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A non-catalytic approach to the synthesis of 5,6-dihydrobenzo[*h*]quinolines

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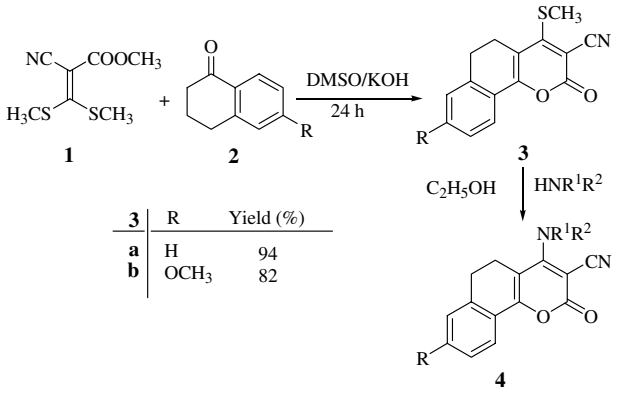
Abstract—A concise synthesis of highly functionalized 5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles is delineated through base induced ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with *S*-methylisothiourea sulfate and 1-carboxamidinepyrazole hydrochloride, separately, in DMF. Under analogous reaction conditions the ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles by formamidine acetate provided 4-*sec*-amino-benzo[*h*]-quinoline-3-carbonitriles in moderate yields, while with benzamidine hydrochloride, the reaction followed the same mechanism to yield 2-phenyl-4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles.

The presence of a benzoquinoline ring system in numerous natural products possessing a wide range of pharmacological activities[1] has attracted a great deal of attention from synthetic as well as medicinal chemists. Besides broad medicinal applications as antimalarials, antibacterial, and anti-inflammatory agents,[2] they are also useful as agrochemicals.[3] The DNA topoisomerase inhibitory activity of benzoquinolines is due to their high binding affinity with DNA and hence they can display cytotoxic and antitumor activities.[4] Numerous synthetic strategies have been developed for the construction of quinolines[5–7] and benzoquinolines[8] due to their therapeutic importance. The quest for new, simple, efficient, and cost effective syntheses is undiminished due to limitations of the earlier procedures, which include (a) harsh reaction conditions,[9] (b) multistep syntheses,[10] and (c) use of large amounts of promoters such as bases,[11] expensive and harmful metals[12] as catalysts, oxidants for aromatization[13] as well as other additives.[3]

Among various approaches for the construction of benzoquinolines the Vilsmeier approach is versatile and involves the reaction of enamines[14] or tautomeric imines[15] with Vilsmeier reagents. Katritzky reported[15] a one-pot synthesis of fused quinolines involving cyclocondensation of imines with Vilsmeier reagents.



3	R	Yield (%)
a	H	94
b	OCH_3	82

Scheme 1.

Table 1. Yields of the different 4-*sec*-amino-2-oxo-5,6-dihydrobenzo[*h*]chromenes **4**

4	NR^1R^2	R	Yields (%)
a	Piperidin-1-yl	H	96
b	4-Methylpiperidin-1-yl	H	91
c	4-Benzylpiperidin-1-yl	H	81
d	4-Benzylpiperazin-1-yl	H	79
e	4-Morpholin-1-yl	H	88
f	Tetrahydroisoquinolin-2-yl	H	82
g	Piperidin-1-yl	OCH_3	85
h	4-Methylpiperidin-1-yl	OCH_3	71

Keywords: Benzo[*h*]quinoline; 2-Oxo-5,6-dihydro-2H-benzo[*h*]chromene; Ring transformation.
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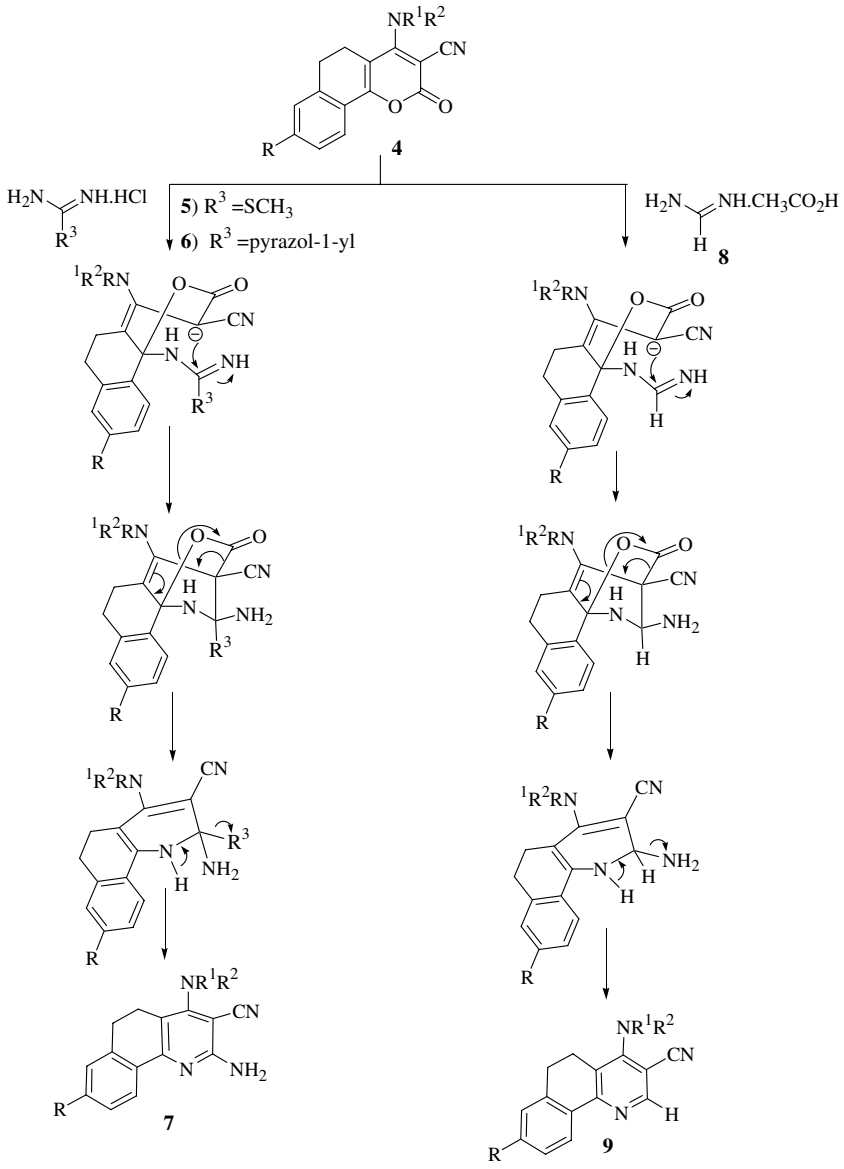


Product	NR^1R^2	R	Yields (%)
7a	Piperidin-1-yl	H	94
7b	4-Methylpiperidin-1-yl	H	82
7c	4-Benzylpiperidin-1-yl	H	96
7d	4-Benzylpiperazin-1-yl	H	91
7e	4-Morpholin-1-yl	H	81
7f	Tetrahydroisoquinolin-2-yl	H	82
7g	Piperidin-1-yl	OCH_3	71
9a	Piperidin-1-yl	H	54
9b	4-Methylpiperidin-1-yl	H	47
9c	Piperidin-1	OCH_3	57
9d	4-Methylpiperidin-1-yl	OCH_3	52

Scheme 2. Mechanism for the formation of 5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **7** and 4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **9**.

Recently, they have been prepared by reaction of an α-oxoketene *N*,*S*-acetal with Vilsmeier reagents.[3]

Herein, we report a concise approach to the synthesis of 5,6-dihydrobenzo[*h*]quinolines through base induced ring transformation of suitably functionalized 2-oxo-5,6-dihydrobenzo[*h*]chromenes **4** with *S*-methylisothiourea sulfate **5** or 1-carboxamidinepyrazole hydrochloride **6** in DMF using powdered KOH as the base. It is conspicuous that both reagents **5** and **6** gave 2-amino-4-

sec-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **7**. Further, the ring transformation of **4** by formamidine acetate **8** under analogous reaction conditions provided 4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **9** in moderate yields while with benzamidine hydrochloride **10** the products isolated were characterized as 2-phenyl-4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **11**. The precursors, 4-*sec*-amino-2-oxo-5,6-dihydrobenzo[*h*]chromenes **4** were prepared by stirring an equimolar mixture of methyl 2-cyano-3,3-dimethylthioacrylate **1**, 1-tetralone **2**, and powdered KOH in DMSO. Work-up involved pouring the reaction mixture onto crushed ice with vigorous stirring which led to 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3**, which on amination with a secondary amine in boiling ethanol afforded 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** in good yields (Scheme 1 and Table 1).

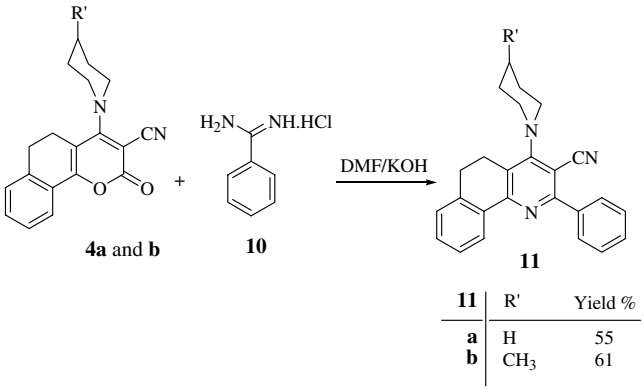
Reaction of **4** with *S*-methylisothiourea **5** in DMF using powdered KOH as base at room temperature gave 2-amino-4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **7** in excellent yields. A plausible reaction mechanism is depicted in Scheme 2. Under analogous conditions, reaction of **4** with 1-carboxamidinepyrazole hydrochloride **6** afforded the same product **7** with loss of 1*H*-pyrazole, being a good leaving group, as shown in Scheme 2.

As is evident from the topography of 4-*sec*-amino-2-oxo-5,6-dihydrobenzo[*h*]chromene-3-carbonitriles **4**, positions C-2, C-4, and C-10b are electrophilic in nature in which the latter is highly prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the chromene ring. The initial step in the formation of **7** is attack of the amino group of the amidine moiety at C-10b of the chromene with ring closure involving C-3 of the chromene and the carbon of *S*-methylisothiourea with loss of carbon dioxide and methyl mercaptan.

Attempts were also made to obtain 4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles by using different bases, solvents of high dielectric constant and harsh reaction conditions, but without success. The ring transformation of **4** by cyanamide did not proceed in the way we anticipated, affording a complex mixture.

It is interesting to note that the ring transformation of **4** by formamidine acetate **8** did not yield **7** but instead provided 4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **9** with loss of ammonia.

Also in this reaction the amino group of formamidine attacks at C-10b of **4** with ring closure involving C-3 of the chromene and the carbon of the amidine to form a dihydro intermediate followed by elimination of ammonia to produce 4-*sec*-amino-5,6-dihydrobenzo-[*h*]quinoline-3-carbonitriles **9** in good yields. Elimination of ammonia in this reaction is preferred over hydrogen due to the lower bond energy of C–N compared to C–H. A plausible mechanism is shown in Scheme 2.



11	R'	Yield %
a	H	55
b	CH_3	61

Scheme 3. Synthesis of 2-phenyl-4-*sec*-amino-5,6-dihydrobenzo[*h*]-quinoline-3-carbonitriles **11**.

The reaction of **4** with benzamidine hydrochloride **10** under analogous reaction conditions followed the same reaction course to yield 2-phenyl-4-*sec*-amino-5,6-dihydrobenzo[*h*]quinoline-3-carbonitriles **11** in moderate yields. In this reaction loss of ammonia is also preferred over benzene because of the lower bond energy of a C–N bond compared to a C–C bond (Scheme 3).

All the synthesized compounds were characterized by spectroscopic analysis.[16]

In summary, a synthetic protocol has been reported for the concise and efficient synthesis of congested 5,6-dihydrobenzo[*h*]quinolines **7**, **9**, and **11**, using 2-oxo-5,6-dihydrobenzo[*h*]chromenes **4** as precursors in moderate to excellent yields. The advantages of the procedure are the use of economical reagents without the requirement of catalyst or source of external energy.

Acknowledgements

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16. *General procedure for the synthesis of* **4**: 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles obtained in two steps:
Synthesis of 4-methylsulfanyl-2-oxo-5,6-dihydro-2H-benzo-[h]chromene-3-carbonitriles (**3**): These were obtained by stirring an equimolar mixture of methyl 2-cyano-3,3-dimethylthioacrylate **1** (0.05 mol, 10.1 g) and 1-tetralone **2** (0.05 mol, 7.3 mL) in the presence of powdered KOH (0.06 mol, 3.3 g) in DMSO (50 mL) for 5–6 h. The reaction mixture was poured onto crushed ice with vigorous stirring and the resulting precipitate was filtered, washed with water, dried, and purified by crystallization from methanol. Compound **3a**: Yellow solid, yield: 94%; mp: 204–206 °C; IR (KBr): 2922, 2370, 2207, 1699, 1612, 1570, 1508, 1446, 1372, 1279, 1257, 1221, 1155, 1132, 1092, 1037, 968, 900, 784, 742 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): δ 2.77–2.83 (m, 2H, CH_2), 2.88–2.96 (m, 2H, CH_2), 2.98 (s, 3H, SCH_3), 7.23–7.27 (m, 1H, ArH), 7.31–7.44 (m, 2H,

ArH), 7.86–7.88 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.26, 20.37, 25.56, 110.89, 113.69, 123.70, 125.19, 126.18, 126.69, 130.88, 139.01, 153.23, 157.07, 167.07; MS *m*/*z* 270 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{15}H_{11}NO_2S$ 269.05105 (M^+) found *m*/*z* 269.05153.

4-sec-Amino-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitriles (**4**): A mixture of **3** (0.01 mol, 2.7 g) and *sec*-amine (0.012 mol) in ethanol (50 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature, and the precipitate obtained was filtered, washed with ethanol, dried, and crystallized from ethanol. Compound **4a**: Yield: 96%; mp: 238–240 °C; IR (KBr): 2938, 2855, 2208, 1702, 1611, 1513, 1452, 1349, 1302, 1245, 1145, 1095, 1049, 1003, 974, 939, 896, 760, 709 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$): δ 1.76 (br s, 6H, CH_2), 2.65–2.70 (m, 2H, CH_2), 2.86–2.91 (m, 2H, CH_2), 3.51–3.53 (m, 4H, CH_2), 7.21–7.24 (m, 1H, ArH), 7.30–7.41 (m, 2H, ArH), 7.82–7.86 (m, 1H, ArH); MS *m*/*z* 307 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{19}H_{18}N_2O_2$ 306.1360 (M^+) found *m*/*z* 306.1358.

General procedure for the synthesis of 2-amino-4-sec-amino-5,6-dihydro-benzo[h]quinoline-3-carbonitriles (**7**): A mixture of 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitrile **4** (0.5 mmol), 1-carboxamidinepyrazole hydrochloride or *S*-methylisothiourea sulfate (0.6 mmol) in DMF (5.0 mL) and powdered KOH (0.7 mmol) was stirred for 2–3 h. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl (4.0 mL). The precipitate obtained was filtered, washed with water and purified by neutral alumina column chromatography using 2% ethyl acetate in hexane as eluent. Compound **7d**: White solid, yield: 91%; mp: 120–122 °C; IR (KBr): 3402, 3333, 2932, 2319, 2216, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 2.60 (t, J = 4.38 Hz, 4H, CH_2), 2.67–2.72 (m, 2H, CH_2), 2.78–2.83 (m, 2H, CH_2), 3.38 (t, J = 4.68 Hz, 4H, CH_2), 3.58 (s, 2H, CH_2), 5.05 (br s, 2H, NH_2), 7.18–7.38 (m, 8H, ArH), 8.08–8.10 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.05, 27.01, 49.52, 52.27, 61.80, 82.17, 114.90, 116.95, 124.50, 125.73, 125.93, 127.04, 127.85, 128.38, 133.15, 136.63, 137.31, 153.98, 158.60, 159.05; MS (ESI): 396 (M^++1); $C_{25}H_{25}N_5$ (395.21) calcd: C, 75.92; H, 6.37; N, 17.71, found: C, 76.07; H, 6.21; N, 17.77.

General procedure for the synthesis of 4-sec-amino-5,6-dihydro-benzo[h]quinoline-3-carbonitriles (**10**): A mixture of **4** (0.5 mmol) and formamidine acetate **9** (0.6 mmol) in DMF (5.0 mL) in the presence powdered KOH (0.8 mmol) was stirred for 2–3 h. Excess DMF was removed under reduced pressure and the reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl (4.0 mL). The precipitate obtained was filtered, washed with water and purified on a neutral alumina column using 3% ethyl acetate in hexane as eluent. Compound **10a**: White solid, yield: 54%; mp: 134–136 °C; IR (KBr): 2932, 2819, 2369, 2198, 1595, 1435, 1382, 1351, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.70–1.75 (m, 6H, CH_2), 2.86 (s, 4H, CH_2), 3.33 (t, J = 4.95 Hz, 4H, CH_2), 7.21–7.24 (m, 1H, ArH), 7.32–7.39 (m, 2H, ArH), 8.20–8.23 (m, 1H, ArH), 8.6 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.45, 22.66, 25.10, 28.40, 51.01, 124.75, 126.06, 128.69, 152.13; (ESI): 290 (M^++1); $C_{19}H_{19}N_3$ (289.16) calcd: C, 78.86; H, 6.62; N, 14.52, found: C, 78.67; H, 6.71; N, 14.55.

General procedure for the synthesis of 2-phenyl-4-sec-amino-5,6-dihydro-benzo[h]quinoline-3-carbonitriles (**11**): A mixture of 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitrile **4** (0.5 mmol), benzamidine hydrochloride **10** (0.6 mmol) and KOH (0.7 mmol) was stirred in DMF (5.0 mL) for 3–4 h. Excess DMF was removed under reduced pressure. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl (4.0 mL). The precipitate obtained was filtered, washed with water and purified by neutral alumina column chromatography using 1.5% ethyl acetate in hexane as eluent. Compound **12b**: White solid, yield: 61%; mp: 148–150 °C; IR (KBr): 2925, 2835, 2341, 2197, 1599, 1435, 1380, 1351, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.01 (d, J = 6.39 Hz, 3H, CH_3), 1.32–1.45 (m, 2H, CH_2), 1.57–1.71 (m, 1H, CH),1.74–1.78 (m, 2H, CH_2), 2.79–2.90 (m, 4H, CH_2), 2.94–2.99 (m, 2H, CH_2), 3.90 (d, J = 14.11 Hz, 2H, CH_2), 7.22–7.24 (m, 1H, ArH), 7.32–7.48 (m, 5H, ArH), 8.42 (dd, J = 1.36, 1.83 Hz, 1H, ArH), 8.55 (dd, J = 1.83, 2.01 Hz, 2H, ArH); MS (ESI): 380 (M^++1); $C_{26}H_{25}N_3$ (379.20) calcd: C, 82.29; H, 6.64; N, 11.07, found: C, 82.41; H, 6.52; N, 11.28.