Novel Synthesis of New Thieno [2,3-b]quinoline-2-carboxylates

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(Received on: March 15, Accepted: March 17, 2017)

ABSTRACT

A new method for the synthesis of substituted condensed thieno[2,3-b]quinoline-2-carboxylates derivatives has been achieved. Very first, 2-chloro-3-formylquinolines 2a-d are synthesized from substituted acetanilides 1a-d. Thus obtained 3-formyl-2-chloro-quinolines 2a-d are converted into substituted 2-mercapto-3-formylquinolines 3a-d. Mercapto quinolines thus obtained on refluxing with chloroacetic acid gave 3-Formylquinolin-2-ylthio acetic acids 4a-d. Thus obtained on refluxing with methanol, ethanol and isopropanol in presence of POCl3 gave uncyclised substituted [(3-formylquinolin-2-yI)thio]acetates 5a-d in quantitative yield. The cyclisation was achieved on refluxing with Methanol, Ethanol and Isopropyl alcohol with DMF at room temperature forms 6a-b, 7a-d and 8a-d. The structures of all the newly synthesized compounds were elucidated on the basis of elemental analysis, IR, 1H NMR and mass spectral data.

Keywords: 3-Formyl-2-mercaptoquinolines; 3-Formyl-2-chloroquinolines; Thieno [2,3-b]quinolines; 3-Formylquinolin-2-ylthio acetic acids; Methyl thieno[2,3-b]quinoline-2-carboxylates.

INTRODUCTION

Quinoline ring system is an essential structural fragment of a large number of natural and unnatural compounds displaying interesting biological activities such as antimalarial, antibacterial, anti-asthmatic, antihypertensive, and anti-inflammatory1-4. Quinolines and their derivatives have been found applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks5-8. Quinolines and their derivatives are receiving increasing importance due to their wide range of biological activities.

Thieno derivatives are known to exhibit array of biological activites including analgesic and antiinflammatory activites9-13. It is evident from the literature that thieno
derivatives are well known for their varied biological activities such as high affinity selective 5-HT\textsubscript{1A} receptor ligands\textsuperscript{14} potential antihypertensive agents\textsuperscript{15} molluscicidal and larvicidal activites\textsuperscript{16,17}

The key intermediate 3-formyl-2-chloro-quinolines have been prepared by reported method\textsuperscript{18}. In continuation of our program directed towards the study in novel heterocycles\textsuperscript{19-27} and synthesis of new potentially bioactive molecules. We were in need a rapid, cost effective and commercial method for the synthesis of quinolines based sulfur compounds. The methods described for the synthesis of key intermediate 3-formyl-2-chloro-quinolines from substituted acetanilide provide a short period of time in high yield.

RESULTS AND DISCUSSION

The required 3-formyl-2-mercaptoquinoline 3a was prepared from 3-formyl-2-chloroquinoline by reported method\textsuperscript{22} from our laboratory.

When 3-formylquinolin-2-yl-thioacetic acid 4a on refluxing with POCl\textsubscript{3} in methanol afforded methyl(3-formylquinolin-2-yl)thioacetate 5a intermediate. This intermediate on stirring with DMF underwent smooth cyclisation at room temperature produced methyl thieno[2,3-b]quinoline-2-carboxylates 6a-b at room temperature. Similarly, 5b-d on refluxing with ethanol and isopropyl alcohol gave 7a-d and 8a-d.

The \textsuperscript{1}H NMR spectrum of 5a exhibits singlet at \(\delta 10.31\) ppm corresponding to –CHO proton, which was found absent in 6a. In addition to these, the singlet at \(\delta 4.25\) ppm corresponding to –S-CH\textsubscript{2} of 5a was found to be absent. In IR spectrum, absence of band at 1640-1644 cm\textsuperscript{-1} corresponds -CHO group and reappearance of band at 1735 cm\textsuperscript{-1} confirms the ring cyclisation. Further, the structure assigned was confirmed by its mass spectrum. It gave molecular ion peak at 243.

EXPERIMENTAL

IR spectra were taken on a Perkin Elmer 157 Infrared spectrophotometer. The \textsuperscript{1}H NMR spectra (300 MHz) were recorded on a Bruker supercon FT NMR instrument using TMS as internal standard and mass spectra on a Jeol JMS-D 300 Mass spectrometer operating at 70 eV. Melting points were determined in open capillary and are uncorrected. Purity of the compounds was checked by TLC on silica gel and were purified by column chromatography.

Preparation of [(3-formylquinolin-2-yl)thio]acetic acid 4a

A mixture of 3a (1890 mg, 10 mmole), Chloroaceticacid (1461 mg 15 mmole) and K\textsubscript{2}CO\textsubscript{3} (2760 mg 40 mmol) in dry acetone (50ml) was refluxed on water bath for 4-5 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was filtered solvent was evaporated and dried. Finally solid obtained was purified by column chromatography. Resulting solid obtained was recrystallized (1778 mg, 72\%) from alcohol. In a similar way, the same procedure was followed for the synthesis of 4b-e (65-72\%).
[(3-Formylquinolin-2-yl)thio]acetic acid 4a

1H NMR (300 MHz, DMSO-d6) δ (ppm): 4.25 (2H, s, -SCH2-), 7.59-9.58 (5H, m, Ar-H), 10.31 (1H, s, CHO); IR (KBr) ν (cm⁻¹): 1680. [M+], 247. Calcd. (%) for C₁₀H₁₁NO₃S: C; 58.29, H; 3.67, N; 5.66, S, 12.97. Found: C; 58.23, H; 3.59, N; 5.57, S, 12.86

[(3-formyl-6-methylquinolin-2-yl)thio]acetic acid 4b

1H NMR (300 MHz, DMSO-d6) δ (ppm): 2.55 (3H, s, CH₃), 4.26 (2H, s, -SCH2-), 7.58-9.56 (5H, m, Ar-H), 10.30 (1H, s, CHO); IR (KBr) ν (cm⁻¹): 1681. [M+], 261. Calcd. (%) for C₁₃H₁₄NO₃S: C; 59.76, H; 4.24, N; 5.36, S, 12.27. Found: C; 59.68, H; 4.16, N; 5.28, S, 12.23.

[(7-Chloro-6-fluoro-3-formylquinolin-2-yl)thio]acetic acid 4c

1H NMR (300 MHz, DMSO-d6) δ (ppm): 4.25 (2H, s, -SCH2-), 7.57-9.53 (4H, m, Ar-H), 10.30 (1H, s, CHO); IR (KBr) ν (cm⁻¹): 1680. [M+], 299. Calcd. (%) for C₁₂H₆ClFNO₃S: C; 48.09, H; 2.35, N; 4.67, S, 10.70. Found: C; 48.01, H; 2.29, N; 4.56, S, 10.61.

[(6-Chloro-3-formylquinolin-2-yl)thio]acetic acid 4d

1H NMR (300 MHz, DMSO-d6) δ (ppm): 4.27 (2H, s, -SCH2-), 7.54-9.58 (4H, m, Ar-H), 10.32 (1H, s, CHO); IR (KBr) ν (cm⁻¹): 1682. [M+], 281. Calcd. (%) for C₁₂H₆ClNO₃S: C; 51.16, H; 2.86, N; 4.97, S, 11.38. Found: C; 51.32, H; 2.75, N; 4.86, S, 11.25.

Preparation of [(3-formylquinolin-2-yl)thio]acetate 5a

A mixture of 4a (2472 mg, 10 mmol), methanol (50 ml) in presence of POCl₃ (15 ml) was refluxed on water bath for 2h. The completion of the reaction was monitored by TLC. After the completion of the reaction, the excess of POCl₃ was distilled off under reduced pressure. Then the residue obtained was poured into ice water, the solid obtained was filtered, dried. The crude product was recrystallized from DMF to provide 1992 mg (82%) of pure 5a. In a similar way, 5b-d were prepared in 73-82% yield and purified by column chromatography.

[(3-Formylquinolin-2-yl)thio]acetate 5a

1H NMR (300 MHz, DMSO-d6) δ (ppm): 3.85 (3H, s, OCH₃), 4.23 (2H, s, -SCH2-), 7.62-9.63 (4H, m, Ar-H), 10.33 (1H, s, CHO); IR (KBr) ν (cm⁻¹): 1682. [M+], 261. Calcd. (%) for C₁₃H₁₁NO₃S: C; 59.76, H; 4.24, N; 5.36, S, 12.27. Found: C; 59.67, H; 4.23, N; 5.28, S, 12.12.

[(3-Formyl-6-methylquinolin-2-yl)thio]acetate 5b

1H NMR (300 MHz, DMSO-d6) δ (ppm): 2.55 (s, CH₃), 3.83 (3H, s, OCH₃), 4.24 (2H, s, -SCH2-), 7.64-9.61 (5H, m, Ar-H), 10.33 (1H, s, CHO); IR (KBr) ν (cm⁻¹): 1683, [M+], 275. Calcd. (%) for C₁₄H₁₃NO₃S: C; 61.07, H; 4.76, N; 5.09, S, 11.65. Found: C; 61.04, H; 4.62, N; 5.02, S, 11.58.

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[(7-Chloro-6-fluoro-3-formylquinolin-2-yl)thio]acetate 5c

\[ ^{1}H \text{NMR (300 MHz, DMSO-d}_6 \delta (\text{ppm}): 3.82 (3H, s, OCH}_3), 4.26 (2H, s, -SCH}_2), 7.62-9.64 (3H, m, Ar-H), 10.31 (1H, s, CHO); IR (KBr) \nu (\text{cm}^{-1}): 1680. [M+], 313. \text{Calcd. (}) \% \text{for } C_{15}H_{10}ClFNO}_3S: C; 49.77, H; 2.89, N; 4.46, S; 10.22. \text{Found: } C; 49.68, H; 2.78, N; 437, S; 10.14. \]

[(6-Chloro-3-formylquinolin-2-yl)thio]acetate 5d

\[ NMR (300 MHz, DMSO-d}_6 \delta (\text{ppm}): 3.84 (3H, s, OCH}_3), 4.25 (2H, s, -SCH}_2), 7.64-9.61 (4H, m, Ar-H), 10.30 (1H, s, CHO); IR (KBr) \nu (\text{cm}^{-1}): 1684. [M+], 295. \text{Calcd. (}) \% \text{for } C_{15}H_{10}ClN}_3O}_3S: C; 52.80, H; 3.41, N; 4.74, S; 10.84. \text{Found: } C; 52.71, H; 3.32, N; 4.64, S; 10.73. \]

**Preparation of methyl thieno[2,3-b]quinoline-2-carboxylate 6a**

A mixture of 5a (2612 mg, 10 mmol), DMF (30 ml) was stirred by means of magnetic stirrer. The completion of the reaction was monitored by TLC. After the completion of the reaction, the excess of DMF was distilled off under reduced pressure. Then the reaction mixture was poured into crushed ice, the solid obtained was filtered, dried. The crude product was and purified by column chromatography ethyl acetate-carbon tetrachloride (9:1) to provide 2055 mg (85%) of pure 6a. In a similar way, 6b-d, 7a-d and 8a-d were prepared in 70-85% yield.

**Methyl thieno[2,3-b]quinoline-2-carboxylate 6a**

\[ ^{1}H \text{NMR (300 MHz, DMSO-d}_6 \delta (\text{ppm}): 3.86 (3H, s, OCH}_3), 7.62-9.67 (5H, m, Ar-H), IR (KBr) \nu (\text{cm}^{-1}): 1682. [M+], 243. \text{Calcd. (}) \% \text{for } C_{13}H_{10}N}_3O}_3S: C; 64.18, H; 3.73, N; 5.76, S; 13.18. \text{Found: } C; 64.26, H; 3.67, N; 63, S; 13.26. \]

**Methyl 6-methylthieno[2,3-b]quinoline-2-carboxylate 6b**

\[ ^{1}H \text{NMR (300 MHz, DMSO-d}_6 \delta (\text{ppm}): 2.55 (s, CH}_3), 3.84 (3H, s, OCH}_3), 7.61-9.65 (5H, m, Ar-H), IR (KBr) \nu (\text{cm}^{-1}): 1682. [M+], 257. \text{Calcd. (}) \% \text{for } C_{14}H_{11}N}_3O}_3S: C; 65.35, H; 4.31, N; 5.44, S; 12.46. \text{Found: } C; 65.26, H; 4.20, N; 5.33, S; 12.35. \]

**Methyl 7-chloro-6-fluorothieno[2,3-b]quinoline-2-carboxylate 6c**

\[ ^{1}H \text{NMR (300 MHz, DMSO-d}_6 \delta (\text{ppm}): 3.81 (3H, s, OCH}_3), 7.63-9.62 (4H, m, Ar-H), IR (KBr) \nu (\text{cm}^{-1}): 1680. [M+], 295. \text{Calcd. (}) \% \text{for } C_{13}H_{10}ClFNO}_3S: C; 52.80, H; 2.39, N; 4.74, S; 10.84. \text{Found: } C; 52.80, H; 2.39, N; 4.74, S; 10.84. \]

**Methyl 6-chlorothieno[2,3-b]quinoline-2-carboxylate 6d**

\[ ^{1}H \text{NMR (300 MHz, DMSO-d}_6 \delta (\text{ppm}): 3.82 (3H, s, OCH}_3), 7.62-9.65 (5H, m, Ar-H), IR (KBr) \nu (\text{cm}^{-1}): 1682. [M+], 277. \text{Calcd. (}) \% \text{for } C_{15}H_{10}ClNO}_3S: C; 56.22, H; 2.90, N; 5.04, S; 11.55. \text{Found: } C; 56.32, H; 2.79, N; 5.01, S; 11.47. \]
Ethyl thieno[2,3-b]quinoline-2-carboxylate 7a

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.32 (3H, t, CH$_3$), 4.33 (2H, q, -OCH$_2$), 7.61-9.68 (5H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1682. [M$^+$.], 257. Calcd. (%) for C$_{14}$H$_{11}$NO$_2$S: C; 65.35, H; 4.31, N; 5.44, S, 12.46. Found: C; 65.27, H; 4.23, N; 5.36, S, 12.46.

Ethyl 6-methylthieno[2,3-b]quinoline-2-carboxylate 7b

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.32 (3H, t, CH$_3$), 2.55 (1H, s, CH$_3$), 4.33 (2H, q, -OCH$_2$), 7.61-9.65 (4H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1682. [M$^+$.], 271. Calcd. (%) for C$_{13}$H$_{13}$NO$_2$S: C; 66.40, H; 4.83, N; 5.16, S, 11.82. Found: C; 66.32, H; 4.73, N; 5.26, S, 11.74.

Ethyl 7-chloro-6-fluorothieno[2,3-b]quinoline-2-carboxylate 7c

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.32 (3H, t, CH$_3$), 4.33 (2H, q, -OCH$_2$), 7.61-9.65 (4H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1682. [M$^+$.], 309. Calcd. (%) for C$_{13}$H$_{10}$ClFNO$_2$S: C; 54.29, H; 2.93, N; 4.52, S, 10.35. Found: C; 54.17, H; 2.82, N; 4.41, S, 10.46.

Ethyl 6-chlorothieno[2,3-b]quinoline-2-carboxylate 7d

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.32 (3H, t, CH$_3$), 4.33 (2H, q, -OCH$_2$), 7.61-9.65 (5H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1682. [M$^+$.], 291. Calcd. (%) for C$_{13}$H$_{13}$NO$_2$S: C; 57.63, H; 3.45, N; 4.80, S, 10.99. Found: C; 57.52, H; 3.36, N; 4.71, S, 10.84.

Isopropyl thieno[2,3-b]quinoline-2-carboxylate 8a

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.45 (6H, d, CH$_3$), 3.55 (1H, s, -CH$_3$), 7.62-9.64 (6H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1680. [M$^+$.], 271. Calcd. (%) for C$_{15}$H$_{13}$NO$_2$S: C; 66.40, H; 4.83, N; 5.16, S, 11.82. Found: C; 66.33, H; 4.74, N; 5.26, S, 11.73.

Isopropyl 6-methylthieno[2,3-b]quinoline-2-carboxylate 8b

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.45 (6H, d, 2CH$_3$), 2.55 (s, Ar-CH$_3$) 3.55 (1H, s, -CH$_3$), 7.63-9.64 (5H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1682. [M$^+$.], 285. Calcd. (%) for C$_{15}$H$_{13}$NO$_2$S: C; 67.34, H; 5.30, N; 4.91, S, 11.24. Found: C; 67.24, H; 5.21, N; 4.82, S, 11.16.

Isopropyl 6-chloro-7-fluorothieno[2,3-b]quinoline-2-carboxylate 8c

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.45 (6H, d, 2CH$_3$), 2.55 (s, Ar-CH$_3$) 3.55 (1H, s, -CH$_3$), 7.63-9.64 (4H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1682. [M$^+$.], 323. Calcd. (%) for C$_{15}$H$_{11}$ClFNO$_2$S: C; 55.64, H; 3.42, N; 4.33, S, 9.90. Found: C; 55.55, H; 3.31, N; 4.21, S, 9.79.

Isopropyl 7-chlorothieno[2,3-b]quinoline-2-carboxylate 8d

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 1.46 (6H, d, 2CH$_3$), 3.57 (1H, s, -CH$_3$), 7.61-9.67 (4H, m, Ar-H), IR (KBr) $\nu$ (cm$^{-1}$): 1680. [M$^+$.], 305. Calcd. (%) for C$_{15}$H$_{12}$ClNO$_2$S: C; 58.92, H; 3.96, N; 4.58, S, 10.49. Found: C; 58.81, H; 3.86, N; 4.48, S, 10.38.
ACKNOWLEDGEMENT

The authors are also thankful to the Convenor, SIF, IISc, Bangalore for Spectral data.

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