Polyphosphoric acid trimethylsilylester: a useful reagent for organic synthesis

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This review describes the composition, preparation and applications in organic synthesis of polyphosphoric acid trimethylsilylester (PPSE). It covers the literature since it first appeared in the eighties until the first trimester of 2007. A discussion of the synthetic utility of PPSE, compared to other related reagents such as polyphosphoric acid (PPA) and polyphosphoric acid ethyl ester (PPE) as well as various Lewis acids, is also included.

Keywords: polyphosphoric acid trimethylsilylester, PPSE, organic synthesis, condensation, cyclodehydration, heterocycles

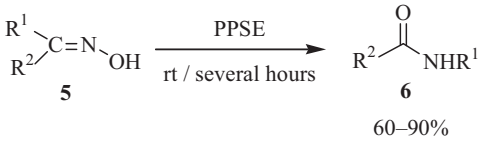
The polyphosphoric acid trimethylsilylester (PPSE) is a derivative of polyphosphoric acid, first synthesised by Imamoto and coworkers in 1981.[1] It is an oxygen-activating agent by its interaction through the phosphorus atom or the trimethylsilyl group. PPSE is essentially an aprotic liquid which possess a strong dehydrating power as well as being a solvent.[2] It is a synthetically useful reagent for the induction of a diversity of reactions such as: dehydration of amides into nitriles,[3] pinacolic rearrangement,[4] synthesis of heterocycles,[5,6] aldol-like condensations,[2] preparation of alkyl iodides from alcohols,[7] synthesis of dithioketals[8] and the formation of enynes and enediynes from propargyl alcohol.[9] Now commercially available, this flammable reagent, which is a mild irritant, is synthesised from phosphorus pentoxide and hexamethyldisiloxane (HMDS) in solvents such as benzene, chloroform, dichloromethane or toluene under reflux in an inert atmosphere. It is a colourless or light yellow oil, viscous and soluble in diverse organic solvents.[3] Yamamoto and Watanabe described the composition of PPSE based on ^{31}P NMR experiments,[6] as being composed basically of a mixture of cyclic and linear tetramers: isocyclotetraphosphate **1** (its principal and most reactive species), cyclotetraphosphate **2**, linear tetraphosphate **3** and a small proportion of tetrakis (trimethylsilyl)diphosphate **4** (Fig. 1).[2-4,6]

Rearrangement reactions

Beckmann rearrangement

Initially observations by Imamoto and coworkers showed that oximes reacted at room temperature in the presence of PPSE, which promotes a Beckmann rearrangement to obtain the corresponding substituted amides in good yields.[1]

A comparison of the effect of several Lewis acids (PCl_5, P_2O_5, $AlCl_3$, $SnCl_4$, $ZnBr_2$) and PPSE in the Beckmann rearrangement and cyclisation of the oxime from 6-methylhept-5-en-2-one **7** to form 3-isopropylidene-2-methyl-Δ^1-pyrroline **8**, showed that PPSE brought about this and similar reactions more cleanly and more rapidly.[10]



5 **6**

60–90%

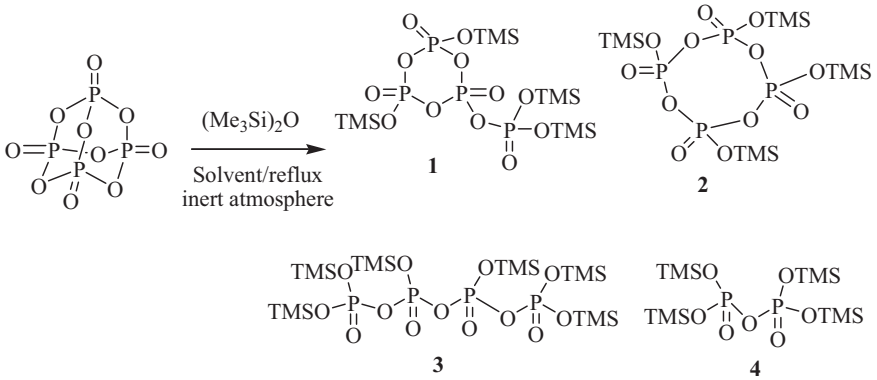
7 **8**

74%

The initiation of the Beckmann rearrangement of enantiomerically pure spirocyclic keto-oximes **9** and **10** by different acidic promoters (PPA,[22] Eaton's reagent,[33] PPE[34] and PPSE[2]) was recently reported.[34] In two cases (PPE and PPSE) the spirocyclic core was fully preserved during the exclusively concerted 1,2-shift of the *anti* carbon, the yields given by PPE being considerably higher.

Meyer–Schuster rearrangement

α,β-Unsaturated thioesters **14** were synthesised in good yields by the Meyer–Schuster rearrangement.[11] The reaction was performed by treating γ-thioalkoxy substituted propargyl alcohols **13** with PPSE, giving also 6–12% of the β-elimination product **15**. However, when tertiary propargyl esters **16** were used, *Z*-thioalkoxy-enynes **17** were obtained in high yields accompanied by small amounts of the α,β-unsaturated esters **18**.



1 **2** **3** **4**

Fig. 1 Preparation and composition of polyphosphoric acid trimethylsilylester (PPSE).

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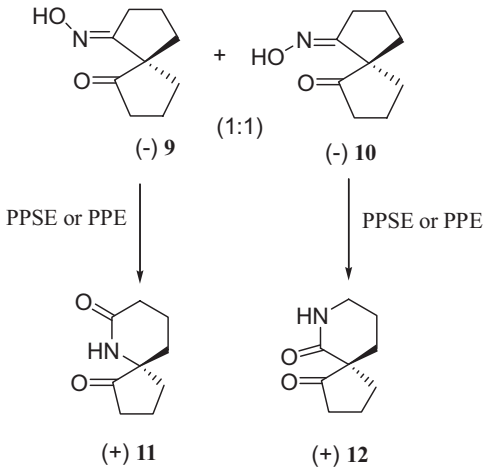
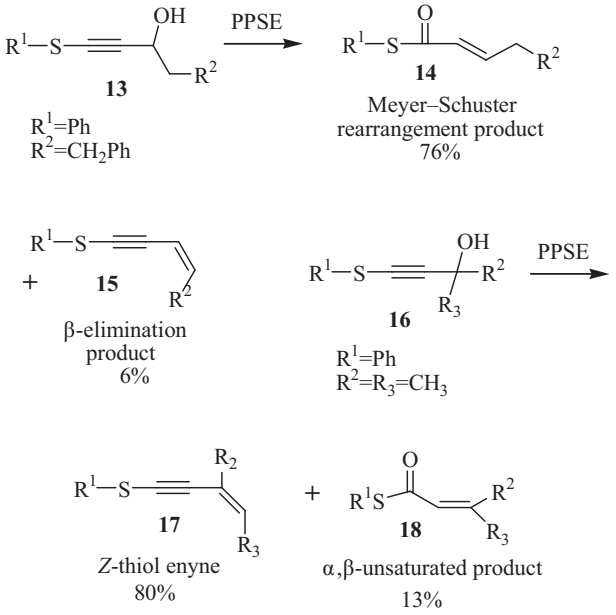
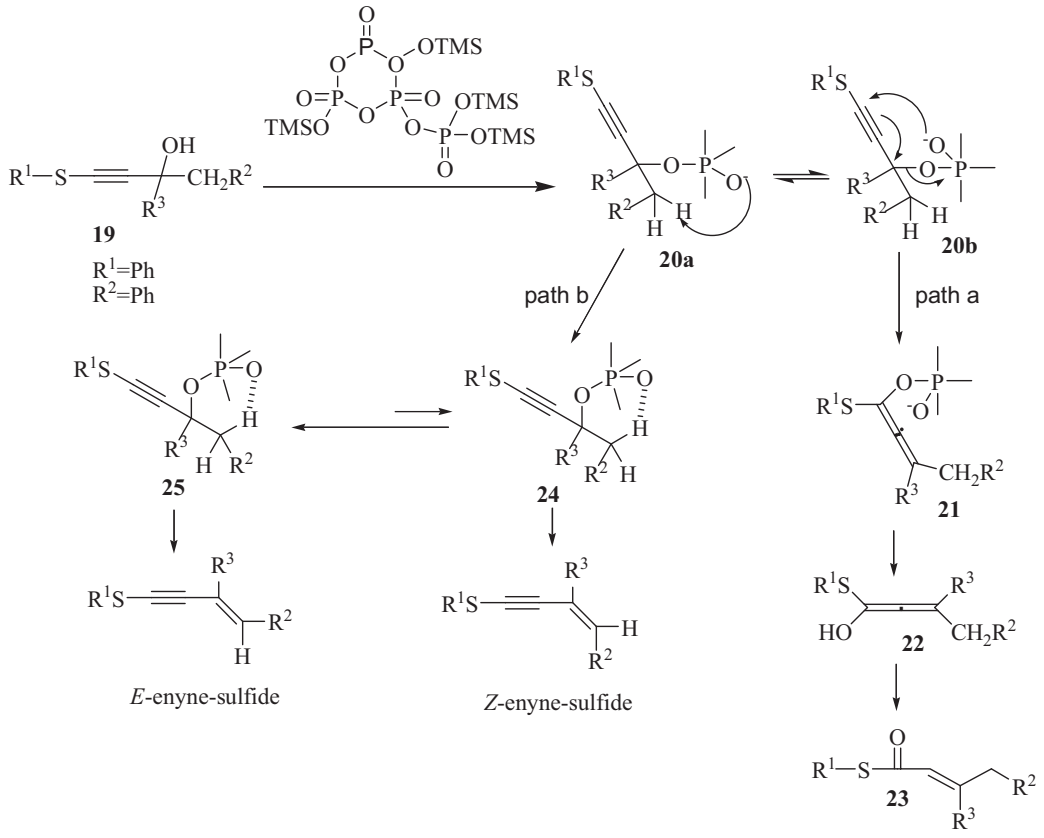




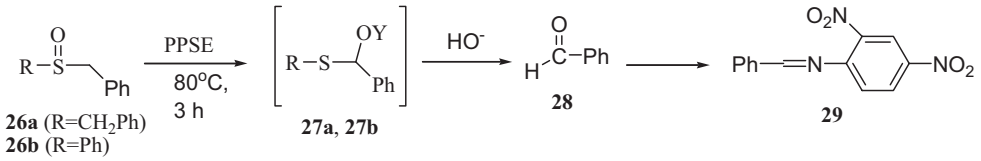
The postulated mechanism for the formation of the Meyer–Schuster type product is shown in Scheme 1. The propargyl alcohol **19** attacks at a phosphorus atom of PPSE to give a pentavalent phosphorane intermediate **20**. The intermediate **20** (R_3 = H), formed from a secondary alcohol, undergoes a Meyer–Schuster rearrangement *via* the intermediate **20b** (path a) rather than dehydration. The resulting phosphate **21** is hydrolysed to give an allenol intermediate **22**, which easily isomerises to an α,β- unsaturated thioester **23**. Alternatively, the propargyl carbon–oxygen bond of the intermediate **19** ($R_3 \neq H$), formed from a tertiary alcohol, is cleaved more readily than that from the intermediate formed from a secondary alcohol (**19**, R_3 = H). Consequently, the intermediate **19** ($R_3 \neq H$) undergoes dehydration through the intermediate **20a** (path b). The dehydration of **20** would proceed through a six-membered transition state (**24**), in which an alkyl and alkynyl group lie opposite the bulky phosphorus units, affording the *Z*-enyne sulfide selectively. When steric hindrance between R_3 and the acetylenic moiety becomes larger, the intermediate **24** transforms into **25** and forms the more stable *E*-isomer.[11]

Pummerer rearrangement

The Pummerer rearrangement of some sulfoxides in the presence of PPSE has been reported.[12] When the dibenzylsulfoxide **26a** was treated with a solution of PPSE in 1,2-dichloroethane at 80°C for 3 h, and the cooled reaction mixture poured into 1M sodium hydroxide solution, the corresponding benzaldehyde



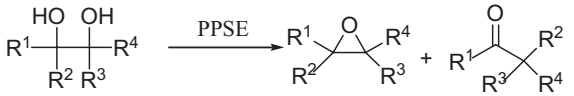
Scheme 1 Postulated mechanism for the formation of the Meyer–Schuster type product by treating γ-thioalkoxy-substituted propargyl alcohols with PPSE.[11]



28 could be isolated as its 2,4-dinitrophenylhydrazone **29** in 91% yield. The reactions seem to proceed *via* phosphorylation of the oxygen atom of the sulfoxides.

Pinacolic rearrangement

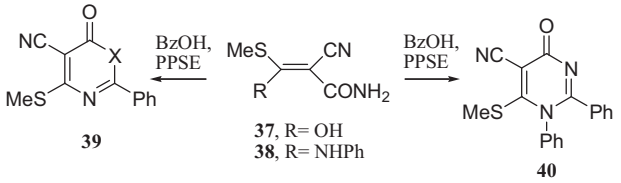
Several pinacolones **32** were prepared from the corresponding pinacols **30** in high yields in the presence of PPSE at a temperature above 80°C in 1,2-dichloroethane.[4] Additionally, tetraphenylethylene oxide ($R^1 = R^2 = R^3 = R^4 = Ph$) **31**, was obtained with benzopinacolone in the reaction of benzopinacol under milder conditions (80°C).

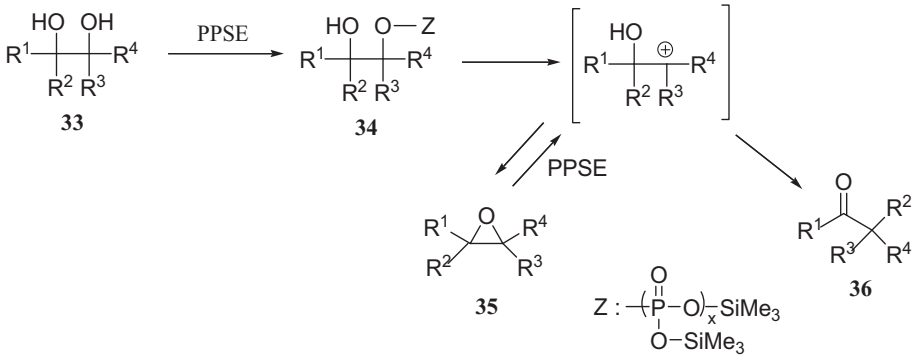


The acceleration effect observed with a polar solvent (tetrahydrothiophene 1,1-dioxide) suggested the rearrangement proceeded through an ionic intermediate, such as a carbocation. The proposed mechanism is shown in Scheme 2. The reaction involves the phosphorylation of a pinacol (**33**) and the formation of a carbonium ion by the loss of the silylated phosphoric acid. Once the carbonium ion is formed, there are two possible paths, the formation of the epoxide **34**, which may be reopened by the action of PPSE, and the direct formation of the pinacolone **36**.

O,N and N,N double rearrangement

The amide **37** condensed with benzoic acid in the presence of PPSE giving a O,N-double rearranged product **39** (77%, X = O), while a similar condensation of **38** with the same acid in the presence of PPSE gave the N,N-double rearranged product **40** (49%). Similar reactions occurred with other aromatic carboxylic acids and the mechanism of these heteroatom rearrangements is analogous to that of S,N-double rearrangement.[13]



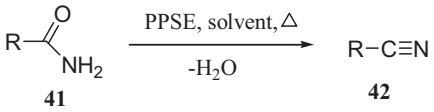


Scheme 2 Proposed mechanism for the Pinacolic rearrangement of several pinacols in the presence of PPSE.[4]

Functional group transformations

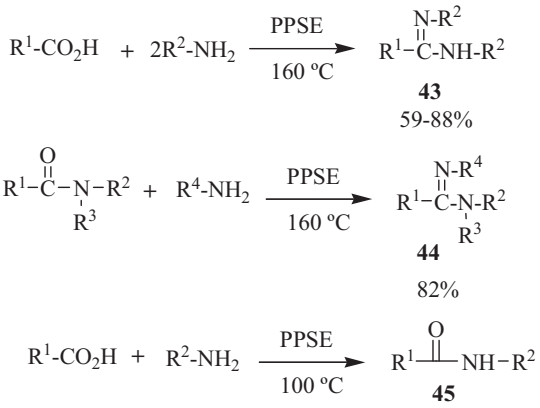
Synthesis of nitriles from carboxamides

Due its strong dehydration power, PPSE may be used for the simple and efficient conversion of several aryl, heteroaryl and alkyl amides **41** into nitriles **42** in good yields.[3] The reaction is performed in 5–180 minutes, depending of the nature of the R substituent. Although PPE may also be used for this reaction, PPSE offers the advantage of a short preparation time when compared with PPE, which requires a long time for the preparation (refluxing for 2–3 days).



Synthesis of amidines and amides from carboxylic acids

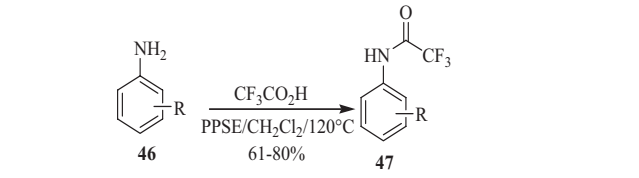
As well as condensation and dehydration properties, PPSE has also a Lewis acid character; due these properties, it is effective in the synthesis of symmetric (**43**) and non-symmetric (**44**) amidines, as well as amides (**45**), by the direct reaction of carboxylic acids and amines or amides in 60–85% yields.[14]



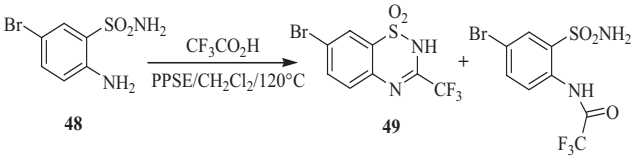
Trifluoroacetylation of aromatic amines

An easy and practical procedure for the trifluoroacetylation of substituted anilines **46** has been recently described by our group, employing trifluoroacetic acid and PPSE.[15] The better yields were obtained for *p*-substituted anilines, while the *o*-substituted ones gave poor results. This method

was also applied to the direct preparation of 3-trifluoromethyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide **49** from 5-bromo-2-aminobenzenesulfonamide **48**, and gave a 6:4 mixture of the desired heterocycle **49** and the trifluoroacetylated benzenesulfonamide **50**.



46 **47**

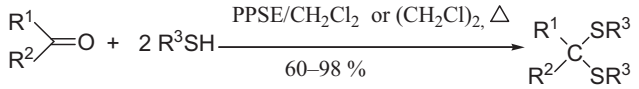


48 **49** **50**

(6:4 ratio)

Synthesis of dithioketals

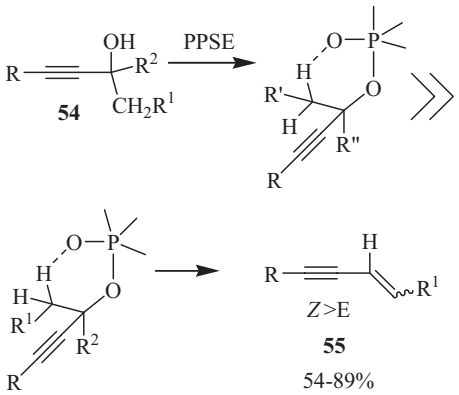
Various dithioketals **53** were synthesised from carbonyl compounds **51** (aldehydes, ketones) and thiols **52** in the presence of PPSE.[8] The reaction can be performed using aromatic, primary, secondary and tertiary thiols. Some reactive functions such as phenol and carboxylic acid did not disturb the dithioketal formation. Although acetal formation using PPSE has been reported,[2] it failed when ethanol or phenol were used under the same conditions as those for dithioketal preparation.[8]



51 **52** **53**

Synthesis of enynes and enediynes from propargyl alcohols

When secondary or tertiary propargyl alcohols and diyne alcohols were treated with PPSE *Z*-enynes and *Z*-enediynes were obtained with both high stereoselectivity and yields.[9] This high stereoselectivity can be explained by the steric hindrance afforded by the PPSE, where the alkyl and alkenyl groups of the alcohol are placed in a six-membered transition state formed between the PPSE and the hydroxy group of the propargyl alcohol, which suffers a dehydration giving mainly the *Z*-olefin.



54 **55**

54-89%

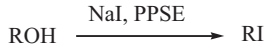
R= Ph, Bu, $BnOCH_2$

R^2= H

R^1= Bu, CH_2Ph, CH_2CH_2Ph, —CΞCH, —CΞCMe

Synthesis of alkyl halides from alcohols

Several alkyl iodides **57** have been prepared using sodium iodide by an induced dehydration of alcohols **56** by the action of PPSE.[7] The reactions proceed cleanly at room temperature and the products were isolated easily for most cases. High yields were obtained for primary, secondary and benzyl alcohols (62–98%), but the method failed with cinnamyl alcohol, *l*-menthol, cyclododecanol, propane-1,2-diol, benzoin, 1,3-diphenyl-3-hydroxypropan-1-one, and 4-hydroxy-4-methylpentan-2-one, where side reactions such as elimination prevailed and the corresponding alkyl iodides were not obtained in good yields.

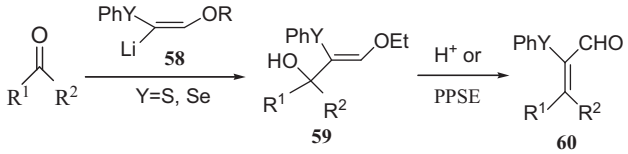


56 **57**

Homologation reactions

α-*Chalcogen-substituted formylolefinations of ketones and aldehydes*

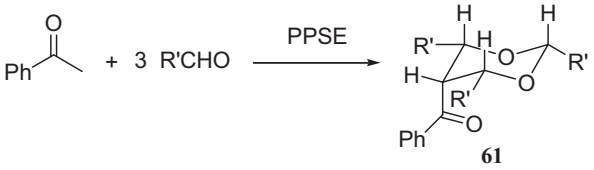
An homologation sequence has been performed using 1-lithio-2-ethoxyvinyl chalcogenides **58** with PPSE or TMSOTf to produce a series of α-chalcogenoformylolefinated products **60** in high yields.[16] Although the alcohols **59** (Y = Se) could be prepared by the same method as that for the sulfur analogues (Y = S), the dehydration of the alcohols by PPSE was not effective with the selenium analogues.



59 **60**

Aldol condensations

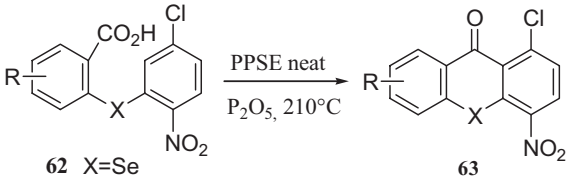
The stereoselective aldol-like synthesis of *meso*-5-acyl-2,4,6-trisubstituted-1,3-dioxanes **61** was achieved by the condensation reaction of aryl methyl ketones with 3 equivalents of aromatic aldehydes in the presence of PPSE.[2] The exact structure and relative stereochemistry of these dioxane products was confirmed by single crystal X-ray analysis. PPSE proved to be critical for this condensation and the use of PPE in place of PPSE resulted in the formation of α,β-unsaturated carbonyl compounds, probably due to the strong dehydration power of PPE.



61

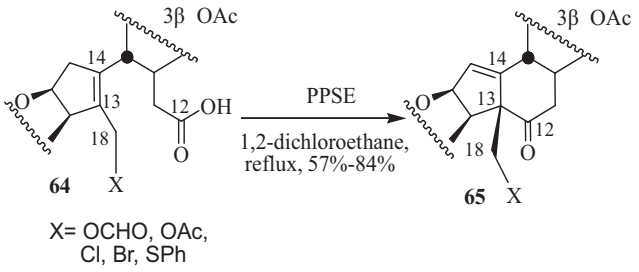
Friedel – Crafts reactions

PPSE has been an excellent alternative for the promotion of Friedel–Crafts acylation reactions.[17,18] Berman compared the effectiveness of PPSE in the Friedel–Crafts cyclisation of different benzoic acid precursors **62** to 9*H*-selenoxanth-9-ones **63**; in general, higher yields were obtained for PPSE when compared with promoters such as PPA, PPE, MSA/P_2O_5, $SOCl_2/AlCl_3$ and TFA/TFAA.[18]



62 X=Se **63**

Fuchs used PPSE to promote a Friedel–Crafts intramolecular cyclisation of unsaturated steroid acids. The procedure involved the addition of the carboxylic acid **64** to a solution of PPSE in 1,2-dichloroethane giving the ketone **65** in 57% yield.[17]



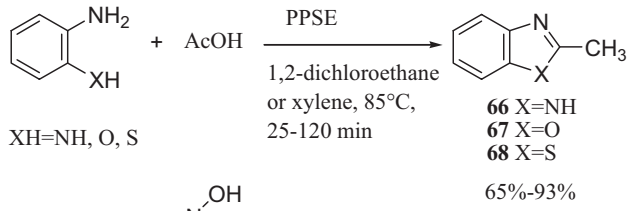
X= OCHO, OAc, Cl, Br, SPh

Synthesis of heterocycles

The use of PPSE in the synthesis of heterocycles was reviewed by Perillo and Hedrera in 2002.[19] Probably, the most interesting use of PPSE in the synthesis of heterocycles arises from its powerful but milder condensating properties compared with PPA, being succesfully employed in those cases where the cyclodehydrations using PPA failed or gave low yields due to its strong acidic character.

Benzimidazoles, benzothiazoles and benzoxazoles

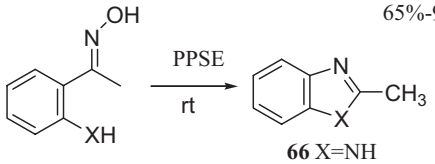
2-Methylbenzimidazole **66**, 2-methylbenzoxazole **67** and 2-methylbenzothiazole **68** were efficiently synthesised from *o*-diaminobenzene, o-aminophenol and *o*-aminothiophenol respectively by means of PPSE.[6] The reaction conditions were improved in all cases by the use of PPSE, which is superior to PPE in ready availability[20,21] and by the milder conditions than those used for PPA.[22] When reaction was carried out using *o*-aminoacetophenone, *o*-hydroxyacetophenone or *o*-mercaptoacetophenone oximes, the same heterocycles were obtained *via* the Beckmann rearrangement[23] in satisfactory (38–86%) yields. Several other substituted benzoxazoles were also synthesised in 67–97% yields from the reaction of aryl, alkyl, styryl and heteroaryl carboxylic acids and *o*-aminophenol in the presence of PPSE.[24]



XH=NH, O, S

66 X=NH
67 X=O
68 X=S

65%-93%



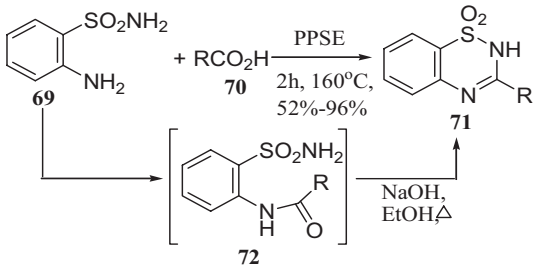
XH=NH, O, S

66 X=NH
67 X=O
68 X=S

38%-86%

1,2,4-Benzothiadiazines

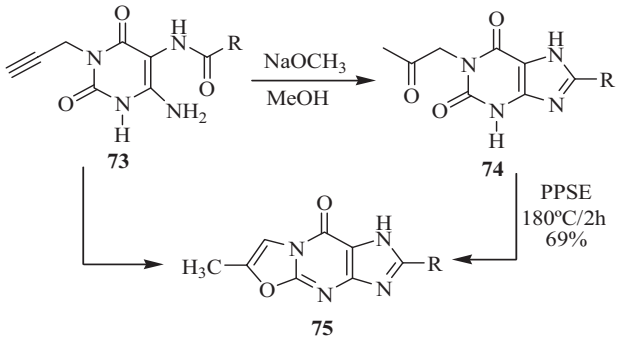
The reaction of 2-aminobenzenesulfonamide **69** with various saturated and unsaturated aliphatic and aromatic carboxylic acids **70** in an excess of PPSE for 2 h at 160°C, afforded 2*H*-1,2,4-benzothiadiazine 1,1-dioxides **71** in good yields.[25] This represents a major contribution in the direct synthesis of these compounds, which are usually prepared in a two step procedure by the cyclodehydration under basic conditions of isolated 2-(*N*-acylamino)benzenesulfonamides **72.** Although the mechanism of this heterocyclisation is not clear in detail, the authors proposed the corresponding amide (**72**) or their silylated analogues as possible intermediates for the ring closure, since when several of the above acids were refluxed in 1,2-dichloroethane for 2 h, a mixture of **71** and **72** was detected. However, when the reaction time was extended to 5 h, **71** was exclusively obtained in >84% yield.



R= C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, H_3C-$(CH_2)_4$-, *c*-C_6H_{11},C_6H_5-CH=CH

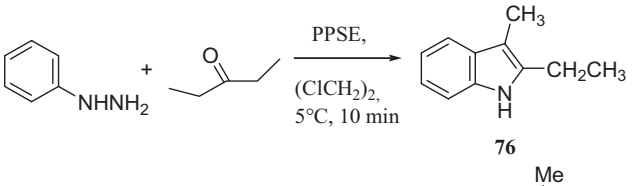
Oxazolopurines

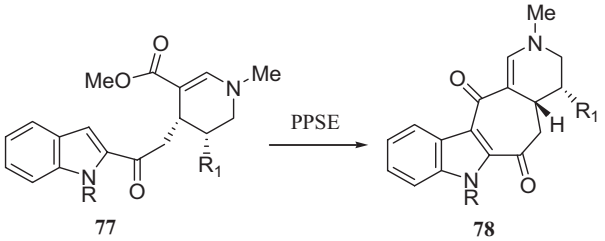
Employing its high condensation power, several oxazolo[3,2-*a*]purinones **75** have been obtained from the treatment of propynyluracil **73** with PPSE.[26] The formation of oxazolopurinones **75** derivatives from 1-(2-propynyl)uracils **73** using PPSE should proceed by a two steps mechanism, which involves the initial hydration of the triple bond followed by a cyclocondensation of **74** to obtain the oxazol ring.

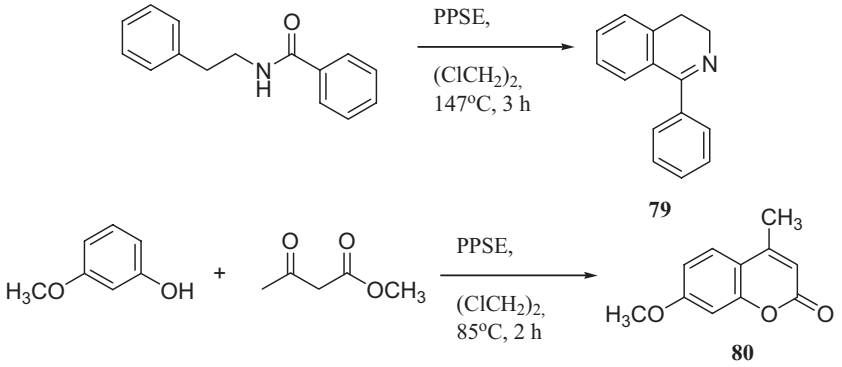


Indoles, isoquinolines and coumarins

PPSE has been succesfully employed for the Fischer Indole synthesis.[6] For example, 2-ethyl-3-methylindole **76** was prepared from phenylhydrazine and diethyl ketone using PPSE at 85°C for 10 minutes in 88% yield. A short route for the construction of the tetracyclic ring system of silicine-methuenine alkaloids was developed,[27] involving a partial hydrogenation followed by cyclocondensation of pyridine derivatives **77** in the presence of PPSE at 100°C, to form the corresponding *trans*-pyrido[3',4':4,5]cyclohept[1,2-b]indoles **78**.



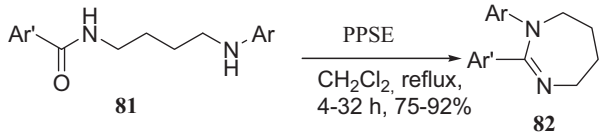




1-Phenyl-3,4-dihydroisoquinoline **79** was also directly obtained through a Bischler–Napieralski PPSE promoted reaction in 82% yield.[6] The Peckman synthesis of coumarin **80** was performed using a hot PPSE solution (1,2-dichloroethane, 85°C, 2 h) of resorcinol monomethyl ether and methyl acetoacetate.[6]

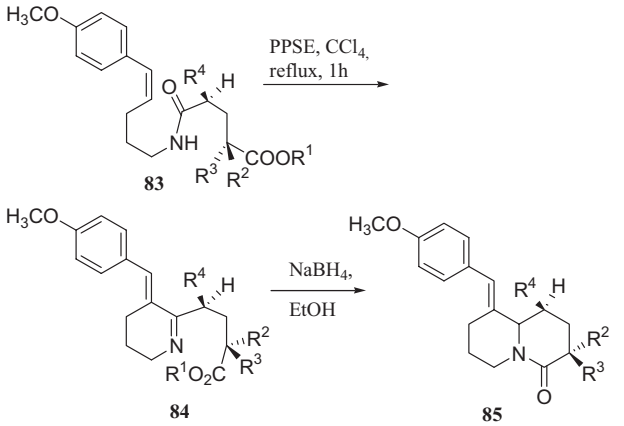
1,3-Tetrahydrodiazepines

The PPSE-promoted cyclodehydration of *N*-aryl-*N*'-benzoyl-tetramethylenediamines **81** gave considerable better yields for the preparation of 1*H*-4,5,6,7-tetrahydro-1,3-diazepines **82**,[19,28] than those obtained when PPE was employed.[29,30] The authors attributed the longer reaction times for PPSE due, probably, to the stronger dehydration power of PPE.[2]



Tetrahydropyridines

The synthetic tetrahydropyridine intermediate **83** was obtained by the PPSE-promoted cyclodehydration of the amide precursor **84** in low to moderate yields (24–80%), during the preparation of quinolizidinones **85** based on a vinylogous Bischler-Napieralski nitrilium ion cyclisation.[31] A strong electron donor, such as a *p*-methoxy group, was necessary in the styryl fragment for the ring generation.



Conclusion

Since the discovery of PPSE in 1981, it has been employed for a variety of useful organic reactions; the strong dehydration power, ease of preparation and the moderate reaction conditions usually required when compared with other dehydrating agents such as PPA and PPE, makes this reagent an important tool to consider for the promotion of heterocyclisation reactions and other important type of organic transformations.

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