SHORT PAPER

J. Chem. Research (S), 2000, 34–35

Selenium dioxide: a selective oxidising agent for the functionalisation of quinolines†

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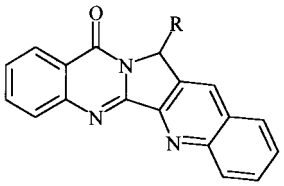
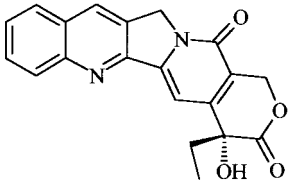
A simple method is described for the preparation of 1,3-dihydrofuro[4,3-b]quinolin-3-ol starting from aniline and methyl acetoacetate using selenium dioxide.

The quinolines are found to be a basic structural unit of several bioactive molecules.[1] Camptothecin[2] and luotonins[3] A and B are the anticancer and anti-inflammatory compounds respectively having this unit. The quinolines are also used in asymmetric synthesis for example, chiral oxazolines derived from quinolines are successfully utilized in organic tranformations.[4]



R= H luotonin A

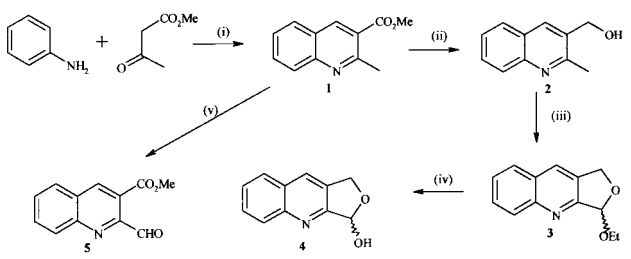
R=OH lutonin B



Camptothecin

Several quinoline-based drugs have occupied places in pharmaceutical market. In our study on synthesis of some biologically active compounds we were interested to construct lactol **4**. The same lactol **4** was prepared earlier as a mixture with the tatomeric 2-formyl-3-(hydroxymethyl)quinoline from formate ester of 2-iodo-3-(hydroxymethyl)quinoline by Narasimhan *et al.*[5] using n-BuLi in the lithium-halogen exchange reaction. We have developed a simple method for the preparation of lactol **4** by avoiding the use of strong base n-BuLi. It is known that selenium dioxide oxidation of the methyl group adjacent to nitrogen heterocyclic compounds give the corresponding aldehyde.[6]

In our approach as shown in Scheme 1, we have started with aniline and methyl acetoacetate to synthesise the lactol **4**.



Scheme 1

(i) Ref. 7 [(a) AcOH, C_6H_6, reflux (b) $POCl_3$, DMF, $CHCl_3$, 70°C] (ii) LAH, THF, rt. (iii) SeO_2, EtOH, cyclohexane, reflux (iv) THF:AcOH:H_2O (1:1:1), 80°C (v) SeO_2, xylene, reflux.

Methyl-2-methyl-3-quinolinecarboxylate (**1**) was prepared by the reported procedure[7] starting from aniline and methyl acetoacetate. The lithium aluminium hydride reduction in THF of the ester **1** gave alcohol **2**. Selenium dioxide oxidation of the alcohol **2** in xylene[8] gave a complex mixture of products. Under a modified condition for the selective oxidation of methyl group of alcohol **2,** selenium dioxide was used with a mixture of cyclohexane and ethanol (5:1) to give acetal **3** in 52% yield. The acetal **3** was then smoothly hydrolysed to the required lactol **4** using a mixture of THF, AcOH and H_2O (1:1:1) in very good yield. In an alternative study the ester **1** on oxidation with SeO_2 in xylene gave a very good yield of aldehyde **5** (Scheme 1).

Experimental

IR spectra were recorded on a Perkin Elmer 137-E spectrometer. The ^{1}H spectra were recorded on a Bruker 200MHz instrument and the chemical shifts were reported with Me_4Si as an internal standard. The mass spectra were recorded on an automatic Finnigan-MAT 1020 C mass spectrometer using ionization energy of 70 eV.

*2-methyl-3-hydroxymethylquinoline (**2**):* The ester **1** (5.5 g, 27.5 mmol), prepared by the known procedure[7] in dry THF (25 ml) was added slowly at 0°C to the suspension of LAH (1 g, 27.5 mmol) in dry THF (10 ml). The reaction mixture was stirred overnight, quenched with ethyl acetate and then poured into ice. Excess of ethyl acetate was added and the precipitate was filtered, washed with ethyl acetate, combined ethyl acetate layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography to give alcohol **2** (2.2 g, 48%) as a dark yellow powder mpt 140–142° C, IR (nujol): 3500, 1600, 720 cm^{-1} ^{1}H NMR (200MHz; Acetone- d_6): δ 2.62 (s, 3H), 2.90 (bs, 1H, OH), 4.83(s, 2H), 7.35-7.91 (m, 4H), 8.05(s, 1H). MS: *m/z* 173(M^+), 155, 144, 115, 77. Analysis. Calc. for $C_{11}H_{11}NO_2$: C,76.30; H,6.35; N,8.09. Found: C,76.52; H,6.22; N,8.21%.

*3-ethoxy-1,3-dihydrofuro[4,3-b]quinoline (**3**):* To the mixture of alcohol **2** (2.0 g, 11.5 mmol) and SeO_2 (1.28, 11.5 mmol) in rectified spirit (5 ml), cyclohexane (25ml) was added and refluxed for 8 h in a Dean Stark apparatus. After the reaction was over the solvent was removed and crude product was purified by column chromatography over silica gel to give product **3** (1.30 g, 52%) as a red sticky solid. IR (nujol): 3000, 1600, 780 cm^{-1} ^{1}H NMR (200 MHz; $CDCl_3$): δ 1.35 (m, 3H), 3.80–4.05 (m, 2H), 5.20 (d, *J* = 7.3Hz, 1H), 5.40 (d, *J* = 7.3 Hz, 1H), 6.20 (s, 1H), 7.60–8.25 (m, 5H). MS: *m/z* 215 (M^+), 187, 171, 92. Analysis calc. for $C_{13}H_{13}NO_2$: C,72.55; H,6.04; N,6.51. Found: C,72.75; H,6.15; N,6.82%.

*1,3-dihydrofuro[4,3-b]quinolin-3-ol (**4**):* The compound **3** (1.5 g, 6 mmol) in THF:H_2O:CH_3CO_2H (2 ml **:** 2ml **:** 2 ml) was heated at 80°C for 24 h. The reaction mixture was then cooled and neutralized with $NaHCO_3$. The solid separated was filtered, dried and recrystalysed from ethanol to give **4**. (1.25 g, 96%) mpt: 153°C (lit[6] mpt: 155°C) IR (nujol): 3500, 1600, 1100 cm^{-1} ^{1}H NMR(200 MHz; Acetone-d_6): δ 5.20 (d, *J* = 7.3 Hz, 1H), 5.40 (d, *J* = 7.3 Hz, 1H), 6.50 (bs, 1H), 6.62 (s,1H), 7.7-8.25 (m,5H); MS: *m/z* 187 (M^+), 171, 169, 113, 59.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Analysis calc. for $C_{11}H_9NO_2$: C,71.00; H,4.61; N,7.45. Found: C,70.58; H,4.81;N,7.48%.

*2-carboxaldehyde 3-quinoline methyl carboxylate (***5***):* To the compound **1** (2.48 g, 12 mmol) in xylene was added SeO_2 (1.36 g; 12 mmol) and refluxed for 8 h. The xylene was removed under reduced pressure and the residue was purified by column chromatography to give aldehyde **5** as yellow oil. (1.85 g, 69%). IR (nujol) 1750, 1600, 1210 cm^{-1} ^1H NMR (200 MHz; $CDCl_3$): δ 4.05 (s, 3H); 7.80–8.30 (m, 4H); 8.62 (s, 1H); 10.9 (s, 1H). MS: *m/z* 215 (M+), 187, 156, 128, 75.

We wish to thank CSIR (New Delhi) for the award of a Senior Research Fellowship to GKJ and Lady Tata Memorial Trust, Mumbai for a fellowship to NSS.

Accepted 11 October 1999
Paper 9/01605C

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