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Economical synthesis of novel class of heteroatom containing partially reduced polycyclic aromatic hydrocarbons

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This Letter is dedicated to late Mr. Rajeev Pratap, for his loving support in my achievements

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ABSTRACT

An efficient and convenient synthesis of 2-oxa- and 2-thia-3,4,7,8-tetrahydro-1*H*-benzo[*c*]phenanthrenes has been described through base-induced ring transformation of 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles by 4-oxotetrahydropyran and 4-oxotetrahydrothiopyran, respectively, in excellent yields.

The toxicity and carcinogenicity studies of polycyclic aromatic hydrocarbons are major areas of investigation of environmentalists and ecologists since the 1970s. Although a rather large body of data on the genotoxicity of homonuclear polycyclic hydrocarbon is available, very little attention has been paid to the oxygen and sulfur polycyclic heteroaromatics because of their lower concentration in the environment.[1] However, recently more attention has been focused on the toxic effect of heteroaromatics on human health and the biosphere.[2] Insertion of heteroatoms in the ring of polycyclic aromatic hydrocarbons enhances the bioavailability of the molecules by increasing their polarity.[3] Thus, it was decided to construct a library of partially reduced polycyclic heteroaromatics for biological evaluation. Based on the literature data on various homonuclear polycyclic aromatic hydrocarbons, it has been concluded that the toxicity of these compounds increases with an increase in number of aromatic rings and their degree of hydrophobicity. The planarity and electrophilic character of polycyclic heteroaromatics also play a significant role on the carcinogenicity of these compounds. There is increasing evidence that the polycyclic sulfur heterocycles are present in tobacco smoke condensate[4] and derivatives,[5,6] and shale fuels[7] and that such species display high carcinogenicity[8].

The main focus of the present investigation is to understand the structural features responsible for metabolic activation and consequently their mutagenic potential. Benzo[*c*]phenanthrene (BcP) **I**, a potent carcinogen possessing a 'fjord' region, is prone to be metabolized in vivo to diol epoxides by Cytochrome P450 and epoxide hydrolase. The metabolites formed are highly tumorigenic as they covalently bind to the amino function of purine bases of DNA by C–N linkage[9,10] and thereby mutate DNA during replication. The partially reduced oxa- and thiabenzo[*c*]phenanthrenes **II** and **III** have structural analogies with BcP and they may also metabolize analogously to produce potent mutagens (Fig. 1). In this study, we planned to synthesize partially reduced polycyclic heteroaromatics

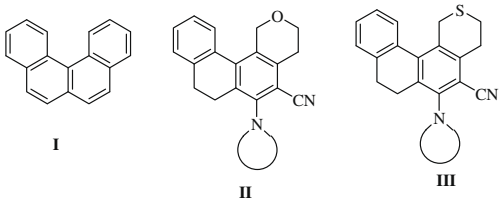

Figure 1. Various polycyclic aromatic hydrocarbons.

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to distort their coplanarity and reduce or eliminate their mutagenic potential.

Our synthetic strategy[11] for the construction of partially reduced 2-oxa- and 2-thia-3,4,7,8-tetrahydro-1*H*-benzo[*c*]phenanthrenes (**6**, **9**) was based on the suggested retrosynthetic pathways as depicted in Figure 2.

Herein, we report an innovative approach to the synthesis of partially reduced oxa- and thiabenzo[*c*]phenanthrenes through base-catalyzed ring transformation of 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles with 4-oxotetrahydropyran and 4-oxotetrahydrothiopyran, respectively.

The 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles used as precursors for the synthesis of various polycyclic heteroaromatics were prepared in two steps. The first step was the synthesis of 2-oxo-4-methylsulfanyl-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles[11,12] **3** by base-catalyzed reaction of 1-tetralone **2** and methyl 2-cyano-3,3-dimethylthioacrylate **1**. Amination[12] of **3** with secondary amines in refluxing ethanol produced 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** (Scheme 1). Use of **4** as a precursor instead of **3** was preferred to avoid the side reactions at position C-4 of the 2-oxo-4-methylsulfanyl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3** as well as to obtain clean partially reduced ring-transformed products. Our synthetic approach was to start with dihydro precursors **4** to obtain various partially reduced polycyclic heteroaromatics, as selective reduction at the final stage is very difficult and it may yield complex mixtures of reduced products.

The molecular makeup of 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles **4**, reveals the presence of the three electrophilic sites C-2, C-4, and C-10b in which the latter is the most electrophilic in nature due to extensive conjugation and the presence of an electron-withdrawing CN substituent at position 3 of the chromene ring. It is, consequently, prone to nucleophilic attack. In situ generated carbanions, obtained from 4-oxotetrahydropyran and 4-oxotetrahydrothiopyran in the presence of powdered KOH in DMF, were the nucleophiles of choice. Thus, a mixture of **4**, 4-oxotetrahydropyran **5,** and powdered KOH in DMF was stirred at room temperature for 1.5–2 h. During this period all the starting material was consumed with the appearance of a new spot on TLC. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring and was neutralized with 10% aqueous HCl. The resulting precipitate was filtered, washed with water, dried and purified by elution through a neutral alumina column, and characterized. Structural elucidation confirmed it to be the 2-oxa-6-*sec*.amino-3,4,7,8-tetrahydro-1*H*-benzo[*c*]phenanthrene-5-carbonitrile **6** product, which was obtained in excellent yields (Scheme 2).

Theoretically, the possibility for the formation of (3,4,7,8-tetrahydro-2,5-dioxa-1*H*-benzo[*c*]phenanthren-6-ylidene)acetonitrile **7** was envisaged, but practically only product **6** was isolated and

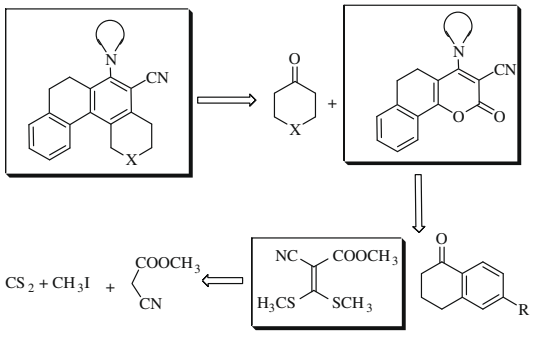
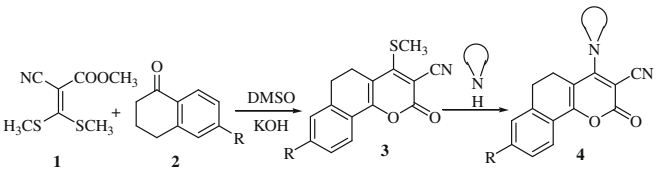
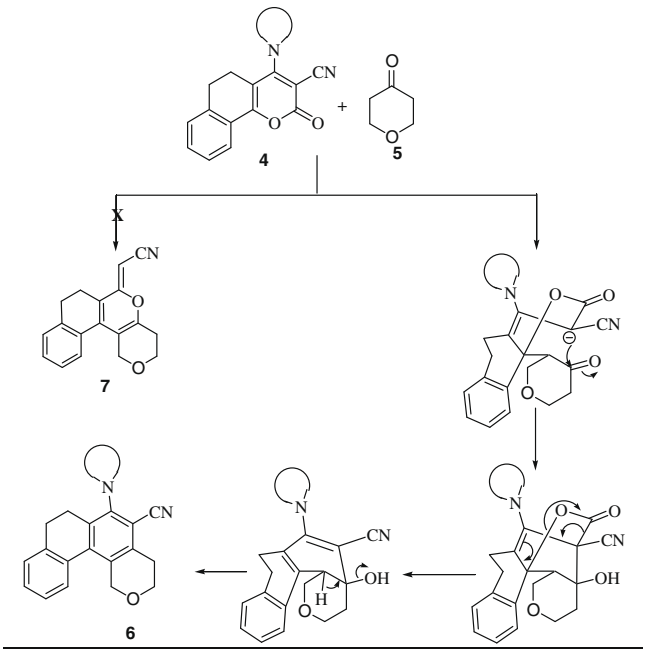


Figure 2. Retrosynthetic route to polycyclic aromatic hydrocarbons.



Scheme 1. Two-step synthesis of oxabenzo[*h*]chromene **4**.



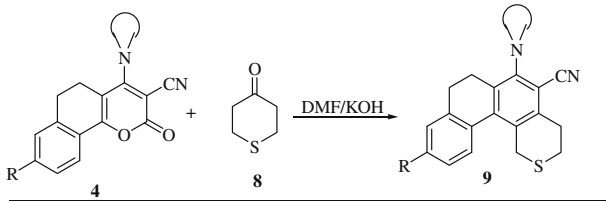
6	N—	R	Yields (%)
a	piperidin-1-yl	H	89
b	4-methylpiperidin-1-yl	H	91
c	4-benzylpiperidin-1-yl	H	94
d	4-benzylpiperazin-1-yl	H	85
e	4-morpholin-1-yl	H	95
f	tetrahydroisoquinolin-2-yl	H	90
g	piperidin-1-yl	OCH_3	87
h	4-methylpiperidin-1-yl	OCH_3	79

Scheme 2. Proposed mechanism involved in the formation of 2-oxa-3, 4, 7, 8-tetrahydrobenzo[*c*]phenanthrenes **6**.

characterized. The instability of the enol intermediate, involved in the formation of **7** is the major reason for the facile formation of **6**. The reaction is initiated by attack of a carbanion at C-10b with Michael addition followed by ring closure involving C-3 of the chromene ring and elimination of carbon dioxide and water as shown in Scheme 2.

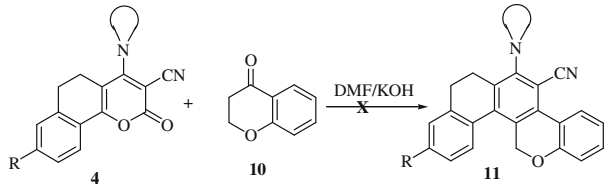
Under analogous reaction conditions the reaction of **4** with 4-oxotetrahydrothiopyran **8** progressed smoothly with the formation of 2-thia-6-*sec*.amino-3,4,7.8-tetrahydro-1*H*-benzo[*c*]phenanthrene-5-carbonitriles in very good yields (Scheme 3). This reaction also follows the same course as shown in Scheme 2. Comparative study of these ring transformation reactions showed that the electronegativity of the different heteroatoms employed does not affect the yields and mode of reaction.

We also attempted to synthesize 6-*sec*.amino-8,13-dihydro-7*H*-14-oxa-benzo[*c*]chrysene-5-carbonitrile **11**, using 4-chromanone **10** as a nucleophile precursor for the ring transformation under analogous experimental conditions, but no reaction was detected



9	N—	R	Yields (%)
a	piperidin-1-yl	H	89
b	4-methylpiperidin-1-yl	H	89
c	4-benzylpiperidin-1-yl	H	84
d	4-benzylpiperazin-1-yl	H	83
e	piperidin-1-yl	OCH_3	77

Scheme 3. Synthesis of 2-thia-3,4,7,8-tetrahydrobenzo[*c*]phenanthrenes **9**.



Scheme 4. Attempt to synthesize 6-*sec*.amino-8,13-dihydro-7*H*-14-oxa-benzo[*c*] chrysene-5-carbonitrile **11**.

(Scheme 4). From this reaction, it was concluded that the presence of fused aryl systems decreased the reactivity of pyran-4-one probably due to conjugation of the carbonyl function with the aromatic ring.

All the compounds synthesized were characterized by spectroscopic techniques and data for a representative compound are presented in the reference section.[13]

In summary, the synthesis of partially reduced oxo- and thia-analogs of benzo[*c*]phenanthrenes (**6**, **9**) is reported for the first time through base-catalyzed ring transformation of suitably functionalized 2-oxobenzo[*h*]chromene by 4-oxotetrahydropyran and 4-oxotetrahydrothiopyran, respectively, through C–C insertion, in excellent yields. The protocol provides an efficient and concise synthesis of polycyclic partially reduced heteroaromatics not easily obtainable by other routes. The process is very simple and viable using very economical reagents.

Acknowledgments

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13. *General procedure for the synthesis of 2-oxa/thia-6-sec.amino-3,4,7,8-tetrahydro-1H-benzo[c]phenanthrene-5-carbonitriles* **6/9**: A mixture of **4** (0.5 mmol), 4-oxotetrahydropyran **5** or 4-oxotetrahydrothiopyran **8** (0.6 mmol), and powdered KOH (34.2 mg, 0.6 mmol) in DMF (4 mL) was stirred at room temperature for 1.5–3 h. During this period all the starting material was consumed with the appearance of a new spot on TLC. Thereafter, the reaction mixture was poured onto crushed ice under vigorous stirring followed by neutralization with 10% HCl (5.0 mL). The resulting precipitate was filtered, washed with water, dried, and purified by elution over neutral alumina using 2% ethyl acetate in hexane as eluents. (**6a**). Yield 89%; mp 188–190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59–1.74 (m, 6H, CH_2), 2.65–2.69 (m, 2H, CH_2), 2.75–2.80 (m, 2H, CH_2), 3.09 (t, J = 6.18 Hz, 2H, CH_2), 3.23 (br s, 4H, CH_2) 4.08 (t, J = 6.27 Hz, 2H, CH_2), 4.89 (s, 2H, CH_2), 7.22–7.33 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.9, 23.4, 25.5, 26.5, 28.1, 51.1, 63.9, 67.5, 106.2, 117.2, 124.7, 126.3, 126.6, 127.0, 27.3, 131.7, 134.1, 135.4, 137.4, 138.9, 151.1; IR (KBr): 2209 (CN) cm^{-1}; mass (ESI-MS) *m/z* 345 [M$^+$+1]; HRMS (70 eV): M$^+$ Calcd for $C_{23}H_{24}N_2O$: 344.18886. Found: 344.18902; Anal Calcd for $C_{23}H_{24}N_2O$: 344.18 C, 80.20; H, 7.02; N, 8.13. Found: C, 80.27; H, 7.11; N, 8.09. (**9d**). Yield 83%; mp 154–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.62 (br s, 4H, CH_2), 2.70–2.75 (m, 4H, CH_2), 2.96 (t, J = 6.48 Hz, 2H, CH_2), 3.24 (t, J = 6.48 Hz, 2H, CH_2), 3.30 (br s, 4H, CH_2), 3.58 (s, 2H, CH_2), 393 (s, 2H, CH_2), 7.22–7.41 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.7, 26.1, 27.4, 28.0, 49.7, 52.7, 62.0, 106.7, 116.6, 124.9, 125.8, 126.3, 126.9, 127.5, 127.9, 129.7, 131.8, 134.5, 137.0, 137.7, 138.9, 140.4, 149.2; IR (KBr): 2211 (CN) cm^{-1}; mass (ESI-MS) *m/z* 452 [M$^+$+1]; HRMS (70 eV): M$^+$ Calcd for $C_{29}H_{29}N_3S$ 451.20822; found 451.20811; Anal Calcd for $C_{29}H_{29}N_3S$: 451.20 C, 77.12; H, 6.47; N, 9.30. Found: C, 77.25; H, 6.47; N, 9.33.