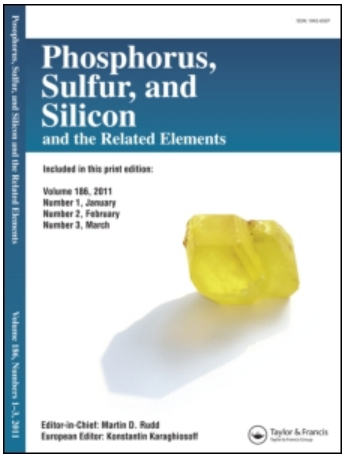

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A Fast and Large-Scale Synthesis of 3-Formyl-2-mercaptoquinolines

Belalakatte P. Nandeshwarappa[a]; Doyijode B. Aruna Kumar[b]; Halehatty S. Bhojya Naik[a]; Kittappa M. Mahadevan[b]

[a] Department of Post Graduate Studies and Research in Industrial Chemistry, Kuvempu University, Shankaraghatta, Karnataka, India [b] Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, Karnataka, India

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Belalakatte P. Nandeshwarappa
Department of Post Graduate Studies and Research in Industrial Chemistry, Kuvempu University, Shankaraghatta, Karnataka, India

Doyijode B. Aruna Kumar
Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, Karnatak, India

Halehatty S. Bhojya Naik
Department of PG Studies and Research in Industrial Chemistry, Kuvempu University, Shankaraghatta, Karnataka, India

Kittappa M. Mahadevan
Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, Karnatak, India

A convenient, efficient, and inexpensive procedure for the synthesis of 3-formyl-2-mercaptoquinolines ***2a–l*** *has been developed by a simple one-pot reaction of 3-formyl-2-chloroquinolines* ***1a–l*** *with sodium sulfide and hydrochloric acid in ethanol. The structures of all the synthesized compounds were elucidated on the basis of elemental analyses and IR,* ^{1} *H NMR, and mass spectral data.*

Keywords 3-formy-2-mercaptoquinoline; 3-formy-2-chloroquinoline; hydrochloric acid; sodium sulfide

INTRODUCTION

The conversion of aryl quinolines into mercaptoquinolines is of vital importance in synthetic organic chemistry. Aryl mercaptols are

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Address correspondence to Kittappa M. Mahadevan, Kuvempu University, Department of PG Studies and Research in Chemistry, Shankaraghatta, Karnatak 577 451, India. E-mail: mady_kmm@yahoo.co.uk

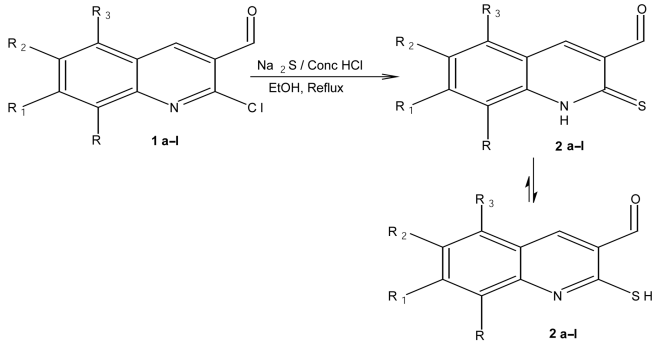
usually prepared via their corresponding halogenated derivatives. More reactive heterocyclic halogenated derivatives, i.e., 3-formyl-2-chloroquinolines into 3-formyl-2-mercaptoquinolines, are known.[1,2] Such procedures are obviously accompanied by poor yields, undesired side products, vigorous reaction conditions, long reaction times, expensive or toxic reagents, and tedious work-up. Therefore, there is still a need to introduce new methods and inexpensive reagents for such functional group transformations. In this context, we wish to report an efficient and inexpensive method for the synthesis of 3-formyl-2-mercaptoquinolines starting from easily accessible 3-formyl-2-chloroquinoline by a reaction with sodium sulfide and hydrochloric acid in a quantitative yield under remarkably soft conditions. We found that the best results were achieved using concentrated hydrochloric acid.

3-formyl-2-mercaptoquinoline compounds and the ring substituted analogues are important starting materials to construct sulfur-containing heterocycles, such as thiophene, thiopyrans, etc., fused with a quinoline moiety, with very important functional groups, such as —COOR, —COR, —CN, and —CONHR, at appropriate positions.[3] These functional groups have been utilized to build various pharmaceutically important heterocycles.[4–9] 2-hydroxy, 2-mercaptoaromatic, and heterocyclic aldehydes, and also their derivatives, such as oximes, and schiff bases, have proven to be an important pharmaceutical agent.[10–16] A number of metal complexes of such compounds have also been reported. Hence, there is a great deal of interest to synthesize 3-formyl-2-mercaptoquinolines.

In continuation of our work on condensed heterocycles[17–19]and in view of a growing interest in the field of anticancer agents, we wish to report an efficient synthesis of novel title compounds **2a–l**.

RESULTS AND DISCUSSION

The reaction is presumed to take place via an in situ formation of H_2S under strong acidic conditions. It was observed that reaction was complete within 10 min. The synthesis of 3-formyl-2-mercaptoquinoline **(2a)** from **1a** with conc. HCl and sodium sulfide resulted in an excellent yield (Scheme 1). The structure of **2a** was assigned on the basis of IR, ^{1}H NMR, and mass spectral studies. As an example, the IR spectrum of **2a** exhibited bands at 3480–3490 cm^{-1}, which correspond to —NH and —SH. This confirms the subsequent substitution by removing chlorine present at the 2-position on the quinoline nucleus of **2a**. Also, the absence of chlorine was confirmed by a Beilstein's test. In



	R	R_1	R_2	R_3
a.	**H**	**H**	**H**	**H**
b.	**H**	**H**	**CH_3**	**H**
c.	**H**	**CH_3**	**H**	**H**
d.	**CH_3**	**H**	**H**	**H**
e.	**H**	**H**	**OCH_3**	**H**
f.	**H**	**OCH_3**	**H**	**H**
g.	**OCH_3**	**H**	**H**	**H**
h.	**H**	**H**	**Br**	**H**
i.	**H**	**H**	**Cl**	**H**
j.	**H**	**Cl**	**H**	**H**
k.	**H**	**OCH_3**	**OCH_3**	**H**
l.	**H**	**OCH_3**	**OCH_3**	**OCH_3**

SCHEME 1 The general synthetic procedure of 3-formyl-2-mercaptoquinolines derivatives 2a–l.

the ^{1}H NMR spectra of **2a**, a broad singlet occurred at δ 11.2 due to the —SH in the product. Furthermore, the structure assigned for **2a** was confirmed by its mass spectrum with a molecular ion peak at 189. In addition, the structure of **2a** was further supported by elemental analysis. Compounds **2b–l** were similarly prepared (see Experimental section).

In conclusion, the present procedure catalyzed by conc. HCl on substituted 3-formyl-2-chloroquinolines **1a–l** provided a convenient and selective method for the synthesis of substituted 3-formyl-2-mercaptoquinolines **2a–l**. The notable advantages of this procedure are (a) a fast reaction, (b) high yields, and (c) good conversions. We believe that this procedure will provide a better and more practical alternative to the existing methodologies for the synthesis of 3-formyl-2-mercaptoquinoline derivatives.

EXPERIMENTAL

General

All mps were recorded in an open capillary and were uncorrected. IR spectra (cm^{-1}) were recorded (as KBr pellets) on a Perkin Elmer 157 infrared spectrophotometer. The ^1H NMR spectra (300 MHz) were measured in DMSO-d_6 with a Bruker supercon FT NMR instrument using TMS as an internal standard. Chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Jeol JMS-D 300 mass spectrometer operating at 70 eV. The purity of compounds was checked by TLC on silica gel, and the compounds were purified by column chromatography (silica gel).

The General Procedure for the Synthesis of 2-Mercapto-3-formylquinolin es 2a–l

A mixture of 3-formyl-2-chloroquinoline (**1a**, 5.73 g, 29.98 mmol) and sodium sulfide (8.4 g, 9.2 mmol) was refluxed for 10 min on a water bath in ethanol (50 mL). Conc. HCl (15 mL) was added dropwise to the reaction mixture. The mercapto compound **2a** precipitated out as a yellow crystalline solid. The mixture was poured into cold water (500 mL); the resulting solid product **2a** was collected by filtration, washed with ethanol, dried, and recrystallized from ethyl acetate and benzene (8:2). In a similar way, the same procedure produced **2b–l**. The synthesized compounds were easily characterized by IR, ^1H NMR, and mass spectroscopy.

3-Formyl-2-mercaptoquinoline (2a)

Obtained in an 80% yield, solid; m.p. $> 193^\circ$C; (Found: C, 63.39; H, 3.71; N, 7.38; S, 16.85. $C_{10}H_7NOS$ requires C, 63.47; H, 3.73; N, 7.40; S, 16.95); ν_{max}/cm^{-1} 3480–3490 (NH), 1640 (C=S); δ_H7.6–8.3 (m, 5H, 6H, 7H, 8H), 8.83 (s, 4H), 10.35 (s, CHO), 11.2 (s, SH); m/z 189 (M^+).

6-Methyl-3-formyl-2-mercaptoquinoline (2b)

Obtained in a 79% yield, solid; m.p. $> 213^\circ$C; (Found: C, 65.07; H, 4.39; N, 6.78; S, 15.68. $C_{11}H_9NOS$ requires C, 65.00; H, 4.46; N, 6.89; S, 15.78); ν_{max}/cm^{-1} 3485–3493 (NH), 1635 (C=S); δ_H 2.55 (s, $-CH_3$), 7.70 (d, J = 9Hz, 7H), 7.82 (s, 5H), 7.86 (d, J = 9Hz, 8H), 8. 68 (s, 4H), 10.44 (s, CHO), 11.3 (s, SH); m/z 203 (M^+).

7-Methyl-3-formyl-2-mercaptoquinoline (2c)

Obtained in an 82% yield, solid; m.p. > 225°C; (Found: C, 65.07; H, 4.39; N, 6.78; S, 15.68. $C_{11}H_9NOS$ requires C, 65.00; H, 4.46; N, 6.89; S, 15.78); ν_{max}/cm^{-1} 3485–3494 (NH), 1642 (C=S); δ_H2.60 (s, $-CH_3$), 7.49 (dd, J = 9Hz, 6H), 7.79 (dd. J = 9Hz, 8H), 7.95 (s, J = 9Hz, 5H), 8.71 (s, 4H), 10.47 (s, CHO), 11.2 (s, SH).

8-Methyl-3-formyl-2-mercaptoquinoline (2d)

Obtained in an 80% yield, solid; m.p. > 223°C; (Found: C, 65.07; H, 4.39; N, 6.78; S, 15.68. $C_{11}H_9NOS$ requires C, 65.00; H, 4.46; N, 6.89, S, 15.78); ν_{max}/cm^{-1} 3487–3492 (NH), 1636 (C=S); δ_H2.73 (s, $-CH_3$), 7.55 (t, J = 8Hz, 6H), 7.75 (dd. J = 8 Hz, 7H), 7.92 (dd, J = 8Hz, 5H), 8.75 (s, 4H), 10.50 (s, CHO), 11.4 (s, SH).

6-Methoxy-3-formyl-2-mercaptoquinoline (2e)

Obtained in an 85% yield, solid; m.p. > 233°C; (Found: C, 60.29; H, 4.15; N, 6.35; s, 14.69. $C_{11}H_9NO_2S$ requires C, 60.26; H, 4.14; N, 6.39; S, 14.62); ν_{max}/cm^{-1} 3488–3498 (NH), 1635 (C=S); δ_H3.94 (s, $-OCH_3$), 7.47 (dd, J = 8Hz, 7H), 7.91 (d, J = 8Hz, 8H), 7.17 (d, J = 8Hz, 5H), 8.75 (s, 4H), 10.50 (s, CHO), 11.3 (s, SH); m/z 219 (M^+).

7-Methoxy-3-formyl-2-mercaptoquinoline (2f)

Obtained in an 88% yield, solid; m.p. > 236°C; (Found: C, 60.29; H, 4.15; N, 6.35; S, 14.69. $C_{11}H_9NO_2S$ requires C, 60.26; H, 4.14; N, 6.39; S, 14.62); ν_{max}/cm^{-1} 3480–3491(NH), 1638 (C=S); δ_H3.97 (s, 4 .02 (s, $-OCH_3$), 7.27 (dd, J = 9Hz, 6H), 7.33 (s. 8H), 8.03 (s, J = 9Hz, 5H), 8.72 (s, 4H), 10.97 (s, CHO), 11.3 (s, SH).

8-Methoxy-3-formyl-2-mercaptoquinoline (2g)

Obtained in an 85% yield, solid; m.p. > 241°C; (Found: C, 60.29; H, 4.15; N, 6.35; S, 14.69. $C_{11}H_9NO_2S$ requires C, 60.26; H, 4.14; N, 6.39; S, 14.62); ν_{max}/cm^{-1} 3485–3493 (NH), 1630 (C=S); δ_H4.10 (s, $-OCH_3$), 7.25 (t, J = 9Hz, 6H), 7.47 (s, 7H), 7.55 (t, J = 9Hz, 5H), 8. 70 (s, 4H), 10.57 (s, CHO), 11.2 (s, SH).

6-Bromo-3-formyl-2-mercaptoquinoline (2h)

Obtained in an 83% yield, solid; m.p. > 243°C; (Found: C, 44.89; H, 2.28; N, 5.24; S, 11.86. $C_{10}H_6BrNOS$ requires C, 44.79; H, 2.26; N, 5.22; S,

11.96); ν_{max}/cm^{-1} 3489–3498 (NH), 1636 (C=S); δ_H7.95 (s, 8H); 7.97 (s, 7H), 10.55 (s, CHO), 8.18 (s, 5H), 8. 68 (s, 4H), 11.3 (s, SH); m/z 268 (M^+).

6-Chloro-3-formyl-2-mercaptoquinoline (2i)

Obtained in an 85% yield, solid; m.p. > 248°C; (Found: C, 53.69; H, 2.69; N, 6.18; S, 14.28. $C_{10}H_6ClNOS$ requires C, 53.70; H, 2.70; N, 6.26; S, 14.34); ν_{max}/cm^{-1} 3485–3496 (NH), 1635 (C=S); δ_H7.80 (dd, J = 9Hz, 7H), 7.96 (s, 5H), 8.03 (d, 8H), 8. 68 (s, 4H), 10.55 (s, CHO), 11.2 (s, SH); m/z 223 (M^+).

7-Chloro-3-formyl-2-mercaptoquinoline (2j)

Obtained in an 87% yield, solid; m.p > 251°C; (Found: C, 53.69; H, 2.69; N, 6.18; S, 14.28. $C_{10}H_6ClNOS$ requires C, 53.70; H, 2.70; N, 6.26; S, 14.34); ν_{max}/cm^{-1} 3486–3495 (NH), 1645 (C=S); δ_H 7.58 (dd, J = 9Hz, 6H), 7.95 (d, J = 9Hz, 5H), 8.01 (s. 8H), 8. 73 (s, 4H), 10.51 (s, CHO), 11.3 (s, SH).

6,7-Dimethoxy-3-formyl-2-mercaptoquinoline (2k)

Obtained in an 85% yield, solid; m.p > 247°C; (Found: C, 57.76; H, 4.37; N, 5.59; S, 12.85. $C_{12}H_{11}NO_3S$ requires C, 57.82; H, 4.45; N, 5.62, S, 12.86); ν_{max}/cm^{-1} 3486–3496 (NH), 1630 (C=S); δ_H 4.00 (s, –OCH_3), 4.02 (s, –OCH_3), 7.07 (s, 5H), 7.30 (s, 8H), 8.84 (s, 4H), 10.42 (s, CHO), 11.4 (s, SH); m/z 249 (M^+).

5,6,7-Trimethoxy-3-formyl-2-mercaptoquinoline (2l)

Obtained in a 76% yield, solid; m.p > 242°C; (Found: C, 55.85; H, 4.75; N, 5.06; S, 11.37. $C_{13}H_{13}NO_4S$ requires C, 55.90; H, 4.69; N, 5.01; S, 11.48); ν_{max}/cm^{-1} 3488–3498 (NH), 1635 (C=S); δ_H4.05 (s, –OCH_3), 4.14 (s, –OCH_3), 4.22 (s, –OCH_3), 7.10 (s, 8H), 8.84 (s, 4H), 10.59 (s, CHO), 11.2 (s, SH); m/z 279 (M^+).

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