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Tetracyclic Heteroaromatic Systems-Synthesis of Ethoxycarbonylphenylpyrido[3′,2′:5,6]Thiopyranoquinolines

Muhammad Naeem Khan[a]*, Misbahul Ain Khan[b], Noreen Aslam[c], Pir Bakhsh Khan[d] and Ehsan ul Haq[d]

[a]Department of Chemistry, Government College of Science, Wahdat Road, Lahore, Pakistan
[b]Department of Chemistry, The Islamia University of Bahawalpur, Pakistan
[c]Department of Chemistry, Govt. Sadiq College for Women University, Bahawalpur, Pakistan
[d]Pakistan Council of Scientific and Industrial Research Laboratories Complex, Lahore, Pakistan

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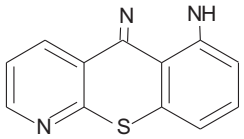
Abstract. 7-benzylideneamino-5H-thiochromeno[2,3-b]pyridin-5-ones and 9-benzylideneamino-5H-thiochromeno[2,3-b]pyridin-5-ones, on reaction with ethyl pyruvate to afford 1-ethoxycarbonyl-3-phenyl-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-ones and 4-ethoxycarbonyl-2-phenyl-7H-pyrido[3′,2′:5,6]thiopyrano[3,2-h]quinoline-7-ones respectively by the two different methods. These products were precipitated by addition of ethanol, water (1:1), were purified by recrystalizing from appropriate solvents and were characterized from their IR, ^{1}H-NMR, mass spectra and elemental analysis data.

Keywords: thiopyranoquinolines, synthesis of ethoxycarbonyl, Schiff's bases

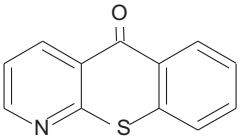
Introduction

Synthesis of new heteroaromatic compounds and their derivatives with the aim to enhance their pharmacological properties or to decrease their side effects, have received special attention (Antonini and Martelli, 1992; Cholody *et al*., 1992; Denny *et al*., 1982). Thiochromones and their analogues possess interesting biological properties which are tested and have been applied as drugs (Geissler *et al*., 1992). Recently much attention is being given to the synthesis of heteroaromatic compounds and their derivatives with the aim to evaluate their antitumor properties (Kucukguzel *et al*., 2004; Tarafder *et al*., 2002; Ittel *et al*., 2000).

We had earlier reported the structures of some selected thiochromones and biological and antioxidant potential of some of the benzylidene amino compounds synthesized in our laboratories (Khan *et al*., 2011 a and b; Khan *et al*., 2009; Khan *et al*., 2008 a and b). Tetracyclic derivatives (1) derived from thiochromenopyridines (2) are reported to be potent cytotoxic agents (Geissler *et al*., 1992).



(1)



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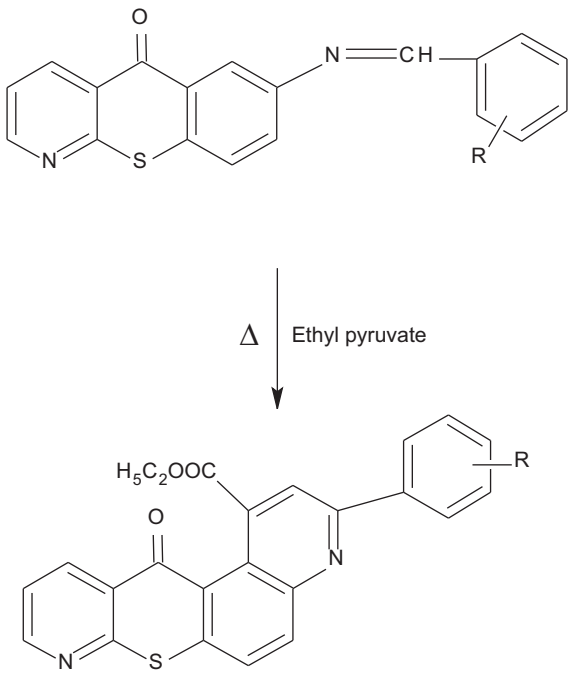
*Author for correspondence; E-mail: changwani_1@yahoo.com, naeemchangwani@gmail.com

Thiochromones functionalities and their analogues are of considerable importance and have been applied as drugs (Antonini and Martelli, 1992; Cholody *et al*., 1992; Denny *et al*., 1982).

(Scheme-1)



(1a-1l)

Materials and Methods

Chemicals and equipments. All chemicals were purchased from E. Merck, BDH or Fluka and used without purification. ^{1}H-NMR spectra were recorded on Bruker DPX instrument at 400 MHz. Chemical shifts are reported in ppm reference to the residual solvent signal. Mass spectra were recorded on Agilent 6890 spectrometer. IR spectra were recorded on Bruker Tensor-27. Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected.

General procedure. Schiff's bases on reaction with ethyl pyruvate was cyclized to 1-ethoxycarbonyl-3-phenyl-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f] quinoline-12-ones and 4-ethoxycarbonyl-2-phenyl-4′-hydroxy-7H-pyrido[3′,2′:5,6]thiopyrano[3,2-h]quinoline-7-one, through the following general procedure. Ethyl pyruvate (0.15 g, 1.20 mmol) was added to a mixture of Schiff' base (0.070 g, 0.21 mmol) in acetic acid, few drops of phosphoric acid was also added. The reaction mixture was heated at a temperature of 100-110 °C (oil bath) for a period of about one and half an hour. The completion of reaction was monitored by TLC. After cooling, a mixture of (ethanol:water 1:1) was added into the reaction mixture along with stirring in order to get precipitates. The precipitates thus obtained were filtered, washed, dried and re-crystallized from appropriate solvent. These cyclized products were obtained in reasonable yields.

1) 1-ethoxycarbonyl-3-phenyl-12H-pyrido[3′,2′:5,6] thiopyrano[3,2-f] quinoline-12-one. (1a).
Yield: 0.58 g, 64%, melting point: 213 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.72 (t, J=7.2 Hz, 3H, CH_3), 7.53 (m, 3H, 3′, 4′, 5′-H), 7.65 (m, 2H, 2′, 6′-H), 8.79 (d, J=6.6 Hz, 1H, 11-H), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1657 (C=O), 1761 ester (C=O) cm^{-1}, MS: m/z 412.
Elemental analysis. Calculated for $C_{24}H_{16}N_2O_3S$: C, 69.90; H, 3.88; N, 6.80%, found: C, 69.37; H, 3.43; N, 6.31%.

2) 1-ethoxycarbonyl-3-phenyl-4′-methoxy-12H-pyrido [3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1b).
Yield: 0.59 g, 68%, melting point: 198 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.37 (t, J=6.8 Hz, 3H, CH_3), 3.80 (s, 3H, 4′-OCH_3), 8.79 (d, J=6.6 Hz, 1H, 11-H), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1657 (C=O), 1761 ester (C=O)/cm, MS: m/z 442.
Elemental analysis. Calculated for $C_{25}H_{18}N_2O_4S$: C, 67.87; H, 4.07; N, 6.33%, found: C, 67.39; H, 3.83; N, 6.04%.

3) 1-ethoxycarbonyl-3-phenyl-2′-fluoro-12H-pyrido [3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1c).
Yield: 0.47 g, 53%, melting point: 219 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.34 (t, J=6.4 Hz, 3H, CH_3), 4.28 (q, J=6.4 Hz, 2H, CH_2), 7.10-7.94 (m, 4H, 3′,4′,5′,6′-H), IR (Neat):1658 (C=O), 1762 ester (C=O)/cm, MS: m/z 430.
Elemental analysis. Calculated for $C_{24}H_{15}N_2O_3S$: C, 66.98; H, 3.49; N, 6.51%, found: C, 66.43; H, 3.11; N, 6.04%.

4) 1-ethoxycarbonyl-3-phenyl-2′,4′-dimethoxy-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1d).
Yield: 0.46 g, 55%, melting point: > 256 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.34 (t, J=7.2 Hz, 3H, CH_3), 3.95 (s, 3H, 2′-OCH_3), 3.98 (s, 3H, 4′-OCH_3), 4.21 (q, J=7.2 Hz, 2H, CH_2), 7.64 (s, 1H, 3′-H), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat):1656 (C=O), 1762 ester (C=O)/cm, MS: m/z 472.
Elemental analysis. Calculated for $C_{26}H_{20}N_2O_5S$: C, 66.10; H, 4.23; N, 5.93%, found: C, 65.93; H, 4.01; N 5.32%.

5) 1-ethoxycarbonyl-3-phenyl-3′-methoxy-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1e).
Yield: 0.52 g, 59%, melting point: 209 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.47 (t, J=6.4 Hz, 3H, CH_3), 3.76 (s, 3H, 3′-OCH_3), 4.21 (q, J=6.4 Hz, 2H, CH_2), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1659 (C=O), 1761 ester (C=O)/cm, MS: m/z 442.
Elemental analysis. Calculated for $C_{25}H_{18}N_2O_5S$: C, 67.87; H, 4.07; N, 6.33%, found: C, 67.32; H, 3.78; N, 6.11%.

6) 1-ethoxycarbonyl-3-phenyl-3′-methoxy-4′hydroxy-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1f).
Yield: 0.64 g, 71%, melting point: 235 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.32 (t, J=6.8 Hz, 3H, CH_3), 3.72 (s , 3H, 3′-OCH_3), 4.21 (q, J=6.4 Hz, 2H, CH_2), 8.79 (d, J=6.6 Hz, 1H, 11-H), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1660 (C=O), 1763 ester (C=O)/cm, MS: m/z 458.
Elemental analysis. Calculated for $C_{25}H_{18}N_2O_5S$: C, 65.50; H, 3.93; N, 6.11%, found: C, 65.06; H, 3.22; N, 5.83%.

7) 1-ethoxycarbonyl-3-phenyl-4′-chloro-3′-nitro-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1g).
Yield: 0.51 g, 58%, melting point: 249 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.40 (t, J=7.2 Hz, 3H, CH_3), 4.21 (q, J=7.2 Hz, 2H, CH_2), 7.42 (s, 1H, 2′-H), 9.39 (d, J=1.8

Hz, 1H, 9-H), IR (Neat): 1660 (C=O), 1762 ester (C=O)/cm, MS: m/z 492 [M^+, 80%].
Elemental analysis. Calculated for $C_{25}H_{14}N_2O_5SCl$: C, 60.91; H, 3.45; N, 5.69%, found: C, 60.34; H, 2.89; N, 5.08%.

8) 1-ethoxycarbonyl-3-phenyl-4′-hydroxy-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1h).
Yield: 0.51 g, 65%, melting point: 196-198 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.36 (t, J=6.8 Hz, 3H, CH_3), 4.21 (q, J=6.8 Hz, 2H, CH_2), 9.26 (s, 1H, 4′-OH), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1659 (C=O), 1761 ester (C=O)/cm, MS: m/z 428.
Elemental analysis. Calculated for $C_{24}H_{17}N_2O_4S$: C, 67.28; H, 3.73; N, 6.54%, found: C, 67.05; H, 3.31; N, 6.25%.

9) 1-ethoxycarbonyl-3-phenyl-2′-hydroxy-12H-pyrido[3′,2′:5,6]thiopyrano[3,2-f]quinoline-12-one. (1i).
Yield: 0.49 g, 63%, melting point: 213 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.34 (t, J=7.2 Hz, 3H, CH_3), 4.24 (q, J=7.2 Hz, 2H, CH_2), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1658 (C=O), 1760 ester (C=O), 3338 (N-H)/cm, MS: m/z 428.
Elemental analysis. Calculated for $C_{24}H_{16}N_2O_4S$: C, 67.28; H, 3.73; N, 6.54%, found: C, 67.02; H, 3.27; N, 6.29%.

10) 4-ethoxycarbonyl-2-phenyl-4′-hydroxy-7H-pyrido[3′,2′:5,6]thiopyrano[3,2-h]quinoline-7-one. (1j).
Yield: 0.47 g, 57%, melting point: 227 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.32 (t, J=6.4 Hz, 3H, CH_3), 4.21 (q, J=6.4 Hz, 2H, CH_2), 6.93-7.12 (m, 2H, 3′, 5′-H), 7.68-7.90 (m, 2H, 2′, 6′-H), 9.24 (s, 1H, 4′-OH), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1657 (C=O), 1761 ester (C=O)/cm, MS: m/z 428.
Elemental analysis. Calculated for $C_{24}H_{16}N_2O_4S$: C, 67.29; H, 3.73; N, 6.54%, found: C, 67.07; H, 3.35; N, 6.31%.

11) 4-ethoxycarbonyl-2-phenyl-4′-chloro-7H-pyrido[3′,2′:5,6]thiopyrano[3,2-h]quinoline-7-one. (1k).
Yield: 0.53 g, 61%, melting point: 183 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.36 (t, J=7.2 Hz, 3H, CH_3), 4.24 (q, J=7.2 Hz, 2H, CH_2), 9.28 (s, J=Hz, 1H, 2′-OH), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1657 (C=O), 1761 ester (C=O)/cm, MS: m/z 446.
Elemental analysis. Calculated for $C_{24}H_{15}N_2O_3SCl$: C, 64.50; H, 3.35; N, 6.27%, found: C, 63.1; H, 2.37; N, 5.18%.

12) 4-ethoxycarbonyl-2-phenyl-3′-methoxy-4′-hydroxy-7H-pyrido[3′,2′:5,6]thiopyrano[3,2-h]quinoline-7-one. (1l).
Yield: 0.64 g, 73%, melting point: 237 °C, ^{1}H-NMR: (DMSO-d_6) δ: 1.32 (t, J=6.8 Hz, 3H, CH_3), 3.72 (s, 3H, 3′-OCH_3), 9.39 (d, J=1.8 Hz, 1H, 9-H), IR (Neat): 1657 (C=O), 1761 ester (C=O)/cm, MS: m/z 458.
Elemental analysis. Calculated for $C_{25}H_{18}N_2O_5S$: C, 65.50; H, 3.93; N, 6.11%, found: C, 65.14; H, 3.37; N, 5.87%.

Results and Discussion

These products were precipitated by addition of ethanol and water (1:1) and were purified by recrystalizing from appropriate solvents, and were characterized from their IR, ^{1}H-NMR and mass spectral data. In the IR spectrum of these compounds the absorption bands in the region of 1761-1762/cm is due to presence of C=O group of ester which is conjugated with phenyl group, while the C=O group of ketone have shown its stretching in the region between 1657-1660/cm. The ^{1}H-NMR spectra of these compounds have shown the appearance of triplet between δ 1.32-1.72 ppm and quartet between δ 3.72-4.23 ppm due to the presence of three and two protons of -CH_3 and -CH_2 of esters respectively. The appearance of multiplet and doublet in the region between δ 6.93-7.92 ppm may be assigned to aromatic protons, while three pyridine protons i.e. 9 (d), 10 (dd) and 11(d) were observed in the region of δ 9.39, 7.86 and 8.79 ppm respectively. It seems that the ester group does not interfere during cyclization to the 6 position. In some of the cyclizations the three components i.e. aryl aldehyde, the amino compound i.e. 7-and 9-amino-5H-thiochromeno[2,3-b]pyridin-5-one and ethyl pyruvate were heated in acetic acid (to give the cyclized products) (1a-1l) (Bergstrom, 1944).

Pyruvic acid adds to the Schiff's base followed by dehydration-cyclization to give a dihydro product which aromatized by air oxidation.

It has been observed in most cases of such cyclizations that "angular" products were obtained in preference to the linear ones for example the synthesis of benzo[f] quinoline from 2-naphthylamine. Another example of angular cyclizations is given below (Wang *et al*., 2008; Fujiwara and Kitagawa, 2000; Fujiwara, 1997).

Similarly 4-ethoxycarbonyl-2-phenyl-7H-pyrido [3′,2′:5,6]thiopyrano[3,2-h]quinoline -7-ones (1j-1l) were prepared by the reaction of 9-benzylideneamino-

5H-thiochromeno[2,3-b]pyridin-5-one and ethyl pyruvate. They were characterized from their IR, ^{1}H-NMR and mass spectral data. In the IR spectrum of these compounds the absorption bands appear in the region between 1761-1762/cm is due to presence of C=O group of ester, while the C=O group of ketone have shown its stretching in the region between 1657-1660/cm. The ^{1}H-NMR spectra of these compounds may be described on the baises of similar justifications as discussed for (1a-1i).

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Conflict of Interest. The authors declare no conflict of interest.

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