A CONVENIENT METHOD FOR THE SYNTHESIS OF THIOPYRANO[4,3-*c*]QUINOLINE, A NEW HETEROCYCLIC SYSTEM

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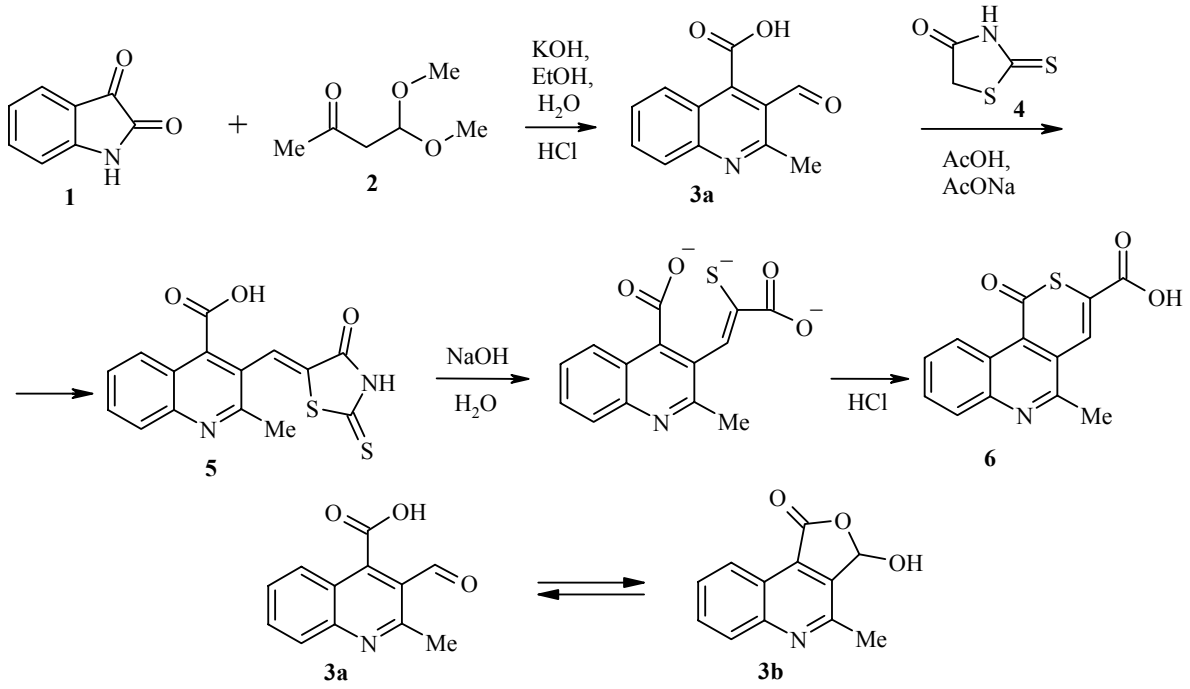
1H-Benzothiopyrans (1H-isothiochromenes) form a class of heterocyclic compounds that has not been studied extensively, largely due to the difficulty of obtaining the starting compounds for their synthesis [1-6].

Some 1H-2-benzothiopyran derivatives display biological activity [7] and cited there works. It has been difficult to obtain a library of these compounds using the cited methods for the synthesis of 1H-2-benzothiopyranes and thioisocoumarins, which has hindered the study of their biological activity. This is also true for heterocyclic compounds with a fused thiopyran ring.



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In the present work, we describe a convenient method for fusion of a thiopyran ring to the quinoline fragment. The reaction of isatin **1** with the dimethylacetal of acetaldehyde (4,4-dimethoxy-2-butanone) **2** under conditions of the Pfitzinger reaction gives 3-formyl-2-methyl-4-quinolinecarboxylic acid **3a**, which, is converted in acid media to the cyclic form, namely, 3-hydroxy-4-methyl-3H-furo[3,4-*c*]quinoline-1-one **3b**. This result is supported by ^{1}H NMR spectroscopy.

In a study of the reaction of compound **3** with rhodanine (2-thioxothiazolidin-4-one) **4**, we found that the condensation product **5** forms a thiopyran ring due to recyclization upon hydrolysis conditions. Thus, we have obtained the first thiopyrano[4,3-*c*]quinoline **6**.

The synthesis of acids **6** with various substituents in the quinoline fragment should be possible by varying reagents **1** and **2**. Acid **6** may be used in combinatorial synthesis.

The ^{1}H NMR spectra were taken on a Varian Unity +400 spectrometer at 400 MHz in DMSO-d_6 with TMS as the internal standard. The mass spectra were obtained on an Agilent 1100LC/MSD instrument with chemical ionization.

3-Hydroxy-4-methylfuro[3,4-*c*]quinoline-1(3H)-one (3b). Isatin **1** (5.5 g, 37.4 mmol) was dissolved upon heating in a solution of KOH (10.9 g, 194.6 mmol) in water (50 ml) and ethanol (10 ml). Then, 4,4-dimethoxy-2-butanone **2** (5 ml, 37.5 mmol) was added and heated at reflux for 7 h. The reaction mixture was cooled, combined with water (100 ml), and brought to pH 6-7 by adding acetic acid. The precipitate was filtered off and dissolved in dioxane (~2 g in 10 ml). Then, 0.5 ml concentrated hydrochloric acid was added. The mixture was heated at reflux for 1 min, diluted with water, and neutralized. The precipitate formed was filtered off and purified by recrystallization from ethanol to give compound **3b** in 76% yield; mp 243-244°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.94 (3H, s, CH_3); 7.77 (1H, t, ^3J = 7.8, quinoline H-6); 7.94 (1H, t, ^3J = 7.8 quinoline H-7); 8.06 (1H, s, CH); 8.37 (1H, d, ^3J = 7.8, quinoline H-5); 8.74 (1H, d, ^3J = 8.8, quinoline H-8). Mass spectrum, *m/z* (I_{rel}, %): 216 $[M+H]^+$. Found, %: C 66.79; H 4.07; N 6.71. $C_{12}H_9NO_3$. Calculated, %: C 66.97; H 4.22; N 6.51.

2-Methyl-3-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-4-quinolinecarboxylic Acid (5). A mixture of compound **3** (2.2 g, 10 mmol), rhodanine **4** (1.3 g, 10 mmol), and triethylamine (2 ml) in acetic acid (25 ml) was heated at reflux for 2 h. The precipitate formed upon cooling was filtered off and after drying in the air, recrystallized from acetic acid to give compound **5** in 76% yield; mp 287-288°C. Mass spectrum, *m/z* (I_{rel}, %): 331 $[M+H]^+$. Found, %: C 54.79; H 3.07; N 8.31. $C_{19}H_{15}N_2O_3S_2$. Calculated, %: C 54.53; H 3.05; N 8.48.

5-Methyl-1-oxo-1H-thiopyrano[4,3-*c*]quinoline-3-carboxylic Acid (6). Acid **5** (3.3 g, 10 mmol) was added to a solution of KOH (2.24 g, 40 mmol) in water (50 ml) and heated at reflux for 3 h. The reaction mixture was poured into concentrated hydrochloric acid (15 ml) and ice (75 ml). The precipitate formed was filtered off and recrystallized from ethanol to give compound **6** in 69% yield; mp 246-247°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (3H, s, CH_3); 7.56 (1H, t, ^3J = 8.8, quinoline H-6); 7.71 (1H, t, ^3J = 7.8, quinoline H-7); 7.79 (1H, s, thiopyran); 7.95 (1H, d, ^3J = 8.8, quinoline H-5); 8.69 (1H, d, ^3J = 7.8, quinoline H-8). Mass spectrum, *m/z* (I_{rel}, %): 272 $[M+H]^+$. Found, %: C 62.09; H 3.09; N 5.11; S 11.67. $C_{14}H_9NO_3S$. Calculated, %: C 61.98; H 3.34; N 5.16; S 11.82.

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