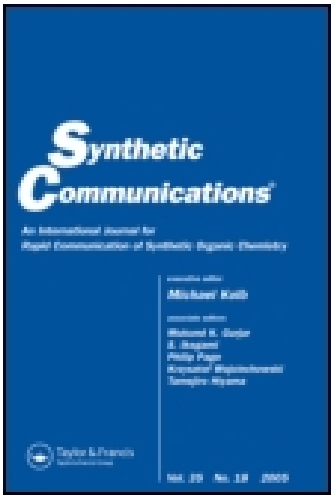

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Regioselective Synthesis of Polyheterocycles From 4-Cyclohex-2-ENYL-3-Hydroxy-1-Methylquinolin-2(1H)-One

K. C. Majumdar [a] & A. K. Kundu [a]
[a] Department of Chemistry , University of Kalyani , Kalyani, 741 235, W.B, INDIA
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REGIOSELECTIVE SYNTHESIS OF POLYHETEROCYCLES FROM 4-CYCLOHEX-2-ENYL-3-HYDROXY-1-METHYLQUINOLIN-2(1*H*)-ONE

K.C. Majumdar* and A.K. Kundu
Department of Chemistry, University of Kalyani,
Kalyani-741 235, W.B., INDIA

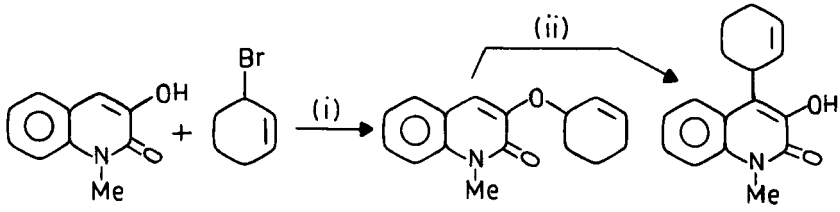
Abstract: 4-Cyclohex-2-enyl-3-hydroxy-1-methylquinolin-2(1*H*)-one (4) was prepared in 90% yield by the thermal [3,3]sigmatropic rearrangement of 3-cyclohex-2-enyloxy-1-methylquinolin-2(1*H*)-one (3) in refluxing chlorobenzene for 10 h. Compound (4) was cyclised through a sequence of reactions *viz.* i) acetylation ii) addition of bromine and iii) treatment of the acetyl dibromo compound (6) with base to give a bicyclic product (7) in 90% yield. Treatment of compound 4 with pyridine hydrobromide perbromide in dichloromethane at 0-5° C afforded a cyclic product 8 in excellent yield. Compound 4 when treated with cold conc. sulphuric acid at 0-5° C furnished the bicyclic product 12 in 89% yield.

Furo[2,3-c]quinolin-4(5*H*)-one and 2*H*-pyrano[3,2-c]quinolin-5(6*H*)-one derivatives are abundantly distributed in nature[1,2] and a number of syntheses for these heterocycles have been reported[3,4] which also includes our own work.[5,6] However, the synthesis of isomaric 3*H*-pyrano[2,3-c]quinolin-5(6*H*)-ones remained unreported till our recent communication[7] whereas the synthesis of furo[2,3-c]quinolin-4(5*H*)-ones has been

* To whom correspondence should be addressed.

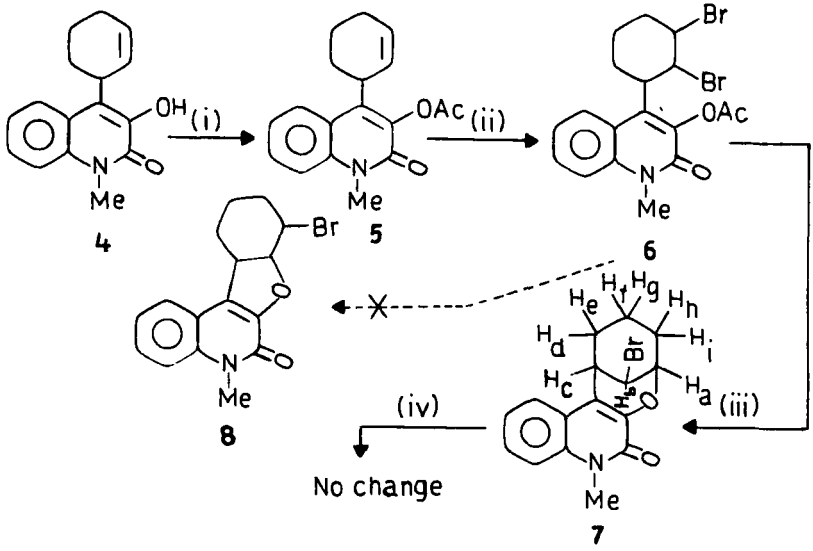
reported in low yield from the photochemical cyclisation of furan-2-carboxanilide[8,9] and in five steps from *o*-nitrotoluene[10] also in overall low yield. This paucity of literature reports for the synthesis of heterocycles from 3-hydroxyquinolin-2(1*H*)-one, **1** prompted us to undertake the present investigation on the cyclisation of 4-[cyclohex-2-enyl]-3-hydroxy-1-methylquinolin-2(1*H*)-one (**4**) towards the synthesis of a number of hitherto unreported polyheterocycles. Here we report the results of this investigation.

The starting material for this study 4-[cyclohex-2-enyl]-3-hydroxy-1-methylquinolin-2(1*H*)-one **4** was obtained in 94% yield by the thermal rearrangement of 3-[cyclohex-2-enyloxy]-1-methylquinolin-2(1*H*)-one **3** in refluxing chlorobenzene. The compound **3** in turn was obtained by the reaction of 3-hydroxy-1-methylquinolin-2(1*H*)-one **1** with 3-bromocyclohexene in refluxing acetone in the presence of anhydrous potassium carbonate (scheme 1).



Scheme 1 Reasents: (i) Me_2Co_3/K_2CO_3, reflux, 8–10 h
(ii) C_6H_5Cl, reflux, 10 h

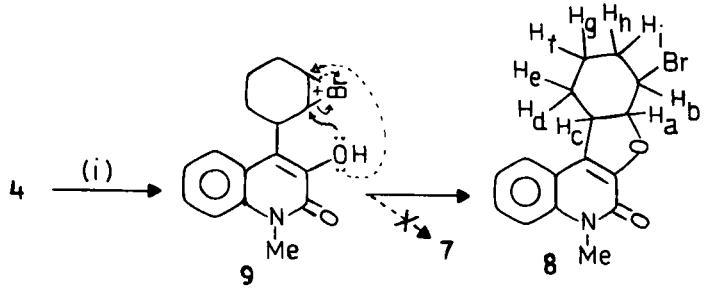
Our first approach for the cyclisation of compound **4** was to deactivate the compound **4** towards electrophilic substitution by converting **4** into its acetate **5** with acetic anhydride-sodium acetate. Brominating **5** by addition of bromine to the cyclohexenyl double bond to afford the dibromo acetate derivative **6**. Compound **6** was then treated with alcoholic potassium hydroxide to give the hitherto unreported bicyclic compound **7** in 90% yield (scheme 2).



Scheme 2 Reasents: (i) Ac_2O, NaOAc, Δ, 4 h (ii) Br_2/AcOH (iii) KOH/EtOH, Δ, 2 h (iv) KOH/EtOH or, KCN, KI/Me_2CO or,Pd-C,Ph_2O, Δ

The alternative structure **8** for the cyclisation product was ruled out as the cyclisation product **7** remain unchanged when refluxed in alcoholic potassium hydroxide or with potassium cyanide in acetone. This

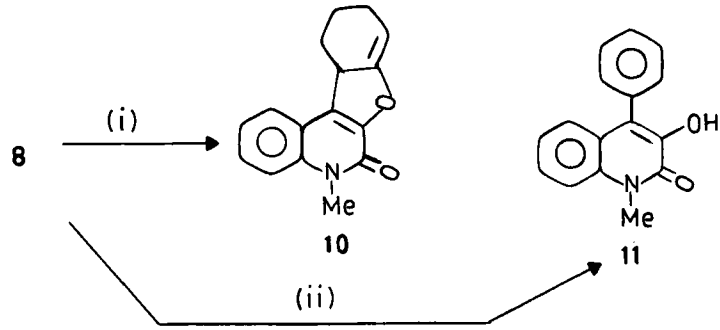
product also remains unaffected when refluxed with palladised charcoal in diphenyl ether. Recently we have reported a regio- and chemoselective cyclisation of *o*-cyclohexenyl phenol with pyridine hydrobromide perbromide[11] and also with hexamethylene tetramine hydrotribromide.[12] So we have attempted cyclisation of compound **4** with pyridine hydrobromide perbromide or hexamethylene tetramine hydrotribromide in dichloromethane at 0-5° C. The starting material disappeared within 1.5 h as indicated by tlc and a new product **8** was obtained in 98% yield. When hexamethylene tetramine hytribromide was used in this reaction instead of pyridine hydrobromide perbromide the reaction was completed in 30 minutes (scheme 3).



Scheme 3 Reasents: (i) $PyHBr_3, CH_2Cl_2$, 0-5° C, 1.5 h.
or, $C_{16}H_{12}N_4HBr_3/CH_2Cl_2$, 0-5° C,
30 minutes

Compound **8** when refluxed with alcoholic potassium hydroxide furnished the dehydrobrominated product **10** in 90% yield. Attempt to dehydrogenate of compound **8** with

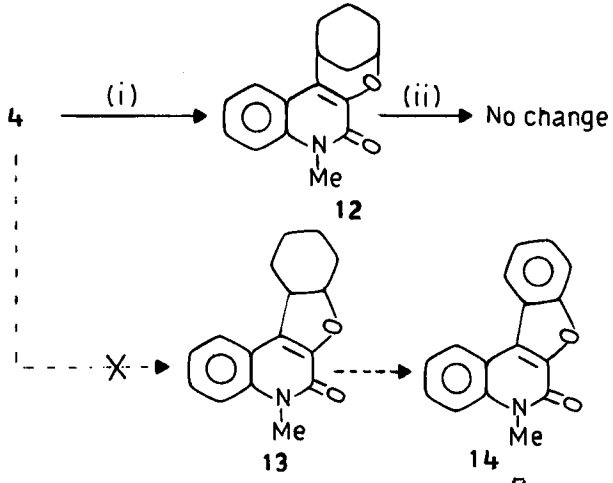
Pd-C in refluxing diphenyl ether[13] cleaved the furan ring to give compound 11



Scheme 4 Reasents: (i) EtOH/KOH, Δ, 40 minutes

(ii) Pd-C/Ph_2O, Δ

Next we have studied the cyclisation of 4 with cold conc. sulphuric acid.[14] Treatment of 4 with cold conc. sulphuric acid gave a single product 12 a gummy mass in 89% yield. Compound 12 resisted dehydrogenation



Scheme 5 Reasents (i) Conc. H_2SO_4, 0-5° C, 2 h

(ii) Pd-C/Ph_2O, reflux, 2 h

when refluxed with palladised charcoal in diphenyl ether indicating its bicyclic nature (schem 5).

In conclusion, 4-cyclohex-2-enyl-3-hydroxy-1-methylquinolin-2(1H)-one, 4 has been successfully cyclised under different reaction conditions to give different polyheterocycles in excellent yields.

Experimental

Melting points were determined in a sulphuric acid-bath and are uncorrected. UV absorption spectra were recorded on a Hitachi 200-20 spectrometer for solution in ethanol. IR spectra were run in KBr discs on a Perkin-Elmer 1330 apparatus. PMR spectra were determined for solutions in deuteriochloroform with $SiMe_4$ as internal standard on a Jeol Fx-100 (100 MHz) instrument at the Indian Institute of Chemical Biology,Calcutta and Bruker 250 MHz instrument at the University of Konstanz, Germany. Elemental analysis and recording of mass spectra were carried out by RSIC (CDRI), Lucknow. Silica gel (60-120 mesh) was obtained from Qualigen. Extracts were dried over anhydrous sodium sulphate.

Preparation of 4-Cyclohex-2-enyl-3-hydroxy-1-methylquinolin-2(1*H*)-one (3).

A mixture of 3-hydroxy-1-methylquinolin-2(1*H*)-one (0.01 mol), 3-bromocyclohexene (0.01 mol) and anhydrous potassium carbonate (5 g) was refluxed in dry acetone (100 ml) on a water-bath for 8-10 h. The reaction mixture was then cooled, filtered and evaporated and the

residue extracted with chloroform. The chloroform extract was washed with water (twice) and dried (Na_2SO_4). Evaporation of the solvent gave the crude product which was then chromatographed over silica gel (60-120 mesh) using pet.ether (60-80° C)-ethylacetate (3:1) as eluant to give the compound 3.

Compound 3, viscous liquid (90%); UV (EtOH): λ_{max} 224 (log ε 4.28), 278 (log ε 3.56) and 319 (log ε 3.69) nm; IR (KBr): υ_{max} 1700, 1610, 1580, 1440 and 1270 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 1.84-2.24 (m, 6H), 3.76 (s, 3H), 4.80-5.00 (m, 1H), 5.96 (s, 2H), 6.99 (s, 1H) and 7.26-7.60 (m, 4H); m/z 255 (M^+). Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%; found C, 75.40; H, 6.42; N, 5.61%.

Rearrangement of Compound 3: Formation of 4-[Cyclohex-2-enyl]-3-hydroxy-1-methylquinolin-2(1*H*)-one (4).

Compound 3 (1 g) was refluxed in chlorobenzene (10 ml) for 10 h. Chlorobenzene was removed *in vacuo* and the residual mass subjected to column chromatography over silica gel (60-120 mesh). The rearranged product **4** was obtained by eluting the column with pet.ether (60-80° C) -benzene (1:1).

Compound **4**, m.p. 192° C (94%); UV (EtOH): λ_{max} 222 (log ε 3.95), 251 (log ε 3.66) and 329 (log ε 3.50) nm; IR (KBr) υ_{max} 3310, 1710, 1595, 1458 and 1250 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 1.79-2.41 (m, 6H), 3.81 (s, 3H), 4.07-4.39 (m, 1H), 5.59-6.11 (m, 2H), 7.07-7.59

(m, 4H) and 8.00-8.23 (m, 1H); m/z 255 (M^+). Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%; found C, 75.18; H, 6.37; N, 5.79%.

Preparation of Acetate Derivative of Compound 3.

The compound 3 (0.2 g) and a few crystals of freshly fused sodium acetate (0.1 g) was taken in acetic anhydride (4 ml) and was heated on a water-bath for 4 h. The reaction mixture was cooled and poured into excess ice-water, stirred well to decompose the excess acetic anhydride and an insoluble solid was obtained. This was recrystallised from chloroform-pet.ether (60-80° C) to give white crystalline solid **5**, 87%, m.p. 185° C.

Bromination of Compound 5: Formation of Dibromoderivative 6.

The solution of bromine (0.5 m mol) in glacial acetic acid (1 ml) was added dropwise to a well stirred solution of compound **5** (0.5 m mol) in glacial acetic acid (2 ml) at room temperature. After 2 h, the reaction mixture was diluted with water and the gummy mass was collected, which was chromatographed over silica gel. The product **6** was obtained when the column was eluted with benzene.

Compound **6**, m.p. 204° C (91%); UV (EtOH): λ_{max} 226 (log ε 4.32), 274 (log ε 3.59) and 327 (log ε 3.36) nm; IR (KBr): υ_{max} 1770, 1610, 1600, 1515 and 1200 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 1.55-2.27 (m, 6H), 2.38 (s, 3H), 3.74 (s, 3H), 4.15-4.40 (m, 1H), 4.87 (s, 2H),

7.28-7.68 (m, 3H) and 8.10 (d, J=8 Hz, 1H). Anal. calcd. for $C_{18}H_{19}Br_2NO_3$: C, 47.26; H, 4.16; N, 3.06%; found C, 47.38; H, 4.05; N, 3.25%.

Cyclisation of Compound 6.

The compound **6** (0.1 g) was refluxed with ethanolic potassium hydroxide solution (4%) for 2 h. Ethanol was removed to one thired by distillation and water (10 ml) was added to it. The aqueous solution was extracted with chloroform (2 x 25 ml) and the chloroform extract was washed with water (2 x 50 ml) and dried (Na_2SO_4). The solvent was removed and the crude mass was chromatographed over silica gel. The product **7** was obtained when the column was eluted with benzene.

Compound **7**, m.p. 292° C (90%); UV (EtOH): λ_{max} 225 (log ε 4.02), 280 (log ε 3.17) and 321 (log ε 3.47) nm; IR (KBr): υ_{max} 1690, 1670, 1565, 1410 and 1220 cm^{-1}; ^{1}H-NMR (100 MHz: $CDCl_3$/TMS) δ: 1.44-2.60 (m, 6H), 3.64-3.80 (m, 1H), 3.82 (s, 3H), 4.50-4.64 (m, 1H), 4.80-4.96 (m, 1H) and 7.34-7.76 (m, 4H); m/z 335 and 333 (M^+). Anal. calcd. for $C_{16}H_{16}BrNO_2$: C, 57.49; H, 4.79; N, 4.19%; found C, 57.45; H, 4.88; N, 4.32%; ^{1}H-NMR (250 MHz; $CDCl_3$/TMS) δ: 1.25-1.47 (m, 1H, H_g), 1.55-1.63 (m, 1H, H_f), 1.75-1.90 (m, 1H, H_i), 1.94-2.13 (m, 2H, H_d and H_e), 2.36-2.45 (m, 1H, H_h), 3.75 (t, J=2.5 Hz, 1H, H_c), 3.82 (s, 3H, N-CH_3), 4.54-4.56 (dd, J=1.8 and 2.6 Hz, 1H, H_b), 4.85-4.87 (dd, J=1.9 and 3.8 Hz, H_a) and 7.24-7.55 (m, 4H).

Attempted Dehydrobromination of Compound 7.

A mixture of compound 7 (0.05 g) and potassium hydroxide (0.08 g) in rectified spirit (2 ml) was refluxed on a water-bath for 4 h. No change was observed as evidenced from the tlc of the reaction mixture and also from co-tlc with the starting material 7, mixed m.p. etc.

Attempted Functionalisation of Compound 7.

A mixture of compound 7 (0.035 g), powdered potassium cyanide (0.035 g) and 5% potassium iodide in acetone (2 ml) was stirred and heated under reflux for 8 h. No change was observed when examined by tlc.

Attempted Dehydrogenation of Compound 7.

Compound 7 (0.05 g) was refluxed with 10% palladised charcoal in diphenyl ether (2 ml) for 2 h. No change was observed when examined by co-tlc with the starting material 7, mixed m.p. etc.

Pyridine Hydrobromide Perbromide or Hrxamethylene Tetramine Hydrotribromide mediated Cyclisation of Compound 7.

The brominating agent solid pyridine hydrobromide perbromide (0.5 m mol) was added slowly to a dichloromethane solution (20 ml) of the compound 7 (0.5 m mol). The reaction mixture was then stirred for 1.5 h on a magnetic stirrer at 0-5° C, when hexamethylene tetramine hydrotribromide was used in the same condition, the reaction was completed within 30-40 minutes. After completion of the reaction, the reaction mixture was

washed with 5% $NaHCO_3$ solution (2 x 25 ml), water (2 x 25 ml) and dried (Na_2SO_4). The residual mass after removal of solvent was subjected column chromatography over silica gel using benzene as eluant to give the white solid product **8**.

COmpound **8**, m.p. 195° C (98%); UV (EtOH): λ_{max} 227 (log ε 4.31), 2.44 (log ε 3.97) and 326 (log ε 3.85) nm; IR (KBr): υ_{max} 1670, 1635, 1600, 1460 and 1230 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 1.64-2.40 (m, 6H), 3.56-3.74 (m, 1H), 3.79 (s, 3H), 4.94 (d, J=4 Hz, 2H) and 7.38-7.64 (m, 4H); m/z 335 and 333 (M^+). Anal. calcd. for $C_{16}H_{16}BrNO_2$:C, 57.49; H, 4.79; N, 4.19%; found C, 57.86; H, 4.56; N, 4.35%; ^{1}H-NMR (250 MHz; $CDCl_3$/TMS) δ: 1.21-1.33 (m, 1H, H_e), 1.57-1.64 (m, 1H, H_i), 1.81-1.99 (m, 1 H, H_f), 2.12-2.18 (m, 2H, H_h and H_g), 2.22-2.33 (m, 1H, H_d), 3.72-3.78 (dd, J=6.5 and 11 Hz, 1H, H_c), 3.79 (s, 3 H, N-CH_3), 4.92 (s, 1H, H_b), 4.93 (s, 1H, H_a) and 7.31-7.52 (m, 4H).

Attempted Dehydrogenation of Compound 8.

Compound **8** (0.05 g) was refluxed with 10% palladised charcoal in diphenyl ether (2 ml) for 2 h. The compound was breacked into compound **11**.

Compound **11**, m.p. 192° C (60%); IR (KBr): υ_{max} 3270, 1620, 1600, 1465 and 1275 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 3.82 (s, 3H) and 7.08-7.80 (m, 10H); m/z 251 (M^+).

Dehydrobromination of Compound 8.

A mixture of compound **8** (0.05 g) and potassium hydroxide (0.08 g) in rectified sprit (3 ml) was refluxed on water-bath for 40 minutes. Ethenol was removed and the residue was extracted with dietheylether. The ethereal solution was washed repeatedly with salt-water, water and finally dried (Na_2SO_4). Removal of solvent gave a white solid **10** which was recrystallised from chloroform-methanol.

Compound **10**, m.p. 170° C (91%); UV (EtOH): λ_{max} 225 (log ε 4.55) and 326 (log ε 3.68) nm; IR (KBr): υ_{max} 1680, 1615, 1600, 1455 and 1250 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 1.56-2.56 (m, 6H), 2.64-3.00 (m, 1H), 3.78 (s, 3H), 4.68 (s, 1H), 7.20-7.48 (m, 3H) and 7.99 (d, J= 8 Hz, 1H); m/z 253 (M^+). Anal. calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93; N, 5.53%; found C, 75.65; H, 5.85, N, 5.74%.

Cyclisation of Compound 4 in Conc. Sulphuric Acid.

Compound **4** (0.1 g) was added to the well-stirred cold conc. sulphuric acid (1.5 ml) at 0-5° C and the stirring was continued for 2 h at this temperature. The reaction mixture was poured into crushed ice and extracted with chloroform. The chloroform extract was washed with sodium bicarbonate (10%) solution (2 x 25 ml), water (2 x 50 ml) and dried (Na_2SO_4). Removal of solvent gave a viscous oil which was subjected to column

chromatography over silica gel using benzene to give product **12**.

Compound **12**, gummy liquid (89%); UV (EtOH): λ_{max} 226 (log ε 4.33), 281 (log ε 3.55) and 321 (log ε 3.83) nm; IR (KBr): υ_{max} 1660, 1618, 1600, 1453 and 1225 cm^{-1}; ^{1}H-NMR (100 MHz; $CDCl_3$/TMS) δ: 1.52-2.12 (m, 8H), 3.32-3.52 (brs, 1H), 3.78 (s, 3H), 4.76-4.94 (brs, 1H) and 7.32-7.72 (m, 4H); m/z 255 (M^+). Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%; found C, 75.55; H, 6.7; N, 5.24%.

Attempted Dehydrogenation of Compound 12.

Compound **12** (0.05 g) was refluxed with 10% palladised charcoal (0.01 g) in diphenyl ether (2 ml) fpr 2 h. No change was observed as evidenced from tlc of the reaction mixture, co-tlc with the starting material **12** and also superimposable i.r. spectra.

Acknowledgement

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