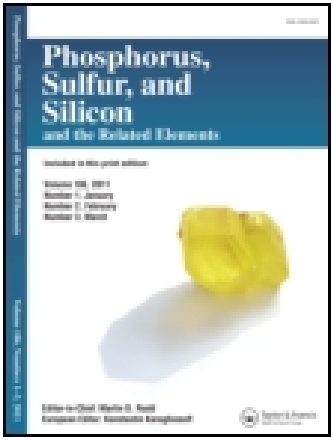

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A Novel Approach Toward the Synthesis and Characterization of Pyrimidyl Chalcogen Compounds

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A variety of hitherto unknown symmetrical and unsymmetrical pyrimidyl chalcogen compounds have been synthesized and characterized by elemental analysis using various spectroscopic techniques viz. NMR ^{1}H, ^{13}C, ^{77}Se and infrared. Two different methodologies were employed. The first method involves the use of hydrazine hydrate as reducing agent to generate dichalcogenide anions followed by reaction with 2, 4-dichloropyrimidine to give the dichalcogenide compounds in good yield. The second method employs chlorine-magnesium exchange of 2,4-dichloropyrimidine using iso propyl magnesium chloride. The synthesis of the mixed phenyl pyrimidyl selenides have been achieved using sodium borohydride in ethanol as a reductive reagent to cleave Se-Se bond followed by alkylation with 2-chloro-4, 6-dimethylpyrimidine and 2, 4-dichloropyrimidine.

Keywords 2,4-dichloropyrimidine; diselenide; pyrimidine; selenium

INTRODUCTION

Hetrocycles are major building blocks in many biologically active molecules and their functionalization is an active field of research.[1] The pyrimidine moiety is widely found in natural products and its compounds are widely used as inhibitors of human immunodeficiency virus,[2] act as effective anti-cancer drugs,[3] and as anti-rejection drugs[4] in transplantations. It is curious to note, however, that the pyrimidine compounds of sulfur and selenium do not occupy the appropriate

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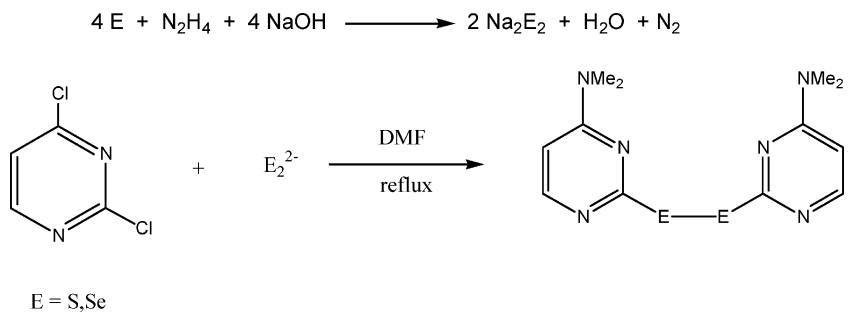


E = S,Se

SCHEME 1

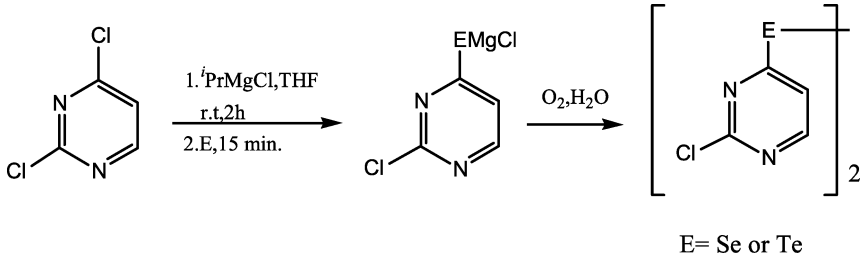
place in the literature as compared to alkyl/aryl/pyridyl chalcogenides. In this paper, we wish to report a mild, convenient and economical method for the synthesis of some newly designed pyrimidyl chalcogen compounds (Scheme 1).

RESULTS AND DISCUSSION

Jerchel et al.[5] were the first to explore the chemistry of pyridyl selenium compounds and synthesize bis (4-pyridyl) diselenide and bis (4-pyridyl) selenide by reacting N-pyridyl (4-pyridinium) chloride with hydrogen selenide. We, therefore, felt it necessary to develop a safe and convenient method for its preparation. Subsequently, the method was improved by reducing elemental selenium with sodium borohydride in different solvents by various coworkers.[6] Different methodologies in the subsequent years explored variations of the published procedures to improve the yield of 2,2'-dipyridyl diselenide. Bhasin et al.[7]have developed and optimized the conditions for the preparation of stable bis (2-pyridyl) diselenide/ditelluride by lithiation of pyridine using BF_3-Et_2O complex followed by insertion of elemental selenium/tellurium and subsequent oxidation.

In pursuance of our work on the synthesis of dipyridyl diselenide, we report herein a convenient, operationally simple and facile synthetic route for the synthesis of hitherto unknown dipyrimidyl dichalcogenide and phenyl pyrimidylselenides (Scheme 2). The starting materials 2-chloro-4, 6-dimethylpyrimidine and 2,4-dichloropyrimidine were prepared by chlorination of 4,6-dimethyl-2-hydroxypyrimidine hydrochloride and 2,4-dihydroxypyrimidine respectively using phosphorus oxychloride.

The synthetic strategy that has been followed to prepare bis [4-dimethylamino-2-pyrimidyl] dichalcogenide employs hydrazine

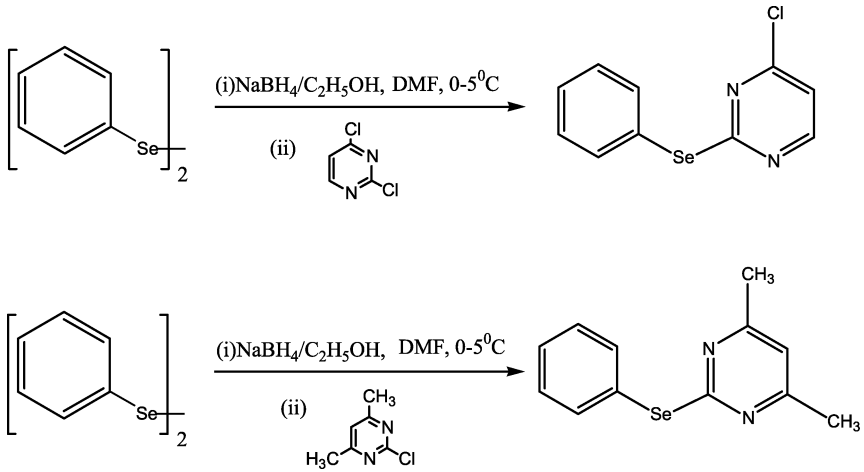


SCHEME 2

hydrate as the reducing reagent for chalcogens (S, Se) in dimethylformamide. It has been found that dimethyl formamide acts both as solvent and a nucleophile, leading to nucleophilic substitution of chlorine at fourth position by dimethyl amino group, -NMe_2.

Attempts to prepare the titled dichalcogenides by chlorine- magnesium exchange reaction employing isoopropylmagnesium chloride at fourth position was not successful.

To synthesize unsymmetrical pyrimidyl selenides, ethanolic sodium borohydride was used for the reductive cleavage of Se–Se bond in diphenyl diselenide (Scheme 3). Dimethyl formamide (DMF) has been employed as co-solvent in this reaction. It has been found that DMF improves the yield of the desired product by solubilizing the phenylselenolate ion, which is otherwise known to exist as a boron complex possessing diminished nucleophilicity.[8,9]



SCHEME 3

The disulfide/diselenide and monoselenides thus prepared are stable enough to be purified by column chromatography (silica gel using hexane-ethyl acetate) on a laboratory bench. The compounds are soluble in conventional organic solvents and have a shelf life of several months without any sign of decomposition even at room temperature. The compounds prepared have been fully characterized with the help of various spectroscopic techniques.

EXPERIMENTAL

All experiments were carried out in dry oxygen–free nitrogen atmosphere. IR spectra were recorded between KBr plates on a Perkin-Elmer Model 1430 ratio recording spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CCl_4/CDCl_3$ using tetramethylsilane as an internal standard and ^{77} Se with dimethylselenide as an external reference on a Jeol 300MHz spectrometer. Carbon, Hydrogen and Nitrogen were estimated micro analytically on a Perkin-Elmer 2400 CHN Elemental analyzer.

Synthesis of 4, 6-Dimethyl-2-hydroxypyrimidine Hydrochloride

Urea (12 g) in 100 ml of boiling ethanol (b.pt. 78°C) was treated with acetyl acetone (20 g) and the hot solution was treated with 27 ml of conc. HCl with stirring. The mixture was refluxed for 24 h after which time 24.0 g (75%) of 4, 6-Dimethyl-2-hydroxypyrimidine hydrochloride was isolated by filtration and subsequent washing with cold ethanol and diethyl ether.

Synthesis of 4, 6-Dimethyl-2-chloropyrimidine

The mixture of 4, 6-Dimethyl-2-hydroxypyrimidine hydrochloride (20.0 g, 0.125 mol) and phosphorous oxychloride (110 ml) was refluxed for 10 h, after which time the residual phosphorous oxychloride was removed in vacuo. The residual oil was poured into 50 g of ice and neutralized below 10°C with a concentrated solution of potassium hydroxide. The resulting mixture and 300 ml diethyl ether was vigorously stirred for 10 h. The organic extract was evaporated to dryness. The residual crude product was recrystallized from a minimal amount of petroleum ether (b.pt. 40–70°C) giving 13.8 g (77%) of colorless 4, 6-Dimethyl-2-chloropyrimidine plates. M.pt.37–38°C. ^{1}H NMR ($CDCl_3/CCl_4$); δ 6.89(s, 1H), 2.37(s, 6 H).

Synthesis of Bis [4-dimethylamino-2-pyrimidyl] Diselenide/Disulfide

To a vigorously stirred mixture of powdered sodium hydroxide (3.0 g, 75 mmol), elemental chalcogen (S = 1.6 g or Se = 4.0 g, 50 mmol) and dimethylformamide (30 ml), 100% hydrazine hydrate was added slowly. After stirring for nearly 6 hr. at room temperature, a solution of 4, 6-dimethyl-2-chloropyrimidine (100 mmol) dissolved in 15 ml DMF was added dropwise. The reaction was refluxed for 2–3 h and monitored by TLC. After completion of reaction, it is diluted with about 250 ml of distilled water and extracted in dichloromethane (3 × 50 ml). The organic layer was separated and solvent evaporated to get the crude product in solid form. The product was subjected to purification on a silica column using hexane as eluant.

General Procedure for Synthesis of Unsymmetrical Pyrimidyl Selenides

To a solution of Ar_2Se_2 (Ar = phenyl) in 50 ml of C_2H_5OH-DMF (3:2) was added 0.456 g (12 mmol) of $NaBH_4$ in parts with continuous stirring at 0–5°C; 10 mmol of alkylating agent (4, 6-dimethyl-2-chloropyrimidine or 2,4-dichloropyrimidine) diluted with equal volume of DMF was added drop wise. Reaction was complete within 1–2 h. Extraction is done in dichloromethane after evaporating ethanol under vacuum. The organic layer was repeatedly washed with distilled water (3 * 40 ml), dried over anhydrous sodium sulfate. Solvent was evaporated on rota evaporator and the product was subjected to purification on a silica column using hexane as eluant.

Bis [4-dimethylamino-2-pyrimidyl] Diselenide

Yield = 65%, Yellow crystalline solid, m.p. = 79–81°C, ^{1}H NMR; δ 7.9 (d, 1H), 6.83 (d, 1 H), 3.14 (s, 6H); ^{13}C NMR; δ161.2, 157.1,154.7,107.3,37.0; ^{77} Se NMR; 431.57; IR (KBr, cm^{-1}): 2924.4, 2853.3, 1566.0, 1521.4,1458, 1405.3, 1340.4, 786.8, 534.3; Anal. Calcd. for $C_{12}H_{16}N_6Se_2$; C, 33.60, H, 3.96, N, 20.79. Found; C, 34.97, H, 3.13, N, 16.32.

Bis [4-dimethylamino-2-pyrimidyl] Disulfide

Yield = 67%, Yellow crystalline solid, m.p. = 130°C, ^{1}H NMR; δ 8.50 (d, 1H), 7.45 (d, 1 H), 3.50 (s, 6H); ^{13}C NMR; δ160.2, 154.1, 150.4, 101.5, 34.0; IR (KBr, cm^{-1}); 2925.4, 1568.3, 1405.4, 1340.6, 1208.3, 790.4, 550.7.

4-6-Dimethyl-2-pyrimidylselenobenzene

Yield = 75%, White crystalline solid, m.p. = 58–62°C, ^{1}H NMR: δ 7.61(d,2H), 7.31(m,3H), 6.58 (s,1H), 2.28 (s,6 H) ; ^{13}C NMR: δ 170.3, 166.9, 136.9, 136.0, 129.6, 128.2, 117.5, 36.8, 23.8; ^{77} Se NMR: δ 486.8; IR (KBr,cm^{-1}): 2924.0, 1578.0, 1529.0, 1438.0, 1341.0, 783.0, 542.0; Anal. Calcd. for $C_{12}H_{12}N_2Se$; C, 54.50; H, 4.54, N, 10.60. Found: C, 37.03, H, 3.36, N, 12.38.

2-Phenylseleno-4-chloropyrimidine

Yield = 75%, White crystalline solid, m.p.= 49–51°C, 1H NMR: δ 8.08 (d, 1H), 7.00(d, 2H), 7.45 (m, 3H); ^{13}C NMR: δ 162.6, 161.3, 160.8, 159.8, 157.2, 120.0; ^{77} Se NMR: δ 500.69; IR (KBr, cm^{-1}): 2924.0,1542.0, 1518.0, 1478.0, 1439.0, 790.0, 592.6: Anal. Calcd. for C_{10} H_7Cl N_2Se; C, 44.28; H, 2.58, N, 10.33. Found: C, 44.42, H, 1.96, N, 9.71.

In summary, in this present paper, we have proposed a simple and convenient methodology to prepare novel pyrimidine chalcogen compounds in good to excellent yields.

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