Asian Journal of Chemistry Vol. 16, Nos. 3–4 (2004), 1594–1598

Synthesis and Spectral Studies of Thieno(2,3-b)Quinoline Derivatives

V. NITHYADEVI, N. SAMPATHKUMAR and S.P. RAJENDRAN*
Department of Chemistry
Bharathiar University, Coimbatore-641 046, India

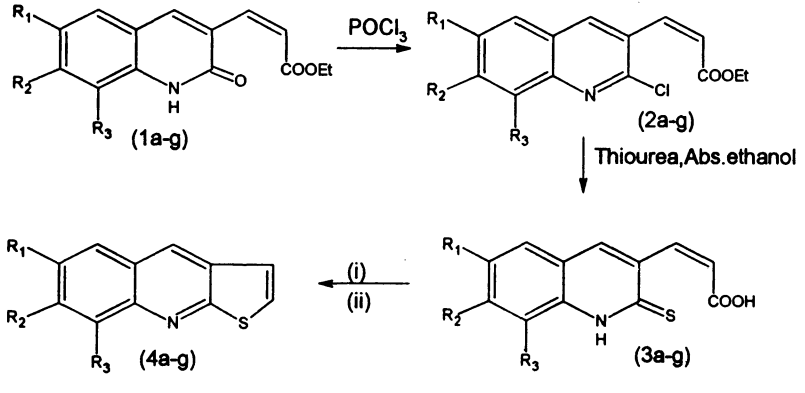
3-(2-Chloro-3-quinolyl)acrylic esters on boiling with thiourea in absolute ethanol yielded the thiones. These on treatment with bromine followed by the reaction with triethylamine afforded the cyclised product thieno(2,3-b)quinolines. The structural elucidations were performed using the elemental analysis, infrared, nuclear magnetic resonance and mass spectral data.

Key Words: Synthesis, Thieno(2,3-b)quinoline derivatives, IR, NMR, Mass spectra.

INTRODUCTION

Numerous thieno(2,3-b)quinoline derivatives are well documented for their pharmacological properties exhibiting antibacterial[1–3], antifungal[3], anti-anaphylactic[4], antiarrhythmic and antiinflammatory activity[5].

Early workers from our laboratory have synthesized thieno(2,3-b)quinolines using 3-vinyl quinolin-2(1H)ones[6–8], 3-(2′-hydroxyethyl)-2-quinolines[9], 4,5-dihydrofuran-3-carboxanilides[10, 11] and 2,3-dihydrothieno(2,3-b) quinoline-S-oxides[12] as starting compounds. Herein we report the synthesis of thieno(2,3-b)quinolines (**4**) from 3-(2-chloro-3-quinolyl)acrylic esters (**2**) which in turn were prepared from 2-chloro-3-formyl quinolines[13] **(Scheme-1).**



Scheme-1.

(i) Br_2, Anhy. $CHCl_3$, (ii) Et_3N, Anhy. $CHCl_3$, (a) $R_1 = R_2 = R_3 = H$, (b) $R_1 = CH_3$, $R_2 = R_3 = H$, (c) $R_1 = R_3 = H$, $R_2 = CH_3$, (d) $R_1 = R_2 = H$, $R_3 = CH_3$, (e) $R_1 = OCH_3$, $R_2 = R_3 = H$, (f) $R_1 = R_3 = H$, $R_2 = OCH_3$, (g) $R_1 = H$, $R_2 = R_3 =$ —CH=CH—CH=CH—

EXPERIMENTAL

Melting points were determined using Raaga melting point apparatus and were uncorrected. The IR spectra were recorded on FTIR 8201(PC)S spectrometer as KBr pellets. Proton NMR spectra were recorded on a Gemini-200 MHz or on a Varian AMX 400 spectrometer in $CDCl_3$. The chemical shifts were expressed in δ(ppm) downfield from tetramethylsilane as an internal standard. Elemental analysis was performed by Perkin-Elmer model 240B CHN analyzer and the values are within the pemnissible limits (±0.5). The mass spectra were recorded by EIMS technique on an Autospec mass spectrometer. The crude products were checked by thin layer chromatography and purified by column chromatography using silica gel (60–120 mesh). 2-Chloro-3-formyl quinoline[13] and 3-(2-oxo-1,2-dihydro-3-quinolyl)acrylic acid[14] were synthesized according to the previously reported procedures.

Preparation of 3-(2-oxo-1,2-dihydro-3-quinolyl)acrylic ethyl esters (1)

The ethyl ester was obtained in an almost quantitative yield by boiling 3-(2-oxo-1,2-dihydro-3-quinolyl)acrylic acid (3 g) with concentrated sulphuric acid (4.5 mL) and absolute ethanol (150 mL). The acid gradually passed into the solution after boiling for 5 to 6 h on steam bath. The solution was then allowed to cool, where a mass of needles of esters was filled within. A considerable quantity was further precipitated by dilution with two volumes of water. The whole solid was collected, washed with water, dried, recrystallized from ethanol and was ready for further use.

Preparation of 3-(2-chloro-3-quinolyl)acrylic ethyl esters (2)

The ester (1) (0.0228 mol) was treated with freshly distilled phosphorus oxychloride (13.6 mL, 0.148 mol) and kept on a steam bath for 5–6 h. On cooling and pouring into crushed ice, the compound separated as a creamy white solid. It was then recrystallised from pet. ether : benzene (4 : 1 v/v) and obtained as yellow coloured needles (Table-1)

TABLE-1
PHYSICAL AND IR DATA OF **2a–g***

Compound	Yield (%)	m.p. (°C)	IR (KBr, cm^{-1})	Mass (m/z)
2a	85	120–121	1710, 1267, 1064	261, 263
2b	87	90–91	1701, 1263, 1041	275, 277
2c	89	135–136	1708, 1265, 1039	275, 277
2d	92	144–145	1711, 1274, 1031	275, 277
2e	80	96–97	1709, 1269, 1049	291, 293
2f	85	115–117	1712, 1261, 1026	291, 293
2g	89	150–151	1718, 1280, 1045	311, 312

*Recrystallized from petroleum ether : benzene (4 : 1 v/v)

Preparation of quinoline-2(1H)-thione-3-acrylic acids (3)

A mixture of (2) (0.00382 mol), thiourea (0.00459 mol) and anhydrous ethanol (30 mL) was heated together under reflux temperature for 5 to 6 h on a steam bath. The yellow coloured solid was collected by evaporation of the solvent and heated with 10% sodium hydroxide solution (15 mL) for 15 min. On cooling and acidification the quinolin-2 (1H)-thione-3-acrylic acid was obtained as yellow powder. The thione obtained was pure enough for further use (Table-2).

TABLE-2
PHYSICAL AND IR DATA OF **3a–g***

Compound	Yield (%)	m.p. (°C)	IR (KBr, cm^{-1})
3a	70	280–281	3395, 1680, 1608, 1130
3b	73	230–231	3418, 1669, 1610, 1135
3c	76	264–265	3408, 1679, 1616, 1145
3d	80	215–216	3413, 1693, 1608, 1110
3e	81	240–241	3415, 1680, 1616, 1168
3f	79	218–219	3401, 1690, 1601, 1180
3g	70	249–250	3425, 1695, 1621, 1165

*Recrystallized from chloroform

Preparation of thieno(2,3-b) quinolines (4)

To a well cooled solution of (3) (0.00378 mole) at 0 to 5°C in 30 mL of anhydrous chloroform, bromine (0.00378 mol) in anhydrous chloroform (15 mL) was added in drops and kept stirring for 2 h. A light brownish yellow powder resulted out by distilling the solvent along with excess bromine.

The dibromide (0.0045 mol) was suspended in 70 mL of anhydrous chloroform, mixed with triethyl amine (0.0665 mol) and refluxed for 6 to 7 h. After the completion of the reaction the solvent together with excess triethyl amine was stripped off. The residue was mixed with chloroform and washed with water. The organic layer was separated, dried with anhydrous sodium sulphate and evaporated. Column chromatography of the residue with 100% petroleum ether (60–80°C) furnished colourless crystals. This was again recrystallised from petroleum ether (Table-3).

RESULTS AND DISCUSSION

Esterification of 8-methyl-3-(2-oxo-1,2-dihydro-3-quinolyl)acrylic acid in presence of absolute ethanol and concentrated sulphuric acid at reflux temperature for 5–6 h furnished the crude compound in an almost quantitative yield. This upon recrystallisation from ethanol furnished shiny needle-shaped crystals with 90% yield. The IR spectrum showed strong peaks at 1707cm^{-1} (—C=O of ester), 1601 cm^{-1} (—C=C— stretching), 3109 cm^{-1} (—NH stretching), broad peak at 3163 cm^{-1} (—OH stretching (tautomerism)) assigning the structure as 8-methyl-3-(2-oxo-3-quinolyl)acrylic ethyl ester (**1d**) to the compound. The compound (**1d**) upon dehydroxychlorination with freshly distilled phosphorus oxychloride resulted in a creamy white compound. This was followed by recrystallization from

pet. ether : benzene (4 : 1 v/v) giving rise to needle-shaped crystals melting at 144–145°C in 92% yield. The spectral values of the compound were found to be as follows:

IR (KBr, cm^{-1}): 1710 (—C=O of ester), 1030 (—C—Cl) and the disappearance of peaks at 3109 and 3163 cm^{-1}.

TABLE-3
PHYSICAL AND SPECTROSCOPIC DATA OF **4a–g***

Compd.	m.p. (°C) Yield (%)	Analysis calcd. (Found) C	H	N	^{1}H NMR ($CDCl_3$) δ(ppm)	Mass (m/z)
4a	107–108 (107–108)[15] (68)	71.30 (71.12)	3.81 (3.61)	7.55 (7.23)	7.28–7.85 (m, 2H, C_6, C_7—H), 7.62 (d, C_2—H, J = 6 Hz), 7.32 (d, C_3—H, J = 6 Hz), 8.52 (s, C_4—H), 7.88 (dd, 1 H, C_5—H, J = 8, 1.5 Hz), 8.27 (dd, 1 H, C_8—H, J = 1.5 Hz)	185
4b	131–132 (131–132)[10] (50)	72.30 (72.41)	4.55 (4.61)	7.02 (7.13)	7.57–7.80 (m, 2H, C_5—H, C_7—H), 7.53 (d, C_2—H, J = 6 Hz), 7.33 (d, C_3—H, J = 6 Hz), 8.43 (s, C_4—H), 8.07 (d, 1H, C_8—H, J = 8 Hz), 2.57 (s, 3H, CH_3)	199
4c	126–127 (70)	72.30 (72.30)	4.55 (4.50)	7.02 (6.72)	7.33–7.93 (m, 4H, C_2, C_5, C_6, C_8—H), 2.61 (s, 3H, —CH_3), 8.51 (s, C_4—H), 7.55 (d, C_3—H, J = 6 Hz)	199
4d	94–95 (93–94)[10] (65)	/2.30 (72.00)	4.55 (4.51)	7.02 (7.00)	7.47–800 (m, 4H, C_2, C_5, C_6, C_7—H), 8.5 (s, C_4—H), 7.4 (d, J = 6 Hz, C_3—H), 2.9 (s, 3H, —CH_3)	199
4e	116–117 (45)	66.93 (66.61)	4.21 (4.21)	6.50 (6.51)	7.22 (d, C_2—H, J = 6 Hz), 7.46 (d, C_3—H, J = 6 Hz), 8.18 (s, C_4—H), 7.16 (d, 1H, C_5—H, J = 2.5 Hz), 7.42 (dd, 1H, C_7—H, J = 2.5 Hz; 8 Hz), 3.96 (s, 3H, OCH_3)	215
4f	111–112 (50)	66.93 (66.88)	4.21 (4.19)	6.50 (6.45)	7.32–7.73 (m, 3H, C_5, C_6, C_8—H), 8.47 (s, C_4—H), 7.85 (d, C_2—H, J = 6 Hz), 7.34 (d, C_3—H, J = 6 Hz)	215
4g	145–146 (60)	76.56 (76.11)	3.86 (3.52)	5.95 (5.89)	8.54 (s, 1H, C_4—H), 7.41–9.41 (m, 9H, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}—H)	235

^{1}H-NMR ($CDCl_3$)δ (ppm): 8.33 (s, C_4—H), 8.15, 6.56 (d, 1H each —CH=CH_{trans}, J = 16 Hz), 7.69 (d, J = 8 Hz, C_7—H), 7.60 (d, J = 7.4 Hz, C_5—H), 7.47 (t, J = 7.4 Hz, C_6—H), 1.49 (t, J = 7 Hz, 3H, —CH_3 (of ester)), 4.44 (q, J = 7 Hz, 2H, —OCH_2).

Mass spectra: m/e = 275 (M^+), 277 (M + 2) which is one-third the intensity of the parent peak, thus confirming the structure of the compound as 8-methyl-3-(2-chloro-3-quinolyl)acrylic ester **(2d)**. The chloro ester **(2d)** furnished a yellow solid on boiling with thiourea and absolute ethanol for 5 to 6 h. This was followed by decomposition of the thiouronium salt with 10% aqueous alkali. The alkaline solution upon acidification furnished a yellow compound with 80% yield.

IR (KBr, cm^{-1}): appearance of strong peaks at 1693 cm^{-1} (—C=O of acid), 1110 cm^{-1} (C=S), 1608 cm^{-1} (—C=C— stretching), 3413 cm^{-1} (—NH stretching), disappearance of peak at 1030 cm^{-1}.

^1H NMR($CDCl_3$) δ (ppm): 2.59 (s, 3H, CH_3), 8.36, 6.56 (d, 1H, each —CH=CH—, J = 16 Hz), 7.30 (t, J = 7.8 Hz, C_6—H), 7.52 (d, J = 6.8 Hz, C_5—H), 7.67 (d, J = 7.8 Hz, C_7—H), 8.52 (s, C_4—H), 12.4 (s, COOH)

The mass spectrum showed molecular ion peak at 245 (M^+). Thus the structure of the compound was identified as 8-methylquinoline-2(1H)-thione-3-acrylic acid **(3d)**. Addition of bromine to **(3d)** in anhydrous chloroform solution at 0–5°C followed by heating the reaction mixture with triethylamine at reflux temperature readily furnished a compound in an almost quantitative yield. Its IR spectrum showed the disappearance of the acid peak at 1693 cm^{-1}.

^1H NMR ($CDCl_3$) δ ppm: 8.5 (s, C_4—H), 7.4 (d, C_3—H, J = 6 Hz), 7.47–8.00 (m, 4H, C_2, C_5, C_6, C_7—H) and singlet at 2.9 (s, 3H, —CH_3) and the mass spectrum showed intense molecular ion peak at 199 (M^+).

Thus the structure of the compound was identified as **8-methyl thieno(2,3-b) quinoline (4d).** The above reaction sequence was extended to synthesize the other derivatives **(4a), (4b), (4c), (4e), (4f)** and **(4g),** respectively.

ACKNOWLEDGEMENTS

We wish to thank Bharathiar University Coimbatore, IICT Hyderabad, IISc Bangalore for recording Proton NMR, IR and Mass spectra.

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(*Received*: 2 January 2004; *Accepted*: 22 April 2004) AJC-3410