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A facile one pot synthesis of 4-methylthieno[2,3-b]quinolin-3(2H)-one and 4-methylseleno[2,3-b]quinolin-3(2H)-one's by microwave irradiation under solvent free condition

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ABSTRACT

A simple and efficient procedure has been developed for the synthesis of quinolines containing thiotetronic ring and selenotetronic ring system. The methodology is based on cyclization reaction of 2-chloro, 2seleno-4-methyl quinoline with thioglycolic acid and chloroacetic acid by microwave irradiation in presence of anhydrous potassium carbonate catalyst under solvent free condition. The new compounds were characterized by elemental analysis, IR, ^{1}H NMR and mass spectral data.

KEYWORDS

Quinoline;
Thiotetronic ring;
Selenotetronic ring;
Microwave irradiation;
Solvent free condition.

INTRODUCTION

In recent years several synthetic methods gaining prominence for accessing sulfur and selenium containing compounds, especially five and six membered heterocycles fused to quinoline ring in linear fashion are found in natural products as well as in the synthetic compounds of biological importance[1-6]. In addition, the basic thiolactone ring(Figure 1) system is integral part of a number of naturally occurring thiotetronic acids which exhibit a wide range of biological activities, such as antibacterial[7,8], antiallergenic[9], antifungal[10], hypocholesteromic, hypolemic[11] and antiviral[12] activities.

Further, it is well known that number of heterocyclic compounds containing S and Se exhibit a wide variety of biological activities[13-15]. Even though sulfur and selenium are considered to be isosteric as defined by Langmuir[16] and Erlenmeyer[17], the reports about selenium-containing heterocyclics are few[18-20]. However, the medicinal application of isosterism has been reviewed by Klayman and Gunther[21]. The antioxidant and anticancer activity of selenium containing compounds have been reported[22-24] recently. Selenium plays an important role in decreasing oxidative stress in HIV-effected cells and possibly suppressing the rate of HIV replication[25,26]. Recent research proposes that HIV may be capable of incorporating host selenium into viral seleno proteins that have glutathione-peroxide activity. Though the significance of these findings require further clarification, they suggest that both human immune system

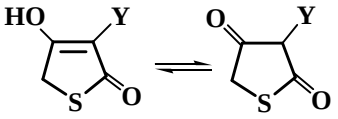

Figure 1: Thiotetronic ring system

and the activity of the virus are affected by selenium nutritional status[27,28]. In recent years, the number of publications devoted to various aspects of fused heterocycles containing sulfur and selenium has sharply increased. More publications have appeared during last two decades, 35-40% of them being patents.

Thus, the heterocycles containing sulfur(thiotetronic ring) and selenium(selenotetronic ring) represent excellent target for a number of research groups, and several procedures for the synthesis of these types of compounds have been found in the literature. The first synthetic approach for the synthesis of 3-substituted thiotetronic acids was reported by Benary[29] in 1913 in which thiolactic acid chlorides were used as acylating agents of active methylene compounds. In later years similar methods has been applied for the synthesis of various thiotetronic acids[30,31]. On the other hand, some of the quinoline derivatives, such as thienoquinolines and benzothienoquinoline are also exhibit antitumor, antimicrobial, hypocholesterolemic, hypolemic, antifungal and antiviral activities[32,35]. The extensive biological properties and pharmaceutical applications have attracted interests in development of such sulfur and selenium containing analogues.

Moreover, the microwave irradiation techniques have been adopted for the synthesis of different heterocyclic analogues mainly because to increase reaction rate, yield and reduce reaction time. Development of microwave irradiation techniques have helped immensely in developing newer, synthetic protocols towards an eco-friendly mode. So a number of research papers have been appeared proving the synthetic utility of microwave-induced organic reaction enhancement (MORE) chemistry in routine organic synthesis[36-39].

Hence, in view of biological importance of sulfur and selenium containing condensed heterocycles and in continuation of our quest on microwave assisted organic synthesis of condensed heterocycles, hitherto undescribed quinoline derivatives[40-42], we have developed a simple eco-friendly solvent free synthesis of 4-methylthieno[2,3-*b*]quinolin-3(2H)-one**(3a-h)** and 4-methylseleno[2,3-b]quinolin-3(2H)-one**(6a-h)** derivatives.

EXPERIMENTAL

The purity of the reactions was checked by thin layer chromatography(TLC) on silica gel plates using petroleum ether:ethyl acetate solvent. Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in KBr pellets on Perkin-Elmer 157 IR spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on EM-390 (300MHz) NMR spectrometer and mass spectra were recorded on MASPEC low resolution instrument operating at 70eV.

General procedure for the synthesis of 4-methyl thieno[2,3-b]quinolin-3(2H)-one's(3a-h)

A mixture of 2-chloro-4-methyl quinoline(1.77g, 0.01mol), thioglycolic acid(1.06g, 0.018mol) and anhydrous potassium carbonate(0.69g, 0.005mol) was taken in beaker and irradiated in a microwave oven for about 2-3 min in an interval of 10sec at 160 Watt. The progress of the reaction was monitored by TLC; further the reaction mixture was irradiated for 1-2min by adding 3-4ml of PPA, the obtained product was poured into ice-cold water, stirred well, basified with sodium hydrogen carbonate. The solid separated out was filtered, washed with water and dried and recrystalized from methanol.

Preparation of sodium selenide

Selenium powder(1g, 0.013mol) was taken in 500ml beaker containing water(25ml). Beaker was kept in the ice water bath to control the heat; sodium borohydride(0.026) was added in small portion, with stirring. Considerable foaming(liberation of hydrogen), occurred immediately. After addition of sodium borohydride water was added(25ml) along the side of the beaker and stirred for 15min, colourless or deep reddish NaHSe resulted and was readily used without further purification.

Preparation of 2-seleno-4-methyl-quinoline(4a-h)

To a solution of hydrogen selenide(0.013mol) and sodium borohydride(0.026mol) in water(5ml) was

added to 2-chloro-4-methyl quinoline(0.01) in ethanol (10ml). The reaction mixture was taken in a beaker and irradiated in MW at 160W for 5-6min, cooled poured into ice(10g) and acidified with dil.(4N)HCl. The resultant solid was washed with 30ml of water and recrystalized from excess of alcohol.

General procedure for the synthesis of 4-methyl seleno[2,3-b]quinolin-3(2H)-one's(6a-h)

A mixture of 2-seleno-4-methyl quinoline(1.77g, 0.01mol), chloro acetic acid(1.22g, 0.013mol) and anhydrous potassium carbonate(0.69g, 0.005mol) was taken in a beaker and irradiated in a microwave oven for about 2-3min in an interval of 10sec at 160 Watt. The progress of the reaction was monitored by TLC; further the reaction mixture was irradiated for 1-2min by adding 3-4ml of PPA, the obtained product was poured into ice-cold water, stirred well, basified with sodium hydrogen carbonate. The solid separated out was filtered, washed with water and dried and recrystalized from methanol.

4-methylthieno[2,3-b]quinolin-3(2H)-one(3a)

Pale yellow solid, 143-146^{0}C; Yield 85%(MW); IR(KBr)(cm^{-1}): 1695(C=O), 3109(C-H). ^{1}H NMR (300Hz, DMSO-d_6) δ(ppm) 7.09-8.1(m, 4H, Ar-H), 1.38(t, 3H, j=7.01, -CH_3), 4.09(s, 2H, CH_2). MS, m/z 315[M$^+$]. Calcd.(%) for $C_{12}H_9NOS$: C; 66.95, H; 4.21, N; 6.51. Found: C; 66.89, H; 4.24, N; 6.48.

4,7-dimethylthieno[2,3-b]quinolin-3(2H)-one(3b).

Yellow solid, mp.151-154^{0}C; Yield 82%(MW); IR(KBr)(cm^{-1}): 1702(C=O), 3091(C-H). ^{1}H NMR (300Hz, DMSO-d_6) δ(ppm) 7.29-8.1(m, 3H, Ar-H), 1.48(m, 6H, j=7.34, -2CH_3), 4.26(s, 2H, CH_2). MS, m/z 229 [M$^+$]. Calcd.(%) for $C_{13}H_{11}NOS$: C; 68.09, H; 4.84, N; 6.11. Found: C; 68.12, H; 4.81, N; 6.07.

6-methoxy-4-methylthieno[2,3-b]quinolin-3(2H)-one(3c)

Yellow solid, mp.135-138^{0}C; Yield 80%(MW); IR(KBr)(cm^{-1}): 1681(C=O), 3051(C-H). ^{1}H NMR (300Hz, DMSO-d_6) δ(ppm) 3.94(s, 3H, -O-CH_3), 7.02-8.2(m, 3H, Ar-H), 1.48(m, 3H, j=7.08, -CH_3), 4.17(s, 2H, CH_2). MS, m/z 245[M$^+$]. Calcd.(%) for $C_{13}H_{11}NO_2S$: C; 63.65, H; 4.52, N; 5.71. Found: C; 63.61, H; 4.54, N; 5.69.

4-methyl-6-nitrothieno[2,3-b]quinolin-3(2H)-one(3d)

Yellow solid, mp.140-143^{0}C; Yield 88%(MW); IR(KBr)(cm^{-1}): 1710(C=O), 3013(C-H). ^{1}H NMR (300Hz, DMSO-d_6) δ(ppm) 8.03(s, 2H, -CH_2), 7.54 (s, 1H, Ar-H), 1.31(m, 3H, j=7.08, -CH_3), 4.27(s, 2H, CH_2). MS, m/z 260 [M$^+$]. Calcd.(%) for $C_{12}H_8N_2O_3S$: C; 55.38, H; 3.10, N; 10.76. Found: C; 55.34, H; 3.13, N; 10.67.

4-methyl-7-nitrothieno[2,3-b]quinolin-3(2H)-one(3e)

Yellow solid, mp.154-157^{0}C; Yield 90%(MW); IR(KBr)(cm^{-1}): 1691(C=O), 3102(C-H). ^{1}H NMR (300Hz, DMSO-d_6) δ(ppm) 7.41(s, 1H, Ar-H), 8.1(s, 2H, -CH_2), 1.38(m, 3H, j=7.08, -CH_3), 4.13(s, 2H, CH_2). MS, m/z 260 [M$^+$]. Calcd.(%) for $C_{12}H_8N_2O_3S$: C; 55.38, H; 3.10, N; 10.76. Found: C; 55.33, H; 3.15, N; 10.7.

7-methoxy-4-methylthieno[2,3-b]quinolin-3(2H)-one(3f)

Pale yellow solid, mp.144-147^{0}C; Yield 81% (MW); IR(KBr)(cm^{-1}): 1697(C=O), 3083(C-H). ^{1}H NMR(300Hz, DMSO-d_6) δ(ppm) 3.79(s, 3H, -O-CH_3), 7.21-7.97(m, 3H, Ar-H), 1.41(m, 3H, j=7.08, -CH_3), 4.17(s, 2H, CH_2). MS, m/z 245 [M$^+$]. Calcd. (%) for $C_{13}H_{11}NO_2S$: C; 63.65, H; 4.52, N; 5.71. Found: C; 63.67, H; 4.55, N; 5.73.

6-chloro-4-methylthieno[2,3-b]quinolin-3(2H)-one(3g)

Yellow solid, mp.133-136^{0}C; Yield 80%(MW); IR(KBr)(cm^{-1}): 1703(C=O), 3112(C-H). ^{1}H NMR (300Hz, DMSO-d_6) δ(ppm) 7.05(s, 2H, -CH_2), 7.61 (s, 1H, Ar-H), 1.44(m, 3H, j=7.08, -CH_3), 4.09(s, 2H, CH_2). MS, m/z 249[M$^+$]. Calcd.(%) for $C_{12}H_8ClNOS$: C; 57.72, H; 3.23, N; 5.61. Found: C; 57.73, H; 3.20, N; 5.78.

4,6-dimethylthieno[2,3-b]quinolin-3(2H)-one(3h)

Pale yellow solid, mp.146-149^{0}C; Yield 79% (MW); IR(KBr)(cm^{-1}): 1678(C=O), 3028(C-H). ^{1}H NMR(300Hz, DMSO-d6) δ(ppm) 7.13-8.25(m, 3H, Ar-H), 1.35(m, 6H, j=7.34, -2CH_3), 4.37(s, 2H, CH_2). MS, m/z 229[M$^+$]. Calcd.(%) for $C_{13}H_{11}NOS$: C; 68.09, H; 4.84, N; 6.11. Found: C; 68.15, H; 4.78,

N; 6.15.

4-methylseleno[2,3-b]quinolin-3(2H)-one(6a)

Pale brown solid, 181-183^{0}C; Yield 69%(MW); IR(KBr)(cm^{-1}): 1678(C=O), 3115(C-H). ^{1}H NMR(300Hz, DMSO-d$_6$) δ(ppm) 7.2-7.9(m, 4H, Ar-H), 1.54(t, 3H, j=7.01, -CH$_3$), 4.15(s, 2H, CH$_2$). MS, m/z 262 [M$^+$]. Calcd.(%) for $C_{12}H_9NOSe$: C; 78.67, H; 4.95, N; 7.65. Found: C; 78.65, H; 4.93, N; 7.66.

4,7-dimethylseleno[2,3-b]quinolin-3(2H)-one(6b).

Brown solid, mp.198-201^{0}C; Yield 73%(MW); IR (KBr)(cm^{-1}): 1690(C=O), 3048(C-H). ^{1}H NMR (300Hz, DMSO-d$_6$) δ(ppm) 7.4-7.9(m, 3H, Ar-H), 1.41(m, 6H, j=7.34, -2CH$_3$), 4.19(s, 2H, CH$_2$). MS, m/z 276 [M$^+$]. Calcd.(%) for $C_{13}H_{11}NOSe$: C; 79.16, H; 5.62, N; 7.10. Found: C; 79.12, H; 5.69, N; 7.15.

6-methoxy-4-methylseleno[2,3-b]quinolin-3(2H)-one(6c)

Brown solid, mp.179-180^{0}C; Yield 65%(MW); IR (KBr)(cm^{-1}): 1663(C=O), 3024(C-H). ^{1}H NMR (300Hz, DMSO-d$_6$) δ(ppm) 3.89(s, 3H, -O-CH$_3$), 7.5-7.9(m, 3H, Ar-H), 1.41(m, 3H, j=7.08, -CH$_3$), 4.22(s, 2H, CH$_2$). MS, m/z 292 [M$^+$]. Calcd.(%) for $C_{13}H_{11}NO_2Se$: C; 73.22, H; 5.20, N; 6.57. Found: C; 73.25, H; 5.18, N; 6.55.

4-methyl-6-nitroseleno[2,3-b]quinolin-3(2H)-one(6d)

Brown solid, mp.205-207^{0}C; Yield 75%(MW); IR (KBr)(cm^{-1}): 1662(C=O), 3083(C-H). ^{1}H NMR (300Hz, DMSO-d$_6$) δ(ppm) 8.24(s, 2H, -CH$_2$), 7.61 (s, 1H, Ar-H), 1.42(m, 3H, j=7.08, -CH$_3$), 4.37(s, 2H, CH$_2$). MS, m/z 307[M$^+$]. Calcd.(%)for $C_{12}H_8N_2O_3Se$: C; 63.16, H; 3.53, N; 12.28. Found: C; 63.11, H; 3.49, N; 12.26.

4-methyl-7-nitroseleno[2,3-b]quinolin-3(2H)-one(6e)

Brown solid, mp.192-194^{0}C; Yield 78%(MW); IR (KBr)(cm^{-1}): 1705(C=O), 3115(C-H). ^{1}H NMR (300Hz, DMSO-d$_6$) δ(ppm) 7.64(s, 1H, Ar-H), 8.3(s, 2H, -CH$_2$), 1.46(m, 3H, j=7.08, -CH$_3$), 4.24(s, 2H, CH$_2$). MS, m/z 307[M$^+$]. Calcd.(%) for $C_{12}H_8N_2O_3Se$: C C; 63.16, H; 3.53, N; 12.28. Found: C; 63.18, H; 3.56, N; 12.30.

7-methoxy-4-methylseleno[2,3-b]quinolin-3(2H)-one(6f)

Pale brown solid, mp.185-188^{0}C; Yield 64% (MW); IR(KBr)(cm^{-1}): 1684(C=O), 3107(C-H). ^{1}H NMR(300Hz, DMSO-d$_6$) δ(ppm) 3.82(s, 3H, -O-CH$_3$), 7.41-7.8(m, 3H, Ar-H), 1.38(m, 3H, j=7.08, -CH$_3$), 4.23(s, 2H, CH$_2$). MS, m/z 292 [M$^+$]. Calcd. (%) for $C_{13}H_{11}NO_2Se$: C; 73.22, H; 5.20, N; 6.57. Found: C; 73.21, H; 5.25, N; 6.60.

6-chloro-4-methylseleno[2,3-b]quinolin-3(2H)-one(6g)

Brown solid, mp.153-155^{0}C; Yield 57%(MW); IR(KBr)(cm^{-1}): 1673(C=O), 2098(C-H). ^{1}H NMR (300Hz, DMSO-d$_6$) δ(ppm) 7.18(s, 2H, -CH$_2$), 7.56 (s, 1H, Ar-H), 1.38(m, 3H, j=7.08, -CH$_3$), 4.15(s, 2H, CH$_2$). MS, m/z 296 [M$^+$]. Calcd.(%) for $C_{12}H_8ClNOSe$: C; 66.22, H; 3.70, N; 6.44. Found: C; 66.20, H; 3.68, N; 6.41.

4,6-dimethylseleno[2,3-b]quinolin-3(2H)-one(6h)

Brown solid, mp.196-198^{0}C; Yield 71%(MW); IR (KBr)(cm^{-1}): 1691(C=O), 3015(C-H). ^{1}H NMR (300Hz, DMSO-d6) δ(ppm) 7.25-7.81(m, 3H, Ar-H), 1.41(m, 6H, j=7.34, -2CH$_3$), 4.35(s, 2H, CH$_2$). MS, m/z 276[M$^+$]. Calcd.(%) for $C_{13}H_{11}NOSe$: C; 79.16, H; 5.62, N; 7.10. Found: C; 79.15, H; 5.61, N; 7.07.

RESULTS AND DISCUSSION

In present study, the quinoline derivatives containing thiotetronic ring**(3a-h)** and selenotetronic ring**(6a-h)** were accessed with excellent yield in one pot reaction between 2-chloro-4-methyl quinolines**(1a-h)**, 2-seleno-4-methyl quinolines**(6a-h)** with thioglycolic acid and chloroacetic acid. The product afforded through cyclization using polyphosphoric acid(PPA) in presence of anhydrous potassium carbonate as catalyst, over crossing through intermediate[(4-methylquinolin-2-yl)sulfanyl]acetic acid**(2a-h)**, by microwave irradiation technique under solvent free condition(SCHEME 1). The structures of new compounds were confirmed on the basis of elemental analysis and other spectral evidences.

As an example, the intermediate **(2a)** shows a sharp

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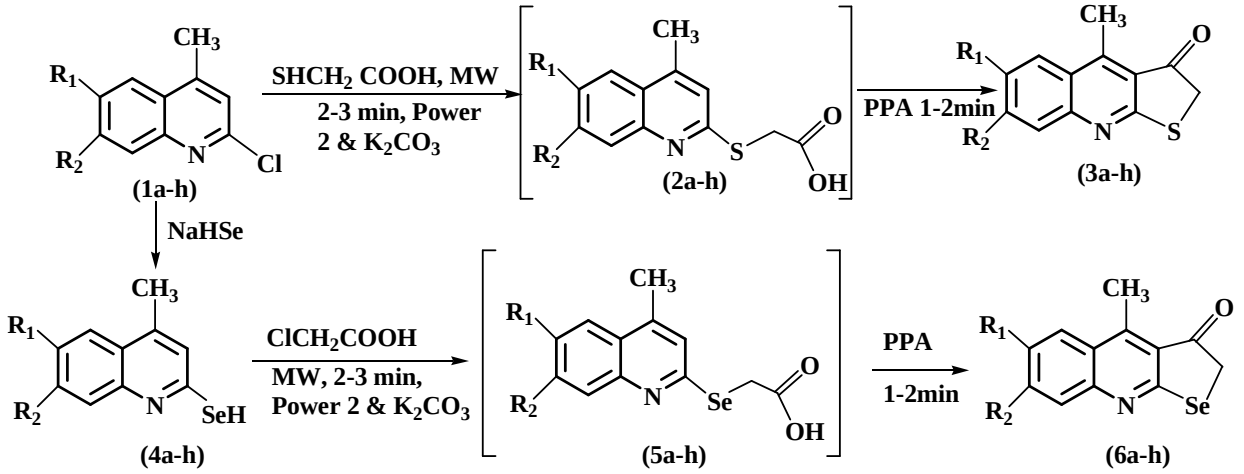

SCHEME 1: Reactions carried out to obtain targeted thieno(3a-h), seleno(6a-h) quinolines

IR absorption band at 1254cm^{-1} of OH(COOH group) and appearance of singlet belongs to 1H proton(COOH group) at 10.2 in IR and ^{1}H NMR spectra confirms the chlorine of quinoline ring replaced by thioglycolic acid. Further, when intermediate**(2a)** treated with PPA, the disappearance and shift of IR absorption frequency from 1254cm^{-1} of OH(COOH group) to1695cm^{-1} and absence of singlet belongs to 1H proton(COOH group) at δ 10.2 in**(3a)** confirms the cyclization of intermediate **(2a)**, which leads to the formation of **(3a)**. Finally, the structure was confirmed by its mass spectrum through the appearance of molecular ion peak at m/z 315[M$^+$]. Similarly other synthesized derivatives**(3b-h)**, were also exhibited such spectral characteristics.

Similarly other intermediate**(5a)** also shows a sharp IR absorption band at 1263 cm^{-1} of OH(COOH group) and appearance of singlet belongs to 1H proton(COOH group) at 10.5 in IR and ^{1}H NMR spectra confirms the of chloroacetic acid coupled to **(4a)**. Further, when intermediate 5a treated the with PPA, the disappearance and shift of IR absorption frequency from 1263 cm^{-1} OH(COOH group) to 1678cm^{-1} and absence of singlet belongs to 1H proton(COOH group) at δ10.5 in **(6a)** confirms the cyclization of intermediate **(5a)**, which leads to the formation of **(3a)**. Finally, the structure was confirmed by its mass spectrum through the appearance of molecular ion peak at m/z 262[M$^+$]. Similarly other synthesized derivatives**(6b-h)**, were also exhibited such spectral characteristics.

All the reactions afforded good yields of target products in shorter reaction time with high purity as on example the IR(KBr) spectra of 4-methylthieno[2,3-b] quinolin-3(2H)-one**(3a-h)**, 4-methylseleno[2,3-b] quinolin-3(2H)-one**(6a-h)** exhibited an absorption band in region 1665-1700cm^{-1}, 1220-1230cm^{-1} and 1226-1234cm^{-1} due to C=O, C-S-C and C-Se-C groups respectively.

When the same reactions carried out in conventional method it took 8-10hrs for completion. And also, it has been found that the reactions yield 55-60% with incomplete consumption of the starting materials even took a longer time. From theses results we found that the microwave-assisted synthetic method is more convenient and beneficial for the synthesis of titled compounds.

CONCLUSION

In conclusion, we developed a versatile and useful new access to different scaffold of biologically importance 4-methylthieno[2,3-b]quinolin-3(2H)-one**(3a-h)**, 4-methylseleno[2,3-b]quinolin-3(2H)-one**(6a-h)** using an efficient and simple methodology based on microwave irradiation technique. The efficiency of employed methodology can explained by the fact that microwave energy is probably much higher than the activation energy necessary for each reaction, so that reaction rate is increased and yields higher.

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