Regioselective Synthesis of 2H-Benzopyrano[3,2-c]quinolin-7(8H)-ones by Radical Cyclization

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Received 19 August 2002; revised 24 October 2002

Abstract: Different 4-hydroxyquinolin-2(1H)-ones were treated with 2-bromobenzyl bromide and 2-bromo-5-methoxybenzyl bromide in the presence of anhydrous potassium carbonate in acetone to afford a number of 4-(2'-bromobenzyloxy)quinolin-2(1H)-one derivatives in 80–85% yield. These 4-(2'-bromobenzyloxy)quinolin-2(1H)-ones were then refluxed with tributyltin chloride and sodium cyanoborohydride in benzene under nitrogen, in the presence of a catalytic amount of AIBN, for 4–5 hours to give 2H-benzopyrano[3,2-c]quinolin-7(8H)-ones in 70–80% yields.

Key words: 2-bromobenzyl bromide, sodium cyanoborohydride, radical cyclization, tributyltin chloride, 2H-benzopyrano[3,2-c]quinolin-7(8H)-ones

Aryl radical cyclization has recently emerged as a valuable tool for organic synthesis.1 In the course of our studies on the application of sigmatropic rearrangements2 for the synthesis of heterocyclic compounds we recently noted the unusual formation of [6,6]pyranopyrans from substrates containing 3-hydroxycoumarin3 and 5-hydroxyuracil4 moieties in the second Claisen rearrangement step. We became interested to investigate whether [6,6] ring fusion could be achieved by tributyltin hydride mediated aryl radical cyclization. The generation and subsequent reaction of radicals formed from aryl halides using tributyltin hydride and AIBN are now well established and the synthesis of a wide range of natural products based on aryl radical cyclization have been reported.5 However, literature reports on heteroaryl radicals are much less in number. Some examples by Snieckus5a,b,6a and Harrowven6b involve pyridine and pyridyl radicals. Sundberg7a reported one example of an indonyl radical7b,c in the synthesis of Iboga alkaloids. The cyclization of radical derived from N-o-bromobenzylanilines to phenanthridine was very recently reported.8 Lack of significant work on the generation of radicals on heteroaromatic systems prompted us to study the synthesis of 2H-benzopyrano[3,2-c]quinolin-7(8H)-ones by aryl radical cyclization and our results are reported here.

The starting materials, 4-(2'-bromobenzyloxy)quinolin-2(1H)-ones were prepared in 80–85% yield by the reaction of 2'-bromobenzyl bromide (2) with 1-alkyl or aryl-4-hydroxyquinolin-2(1H)-ones 1a-c in refluxing acetone in the presence of anhydrous K2CO3 for 4–5 hours (Scheme 1).

Substrate 3a was refluxed in benzene with tributyltin(IV) chloride and sodium cyanoborohydride in the presence of azoisobutyronitrile (AIBN) for 4–5 hours to give compound 4a in 80% yield, which was characterized by elemental analyses and spectroscopic data. The IR spectrum of the compound 4a as 8-phenylbenzopyrano[3,2-c]quinolin-7(8H)-one showed a peak at 2905 cm–1 for the aromatic C–H stretching and at 1650 cm–1 for a carbonyl group. The high-field 1H NMR (300 MHz) spectrum of the product 4a displayed a two proton singlet at δ = 5.37 for OCH2. The 13C NMR chemical shifts of compound 4a and multiplicities were assigned by DEPT experiments. DEPT shows 14 protonated carbons identified as 13 CH, and one CH2. The mass spectrum of compound 4a showed a molecular ion peak at m/z 325 (M+). Encouraged by this result, other substrates 3b–f were also treated similarly to give tetracyclic heterocycles 4b–f in 70–80% yield (Scheme 2).
The formation of products 4a-f from 3a-f may be explained by the generation of an aryl radical 5 which may give the dihydro intermediate 7 by a direct ‘6-endo’ cyclization or a ‘5-exo’ cyclization of radical 5 via the spiroheterocyclic radical 6 (not isolated) followed by a neophyl rearrangement.\(^\text{10}\) The intermediate radical 7 then loses a H-radical to yield the products 4a-f by an unknown mechanism which is usual for this synthetic sequence, i.e., an oxidation step in Bu\(_3\)SnH-mediated cyclizations\(^\text{8b,11}\) (Scheme 3).

In conclusion, we have successfully extended the Bu\(_3\)SnH-mediated radical cyclizations to the regioselective synthesis of tetracyclic heterocycles 2H-benzopyrano[3,2-c]quinolin-7(8H)-ones. This method is a general one and attractive due to its simplicity.

Melting points were determined on a H\(_2\)SO\(_4\) bath and are uncorrected. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401 PC spectrophotometer (\(\lambda_{\text{max}}\) in nm) and IR spectra were recorded on KBr disks on a Perkin-Elmer L120-000A apparatus. \(^1\)H NMR (300 MHz) and \(^13\)C NMR (75.5 MHz) spectra were recorded on a Bruker DPX-300 spectrometer in CDCl\(_3\) at the Indian Institute of Chemical Biology, Kolkata (chemical shift in \(\delta\)). TMS was used as an internal standard. Elemental analyses and recording of mass spectra were carried out by RSIC (CDRI), Lucknow on a Jeol D-300 (El) instrument. Silica gel (60–120 mesh), Spectrochem, India was used for chromatographic separation. Petroleum ether refers to the fraction boiling between 60–80 °C.

4-(2-Bromobenzyloxy)quinolin-2(1H)-ones 3a–f; General Procedure

A mixture of 4-hydroxyquinolin-2(1H)-one 1a–c (5 mmol), 2-bromobenzyl bromide 2a (1.25 g, 5 mmol) or 2-bromo-5-methoxybenzyl bromide 2b (1.40 g, 5 mmol) and anhyd K\(_2\)CO\(_3\) (5 g) was refluxed in anhyd acetone (150 mL) on a water bath for 4–5 h. The reaction mixture was then cooled, filtered, and the solvent was removed. The residue was subjected to column chromatography over silica gel using benzene–EtOAc (9:1) as eluent to give 3a–f, which were then recrystallized from CHCl\(_3\)–petroleum ether.

1-Phenyl-4-(2-bromobenzyloxy)quinolin-2(1H)-one (3a)

Yield: 85%; white solid, mp 145–147 °C.

IR (KBr): 750, 1246, 1645, 2440 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta = 5.30\) (s, 2 H, OCH\(_2\)), 6.22 (s, 1 H, =CH), 6.63–7.42 (m, 7 H, ArH), 7.49–7.66 (m, 5 H, ArH), 8.06–8.09 (m, 1 H, ArH).

MS: \(m/z = 405, 407\) (M\(^+\)).

UV (EtOH): \(\lambda_{\text{max}} = 317, 277, 268, 225\) nm.

Anal. Calcd for C\(_{22}\)H\(_{16}\)BrNO\(_2\): C, 64.86; H, 3.93; N, 3.43. Found: C, 64.98; H, 4.08; N, 3.72.

1-Methyl-4-(2-bromobenzyloxy-5-methoxy)quinolin-2(1H)-one (3d)

Yield: 83%; white solid, mp 138–140 °C.

IR (KBr): 750, 1245, 1640, 2435 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta = 3.68\) (s, 3 H, NCH\(_3\)), 3.89 (s, 3 H, OCH\(_3\)), 5.20 (s, 2 H, OCH\(_3\)), 6.13 (s, 1 H, =CH), 6.78–7.19 (m, 3 H, ArH), 7.35–7.62 (m, 3 H, ArH), 8.06–8.07 (m, 1 H, ArH).

MS: \(m/z = 343, 345\) (M\(^+\)).

UV (EtOH): \(\lambda_{\text{max}} = 317, 277, 268, 228\) nm.

Anal. Calcd for C\(_{21}\)H\(_{14}\)BrNO\(_2\): C, 59.13; H, 4.05; N, 4.05. Found: C, 59.39; H, 4.19; N, 4.23.

Scheme 3

Synthesis 2003, No. 1, 97–100 ISSN 0039-7881 © Thieme Stuttgart · New York
IR (KBr): 725, 1100, 1300, 1650, 2905 cm⁻¹.
Yield: 80%; white solid; mp 118–120 °C.

1-Ethyl-4-(2-bromobenzyloxy)quinolin-2(1H)-one (3e)

Yield: 76%; white solid; mp 105–107 °C.

1H NMR (CDCl₃, 300 MHz): δ = 1.33–1.38 (t, 3 H, J = 6.9 Hz, CH₃), 3.81 (s, 3 H, OCH₃), 4.30–4.37 (q, 2 H, J = 6.9 Hz, NCH₂), 5.19 (s, 2 H, OCH₂), 6.13 (s, 1 H, =CH), 6.77–7.40 (m, 4 H, ArH), 7.54–7.63 (m, 3 H, ArH), 8.07–8.09 (m, 1 H, ArH).

MS: m/z = 375, 359 (M⁺).
UV (EtOH): λ_max = 318, 278, 269, 206 nm.

Anal. Calcd for C₁₈H₁₅NO₂: C, 77.97; H, 5.41; N, 5.05. Found: C, 78.11; H, 5.69; N, 5.28.

8-Phenylbenzopyrano[3,2-c]quinolin-7(8H)-one (4a)

Yield: 80%; white solid; mp 200–202 °C.

IR (KBr): 750, 1235, 1636, 2425 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 1.32–1.37 (t, 3 H, J = 6.9 Hz, CH₃), 4.30–4.37 (q, 2 H, J = 6.9 Hz, NCH₂), 5.24 (s, 2 H, OCH₂), 6.15 (s, 1 H, =CH), 7.21–7.39 (m, 4 H, ArH), 7.54–7.63 (m, 3 H, ArH), 8.07–8.09 (m, 1 H, ArH).

MS: m/z = 375, 359 (M⁺).
UV (EtOH): λ_max = 317, 277, 268, 228 nm.

Anal. Calcd for C₁₈H₁₅BrNO₂: C, 60.16; H, 4.45; N, 3.89. Found: C, 60.36; H, 4.68; N, 4.05.

8-Phenylbenzopyrano[3,2-c]quinolin-7(8H)-one (4b)

Yield: 76%; white solid; mp 160–162 °C.

IR (KBr): 760, 1123, 1241, 1645, 2920 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 3.84 (s, 3 H, OCH₃), 5.34 (s, 2 H, OCH₂), 6.63–6.88 (m, 3 H, ArH), 7.21–7.34 (m, 4 H, ArH), 7.53–7.62 (m, 3 H, ArH), 8.03–8.77 (m, 2 H, ArH).

UV (EtOH): λ_max = 346, 323, 228, 206 nm.

Anal. Calcd for C₂₃H₁₇NO₃: C, 77.76; H, 4.97; N, 4.09.

8-Methylbenzopyrano[3,2-c]quinolin-7(8H)-one (4c)

Yield: 70%; white solid; mp 130–132 °C.

IR (KBr): 800, 1100, 1255, 1625 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 3.77 (s, 3 H, NCH₃), 5.29 (s, 2 H, OCH₂), 7.13–7.43 (m, 5 H, ArH), 7.57–7.62 (m, 1 H, ArH), 8.05–8.08 (m, 2 H, ArH).

MS: m/z = 263 (M⁺).
UV (EtOH): λ_max = 343, 320, 232, 206 nm.

Anal. Calcd for C₁₈H₁₄NO₂: C, 73.77; H, 4.94; N, 5.32. Found: C, 73.77; H, 5.12; N, 5.74.

8-Methylbenzopyrano[3,2-c]4-methoxyquinolin-7(8H)-one (4d)

Yield: 73%; white solid; mp 110–112 °C.

IR (KBr): 751, 1103, 1245, 1633 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 3.78 (s, 3 H, NCH₃), 3.85 (s, 3 H, OCH₃), 5.26 (s, 2 H, OCH₂), 6.69–7.22 (m, 2 H, ArH), 7.36–7.59 (m, 3H, ArH), 8.02–8.78 (m, 2H, ArH).

MS: m/z = 293 (M⁺).
UV (EtOH): λ_max = 345, 328, 230, 206 nm.

Anal. Calcd For C₁₈H₁₄NO₃: C, 73.72; H, 5.11; N, 4.77. Found: C, 73.98; H, 5.32; N, 4.98.

8-Ethylbenzopyrano[3,2-c]quinolin-7(8H)-one (4e)

Yield: 70%; white solid; mp 120–122 °C.

IR (KBr): 785, 1110, 1240, 1645 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 1.25–1.31 (t, 3 H, J = 6.9 Hz, CH₃), 4.39–4.46 (q, 2 H, J = 6.9 Hz, NCH₂), 5.28 (s, 2 H, OCH₂), 6.76–7.31 (m, 4 H, ArH), 7.52–7.63 (m, 2 H, ArH), 8.04–8.83 (m, 2 H, ArH).

MS: m/z = 277 (M⁺).
UV (EtOH): λ_max = 343, 321, 232, 206 nm.

Anal. Calcd for C₁₈H₁₄NO₂: C, 77.97; H, 5.41; N, 5.05. Found: C, 78.11; H, 5.69; N, 5.28.

8-Ethylbenzopyrano[3,2-c]4-methoxyquinolin-7(8H)-one (4f)

Yield: 76%; white solid; mp 128–130 °C.

IR (KBr): 755, 1112, 1245, 1621 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 1.25–1.30 (t, 3 H, J = 6.9 Hz, CH₃), 3.84 (s, 3 H, OCH₃), 4.39–4.46 (q, 2 H, J = 6.9 Hz, NCH₂), 5.25 (s, 2 H, OCH₂), 6.92–7.21 (m, 3 H, ArH), 7.42–7.68 (m, 2 H, ArH), 8.02–8.08 (m, 2 H, ArH).
MS: $m/z = 307$ (M$^+$. 
UV (EtOH): $\lambda_{\text{max}} = 346, 320, 230, 207$ nm.

Anal. Calcd for C$_{19}$H$_{17}$NO$_3$: C, 74.26; H, 5.53; N, 4.56. Found: C, 74.38; H, 5.76; N, 4.73.

Acknowledgments

We thank the CSIR (New Delhi) for financial assistance. One of us (P.P.M) is grateful to CSIR for a Junior Research Fellowship.

References


