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A Facile Route to Quinazolin-4(3H)-ones Functionalised at the 2-Position

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A FACILE ROUTE TO QUINAZOLIN-4(3*H*)-ONES FUNCTIONALISED AT THE 2-POSITION

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ABSTRACT: Treatment of 2-methoxyacetamidobenzonitriles or 2-chloroacetamidobenzonitrile with UHP and K_2CO_3 provides a convenient route to 2-methoxymethyl- or 2-chloromethylquinazolin-4(3*H*)-ones. In addition, demethylation of 2-methoxymethylquinazolin-4(3*H*)-ones with 48% HBr gives 2-hydroxymethylquinazolin-4(3*H*)-ones.

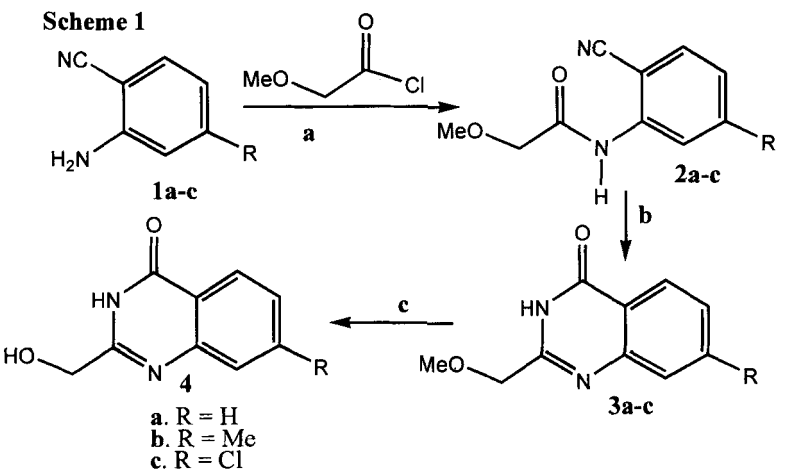
Quinazolin-4(3*H*)-one - based molecules are commonly encountered in many chemotherapeutic areas, and quite often they exhibit interesting pharmacological properties. In cancer chemotherapy, for example, ZD9331 and AG337, two quinazolin-4(3*H*)-one - based compounds, are currently under clinical evaluation.[1,2]

The majority of synthetic routes to 2-substituted quinazolin-4(3*H*)-ones are based on the Niementowski reaction[3] which involves the fusion of analogues of anthranilic acid with amides (e.g. formamide), and it proceeds via an o-

amidobenzamide intermediate.[4,5,6] In a recent report, 2-methyl or 2-phenylquinazolin-4(3*H*)-ones were prepared from o-amidobenzonitriles using urea hydrogen peroxide (UHP) as an oxidising reagent for the conversion of o-amidobenzonitriles to o-amidobenzamides.[7]

In connection with ongoing work aimed at the synthesis of novel anticancer agents we were interested in the synthesis of 2-hydroxymethylquinazolin-4(3*H*)-ones. General synthetic methodologies to this system are limited, though a literature search revealed that compound **4a** has been prepared by four different routes: cyclisation of 2-acetoxyacetamidobenzamide under alkaline conditions,[8] fusion of anthranilamide with ethyl glycolate,[9] reacting 4,1-benzoxazepine-2,5(1*H*,3*H*)-dione with ammonia in methanol,[10] and finally from 5-amino-v-triazolo[1,5-a]quinazoline on treatment with 30% sulphuric acid in 2-ethoxyethanol.[11]

Scheme 1



a. R = H
b. R = Me
c. R = Cl

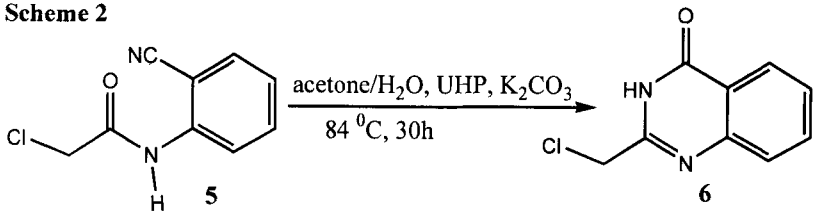
Conditions: (a) pyridine, DMF; (b) acetone/H_2O, UHP, K_2CO_3, 82 ^{0}C, >40h; (c) 48% HBr.

In a recent report, 2-acetoxymethyl-6-methylquinazolin-4(3*H*)-one and 2-acetoxymethyl-6,7-dimethylquinazolin-4(3*H*)-one were prepared from the corresponding anthranilic acid derivative on treatment with chloroacetonitrile and sodium in methanol, followed by the displacement of the chlorine of the resulting 2-chloromethylquinazolin-4(3*H*)-ones with the acetate anion.[12]

In our approach to the synthesis of 2-hydroxymethylquinazolin-4(3*H*)-ones, we envisioned that this class of compounds could be derived from 2-methoxymethylquinazolin-4(3*H*)-ones which could be prepared from 2-methoxyacetamidobenzonitrile derivatives by treatment with urea hydrogen peroxide. Indeed, 2-methoxymethylquinazolin-4(3*H*)-ones **3** were successfully synthesised, when 2-amidobenzonitriles **2** were heated at 82 °C in acetone/H_2O with UHP and K_2CO_3 for approximately 48 hours (Scheme 1). The reaction was followed by TLC (10% MeOH in $CHCl_3$), and in each case it was found that the benzonitrile derivative was completely consumed, only when fresh portions of UHP and K_2CO_3 were added after approximately 24 hours.

Demethylation of the 2-methoxymethyl derivatives **3** was effected by treatment with 48% HBr at 120 °C (Scheme 1).[13] After cooling, the reaction mixture was neutralised with NaOH – under these conditions the product was precipitated from the solution and subsequently isolated by filtration. ^{1}H-NMR of the crude product indicated a ~15% contamination with the corresponding 2-bromomethylquinazolin-4(3*H*)-one. Pure product was obtained either by recrystallisation (compound **4c**) or by column chromatography (compounds **4a** and **4b**). It should be noted that attempted demethylation of **3b** with 1M BBr_3 in

Scheme 2



CH_2Cl_2 at 0 °C afforded 2-bromomethyl-7-methylquinazolin-4(3*H*)-one as the major product rather than **4b**. Compounds **2** were readily prepared in good yields from the commercially available 2-aminobenzonitriles **1**.

In an extension of this methodology, 2-chloroacetamidobenzonitrile (**5**) was also converted to 2-chloromethylquinazolin-4(3*H*)-one (**6**) in 55% yield (Scheme 2).

In conclusion, 2-amidobenzonitriles, readily prepared from commercially available 2-aminobenzonitriles and the appropriate acetyl chloride, were converted in one step to 2-methoxymethyl- or 2-chloromethylquinazolin-4(3*H*)-ones in good yields, though compared to 2-methyl or 2-phenylquinazolin-4(3*H*)-ones[7], the yields were lower. However, the product of this transformation was precipitated from the reaction mixture and subsequently was easily collected by filtration in pure form. Importantly, demethylation of 2-methoxymethylquinazolin-4(3*H*)-ones with 48% HBr provided 2-hydroxymethylquinazolin-4(3*H*)-ones, useful intermediates for further functionalisation of this class of compounds.

EXPERIMENTAL

General: Proton NMR spectra were recorded using a Bruker AC250 spectrometer, and field strengths are expressed in units of δ relative to

tetramethylsilane. Fast atom bombardment (FAB) mass spectra were determined with a VG ZAB-SE spectrometer. Thin layer chromatography (TLC) was performed on precoated sheets of silica $60F_{254}$ (Merck Art 5735), and visualisation was achieved under UV. Merck silica 60 (Art 15111) was used in low pressure column chromatography. Melting points were determined on a Kofler block and are uncorrected. Elemental analysis were determined by C.H.N. Analysis Limited, Leicester, UK. Commercially available chemicals including UHP were purchased from Aldrich Chemical Co, Gillingham, Dorset, UK. Petrol refers to light petroleum (b.p. 60-80 °C).

2-Methoxyacetamidobenzonitrile (2a). To a stirred solution of 2-aminobenzonitrile (3.55 g, 0.03 mol) in anhydrous DMF (20 ml) was added methoxyacetyl chloride (7.13 g, 0.066 mol) followed by anhydrous pyridine (12.20 ml, 0.15 mol). The solution was stirred at room temperature for 24 hrs under argon, then it was partitioned between ethyl acetate (250 ml) and 1 N aqueous HCl (110 ml). The organic layer was washed with more 1 N aqueous HCl (110 ml), and brine (110 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography, on elution with 50% ethyl acetate in petrol, gave the title compound **2a** as a white solid (4.2 g, 74%), m.p. 88-90 °C; ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, 3H, OCH_3), 4.07 (s, 2H, CH_2OMe), 7.20 (t, J = 7.6 Hz, 1H) and 7.60 (m, 2H) (4-H, 5-H, and 6-H), 8.47 (d, J = 8.5 Hz,1H, 3-H), 8.95 (br s, 1H, CONH); MS (FAB, m/z), 213 $(M+Na)^+$, 191 $(M+H)^+$; Found C, 63.12; H, 5.39; N, 14.76; $C_{10}H_{10}N_2O_2$ requires: C, 63.15; H, 5.30; N, 14.73%.

2-Methoxyacetamido-4-methylbenzonitrile (2b). To a stirred solution of 2-amino-4-methylbenzonitrile (0.300 g, 2.27 mmol) in anhydrous DMF (3 ml) was

added methoxyacetyl chloride (0.539 g, 5.0 mmol) followed by anhydrous pyridine (0.91 ml, 11.35 mmol). The solution was stirred at room temperature for 1 h under argon, then the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (110 ml) and 0.5 N aqueous HCl. The organic layer was washed with more 0.5 N aqueous HCl (90 ml), a saturated $NaHCO_3$ solution (100 ml), and brine (100 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography, on elution with 30% ethyl acetate in hexanes, gave the title compound **2b** as a white solid (0.354 g, 76%), m.p. 86-87 °C; ^{1}H-NMR ($CDCl_3$) δ 2.43 (s, 3H, 4-CH_3), 3.56 (s, 3H, OCH_3), 4.07 (s, 2H, CH_2OMe), 7.01 (d, J = 7.9 Hz, 1H, 5-H), 7.48 (d, J = 7.9 Hz, 1H, 6-H), 8.30 (s, 1H, 3-H), 8.96 (br s, 1H, CONH); MS (FAB, m/z), 227 $(M+Na)^+$, 205 $(M+H)^+$; Found C, 64.61; H, 5.98; N, 13.77; $C_{11}H_{12}N_2O_2$ requires: C, 64.69; H, 5.92; N, 13.72%.

2-Methoxyacetamido-4-chlorobenzonitrile (2c). To a stirred solution of 2-amino-4-chlorobenzonitrile (3.05 g, 0.02 mol) in anhydrous DMF (15 ml) was added methoxyacetyl chloride (4.75 g, 0.044 mol) followed by anhydrous pyridine (8.0 ml, 0.10 mol). The reaction mixture was stirred at room temperature for 7 hrs under argon, then it was partitioned between ethyl acetate (200 ml) and 1 N aqueous HCl (100 ml). The organic layer was washed with more 1 N aqueous HCl (100 ml), and brine (100 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography, on gradient elution with ethyl acetate in petrol (25 to 40%), gave the title compound **2c** as a white solid (3.51 g, 78%), m.p. 121-122 °C; ^{1}H-NMR (DMSO-d_6) δ 3.43 (s, 3H, OCH_3), 4.09 (s, 2H, CH_2OMe), 7.45 (dd, J = 1.9, 8.32 Hz, 1H, 5-H), 7.84 (d, J = 2.0 Hz, 1H, 3-H), 7.88 (d, J =

8.44 Hz, 1H, 6-H), 10.00 (s, 1H, CONH); MS (FAB, m/z), 225, 227 [$(M+H)^+$, Cl isotopic pattern]; Found C, 53.46; H, 4.15; N, 12.49, Cl, 15.82; $C_{10}H_9ClN_2O_2$ requires: C, 53.47; H, 4.04; N, 12.47; Cl, 15.78%.

2-Methoxymethylquinazolin-4(3*H*)-one (3a). To a mixture of **2a** (0.247 g, 1.3 mmol) and acetone/H_2O (v/v 1:1, 9 ml) was added K_2CO_3 (0.024 g) and UHP (0.244 g, 2.6 mmol). The reaction flask was fitted with a condenser and then placed in an oil bath preheated to 82 °C. The reaction mixture was stirred at this temperature for 26 hrs, then diluted with acetone/H_2O (v/v 1:1, 6 ml) and more K_2CO_3 (0.024 g) and UHP (0.122 g, 1.3 mmol) were added. Stirring was continued at 82 °C for 24 hrs, then the reaction mixture was allowed to cool to room temperature, diluted with H_2O (5 ml), and allowed to stand in a refrigerator for a few hours. The white precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 to give 0.140 g of the title compound **3a**. The filtrate was extracted with ethyl acetate (3 x 40 ml); the organic extracts were combined, concentrated *in vacuo* and the residue was triturated with H_2O, collected by filtration, washed with H_2O (5 ml), and dried *in vacuo* over P_2O_5 to afford an additional 0.026 g of the product. Total yield 0.166 g (67%), m.p. 183-185 °C; ^{1}H-NMR (DMSO-d_6) δ 3.37 (s, 3H, OCH_3), 4.33 (s, 2H, CH_2OMe), 7.51 (t, J = 7.6 Hz, 1H) and 7.81 (dt, J = 1.50, 8.4 Hz, 1H) (6-H, 7-H), 7.65 (d, J = 7.9 Hz, 1H) and 8.11 (dd, J = 1.4, 8.0 Hz,1H) (5-H, 8-H), 12.18 (br s, 1H, N^3-H); MS (FAB, m/z), 191 $(M+H)^+$; Found C, 62.84; H, 5.39; N, 14.75; $C_{10}H_{10}N_2O_2$ requires: C, 63.15; H, 5.30; N, 14.73%.

2-Methoxymethyl-7-methylquinazolin-4(3*H*)-one (3b). To a mixture of **2b** (0.180 g, 0.88 mmol) and acetone/H_2O (v/v 1:1, 6 ml) was added K_2CO_3 (0.016 g)

and UHP (0.165 g, 1.76 mmol). The reaction flask was fitted with a condenser and then placed in an oil bath preheated to 82 °C. The reaction mixture was stirred at this temperature for 28 hrs, then diluted with acetone/H_2O (v/v 1:1, 4 ml) and more K_2CO_3 (0.016 g) and UHP (0.080 g, 0.88 mmol) were added. Stirring was continued at this temperature for 18 hrs, then the reaction mixture was allowed to cool to room temperature and diluted with H_2O (10 ml). The white precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 to give the title compound **3b** (0.121 g, 67%), m.p. 211 °C; ^{1}H-NMR (DMSO-d_6) δ 2.45 (s, 3H, 7-CH_3), 3.36 (s, 3H, OCH_3), 4.32 (s, 2H, C*H*$_2$OMe), 7.33 (dd, J = 1.2, 8.2 Hz, 1H, 6-H), 7.46 (s, 1H, 8-H), 7.99 (d, J = 8.0 Hz, 1H, 5-H), 12.07 (br s, 1H, N^3-H); MS (FAB, m/z), 227 $(M+Na)^+$, 205 $(M+H)^+$; Found C, 64.60; H, 5.97; N, 13.79; $C_{11}H_{12}N_2O_2$ requires: C, 64.69; H, 5.92; N, 13.72%.

2-Methoxymethyl-7-chloroquinazolin-4(3*H*)-one (3c). To a mixture of **2c** (0.449 g, 2.0 mmol) and acetone/H_2O (v/v 1:1, 14 ml) was added K_2CO_3 (0.037 g) and UHP (0.376 g, 4.0 mmol). The reaction flask was fitted with a condenser and then placed in an oil bath preheated to 82 °C. The reaction mixture was stirred at this temperature for 24 hrs, then diluted with acetone/H_2O (v/v 1:1, 11 ml) and more K_2CO_3 (0.037 g) and UHP (0.188 g, 2.0 mmol) were added. Stirring was continued at this temperature for 26 hrs, then the reaction mixture was allowed to cool to room temperature and diluted with H_2O (7 ml). The white precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 to give the title compound **3c** (0.312 g, 69%), m.p. 224-225 °C; ^{1}H-NMR (DMSO-d_6) δ 3.37 (s, 3H, OCH_3), 4.34 (s, 2H, C*H*$_2$OMe), 7.54 (dd, J = 2.1, 8.6 Hz, 1H, 6-H), 7.71 (d, J

= 2.0 Hz, 1H, 8-H), 8.10 (d, J = 8.50 Hz, 1H, 5-H), 12.31 (s, 1H, N^3-H); MS (FAB, m/z), 225, 227 [$(M+H)^+$, 100% and 35% respectively; Cl isotopic pattern], Found C, 53.45; H, 4.08; N, 12.50, Cl, 15.80; $C_{10}H_9ClN_2O_2$ requires: C, 53.47; H, 4.04; N, 12.47; Cl, 15.78%.

2-Hydroxymethylquinazolin-4(3*H*)-one (4a). A mixture of **3a** (0.061 g, 0.32 mmol) and 48% HBr (6.5 ml) was placed in an oil bath preheated to 120 °C. The reaction mixture was stirred at this temperature under reflux for 11 hrs, then allowed to cool to room temperature, diluted with 2N aqueous NaOH (10 ml), and the pH was adjusted to ~5 using NaOH pellets and 1N HCl with cooling. The mixture was allowed to stand at room temperature overnight, then the white precipitate was collected by filtration, washed with H_2O and dried. This solid was suspended in CH_2Cl_2/MeOH and then Merck silica (Art 7734, 1g) was added. The solvents were removed *in vacuo*, and the free running powder was placed on a silica gel column made up in 4% MeOH in CH_2Cl_2. The column was eluted with a gradient of MeOH in CH_2Cl_2 (4 to 10%) to give the title compound **4a** as a white solid (0.034 g, 61%), m.p. 235-241 °C (melts with decomposition), lit[8] m.p. 215 °C (dec), lit[9] m.p. 232 °C, lit[10] m.p. >214 °C (dec), lit[11] m.p. 214 °C; ^{1}H-NMR (DMSO-d_6) δ 4.39 (br d, J = 3.8 Hz, 2H, C*H*$_2$OH), 5.55 (br s (poorly resolved triplet), 1H, CH$_2$O*H*), 7.48 (t, J = 7.6 Hz, 1H) and 7.80 (t, J = 7.5 Hz, 1H) (6-H, 7-H), 7.62 (d, J = 7.9 Hz, 1H) and 8.10 (d, J = 8.5 Hz, 1H) (5-H, 8-H), 11.86 (br s, 1H, N^3-H); MS (FAB, m/z), 177 $(M+H)^+$; Found C, 61.00; H, 4.58; N, 15.74; $C_9H_8N_2O_2$ requires: C, 61.36; H, 4.58; N, 15.90%.

2-Hydroxymethyl-7-methylquinazolin-4(3*H*)-one (4b). A mixture of **3b** (0.065 g, 0.32 mmol) and 48% HBr (6.5 ml) was placed in an oil bath preheated to 120

°C. The reaction mixture was stirred at this temperature under reflux for 6.5 hrs, then allowed to cool to room temperature, diluted with 2N aqueous NaOH (10 ml), and the pH was adjusted to ~5 using NaOH pellets and 1N HCl with cooling. The mixture was allowed to stand at room temperature for a few hours, then the white precipitate was collected by filtration, washed with H_2O, and dried. This solid was suspended in CH_2Cl_2/MeOH and then Merck silica (Art 7734, 1g) was added. The solvents were removed *in vacuo*, and the free running powder was placed on a silica gel column made up in 4% MeOH in CH_2Cl_2. The column was eluted with a gradient of MeOH in CH_2Cl_2 (4 to 10%) to give in order of elution: a) 2-bromomethyl-7-methylquinazolin-4(3*H*)-one (0.009 g), m.p. 255-256 °C; ^{1}H-NMR (DMSO-d_6) δ 2.45 (s, 3H, 7-CH_3), 4.38 (s, 2H, 2-CH_2Br), 7.37 (d, J = 7.8 Hz, 1H, 6-H), 7.47 (s, 1H, 8-H), 8.00 (d, J = 8.1 Hz, 1H, 5-H), 12.44 (br s, 1H, N^3-H); MS (FAB, m/z), 255, 253 [$(M+H)^+$, 80% and 85% respectively, Br isotopic pattern]; FAB-HRMS, measured: 252.9981, calculated for $C_{10}H_{10}BrN_2O$ $(M+H)^+$: 252.9976; b) the title compound **4b** (0.037 g, 61%), m.p. >203 °C (dec); ^{1}H-NMR (DMSO-d_6) δ 2.44 (s, 3H, 7-CH_3), 4.37 (poorly resolved d, J = 3.8 Hz, 2H, 2-CH_2OH), 5.55 (br s (poorly resolved triplet), 1H, CH_2OH), 7.31 (d, J = 8.1 Hz, 1H, 6-H), 7.43 (s, 1H, 8-H), 7.98 (d, J = 8.1 Hz, 1H, 5-H), 11.70 (br s, 1H, N^3-H); MS (FAB, m/z), 191 $(M+H)^+$; Found C, 62.99; H, 5.32; N, 14.65; $C_{10}H_{10}N_2O_2$ requires: C, 63.15; H, 5.30; N, 14.73%.

2-Hydroxymethyl-7-chloroquinazolin-4(3*H*)-one (4c). A mixture of **3c** (0.072 g, 0.32 mmol) and 48% HBr (6.0 ml) was placed in an oil bath preheated to 120 °C. The reaction mixture was stirred at this temperature under reflux for 6.5 hrs, then

allowed to cool to room temperature, diluted with 2N aqueous NaOH (10 ml), and the pH was adjusted to ~6 using NaOH pellets and 1N HCl with cooling. The mixture was allowed to stand at room temperature for a few hours, then the white precipitate was collected by filtration, washed with H_2O (5ml) and dried *in vacuo* over P_2O_5 to afford the title compound **4c** as a white solid (0.064 g, 95%), m.p. 249-250 °C (from 30% MeOH in $CHCl_3$/ethyl acetate v/v, 1:1); ^{1}H-NMR (DMSO-d_6) δ 4.39 (d, J = 5.6 Hz, 2H, C*H*$_2$OH), 5.61 (t, J = 6.0 Hz, 1H, CH_2O*H*), 7.52 (dd, J = 2.1, 8.6 Hz, 1H, 6-H), 7.68 (d, J = 1.9 Hz, 1H, 8-H), 8.10 (d, J = 8.5 Hz, 1H, 5-H), 12.05 (s, 1H, N^3-H); MS (FAB, m/z), 211, 213 [$(M+H)^+$, Cl isotopic pattern]; A dd at 7.58 ppm and a d at 7.72 ppm indicated the presence of the corresponding 2-bromomethylquinazolin-4(3*H*)-one (~10%). An analytically pure sample was obtained by recrystallisation from 30% MeOH in $CHCl_3$/ethyl acetate (v/v, 1:1): Found C, 51.09; H, 3.46; N, 13.15; $C_9H_7ClN_2O_2$ requires: C, 51.32; H, 3.35; N, 13.30%.

2-Chloroacetamidobenzonitrile (5). This known compound was prepared from 2-aminobenzonitrile (1.4 g, 0.012 mol) by treatment with chloroacetyl chloride (1.7 eq) in DMF, using pyridine (3 eq) as the base. Yield 54% (after column chromatography and recrystallisation from 25% ethyl acetate in hexanes); m.p. 123 °C (lit[14] m.p. 115-116 °C).

2-Chloromethylquinazolin-4(3*H*)-one (6). To a mixture of **5** (0.146 g, 0.75 mmol) and acetone/H_2O (v/v 1:1, 5.5 ml) was added K_2CO_3 (0.015 g) and UHP (0.141 g, 1.5 mmol). The reaction flask was fitted with a condenser and then placed in an oil bath preheated to 84 °C. The reaction mixture was stirred at this

temperature for 23 hrs, then diluted with acetone/H_2O (v/v 1:1, 2.5 ml), and more K_2CO_3 (0.008 g) and UHP (0.071 g, 0.75 mmol) were added. Stirring was continued at 84 °C for 7 hrs, then the reaction mixture was allowed to cool to room temperature, diluted with H_2O (4 ml). The precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 to give the title compound **6** (0.088 g, 55%), m.p. 249-253 °C with decomposition, lit[15], m.p. 246-250 °C, lit[16] m.p. 246-248 °C; ^{1}H-NMR (DMSO-d_6) δ 4.55 (s, 2H, CH_2Cl), 7.55 (t, J = 7.1 Hz, 1H) and 7.84 (dt, J = 1.2, 8.0 Hz, 1H) (6-H, 7-H), 7.68 (d, J = 7.8 Hz, 1H) and 8.12 (dd, J = 1.3, 7.8 Hz,1H) (5-H, 8-H), 12.55 (br s, 1H, N^3-H); MS (FAB, m/z), 195, 197 [$(M+H)^+$,100% and 35% respectively, Cl isotopic pattern]; FAB-HRMS: measured, 195.0332, calculated for $C_9H_8ClN_2O$ $(M+H)^+$: 195.0325.

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