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An efficient and versatile route to the synthesis of 9,10-dihydro-3-formylphenanthrenes☆

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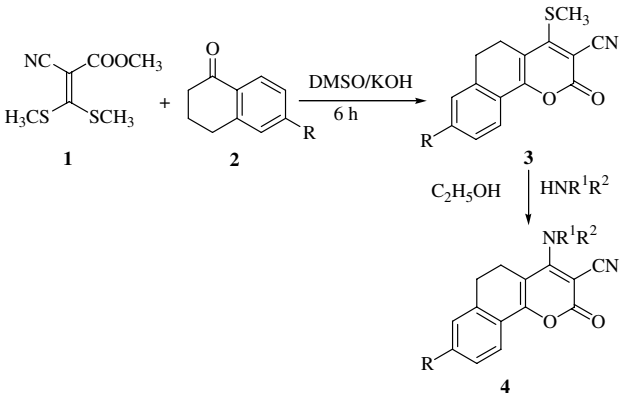
Abstract—An innovative and efficient route to the synthesis of 9,10-dihydro-3-formylphenanthrenes **7** has been delineated through the ring transformation of 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** with methyl glyoxaldimethylacetal **5** to masked 3-dimethoxymethyl-1-*sec*-amino-9,10-dihydrophenanthrene-3-carbonitriles **6** followed by deacetalation with Amberlyst 15 in excellent yields.

The presence of a formyl group in a molecule makes it highly versatile for generating molecular diversity through C–C and C–heteroatom bond formation.[1] Formyl derivatives are invariably used as ligands for the synthesis of metal chelates. They are also useful building blocks for the construction of various synthetic and natural products of therapeutic importance. There are various ways to introduce a formyl group onto an aromatic ring. Among these protocols, Gatterman,[2] Gatterman-Koch[3] and Vilsmeier-Haack[4] reactions are prominent. The use of formylating agents such as orthoformate,[5] formyl fluoride–BF_3[6] and dichloromethyl ether–$AlCl_3$[7] are alternative routes to the synthesis of formyl arenes. These are also obtained by oxidation of methyl or hydroxy methyl arenes,[8] or reduction of nitriles,[9] amides[10] and acid chlorides.[11]

It was a great surprise to us that the chemistry of formylphenanthrenes had not been explored significantly after 1936. The synthesis of 1-formylphenanthrene has been reported[12] from 1-phenanthranilide by conversion into imidoyl chloride followed by reduction with $SnCl_2$ and HCl, while 2- and 3-formylphenanthrenes were prepared[13] by the hydrogenation of the corresponding acid chloride in the presence of 5% Pd–$BaSO_4$ catalyst in very good yields. This route is also useful for the preparation of 9-formyl phenanthrene, which has also been prepared[14] by the reaction of phenanthrene and HCN as well as from the interaction of 9-phenanthrylmagnesium bromide and ethyl orthoformate.

The lack of a concise, straightforward protocol for the construction of 9,10-dihydro-3-formylphenanthrene inspired us to develop a novel, short and efficient synthesis as an alternative to the former procedures.

2-Oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles (**4**), which were used as synthons for the



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

Keywords: Tetralone; Formylphenanthrene; 2-Oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles; Masked aldehyde; Ring transformation.

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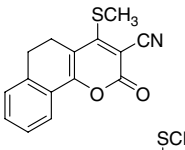
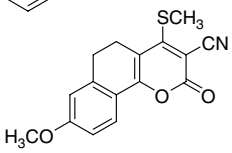
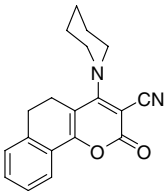
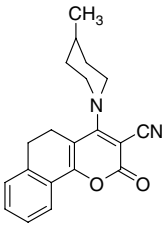
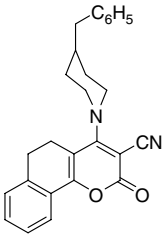
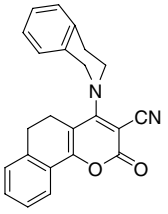
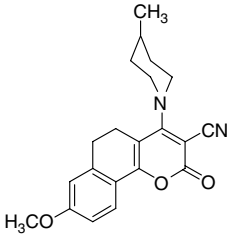
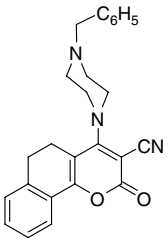
Table 1. Duration of reaction and yields of the various 2-oxo-5,6-dihydrobenzo[*h*]chromenes

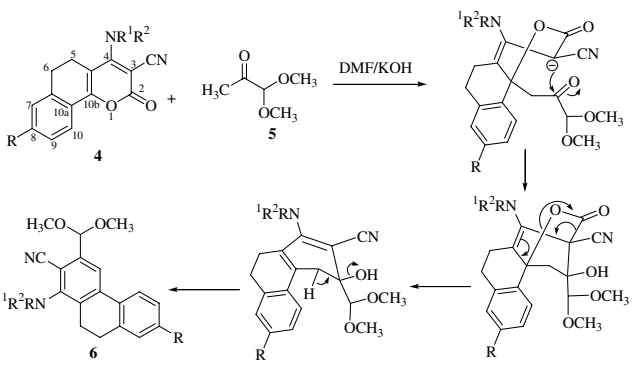
Compound	Structure	Duration of reaction (h)	Yields (%)
3a		6	94
3b		6	82
4a		5.5	96
4b		6.5	91
4c		7	81
4d		6	82
4e		5.5	71
4f		6	79

preparation of 9,10-dihydro-3-formylphenanthrenes were synthesized in two steps. The first step was the synthesis of 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **3**, from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate **1** and 1-tetralone **2** in the presence of powdered KOH in DMSO. The second step was the amination of **3** with a *sec*-amine in refluxing ethanol (Scheme 1 and Table 1).

From the topography of 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** it is evident that the C-2, C-4 and C-10b positions are electrophilic in nature. Position C-10b is highly susceptible to nucleophilic attack due to the extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the chromene ring. The masked 9,10-dihydro-3-formylphenanthrenes **6** were prepared by stirring an equimolar mixture of **4**, methyl glyoxaldimethylacetal **5** and powdered KOH in dry DMF at room temperature for 2.5–4 h, followed by pouring the reaction mixture onto crushed ice with vigorous stirring. Neutralization of the reaction mixture with 10% aqueous HCl provided a precipitate, which was filtered, washed with water and finally purified on a neutral alumina column and characterized as the masked aldehydes **6** in 72–91% yield (Scheme 2 and Table 2). There was also the possibility of formation of (3-dimethoxymethyl-9,10-dihydro-2-oxaphenanthrene-1-ylidene)acetonitrile by cyclization involving the enolic OH and C-4 of the 2-oxobenzo[*h*]chromene through Michael addition followed by elimination of the secondary amine. However, under the applied reaction conditions no such product was isolated possibly due to the presence of the electron-releasing acetal group, which did not facilitate enolization.

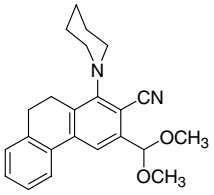
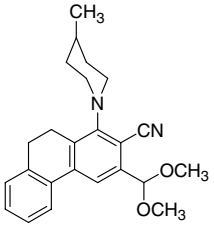
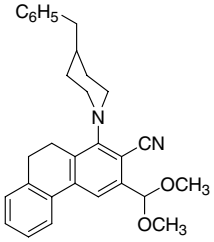
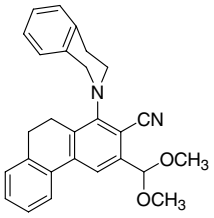
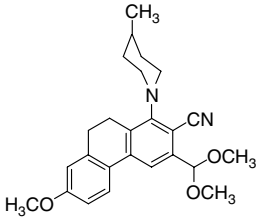
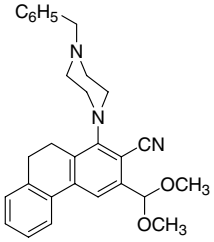
The reaction was possibly initiated by the attack of a carbanion, generated in situ from methyl glyoxaldimethylacetal **5** at C-10b with ring closure followed by decarboxylation and dehydration to yield **6**. The deacetalation of **6** by Amberlyst 15 led to aldehyde **7** in high yields (Scheme 3 and Table 3).

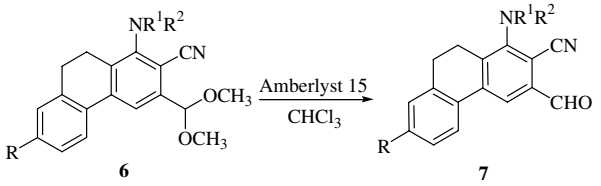
To the best of our knowledge, this is the first report on the synthesis of functionalized 9,10-dihydro-3-formylphenanthrenes using 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** as substrates for



Scheme 2.

Table 2. Duration of reaction and yields of the various masked 9,10-dihydro-3-formylphenanthrene aldehydes

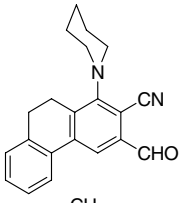
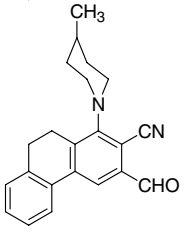
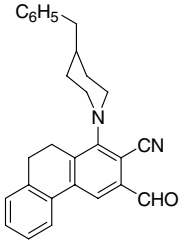
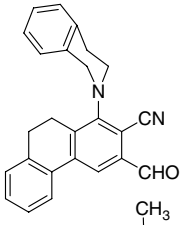
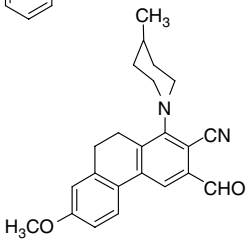
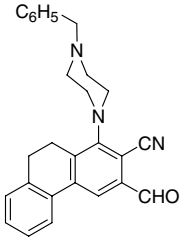
Compound	Structure	Duration of reaction (h)	Yields (%)
6a		3	84
6b		2.5	72
6c		3	86
6d		4	76
6e		3.5	91
6f		2.5	87



6 **7**

Scheme 3.

Table 3. Duration of reaction and yields of the various 9,10-dihydro-3-formylphenanthrene aldehydes

Compound	Structure	Duration of reaction (h)	Yields (%)
7a		3	98
7b		2.5	99
7c		3	97
7d		4	99
7e		3.5	99
7f		3.5	98

ring transformation reactions with methyl glyoxaldimethylacetal **5**. The synthetic strategy is very simple and straightforward. The yields were excellent without the use of any catalyst.

All the compounds synthesized were characterized by spectroscopic techniques.[15] This methodology provided a new avenue for the synthesis of congested 9,10-dihydro-3-formylphenanthrenes in excellent yields.

Acknowledgements

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15. *Representative procedure for the synthesis of 2-oxo-4-sec-amino-5,6-dihydro-2H-benzo[h]chromene-3-carbonitriles* (**4**): *Synthesis of 4-methylsulfanyl-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile* (**3a**): Compound **3a** was obtained by stirring an equimolar mixture of methyl 2-cyano-3,3-dimethylthioacrylate (0.05 mol, 10.15 g) and 1-tetralone (0.05 mol, 7.3 mL) in the presence of powdered KOH (0.06 mol, 3.4 g) in DMSO (50 mL) for 5–6 h. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring. The precipitate was filtered, washed with water then dried and purified by crystallization from methanol. Yield: 94%; mp: 204–206 °C; IR (KBr): 2922, 2370, 2207, 1699, 1612, 1570, 1508, 1446, 1372, 1279, 1257, 1221, 1155, 1132, 1092, 1037, 968, 900, 784, 742 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, 91.60, 110.89, 113.69, 123.70, 125.19, 126.28, 126.69, 130.88, 137.01, 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.
Synthesis of 4-(piperidin-1-yl)-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitrile (**4a**): Compound **4a** was prepared by refluxing a mixture of **3a** (0.01 mol, 2.7 g) and piperidine (0.012 mmol, 1.3 mL) in ethanol (50 mL) for 5 h. The reaction mixture was cooled to room temperature and filtered. The resulting precipitate was crystallized from ethanol, yield: 96%; mp: 238–240 °C; IR (KBr): 2938, 2855, 2208, 1702, 1611, 1513, 1452, 1349, 1302, 1245, 1145, 1095, 1049, 1003, 974, 939, 896, 760, 709 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.
Synthesis of masked formylphenanthrenes (**6**): An equimolar mixture of 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol), methyl glyoxaldimethylacetal (0.5 mmol) and powdered KOH (0.7 mmol) in dry DMF was stirred at room temperature for 2–3 h. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring. Neutralization with 10% aqueous HCl gave a precipitate which was filtered, washed with water and purified by neutral alumina column chromatography using hexane:ethyl acetate (99:1) as the eluent. Compound **6d**: Yield: 76%; mp: 168–170 °C; IR (KBr): 2928,2838, 2367, 2341, 2219, 1658, 1588, 1552, 1427, 1375, 1255, 1216, 1118, 1065, 971, 893, 762 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 2.73–2.78 (m, 2H, CH_2), 2.88 (br s, 2H, CH_2), 3.04 (br s, 2H, CH_2), 3.49 (s, 6H, OCH_3), 3.65 (br s, 2H, CH_2), 4.38 (br s, 2H, CH_2), 5.65 (s, 1H, CH), 7.02–7.05 (m, 1H, ArH), 7.13–7.35 (m, 6H, ArH), 7.78–7.81 (m, 1H, ArH), 7.87 (s, 1H, ArH);^{13}C NMR: (75 MHz, $CDCl_3$): 22.10, 27.07, 29.35, 47.40, 51.46, 53.40, 100.98, 106.02, 115.02, 117.59, 123.66, 124.49, 124.88, 124.97, 125.90, 126.71, 127.60, 127.99, 132.41, 133.28, 133.40, 135.47, 136.62, 138.85, 140.10, 151.56; MS *m*/*z* 411 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{27}H_{26}N_2O_2$ 410.1994 (M^+) found for *m*/*z* 410.1988.
Synthesis of 3-formylphenanthrenes (**7**): These were obtained by stirring a solution of masked formylphenanthrene **6** (0.2 mmol) in chloroform with Amberlyst 15 for 2.5–4 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered and the solvent was removed under reduced pressure. The solid obtained was crystallized from chloroform:methanol (1:1). Compound **7e**: Yield: 99%; mp: 164–166 °C; IR (KBr): 2923, 2848, 2362, 2219, 1698, 1593, 1430, 1384,

1353, 1220, 1152, 1101, 1055, 972, 900, 838, 758, 700 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): 1.01 (d, $J = 6.3$ Hz, 3H, CH_3), 1.41–1.44 (m, 1H, CH), 1.61–1.64 (m, 2H, CH_2), 1.73–1.77 (m, 2H, CH_2), 2.81 (t, $J = 6.69$ Hz, 2H, CH_2), 2.94 (t, $J = 6.48$ Hz, 2H, CH_2), 3.13–3.16 (m, 2H, CH_2), 3.40–3.44 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.81 (d, $J = 2.4$ Hz, 1H, ArH), 6.87 and 6.89 (dd, $J = 2.58$ and 2.58 Hz, 1H, ArH), 7.71 (d, $J = 8.61$ Hz, 1H, ArH), 8.02 (s, 1H, ArH), 10.36 (s, 1H, CHO); ^{13}C NMR: (75 MHz, $CDCl_3$): 20.87, 27.18, 28.42, 29.27, 33.83, 50.15, 54.11, 111.55, 112.08, 118.25, 124.60, 125.26, 135.08, 138.10, 139.29, 140.10, 153.67, 159.29, 188.30; MS m/z 361 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{23}H_{24}N_2O_2$ 360.1837 (M^+) found for m/z 360.1843.