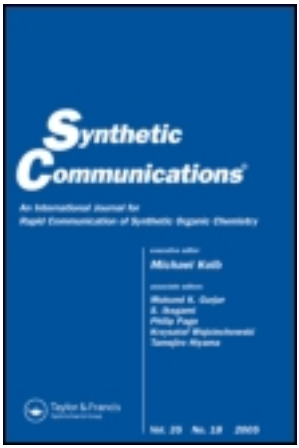

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Regioselective Synthesis of Chromeno[4,3-c] isoquinolin-11-ones by Radical Cyclization

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Regioselective Synthesis of Chromeno[4,3-*c*] isoquinolin-11-ones by Radical Cyclization

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ABSTRACT

A number of 4-tosyloxycoumarins were treated with *N*-methyl,*N*-(2-bromobenzyl)amine, and *N*-methyl,*N*-(2-bromo-5-methoxybenzyl)amine in refluxing ethanol to give different 4-[*N*-(2′-bromobenzyl),*N*-methyl] amino coumarins in 70–75% yield. These tertiary amine substrates were then refluxed in dry benzene under nitrogen with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of 0.5–0.6 mol equiv. of azobisisobutyronitrile(AIBN) for 4–5 hr to give the title compounds in 65–68% yield.

Key Words: 2-Bromobenzyl bromide; AIBN; Sodium cyanoborohydride; Tri-*n*-butyltin chloride; Radicals and radical reactions.

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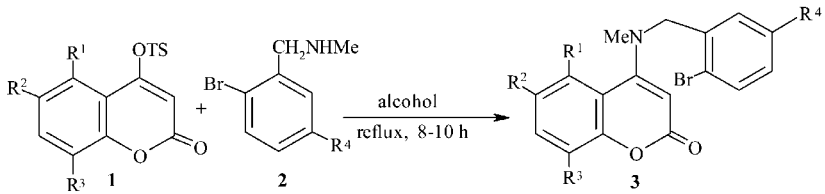
INTRODUCTION

Aryl radical cyclization has recently emerged as a valuable tool for organic synthesis.[1] In the course of our studies on the application of [3,3]-sigmatropic rearrangements[2] for the synthesis of heterocyclic compounds, we recently noted the unusual formation of [6,6]pyranopyrans in case of substrates containing 3-hydroxycoumarin[3] and 5-hydroxy uracil[4] in the second Claisen rearrangement step. We became interested to investigate whether [6,6] ring system could be achieved by tri-*n*-butyltin hydride mediated aryl radical cyclization. The generation and subsequent reactions of aryl radical formed from an aryl halides using tri-*n*-butyltin chloride, sodium cyanoborohydride, and azobisisobutyronitrile (AIBN) is now well-established[5] and synthesis of a wide range of natural products based on aryl radical cyclization have been reported.[6] However, the literature reports on heteroaryl radicals are relatively much less. Some examples by Snieckus[6a,b] and Harrowven[7] involve pyridine and pyridyl radicals. Sundberg[8a] reported one example of indonyl radical[8b,c] in the synthesis of iboga alkaloids. The cyclization of radical derived from *N*-*o*-bromobenzylanilines to phenanthridine[9] was very recently reported. Lack of significant work on the generation of radical on heteroaromatic systems has prompted us to undertake a study on the radical cyclization of 4-(2′-bromobenzyl)amino[1]benzopyran-7-ones to achieve the synthesis of [6,6]pyranoisoquinoline ring system.

RESULTS AND CONDITIONS

4-Tosyloxy[1]benzopyran-2-ones(**1a–d**) were synthesized following published procedure. The compounds **1a–d** were refluxed with *N*-(2-bromobenzyl),*N*-methylamine(**2a**), and *N*-(2-bromo-5-methoxybenzyl),*N*-methylamine(**2b**) in ethanol for 8–10 hr to give 4[*N*-(2′-bromobenzyl),*N*-methyl]amino[1]benzopyran-7-ones(**3a–h**) in 70–75% yield (Sch. 1).

Compounds **3a–h** were characterized from their elemental analyses and spectroscopic data (vide Experimental). The substrate **3a** was then refluxed in dry benzene under nitrogen atmosphere with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of 0.5–0.6 mol equiv. of AIBN for 4–5 hr to afford a cyclic product **4a**, m.p. 128°C, yield 65%. Compound **4a** was characterized from its elemental analysis and spectroscopic data. The IR spectrum of the compound **4a** showed ν_{max} at 2950, 1710, 1580, and 1390 cm^{-1}. The high field (300 MHz) ^{1}H-NMR of the product **4a** exhibited a nine-proton singlet at δ 1.38 for $-C(C\mathbf{H_3})_3$ protons, a three proton singlet at δ 3.15 for $-NC\mathbf{H}_3$ group, a two proton singlet at δ 4.29 for $-NC\mathbf{H_2}$ group and rest are aromatic protons. The ^{13}C-chemical shifts of



1. a) $R^1 = R^3 = H$, $R^2 = CMe_3$
b) $R^1 = R^3 = H$, $R^2 = CH_3$
c) $R^1 = R^2 = H$, $R^3 = CH_3$
d) $R^1 = R^2 = R^3 = H$

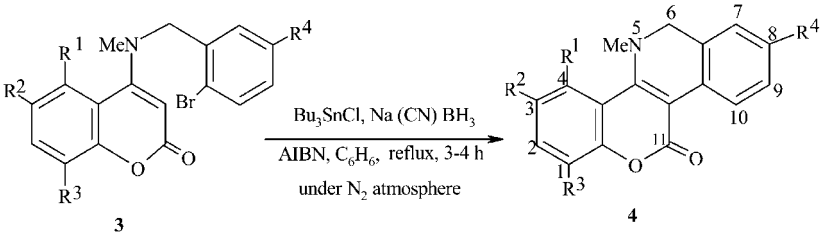
2.a) $R^4 = H$
b) $R^4 = OCH_3$

3.a) $R^1 = R^3 = R^4 = H$, $R^2 = CMe_3$
b) $R^1 = R^3 = H$, $R^2 = CMe_3$, $R^4 = OCH_3$
c) $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$
d) $R^1 = R^3 = H$, $R^2 = CH_3$, $R^4 = OCH_3$
e) $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
f) $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = OCH_3$
g) $R^1 = R^2 = R^3 = R^4 = H$
h) $R^1 = R^2 = R^3 = H$, $R^4 = OCH_3$

Scheme 1.

compound **4a** are assigned by DEPT experiment. Multiplicity are also established by DEPT experiment. DEPT shows 12 protonated carbons among which seven >CH–, four $-CH_3$, and one $-CH_2-$. ^{13}C-NMR displayed the following peaks: δ_c: 29.66 ($-\mathbf{C}(Me)_3$), 31.38 ($-C(\mathbf{C}H_3)_3$), 41.66 ($-N\mathbf{C}H_3$), 54.51 (C-6), 107.89 (C-4a), 115.93 (C-1), 116.80 (C-9), 121.38 (C-8), 125.16 (C-7), 125.27 (C-10), 127.82 (C-4), 127.90 (C-10a), 128.93 (C-6a), 129.02 (C-4), 129.26 (C-4), 146.40 (C-11a), 151.33 (C-1a), 155.25 (C-11b), 160.46 (C-11). The mass spectrum of the product **4a** showed a molecular ion peak at m/z 319(M^+). The generality of the reaction was tested by subjecting seven other substrates **3b–h** under the same reaction condition to give products **4b–h** in 65–68% yield (Sch. 2).

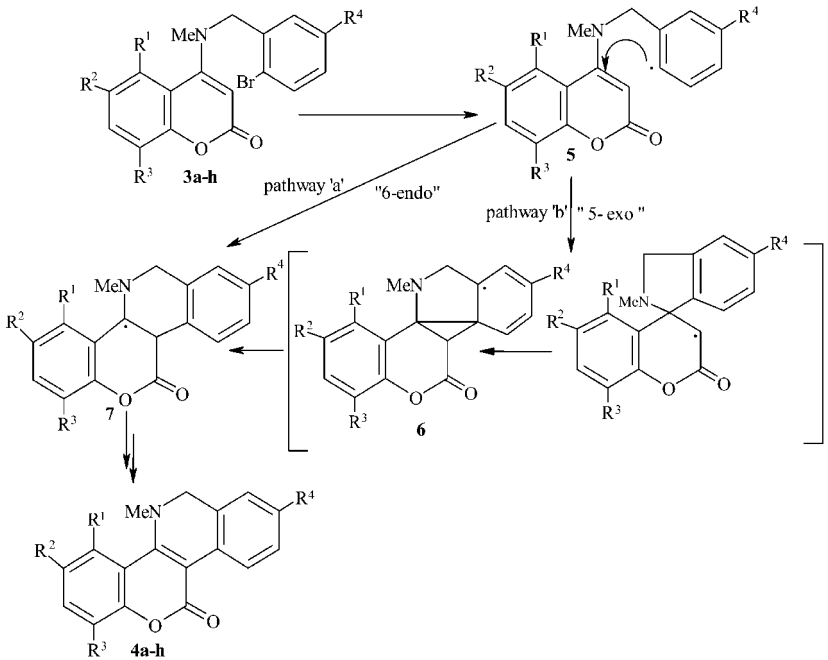
The formation of products **4a–h** from substrates **3a–h** may be easily explained by the generation of an aryl radical **5** in the tri-*n*-butyltin hydride and AIBN mediated reaction.The aryl radical **5** may undergo cyclization by



Scheme 2.

two different modes, a 6-endo trig cyclization[10] to afford the heterocyclic radical **7** ("pathway a") or a 5-exo trig cyclization to give the spiroheterocyclic radical[11] **6** (not isolated, "pathway b"). The relatively more stable heterocyclic radical **7** (benzyl radical) may form a conjugated double bond to yield the products **4a–h** by an unknown mechanism which is usual for this type of synthetic sequence i.e. an oxidation step in a Bu_3SnH mediated cyclizations.[9b,12] The possibility for the formation of heterocyclic radical **7** via spirocyclic radical **6** by a neophyl rearrangement[13] cannot be ruled out (Sch. 3).

It is known that radical cyclizations leading to six-membered rings are usually less general than cyclization leading to five-membered rings. Six membered ring forming reactions are also slower than five membered ring forming reactions and are subject to competitive formation of reduced uncyclized by-products. However, appropriately substituted five hexenyl radicals are known to undergo 6-endo cyclization to give six membered rings. It is interesting to note that regioselectively six membered heterocyclic ring is formed in all the cases studied at the present instance. The reaction is mild, and regioselective. This is an attractive and simple methodology for the synthesis of [6,6]pyrano isoquinoline ring system.



Scheme 3.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401 PC spectrophotometer (λ_{max} in nm) and IR spectra in KBr discs on a Perkin Elmer L 120-000A apparatus (ν_{max} in cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were run in $CDCl_3$ with TMS as an internal standard on a Bruker DPX-300 MHz and 75.5 MHz instrument at the Indian Institute of Chemical Biology, Kolkata (chemical shifts in δ ppm). Elemental analyses and mass spectra were recorded by RSIC (CDRI), Lucknow on a JEOL D-300 (E1) instrument. Silica gel (60–120 mesh) was obtained from Spectrochem, India. Extracts were dried over anhydrous sodium sulfate. Petroleum ether refers to the fraction boiling between 60°C and 80°C.

The starting materials **(1a–d)** for this study were prepared according to our earlier published procedure.[14] The substrates **1a** and **1c** were newly prepared from the 6-tertiarybutyl-4-hydroxycoumarin and 8-methyl-4-hydroxycoumarin for which characterization datas are given as follows.

6-Tertiarybutyl-4-tosyloxy[1]benzopyran-2-one (1a). M.p. 177°C; yield 90%; UV(EtOH) λ_{max}: 217, 274, 314 nm; IR(KBr) ν_{max}: 1740, 1620, 1250 cm^{-1}; ^{1}H-NMR (300 MHz): δ 1.34 (s, 9H), 2.47 (s, 3H), 6.31 (s, 1H), 7.24–7.91 (m, 7H); Anal. calcd for $C_{20}H_{20}O_5S$: C, 64.52; H, 5.37; found C, 64.66; H, 5.21 %.

8-Methyl-4-tosyloxy[1]benzopyran-2-one (1c). M.p. 124°C; yield 90%; UV(EtOH) λ_{max}: 217, 275, 323 nm; IR(KBr) ν_{max}: 1725, 1615, 1240 cm^{-1}; ^{1}H-NMR (300 MHz): δ 2.39 (s, 3H), 2.47 (s, 3H), 6.25 (s, 1H), 7.19–7.91 (m, 7H); Anal. calcd for $C_{17}H_{14}O_5S$: C, 61.82; H, 4.24; found C, 61.95; H, 4.38 %.

General Procedure for the Preparation of 4-[*N*-Methyl-*N*-(2-bromobenzyl)]aminobenzopyran-7-ones (3a–h)

4-Tosyloxy[1]benzopyran-2-ones (**1a–d**) (4 mmol) were refluxed with *N*-methyl,*N*-(2-bromobenzyl)amine (**2a**) (4 mmol) or *N*-methyl,*N*-(2-bromo-5-methoxybenzyl)amine (**2b**) (4 mmol) in alcohol (100 mL) for 8–10 hr. The alcohol was removed under reduced pressure. The residual mass was extracted with $CHCl_3$ (3 × 50 mL) and the extract was washed with water (2 × 50 mL) and dried (Na_2SO_4). The residual mass after removal of the solvent ($CHCl_3$) was subjected to column chromatography over silica gel using petroleum ether–ethylacetate (2 : 1) as eluant to give compounds **3a–h** which were then recrystallized from chloroform–petroleum ether.

4-[*N*-Methyl,*N*-(2-bromobenzyl)]amino-6-tertiarybutylbenzopyran-7-one (3a). Yield 75%, white solid, m.p. 138°C; [Found C, 63.16; H, 5.41; N, 3.62%. $C_{21}H_{22}NO_2Br$ requires C, 63.01; H, 5.50; N, 3.50%]; ν_{max} (KBr) 2980, 1705, 1620, 1405, 1360 cm^{-1}; λ_{max} 218, 304 nm; δ_H (300 MHz, $CDCl_3$) 1.35 (s, 9H, $-C(CH_3)_3$), 2.96 (s, 3H, $-NCH_3$), 4.66 (s, 2H, $-NCH_2$), 5.67 (s, 1H, =CH), 6.92–6.94 (m, 1H, ArH), 7.24–7.32 (m, 2H, ArH), 7.38–7.44 (m, 1H, ArH), 7.53–7.55 (m, 2H, ArH), 7.67–7.69 (m, 1H, ArH); m/z 399, 401 (M^+).

4-[*N*-Methyl-*N*-(2′-bromo-5′-methoxybenzyl)]amino-6-tertiarybutylbenzopyran-7-one (3b). Yield 73%, white solid, m.p. 122°C; [Found C, 61.33; H, 5.47; N, 3.38%. $C_{22}H_{24}NO_3Br$ requires C, 61.41; H, 5.58; N, 3.26%]; ν_{max}(KBr) 2950, 1705, 1610, 1405, 1350 cm^{-1}; λ_{max} 215, 302 nm; δ_H (300 MHz, $CDCl_3$) 1.31 (s, 9H, $-C(CH_3)_3$), 2.81 (s, 3H, $N-CH_3$), 3.80 (s, 3H, $O-CH_3$), 4.53 (s, 2H, $N-CH_2$), 5.62 (s, 1H, =CH), 6.86–6.89 (m, 1H, ArH), 7.09–7.11 (m, 1H, ArH), 7.29–7.31 (m, 1H, ArH), 7.40–7.43 (m, 1H, ArH), 7.56–7.59 (m, 1H, ArH), 7.69–7.70 (m, 1H, ArH).

4-[*N*-Methyl-*N*-(2′-bromobenzyl)]amino-6-methylbenzopyran-7-one (3c). Yield 70%, white solid, m.p. 102°C; [Found C, 60.26; H, 4.54; N,3.83%. $C_{18}H_{16}NO_2Br$ requires C, 60.35; H, 4.47; N, 3.91%]; ν_{max} (KBr) 2980, 1710, 1620, 1410, 1380 cm^{-1}; λ_{max} 218, 305 nm; δ_H (300 MHz, $CDCl_3$) 2.41 (s, 3H, $C-CH_3$), 2.99 (s, 3H, $-NCH_3$), 4.67 (s, 2H, $-NCH_2$), 5.66 (s, 1H, =CH), 7.11–7.23 (m, 2H, ArH), 7.22–7.27 (m, 1H, ArH), 7.38–7.42 (m, 2H, ArH), 7.45–7.47 (m, 1H, ArH), 7.67–7.69 (m, 1H, ArH).

4-[*N*-Methyl-*N*-(2-bromo-5-methoxybenzyl)]amino-6-methylbenzopyran-7-one (3d). Yield 73%, white solid, m.p. 118°C; [Found C, 58.69; H, 4.78; N, 3.72%. $C_{19}H_{18}NO_3Br$ requires C, 58.78; H, 4.64; N, 3.61%]; ν_{max} (KBr) 2950, 1705, 1635, 1400, 1350 cm^{-1}; λ_{max} 215, 302 nm; δ_H (300 MHz, $CDCl_3$) 2.46 (s, 3H, $C-CH_3$), 2.96 (s, 3H, $-NCH_3$), 3.79 (s, 3H, $O-CH_3$), 4.51 (s, 2H, $-NCH_2$), 5.73 (s, 1H, =CH), 6.77–6.81 (m, 2H, ArH), 6.99–7.04 (m, 1H, ArH), 7.04–7.09 (m, 1H, ArH), 7.32–7.35 (m, 1H, ArH), 7.50–7.53 (m, 1H, ArH).

4-[*N*-Methyl-*N*-(2-bromobenzyl)]amino-8-methylbenzopyran-7-one (3e). Yield 75%, white solid, m.p. 92°C; [Found C, 60.26; H, 4.54; N,3.83%. $C_{18}H_{16}NO_2Br$ requires C, 60.35; H, 4.47; N, 3.91%]; ν_{max} (KBr) 2965, 1720, 1630, 1420, 1360 cm^{-1}; λ_{max} 215, 305 nm; δ_H (300 MHz, $CDCl_3$) 2.47 (s, 3H, $C-CH_3$), 2.97 (s, 3H, $-NCH_3$), 4.61 (s, 2H, $-NCH_2$), 5.67 (s, 1H, =CH), 7.17–7.20 (t, $J = 7.6$ Hz, 1H, ArH), 7.25–7.29 (m, 1H, ArH), 7.37–7.42 (m, 2H, ArH), 7.51–7.53 (d, $J = 7.6$ Hz, 1H, ArH), 7.63–7.65 (d, $J = 7.9$ Hz, 1H, ArH), 7.73–7.74 (d, $J = 7.9$ Hz, 1H, ArH).

4-[*N*-Methyl-*N*-(2-bromo-5-methoxybenzyl)]amino-8-methylbenzopyran-7-one (3f). Yield 73%, white solid, m.p. 110°C; [Found C, 58.65; H, 4.73; N, 3.79% $C_{19}H_{18}NO_3Br$ requires C, 58.78; H, 4.64; N, 3.61%]; ν_{max}(KBr) 2960, 1700, 1620, 1430, 1350 cm^{-1}; λ_{max} 216, 305 nm;

δ_H (300 MHz, $CDCl_3$) 2.49 (s, 3H, C–C**H**$_3$), 2.91 (s, 3H, –NC**H**$_3$), 3.81 (s, 3H, O–C**H**$_3$), 4.55 (s, 2H, –NC**H**$_2$), 5.61 (s, 1H, =C**H**), 6.80–6.83 (dd, $J = 2.90$, 8.77 Hz, 1H, Ar**H**), 7.06–7.07 (d, $J = 2.90$ Hz, 1H, Ar**H**), 7.17–7.20 (t, $J = 7.6$ Hz, 1H, Ar**H**), 7.42–7.44 (d, $J = 7.1$ Hz, 1H, Ar**H**), 7.51–7.53 (d, $J = 8.77$ Hz, 1H, Ar**H**), 7.73–7.75 (d, $J = 7.1$ Hz, 1H, Ar**H**).

4-[*N*-Methyl-*N*-(2-bromobenzyl)]aminobenzopyran-7-one (3g). Yield 70%, white solid, m.p. 112°C; [Found C, 59.47; H, 4.14; N, 3.95%. $C_{17}H_{14}NO_2Br$ requires C, 59.32; H, 4.07; N,4.07%]; ν_{max} (KBr) 2943, 1697, 1603, 1438,1353 cm^{-1}; λ_{max} 216, 302 nm; δ_H (300 MHz, $CDCl_3$) 2.97 (s, 3H, –NC**H**$_3$), 4.59 (s, 2H, NC**H**$_2$), 5.72 (s, 1H, =C**H**), 7.09–7.14 (m, 1H, Ar**H**), 7.22–7.27 (m, 2H, Ar**H**), 7.34–7.53 (m, 4H, Ar**H**), 7.63–7.65 (m, 1H, Ar**H**).

4-[*N*-Methyl-*N*-(2-bromo-5-methoxybenzyl)]aminobenzopyran-7-one (3h). Yield 72%, white solid, m.p. 130°C; [Found C, 57.63; H, 4.28; N, 3.83%. $C_{18}H_{16}NO_3Br$ requires C, 57.77; H, 4.28; N, 3.74%]; ν_{max} (KBr) 2950, 1700, 1620, 1430, 1360 cm^{-1}; λ_{max} 215, 300 nm; δ_H (300 MHz, $CDCl_3$) 2.93 (s, 3H, N–C**H**$_3$), 3.80 (s, 3H, O–C**H**$_3$), 4.51 (s, 2H, –NC**H**$_2$), 5.73 (s, 1H, =C**H**), 6.80–6.85 (m, 1H, Ar**H**), 7.05–7.12 (m, 1H, Ar**H**), 7.25–7.33 (m, 2H, Ar**H**), 7.52–7.59 (m, 2H, Ar**H**), 7.74–7.76 (m, 1H, Ar**H**).

General Procedure for the Preparation of (4a–h)

A suspension of the compounds **3a–h** (0.5 mmol), *n*Bu_3SnCl (0.075 mL), $Na(CN)BH_3$ (1 mmol) and AIBN (0.5–0.6 mol equiv.) in 7 mL of dry benzene were refluxed for 4–5 hr under N_2 atmosphere. Solvent was evaporated under reduced pressure and the residue was taken in 10 mL of water and was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extract was washed with 1% aqueous NH_4OH (2 × 10 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the residual mass which was then magnetically stirred with saturated solution of potassium fluoride (5 mL) for 24 hr. It was then extracted with $CHCl_3$ (3 × 10 mL) and was washed with water for several times and dried (Na_2SO_4). The residual mass after removal of the solvent ($CHCl_3$), was subjected to column chromatography using petroleum ether–ethyl acetate (3 : 1) as eluant to give cyclized products **4a–h** which were then recrystallized from chloroform–petroleum ether.

3-Tertiarybutyl-5-methylchromeno[4,3-*c*]isoquinolin-11-one (4a). Yield 65%, solid, m.p. 128°C; [Found C, 78.81; H, 6.63; N, 4.23%. $C_{21}H_{21}NO_2$ requires C, 78.99; H, 6.58; N, 4.39%]; ν_{max} (KBr) 2950, 1710, 1580, 1390 cm^{-1}; λ_{max} 218, 263 nm; δ_H (300 MHz, $CDCl_3$) 1.38 (s, 9H, C(C**H**$_3$)$_3$), 3.15 (s, 3H, –NC**H**$_3$), 4.29 (s, 2H, –NC**H**$_2$), 7.15–7.17 (s, 1H, Ar**H**), 7.28–7.40 (m, 4H, Ar**H**), 7.53–7.57 (m, 1H, Ar**H**), 8.01–8.04 (m, 1H, Ar**H**); ^{13}C-NMR(75.5 MHz, $CDCl_3$) δ_c:

29.66 (–**C**(Me)$_3$), 31.38 (–C(CH$_3$)$_3$), 41.66 (–N**C**H$_3$), 54.51 (C-6), 107.89 (C-4a), 115.93 (C-1), 116.80 (C-9), 121.38 (C-8), 125.16 (C-7), 125.27 (C-10), 127.82 (C-4), 127.90 (C-10a), 128.93 (C-6a), 129.02 (C-4), 129.26 (C-3), 146.40 (C-11a), 151.33 (C-1a), 155.25 (C-11b), 160.46 (C-11); m/z 319 (M^+).

3-Tertiarybutyl-8-methoxy-5-methylchromeno[4,3-*c*]isoquinolin-11-one (4b). Yield 67%, solid, m.p. 127°C; [Found C, 75.45; H, 6.71; N, 4.16%. $C_{22}H_{23}NO_3$ requires C, 75.64; H, 6.59; N, 4.01%]; ν_{max} (KBr) 2930, 1720, 1570, 1390 cm^{-1}; λ_{max} 218, 263 nm; δ_H (300 MHz, $CDCl_3$) 1.35 (s, 9H, C(C**H$_3$**)$_3$), 3.09 (s, 3H, –NC**H$_3$**), 3.75 (s, 3H, –OC**H**$_3$), 4.21 (s, 2H, –NC**H**$_2$), 6.92–6.94 (m, 1H, Ar**H**), 7.04–7.05 (m, 1H, Ar**H**), 7.13–7.14 (m, 2H, Ar**H**), 7.22–7.23 (m, 1H, Ar**H**), 7.87–7.91 (m, 1H, Ar**H**); m/z 349 (M^+).

3,5-Dimethylchromeno[4,3-*c*]isoquinolin-11-one (4c). Yield 70% white solid, m.p. 165°C; [Found C, 77.82; H, 5.33; N, 5.12%. $C_{18}H_{15}NO_2$ requires C, 77.98; H, 5.41; N, 5.05%]; ν_{max} (KBr) 2905, 1705, 1570, 1380 cm^{-1}; λ_{max} 218, 290 nm; δ_H(300 MHz, $CDCl_3$) 2.44 (s, 3H, C–C**H**$_3$), 3.16 (s, 3H, –NC**H**$_3$), 4.29 (s, 2H, –NC**H$_2$**), 7.30–7.33 (m, 4H, Ar**H**), 7.37–7.59 (m, 2H, Ar**H**), 8.05–8.08 (m, 1H, Ar**H**); m/z 277 (M^+).

8-Methoxy-3,5-dimethylchromeno[4,3-*c*]isoquinolin-11-one (4d). Yield 67 %, solid, m.p. 104°C; [Found C, 74.36; H, 5.42; N, 4.63%. $C_{19}H_{17}NO_3$ requires C, 74.27; H, 5.53; N, 4.56%]; ν_{max} (KBr) 2956, 1699, 1541, 1369 cm^{-1}; λ_{max} 224, 245 nm; δ_H (300 MHz, $CDCl_3$) 2.48 (s, 3H, C–C**H**$_3$), 3.14 (s, 3H, –NC**H$_3$**), 3.84 (s, 3H, O–C**H**$_3$), 4.27 (s, 2H, –NC**H**$_2$), 6.87–6.90 (dd, $J = 2.50$, 8.40 Hz, 1H, Ar**H**), 7.09–7.12 (d, $J = 2.50$ Hz, 1H, Ar**H**), 7.19–7.22 (d, $J = 8.40$ Hz, 1H, Ar**H**), 7.28–7.38 (m, 2H, Ar**H**), 7.87–7.89 (m, 1H, Ar**H**); m/z 307 (M^+).

1,5-Dimethylchromeno[4,3-*c*]isoquinolin-11-one (4e). Yield 66%, solid, m.p. 108°C; [Found C, 77.82; H, 5.33; N, 5.12%. $C_{18}H_{15}NO_2$ requires C, 77.98; H, 5.41; N, 5.05%]; ν_{max} (KBr) 2925, 1720, 1596, 1380 cm^{-1}; λ_{max} 216, 259 nm; δ_H (300 MHz, $CDCl_3$) 2.42 (s, 3H, C–C**H**$_3$), 3.14 (s, 3H, –NC**H$_3$**), 4.21 (s, 2H, –NC**H**$_2$), 7.29–7.32 (m, 2H, Ar**H**), 7.37–7.40 (m, 2H, Ar**H**), 7.44–7.49 (m, 1H, Ar**H**), 7.57–7.59 (m, 1H, Ar**H**), 8.04–8.06 (m, 1H, Ar**H**); m/z 277 (M^+).

8-Methoxy-1,5-dimethylchromeno[4,3-*c*]isoquinolin-11-one (4f). Yield 69%, solid, m.p. 122°C; [Found C, 74.36; H, 5.42; N, 4.63%. $C_{19}H_{17}NO_3$ requires C, 74.27; H, 5.53; N, 4.56%]; ν_{max} (KBr) 2900, 1720, 1590, 1370 cm^{-1}; λ_{max} 218, 265 nm; δ_H (300 MHz, $CDCl_3$) 2.45 (s, 3H, C–C**H**$_3$), 3.01 (s, 3H, –NC**H$_3$**), 3.81 (s, 3H, –OC**H**$_3$), 4.20 (s, 2H, –NC**H**$_2$), 6.91–6.94 (m, 1H, Ar**H**), 7.20–7.22 (m, 2H, Ar**H**), 7.36–7.43 (m, 2H, Ar**H**), 7.91–7.93 (m, 1H, Ar**H**); m/z 307 (M^+).

5-Methylchromeno[4,3-*c*]isoquinolin-11-one (4g). Yield 68%, solid, m.p. 117°C; [Found C, 77.51; H, 5.01; N, 5.25%. $C_{17}H_{13}NO_2$ requires C, 77.57; H, 4.94; N, 5.32%]; ν_{max} (KBr) 2920, 1719, 1565, 1393 cm^{-1}; λ_{max} 217, 264 nm; δ_H (300 MHz, $CDCl_3$) 3.17 (s, 3H, $-NCH_3$), 4.30 (s, 2H, $-NCH_2$), 7.14–7.16 (m, 2H, ArH), 7.27–7.41 (m, 3H, ArH), 7.48–7.53 (m, 2H, ArH), 8.02–8.04 (m, 1H, ArH); m/z 263 (M^+).

8-Methoxy-5-methylchromeno[4,3-*c*]isoquinolin-11-one (4h). Yield 65%, solid, m.p. 132°C; [Found C, 73.64; H, 5.16; N, 4.94%. $C_{18}H_{15}NO_3$ requires C, 73.72; H, 5.12; N, 4.78%], ν_{max} (KBr) 2900, 1720, 1580, 1400 cm^{-1}; λ_{max} 217, 264 nm; δ_H (300 MHz, $CDCl_3$) 3.08 (s, 3H, $-NCH_3$) 3.92 (s, 3H, $-OCH_3$), 4.23 (s, 2H, $-NCH_2$), 6.90–6.94 (dd, $J = 2.50$, 8.40 Hz, 1H, ArH), 7.13–7.14 (d, $J = 2.50$ Hz, 1H, ArH), 7.20–7.23 (d, $J = 8.40$ Hz, 1H, ArH), 7.31–7.36 (m, 1H, ArH), 7.39–7.42 (m, 1H, ArH), 7.53–7.59 (m, 1H, ArH), 7.93–7.94 (m, 1H, ArH); m/z 293 (M^+).

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