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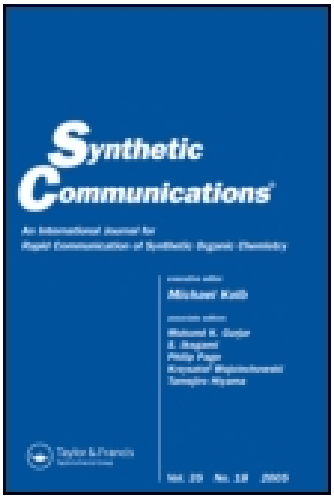

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Aryl Radical Cyclization: Regioselective Synthesis of 6a,7,8,12b-Tetrahydro-6H-chromeno[3,4-c]quinc

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Aryl Radical Cyclization: Regioselective Synthesis of 6a,7,8,12*b*-Tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one

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Abstract: Regioselective synthesis of 6a,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-ones **4** in good to excellent yields from 3-(2-bromoanilinomethyl)coumarins **3** by aryl radical cyclization is described. The cyclization precursors **3** were prepared by the reaction of 3-chloromethyl coumarin with different 2-bromoaniline.

Keywords: Aryl radical cyclization, coumarin derivatives, 6-*endo* trig, organotin reagent, tetrahydroquinolines

INTRODUCTION

Substituted coumarin rings are common structural motifs in natural products,[1] and they constitute attractive synthetic targets because of their interesting biological and physiological activities.[2] In particular, those coumarins fused to pyridines have been reported to possess antialergic,[3a] antidiabetic,[3b] and analgesic properties.[3c] Several efforts have been made to synthesize them.[4] Galariniotou et al.[5] reported the synthesis of some pyrido coumarins and benzo-fused azacoumarins. Recently, aryl radical cyclization has been developed as a potential method for preparing various types of cyclic compounds via intramolecular carbon–carbon bond-forming processes.[6] The synthesis of nitrogen heterocycles[7] using radical intermediates has become an invaluable tool in modern chemistry. In the interest of

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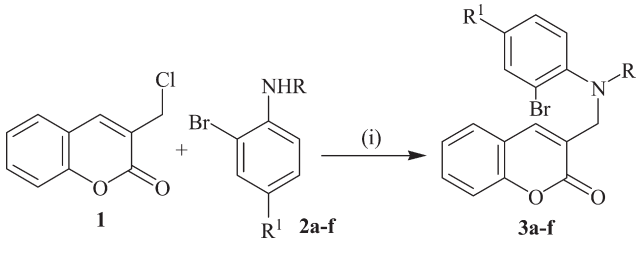
synthesizing new coumarin ring systems of biological interest, we have prepared a variety of coumarins such as furocoumarin, pyranocoumarin,[8] and spirocoumarin[9] by using a radical cyclization strategy. In continuation of our work, we describe here the synthesis of quinoline fused coumarins via aryl radical cyclization reaction of 3-(2-bromoanilinomethyl)coumarins.

RESULTS AND DISCUSSION

The requisite radical precursors 3-(2-bromoanilinomethyl)coumarins **3a**–**f** were prepared in 80–92% yields by treating 3-chloromethyl coumarin (**1**) with different 2-bromoaniline (**2a**–**f**) in refluxing acetone in the presence of anhydrous potassium carbonate for 5–6 h (Scheme 1). Compounds **3a**–**f** were characterized from their elemental analyses and spectroscopic data.

A preliminary attempt to effect the desired radical cyclization was carried out with the substrate **3a**. Compound **3a**, when heated at 80 °C with $^{n}Bu_3SnH$ in dry degassed toluene in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 2.5 h, afforded cyclized product tetrahydropyrido[3,4-*c*]coumarin **(4a)** in 81% yield (Scheme 2). Other substrates **3b** and **3c** were also similarly treated to give cyclic products **4b** and **4c** in 85% and 88% yields, respectively. To extend the scope of this reaction, we also attempted a similar radical reaction with 3-[2-bromo(N-methyl)anilinomethyl]coumarins **3d**, employing similar reaction conditions. Unfortunately, we were unable to obtain any cyclized product because the starting material decomposed under the reaction condition. Changing the solvent (benzene) and lowering the reaction temperature (50–60 °C) did not divert the reaction away from the observed decomposition. However, changing the tin reagent eliminated the decomposition of the starting material. The compound **3d** was heated at 60 °C in dry degassed toluene under a nitrogen atmosphere with radical initiator AIBN, $^{n}Bu_3SnCl$, and $Na(CN)BH_3$ for 1 h. Isolation of the product by flash chromatography furnished solid **4d** in 74% yield. Similarly, other substrates **3e** and **3f** gave **4e** and **4f** in 82% and 78% yields, respectively (Scheme 2). The structure of the product **4** was readily elucidated



Scheme 1. Reagents and conditions: (i) dry acetone, anhyd, K_2CO_3, reflux, 5–6 h.

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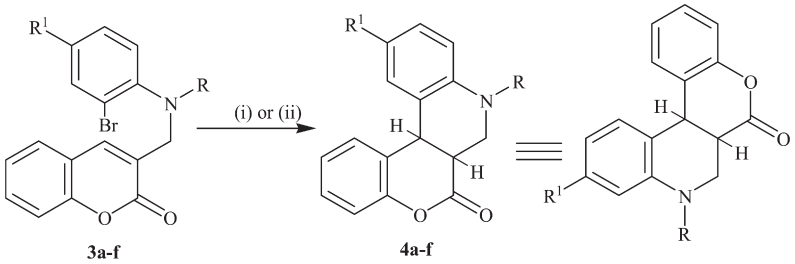

	R	R^1	Yield(%)
4a	H	H	81
4b	H	CH_3	85
4c	H	C_2H_5	88

	R	R^1	Yield(%)
4d	CH_3	H	74
4e	CH_3	CH_3	82
4f	CH_3	C_2H_5	78

Scheme 2. Reagents and conditions: (i) $^{n}Bu_3SnH$, AIBN, toluene, 80 °C, 2–2.5 h; (ii) $^{n}Bu_3SnCl$, $Na(CN)BH_3$, AIBN, toluene, 60 °C, 1 h

from ^{1}H NMR spectroscopy. Compound **4a** exhibited one proton multiplet at δ 3.18–3.22 and another one proton doublet at δ 4.32 ($J = 5.6$ Hz) due to ring juncture protons. The stereochemistry of the ring juncture protons can be surmised from the molecular model (Dreiding model), which showed a strain-free *cis*[10] arrangement, and also from the small coupling constant value ($J = 5.6$ Hz) of the ring juncture protons of **4**. The ^{13}C NMR spectra of **4a** also supported the proposed structure. The mass spectrum of compound showed a molecular ion peak at $m/z = 251$ (M^+).

The formation of the products **4** from **3** may be explained by the generation of aryl radical **5**, which may undergo either a 5-*exo* trig or a 6-*endo*-trig cyclization at the double bond of the pyrone ring of the coumarin moiety. A 6-*endo* trig cyclization of radical **5** may produce the intermediate radical **8**, whereas 5-*exo* trig cyclization may give the spirocycle radical **6** (not isolated), followed by neophyl rearrangement[11] to radical intermediate **7**. Abstraction of hydrogen by **8** from $^{n}Bu_3SnH$ may afford **4** (Scheme 3). However, 5-*exo* cyclization with subsequent neophyl rearrangement is unlikely with the present system. The stability and nonnucleophilicity[12] of the intermediate bezylic radical due to excellent overlapping[13] of *p*-orbital of radical center with the adjacent aromatic π-system might prevent further attack to produce the intermediate cyclohexadienyl radical **7**. The stabilization of the intermediate tertiary radical **8** by the adjacent carbonyl group may also be responsible for the formation of 6-*endo* products.

In conclusion, we have successfully described the $^{n}Bu_3SnH$-mediated mild and efficient synthesis of coumarin-annulated [6,6] fused nitrogen heterocycles. The use of 2-bromoaniline provides easy access to tetrahydroquinoline derivatives, which are of synthetic utility in organic synthesis.

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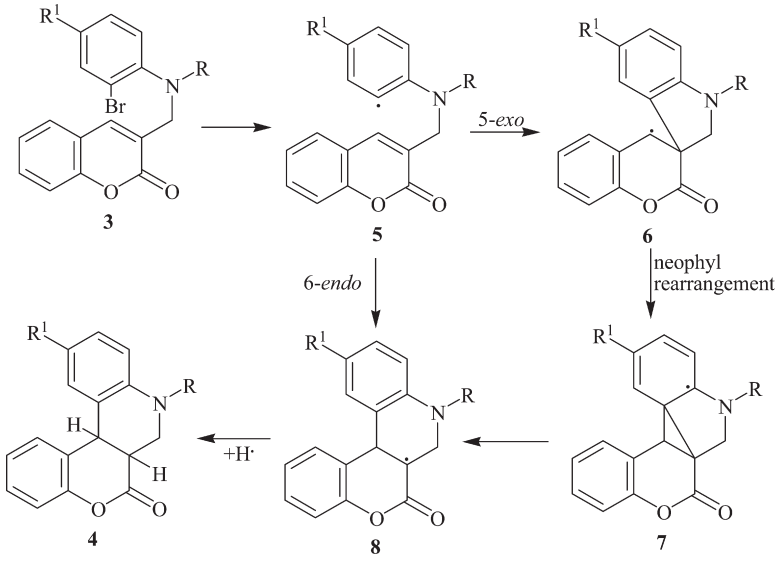

Scheme 3. Mechanism of the cyclization reaction.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer (γ_{max} in cm^{-1}) using samples as neat liquids, and solid samples were recorded in KBr disks ^1H NMR (300 MHz, 400 MHz, 500 MHz) and ^{13}C NMR (100 MHz, 125 MHz) spectra were recorded on Bruker DPX-300, Varian-400, and Bruker DPX-500 spectrometers in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Silica gel (60–120 mesh, Spectrochem, India) was used for chromatographic separation. Silica gel G (E-Merck, India) was used for thin-layer chromatography (TLC). Petroleum ether refers to the fraction boiling between 60 °C and 80 °C.

General Procedure for the Preparation of 3-(2-Bromoanilinomethyl)coumarins 3a–f

2-Bromoaniline **2a–f** (5.15 mmol) and anhydrous potassium carbonate (2 g) were added to a solution of 3-chloromethylcoumarin (**1**) (1 g, 5.15 mmol) in dry acetone (100 mL), and the reaction mixture was refluxed for 5–6 h. The reaction mixture was then cooled and filtered, and the solvent was removed. The residual mass was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water (3 × 20 mL) and finally with brine (20 mL). After removal of the solvent, the residue was subjected to column

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chromatography over silica gel. Elution of the column with 5% ethyl acetate in petroleum ether afforded 3-(2-bromoanilinomethyl)coumarins **3a**–**f**. All the compounds were recrystalized from chloroform–methanol.

Data

3-[(2-Bromoanilino)methyl)]-2*H*-chromen-2-one (3a)

Yield: 82%; colorless solid; mp 105–106; IR (KBr): $\nu_{max} = 3413$, 1714, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 4.40$ (s, 2H, -NCH_2), 4.97 (brs, 1H, NH), 6.54 (d, $J = 8.3$ Hz, 1H, ArH), 6.61 (t, $J = 7.8$ Hz, 1H, ArH), 7.12 (t, $J = 8.6$ Hz, 1H, ArH), 7.27–7.29 (m, 1H, ArH), 7.35 (d, $J = 8.3$ Hz, 1H, ArH), 7.43–7.54 (m, 3H, ArH), 7.63 (s, 1H, vinylic H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_c = 43.2$, 109.9, 111.5, 116.5, 118.7, 119.1, 124.5, 125.7, 127.8, 128.6, 131.2, 132.6, 138.2, 144.0, 153.1, 161.1; MS: $m/z = 329$, 331 (M^+). Anal. calcd. for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; N, 4.24%. Found: C, 58.35; H, 3.59; N, 4.28%.

3-[(2-Bromo-4-methylanilino)methyl)]-2*H*-chromen-2-one (3b)

Yield: 88%; colorless solid; mp 122–123 °C; IR (KBr): $\nu_{max} = 3410$, 1715, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.24$ (s, 3H, $ArCH_3$), 4.38 (s, 2H, -NCH_2), 4.82 (brs, 1H, NH), 6.45 (d, $J = 8.3$ Hz, 1H, ArH), 6.94 (d, $J = 2.5$ Hz, 1H, ArH), 7.25–7.38 (m, 3H, ArH), 7.44 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.49–7.54 (m, 1H, ArH), 7.63 (s, 1H, vinylic H); MS: $m/z = 343$, 345 (M^+). Anal. calcd. for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07%. Found: C, 59.15; H, 4.18; N, 4.10%.

3-[(2-Bromo-4-ethylanilino)methyl)]-2*H*-chromen-2-one (3c)

Yield: 80%; colorless solid; mp 98–99 °C; IR (KBr): $\nu_{max} = 3408$, 1713, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.16$ (t, $J = 7.5$ Hz, 3H, $ArCH_2CH_3$), 2.49 (q, $J = 7.5$ Hz, 2H, $ArCH_2CH_3$), 4.36 (s, 2H, -NCH_2), 4.80 (brs, 1H, NH), 6.46 (d, $J = 8.5$ Hz, 1H, ArH), 6.94 (dd, $J = 2.0$, 8.5 Hz, 1H, ArH), 7.23–7.35 (m, 3H, ArH), 7.42 (dd, $J = 1.5$, 7.5 Hz, 1H, ArH), 7.47–7.51 (m, 1H, ArH), 7.62 (s, 1H, vinylic H); MS: $m/z = 357$, 359 (M^+). Anal. calcd. for $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91%. Found: C, 60.42; H, 4.55; N, 4.02%.

3-[(2-Bromo-*N*-methylanilino)methyl)]-2*H*-chromen-2-one (3d)

Yield: 90%; viscous liquid; IR (KBr): $\nu_{max} = 1704$, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.79$ (s, 3H, NCH_3), 4.13 (s, 2H, -NCH_2), 6.91 (t, $J = 7.2$ Hz, 1H, ArH), 7.18 (d, $J = 7.4$ Hz, 1H, ArH), 7.24

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(t, $J = 7.4$ Hz, 2H, ArH), 7.31 (d, $J = 8.1$ Hz, 1H, ArH), 7.46–7.51 (m, 2H, ArH), 7.56 (d, $J = 7.6$ Hz, 1H, ArH), 8.03 (s, 1H, vinylic H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_c = 41.5$, 54.7, 116.5, 119.5, 120.0, 122.0, 124.4, 124.8, 125.7, 127.8, 128.4, 130.9, 132.7, 133.9, 139.6, 152.9, 161.5; MS: $m/z = 343$, 345 (M^+). Anal. calcd. for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07%. Found: C, 59.46; H, 4.13; N, 4.02%.

3-[(2-Bromo-4-dimethylanilino)methyl)]-2*H*-chromen-2-one (3e)

Yield: 92%; viscous liquid; IR (KBr): $\nu_{max} = 1717$, 1608 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.31$ (s, 3H, $ArCH_3$), 2.77 (s, 3H, -NCH_3), 4.11 (s, 2H, -NCH_2), 7.07–7.10 (m, 2H, ArH), 7.25–7.28 (m, 1H, ArH), 7.32 (d, $J = 8.3$ Hz, 1H, ArH), 7.41 (s, 1H, ArH), 7.46–7.52 (m, 2H, ArH), 8.03 (s, 1H, vinylic H); MS: $m/z = 357$, 359 (M^+). Anal. calcd. for $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91%. Found: C, 60.56; H, 4.34; N, 3.95%.

3-[(2-Bromo-4-ethyl-*N*-methylanilino)methyl)]-2*H*-chromen-2-one (3f)

Yield: 87%; viscous liquid; IR (KBr): $\nu_{max} = 1710$, 1606 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.18$ (t, $J = 7.1$ Hz, 3H, $ArCH_2CH_3$), 2.55 (q, $J = 7.6$ Hz, 2H, $ArCH_2CH_3$), 2.78 (s, 3H, NCH_3), 4.11 (s, 2H, -NCH_2), 7.08 (dd, $J = 1.9$, 8.1 Hz, 1H, ArH), 7.12 (d, $J = 8.1$ Hz, 1H, ArH), 7.25–7.28 (m, 1H, ArH), 7.32 (d, $J = 7.8$ Hz, 1H, ArH), 7.42 (d, $J = 1.7$ Hz, 1H, ArH), 7.47–7.52 (m, 2H, ArH), 8.04 (s, 1H, vinylic H); MS: $m/z = 371$, 373 (M^+). Anal. calcd. for $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87; N, 3.76%. Found: C, 61.58; H, 4.99; N, 3.86%.

General Procedure for the Radical Cyclization of Compound 3a–f

^{n}Bu$_3$SnH Procedure

^{n}Bu$_3$SnH (0.12 mL, 0.33 mmol) was added dropwise under a nitrogen atmosphere to a magnectically stirred solution of **3**(**a**–**c**) (0.30 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (5 mL). The reaction mixture was heated at 80 °C for 2–2.5 h. After completion of the reaction, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and stirred with 10% KF solution (20 mL) for 1 h. The organic phase was washed with water (3 × 10 mL) and brine (1 × 20 mL) and dried (Na_2SO_4). The solvent was distilled off, and the crude solid was purified by column chromatography over silica gel (230–400 mesh). Elution of the column with petroleum ether–ethyl acetate (9:1) gave pure solids **4a**–**c**.

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$^{n}Bu_3SnCl$ and $Na(CN)BH_3$ Procedure

This procedure is the same as the procedure described previously except that $^{n}Bu_3SnCl$ (1.5 equiv.) and $Na(CN)BH_3$ (1.5 equiv.) were added in one portion instead of $^{n}Bu_3SnH$ at the beginning to the reaction mixture of **3**(**d**–**f**).

Data

6a,7,8,12*a*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one (4a). Yield: 81%; colorless solid; mp 132–133 °C; IR (KBr): $\nu_{max} = 3390, 1745, 1604\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta_H = 3.18–3.22$ (m, 1H, ring juncture H), 3.51 (dd, $J = 3.5, 11.9$ Hz, 1H, -NCH_2), 3.82 (dd, $J = 4.7, 11.9$ Hz, 1H, -NCH_2), 4.02 (brs, 1H, NH), 4.32 (d, $J = 5.6$ Hz, 1H, ring juncture H), 6.52–6.61 (m, 2H, ArH), 6.81 (d, $J = 7.5$ Hz, 1H, ArH), 7.00–7.08 (m, 2H, ArH), 7.16 (t, $J = 7.4$ Hz, 1H, ArH), 7.29–7.34 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_c = 37.4, 37.9, 40.5, 115.3, 117.6, 117.7, 117.8, 124.9, 125.9, 128.9, 129.2, 129.6, 130.0, 143.2, 150.9, 167.8$; MS: $m/z = 251$ (M^+). Anal. calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57%. Found: C, 76.77; H, 5.27; N, 5.48%.

11-Methyl-6a,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one (4b). Yield: 85%; colorless solid; mp 117–119 °C; IR (KBr): $\nu_{max} = 3394, 1746, 1617\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta_H = 2.13$ (s, 3H, $ArCH_3$), 3.15–3.20 (m, 1H, ring juncture H), 3.47 (dd, $J = 3.6, 12.0$ Hz, 1H, -NCH_2), 3.79 (dd, $J = 5.0, 12.0$ Hz, 1H, -NCH_2), 4.29 (d, $J = 5.6$ Hz, 1H, ring juncture H), 6.46 (d, $J = 8.1$ Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.83 (d, $J = 7.0$ Hz, 1H, ArH), 7.06 (d, $J = 7.9$ Hz, 1H, ArH), 7.17–7.25 (m, 1H, ArH), 7.30–7.34 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_c = 20.9, 37.5, 38.2, 40.6, 115.7, 117.7, 117.8, 124.9, 125.9, 127.2, 129.2, 129.7, 129.9, 130.0, 140.8, 150.9, 169.1$; MS: $m/z = 265$ (M^+). Anal. calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%. Found: C, 76.88; H, 5.86; N, 5.31%.

11-Ethyl-6a,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one (4c). Yield: 88%; colorless solid; mp 161–163 °C; IR (KBr): $\nu_{max} = 3392, 1748, 1618\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.07$ (t, $J = 7.6$ Hz, 3H, $ArCH_2CH_3$), 2.39 (q, $J = 7.5$ Hz, 2H, $ArCH_2CH_3$), 3.16–3.20 (m, 1H, ring juncture H), 3.48 (dd, $J = 3.0, 11.9$ Hz, 1H, -NCH_2), 3.76 (dd, $J = 4.6, 12.0$ Hz, 1H, -NCH_2), 3.89 (brs, 1H, NH), 4.30 (d, $J = 5.5$ Hz, 1H, ring juncture H), 6.48 (d, $J = 8.1$ Hz, 1H, ArH), 6.65 (s, 1H, ArH), 6.87 (d, $J = 7.9$ Hz, 1H, ArH), 7.05 (d, $J = 7.9$ Hz, 1H, ArH), 7.17–7.25 (m, 1H, ArH), 7.29–7.32 (m, 2H, ArH); MS: $m/z = 279$ (M^+). Anal. calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01%. Found: C, 77.53; H, 6.18; N, 5.09%.

8-Methyl-6a,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one (4d). Yield: 74%; colorless solid; mp 144–145 °C; IR (KBr): $\nu_{max} = 1750, 1602\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.97$ (s, 3H, -NCH_3),

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3.28–3.32 (m, 1H, ring juncture H), 3.54 (dd, $J = 4.5$, 11.4 Hz, 1H, NCH_2), 3.70 (dd, $J = 5.2$, 11.5 Hz, 1H, -NCH_2), 4.33 (d, $J = 5.2$ Hz, 1H, ring juncture H), 6.59–6.65 (m, 2H, ArH), 6.78 (d, $J = 7.3$ Hz, 1H, ArH), 7.06 (d, $J = 8.0$ Hz, 1H, ArH), 7.13–7.19 (m, 2H, ArH), 7.27–7.33 (m, 2H, ArH); MS: $m/z = 265$ (M^+). Anal. calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%. Found: C, 77.03; H, 5.66; N, 5.23%.

8,11-Dimethyl-6a,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one (4e). Yield: 82%; colorless solid; mp 168–170 °C; IR (KBr): $\nu_{max} = 1765$, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.30$ (s, 3H, $ArCH_3$), 2.95 (s, 3H, -NCH_3), 3.26–3.30 (m, 1H, ring juncture H), 3.48 (dd, $J = 4.2$, 11.7 Hz, 1H, -NCH_2), 3.67 (dd, $J = 5.2$, 11.9 Hz, 1H, -NCH_2), 4.32 (d, $J = 5.3$ Hz, 1H, ring juncture H), 6.55 (d, $J = 8.2$ Hz, 1H, ArH), 6.61 (d, $J = 7.9$ Hz, 1H, ArH), 7.01–7.12 (m, 2H, ArH), 7.17–7.22 (m, 1H, ArH), 7.27–7.31 (m, 2H, ArH); MS: $m/z = 279$ (M^+). Anal. calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01%. Found: C, 77.62; H, 6.24; N, 5.04%.

11-Ethyl-8-methyl-6a,7,8,12*b*-tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one (4f). Yield: 78%; colorless solid; mp 141–143 °C; IR (KBr): $\nu_{max} = 1746$, 1615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.10$ (t, $J = 7.5$ Hz, 3H, $ArCH_2CH_3$), 2.43 (q, $J = 7.5$ Hz, 2H, $ArCH_2CH_3$), 2.93 (s, 3H, -NCH_3), 3.30–3.34 (m, 1H, ring juncture H), 3.46 (dd, $J = 4.5$, 11.4 Hz, 1H, -NCH_2), 3.62 (dd, $J = 5.8$, 11.4 Hz, 1H, -NCH_2), 4.29 (d, $J = 5.6$ Hz, 1H, ring juncture H), 6.57 (d, $J = 8.3$ Hz, 1H, ArH), 6.65 (d, $J = 8.6$ Hz, 1H, ArH), 6.98 (dd, $J = 1.8$, 8.3 Hz, 1H, ArH), 7.07 (d, $J = 8.0$ Hz, 1H, ArH), 7.15–7.19 (m, 1H, ArH), 7.24–7.33 (m, 2H, ArH); MS: $m/z = 293$ (M^+). Anal. calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%. Found: C, 77.89; H, 6.55; N, 4.86%.

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REFERENCES

1. (a) Coumarin biological activities: For an extensive bibliography, see Wu, J.; Liao, Y.; Yang, Z. Synthesis of 4-substituted coumarins via the palladium-catalyzed cross-coupling of 4-tosylcoumarins with terminal acetylenes and organozinc reagents. *J. Org. Chem.* **2001**, *66*, 3642; (b) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963;

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(c) Murray, D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; J. Wiley & Sons: New York, 1982.

2. (a) Raski, S. R.; Williams, R. M. DNA cross-linking agents as antitumor drugs. *Chem. Rev.* **1998**, *98*, 2723; (b) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahasi, D.; Koshimizu, K.; Ohigashi, H. 1,1-Dimethylallylcoumarins potently supress both lipopolysaccharide- and interferon-γ-induced nitric oxide generation in mouse macrophage RAW 264.7 cells. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59; (c) Guilet, D.; Helesbeux, J. J.; Seraphin, D.; Sevenet, T.; Richomme, P.; Bruneton, J. Novel cytotoxic 4-phenylfuranocoumarins from *Calophyllum dispar*. *J. Nat. Prod.* **2001**, *64*, 563; (d) Kang, S. Y.; Lee, K. Y.; Sung, S. H.; Park, M. J.; Kim, Y. C. Coumarins isolated from *Angelica gigas* inhibit acetylcholinesterase: Structure–activity relationships. *J. Nat. Prod.* **2001**, *64*, 683; (e) Feuer, G. In *Progress in Medicinal Chemistry*; Ellis, G. P. and West, G. B., Eds.; North-Holland Publishing Compeny: New York, 1974; (f) Audus, L. J.; Quastel, J. H. Coumarin as a selective phytocidal agent. *Nature* **1947**, *159*, 320.
3. (a) Ukawa, K.; Ishiguro, T.; Wada, Y.; Nohara, A. Synthesis of 5-oxo-5*H*-[1]benzopyrano[4,3-*b*]pyridine derivatives. *Heterocycles* **1986**, *24*, 1931; (b) Heber, D. Reactions at heterocyclen with 2-acyl-2-propenon-teilstruktur; 3; Memo, pyrido [3,2-c] cumarine from 3-substituierten 1-Benzopyranen and Enaminen. *Arch. Pharm.* **1987**, *320*, 402; (c) Heber, D.; Berghaus, T. Synthesis of 5H [1] benzopyrano [4,3-b] pyridin-5-ones containing an azacannabinoidal structure. *J. Heterocycl. Chem.* **1994**, *31*, 1353.
4. (a) Trecourt, F.; Marsais, F.; Gungor, T.; Queguiner, G. Improved synthesis of 2,3-disubstituted pyridines by metallation of 2-chloropyridine: A convenient route to fused polyheterocycles. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409; (b) Yavari, I.; Adib, M.; Hojabri, L. Vinyltriphenylphosphonium salt mediated synthesis of 1,4-benzoxazine and coumarin derivatives. *Tetrahedron* **2002**, *58*, 6895; (c) Billeret, D.; Blondeau, D.; Silwa, H. Convenient synthesis of 5-azacoumarins. *J. Heterocycl. Chem.* **1993**, *30*, 671.
5. Galariniotou, E.; Fragos, V.; Makri, A.; Litinas, K. E.; Nicolaides, D. N. Synthesis of novel pyridocoumarins and benzo-fused 6-azacoumarins. *Tetrahedron* **2007**, *63*, 8298.
6. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: New York, 1986; (b) Renaud, P.; Sibi, M. P. Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001; Vol. 1; (c) Malacria, M. Selective preparation of complex polycyclic molecules from acyclic precursors via radical mediated- or transition metal-catalyzed cascade reactions. *Chem. Rev.* **1996**, *96*, 289; (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. Radical reactions in natural product synthesis. *Chem. Rev.* **1991**, *91*, 1237; (e) Majumdar, K. C.; Basu, P. K. Formation of five- and six-membered heterocyclic rings by radical cyclization. *Heterocycles* **2002**, *57*, 2413; (f) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. Fomation of five- and six-membered heterocyclic rings under radical cyclization conditions. *Tetrahedron* **2004**, *60*, 6239; (g) Majumdar, K. C.; Alam, S. Regioselective unusual formation of spirocyclic 4-{2′-benzo(2′,3′-dihydro)furo}-9-methyl-2,3,9-trihydrothiopyrano[2,3-*b*]indole by 4-exo-trig aryl radical cyclization and rearrangement. *Org. Lett.* **2006**, *8*, 4059; (h) Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. Fomation of five- and six-membered heterocyclic rings under radical cyclization conditions. *Tetrahedron* **2007**, *63*, 793.
7. (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. Synthesis of heterocycles by radical cyclisation. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1; (b) Bowman, W. R.;

Cloonan, M. O.; Krintel, S. L. Synthesis of heterocycles by radical cyclisation. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885; (c) Kappe, T.; Kappe, C. O. In *Progress in Heterocyclic Chemistry*; Suschitzky, H. and Gribble, G., Eds.; Elsevier Science: New York, 1996; Vol. 8; (d) Aldabbagh, F.; Bowman, W. R. Synthesis of heterocycles by radical cyclisation. *Contemp. Org. Synth.* **1997**, *4*, 261; (e) Navarro-Vazquez, A.; Garcia, A.; Dominguez, D. A study of aryl radical cyclizatior. *J. Org. Chem.* **2002**, *67*, 3213, and references therein.

8. Majumdar, K. C.; Debnath, P.; Maji, P. K. Thiophenol-catalyzed Claisen rearrangement and radical cyclization: Formation of furo- and pyrano coumarin derivatives. *Tetrahedron Lett.* **2007**, *48*, 5265.
9. Majumdar, K. C.; Chattopadhyay, S. K. Unusual reduction of a lactone carbonyl in a Bu_3SnCl and $Na(CN)BH_3$ mediated radical cyclization of 3-(*o*-bromophenoxymethyl)coumarins. *Tetrahedron Lett.* **2004**, *45*, 6871.
10. Majumdar, K. C.; Mukhopadhyay, P. P.; Biswas, A. Regioselective synthesis of quinolone-annulated sulfur heterocycles by aryl radical cyclisation. *Tetrahedron Lett.* **2005**, *46*, 6655.
11. Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. Consecutive ring closure and neophyl rearrangement of some alkenylaryl redicals. *J. Org. Chem.* **1987**, *52*, 4072.
12. Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. Regiochemistry in aryl radical cyclization onto methylenecycloalkanes. *J. Org. Chem.* **2000**, *65*, 9022.
13. (a) Spellmeyer, D. C.; Houk, K. N. Force-field model for intramolecular radical additions. *J. Org. Chem.* **1987**, *52*, 959; (b) Beckwith, A. L. J.; Schiesser, C. H. Regio- and stereo-selectivity of alkenyl radical ring closure: A theoretical study. *Tetrahedron* **1985**, *41*, 3925; (c) Giese, B. Formation of C-C bonds by addition of free radicals to alkenes. *Angew. Chem. Int. Ed.* **1983**, *22*, 753.

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