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NOTE

Functionalization of Quinolines: Preparation of 2-Formyl-4- methoxy Quinolines

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4-Methoxy-2-methyl quinolines (2) on oxidation by selenium dioxide under various conditions yield the hitherto unreported 2-formyl-4-methoxy quinolines (3), a useful synthon for the synthesis of higher nitrogen heterocycles.

Key Words: 4-Methoxy-2-methyl quinolines, Selenium dioxide, Functionalization.

Methyl quinolines can be oxidized to aldehyde by selenium dioxide[1], chromic acid or vapour-phase oxidation methods[2]. Selenium dioxide is the most frequently used reagent. In the course of oxidation, selenium dioxide is reduced to selenium, which can be removed by filtration. The preparation of the reagent is an important factor and emphasis is on freshly prepared one[3]. In contrast to the chromic acid oxidation methyl groups at the second position are readily oxidized by SeO_2. Herein we report the functionalisation of (2) to 2-formyl-4-methoxy quinoline (3) which is a useful synthon for the synthesis of higher nitrogen heterocycles.

Melting points were determined on a Boetius microheating table and are uncorrected. IR spectra were recorded on a Perkin-Elmer-597 infrared spectrophotometer as KBr discs. ^1H NMR spectra were recorded on a DRX 500 MHz spectrophotometer using Me_4Si as internal standard and chemical shifts are quoted in δ ppm. Mass spectra were recorded on an EI-Autospec mass spectrophotometer.

Preparation of 4-methoxy-2-methyl quinoline (2): It was prepared by the action of $POCl_3$ followed by sodium methoxide on 1-hydroxy-2-methyl quinoline (1) which in turn have been prepared by the method of Leonard *et al.*[4]

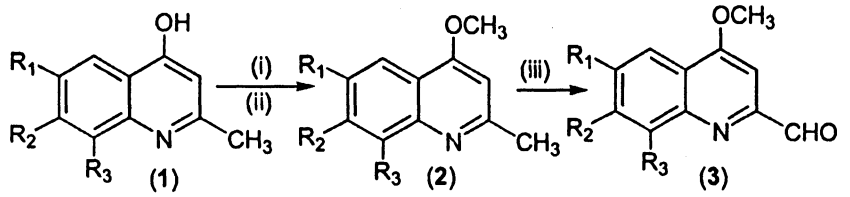
Preparation of 2-formyl-4-methoxy quinolines (3a–i)

Method A: To 0.014 mol of freshly prepared SeO_2 in absolute alcohol (15 mL) was added 0.012 mol of (2) and the whole of the reaction mixture was refluxed. After 6 h the precipitated selenium was filtered off and the alcohol was removed under reduced pressure, which yielded a reddish brown precipitate. The whole of the mixture was column chromatographed over silica gel with (96 : 4) petroleum ether : ethyl acetate as eluent which furnished a white crystalline compound (m.p. 82°C, yield 11%).

Method B: To 1,4-dioxane 25 mL containing 2.5 mL (10%) of water was added 0.015 mol of freshly prepared SeO_2 and the mixture was warmed at 45°C. To the warmed mixture were added 0.01 mol of **(2)** in 7 mL of dioxane over a period of 15 min and the whole of the mixture was refluxed at 110°C with stirring for 1 h whereby the reduced selenium was filtered off. The dioxane was distilled off under reduced pressure and the whole of the mixture was column chromatographed over silica gel at (96 : 4) petroleum ether : ethyl acetate as eluant affording **(3)** in 28% yield.

Method C: To 0.01 mole of **(2)** was added 0.015 mol of selenium dioxide and the whole of the mixture was heated at 180°C whereby the mixture melted and fused. This was continued for about 1 h. The reaction mixture was cooled, put up in water and extracted with chloroform (2 × 50 mL). After drying the organic solvent using anhydrous sodium sulphate, the chloroform was distilled off and the residue was chromatographed over silica gel at (96 : 4) petroleum ether : ethyl acetate as eluant yielding **(3)** in 4% yield.

The oxidation of **(2)** using SeO_2 to the hitherto unreported 2-formyl-4-methoxy quinoline **3** was carried out in three different methods under various conditions. In alcohol medium prolonged oxidation after 6 h decreased the recovery of the aldehyde **(3)**. Even in the best of the conditions the yield could not be improved beyond (11–17)%. In dioxane containing 10% of water the oxidation was very smooth compared to alcohol. By 1 h most of the product has been converted to the aldehyde **(3)** (28–43%) and reflux beyond 1 h decreased the yield of the aldehyde. In method C by fusion 0.012 mol of **(2)** and 0.014 mol of SeO_2 was fused at about 180°C and heated for a further 1 h. The mixture on work up furnished only 4% of **(3)**. Further heating of the mixture resulted only in charring. The time factor is very important as a prolonged reflux decreases the yield of aldehyde greatly. The stirring of the reaction mixture while in reflux in dioxane markedly improves the yield of aldehyde. In all the three methods except the 2-methyl group the other methyl groups remained untouched. The physical and spectroscopic data have been tabulated (Table-1).



(i) $POCl_3$, N,N-dimethyl aniline (4.5h)
(ii) NaOMe (6h)
(iii) SeO_2, / db.Ethanol (6h) (11-17%)
1,4-Dioxane (1h) (28-43%)
Fusion (1h) (0-4%)

3a. $R_1 = R_2 = R_3 = H$
3b. $R_1 = CH_3$, $R_2 = R_3 = H$
3c. $R_1 = H$, $R_2 = CH_3$, $R_3 = H$
3d. $R_1 = R_2 = H$, $R_3 = CH_3$
3e. $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$
3f. $R_2 = -CH_2-CH=CH-CH_2- = R_3$, $R_1 = H$

Scheme-1

TABLE-1
PHYSICAL AND SPECTROSCOPIC DATA OF COMPOUNDS (**3a–3f**)

Compd	m.p. (°C) (Yield* %)	IR ν (cm^{-1})	^1H NMR (δ) ppm ($CDCl_3$) (J = Hz)
3a	82 (11, 28, 4)	1706 1593	10.1 (s,1H, CHO), 8.1 (d, C_8-H, J = 8), 8.1 (d, C_5-H, J = 8), 7.7 (t, C_7-H, J = 7.5), 7.5 (t, C_6-H, J = 7.5), 7.3 (s, 1H, C_3-H), 3.98 (s, 3H, C_4-OCH_3)
3b	140 (14, 38. 3)	1689 1585	10.1 (s, 1H, CHO), 8.2 (d, 1H, C_8-H, J = 7.2), 7.9 (s, 1H, C_5H), 7.8 (d, 1H, C_7-H), 7.3 (s, 1H, C_3-H), 4.0 (s, 3H, C_4-OCH_3), 2.5 (s, 3H, C_6-CH_3)
3c†	114 (15, 29, 0)	1706 1590	10.1 (s, 1H, CHO), 8.2 (d, 1H, C_8-H), 7.85 (d, 1H, C_5-H, J = 8), 7.7 (d, 1H, C_6-H, J = 7.8), 7.35 (s, 1H, C_3-H), 3.95 (s, 3H, C_4-OCH_3), 2.7 (s, 3H, C_7-CH_3)
3d	131 (17, 43, 4)	1706 1593	10.2 (s, 1H, CHO), 7.9 (d, 1H, C_5-H, J = 7.2), 7.82 (d, 1H, C_7-H, J = 6.9), 7.7 (t, 1H, J = 6.9), 7.4 (s, 1H, C_3-H), 4.0 (s, 3H, C_4-OCH_3), 2.8 (s, 3H, C_8-CH_3)
3e	164 (14, 40, 3)	1706 1618	10.1 (s, 1H, CHO), 8.1 (s, 1H, C_5-H), 7.9 (s, 1H, C_7-H), 7.5 (s, 1H, C_3-H), 3.9 (s, 3H, C_4-OCH_3), 2.8 (s, 3H, C_8-CH_3), 2.5 (s, 3H, C_6-CH_3)
3f	143 (11, 30, 2)	1703 1620	10.2 (s, 1H, CHO), 9.39 (d, 1H, C_{10}-H, J = 7.9), 8.1 (d, 1H, C_7H, J = 9), (7.94–7.91) (m, 2H, C_8-H, C_9-H), 7.8–7.7 (m, 2H, C_5-H, C_6-H), 7.5 (s, 1H, C_3-H), 4.1 (s, 3H, C_4-OCH_3)

*In (Method A, Method B, Method C) respectively after separation from chromatography.
†Mass (**3c**) m/z (%) 202 (15) M + 1, 201 (100) M^+, 173 (98), 158 (43), 142 (50), 129 (29), 115 (48), 103 (57), 89 (24), 77 (40), 63928), 51 (25)

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