Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4379–4382

2-Oxobenzo[*h*]chromene: a novel entry for the concise and efficient synthesis of indeno[1,2-*c*]phenanthrenes☆

Ramendra Pratap and Vishnu Ji Ram*

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

Received 20 March 2007; revised 11 April 2007; accepted 18 April 2007
Available online 22 April 2007

This Letter is dedicated to Professor R. P. Rastogi, on the occasion of his 81st birthday

Abstract—An efficient and concise synthesis of 7-*sec*-amino-5,13-dihydro-6*H*-indeno[1,2-*c*]phenanthrene-8-carbonitriles is described through base catalyzed ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with 1-indanone in moderate to good yields.

Polycyclic aromatic hydrocarbons (PAHs) are environmental pollutants and can be introduced into the atmosphere through incomplete combustion of organic matters,[1] fossil fuels,[2] and also from tobacco smoke.[2] Most PAHs are potent carcinogens and are metabolized by cytochrome P-450 and epoxide hydrolase to bay region epoxides responsible for carcinogenicity.[3–5] These metabolites covalently bind to cellular DNA through a C–N linkage, resulting in mutations, leading to tumor induction.

The steric constraints in the bay region are believed to enhance the carcinogenicity.[6,7] More polar metabolites play a significant role in carcinogenesis, particularly those which have more than one bay or fjord region.

Through an extensive literature survey it is evident that the chemistry of 9*H*-indeno[2,1-*c*]phenanthrene (**I**) is little developed[8] in comparison to 13*H*-indeno[1,2-*c*]-phenanthrene (**II**). The derivatives of 9*H*-indeno[2,1-*c*]-phenanthrene (**I**) are mostly noncarcinogenic but the mutagenic properties of 13*H*-indeno[1,2-*c*]phenanthrenes has not been explored enough due to the non-availability of compounds of this ring system. Through extensive study of the carcinogenic properties of various polycyclic aromatic hydrocarbons, it was found that the planarity of the ring is one of the factors behind their mutagenic property. We decided to prepare partially reduced indeno[1,2-*c*]phenanthrenes (**III**) to distort the planarity and to reduce the binding affinity of their metabolites with cellular DNA in order to diminish the mutagenic properties (Fig. 1). Thus, we planned to prepare 7-*sec*-amino-5,13-dihydro-6*H*-indeno[1,2-*c*]phenanthrene-8-carbonitriles (**III**). Reduction of the olefinic bond between C5–C6 in **II** would result in compound **III**. Partial catalytic reduction of **II** is not easy and may lead to a complex mixture. Thus, we planned our synthetic strategy to start with a precursor having a reduced olefinic bond. We contemplated achieving our objective by using 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** as precursors for the ring transformation reactions. The precursors were prepared in two steps through base induced condensation–cyclization of 1-tetralone **2** and methyl 2-cyano-3,3-dimethylthioacrylate **1** followed by amination of

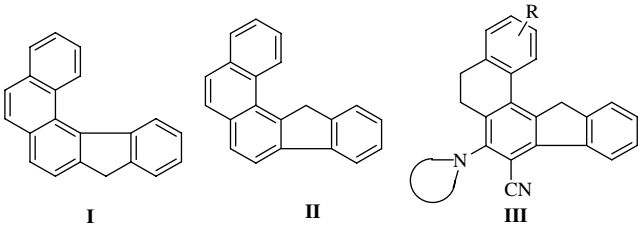
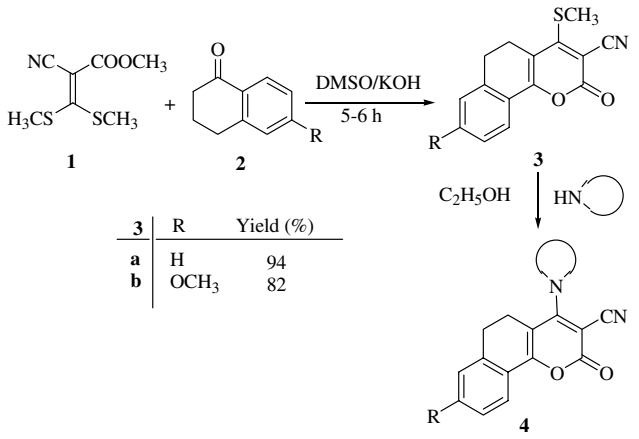


Figure 1. 9*H*-Indeno[2,1-*c*]phenanthrene (**I**), 13*H*-indeno[1,2-*c*]phenanthrene (**II**), 5,13-dihydro-6*H*-[1,2-*c*]phenanthrenes (**III**).

Keywords: Indeno[1,2-*c*]phenanthrenes; 2-Oxobenzo[*h*]chromenes; Ring transformation.
☆ CDRI Communication No. 7182.
* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405; e-mail: vjiram@yahoo.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.087

the resulting 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3** with a secondary amine in refluxing ethanol in excellent yields (Scheme 1, Table 1).[9]

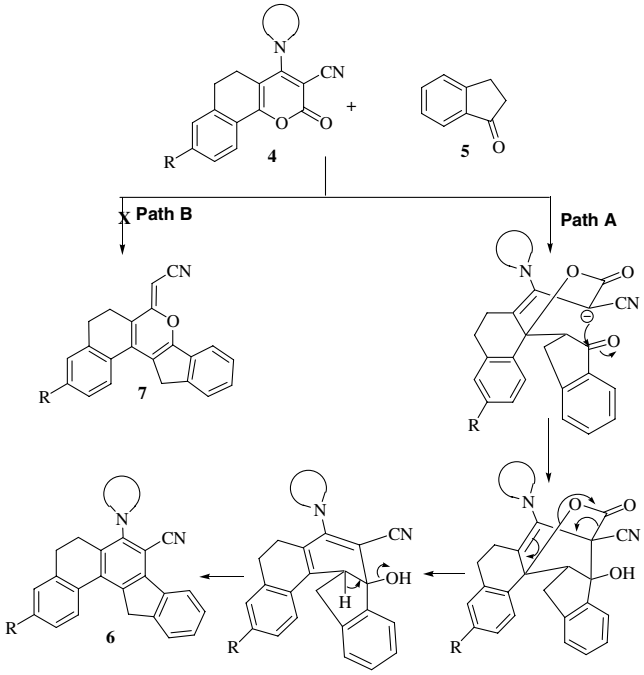


3	R	Yield (%)
a	H	94
b	OCH_3	82

Scheme 1.

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

4		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



Scheme 2. Mechanism involved in the formation of **6** and alternative product **7**.

Table 2. Yields of 7-*sec*-amino-5,13-dihydro-6*H*-indeno[1,2-*c*]phenanthrene-8-carbonitriles **6**

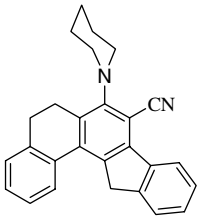
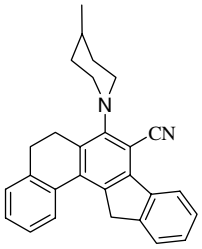
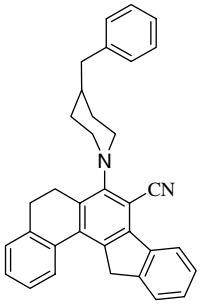
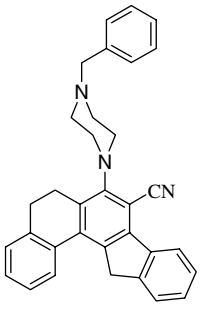
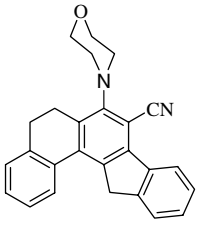
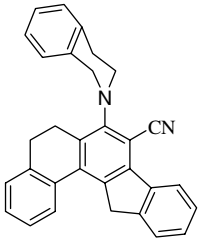
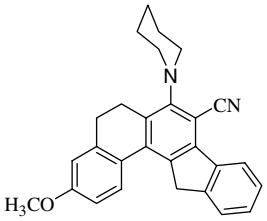
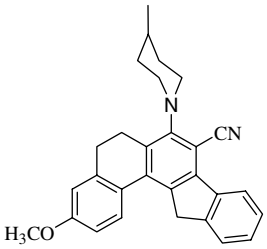
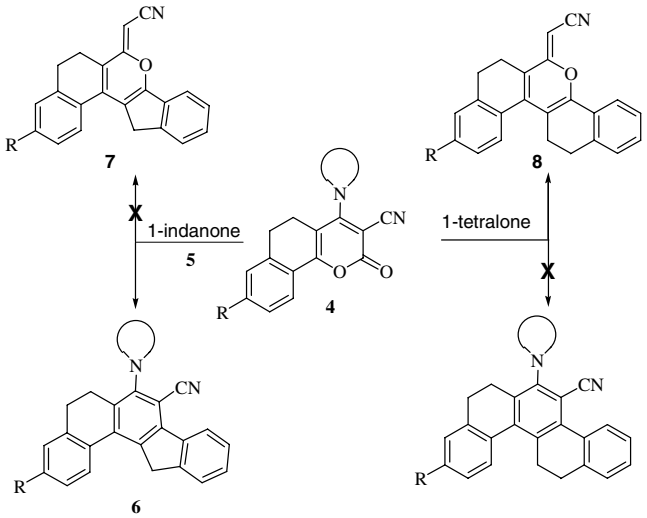
6	Product	Yield (%)
a		68
b		71
c		66
d		75
e		64
f		60

Table 2 (*continued*)

6	Product	Yield (%)
g		77
h		74

The topography of compound **4** reveals the presence of three electrophilic centers C-2, C-4, and C-10b, in which the latter is highly electrophilic due to extended conjugation and the presence of an electron withdrawing CN substituent at position 3 of the chromene ring and is consequently prone to nucleophilic attack. The nucleophile used was a carbanion generated in situ from 1-indanone.

Thus, a mixture **4**, 1-indanone **5** and NaH in DMF was stirred at room temperature for 1–2 h. During this period, all the starting material was consumed with the appearance of a new product on TLC. The reaction mixture was poured onto crushed ice with vigorous stirring and thereafter neutralized with 10% aqueous HCl. The resulting precipitate was filtered washed with water and dried. The crude product, on purification by column chromatography, gave a product which was characterized as 7-*sec*-amino-5,13-dihydro-6*H*-indeno[1,2-*c*]phenanthrene-8-carbonitrile **6**. There was also the possibility of formation of product **7** from this reaction. The initial step is possibly an attack of the carbanion generated in situ from 1-indanone at C-10b of **4** with formation of a Michael adduct and thereafter the reaction may follow either path A or B. If the reaction follows path A, the Michael adduct formed in situ undergoes cyclization involving C-3 and the carbonyl function of 1-indanone with concomitant loss of carbon dioxide and water to yield **6** as shown in Scheme 2 (Table 2). In the formation of product **7** the Michael adduct may undergo enolization followed by cyclization involving the enolic OH and C-4 of the chromeme ring with elimination of the secondary amine to yield product **7**.



Scheme 3. A comparative study of 1-indanone and 1-tetralone on the ring transformation of **4**.

It is surprising to note that under analogous conditions the reaction of **4** with 1-tetralone followed path **B** to produce only oxachrysene **8**. The only difference in the bicyclic ketones is the presence of the fusion of a benzene ring with cyclopentanone in indanone and with a cyclohexanone in 1-tetralone. The cyclopentanone ring in indanone is highly strained, which makes it very reactive. Enolization of the indanone ring in the first intermediate may increase the strain further and hence disfavors further enolization to attain a stable conformation, Scheme 3.

All the synthesized compounds were characterized by spectroscopic analysis.[10]

In summary, this protocol provides an easy and concise access to partially reduced 7-*sec*-amino-5,13-dihydro-6*H*-indeno[1,2-*c*]phenanthrene-8-carbonitriles through the ring transformation of suitably functionalized 2-oxo-5,6-dihydrobenzo[*h*]chromenes with 1-indanone in good yields.

Acknowledgments

V.J.R. and R.P. are thankful to the CSIR, New Delhi, for financial support. The authors also thank SAIF, CDRI, Lucknow for spectroscopic data.

References and notes

1. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons. Chemistry and Carcinogenicity*; Cambridge University Press: England, 1991, Chapter 3; (a) Kumar, S. *J. Org. Chem.* **1997**, *62*, 8535–8539.
2. Harvey, R. G.; Dia, W.; Zhang, J.-T.; Cortez, C. *J. Org. Chem.* **1998**, *63*, 8118–8124.
3. Lehr, F.; Kumar, S.; Levin, W.; Wood, A. W.; Chang, R. L.; Conney, A. H.; Yagi, H.; Sayer, J. M.; Jerina, D. M. In *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 63–84.
4. Thakker, D. R.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Jerina, D. M. *Bioact. Foreign Compd.* **1985**, *7*, 117.
5. Harvey, R. G.; Geaintov, N. E. *Acc. Chem. Res.* **1988**, *21*, 66.

6. Hecht, S. S.; El-Bayoumy, K.; Rovinson, A.; Amin, S. *Cancer Res.* **1994**, *54*, 21.
7. Hecht, S. S.; Amin, S.; Hule, K.; Melikian, A. A.; Harvey, R. G. *Cancer Res.* **1987**, *47*, 5310.
8. (a) Marrocchi, A.; Minuti, L.; Morozzi, G.; Pampanella, L.; Taticchi, A. *Carcinogenesis* **1996**, *17*, 2009–2012; (b) Heller, H. G.; Salisbury, K. *J. Chem. Soc. (C)* **1970**, 1997–2000; (c) Heller, H. G.; Salisbury, K. J. *Tetrahedron Lett.* **1968**, *17*, 2033–2035.
9. Pratap, R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 1715–1719.
10. *General procedure for the synthesis of 7-sec-amino-5,13-dihydro-6H-indeno[1,2-c]phenanthrene-8-carbonitriles* (**6**): A mixture of 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitrile **4** (0.5 mmol), 1-indanone (0.6 mmol) in DMF (5.0 mL) and sodium hydride (0.7 mmol) was stirred for 1–2 h. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl (4.0 mL). The resulting precipitate was filtered, washed with water, and purified by neutral alumina column chromatography using 2% ethyl acetate in hexane as eluent. Compound (**6b**). White solid; yield: 71%; mp 200–202 °C; IR (KBr): 2214 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.04 (d, $J = 5.94$ Hz, 3H, CH_3), 1.47 (br s, 1H CH), 1.62 (br s, 2H, CH_2), 1.74 (d, $J = 11.16$ Hz, 2H, CH_2), 2.72–2.77 (m, 2H, CH_2), 2.91 (br s, 2H, CH_2), 3.19 (br s, 2H, CH_2), 3.47 (br s, 2H, CH_2), 4.15 (s, 2H, CH_2), 7.29–7.47 (m, 5H, ArH), 7.56 (d, $J = 7.29$ Hz, 1H, ArH), 7.94 (d, $J = 7.53$ Hz, 1H, ArH), 8.55 (d, $J = 7.62$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.15, 30.74, 35.37, 38.01, 51.56, 122.17, 124.34, 126.48, 126.83, 127.14, 127.80, 127.85, 128.28, 134.23, 135.55, 135.91, 137.06, 139.10, 143.37, 144.03, 153.17; Mass (ESI): 391 (M^++1); $C_{28}H_{26}N_2$ (390.51) calcd: C, 86.12; H, 6.71; N, 7.17, found: C, 86.43; H, 6.67; N, 7.31. Compound (**6h**). White solid; yield: 74%; mp 196–198 °C; IR (KBr): 2210 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.03 (d, $J = 5.91$ Hz, 3H, CH_3), 1.40–1.44 (m, 1H, CH), 1.59–1.62 (m, 2H CH_2), 1.73 (d, $J = 11.07$ Hz, 2H, CH_2), 2.69–2.73 (m, 2H, CH_2), 2.90 (br s, 2H, CH_2), 3.16 (br s, 2H, CH_2), 3.49 (br s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2), 6.85–6.92 (m, 2H, ArH), 7.32–7.45 (m, 2H, ArH), 7.54 (d, $J = 7.32$ Hz, 1H, ArH), 7.86 (d, $J = 8.58$ Hz, 1H, ArH), 8.54 (d, $J = 7.68$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.0, 28.43, 29.44, 34.05, 36.97, 50.29, 54.05, 110.41, 112.09, 117.60, 120.92, 123.06, 125.66, 125.85, 126.46, 126.99, 133.51, 134.02, 135.77, 137.88, 140.64, 141.96, 142.73, 157.79, 158.16; Mass (ESI): 421 (M^++1); $C_{29}H_{28}N_2O$ (420.54) calcd: C, 82.82; H, 6.71; N, 6.66, found: C, 89.05; H, 6.81; N, 6.51.