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Synthesis and characterization of 4-methoxy-1H-quinolin-2-thiones

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ABSTRACT

The synthesis of various substituted 4-methoxy-1H-quinolin-2-thiones from various substituted aniline with malonicacid, phosphorous-oxychloride, sodium methoxide glacial acetic acid and thiourea under different conditions is described. The title compounds were synthesized from four steps; the first step involved the synthesis of substituted 2, 4-dichloro quinoline from aniline (substituted), with malonicacid and phosphorous-oxychloride. In the second step, the substituted 2, 4 Dichloro compound was heated with freshly prepared methanolic sodium methoxide solution to give 2, 4-dimethoxy quinoline compounds, it was then refluxed with glacial acetic acid and hydrochloric acid to get the substituted 4-methoxy-1H-quinolin-2-one. The final steps involves with an objective of introducing a chloro in the position 2 of the quinolone system, the substituted 4-methoxy-1H-quinolin-2-one was refluxed with distilled $Pocl_3$ chloroform. The substituted 2-chloro-4-methoxy quinoline was then refluxed with thiourea and alcohol to get the titled compounds. The purity of the synthesized compound was judged by their C, H and N analysis and the structure was analyzed on the basics of Mass, FT-IR, and ^{1}H NMR.

Introduction

Heterocyclic compounds have different types of pharmacological properties[1-2]. Several quinolones like ciprofloxacin, pefloxacin, levofloxacin, spafloxacin are released in the clinical world. Synthesis of various substituted quinolone intermediate compounds is of current interest because of their therapeutically potential in the area of human and animal health such as antibacterial[3-5], antimicrobial[6] and antituberculosis [7-9] activities. Combe's et al[10] synthesized the 2,4 disubstituted quinolone.A reaction relates to Skarup and Doebner-Von Miller Synthesis was discovered by comb's in 1888.He condensed an aromatic amine with a 1,3 diketone under acid condition to give 2,4 disubstituted quinolone. These biological data prompted us to synthesis 4- methoxy-1H-quinolin-2-ones.Earliar publications described the synthesis of substituted quinolone,[11-17] by cyclocondensation.

The classical synthetic protocols for the quinoline intermediates and natural products suffer some of disadvantages such as low yield,[18] lack of easy availability/preparation of the reagent,[19-20] prolonged reaction time(24 hours), multiple steps, requirement of excess of reagents/catalyst, need for special apparatus and harsh condition.[19] Hence we felt that it is worthwhile to synthesis a 4-methoxy-1H- quinoline-2-thione compounds in a convenient, efficient approach, the structure and characterization of these compounds are confirmed by FT-IR, Mass, and ^{1}H NMR.

Experimental

All the chemicals were purchased from Loba chemical. The reagents and solvents were analytical grade and were used without further purification unless otherwise mentioned. Carbon, Hydrogen and Nitrogen were determined by Perkin-Elmer 2400 instrument. All the melting points were taken in open in capillaries and were uncorrected. Chromatographic purifications were carried out Silica gel 60(230-400 mesh) and TLC (silica gel) was done on silica gel coated (Merck Kiesel 60 F 254, 0.2mm thickness) sheets.

Electronic absorbance spectra were recorded on a Varian Cary 5E UV-VIS spectrophotometer. Mass spectra were recorded at 70ev on a Joel JMS-D-300instument.IR Spectra were recorded as KBr pellet on a Perkin-Elmer-1700 Spectrophotometer ^{1}H NMR were recorded on 500 MHZ Bruker FT-NMR spectrometer using tetra methyl silane as internal standard and the chemical shifts were reported in δ ppm units.

General procedure for the synthesis:

Synthesis of 2, 4-dichloro quinoline

An equimolar mixture of (0.1m) aniline/substituted aniline (I: aniline 9.31gm, and an equimolar volume of phosphoryl chloride (60ml) were taken in a RB flask fitted with a double surface surface reflux condenser. An equimolar malonic acid (10.420gm) was added carefully and the mixture was heated at 150^{o}c for 5 hrs. The reaction mixture was cooled, poured into ice with vigorous stirring, neutralized with sodium carbonate, filtered, dried and recrystallized from ethanol to afford the desired substituted 2,4-dichloro quinoline (IIa)product as yellow powdered in good yield. Column chromatography (95:5 hexane: EtOAc) yielded the pure dichloroquinoline as off-white needled (6.8g,62%),mp66-67^{0}c(lit.[21]66^{0}c);R_f(95:5 hexane: EtOAc) 0.51.

Synthesis of 2, 4-Dimethoxy quinoline

The substituted 2, 4 Dichloro compound (2.8g, 14mmol of II:2,4 Dichloro-quinoline, was heated with freshly prepared methanolic sodium methoxide solution(from 2.0g,86mmol Na in 50 ml MeOH) in water bath for 5hrs .The reaction mixture was cooled , the contents were poured into ice, neutralized with acetic acid, and the resulting white precipitate was filtered off. The compound 2, 4-Dimethoxy quinoline (III) was washed with water and recrystalized from methanol. Columnchromatography

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(9:1hexane: EtOAc) yielded the2, 4dimethoxyquinoline, (2.65g, 62%) as white needles.M.p78-80^{0}c (lit.[22] 81-82 ^{0}c).

Synthesis of 4-methoxy-1H-quinolin-2-one

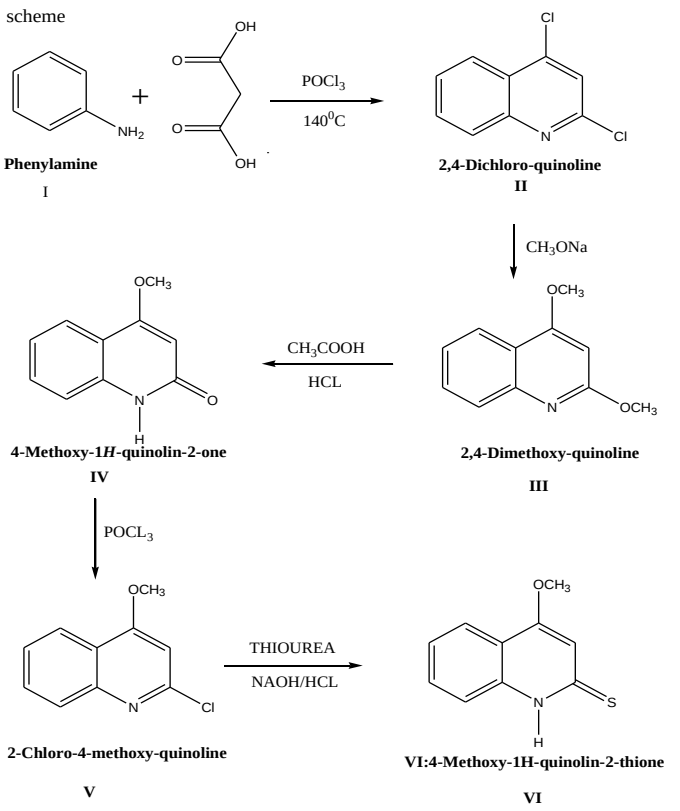
The substituted 2,4-dimethoxy quinoline (2.0g, 11 mmol of III:2,4-Dimethoxy-quinoline, was refluxed with glacial acetic acid and con.Hcl in a R.B flask for 4hrs.The reaction mixture was concentrated and poured into the beaker containing crushed ice and neutralized with sodium carbonate. The compound was filtered, dried, purified by recrystallisation from hot ethanol-water and again chromotogrphed to yield the pure compound 4-methoxy-1H-quinolin-2-one[26](IVa) (1.60 g, 60%), mp249-252^{0}c lit.[23]250-253^{0}c). The spectral and analytical data of the compound was confirmed the structure.

Synthesis of 4-methoxy-1H-quinolin-2-thione

The substituted 4-methoxy-1H-quinolin-2-one (1.6g, 12mmol of 4-methoxy-1H-quinolin-2-one Iv) was refluxed with distilled Pocl3 over water bath for about 4hrs.. It was collected by filtration and recrytallised from chloroform. The substituted 2-chloro-4-methoxy quinoline was refluxed with thiourea and alcohol (distilled) over a water bath for 6hrs.It was then decomposed with NaoH.Then the mass was poured onto crushed ice and neutralized with HCl. Then yellow solid obtained was chromatographed over a column of neutral alumina with chloroform as a eluent to afford a yellow colored solid which was further recrystalised from chloroform. The spectral and analytical data of the substituted 4-methoxy-1H-quinolin-2-thione compounds (VI) (1.5g, m.p2500C.lit24, and 250-254^{0}C) was confirmed the structure of the titled compounds. Elemental analysis corroborated the proposed molecular formula, $C_{10}H_9ONS$.

Exactmass: 191.04, Mol.wt.191.25Found: C-62.36; H-4.70; N-7.31; O-8.35; S- 16.72.Calculated: C-62.80, H-4.74, N-7.32, O-8.37, and S-16.77.Moreover the m.pt of the solid is consistent with the Lit.[24] m.pt of 4-methoxy-6-methyl-1H-quinolin-2-thione as 251^0 c.

SYNTHESIS OF SUBSTITUTED-4-METHOXY-1H-QUINOLIN-2-THIONES



Results and discussion

Reaction of aniline with malonic acid in an excess of phosphorous oxychloride at reflux to give 2,4-dichloroquinoline(I) was reported by Ziegler and Gelfer,[24] Although a reaction time of 24 to40 hours has been reported.

We found that the best yield of (II), 62% was obtained after only 6 hours at reflux. Reaction of 2, 4 dichloroquinoline (II) with sodium methoxide at reflux for 5 hours gave 2, 4 dimethoxyquinoline (III) in 72%yield.

Reaction of (III) with acetic acid and con.hydrochloric acid at reflux for 4 hours gave 4-methoxy-1H-quinolin-2-one (IV), 60% yield. .The spectral and analytical data of the substituted 4-methoxy-1H-quinolin-2-one compounds were analyzed.

With an objective of introducing a chloro in the position C-2 of the quinolone system is known to be favored kinetically the Iv 4-methoxy-1H-quinolin-2-one was refluxed with distilled $Pocl_3$ over water bath for about 4hrs get 2-chloro-4-methoxy quinoline (V).

The substituted 2-chloro-4-methoxy quinoline (V) was refluxed with thiourea and alcohol (distilled) over a water bath for 6hrs.It was then decomposed with NaoH and neutralized with HCl. The titled compound 4-methoxy-1H-quinolin-2-thione (VI) 60%was obtained after recrystallisation. The spectral and analytical data of the substituted 4-methoxy-1H-quinolin-2-thione compounds were analyzed.

The 4-methoxy -1H-quinolin-2-thione solid showed absorption bands at 1600cm^{-1} , 3000--3300cm^{-}1,1563-700 (N-C=S), 2950-2853(CH-Stretch), 800-700 (CH-bend), 1250 (-C-O-C Stretch),880(-C-N-Stretch) attributable to 2-quinolone and NH stretching vibrations respectively. The ^{1}H NMR spectrum represented a singlet at δ 3.12 for aromatic C-SH.

This confirms the attachment of the thione. Elemental analysis corroborated the proposed molecular formula, $C_{10}H_9ONS$.

The spectroscopic properties of our synthetic material II, III, Iv andV agreed well with those reported in literature[24].

4-methoxy-1H-quinolin-2-thione (VIa): ν_{max} (KBr)/cm-1:3150(w,N-H); 1680 (S,C=O);1615 (S,C=C); 1563-700 (N-C=S),1250 (s,-C-O-C),880 (s,-C-N-). ^{1}HNMRδ(ppm):2.41(s,3H,C_6-CH_3),3.87(s,3H,C_4-OCH_3),10.30(s,1H,-NH),6.02 (s,1H,C_3-H),7.20-7.62(2d,2H,C_7-H&C_8-H),7.90(s,1H,C_5H),3.12(s,1H,C-SH). Elemental analysis corroborated the proposed molecular formula, $C_{10}H_9ONS$.

Conclusion

We have clarified the synthesis of 4-methoxy-1H-quinolin-2-thione.The advantage of this new approach is that the reaction procedure is convenient, involves simple experimental procedure and the product isolation is easy. Hence it is the useful modification to the existing method. The reaction is carried out without using any catalyst. The reaction time is short, operable on a large scale. Work up is simple and the yields are excellent

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