Asian Journal of Chemistry; Vol. 24, No. 10 (2012), 4726-4728

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

# Synthesis and Characterization of Substituted 4-Methoxy-1*H*-quinolin-2-thiones

A.K. RAMASAMY[1], V. BALASUBRAMANIAM[2] and K. MOHAN[3,*]

[1]Department of Chemistry, Periyar University, Salem-636 011, India
[2]Department of Chemistry, AMET University, Chennai-603 112, India
[3]Department of Chemistry, Sakthi Polytechnic College, Sakthinagar-638 315, India

*Corresponding author: E-mail: kmohanchitra01@gmail.com

(*Received*: 2 September 2011; *Accepted*: 12 May 2012) AJC-11478

The synthesis of various substituted 4-methoxy-1*H*-quinolin-2-thiones from various substituted aniline with malonic acid, phosphorous-oxychloride, sodium methoxide glacial acetic acid and thiourea under different conditions is described. All these substituted 4-methoxy-1*H*-quinolin-2-thiones were synthesized from four steps; the first step involved the synthesis of substituted 2,4-dichloro quinoline from aniline (substituted), with malonic acid 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-1*H*-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-1*H*-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 substituted 4-methoxy-1*H*-quinolin-2-thiones. 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.

**Key Words: Substituted anilines, Malonic acid, Phosphoryl chloride, Sodium methoxide, Glacial acetic acid, Hydrochloric acid and thiourea.**

## 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 synthesize some new substituted 4-methoxy-1*H*-quinolin-2-ones. Earlier 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 h), multiple steps, requirement of excess of reagents/catalyst, need for special apparatus and harsh condition[19]. Hence it is worthwhile to synthesize some substituted 4-methoxy-1*H*-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 $F_{254}$, 0.2 mm thickness) sheets.

Electronic absorbance spectra were recorded on a Varian Cary 5E UV-VIS spectrophotometer. Mass spectra were recorded at 70 eV on a Joel JMS-D-300 instument. 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 substituted 2,4-dichloro quinoline:** An equimolar mixture of (0.1 m) aniline/substituted aniline (**Ia**: aniline 9.31 g, **Ib:** *p*-touldine 10.716 g and an equimolar volume of phosphoryl chloride (60 mL) were taken in a round bottom flask fitted with a double surface reflux condenser. An equimolar malonic acid (10.420 g) was added carefully and the mixture was heated at 150 ºC for 5 h. 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 (6.8 g, 62 %), m.p. 66-67 ºC (lit.[21] 66 ºC); $R_f$ (95:5 hexane:EtOAc) 0.51.

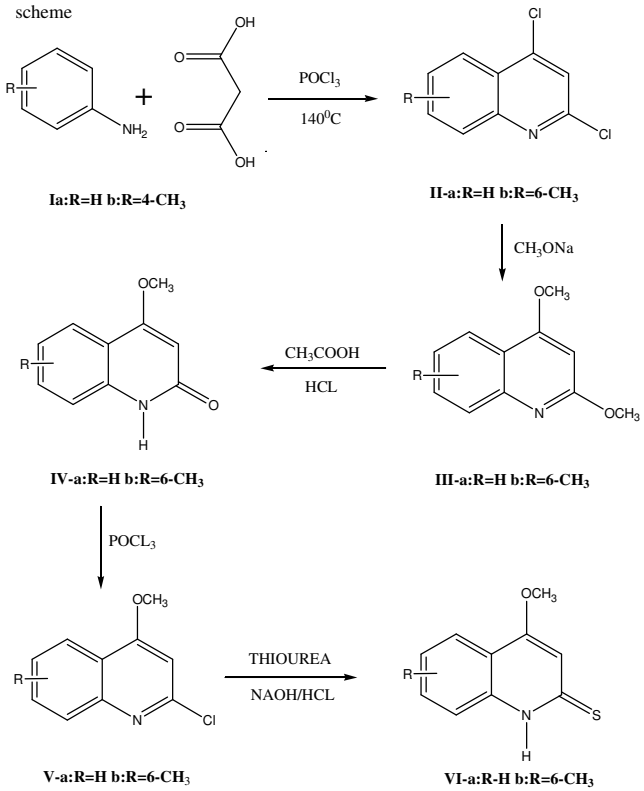
**Synthesis of substituted 2,4-dimethoxy quinoline:** The substituted 2,-4dichloro compound (2.8 g, 14 mmol of **IIa**: 2,4-dichloro-quinoline, **IIb:** 2,4-Dichloro-6-methyl-quinoline, was heated with freshly prepared methanolic sodium methoxide solution (from 2.0 g, 86 mmol Na in 50 mL MeOH) in water bath for 5 h. 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 (**IIIa**) was washed with water and recrystalized from methanol. Columnchromatography (9:1 hexane:EtOAc) yielded the 2,4-dimethoxyquinoline, (2.65 g, 62 %) as white needles. m.p. 78-80 ºC (lit.[22] 81-82 ºC).

**Synthesis of substituted 4-methoxy-1*H*-quinolin-2-one:** The substituted 2,4-dimethoxy quinoline (2.0 g, 11 mmol of **IIIa:** 2,4-Dimethoxy-quinoline, **IIIb:** 2,4-dimethoxy-6-methyl-quinoline was refluxed with glacial acetic acid and con. HCl in a RB flask for 4 h. 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-1*H*-quinolin-2-one[23] (**IVa**) (1.60 g, 60 %), m.p. 249-252 ºC lit.[24] 250-253 ºC). The spectral and analytical data of the compound was confirmed the structure.

**Synthesis of substituted 4-methoxy-1*H*-quinolin-2-thione:** The substituted 4-methoxy-1*H*-quinolin-2-one (1.6 g, 12 mmol of 4-methoxy-1*H*-quinolin-2-one **Iva**) was refluxed with distilled $PoCl_3$ over water bath for about 4 h. 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 6 h. 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 coloured solid which was further recrystalised from chloroform. The spectral and analytical data of the substituted 4-methoxy-1*H*-quinolin-2-thione compounds (**VIa**) (1.5 g, m.p. 250 ºC. lit[24] and 250-254 ºC) was confirmed the structure of the titled compounds. Elemental analysis corroborated the proposed molecular formula, $C_{10}H_9NOS$.

**Exact mass:** 191.04, m.w. 191.25 found (%): C-62.36; H-4.70; N-7.31; O-8.35; S-16.72. Calcd. (%): C-62.80, H-4.74, N-7.32, O-8.37 and S-16.77. Moreover the m.p. of the solid is consistent with the lit.[23] m.p. of 4-methoxy-6-methyl-1*H*-quinolin-2-thione as 251 ºC.

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




**VI**
**a: 4-Methoxy-1H-quinolin-2-thione**
**b: 4-Methoxy-6-methyl-1H-quinolin-2-thione**

## RESULTS AND DISCUSSION

Reaction of aniline with malonic acid in an excess of phosphorous oxychloride at reflux to give 2,4-dichloroquinoline (**Ia**) was reported by Ziegler and Gelfer[24], Although a reaction time of 24-40 h has been reported.

We found that the best yield of (**IIa**), 62 % was obtained after only 6 h at reflux. Reaction of 2,4-dichloroquinoline (**IIa**) with sodium methoxide at reflux for 5 h gave 2,4-dimethoxy-quinoline (**IIIa**) in 72 % yield. Reaction of (**IIIa**) with acetic acid and con. hydrochloric acid at reflux for 4 h gave 4-methoxy-1*H*-quinolin-2-one (**IVa**), 60 % yield. The spectral and analytical data of the substituted 4-methoxy-1*H*-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 favoured kinetically the **IVa** substituted 4-methoxy-1*H*-quinolin-2-one was refluxed with distilled $PoCl_3$ over water bath for about 4 h get 2-chloro-4-methoxy quinoline (**Va**).

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

The 4-methoxy-1*H*-quinolin-2-thione solid showed absorption bands ($cm^{-1}$) at 3300-3000, 1600, 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, $C_{10}H_9NOS$.

The spectroscopic properties of our synthetic material **IIa**, **IIIa**, **Iva** and **Va** agreed well with those reported in literature[25].

**4-Methoxy-6-methyl-1*H*-quinolin-2-one (IVb):** (KBr, $\nu_{max}$, $cm^{-1}$): 3150 (w, N-H), 1680 (S, C=O), 1635, 1608 (S, C=C); 1514 (amide11); $^1$H NMR δ (ppm): 2.42 (s, 3H, $C_6$-$CH_3$), 3.98 (s, 3H, $C_4$-$OCH_3$), 10.33 (s, 1H, -NH), 6.02 (s, 1H, $C_3$-H), 7.20-7.62 (2d, 2H, $C_7$-H amd $C_8$-H), 7.90 (s, 1H, $C_5$-H); anal. found (%); C, 69.81; H, 5.88, N, 7.43; calcd. (%) for; $C_{11}H_{11}NO_2$; C, 69.83; H, 5.86; N, 7.40; MS (M/Z): 189 ($M^+$).

**4-Methoxy-1*H*-quinolin-2-thione (VIa):** (KBr, $\nu_{max}$, $cm^{-1}$): 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-). $^1$H NMR δ (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 and $C_8$-H), 7.90 (s, 1H, $C_5$-H), 3.12 (s, 1H, C-SH). Elemental analysis corroborated the proposed molecular formula, $C_{10}H_9NOS$.

**4-Methoxy-6-methyl-1*H*-quinolin-2-thione (VIb):** (KBr, $\nu_{max}$, $cm^{-1}$): 3148 (w, N-H); 1670 (S, C=O); 1620 (S, C=C); 1550-700 (N-C=S), 1250 (s, -C-O-C), 880 (s, -C-N-). $^1$H NMR δ (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 and $C_8$-H), 7.90 (s, 1H, $C_5$H), 3.08 (s, 1H, C-SH). Elemental analysis corroborated the proposed molecular formula, $C_{11}H_{11}NOS$.

## Conclusion

We have clarified the synthesis of substituted of 4-methoxy-1*H*-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.

## ACKNOWLEDGEMENTS

The authors thank the Sophisticated Analytical Instrument Facility, Indian institutes of Technology, Chennai for recording NMR, UV, Bharathiar University, Coimbatore for recording IR spectra and Periyar University, Salem for providing necessary research facilities.

## REFERENCES

1. V.K. Singh R. Pandey and R.C. Srimal, *Indian J. Pharm. Sci.*, **54**, 4 (1992).
2. D.W. Henry, In ed.: R.M. Acheson, Heterocyclic Compounds, Interscience Publishers, New York, Vol. 9, p. 815 (1972).
3. R. Libel, R. Randle, H. Mildenberger, K. Bauer and H. Biernger, *Chem. Abstr.*, **108**, 6018 (1988).
4. E.A. Harrison and K.C. Rice, *J. Heterocycl. Chem.*, **14**, 909 (1977).
5. C.A. Mitsos, A.L. Zografos and O. Igglessi-Markopoulou, *J. Org. Chem.*, **68**, 4567 (2003).
6. D.S. Narsinh and Anamik, *Indian J. Heterocycl. Chem.*, **10**, 69 (2000).
7. N.B. Patel, A.L. Patel and H.I. Chauhan, *Indian J. Chem.*, **46B**, 126 (2007).
8. World Health Organisation,Tuberculosis Fact Sheet, No. 104 (2006).
9. A. Nayayar, A. Malde and E. Coutinho, *Bioorg. Med. Chem.*, **15**, 7302 (2007).
10. A. Combes, *Bull. Soc. Chim. France*, **49**, 89 (1888).
11. A.C.R. Dean, In ed.: R.M. Acheson, Heterocyclic Compounds, Interscience Publishers, New York, Vol. 9, p. 789 (1972).
12. Y. Mukisumi and A. Murabayashi, *Tetrahedron Lett.*, **10**, 2449 (1969); **10**, 2453 (1969).
13. L. Bauer and L.A. Gardella, *J. Org. Chem.*, **28**, 1320 (1963).
14. V. Nadaraj, S.T. Selvi and R. Sasi, *Arkivoc*, 82 (2006).
15. K. Arya and M. Agarwal, *Bioorg. Med. Chem. Lett.*, **17**, 86 (2007).
16. P. Shanmugam, N. Soundararajan and A. Gnansekaran, *J. Chem. Soc. Perkin I*, 2024 (1977); G.M. Coppolla, *J. Hetrocycl. Chem.*, **20**, 1217 (1983).
17. R. Srorer and D.W. Young, *Tetrahedron*, **29**, 1215 (1973).
18. M.D. Manandhar, F.A. Hussaini, R.S. Dapil and A. Shob, *Phytochemistry*, **24**, 199 (1985).
19. B. Bhudevi, P.V. Ramana, A. Mudiraj and A.R. Reddy, *Indian J. Chem.*, **48B**, 255 (2009).
20. D.G. Vidya, B. Jyothi, G.T. Santhosh and S.M. Ragho, *J. Chem. Res.*, **10**, 628 (2003).
21. A.G. Osborne and J.M. Buely, H. Clarke, R.C.H. Darkin and P.I. Price, *J. Chem. Soc. Perkin Trans. I*, 2747 (1993).
22. A.G. Osborne and J.F. Warmsley, *J. Nat. Prod.*, **55**, 589 (1992).
23. A.K. Ramasamy, V. Balasubramaniam and K. Mohan, *E-J. Chem.*, **7**, 1066 (2010).
24. K. Nickisch, W.K. Lose, E. Nordhoff and F. Bohlmann, *Chem. Ber.*, **113**, 3086 (1980).
25. K. Jones, X. Roset, S. Rossiter and P. Whittiels, *Org. Biomol. Chem.*, **1**, 4380 (2003).