SHORT PAPER

J. Chem. Research (S),
2003, 704–705

A useful 8-hydroxyquinoline synthon†

Jason P. Cross and Peter G. Sammes*

Department of Chemistry, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK

The preparation of 2-bromomethyl-8-(2,2-dimethylpropanoyloxyquinoline) is described and its use as a synthon for the incorporation of 8-hydroxyquinoline units into aza-crowns is exemplified.

Keywords: 8-hydroxyquinoline synthon, cyclen, chelating agents

8-Hydroxyquinoline ('oxine') is a powerful metal chelating agent.[1] Despite this property, there are few reports of the incorporation of the 8-hydroxyquinoline unit into matrices such as aza-crown systems. This is because, hitherto, no synthons for the incorporation of the 8-hydroxyquinoline unit have been developed. Herein we describe the preparation of the simple derivative, 2-bromomethyl-8-(2,2-dimethyl-propanoyloxy)quinoline **9** and, as an example of its utility, the use of this synthon in preparing the aza-crown derivative **11**.

In order to attach the 8-hydroxyquinoline unit onto a substrate a short handle is required and the 2-methyl derivative, **1**, also known as quinaldine, which is commercially available, was chosen. Functionalisation of this methyl group requires protection of the 8-hydroxy group and, initially, the methylated species **2** was prepared. Oxidation of this gave the corresponding *N*-oxide **3** but attempts to effect an acid-catalysed rearrangement,[2] using tosyl chloride, failed to give any of the desired chloromethyl derivative **4**.

Attempted bromination of the 8-methoxy-derivative, using *N*-bromosuccinimide in carbon tetrachloride, afforded mixtures in which aromatic bromination predominated, to give products such as the 5-bromo-derivative **6** and small quantities of the 2-bromomethyl-5-bromo-compound **7** but none of the required 2-bromomethyl derivative **5**.

A means for deactivating the phenolic ring of the quinoline was required and an ester derivative was considered. The choice of the ester derivative is important since the ester group had to be unaffected by primary or secondary amines used in subsequent alkylations. After several attempts it was found that the pivaloyl ester **8** satisfied this requirement. Bromination of the ester **8**, using *N*-bromosuccinimide in carbon tetrachloride, afforded a modest yield of the required bromomethyl-compound **9**.

The synthon **9** was relatively stable and no evidence for self-quaternisation of the quinoline nitrogen was observed. Presumably the adjacent pivaloyl group acts as a steric buttress to shield the nitrogen and thus prevent this potential reaction.

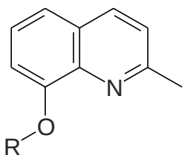
In order to apply the synthon **9**, its reaction with 1,4,7-triazacyclononane was attempted. Stirring the bromide with the triazacyclononane in acetonitrile at room temperature overnight, in the presence of triethylamine to neutralise the hydrogen bromide side product, gave the desired tris-substituted product **10**.

Attempts to remove the pivaloyl group by hydrolysis with ethanolic potassium hydroxide[3] failed, the compound **10** degrading under these conditions. Eventually it was found that a reductive method, using lithium aluminium hydride in anhydrous THF afforded the required product **11** in high yield. Compound **11** is potentially a powerful chelating agent whose properties need to be fully explored.

The synthon **9** is thus of possible use as an alkylating agent, allowing the incorporation of the oxine group into a range of substrates.

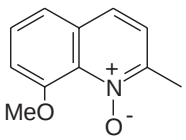
Experimental

8-(2,2-Dimethylpropanoyloxy)-2-methylquinoline **8:** 8-Hydroxy-2-methylquinoline (20g, 0.13mmol) and triethylamine (20.94 g, 0.21 mmol) were dissolved in dry dichloromethane (250 cm^3) and stirred under argon at 0 °C whilst adding, dropwise over 1 h, pivaloyl chloride (16.7 g, 0.138 mmol). Stirring was continued for a further 72 h at room temperature and the reaction mixture worked up by adding water (150 cm^3), separating and washing the organic phase

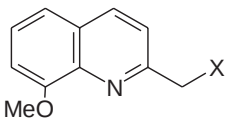


1, R = H

2, R = Me

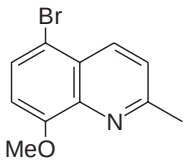


3

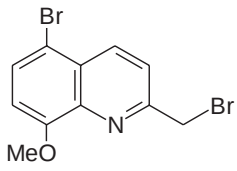


4, X = Cl

5, X = Br



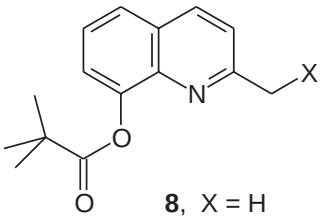
6



7

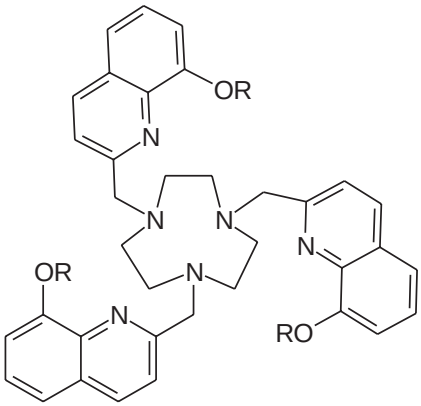
* To receive any correspondence. E-mail: p.sammes@surrey.ac.uk

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



8, X = H

9, X = Br



10, R = $CO.C(CH_3)_3$

11, R= H

with 2M sodium hydroxide solution (150 cm^3). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness at a rotary evaporator. The brown oil was cooled to 5°C and crystallised by trituration with hexane. The white solid obtained was collected and dried to give the title ester (26.54 g, 86%), m.p. 49–51 °C. Found: C, 74.3; H, 7.1; N, 6.1; $C_{15}H_{17}NO_2$ requires C, 74.0; H, 7.0; N, 5.8 %.

ν_{max} (film/cm^{-1}) 1753, 1703, 1505, 1472, 1107; δ_H (300 MHz, $CDCl_3$) 1.51 (9H, s, ^{t}Bu), 2.67 (3H, s, 2-C*H*$_3$), 7.24 (1 H, d, *J* 8, 3-H), 7.36 (1 H, dd, *J* 1, 7, 5-H), 7.43 (1 H, t, *J* 8, 6-H), 7.63 (1 H, dd, *J* 1, 8, 7-H), 8.01 (1 H, d, *J* 8, 4-H);*m/z* (EI) 243 (M^+, 100%).

8-(2,2-Dimethylpropanoyloxy)-2-bromomethylquinoline **9**: A mixture of the pivalate ester **8** (20 g, 82 mmol), *N*-bromosuccinimide (16.56 g, 92 mmol) and benzoyl peroxide (200 mg) in carbon tetrachloride (200 cm^3) was heated to reflux for 24 h, then cooled and the mixture filtered. The solution was evaporated to dryness (rotary evaporator) and the residue chromatographed through silica gel (loading 1:60) eluting with dichloromethane to afford the title monobromide (4.11 g, 16%) as a white, crystalline solid, m.p. (hexane) 58–60 °C; ν_{max} (Nujol/cm^{-1}) 2360, 1753, 1703, 1598, 1568, 1275, 1107, 838, 762 and 721; δ_H (300 MHz, $CDCl_3$) 1.52 (9 H, ^{t}Bu), 4.63 (2 H, s, C*H*$_2$Br), 7.42 (1 H, d, *J* 9, 3-H), 7.55 (2H, m, 5-H, 6-H), 7.67 (1 H, dd, *J* 1, 8.5, 7-H), 8.13 (1 H, d, *J* 9, 4-H). Found: MH^+ 322.0446, $C_{15}H_{17}NO_2Br^{79}$ requires 322.044265.

1,4,7-Tris-[2-(8-(2,2-dimethylpropranoyloxy)quinolinyl)methyl]-1,4,7-triazacyclononane **10:** A solution of 1,4,7-Triaazacyclononane (376 mg, 2.9 mmol), the bromide **9** (3.0 g, 9.3 mmol) and triethylamine (1.62 cm^3, 11.6 mmol) in dry acetonitrile (20 cm^3) was stirred at room temperature for 24 h. the solvent was removed and the residue extracted with dichloromethane and washed with 10% w/v aqueous sodium carbonate solution, backwashing with more dichloromethane. The organic extract was dried over anhydrous sodium sulfate, filtered and the solvent remobved to leave an off-white solid. The crude product was purified by chromatography through silica gel, eluting with 1:9 methanol-dichloromethane, to afford, as a pale yellow solid, the *title compound* (1.31 g, 53%), m.p. 61–63 °C. Found: C, 67.6; H, 7.3; N, 9.3. $C_{51}H_{60}N_6O_6.3H_2O$ requires C, 67.5; H, 7.3; N, 9.3 %; ν_{max} (film/cm^{-1}) 3404, 1747, 1704, 1600, 1571, 1507, 1472, 1216, 1123, 841, 667; δ_H (300 MHz, $CDCl_3$) 1.46 (27 H, 3 x ^{t}Bu), 2.874.63 (12 H, m, aza-C*H*$_2$), 3.90 (6 H, s, 3 x C*H*$_2$), 7.35 (3 H, d, *J* 7.5, 3-H), 7.46 (3 H, m, 5-H), 7.64 (6 H, m, 6-H and 7-H), 8.04 (3 H, d, *J* 8, 4-H); *m/z* (FAB) 853 (MH^+; 100%).

1,4,7-Tris-[2-(8-hydroxyquinolinyl)methyl]-1,4,7-triazacyclononane **11**: The pivaloyl-protected quinaldine derivative **10** (0.80 g, 0.94 mmol) was stirred in freshly distilled tetrahydrofuran (10 cm^3) under argon in an ice bath. To the solution was cautiously added lithium aluminium hydride (95 mg, 2.51 mmol) and the mixrture stirred for 1 h, allowing the mixture to reach ambient temperature. The mixture was quenched by the slow addition of water and the pH adjusted to 7 with dilute hydrochloric acid. The mixture was then treated to a solution of aqueous tartaric acid (20 cm^3) and stirred for 6 h. The mixture was neutralised with aqueous sodium hydrogen carbonate solution, the tetrahydrofuran removed under reduced pressure and the residual aqueous fraction treated with chloroform (10 cm^3) before filtering through Celite and the aqueous chloroform filtrate washed with brine, all aqueous fractions being back extracted with two further portions of chloroform. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The obtained residue was triturated with ether to give the *title compound* as a pale yellow solid (241 mg, 57%), m.p. 67–69 °C; ν_{max} (Nujol/cm^{-1}) 3500–3300, 1662, 1599, 1570, 1505, 1325, 1246, 1086, 837 and 751; λ_{max} (CH_3OH/nm 298 (ε/$dm^3mol^{-1}cm^{-1}$ 7310); δ_H (300 MHz, $CDCl_3$) 2.96 (12 H,m, aza-C*H*$_2$), 3.96 (6 H, s, 3 x C*H*$_2$), 7.14 (3 H, d, *J* 8, 7-H), 7.28 (3 H, d, *J* 8, 5-H), 7.41 (3 H, t, *J* 8, 6-H), 7.58 (3 H, d, *J* 8, 3-H), 8.03 (3 H, d, *J* 8, 4-H); δ_C (75 MHz, $CDCl_3$) 53.3, 60.0, 117.1, 118.7, 120.9, 126.2, 128.2, 128.7, 131.3, 136.1, 157.1. Found (FAB): MH^+ 601.2934; $C_{36}H_{36}N_6O_6$ requires 601.2927.

We thank Amersham plc and the EPSRC for support of this work by means of a CASE award (J. P.C.)

Received 14 August 2003; accepted 26 August 2003
Paper 03/2038

References

1 J.P. Phillips, *Chem. Rev.*, 1956, **56**, 271; R.G. W. Hollingsworth, *Oxine and its Derivatives*, Vols **I - IV**, Butterworths, London, 1954 - 1956; A. Shulman and F.P. Dwyer in *Chelating Agents and Metal Chelates*, ed. F.P. Dwyer and D.P. Mellor, Academic Press, New York, N. Y., 1964, p383.

2 H. Tanida, *J. Pharm. Soc. Japan*, 1958, **78**, 611; M. Hamana and M. Yamazaki, *Chem. Pharm Bull. (Tokyo)*, 1963, **11**, 415.

3 T.W. Greene, in *Protecting Groups in Organic Synthesis*, J. Wiley and Sons, New York, 1981, 102.