Indian Journal of Chemistry
Vol. 46B, February 2007, pp. 303-307

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

A Srivastava, Atish Chandra & R M Singh*

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221 005, India

E-mail: rmohan@bhu.ac.in

Received 30 December 2005; accepted (revised) 31 July 2006

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 H_2O_2 in acetic acid yields 3(2*H*)-one-1, 1-dioxideisothiazolo [5, 4-*b*] quinolines **3**.

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

IPC: Int.Cl.[8] C07D

Isothiazoles and their benzo/hetero-fused derivatives exhibit wide variety of pharmacological activities such as bactricide, fungicide and nematocide properties[1]. In particular isothiazolo[5,4-*b*]quinolines are known to possess antibacterial activity[2]. A number of methods are available for isothiazoles[3] and their benzoanalogues[4] because of their great synthetic and medicinal importances, a few syntheses are known for isothiazolo-fused quinolines[5]. Recently, Choi *et al.*[6] 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* Vilsmeier approach from the reaction of $-CH_2-CO-C<$ group containing compounds with Vilsmeier reagent, are important synthons used for the synthesis of variety of heterocyclic systems like pyran-2-ones[7], isothizoles[4c], pyrazolo[3,4-*b*]pyridines[8], pyrazolo[3,4-*b*]quinolines[9] *etc*. The present work involves the search of Vilsmeier aided synthesis of heterocyclic compounds[10] 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 Vilsmeier-Haack reagent and transformation of their formyl group into cyano and alkoxycarbonyl 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[9b,c] 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[2*H*]-one-1,1-dioxide-isothiazolo[5,4-*b*]quinolines **3** from 2-chloro-3-formyl-quinolines **1** is now reported.

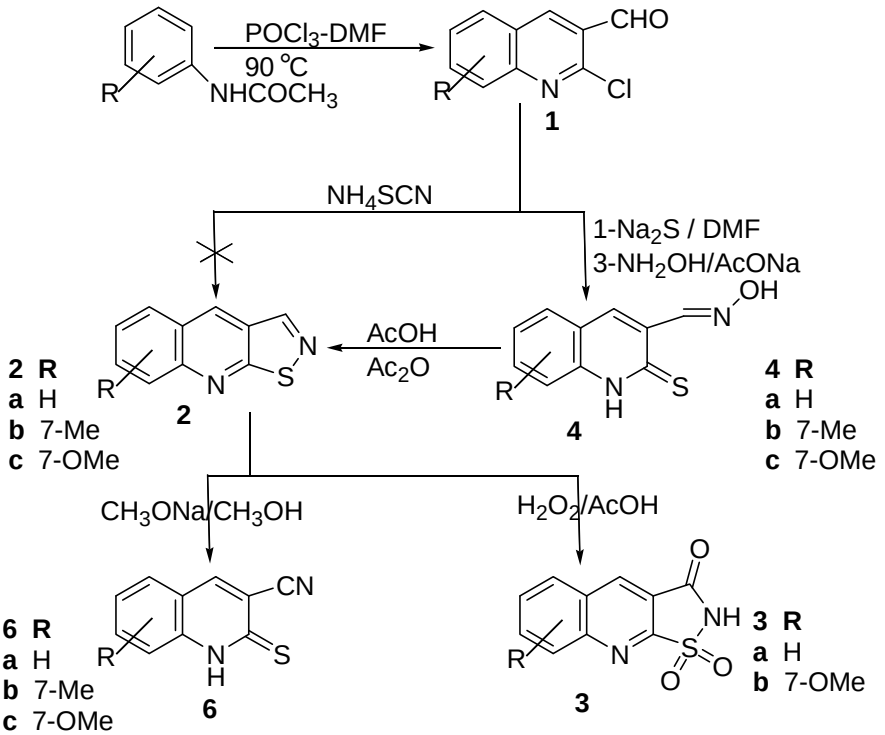
Generally isothiazole derivatives were prepared from β-chlorovinylaldehydes either with ammonium thiocyanate[3c] in acetone or with sodium sulfide/-hydroxylamine hydrochloride sequence followed by cyclisation[12]. The existence of similar precursor in the present system, 2-chloro-3-formylquinolines **1** 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(1*H*) 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

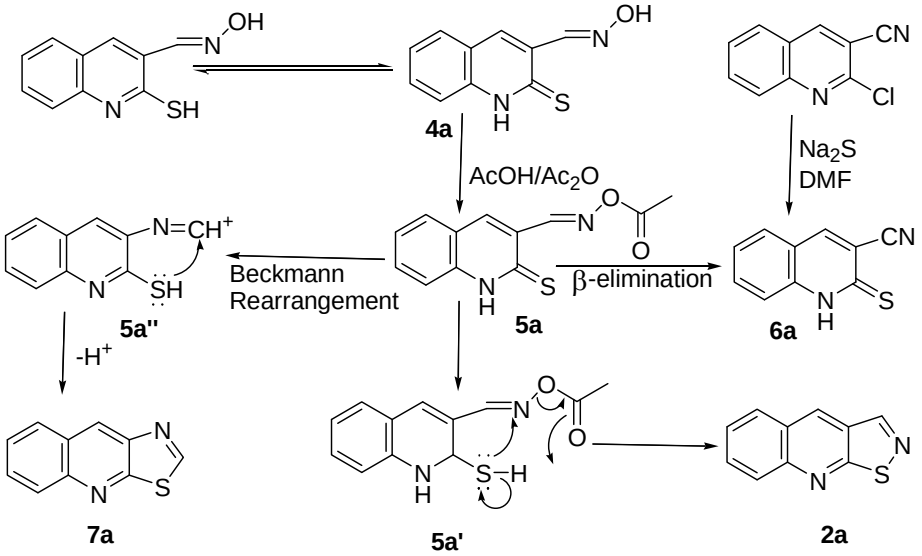
2-chloro-3-formylquinoline **1a** and sodium sulfide in DMF involved *in situ* generation of 3-formyl-quinoline-2(1*H*) thiones, which on subsequent addition of hydroxylamine hydrochloride and sodium acetate in DMF afforded compound **4a**. The cyclisation reaction of compound **4a** was carried out 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**). ^{1}H 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(1*H*) 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(1*H*) 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, $C_{10}H_6N_2S$.

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 reaction[12a] of sodium methoxide onto isolated product **2a**) isothiazole-fused quinoline structure **2a** (**Scheme II**). Thus, the methanolysis reaction product of **2a** upon spectral investigation is found to be a ring cleaved product, 3-cyanoquinoline-2(1*H*) thione **6a** (**Scheme II**), identical to the product obtained from the reaction of 2-chloro-3-cyanoquinoline[11] with sodium sulfide in DMF[13], supports the structure **2a**.



Scheme I



Scheme II

Isothiazoles are known to be easily oxidized to isothiazolo-3(2*H*)-one-1,1-dioxide from H_2O_2 in acetic acid[3c]. Similarly, 2,3-dihydro-1,2-benzisosulfonazol-3-ol[14], 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(2*H*)-one-1,1-dioxideisothiazolo[5,4-*b*]quinolines. Thus, the reaction of compound **2a** with 30% H_2O_2 in acetic acid at reflux temperature completed in a short time afforded the desired 1,1-dioxideisothiazolo[5,4-*b*]quinolines **3** (**Scheme I**). The ^{1}H 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 >SO_2 group and absorptions at 1356 and 1167 cm^{-1} for the >SO_2-N< stretching.

In conclusion, the synthesis of isothiazolo[5,4-*b*]quinolines from easily synthesized 2-chloro-3-formylquinolines and their oxidation products, 3(2*H*)-one-1,1-dioxideisothiazolo[5, 4-*b*]quinolines have 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; ^{1}H NMR spectra in $CDCl_3$/DMSO-d_6 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 $PF_{254+366}$ as an adsorbent and ethyl acetate-hexane in different ratios as eluent.

Synthesis of 3-hydroxyiminomethylquinoline-2(1*H*)-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(1*H*)-thione, 4a: Yield 86%, m.p. 197-98°C [lit[5d] m.p. 198°C]; IR (KBr): 3273, 3124, 1601, 1186 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 13.97 (s, 1H, NH D_2O exchangeable), 11.59 (s, 1H, OH, D_2O 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-Hydroxyiminomethyl-7-methylquinoline-2(1H)-thione, **4b**: Yield 88%, m.p. 184-85°C; IR (KBr): 3342, 3136, 1612, 1193 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 14.4 (s, 1H, NH D_2O exchangeable), 11.72 (s, 1H, OH, D_2O exchangeable), 8.96 (s, 1H, H-4), 8.91 (s,

1H, HC=N), 7.82 (m, 2H, H-5 & H-8), 7.44 (d, 1H, H-6), 2.6 (s, 3H, CH_3).

3-Hydroxyiminomethyl-7-methoxyquinoline-2(1*H*)-thione, **4c**: Yield 86%, m.p. 182-83°C; IR (KBr): 3336, 3123, 1619, 1187 cm^{-1}; ^1H NMR (DMSO-d_6):δ 14.32 (s, 1H, NH D_2O exchangeable), 11.65 (s, 1H, OH, D_2O exchangeable), 8.92 (s, 1H, H-4), 8.88 (s, 1H, HC=N), 7.9 (d, 1H, H-5), 7.4 (s, 1H, H-8), 7.2 (d, 1H, H-6), 4.0 (s, 3H, OCH_3).

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

To the thioneoximes **4** (1 mmole) dissolved in hot acetic acid (15 mL), acetic anhydride (5 mmoles) was added and refluxed for 1.5-2hr. 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*N* HCl and filtered into cold 5*N* 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.[5d] m.p. 169-70°C]; IR (KBr): 1672, 1616 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.2 (s, 1H, H-4), 8.9 (s, 1H, HC=N), 8.5 (d, 1H, H-5), 8.2 (d, 1H, H-8), 7.9 (t, 1H, H-6), 7.7 (t, 1H, H-7); MS: m/z 186($M^{+\bullet}$). Anal. Calcd: C, 64.50; H, 3.25; N, 15.04. Found: C, 64.47; H, 3.19; N, 15.09%.

7-Methylisothiazolo[5,4-*b*]quinoline, **2b**: Yield 68%, m.p. 189°C; IR (KBr): 1678, 1616 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.1 (s, 1H, H-4), 8.8 (s, 1H, HC=N), 7.9 (d, 1H, H-5), 7.9 (s, 1H, H-8), 7.5 (d, 1H, H-6), 2.6 (s, 3H, CH_3). 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 ($CDCl_3$): δ 9.04 (s, 1H, H-4), 8.76 (s 1H, HC=N), 7.91 (d, 1H, H-5), 7.4 (s, 1H, H-8), 7.28 (d, 1H, H-6), 4.0 (s, 3H, OCH_3). Anal. Calcd: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.08; H, 3.76; N, 12.88%.

Synthesis of 3 (2*H*)-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 recrystallisation from acetic acid.

3(2*H*)-one-1, 1-dioxideisothiazolo[5, 4-*b*]quinoline, **3a**: Yield 52%, m.p. 218-22°C (d); IR (KBr): 3428, 1714, 1356, 1330, 1167, 1126 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.49 (br s, 1H, NH, D_2O 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, 51.28; H, 2.58; N, 11.96. Found: C, 51.26; H, 2.54; N, 11.97%.

3(2*H*)-one-1,1-dioxide-7-methoxyisothiazolo[5,4-*b*]quinoline 3b: Yield 54%, m.p. 253°C (d); IR (KBr): 3396, 1716, 1342, 1328, 1168, 1120 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.2 (br s, 1H, NH, D_2O 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, OCH_3). Anal. Calcd: C, 50.00; H, 3.05; N, 10.60. Found: C, 50.02; H, 3.08; N, 10.60 %.

Acknowledgement

Authors thank the Council of Scientific and Industrial Research, New Delhi for financial support.

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