Utility of Alkylthiopyrimidines in Heterocyclic chemistry

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1. Introduction

The chemistry of alkylthiopyrimidine derivatives is interesting both from theoretical and applied points of view. In spite of enormous literature and patents on both chemistry and utility of these compounds but several aspects of the chemistry of this interesting class of compounds are still unsettled. The pyrimidine ring system is present in many natural products, pharmaceuticals, agrochemicals, etc. Thus, there is a continuous quest for efficient methods of synthesis of pyrimidine derivatives \[1,2\]. On the other hand, alkylthiopyrimidines are widely used as agrochemicals. Particularly, 4-alkylthiopyrimidine derivatives have shown excellent broad spectrum herbicidal activity in transplanted paddy rice \[3\]. Alkylthiopyrimidones are precursors for the preparation of anilinopyrimidones, which are useful as insecticidal and acaricidal agents capable of controlling pest of agrohorticultural plants \[4\]. 2-Alkylthiopyrimidine derivatives have found application as agrochemical fungicides \[5,6\] and exhibit remarkable activity as rubella virus inhibitors \[7,8\]. Herbicidal compositions based on 5-alkylthiopyrimidines are used as postemergence herbicides for cereals \[9,10\]. Recent investigations have demonstrated that substituted 6-methylthiopyrimidones present antimicrobial activity against pathogenic bacteria agents including Mycobacterium tuberculosis \[11\] and against the Gram positive bacterium, Nocardia farcinica, and against the parasite Trypanosoma brucei brucei \[12\].

2. Synthesis of Alkylthiopyrimidines

2.1. Using \(\alpha\)-halo carbonyl compounds

Reaction of 5-ethoxycarbonyl-4-methyl-2-phenylpyrimidine-6(1H)-thione 1, with a series of \(\alpha\)-halo carbonyl compounds gave S-alkyl derivatives 2 \((R = \text{EtO}, \text{Ph}, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, \text{PhNH}, 4-\text{ClC}_6\text{H}_4\text{NH}, 4-\text{MeOC}_6\text{H}_4\text{NH})\) \[13\].

2.2. Using 2,6-difluorobenzyl bromide

Treatment of 4-amino-6-hydroxy-2-mercaptopyrimidine 3 in 50% EtOH with solid NaOH followed by addition of 2, 6-difluorobenzyl bromide 4 afforded 6-amino-2-(2, 6-difluorophenylthio) pyrimidin-4-ol 5 \[14\].
2.3. Using bromoacetaldehyde acetals

S-alkylation of 5-alkyl-6-(arylmethyl)-2-thiouracils 6 was performed with 2-bromoacetaldehyde acetal to furnish the S-[bis(alkoxy)ethyl] derivatives (R3 = Me, Et, CH2CH2) 7 and with allyl bromide to furnish S-allyl derivatives 9 [15].

2.4. Thioetherification

Thioetherification reaction of Me 2-(4,6-dichloro-2-methyl-5-pyrimidinyl)acetate 10 by MeSNa followed by etherification by 2-(NC)C6H4OC6H4(OH)-3 11 afforded α-(4-alkythio-5-pyrimidinyl)-α-methoximinoacetates and β-methoxyacrylates 12 [R1 = R3 = Me, R2 = C6H4[OC6H4(CN)-2]-3] which used as agrochemical fungicides [16].

2.5. Photochemical reactions

Reaction of 3-isothiocyanato-2-propeniminium perchlorates Ar-C(NCS):CH:N’Me2 ClO4 [Ar = (un)substituted phenyl] with hydroxylamine gave 1-hydroxy-2(1H)-pyrimidine-2-thiones 13 [R=H] which can be O-acylated with RCOCI [R= Bu, Me, Pr, pentadecyl, benzyl, phenyl] to give 1-acyloxy-4-aryl-2(1H)-pyrimidine-2-thiones 13 [R = R1CO], which underwent photochemical homolysis affording 2-alkylthiopyrimidines 14 [17].

Photochemical addition reactions of pyrimidine-4(3H)-thione 15, in the presence of electron-poor alkenes e.g. (R = Ph, R1 = H, R2 = R3 = Me), gave 4-alkylthiopyrimidines 16 (R2 = SCH2CHR1). Similar irradiation of quinazoline-4(3H)-thiones with electron-rich alkenes (R = CO2Me, CN, R1 = Me) gave 4-substituted quinazolines e.g. 17 (R3 = H, Me) [18].

2.6. Using dimethyl sulfate

Treating sodium 4-amino-6-hydroxypyrimidine-2-thiolate with di-methylsulfate in H2O while adjusting the mixture to pH 2-7 with aqueous sodium hydroxide gave a 99.9% yield of 4,6-dihydroxy-2-methylthiopyrimidine 9 with purity 96.9% [19].

2.7. Cyclocondensation reactions

Cyclocondensation of 2-(amino(alkylthio)methylene)malononitrile 20 with CS2 gave thiopyrimidine derivatives 21, followed by alkylation with XCH2R1 (X = Cl, Br, Iodo) to give 2,4,6-tris(alkylthio)pyrimidine-5-carbonitriles 22 [R = R1 = R2 = alkyl, (halo)aryl, cyano, secondary carbamoyl, PhCO] which is useful as gastroprotectants and as intermediates for other drugs [20].

Cyclocondensation of a ternary mixture of RCHO 23 (R = 3-indolyl, 2-pyrrolyl), ethyl cyanoacetate, and S-methylthiourea in pyridine yielded methylthiopyrimidinones 24 (same R, R1 = Me, R2 = H) [21]. The reaction seemed to be performed in one pot using sodium carbonate as catalyst with good yield [22].
Condensation of thioesters, S-Alkyl and S-aryl thioesters with nitriles in the presence of triflic anhydride to form substituted 4-alkylthio-25 and 4-arylthiopyrimidines 26[23].

2.8. Using halogenated active methylene compounds

Reactions of 4-mercaptopyrimidines 27 (R = 2-furyl, 4-MeOC6H4) with halogenated active methylene compounds in aqueous sodium carbonate gave alkylthiopyrimidines derivatives 28 (R1 = Me, Et, CH2CO2Et, CH2CO2H, PhCH2)[24].

On the other hand, protection of thiol group of 2-thiouracil with various alkylating agents in presence of base furnished 2-alkylthiouracils 30, which on reaction with phenylselenenyl chloride in pyridine under anhydrous conditions yielded 5-phenylselenenyl-2-alkylthiopyrimidines 31. Chlorination of 31 with excess POCI3 under reflux furnished 5-phenylselenenyl-4-chloro-2-alkylthiopyrimidines 32, which underwent aromatic nucleophilic substitution reaction with oxygen nucleophiles like sodium phenoxides furnished the 5-phenylselenenyl-2,4-disubstituted pyrimidines 33 in 60-75% yield. All the synthesized compounds were evaluated for antimicrobial activities [25].

2.9. Alkali metal hydroxides

Treatment of 2-mercaptopyrimidines 34 (R1 = H; X, Y = OH, alkoxy, NH2) and/ or their S-alkyl derivatives with (R1O)2SO2 (R1 = alkyl) or by heating 1-alkylpyrimidinones 35 (R2 = H, alkyl; X = OH, alkoxy, NH2, R3 = alkyl), respectively, in aqueous solutions of alkali metal hydroxides or alcohols in the presence of alkali metal or alkaline earth sulfites or hydrogen sulfites afforded compounds 36 and/ or their S-alkyl derivatives [26].

Treatment of tert-butyl((E)-prop-1-enyl)carbamic chloride 37 with a soln. of NH4SCN in Me2CO, and then alkylated with EtI in MeCOEt containing K2CO3 gave 4-mercapto-2(1H)-pyrimidinones 38 (R1 = Me, R2 = Et) which used as herbicides[27].

Cyclocondensation of ethylacetoacetae 39 with thiourea in MeOH containing NaOMe gave pyrimidines 40 which was alkylated by RX (R = Me, Et, Pr, Me2CH, PhCH2, X = I for Me, undefined for others) in aqueous NaOH to give 78-95% alkylthiopyrimidinols (6-methyl-2-thiouracil derivatives) 41[28].
2.10. Using aryl and/or heteroaryl-thioamide

2-Aryl-4,6-dimercaptopypyrimidines 42 [R = (un)substituted aryl, heteroaryl; R₁ = alkoxy carbonyl, cyano; R₂ = alkyl, PhCH₂, aryl, heteroaryl] were prepared as potential pharmaceutical intermediates in a 2-step process by treating alkylthiobutenenitril 43 R₂SCR₃:CR₁CN (R₃ = alkylthio, amino) with RCSNH₂ in the presence of a mineral or Lewis acid, followed by treatment with a base [29].

2.11. Using alkoxyalkylamines

2,4-Diamino-6-halo-5-alkylthiopyrimidines 44 (R = halo; R₁ = alkyl, haloalkyl; R₂, R₃ = H, alkyl, R₄ = alkyl; Z = alkylene) were prepared by the condensation reaction of trihalopyrimidines with the alkoxyalkylamines HNR₄(ZOR₅) and further reaction with the amines HNR₂R₃, which could be applied as herbicides and fungicides [30].

2.12. Using alcohols

Reaction of 2,4,6-trichloro-5-alkylthiopyrimidine 45 with lower alcohols in the presence of bases followed by reaction of the resulting compound with nucleophiles to give 5-alkylthiopyrimidine derivatives 46 (R, R₁ = Me, Me, N₃; Me, Et, MeO; Me, Et, HCAcCH₂; Me, Me₂CH, MeO; Me, Me, FCH₂CH₂O; Me, Me, ClCCH₂O; Me, Me, F,CCH₂O; Me, Me, Me₂C:CHCH₂CH₂CMe₂:CHCH₂O; Et, Me₂CH, Me₂CH) [31].

Condensation of 5-(ethylthio)barbituric acid 47 with POC₁₃ and PhNMe₂ gave 5-ethylthio-2,4,6-trichloropyrimidine 48 which was treated with 95% NaOH in MeOH to give the alkylthiopyrimidine derivatives 49 (R = Cl, R₁ = Me, R₂ = Et) [32].

Treating of 2-Chloro-5-(trifluoromethyl)pyrimidine 50 with ethanethiol and KOCMe₂ to give 51 (R₁ = Et, n = 0) [33].

2.13. Using n-alkanesulfenyl halides

The reaction of n-alkanesulfenyl halides with a number of pyrimidines, in which the pyrimidine 5-position is unsubstituted but which carry at least two strongly electron-releasing substituents, gave 5-alkylthiopyrimidines 52 in good yield [34].

2.14. Nucleophilic displacement reaction

Tosylation reaction of pyrimidinone 53 gives the tosylate 54 which undergoes nucleophilic displacement with a series of different secondary amines to give 2-alkylthio-4-dialkylaminopyrimidines 55 which exhibits remarkable activity as rubella virus inhibitors, where introducing a halogen atom at C-5 will increase the chemical diversity of these compounds [35].
3. Reactions of alkylthiopyrimidines

It was reported that, 2-alkylthiopyrimidine derivatives underwent nucleophilic substitution at the 2-position in >70% yield with RSH in basic medium. A 5-halogen or 6-NH₂ substituent hindered the reaction, but a 1-Me or 6-OH group facilitated it by influencing tautomerization [36]. Hereby the general reactions of alkylthiopyrimidines will be mentioned.

3.1. Reaction with hydrazines

Treatment of 2-alkylthiopyrimidinium salts 56 (R₃ = alkyl, X = acid residue) with H₂NNHR₂ gave 2(1H)-1-amino-2-iminopyrimidines 57 as intermediates for cardiovascular agents (R, R₁ = alkyl, aryl, heteroaryl; R₂ = H, alkyl, aryl), useful as intermediates for cardiovascular agents [37].

Hydrazino (or azido)-5-alkylthiopyrimidines 58 (R = Me, R₁ = NHNNH₂, R₂ = Cl; R = Me, R₁ = Cl, R₂ = NHNNH₂) were prepared by treatment of pyrimidine derivatives (R = alkyl; R₁ = Cl, hydrazino; one of R₁ and R₂ = Cl or amino and the other is N₁ or hydrazino) with N₂H₄. The synthesized compounds used as pesticides [38,39].

Reactions of alkylthiopyrimidines derivatives 59 (R = 2-furyl, 4-MeOC₆H₄; R₁ = CH₂CO₂Et) with hydrazine hydrate in ethanol gave the acid hydrazides 60. The latter compounds condensed with aromatic aldehydes and ketones to give the hydrazones 61 (R₂ = H, Me; R₃ = H, MeO, NO₂, Cl)[23].

3.2. Reaction with pyrazole

Treatment of 4-(4-tert-butylphenoxy)-2-propylthiopyrimidine-5-carboxylic acid 62 with pyrazole, 4-(1-pyrrolidino)pyridine, and DCC gave 4-(4-tert-butylphenoxy)-2-alkylthiopyrimidinecarboxylic acid pyrazolamides 63 (R = Pr) used as agrochemical fungicides [40].

3.3. Reaction with aniline

Reaction of 4,6-difluoro-2-methylthiopyrimidine 64 in AcNMe₂ with PhNH₂ and Et₃N gave 4-anilino-6-fluoro-2-alkylthiopyrimidine derivatives 65 (R₁ = C₁-3 alkyl; R₂ = H, C₁-3 alkyl; R₃ = H, lower alkyl, Q; Z = H, halo, lower alkyl, lower alkenyl, lower alkoxy, CF₃, (alkyl)amino; n, m = 0-12; when m = 2, Z may represent different groups) used as agricultural and horticultural fungicides [41].

3.4. Oxidation

Oxidation of 4-alkylthiopyrimidines 66 (R = Me, H; R₁ = Me, Et) with H₂O₂ and HCO₂H gave the corresponding pyrimidinones derivatives 67 [42].
3.5. Reaction with furaldehyde derivatives

Treating of 2-alkylthio-4-methylpyrimidine 68 with 5-nitro-2-furaldehyde 69 (or its diacetate) in the presence of CrCl₂·AcOH gave 2-alkylthiopyrimidine derivatives 70 with nitrofuran nucleus which showed antibacterial activity against Escherichia coli and Staphylococcus aureus [43].

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{68} \\
\text{SCH}_3 & \quad \text{69} \\
\text{O} & \quad \text{70}
\end{align*}
\]

3.6. Reaction with potassium thiocyanate

Refluxing of 2-alkylthio-4-chloro-6-methylpyrimidines 71 with potassium thiocyanate in ethanol gave mixtures of corresponding thio- and isothiocyanates, which on heating in dry xylene isomerized completely to isothiocyanates 72. The latter reacted with 4-alkoxyanilines to give N-(4-alkoxyphenyl)-N'-(2-methylthio-6-methyl-4-pyrimidinyl) thiocarbamides 73. The thiocarbamides possessing methylthio group at the 2nd position of pyrimidine ring exhibited anti-inflammatory activity [44].

\[
\begin{align*}
\text{N} & \quad \text{71} \\
\text{Cl} & \quad \text{KSCN} \\
\text{RS} & \quad \text{EtOH} \\
\text{O} & \quad \text{72} \\
\text{NH}_2 & \quad \text{R}_1\text{O}
\end{align*}
\]

3.7. Cyclization reaction

Cyclization reaction of S-alkyl derivatives 74 (R = EtO, Ph, 4-ClC₆H₄) with sodium ethoxide afforded the thienopyrimidines 75 [13].

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{74} \\
\text{SCH}_3 & \quad \text{75}
\end{align*}
\]

3.8. Reaction with α-bromoacetophenone

Reaction of p-substituted α-bromoacetophenone 76 (R; H, CH₃, OCH₃, NO₂, Cl) with 4-alkyl-5- amino-6-thiopyrimidines 77 [R; N(CH₃)₂, OCH₃] leads to the formation of 5-alkyl-(4-substituted phenyl)-2H-pyrimidino[5, 6-d]-1,4-thiazines 78 [45].

\[
\begin{align*}
\text{COCH}_2\text{Br} & \quad \text{R} \\
\text{R} & \quad \text{76} \\
\text{Na}_2\text{CO}_3 & \quad \text{77} \\
\text{CH}_3 & \quad \text{78}
\end{align*}
\]

3.9. Reactions with 2-bromodimedone derivatives

Reaction of 5-amino-6-mercaptopypirimidines 79 with 2-bromodimedone 80 leads to form 5-amino-6-(4,4-dimethyl-1,3-dioxocyclohexyl)thiopyrimidines, which when heated or treated with acids undergo ring closure to form 9-oxo-5H-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]thiazines 81 [46,47]. These reactions were carried out in ethanol at 18-20°C in the presence of an equimolar amount of KOH. The products were reported to have antifolic, cytotoxic, and cytostatic activity [48].

\[
\begin{align*}
\text{COCH}_2\text{Br} & \quad \text{R} \\
\text{R} & \quad \text{79} \\
\text{KOH} & \quad \text{80} \\
\text{CH}_3 & \quad \text{81}
\end{align*}
\]

3.10. Complex formation

2-Thione-4,6-diamino-5-hydroxypyrimidine (HTDAHP) 82 behaves as a bidentate ligand, forming five membered hydroxyl-amino chelates or four-membered cyclic nitrogen-sulphur chelates 83, 84 without any participation of the pendant amino or hydroxy groups, in complexation with Fe(III), Ni(II), Ag(I) and Ru (II). The Ag (I) complexes showed inhabitation activity against fungi (Aspergillus niger and Candida albicans) and bacteria (Staphylococcus aureus and Pseudomonas aeruginosa) have been investigated [50].

\[
\begin{align*}
\text{N} & \quad \text{73} \\
\text{S} & \quad \text{82} \\
\text{H} & \quad \text{83}
\end{align*}
\]

3.11. Claisen rearrangement reaction

Preparation of pyrido[2,3-d]pyrimidines from 2-alkylthiopyrimidines 85, the formation of a new carbon-carbon bond at C5 is required, a reaction, that is, very limited in scope. However Claisen type rearrangement of simple 4-allylic ethers

\[
\begin{align*}
\text{N} & \quad \text{82} \\
\text{S} & \quad \text{83} \\
\text{H} & \quad \text{84}
\end{align*}
\]
affords C5 substituted pyrimidines 86 readily; in cases with an ester substituent, rearrangement occurs at room temperature. Subsequent cyclisation to afford 6-methylpyrido[2,3-d]pyrimidin-7(8H)-ones 87 was achieved in high yield. Using allylic ethers derived from 3-chloromethyl-4-arylbut-3-en-2-ones as substrates, a new titanium[IV]chloride catalysed reaction affording 6-aryl[(1H)-methylpyrido[2,3-d]pyrimidin-7(8H)-ones 88 was discovered. In biological assays unexpected hits were found for activity against the Gram positive bacterium, Nocardia farcinia, and against the parasite Trypanosoma brucei brucei, illustrating the value of diversity oriented synthesis in the discovery of biologically active compounds [12].

4. Conclusion

Alkylthiopyrimidines are easily available and offer countless modifications by numerous reaction modes in various positions due to their high reactivity. This has been comprehensively documented. Apart from the synthetic interest, the known and expected biological or medicinal activities of the numerous derivatives deserve particular mention. The field is far from being exhausted in all of its subdivisions and many new developments and uses. In fact, more recent work used some of the title compounds for reactions both at the thione function and further modifications by numerous reaction modes in various positions. In biological assays unexpected hits were found for activity against the Gram positive bacterium, Nocardia farcinia, and against the parasite Trypanosoma brucei brucei, illustrating the value of diversity oriented synthesis in the discovery of biologically active compounds [12].

References