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An efficient and novel approach to the synthesis of tetrahydrophenanthro[4,3-*b*]thiophenes☆

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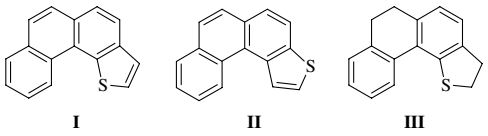
Abstract—An elegant approach to the synthesis of 2,3,6,7-tetrahydrophenanthro[4,3-*b*]thiophenes has been described through base catalyzed ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with tetrahydrothiophen-3-one in very good yields.

Several sulfur analogs of polynuclear aromatic hydrocarbons have been identified in cigarette smoke condensate,[1] coal derived products,[2,3] shale fuels,[3,4] lubricant oils, and exhaust from diesel engines.[5] Like polycyclic aromatic hydrocarbons (PAHs) their respective thia analogs are present in the environment as contaminants and are known for their mutagenic as well as carcinogenic properties.[6–8]

Among these, phenanthro[4,3,-*b*]thiophenes **I** and phenanthro[3,4-*b*]thiophenes **II** are prominent and differ in their mutagenic potency. It is quite surprising that phenanthro[3,4-*b*]thiophene is as mutagenic as benzo[*a*]-pyrene while its isostere **II** is nonmutagenic though it forms a fjord region diol epoxide responsible for tumorigenic property. Based on a comprehensive study on mutagenic properties of numerous polycyclic aromatic hydrocarbons it has been demonstrated that the planarity of the aromatic rings contributes significantly to their mutagenicity and thus, any distortion in the planar conformation either by partial reduction or introduction of a substituent may reduce or destroy its mutagenicity.[8b] Thus, distortion in the planarity of **I** was induced through partial reduction resulting in 2,3,6,7-tetrahydrophenanthro[4,3-*b*]thiophene **III**, which may have reduced cellular DNA binding affinity (Fig. 1).



I II III

Figure 1. Phenanthro[4,3-*b*]thiophene **I**, phenanthro[3,4-*b*]thiophene **II** and tetrahydrophenanthro[4,3-*b*]thiophene **III**.

It is evident from the literature that there are very limited approaches for the construction of phenanthro[4,3-*b*]thiophenes. Earlier, compounds possessing this ring system had been prepared by the reaction of 2-formylnaphthalene with diethyl 3-thienylphosphonate followed by photocyclization in 17% yield[1b] or by Suzuki cross coupling reaction of formylthiophene boronic acid with a naphthyl halide or triflate.[1a]

In search of an efficient and novel route for the construction of 2,3,6,7-tetrahydrophenanthro[4,3-*b*]thiophenes, 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** have been identified as appropriate precursors for efficient and cost effective synthesis. The synthetic potential of **4** is enormous for generating molecular diversity and they have been prepared by base induced condensation–cyclization of 1-tetralone **2** and methyl 2-cyano-3,3-dimethylthioacrylate[9] **1**, which led to 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles **3**.[10] Amination of **3** was affected by refluxing with a *sec*-amine in ethanol (Scheme 1 and Table 1).[10] Indeed, we were interested in synthesizing partially reduced phenanthro[4,3-*b*]-thiophenes to perturb the planarity of the molecule to reduce or destroy its mutagenic and carcinogenic

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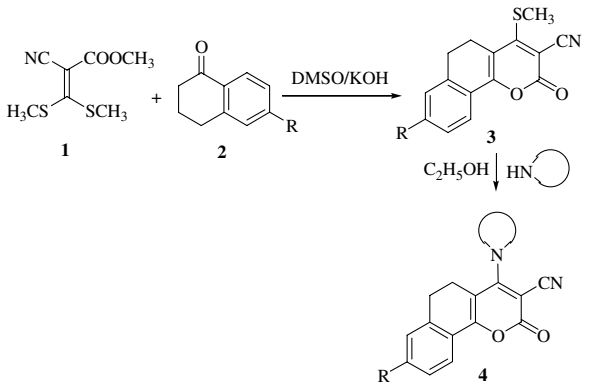


Scheme 1. Synthesis of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles.

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

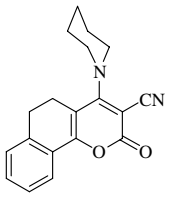
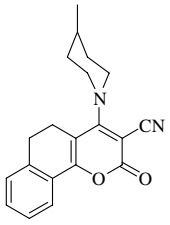
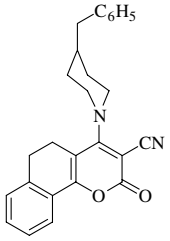
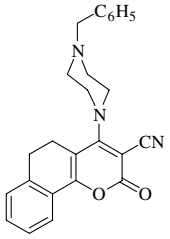
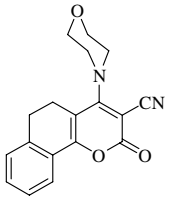
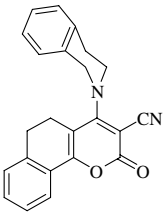
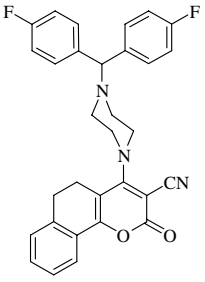
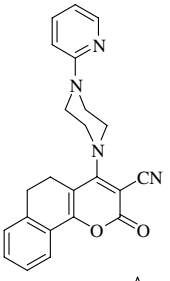
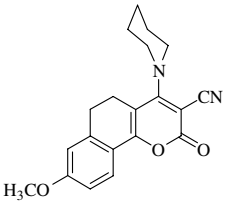
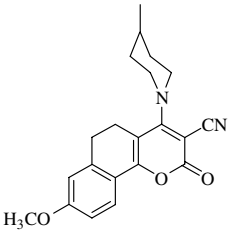
4	Product	Yield (%)
a		96[10]
b		91[10]
c		81[10]
d		79[10]
e		88

Table 1 (*continued*)

4	Product	Yield (%)
f		82
g		79
h		69
i		85
j		71[10]

properties. With this objective in mind, the synthetic strategy was planned to start with dihydro precursors to obtain partially reduced phenanthro[4,3-*b*]thiophenes, as selective partial catalytic reduction is very difficult at the final stage. Thus, 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles were used as precursors for the construction of phenanthro[4,3-*b*]thiophenes **6** (Table 2).

4-*sec*-Amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles possess 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

Table 2. Yields of the different 2,3,6,7-tetrahydro-5-*sec*-amino-phenanthro[4,3-*b*]thiophenes **6**

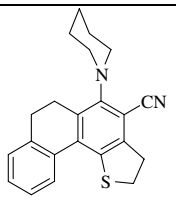
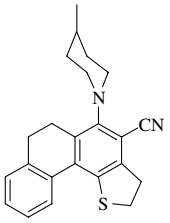
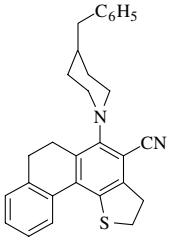
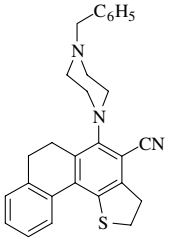
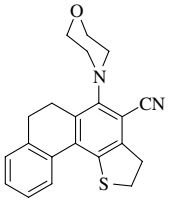
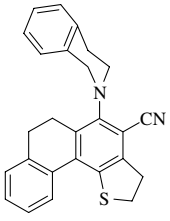
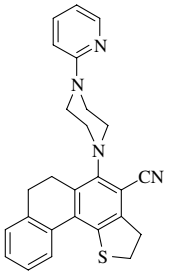
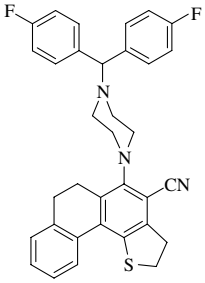
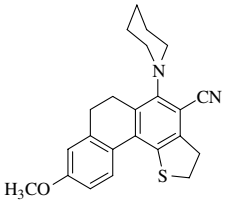
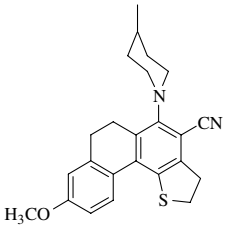
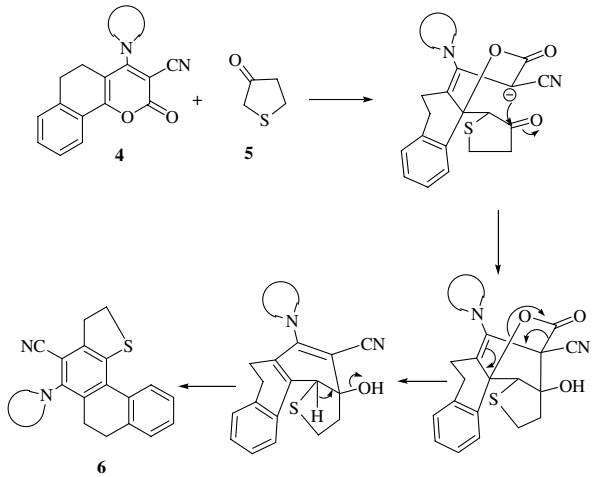
6	Product	Yield (%)
a		82
b		85
c		87
d		77
e		81
f		76
g		71

Table 2 (*continued*)

6	Product	Yield (%)
h		66
i		80
j		76

attack. The nucleophile used was a carbanion generated in situ from tetrahydrothiophen-3-one. Thus, a mixture **4**, tetrahydrothiophen-3-one and powdered KOH 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 through column chromatography, gave 2,3,6,7-tetrahydro-5-*sec*-amino-phenanthro[4,3-*b*]thiophenes **6** in very good yields (Scheme 2, Table 2).



Scheme 2. Mechanism involved in the formation of 2,3,6,7-tetrahydro-5-*sec*-amino-phenanthro[4,3-*b*]thiophenes **6**.

The reaction is possibly initiated by the attack of a carbanion, generated in situ from tetrahydrothiophen-3-one **5** with ring closure followed by decarboxylation and dehydration to yield **6** (Scheme 2).

All the compounds synthesized were characterized by spectroscopic techniques.[11]

To the best of our knowledge, this is the first report on the synthesis of functionalized 2,3,6,7-tetrahydrophenanthro[4,3-*b*]thiophenes using 2-oxo-5,6-dihydrobenzo[*h*]-chromenes as precursors for the ring transformation reaction by tetrahydrothiophen-3-one. The methodology is very simple and efficient and requires no catalyst. It provides a new avenue for the synthesis of polycyclic sulfur-containing heteroaromatics.

Acknowledgments

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11. *General procedure for the synthesis of 2,3,6,7-tetrahydro-5-sec-aminophenanthro[4,3-b]thiophenes* (**6**): A mixture of **4** (0.5 mmol) and tetrahydrothiophen-3-one **5** (0.6 mmol) in DMF (8.0 mL) in the presence of 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 then neutralized with 10% HCl (4.0 mL). The precipitate obtained was filtered, washed with water, and purified on a neutral alumina column using 40% chloroform in hexane as eluent. Compound **6b**: White solid; yield: 85%; mp 122–124 °C; IR (KBr): 2222 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.01 (d, $J = 6.3$ Hz, 3H, CH_3), 1.36–1.41 (m, 2H, CH_2), 1.54–1.56 (m, 1H, CH), 1.70 (d, $J = 11.97$ Hz, 2H, CH_2), 2.70–2.74 (m, 2H, CH_2), 2.81 (d, $J = 6.45$ Hz, 2H, CH_2), 3.06 (br s, 2H, CH_2), 3.31–3.36 (m, 4H, CH_2), 3.50 (t, $J = 7.71$ Hz, 2H, CH_2), 7.25–7.35 (m, 3H, ArH), 7.88 (d, $J = 7.29$ Hz, 1H, ArH); mass (ESI): 361 (M^++1); $C_{23}H_{24}N_2S$ (360.51) Calcd: C, 76.63; H, 6.71; N, 7.77. Found: C, 76.67; H, 6.71; N, 7.55. Compound **6i**: White solid; yield: 80%; mp 148–150 °C; IR (KBr): 2219 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.70 (br s, 6H CH_2), 2.67–2.73 (m, 2H, CH_2), 2.79–2.84 (m, 2H, CH_2), 3.10–3.18 (m, 4H, CH_2), 3.32 (t, $J = 7.5$ Hz, 2H, CH_2), 3.49 (t, $J = 7.60$ Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.80–6.88 (m, 2H, ArH), 7.83 (d, $J = 8.58$ Hz, 1H, ArH); mass (ESI): 377 (M^++1); $C_{23}H_{24}N_2OS$ (376.51) Calcd: C, 73.37; H, 6.42; N, 7.44. Found: C, 73.57; H, 6.47; N, 7.31.