Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4715–4718

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

Ramendra Pratap and Vishnu Ji Ram*

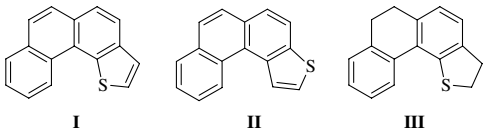
Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, India

Received 15 March 2007; revised 23 April 2007; accepted 2 May 2007
Available online 10 May 2007

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

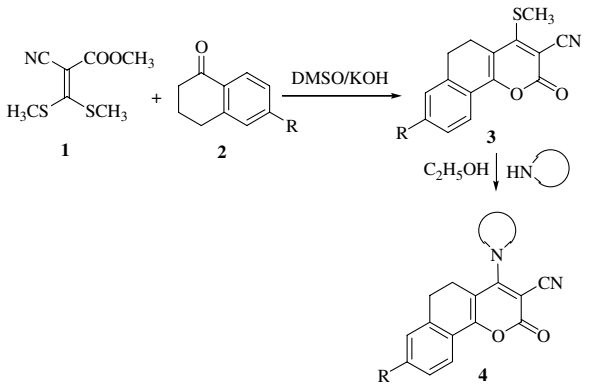
Figure 1. Phenanthro[4,3-*b*]thiophene **I**, phenanthro[3,4-*b*]thiophene **II** and tetrahydrophenanthro[4,3-*b*]thiophene **III**.

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

Keywords: Tetrahydrophenanthro[4,3-*b*]thiophenes; 2-Oxobenzo[*h*]-chromenes; Ring transformation.
☆CDRI Communication No. 7218.
* 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.2007.05.024



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**

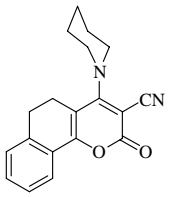
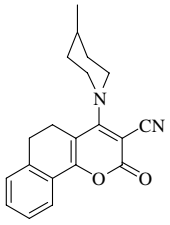
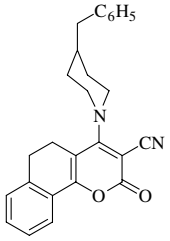
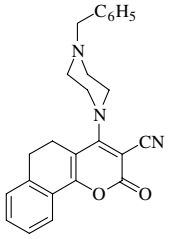
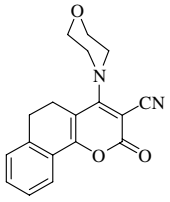
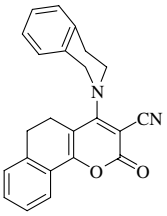
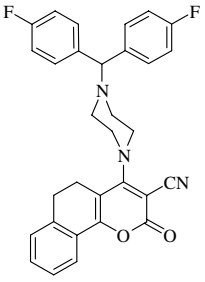
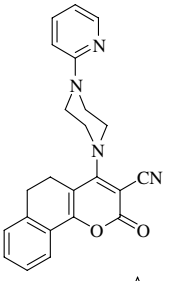
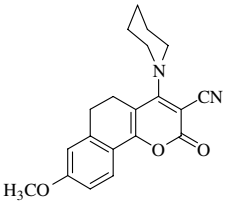
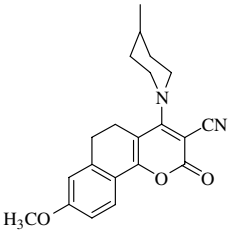
4	Product	Yield (%)
a		96[10]
b		91[10]
c		81[10]
d		79[10]
e		88

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