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An unusual synthesis of tetrahydrobenzo[*f*]isoquinolines☆

Ramendra Pratap,[a] Resmi Raghunandan,[b] P. R. Maulik[b] and Vishnu Ji Ram[a,*]

[a]*Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India*
[b]*Molecular and Structural Biology Division, Central Drug Research Institute, Lucknow 226 001, India*

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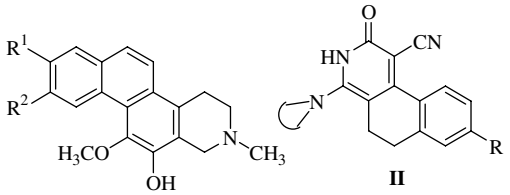
Abstract—A facile and short synthesis of 2-oxo-4-*sec*-amino-2,3,5,6-tetrahydrobenzo[*f*]isoquinoline-1-carbonitriles has been delineated through base catalyzed ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitrile by cyanoacetamide in excellent yields.

1. Introduction

Isoquinoline ring systems have been identified as major structural motifs, widely present in various natural products of chemical and therapeutic importance.[1] Annoretine[2] (**Ia**) and litabamine[3] (**Ib**) are the two phenanthrene alkaloids isolated from Annota Montana and Litsea cubeba, respectively, in Figure 1, in which the former exhibits cytotoxic activity[4] against different human cell cultures whilst the latter is active as a platelet anti-aggregant[5] and against acetyl choline esterase.[6] These alkaloids belong to the family of [2,1-*f*]isoquinolines and, surprisingly, have received little attention towards the development of their chemistry. An extensive literature survey revealed that the chemistry of highly functionalized benzo[*f*]isoquinoline ring systems is meagerly explored.



Ia) $R^1 = R^2 = H$ (Annoretine)
Ib) $R^1 = OH$; $R^2 = OCH_3$ (Litebamine)

Figure 1.

These diverse pharmacological activities and limited synthetic procedures inspired us to develop a novel and facile synthetic route, which could provide compounds with the benzo[*f*]isoquinoline motif.

A multistep synthesis of [2,1-*f*]isoquinolines has been reported[7] from [2-(2-styrylphenyl)ethyl]methylcarbamic acid ethyl ester through a Bischler–Napieralski cyclization followed by photocyclization. Pyrolysis of 4-(2-ethynylphenyl)pyridine at 810 °C and 0.5 mbar pressure resulted in benzo[*f*]isoquinolines as the major product.[8] This procedure is only of theoretical importance. Cyclization of stilbenes by tributyltin hydride and AIBN in toluene at 80 °C produced[9] benzo[*f*]isoquinoline as a major product. Junjappa and co-workers[10] have also reported the synthesis of this class of compounds from the reaction of the oxoketene dithioacetal derived from 1-tetralone and enol acetals in the presence of phosphoric acid. A base catalyzed condensation of 1,2-(dibromomethylene)naphthalene with ethyl acetamidocyanoacetate is also an alternative route[11] for the construction of tetrahydrobenzo[*f*]isoquinolines. They have also been prepared[12] by electrocyclization of 1-vinyl-3,4-dihydronaphthalene-2-carboxaldehyde and *N*,*N*-dimethylhydrazones with the loss of dimethylamine. Recently, there is a thermolytic transformation of benzocyclobutenes into quinodimethane intermediates as dienes, which undergo intramolecular Diels–Alder cyclization reaction to produce[13] benzo[*f*]isoquinolines. A new approach for

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* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405; e-mail: vjiram@yahoo.com

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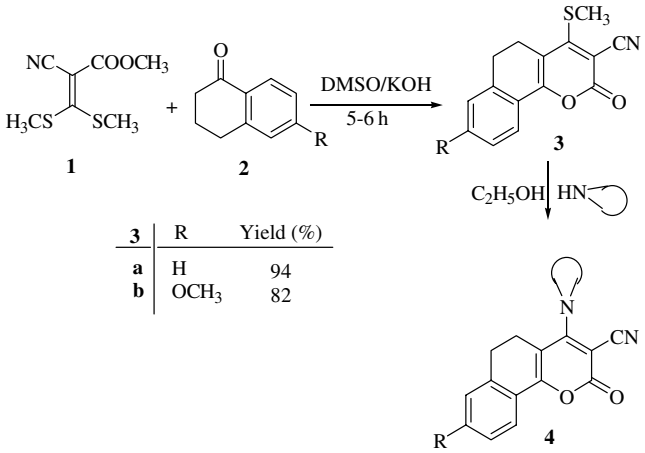
the synthesis of 5,6-dihydrobenzimidazo[1,2-*b*]benzo[*f*]-isoquinolines has been reported[14] through condensation–cyclization of the oxoketene dithioacetal derived from 1-tetralone with 2-methyl/cyanomethylbenzimidazole but this procedure has the limitation of providing only methylsulfanyl substituted fused benzo[*f*]isoquinolines.

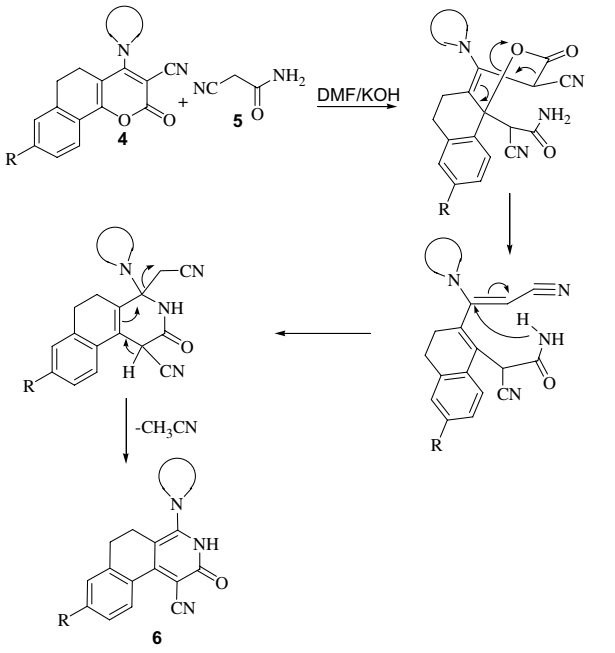
Herein, we report an efficient synthesis of 2-oxo-4-*sec*-amino-2,3,5,6-tetrahydrobenzo[*f*]-isoquinoline-1-carbonitriles **6** through base catalyzed ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles **4** by cyanoacetamide using powdered KOH as a base in DMF. However, we failed to effect the analogous ring transformation of 2-oxo-4-methylsulfanyl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3** by cyanoacetamide, possibly due to the preference of a substitution reaction at C-4 of the chromene ring rather than the attack at C-10b for the ring transformation. To avoid these side reactions, 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles were considered more appropriate precursors for the ring transformation reaction and were synthesized in two steps. The first step was the synthesis of 2-oxo-4-methylsulfanyl-5,6-dihydro-2*H*-benzo[*h*]chromenes **3** from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate **1** and 1-tetralone **2** in DMSO using powdered KOH as a base. Amination[15] of **3** was affected by refluxing with a secondary amine in ethanol (Scheme 1).

The topography of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitriles **4** revealed the presence of three electrophilic centre C-2, C-4 and C-10b in which the latter is highly prone to nucleophilic attack due to extended conjugation and the presence of an electron withdrawing CN substituent at C-3 position of the chromene ring. The nucleophile used as a carbanion was generated in situ from cyanoacetamide. Thus, a mixture of **4**, cyanoacetamide **5** and powdered KOH in DMF was stirred at room temperature for 2–3 h. During this period all the precursors were consumed with the appearance of a new spot on TLC. The reaction mixture was poured onto crushed ice with vigorous stirring and thereafter neutralized with 10% HCl. The resulting



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

Scheme 1. Two step synthesis of 4-*sec*-amino-2-oxobenzo[*h*]chromene-3-carbonitriles (**4**).



6	R	N—	Duration	Yields (%)
a	H	piperidin-1-yl	2	95
b	H	4-methyl-piperidin-1-yl	1.5	92
c	H	4-benzyl-piperidin-1-yl	2	97
d	H	tetrahydroisoquinolin-2-yl	2	95
e	H	4-benzyl-piperazine-1-yl	2.5	91
f	H	marpholin-4-yl	1.5	90
g	OCH_3	piperidin-1-yl	1.5	97
h	OCH_3	4-methyl-piperidin-1-yl	2	89

Scheme 2. A plausible mechanism for the synthesis of 2-oxo-4-*sec*-amino-2,3,5,6-tetrahydrobenzo[*f*]isoquinoline-1-carbonitriles (**6**).

precipitate was filtered, washed with water and dried. The crude products were purified by crystallization from chloroform–methanol and characterized as 2-oxo-4-*sec*-amino-2,3,5,6-tetrahydrobenzo[*f*]-isoquinoline-1-carbonitriles **6**.

A plausible reaction mechanism is shown in Scheme 2. The reaction is initiated by the attack of a carbanion generated in situ from cyanoacetamide at C-10b through the Michael addition followed by ring closure involving the amide nitrogen and C-4 of the chromene ring with the loss of carbon dioxide and acetonitrile to yield **6** (Scheme 2).

2. X-ray structural analysis

X-ray diffraction studies[16] of 2-oxo-4-piperidin-1-yl-2,3,5,6-tetrahydrobenzo[*f*]isoquinoline-1-carbonitrile **6a** revealed that the compound has a non-planarity induced chirality due to distortion in the aromatic rings. The conformation with arbitrary numbering is shown as an ORTEP diagram in Figure 2.

The presence of a cyano group in the bay region forces the molecule to buckle from the most favourable planar

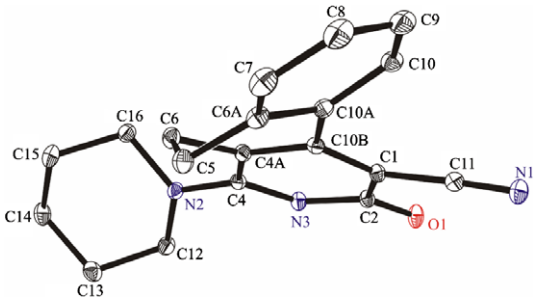


Figure 2. Displacement ellipsoid plot (30% probability) showing the molecular structure of **6**.

arrangement through the bending of the aromatic rings out of the plane. The cyano group and the rings are also in different planes and in this situation the molecule acquires a helical conformation. The average mean plane angle for the twist between the terminal rings is 33.22° and the distance between the non-bonded carbon atoms in two molecules present in an asymmetric unit is 3.060 Å and 3.093 Å.

The X-ray studies further showed that the terminal rings are nearly planar while the central ring adopts a half chair conformation with a torsion angle C1–C10B–C10A–C10, −34.28°. It has structural analogy with the X-ray structure of methyl 1-(4-chlorophenyl)-3-hydroxy-7-methoxy-9,10-dihydrophenanthrene-4-carboxylate.[17] The torsional angle C4–C4A–C4B–C5 in the phenanthrene-4-carboxylate of the previously reported compound is 28.24° and the twist between the terminal rings is 28° while the distance between the non-bonded carbon atoms is 3.025 Å. From these observations, it is inferred that the presence of an isoquinoline ring with cyano substituent increases the degree of distortion and non-planarity induced helicity in the molecule (Fig. 3).

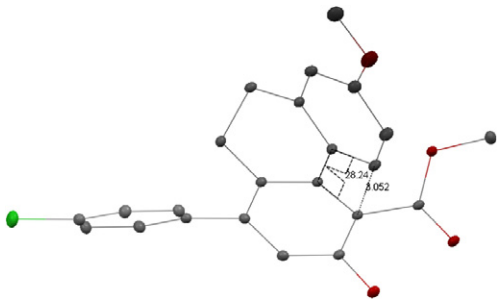


Figure 3. Methyl 1-(4-chlorophenyl)-3-hydroxy-7-methoxy-9,10-dihydrophenanthrene-4-carboxylate.

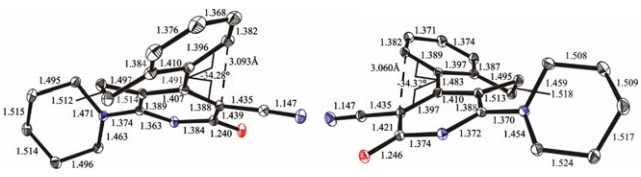


Figure 4. Diastereomers of the benzo[*f*]isoquinoline present in the asymmetric unit showing bond distances and torsion angles.

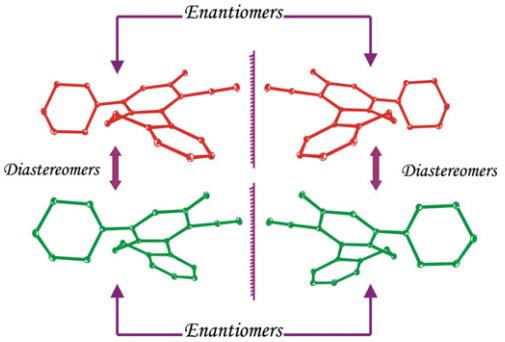


Figure 5. Structures of the benzo[*f*]isoquinoline showing the presence of both enantiomers and diastereomers.

The benzo[*f*]isoquinoline **6a** crystalized in a space group of *C*2/*c*. The crystal packing reveals the presence of two non-equivalent molecules in the asymmetric unit, Figure 4.

There are 16 molecules in the unit cell with two pairs of P and M enantiomers as shown in Figure 5. Out of the 16 molecules, 8 conformers have same bond distances as well as torsion angles, while the other 8 have different bond distances as well as torsion angles. This confirmed the presence of both enantiomeric as well as diastereomeric pairs in the unit cell.

Semi-empirical calculations were also performed for both benzo[*f*]isoquinoline and methyl 1-aryl-3-hydroxy-5,6-dihydrophenanthrene-4-carboxylate. Theoretical calculations were performed in order to study the influence of carbonyl as well as CN/$COOCH_3$ substituents. The semi-empirically optimized structures were then compared with the X-ray crystal structure. The structural parameters matched excellently with those previously obtained through X-ray structure analyses. All the molecules were fully optimized by the AM1 method. The geometry optimization showed that in the presence of a CN substituent in the bay region of benzo[*f*]isoquinoline, the torsion angle C1–C10B–C10A–C10 is 33.11° whereas the experimental value is −34.28°. When CN is replaced by $COOCH_3$ the torsion angle decreases to 28° both experimentally and theoretically. The theoretical calculation showed that the torsion angles of phenanthrene derivatives with CN and $COOCH_3$ substituents in the bay region are 29° and 28°, respectively. The theoretical calculation and X-ray structure analysis revealed that in presence of a CN substituent in the bay region increases the distortion and non-planarity of the rings.

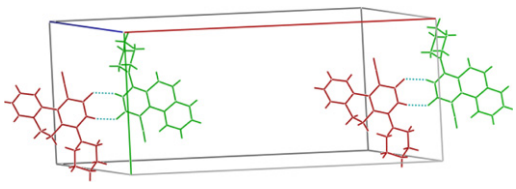


Figure 6. Crystal packing of benzo[*f*]isoquinoline showing the presence of intermolecular N–H···O interactions.

The crystal structure of benzo[*f*]isoquinoline demonstrated supramolecular assembly through intermolecular N–H···O interactions [N3–O1:2.785 Å; H3–O1:1.94 Å and N3–H3–O1:167°] with the formation of an eight-membered ring as indicated in Figure 6.

All the compounds synthesized were characterized by spectroscopic analysis.[18]

In summary, this is the first protocol for an efficient and convenient synthesis of 2-oxo-4-*sec*-amino-2,3,5,6-tetrahydrobenzo[*f*]isoquinoline-1-carbonitriles **6** through base catalyzed ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H*-benzo[*h*]chromene-3-carbonitrile by cyanoacetamide.

Acknowledgement

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16. *The crystal data of* **6a**: $C_{21.71}H_{21.71}N_{3.43}O_{1.14}$, $M = 349.00$, monoclinic, $C2/c$, $a = 28.997(3)$ Å, $b = 13.1900(1)$ Å, $c = 18.057(2)$ Å, $\beta = 116.480(1)°$, $V = 6181.7(1)$ Å^3, $Z = 16$, $D_c = 1.312$ g cm^{-3}, μ(Mo-Kα) = 0.083 mm^{-1}, $F(000) = 2592$, rectangular block, yellow, size = 0.5 × 0.16 × 0.345 mm, 6350 reflections measured ($R_{int} = 0.0187$), 5445 unique, $wR_2 = 0.1448$ for all data, conventional $R = 0.0501$ [$(\Delta/\sigma)_{max} = 000$)] on F-values of 3615 reflections with $I > 2\sigma(I)$, $S = 0.944$ for all data and 415 parameters. Unit cell determination and intensity data collection ($2\theta = 50°$) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (Deposit No: 661402) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: (internat.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk.
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18. *General procedure for the synthesis of 2-oxo-4-sec-amino-2,3,5,6-tetrahydrobenzo[f]isoquinoline-1-carbonitriles* **6**: A mixture of **4** (0.5 mmol), cyanoacetamide **5** (0.6 mmol) and powdered KOH in DMF was stirred at room temperature for 2–3 h. During this period all the starting materials were consumed with the appearance of a new spot on TLC. Thereafter the reaction mixture was poured on crushed ice with vigorous stirring followed by neutralization with 10% HCl. The resulting precipitate was filtered, washed with water, dried and purified through neutral alumina column chromatography using chloroform as an eluent. Compound (**6a**): Yield 95%; mp >250°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74–1.76 (m, 6H, CH_2), 2.48–2.52 (m, 2H, CH_2), 2.71–2.75 (m, 2H, CH_2), 3.36–3.38 (m, 4H, CH_2), 7.26–7.29 (m, 1H, ArH), 7.37–7.39 (m, 2H, ArH), 8.17–8.22 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5, 22.9, 24.6, 28.4, 49.3, 86.6, 104.5, 117.1, 125.6, 126.3, 129.3, 130.1, 138.1, 152.6, 153.1, 162.8; IR (KBr): 2214 (CN) cm^{-1}; mass (ESI-MS) m/z 306 [M$^+$+1]; HRMS (70 eV): M$^+$ Calcd for $C_{19}H_{19}N_3O$ 305.15281, found: 305.15269.