-171** respectively (**Scheme 28**). The resulting pyrroles suffer rearrangement with PPA at 110ºC to yield 2,4-disubstituted pyrroles **172-175** which are subjected to SNAr reaction using 1-fluro-2-nitrobenzene **176** , potassium *t*-butoxide (as base) and DMSO (as solvent) to obtain [1-(2-nitrophenyl)-4-phenyl-1H-pyrrol-2-2yl(phenyl)methanone **177-180**. These methanones undergo cyclization with Fe (5 equiv), MeCOOH at 110 ºC to yield 2,4-disubstituted pyrrol [1,2-a] quinoxalines **181-184** respectively. The cyclization tried with sodium borohydride and nickel chloride and sodium dithionate does not afford satisfactory yield.



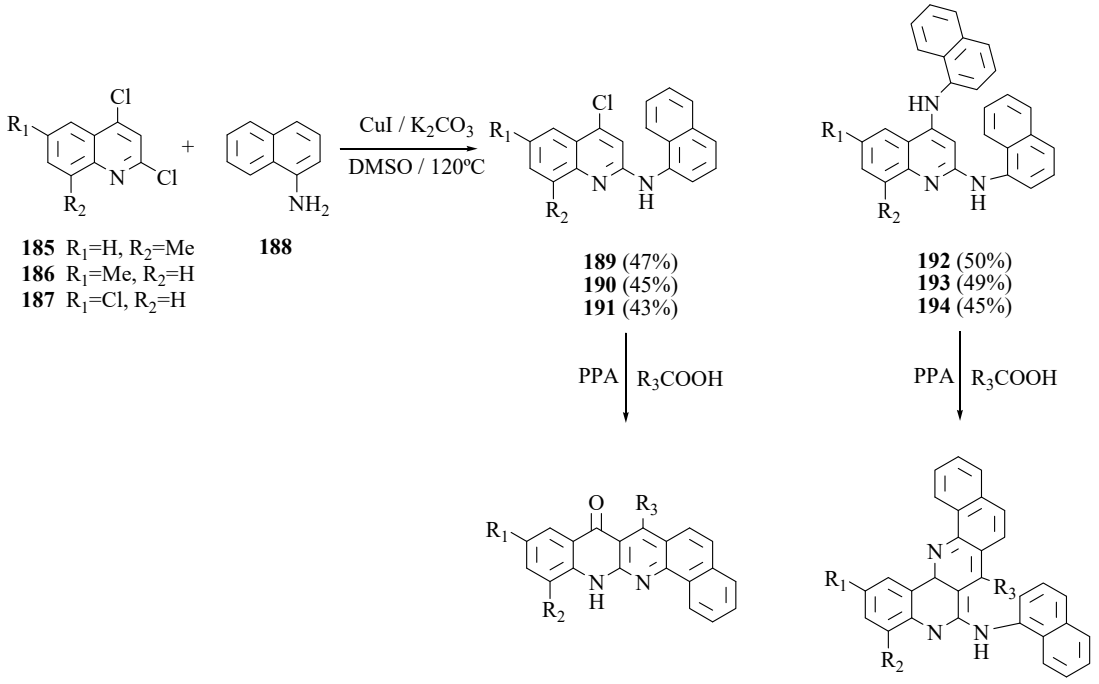
164, 168, 172, 177, 181 $R_1 = R_2 =$ Ph
165, 169, 173, 178, 182 $R_1 =$ Ph, $R_2 =$ *p*-MePh
166, 170, 174, 179, 183 $R_1 =$ Ph, $R_2 =$ *p*-OMe-Ph
167, 171, 175, 180, 184 $R_1 =$ Me, $R_2 =$ Ph

Scheme 28. Synthesis of pyrrol [1,2-a] quinoxalines from chalcones

6 (vii). Synthesis of Benzonaphtho Naphthyridines

The use of PPA has been recorded (Prabha*etal*., 2021) during the synthesis of benzonaphtho naphthyridines from 2,4-dichloroquinolines. The synthetic route is depicted in **Scheme 29**.

Amination of 2,4-dichloroquinolines (**185-187**) with 1-naphthylamine **188** using CuI as catalyst leads the formation monosubstuted (**189-191**) and disubstituted (**192-194**) naphthylamino quinolines respectively. The aminoquinolines (**189-191**) are converted into the linear benzo [g]naphtho[1,2-b][1,8]naphthyridines (**195-200**) respectively by heating with PPA and acetic acid. *p*-toluic can also beused instead of acetic acid. On similar treatment disubstituted (**192-194**) aminoquinolines yield angular benzo[b]naptho[2,1-h][1,8]naphthyridines (**201-206**) respectively. The naphthyridines, benzonaphthyridines and dibenzonaphthyridines display notable biological activities such as CB2 selective agonists, anti-HIV, anticancer, selective 3-phosphoinositide-dependent kinase-1 inhibitors.



185 R_1=H, R_2=Me
186 R_1=Me, R_2=H
187 R_1=Cl, R_2=H

188

189 (47%)
190 (45%)
191 (43%)

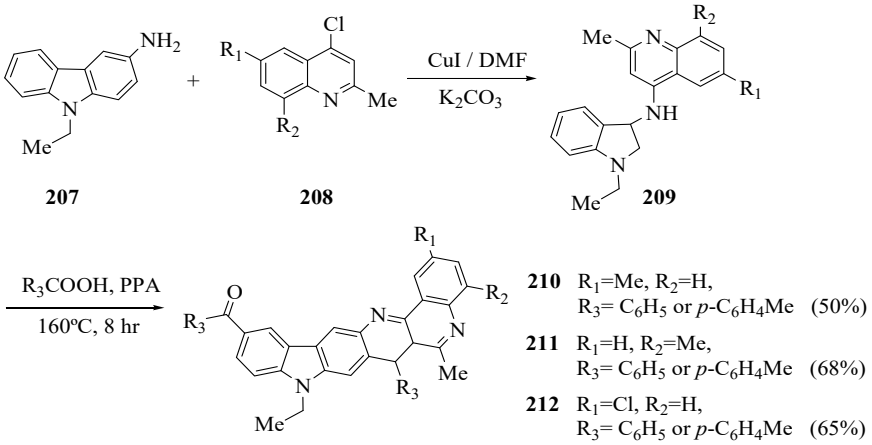
192 (50%)
193 (49%)
194 (45%)

195	R_1=H, R_2=Me, R_3= *p*-MeC_6H_4	(59%)	**201**	R_1=H, R_2=Me, R_3= *p*-MeC_6H_4	(73%)
196	R_1=Me, R_2=H, R_3= *p*-MeC_6H_4	(54%)	**202**	R_1=Me, R_2=H, R_3= *p*-MeC_6H_4	(69%)
197	R_1=Cl, R_2=H, R_3= *p*-MeC_6H_4	(61%)	**203**	R_1=Cl, R_2=H, R_3= *p*-MeC_6H_4	(66%)
198	R_1=H, R_2=Me, R_3= Me	(41%)	**204**	R_1=H, R_2=Me, R_3= Me	(59%)
199	R_1=Me, R_2=H, R_3= Me	(38%)	**205**	R_1=Me, R_2=H, R_3= Me	(56%)
200	R_1=Cl, R_2=H, R_3= Me	(43%)	**206**	R_1=Cl, R_2=H, R_3= Me	(53%)

Scheme 29. Synthesis of benzonaphtho naphthyridines

6(viii) Synthesis of Benzo[h]carbazole [3,2-b] [1,6]Naphthyridines

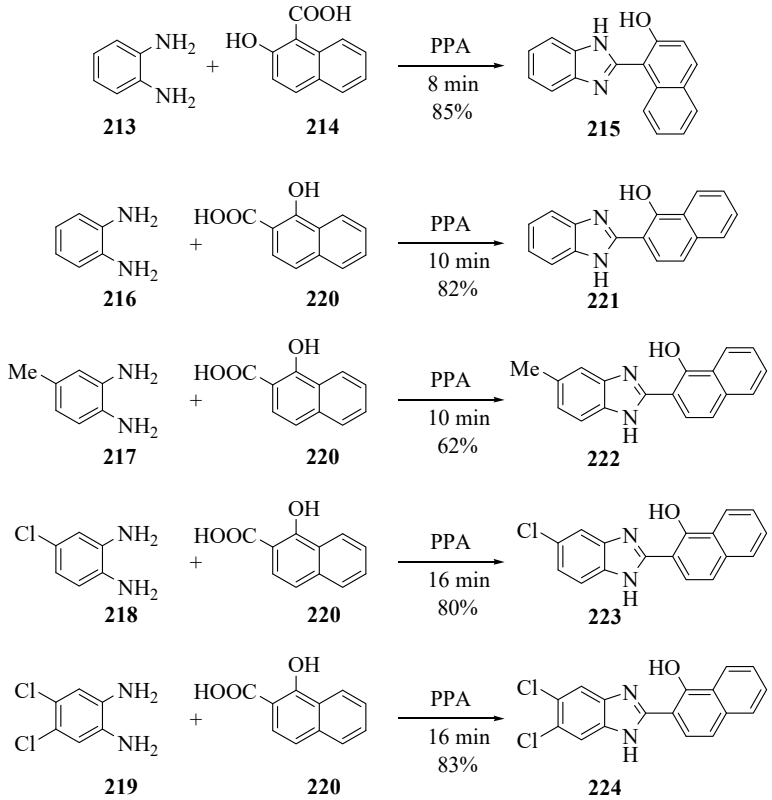
PPA has been utilized in the development of an efficient synthesis (Ezhumalai *etal.,* 2022),of benzo [h]carbazole [3,2-b] 1,6] naphthyridines which are useful for the synthesis of heterocyclic drugs. In order to achieve the desired product, the 3-amino-9-ethylcarbazole **207** in DMF is made to react with 2-methyl-4-chloroquinoline **208** using CUI as promoter to obtain 3-(N-(2-methylquinoline-4-yl)amino)-9-ethyl-9H-carbazole **209** (R_1=Me, R_2= H) (**Scheme 30**). The resulting carbazole is cyclized by heating with benzoic acid in presence of catalytic amount of PPA to obtain only linear1,6-naphthyridine **210**. By similar procedure the naphthyridines **211** and **212** can be prepared. No angular naphthyridine is obtained. The cyclization carried out without benzoic acid affords no desired result. The benzoic acid can be replaced by *p*-toluic acid. The reaction time should be significantly reliant on benzoic acid substituent. The presence of a methyl group at *para* position of the phenyl ring aids reaction rate and increases product yield significantly.



Scheme 30. Synthesis of 12-aryl-9-ethyl-6-methyl-7.phenyl-9H-benzo[h]carlazol[3,2-b][1,6]naphthyridines(4,5)

6(ix) Synthesis of Benzimidazoles with Naphthalene Moiety

The utility of PPA as catalyst has been recorded in relation to the synthesis (Ersan *eta*l., 2020) of naphthyl-substituted benzimidazole under microwave irradiation and conventional synthetic methods. These compounds show antimicrobial activity. In order to develop the synthesis of benzimidazole derivative, a mixture of the diamine **213**, naphthalene carboxylic acid **214**and PPA is stirred and irradiated (100-150 W) to obtain the naphthalene substituted benzimidazole **215**. Similarly the diamines (**216-219**) are mixed with hydroxy diacid **220** in presence of PPA and irradiated to obtain the naphthalene substituted imidazoles (**221-224**) respectively (**Scheme 31**).

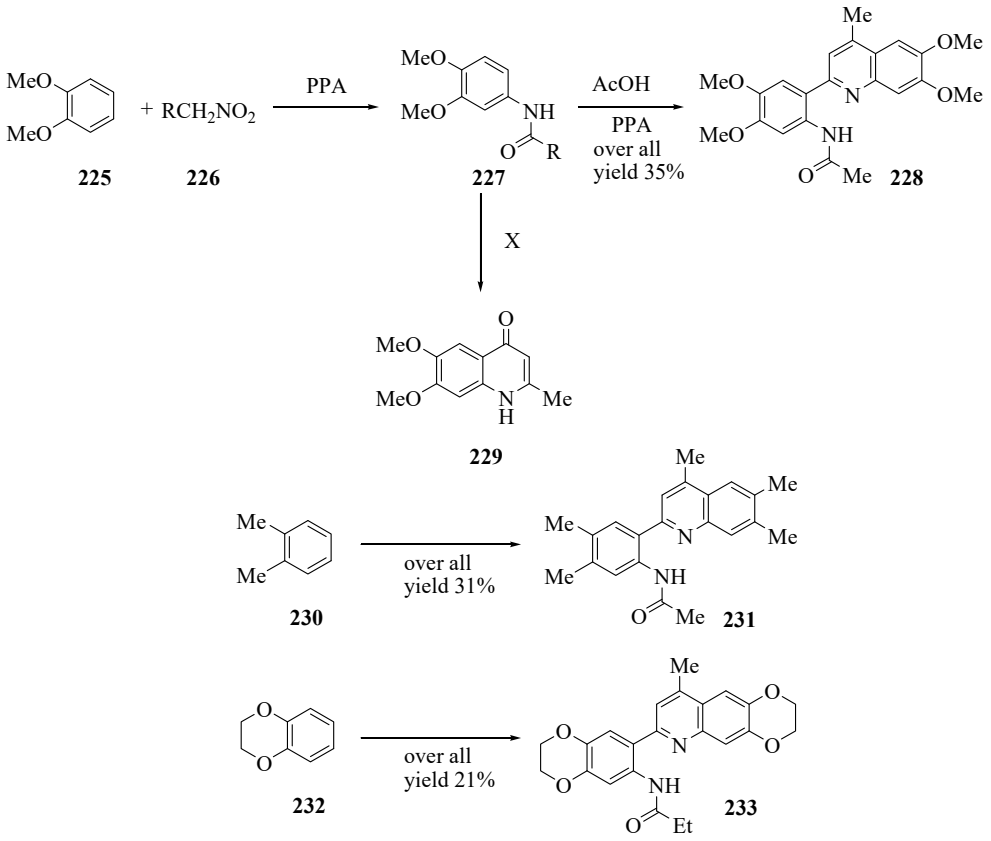


Scheme 31. Synthesis ofbenzimidazoles with naphthalene moiety compounds

The condensation carried out by conventional heating affords low yield and requires more time. The structures of the products have been established on the basis of spectral data. The compounds also have been screened for their antimicrobial activity.

6(x) Synthesis of 2-arylquinolines

The importance of quinoline derivatives in the development of new pharmaceuticals is well known. Several alkaloides contain the quinoline fragment and most of these structures exhibit varied biological activity. Many approaches have been developed for the synthesis of quinoline ring. It has been observed (Grishin *etal*., 2022 that direct acylamination of arenes with nitro alkenes in PPA followed by acylation leads the formation of 2-arylquinolines. Under this condition the disubstituted arene **225** (**Scheme 32**) reacts with nitroalkene **226** (R=Et or Me) in PPA and yield the acetanilide **227** which with acetic acid in PPA medium furnishes quinoline **228**. The formation of the quinoline **229** has not been detected. Following the similar procedure the transformations of the arenes **230** and **232** to the quinolines **231** and **233**respectively have been achieved. The O-acetylacetanilides generated *in situ* undergo a series of cascade transformations leading the formations of 2-(2-acylaminooary)quinolines.



Scheme 32. Synthesis of 2-aryl-quinolines

7. Conclusion

It can be observed that PPA has been utilized to achieve many important organic reactions. PPA has been widely used for the cyclization of acids to obtain the cyclic ketones and some of them have been utilized for the synthesis of natural products like tavacpallescenicine, sesquiterpene lacinilene C methyl ether, desoxypodocarpic acid, emmotin H, Pterosin E and many others. The acylation and isopropylation promoted by PPA proved useful in the synthesis of emmotin G methyl ether, potential intermediates for diterpene ferruginol, xanthoperol, miltirone and carnosic acid. The hydrolysis of esters into acids and cleavage of epoxides (chalcone epoxides, nitrostyrene epoxides, nitrochromene epoxides) have been easily carried out with PPA. The carbonyl containing O-allyl phenols and O-prenyl phenols have been cyclized with PPA to yield dihydrobenzofurans and dihydrobenzopyrans. The importance of PPA has been recorded during the synthesis of several substituted coumarins, benzofuro quinoline, pyrroloquinoxalines and benzo naphtho naphyridines. It also been shown for the first time the possibility of performing the reaction the of direct electrophilic acylamination of arenes with nitroalkenes in PPA together with acylation as a one-pot synthesis. o-Acetylacetanilides generate*d in situ* undergo a series of cascade transformations leading the formation of 2-(2-acylaminoary) quinolines.

References

Aksenov, D. A., Arutyunov, N. A., Gasanova, A. Z., Aksenov, N. A., Aksenov, A. V., Lower, C., & Rubin, M. (2021). Synthetic studies towards benzofuro[2,3-b]quinoline and 6H-indolo[2,3-b] quinoryptolepine.line cores/:Total synthesis of norneocryptolepine and neocryptolepine..*Tetrahedron Letts*., *82*, 153395-153398.

https://doi.org/10.1016/j.tetlet.2021.153395

Bachute, M. T., &Mane, R. B. (1981). Synthesis of an intermediate ,7,8-dimethyl-2-tetralone for occidolisomer-1 and occidol isomer-2. *IndianJ.Chem*., *30B*, 1145-1147.

Banerjee, A. K., Mendoza, Briceno, B., Vera, W. J., Maldondo, A., Cabrera, E. V., &Arriechi, D. (2022). Sulfuric acid promoted molecular rearrangement: applications in synthesis of terpenoid compounds in Terpenes and terpenoids, ed Davies, C.A., Nove Sience Publishers, Inc, 2022, p. 154-185.

Banerjee, A. K., Vera, W. J., & Laya, M .S. (2002).Alternative procedure for the synthesis(±)tavacpallescencine precursor.*Russ. J. Org. Chem., 38*, 855-857. https://doi.org/10.1023/A:1020399306698

Banerjee, A. K., Vera, W., & Laya, M. S. (2004). A new synthesis of 5,8-dimethyl-2-tetralone-a potential intermediate for the synthesis of an aromatic sesquiterpene. Novel transformation duringacetoxylation of 5,8-dimethyldihydronaphthalene. *Synth.Commun., 34*, 2301-2308. https://doi.org/10.1081/SCC-120038516

Bowers, A., Halsall, T. G., Jones, E. R. H., & Lemin, A. J. (1953). The chemistry of triterpenes and relatedcompounds. Elucidation of the structurer of polyporenic acid C. *J. Chem. Soc. Perkin Trans., 1*, 2548-2555.https://doi.org/10.1039/jr9530002548

Cabrera, E. V., & Banerjee, A. K. (2010). A simple synthesis of 8-methoxy-1-tetralone. *Org. Prep. Proc. Int., 42*, 499-502. https://doi.org/10.1080/00304948.2010.514837

Cabrera, E. V., Gil, A. C., Ortega, J. G., Bedoya, L., Sanchez, J., & Banerjee, A. K. (2014). A one pot synthesis of6-isopropyl-7-tetralone. *Org. Prep. Proc. Int., 46*, 272-276. https://doi.org/10.1080/00304948.2014.903146

Cocker, W., & Sainsbury, D. M. (1965). Synthesis of 1,2,34-tetrahydro-7-hydroxy-4-isopropyl-1,6-dimethylnaphthalene, a degradation product. Of copaene. *J. Am. Chem. Soc.,* 3319-3994. https://doi.org/10.1039/jr9650003319

Dodd, J. H. (1991). Polyphosphoric acid. Encyclopedia of reagents for Organic Synthesis John Wiley& Sons, New York.,p 4169-4175.

Dodd, J. H. (2001). Polyphosphoric acid .Encyclopedia of reagents for Organic Synthesis John Wiley & Sons, New York., p 1-6. https://doi.org/10.1002/047084289X.rp186

Edward, Y., Tasdemir, Y., & Isacsson, U. (2007). Rheological effects of commercial waxes and polyphosphoric acid in 160/220-high and medium temperature performance.*Construction and Building materials, 21*, 1899-1908. https://doi.org/10.1016/j.conbuildmat.2006.07.012

Ersan, R. H., Yuksel, A., Ertan-Bolelli, T., Dogen, Burmaoglu, S., & Algul, O. (2021). One-pot synthesis of novel benzimidazoles with a naphthalene moiety as antimicrobial agents and molecular docking studies. *J. Chin. Chem. Soc..,* 1-10. https://doi.org/10.1002/jccs.202000125

Ezhumalai, Y., Kumaresan, P., Matthias, Z., & Jayarampillai, R. P. K. (2022). Efficient synthesis of benzo[h]carbazole[3,2-b][1,6]naphthyridines. *J.Het.Chem., 59*, 1191-1197. https://doi.org/10.1002/jhet.4459

Giarruso, F., & Ireland, R. E. (1968). A. stereoselective synthesis of (±) desoxypodocarpic acid. *J. Org. Chem*., *58*, 3560-3563. https://doi.org/10.1021/jo01273a045

Grishin, I. Y., Malyuga, V. N., Aksenov, D. A., Kirilov, N. K., Abakarov, G. M., Ovcharov, S. N., … & Aksenov, A. V. (2022). *Chemistry of Heterocyclic Compounds*., *58*, 313-318.

He, X., Li, Z., & You, Q. (2002). Use of polyphophoric acid in the hydrolysis of chromone esters. *Synth*. *Commun*., *32*, 709-714. https://doi.org/10.1081/SCC-120002508

Ho, T. L., &, Lin, Y. J. (1999). Synthesis of tavacpallescencineand occidol via a commonintermediate. *J. Chem. Soc. Perkin Trans., 1*, 1201-1207. https://doi.org/10.1039/a900465c

Mane, R. B., & Kadam, A. J. (1998). A new synthesis of occidol. *Collect. Czechoslovakia Chem. Comm., 64,* 533-538. https://doi.org/10.1135/cccc19990533

Manolov, S., Nikolova, S., & Ivanov, I. (2013). Silica-supported polyphosphoric acid in synthesis of 4-substituted tetrahydro -isoquinoline derivatives. *Molecules*, *18*, 1869-1880. https://doi.org/10.3390/molecules18021869

Masson, J. F. (2008). Brief review of the chemistry of polyphosphoic acid (PPA) and bitumen. *Energy & Fuels, 22*, 2637-2640. https://doi.org/10.1021/ef800120x

Masson, J. F., Gagne, M., Robertson, G., & Collins, P. (2008). Reactions of polyphosphoric acid and bitumen model compounds with oxygenated functional groups: where is the phosphorylation?. *Energy & Fuels, 22*, 4151-4157. https://doi.org/10.1021/ef800511v

McCormick, J. P., Pachtatko, J. P., & Schafer, T. R. (1978). Total synthesis of lacinlene C methyl ether,a robable byssinotic agent. *Tetrahedron Lett.*, 3993-3994. https://doi.org/10.1016/S0040-4039(01)95120-2

Nambudiry, E. N. M., & Krishna Rao, G. S. (1974). Synthesis of pterosin E, a sesquiterpene from Bracken. *J. Chem. Soc. Perkin Trans., 1*, 317-319. https://doi.org/10.1039/p19740000317

Pathe, G. H., & Ahmed, N. (2015). Anefficientprotocol for the elimiative deoxygenation of aliphatic and aromatic epoxides to olefins with polyphosphoric acid as a promoter. *Tetrahedron. Lett*., *56*, 6202-6206. https://doi.org/10.1016/j.tetlet.2015.09.083

Popp, F. D., & McEwen, W. E. (1958). Polyphosphoric acid as reagent in organic synthesis. *Chem*. *Rev*., *58*, 321-401. https://doi.org/10.1021/cr50020a004

Prabha, K., Satheeshkumar, R., & Prasad, K. J. R. (2021). Synthesis of novel benzo naphtho naphthyridines from 2,4-dicloroquinolines. *J. Het. Chem., 58,* 1809-1824. https://doi.org/10.1002/jhet.4312

Rand, L., & Dollinski, R. J. (1966). The acylation of cycloheptene. *J. Org. Chem., 31*, 3063-3065. https://doi.org/10.1021/jo01347a512

Reddy, P. A., & Krishna Rao, G. S. (1979). Synthesis of 3-(2-hydroxyisopropyl)-5,8-dimethyl-1,2-naphthoquinone(Emmotin-H*). J. Chem. Soc. Perkin Trans., 1*, 237-240. https://doi.org/10.1039/p19790000237

Renault, O., Dallemagne, P., & Rault, S. (1999). Friedel-Crafts acylation with malonicacids in polyphosphoric acid. *Org. Prep. Proced. Int.*, *31*, 324-328. https://doi.org/10.1080/00304949909458327

Smith, G. F. (1954). The formylation of indole and some reactions of 3-formylindole. *J. Chem. Soc.,* 3842-3846. https://doi.org/10.1039/jr9540003842

Snyder, H. R., & Werber, F. X. (1950). Polyphosphoric acid as a dehydrating agent. The cyclodehydration of some α-acylamino-β-arylpropionic acid. *J. Am*. *Chem*. *Soc*., *72*, 2962-2965. https://doi.org/10.1021/ja01163a041

Stanisheva, D. V., Gerova, M. S., & Petrov, O. I. (2017). Synthesis of a new polycyclic heterocyclic ring system. Benzo[b] imidazo[1,5-d] [1,4]oxazepane-1,4-(2H, 5H)-diones. *Heterocyel. Commun., 23*, 23-27. https://doi.org/10.1515/hc-2016-0236

Togiti, U. K., Shukla, A. K., & Bhattacharya, A. (2021). Pyrrolo[1,2-a]quinoxalines from chalcones: An alternate route. *Tetrahedron Lett*., *81*, 153008-153011. https://doi.org/10.1016/j.tetlet.2021.153008

Venkov, A. P., & Ivanov, I. I. (1996). Synthesis of isoquinolines from 2-phenylethylamines, amides, nitriles and carboxylic acids in polyphosphoric acid. *Tetrahedron., 52*, 12299-12308. https://doi.org/10.1016/0040-4020(96)00716-8

Vuligonda, V., Roshantha, Y. L., & Chandraratna, R. A. S. (1996). Selective conversion of α-tetralone todihydronaphthalenes. *Tetrahedron. Lett., 37*, 1941-1944. https://doi.org/10.1016/0040-4039(96)00309-7

Whaley, W. M., & Govindachari, T. R. (1951). The Pictet-Spengler synthesis of tetrahydroisoquinolines and related compounds. *Org. React., 6*, 151-190. https://doi.org/10.1002/0471264180.or006.03

Whaley, W. M., & Govindachari, T. R. (1951). The preparation of 3,4-dihydroisoquinoline. *Org. React*., *6*, 74-150.

Wollinsky, J., Lau, R., Hamsher, J. J., & Cimarusti, M. C. (1972). A Convenient synthesisofferruginol and xanthoperol. *Synth. Commun., 2*, 327-330. https://doi.org/10.1080/00397917208061989

Yang, L. S., Wang, Y., Wang, E. H., Yang, J., Pan, X., Liao, X., &Yang, X. S. (2020). Polyphosphoric acid -promoted synthesis of coumarins lacking substituents at position 3 and 4. *Synth*.*Communs*., *50*, 3080-3085 and related references. https://doi.org/10.1080/00397911.2020.1792498

Yang, Q., Wang, Y., Yang, J., Wu, Y., Li, L. Q., Chen, F. J., … & Yang, X. S. (2021). Activation of phenolicoxygen atom using polyphosphoricacid : Synthesis of carbonyl-containing dihydrobenzofurans/dihydrobenzopyrans. *Synth. Communs*., *51*, 1723-1730 and related references. https://doi.org/10.1080/00397911.2021.1902537

Yoshira, K., Fukuoka, M., K.uroyanagi, M., & Natori, S. (1971). Indanone derivative from Bracken,Pteidium aquilinium var. latusculum. *Chem. Pharm. Bull., 19*, 1491-1495. https://doi.org/10.1248/cpb.19.1491

Zhao, Y., Zhao, Y., Zhang, J., Liu, H., & Liang, L. (2015). Polyphosphoric acid catalystfor one- pot synthesis of 3,4-dihydropyrimidin 2(1H). *Indian J. Chem*., *54B,* 139-141.