Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3311–3314

Versatility of 2-oxobenzo[*h*]chromene for the synthesis of oxabenzo[*c*]chrysenes

Ramendra Pratap,[a] Rishi Kumar,[b] Prakas 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*

Received 18 January 2007; revised 15 February 2007; accepted 23 February 2007
Available online 28 February 2007

Abstract—An innovative and concise synthesis of (7,8-dihydro-5-oxabenzo[*c*]chrysene-6-ylidene)acetonitriles is described through base catalyzed ring transformation of 2-oxo-4-piperidin-1-yl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with 1-tetralone in very good yields.

Polycyclic aromatic hydrocarbons (PAHs) are widely distributed in the environment as pollutants, produced by the combustion of organic matter.[1,2] Some PAHs such as chrysene are potent carcinogens because of their rigid planer structure but distortion in the planarity results in reduction in tumorigenesis. The process of carcinogenesis involves the metabolic activation of PAHs by P450 and epoxide hydrolase to diol epoxides that covalently bind to the DNA bases, adenine and guanine through CN linkages to form stable adducts.[3,4]

When repair enzymes do not excise these lesions, mutation may occur upon DNA replication, resulting in initiation of carcinogenesis.

It is evident from the topography of benzo[*c*]chrysene that it possesses a 'bay' as well as 'fjord' regions which are important in activation to ultimate carcinogenic diol epoxide metabolites. The 'fjord' region diol epoxides are among the most potent mammalian cell mutagens.[5] The presence of a heteroatom in the chrysene ring greatly influences the biological responses. Benzo[*c*]oxachrysenes **II** have a structural relationship with chrysene **I** which is similar to that of benzo[*c*]phenanthridine chloride **III** and therefore, like the latter, might display antineoplastic activity.[6] Introduction of a nitrogen to the chrysene ring changes entirely its biological profile leading to anticancer activity. This observation inspired us to introduce oxygen in lieu of nitrogen to the chrysene ring to reduce the toxicity and enhance the anticancer efficacy[7] of the synthesized compounds by modifying the overall electronic distribution of the chrysene ring. Thus prototypes of **II** were to be synthesized by replacing the CH_2 group at C-5 with oxygen in order to assess the influence on the biological activity (Fig. 1).

Herein, we report a novel strategy for the synthesis of partially reduced oxabenzo[*c*]chrysenes of type **II** through base catalyzed ring transformation of suitably functionalized 2-oxobenzo[*h*]chromenes **3** with 1-tetralone **2**. However, we failed to isolate oxachrysenes, inseparable complex mixtures were obtained possibly

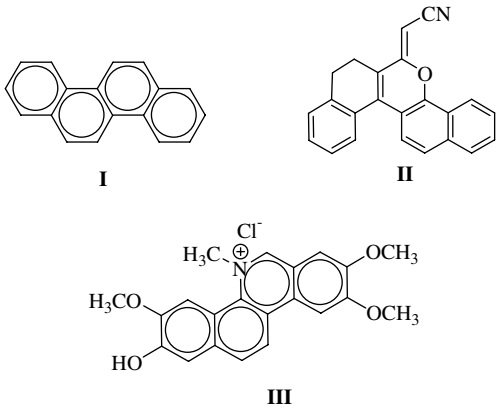


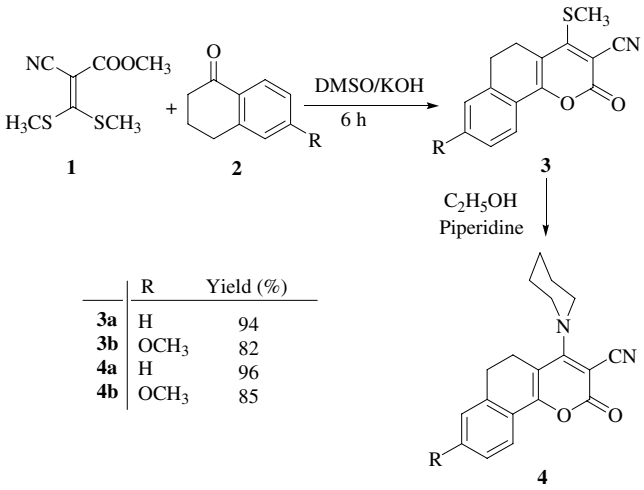
Figure 1. Chrysene **I**, benzo[*c*]oxachrysene **II** and benzo[*c*]phenanthridine chloride **III**.

Keywords: Chrysene; 2-Oxobenzo[*h*]chromenes; Ring transformation.
* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405; e-mail: vjiram@yahoo.com

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.02.106

due to side reactions at C-4. To avoid the side reactions, 2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** were used as precursors and synthesized in two steps. The first step was the synthesis of 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3** from the reaction of 1-tetralone **2** and methyl 2-cyano-3,3-dimethylthioacrylate **1** with powdered KOH in DMSO. Amination of **3** was affected by refluxing with a secondary amine in ethanol (Scheme 1). Indeed, we were interested in synthesizing partially reduced benzo[*c*]oxachrysenes to perturb their planarity to reduce or destroy their carcinogenicity. With this consideration the synthetic strategy was planned to start with dihydro precursors to give partially reduced oxachrysenes, as selective catalytic partial reduction is very difficult at the final stage. Thus, 4-piperidin-1-yl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** were contemplated as precursors.

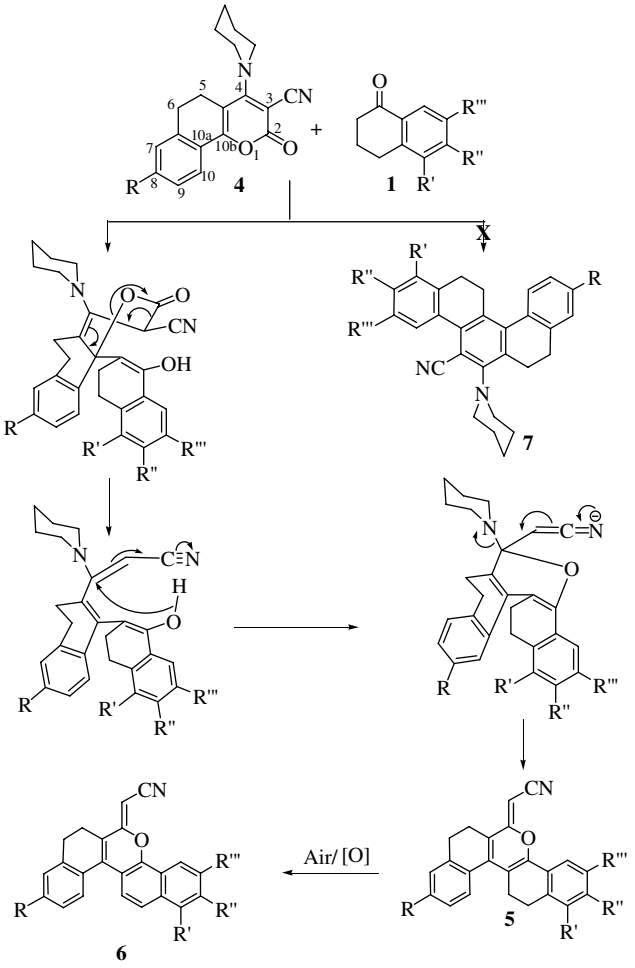
4-(Piperidin-1-yl)-2-oxo-5,6-dihydrobenzo[*h*]chromene-3-carbonitriles **4** possess three electrophilic centers C-2, C-4 and C-10b in which the latter is highly electrophilic in nature due to extended conjugation and the presence of an electron-withdrawing CN substituent at position 3 of the chromene ring and is consequently prone to nucleophilic attack. The nucleophiles used were carbanions generated in situ from 1-tetralones. Thus, a mixture of **4**, 1-tetralone **2** and powdered KOH in DMF was stirred at room temperature for 2–4 h. During this period all the starting material was 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 precipitate was filtered washed with water several times and then dried. The crude product on purification through column chromatography gave (7,8-dihydro-5-oxabenzo[*c*]chrysen-6-ylidene)acetonitriles **6**. However, it was interesting to note that the tetrahydro intermediate **5** formed in situ was easily aromatized in air without the use of any catalyst to yield **6**. The structures of the isolated compounds were confirmed on the basis of NMR and HRMS data as (10-methoxy-1,3-dimethyl-7,8-dihydro-5-oxabenzo[*c*]chrysene-6-ylidene)acetonitriles **6**.[8]



	R	Yield (%)
3a	H	94
3b	OCH_3	82
4a	H	96
4b	OCH_3	85

Scheme 1.

In fact, the reaction of **4** with **2** had been carried out to obtain 6-(piperidin-1-yl)-7,8,13,14-tetrahydrobenzo[*c*]chrysene-5-carbonitriles **7** through cyclization involving C-3 and the carbonyl group of 1-tetralone, but the isolated product turned out to be **6** as shown in Scheme 2. Possibly the extended conjugation of the carbonyl group with the fused aromatic ring modifies the overall electronic distribution and favors enolization followed by cyclization to yield **6** rather than condensed product **7**. The reaction is initiated by the attack of a carbanion generated in situ from 1-tetralone at C-10b followed by cyclization involving the enolic OH and the C-4 carbon with loss of piperidine, affording partially reduced oxabenzo[*c*]chrysenes in very good yields. The stereochemistry of isolated geometrical isomer **6f** was ascertained on



6	R	R'	R''	R'''	Yield(%)
a	H	H	H	H	78
b	H	H	OCH_3	H	81
c	H	CH_3	H	CH_3	72
d	OCH_3	H	H	H	85
e	OCH_3	H	OCH_3	H	72
f	OCH_3	CH_3	H	CH_3	77
g	H	OCH_3	H	H	67
h	OCH_3	OCH_3	H	H	65

Scheme 2. Mechanism for the formation of 5,6-dihydrobenzo-[*c*]chrysene.

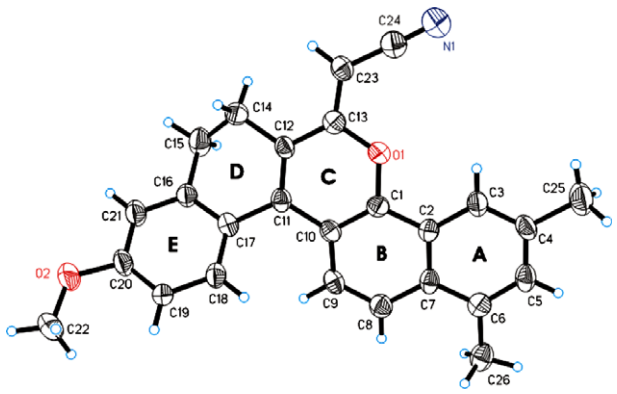


Figure 2. The ORTEP diagram of **6f** at 30% probability showing the (*Z*)-geometry.

the basis of X-ray diffraction analysis as (*Z*)-(1,3-dimethyl-10-methoxy-7,8-dihydro-5-oxabenzo[*c*]chrysene-6-ylidene)acetonitrile.[9] The ORTEP diagram of **6f** at 30% probability level, showing the molecular conformation is depicted in Figure 2. The molecule consists of five fused rings, in which rings A, B and E are planar and ring C is nearly planar. Ring D is puckered with deviations of the atoms C14 and C15 by 0.1873(99) Å and –0.5367(99) Å, respectively, from the least-squares plane through C12, C11, C17, and C16.

In summary this protocol provides an easy access to partially reduced oxabenzo[*c*]chrysenes through ring transformation of suitably functionalized 2-oxobenzo-[*h*]chromene with 1-tetralone in very good yields. The synthetic strategy provides a general route to the synthesis of novel oxabenzochrysenes.

Acknowledgments

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

References and notes

1. (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Cambridge University Press: Cambridge, UK, 1991; (b) Harvey, R. G. In *The Handbook of Environmental Chemistry*, *PAHs and Related Compounds*; Hutzinger, O. (Editor-in-Chief); Neilson, A. (Volume Ed.); Springer: Berlin, Heidelberg, 1997; Chapter 1, Vol. 3. Part I: pp 1–54.
2. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Wiley–VCH: New York, 1997.
3. (a) Denisenko, M. F.; Pao, A.; Tang, M.; Pfeifer, G. P. *Science* **1996**, *274*, 430–432; (b) Pfeifer, G. P.; Denissenko, M. F. *Environ. Mol. Carcin.* **1998**, *31*, 197–205; (c) Denissenko, M. F.; Cheng, J. X.; Tang, M.; Pfeifer, G. P. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 3893–3898; (d) Cheng, J. X.; Zheng, Y.; West, M.; Tang, M. *Cancer Res.* **1998**, *58*, 2170–2175.
4. Cheng, C. C. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Structural Aspects of Antineoplastic Agents—A New Approach; Elsevier Science, BV (Biomedical Division): Amsterdam, 1988; Vol. 25, pp 35–83.
5. Butch, E. R.; Yagi, H.; Jarina, D. M.; Amin, S.; Baird, W. M. *Polycyclic Aromat. Compd.* **1994**, *6*, 63–70.
6. Pampin, M. C.; Estevez, J. C.; Estevez, R. J.; Maestro, M.; Castedo, L. *Tetrahedron* **2003**, *59*, 7231–7243.
7. (a) Zee-Cheng, K. Y.; Cheng, C. C. *J. Heterocycl. Chem.* **1973**, *10*, 867–870; (b) Zee-Cheng, K. Y.; Cheng, C. C. *J. Med. Chem.* **1975**, *18*, 66–71; (c) Stermitz, F. R.; Gillespie, L. G.; Amoros, L. G.; Romero, R.; Stermitz, T. A.; Larson, K. A.; Earl, S.; Ogg, J. E. *J. Med. Chem.* **1975**, *18*, 708–713; (d) Huang, A.-X.; Li, Z.-H. *Acta Chim. Sin.* **1980**, *38*, 535–538; (e) Fang, S.-D.; Wang, L.-K.; Hetch, S. M. *J. Org. Chem.* **1993**, *58*, 5025–5027; (f) Taira, Z.; Matsumoto, M.; Ishida, S.; Icikawa, T.; Sakiya, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1556–1561.
8. *General procedure for the synthesis of 2-oxo-4-sec-amino-5,6-dihydro-2H-benzo[h]chromene-3-carbonitriles* (**4**): 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 (0.5 mol), and 1-tetralone (0.5 mol) in the presence of powdered KOH (0.6 mol) in DMSO (50 mL) for 5–6 h. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring and the precipitate obtained was filtered, washed with water, dried, and purified by crystallization from methanol. Compound (**3a**). Yield: 94%; mp: 204–206 °C; IR (KBr): 2922, 2370, 2207, 1699, 1612, 1570, 1508 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 for *m/z* 269.05153.
Representative procedure for the synthesis of 4-piperidin-1-yl-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile (**4a**): A mixture of **3a** (0.01 mol) and piperidine (0.012 mol) in ethanol (50 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature, and the precipitate obtained filtered, washed with ethanol, dried, and then crystallized from ethanol. Yield: 96%; mp: 238–240 °C; IR (KBr): 2938, 2855, 2208, 1702, 1611, 1513 cm^{-1}; ^1H 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 for *m/z* 306.1358.
Representative procedure for the synthesis of (7,8-dihydro-5-oxa-benzo[c]chrysen-6-ylidene)acetonitrile (**6a**). A mixture of 4-piperidin-1-yl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (**4**, 1 mmol), tetralone (**2**, 1.2 mmol), and powdered KOH in DMF was stirred for 2–4 h at room temperature. Thereafter, the reaction mixture was poured on to crushed ice with vigorous stirring and neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and dried. The crude product was purified by neutral alumina column chromatography using 5% ethyl acetate in hexane as eluent. Compound (**6a**). Yellow solid; Yield: 78%; mp: 170–172 °C; IR (KBr): 2212 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): δ 2.44 (t, J = 7.26 Hz, 2H, CH_2), 2.87 (t, J = 7.26 Hz, 2H, CH_2), 4.68 (s, 1H, CH), 7.35–7.39 (m, 3H, ArH), 7.55–7.66 (m, 3H, ArH), 7.78–7.90 (m, 3H, ArH), 8.58–8.61 (m, 1H, ArH); MS *m/z* 322 (M^++1); HRMS: (EI, 70 eV) calcd for

$C_{23}H_{15}NO$ 321.11536 (M^+) found for m/z 321.11545; Anal. Calcd for $C_{23}H_{15}NO$ (321.11) C, 85.96; H, 4.70; N, 4.36. Found C, 86.02; H, 4.74; N, 4.27.

9. *Crystal data for* **6f**: $C_{26}H_{21}NO_2$, $M = 379.44$, monoclinic, $P2_1/c$, $a = 10.871(1)$, $b = 12.823(2)$, $c = 14.329(3)$ Å, $\beta = 99.79(2)°$, $V = 1968.4(5)$ Å^3, $T = 293(2)$ K, $Z = 4$, $D_c = 1.280$ g cm^{-3}, $\mu = 0.081$ mm^{-1}, $F_{(000)} = 800$, λ (Mo K_α) = 0.71073 Å, yellow colored block, crystal size $0.275 \times 0.250 \times 0.200$ mm, 4629 reflections measured ($R_{int} = 0.0516$), 3456 unique, $R1 = 0.0713$ for 1132 $F_0 > 4\sigma(F_0)$ and 0.2411 for all 3456 data, $S = 0.928$ for all data and 265 parameters. Unit cell determinations ($2\theta = 42.17°$) and intensity data collection was 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 Instruments: Madison, Wisconsin, USA 1996) was used for data collection and data processing], SHELXTL-NT [(Bruker AXS: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC Deposit No. 636306).