Isothiazolo-fused quinoline analogues: Synthesis of isothiazolo [5, 4-b] quinolines and their oxidation products, 3[2H]-one-1, 1-dioxideisothiazolo [5, 4-b] quinolines from 2-chloro-3-formylquinolines

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A convenient synthesis of isothiazolo[5,4-b]quinolines 2 is achieved in two steps from the reaction of 2-chloro-3-formylquinolines 1 with sodium sulfide and hydroxylamine sequences followed by cyclisation with acetic anhydride. The subsequent oxidation of 2 with H₂O₂ in acetic acid yields 3(2H)-one-1, 1-dioxideisothiazolo [5, 4-b] quinolines 3.

Keywords: Cyclisation, oxidation, oxime, sodium sulfide, hydrogen peroxide

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Isothiazoles and their benzo/hetero-fused derivatives exhibit wide variety of pharmacological activities such as bactricide, fungicide and nematocide properties. In particular isothiazolo[5,4-b]quinolines are known to possess antibacterial activity. A number of methods are available for isothiazoles and their benzoanalogues because of their great synthetic and medicinal importance, a few syntheses are known for isothiazolo-fused quinolines. Recently, Choi et al. have reported the synthesis of 3-methyl-9-alkyl-4, 9-dihydroisothiazolo[5,4-b]quinolin-4-ones involving the reaction of substituted 2-alkylthio-3-acyl-4-quinolones with O-(mesitylenesulfonyl) hydroxylamine in DMF. Similarly, chlorovinylaldehydes, easily prepared via Wilsmeier approach from the reaction of –CH₂-CO-C< group containing compounds with Wilsmeier reagent, are important synths used for the synthesis of a variety of heterocyclic systems like pyran-2-ones, isothiazoles, pyrazolo[3,4-b]pyridines, pyrazolo[3,4-b]quinolines etc. The present work involves the search of Wilsmeier aided synthesis of heterocyclic compounds and their reactions with appropriate reagents. Recently, the synthesis of substituted 2-chloro-3-formylquinolines (ref. 11) 1 has been reported from the reaction of easily available acetanilides with Wilsmeier-Haack reagent and transformation of their formyl group into cyano and alkoxy carbonyl groups respectively. The easy accessibility of these functionalities in the synthesized quinolines makes them attractive for their further elaborations. Previously, it has been reported that the fused sulfur and nitrogen fused-quinolines with different functionalities are accessible from these precursors via nitrogen and sulphur nucleophiles. In continuation to these studies on sulfur and nitrogen-fused quinolines, the synthesis of isothiazolo[5,4-b]quinolines 2 and 3(2H)-one-1, 1-dioxide-isothiazolo[5,4-b]quinolines 3 from 2-chloro-3-formylquinolines 1 is now reported.

Generally isothiazole derivatives were prepared from β-chlorovinylaldehydes either with ammonium thiocyanate in acetone or with sodium sulfide/hydroxylamine hydrochloride sequence followed by cyclisation. The existence of similar precursor in the present system, 2-chloro-3-formylquinolines 1 were examined by these routes with a view to synthesize isothiazolo[5,4-b]quinolines 2.

Firstly, the reaction of 2-chloro-3-formylquinolines 1 was attempted with ammonium thiocyanate in acetone under the similar reaction conditions to afford compounds 2 and was found to be unsuccessful. Then, an alternative route was examined, firstly, the preparation of 2(1H) thioquinoline-3-carboaldoximes 4 and secondly, the cyclisation of carboaldoxime 4 with acetic anhydride to afford isothiazolo[5,4-b] quinolines 2. Thus, the reaction of equimolar ratio of
2-chloro-3-formylquinoline 1a and sodium sulfide in DMF involved in situ generation of 3-formylquinoline-2(1H) thiones, which on subsequent addition of hydroxylamine hydrochloride and sodium acetate in DMF afforded compound 4a. The cyclisation reaction of compound 4a was carried out by dissolving it in hot acetic acid followed by refluxing with excess of acetic anhydride. The product isolated was characterized as isothiazolo[5,4-b]quinoline 2a on the basis of its spectral and analytical data (Scheme I). 1H NMR spectrum of the compound 2a showed a singlet for the H-C=N proton at δ 8.9, a singlet at δ 9.2 for the H-4 proton along with the signals for other aromatic protons. The IR spectrum showed no specific functional group absorption.

The probable mechanistic pathway for the formation of product 2a is shown in Scheme II. The initially formed 3-O-acetyl-2(1H) thioquinoline carboaldoxime 5a (anti form) from 4a undergoes intramolecular transfer of proton from thiol group to the acetate oxygen (structure 5a') followed by nucleophilic attack of sulfur anion onto the nitrogen with loss of acetic acid affords the isothiazolo[5,4-b]quinoline 2a. Similarly, two other transformations seem to be equally possible in this mechanism leading to formation of 3-cyanoquinoline-2(1H) thione 6a and thiazolo-fused quinoline 7a, respectively. The compound 6a is a simple β-elimination product of compound 4a, in which an aldoxime group (anti form), is transformed into a nitrile group, when compound 4a is treated with acetic anhydride. Whereas compound 7a is the Beckmann rearrangement product of 4a (syn form) under the acidic condition of the reaction followed by intramolecular nucleophilic attack of the sulfur onto the newly generated carbonium ion (structure 5a'') leading to the formation of thiazole nucleus. All possible compounds (2a, 6a and 7a) formed from compound 4a shown in Scheme II have the same molecular formula, C10H6N2S.

However, the observed spectral data of the isolated product 2a neither support the structure 6a nor able to distinguish between the structures 2a and 7a in Scheme II. The chemical evidence was then considered and attempt was made to react isolated product 2a with sodium methoxide in methanol to further prove the (from the reaction12 of sodium methoxide onto isolated product 2a) isothiazole-fused quinoline structure 2a (Scheme II). Thus, the methanalysis reaction product of 2a upon spectral investigation is found to be a ring cleaved product, 3-cyanoquinoline-2(1H) thione 6a (Scheme II), identical to the product obtained from the reaction of 2-chloro-3-cyanoquinoline11 with sodium sulfide in DMF13, supports the structure 2a.

![Scheme I](image-url)
Isothiazoles are known to be easily oxidized to isothiazolo-3(2H)-one-1,1-dioxide from H₂O₂ in acetic acid.

Similarly, 2,3-dihydro-1,2-benzisosulphonazol-3-ol, commercially known as saccharine, has attracted great importance because of its sweet taste, are the oxidation product of benzisothiazoles. With the similar hetero-fused isothiazoles in hand, the oxidation reaction was further explored with a view to synthesize 3(2H)-one-1,1-dioxideisothiazolo[5,4-b]quinolines. Thus, the reaction of compound 2a with 30% H₂O₂ in acetic acid at reflux temperature completed in a short time afforded the desired 1,1-dioxideisothiazolo[5,4-b]quinolines.

The 1H NMR spectrum of 3a showed broad singlet at δ 12.49 for the NH proton, singlet at δ 8.74 for the H-4 proton of the quinoline nucleus along with other aromatic protons. The IR spectrum showed absorption at 1774 cm⁻¹ for lactam carbonyl, strong absorptions at 1330 and 1126 cm⁻¹ for the >SO₂ group and absorptions at 1356 and 1167 cm⁻¹ for the >SO₂-N< stretching.

In conclusion, the synthesis of isothiazolo[5,4-b]quinolines from easily synthesized 2-chloro-3-formylquinolines and their oxidation products, 3(2H)-one-1,1-dioxideisothiazolo[5, 4-b]quinolines has been described. The mild reaction conditions, cheap chemicals and simple experimental procedures make it a useful and attractive route for the preparation of isothiazolo-fused quinolines.

### Experimental Section

Melting points were measured in an open capillary tube with a Buchi melting point apparatus and are uncorrected. Elemental analysis was obtained using Perkin-Elmer 24°C CHN-analyzer. IR spectra were recorded on a FT/IR-5300 (JASCO) spectrophotometer; ¹H NMR spectra in CDCl₃/DMSO-d₆ at 300 MHz on a Jeol AL-300 spectrometer (chemical shifts in δ, ppm) relative to TMS as an internal standard. Reactions were monitored by TLC, using silica gel PF₂₅₄₃₆₆ as an adsorbent and ethyl acetate-hexane in different ratios as eluent.

### Synthesis of 3-hydroxyiminomethylquinoline-2(1H)-thiones, 4.

To 2-chloro-3-formylquinolines 1 (1.5 mmoles) in DMF (5 mL), sodium sulfide (1.5 moles) was added and stirred for 2 h at RT. On completion of reaction (monitored by TLC) hydroxylamine hydrochloride and sodium acetate (1.5 mmoles each) were added and further stirred for 3-4 hr. Water was added to the reaction mixture and precipitates obtained were filtered, washed with water, dried and purified by recrystallization from aqueous ethanol.

#### 3-Hydroxyiminomethylquinoline-2(1H)-thione, 4a: Yield 86%, m.p. 197-98°C [lit 5d m.p. 198°C]; IR (KBr): 3273, 3124, 1601, 1186 cm⁻¹; ¹H NMR (DMSO-d₆): δ 13.97 (s, 1H, NH D₂O exchangeable), 11.59 (s, 1H, OH, D₂O exchangeable), 8.77 (s, 1H, H-4), 8.33 (s, 1H, HC=N), 7.97-7.94 (d, 1H, H-5), 7.68 (m, 2H, H-8 & H-6), 7.42 (m, 1H, H-7).

#### 3-Hydroxyiminomethylquinoline-2(1H)-thione, 4b: Yield 88%, m.p. 184-85°C; IR (KBr): 3342, 3136, 1612, 1193 cm⁻¹; ¹H NMR (DMSO-d₆): δ 14.4 (s, 1H, NH D₂O exchangeable), 11.72 (s, 1H, H-4), 8.33 (s, 1H, HC=N), 7.97-7.94 (d, 1H, H-5), 7.68 (m, 2H, H-8 & H-6), 7.42 (m, 1H, H-7).
1H, HC=NH, 7.82 (m, 2H, H-5 & H-8), 7.44 (d, 1H, H-6), 2.6 (s, 3H, CH3).

3-Hydroxyiminomethyl-7-methoxyquino-line-2(1H)-thione, 4c: Yield 86%, m.p. 182-83°C; IR (KBr): 3336, 3123, 1619, 1187 cm⁻¹; ¹H NMR (CDCl₃): δ 9.2 (s, 1H, H-4), 8.9 (s, 1H, HC=NH), 7.82 (m, 2H, H-5 & H-8), 7.44 (d, 1H, H-6), 7.7 (t, 1H, H-7); MS: m/z 206 (M⁺).

Synthesis of isothiazolo[5,4-b]quinolines, 2.

To the thionoimines 4 (1 mmole) dissolved in hot acetic acid (15 mL), acetic anhydride (5 mmol) was added and refluxed for 1.5-2 hr. After completion the reaction mixture was poured into ice-water and neutralized with 50% NaOH solution with cooling. The precipitates thus obtained were treated with hot 5% HCl and filtered into cold 5% NaOH solution. The precipitates obtained were filtered, washed well with water, dried and purified by recrystallization from ethyl acetate-petroleum ether.

Isothiazolo[5,4-b]quinoline, 2a: Yield 74%, m.p. 169°C [lit. 4th m.p. 169-70°C]; IR (KBr): 1672, 1616 cm⁻¹; ¹H NMR (CDCl₃): δ 7.5 (s, 1H, H-4), 8.5 (s, 1H, H-8), 7.4 (s, 1H, H-6); MS: m/z 186(M⁺). Anal. Calcd: C, 64.50; H, 3.25; N, 15.04. Found: C, 64.47; H, 3.19; N, 15.09%.

7-Methyloisothiazolo[5,4-b]quinoline, 2b: Yield 68%, m.p. 189°C; IR (KBr): 1678, 1616 cm⁻¹; ¹H NMR (CDCl₃): δ 9.1 (s, 1H, H-4), 8.8 (s, 1H, HC=NH), 7.9 (d, 1H, H-5), 7.9 (s, 1H, H-8), 7.5 (d, 1H, H-6), 2.6 (s, 3H, CH3). Anal. Calcd: C, 65.98; H, 4.03; N, 13.99. Found: C, 65.97; H, 4.03; N, 13.95%.

7-Methoxyisothiazolo[5,4-b]quinoline, 2c: Yield 66%, m.p. 223°C; IR (KBr): 1674, 1613 cm⁻¹; ¹H NMR (CDCl₃): δ 9.04 (s, 1H, H-4), 8.76 (s 1H, HC=NH), 7.91 (d, 1H, H-5), 7.4 (s, 1H, H-8), 7.28 (d, 1H, H-6), 4.0 (s, 3H, OCH3). Anal. Calcd: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.08; H, 3.76; N, 12.88%.

Synthesis of 3 (2H)-one-1, 1-dioxideisothiazolo[5, 4-b]quinolines, 3.

To a suspension of isothiazolo quinolines (1 mmole) in acetic acid (1 mL) at 80°C was added hydrogen peroxide (30%) (1 mL) and refluxed for 20-30 min. Upon evaporating the solvent a solid product was obtained, which was washed well with ethanol, dried and purified by recrystallization from acetic acid.

3(2H)-one-1, 1-dioxideisothiazolo[5, 4-b]quinoline, 3a: Yield 52%, m.p. 218-222°C (d); IR (KBr): 3428, 1714, 1356, 1330, 1167, 1126 cm⁻¹; ¹H NMR (DMSO-d₆): δ 12.49 (br s, 1H, NH, D₂O exchangeable), 8.7 (s, 1H, H-4), 8.6 (d, 1H, H-5), 8.1 (d, 1H, H-8), 7.9 (t, 1H, H-6), 7.7 (t, 1H, H-7). Anal. Calcd: C, 51.26; H, 2.54; N, 11.97%.

3(2H)-one-1,1-dioxide-7-methoxyisothiazolo[5,4-b]quinoline 3b: Yield 54%, m.p. 253°C (d); IR (KBr): 3396, 1716, 1342, 1238, 1168, 1120 cm⁻¹; ¹H NMR (DMSO-d₆): δ 11.2 (br s, 1H, NH, D₂O exchangeable), 8.9 (s, 1H, H-4), 7.8 (d, 1H, H-5), 7.3 (s, 1H, H-8), 7.1 (d, 1H, H-6), 3.9 (s, 3H, OCH₃). Anal. Calcd: C, 50.00; H, 3.05; N, 10.60. Found: C, 50.02; H, 3.08; N, 10.60%.

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