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Acetyltrimethylsilane mediated synthesis of dihydrophenanthrenes☆

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Abstract—An easy and efficient synthesis of phenanthrene derivatives through base catalyzed ring transformation of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with acetyltrimethylsilane is described in good yields. The advantage of this reaction is the direct transformation of 2-oxobenzo[*h*]chromene into phenanthrene via C–C insertion from acetyltrimethylsilane.

The synthetic potential of organosilicon reagents for the regio- and stereocontrolled synthesis[1] of natural products and their use as mild reagents in the preparation of various compounds has been explored extensively. Organosilicons such as aryl, alkenyl-, allyl- and alkylsilanes have been developed as coupling reagents and alternatives to magnesium, boron, zinc and tin alkyls.[2] In addition, aryltrialkoxysilanes have also been developed as coupling reagents for the synthesis of biaryls on reaction with aryl halides.[3] Among the various organosilanes, alkanoyl- and aroylalkylsilanes are very prominent and useful in organic synthesis. These reagents behave like ketones and can be very reactive depending upon the group attached to the silicon.[4] Acyl silanes are considered as poor substrates for functionalization due to their high sensitivity to air and light and are used as aldehyde equivalents especially in the case of lower aldehydes, which are gases at room temperature. They can also be used as a source of carbanions and as acetylating agents.[5] To the best of our knowledge acetyltrimethylsilane has not been used so far as a reagent for the synthesis of phenanthrene derivatives, which are considered to be building blocks for polycyclic aromatics and heteroaromatics.[6]

The diverse pharmacological activities associated with phenanthrene derivatives include antimicrobial,[7] antimalarial,[8] anticancer,[9] anti-HIV,[10] and emetic.[11] Besides these, 9,10-dihydrophenanthrenes with a pendant ester group are reported to behave as liquid crystals[12] and the corresponding acids act as 5α-reductase inhibitors.[13]

Numerous approaches have been reported for the synthesis of phenanthrenes[14] and dihydrophenanthrenes[15] through ring annulation[16] and intermolecular[17] and intramolecular[18] cyclization. The majority of the procedures suffer from limitations such as accessibility of the precursors, multisteps, harsh reaction conditions, functional group tolerance, relatively low overall yields, and lack of well defined regiocontrol.

2,2′-Disubstituted biphenyls have been used as precursors for the preparation of phenanthrene by intramolecular condensation.[18] Palladium catalyzed reaction[19] of *o*-substituted aryl iodides and biphenyl or alkylphenylacetylenes is an alternative route to the synthesis of phenanthrenes. They are also prepared[20] through base catalyzed ring transformation of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylate with 1-tetralone in moderate yield. The pharmacological importance and lack of convenient and efficient procedures, prompted us to develop a concise, straightforward, and economical route for the construction of phenanthrenes possessing electron withdrawing or donating substituents. The immense synthetic potential of organosilicon reagents prompted us to use acetyltrimethylsilane as a source of carbanions for the base catalyzed ring transformation of 2-oxo-5,6-dihydrobenzo[*h*]chromenes **4** to give phenanthrene derivatives through C–C insertion.

Herein, we report an efficient, concise and novel approach for the synthesis of phenanthrene derivatives.

Keywords: Acetyltrimethylsilane; Dihydrophenanthrene; 2-Oxobenzo[*h*]-chromenes; Ring transformation.
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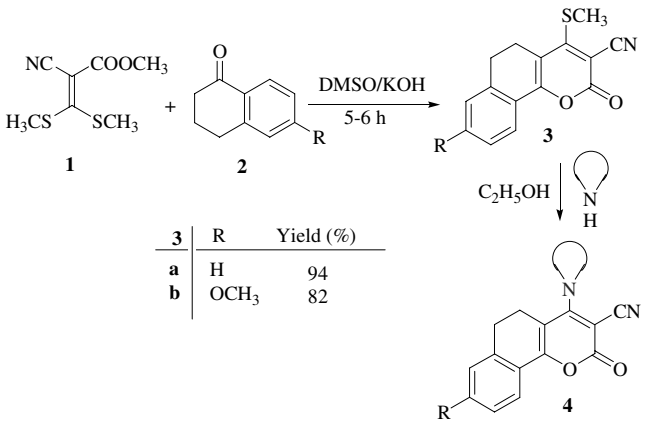


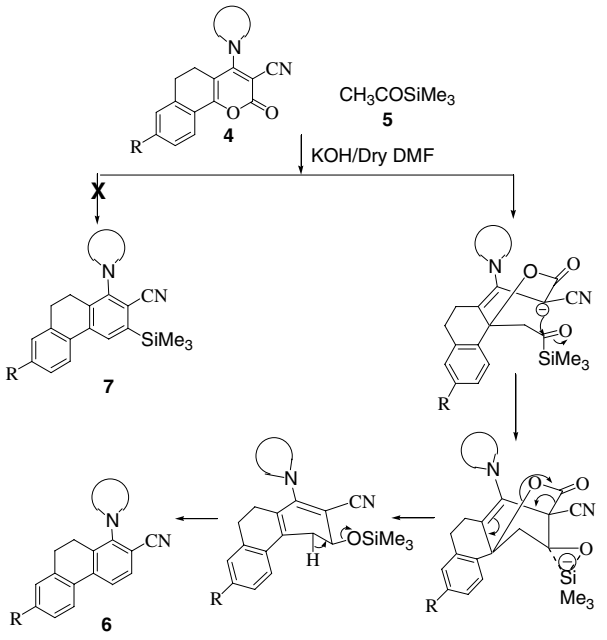
Scheme 1. Synthesis of 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo-[*h*]chromene-3-carbonitriles **4**.

2-Oxo-5,6-dihydrobenzo[*h*]chromenes **4** used in the synthesis were prepared in two steps. The first step was the synthesis of 4-methylsulfanyl-2-oxo-5,6-dihydrobenzo[*h*]chromenes **3** via the base catalyzed reaction of methyl 2-cyano-3,3-dimethylthioacrylate **1** and 1-tetralone **2** in DMSO. The reaction mixture was poured onto crushed ice with vigorous stirring to yield **3**. Amination of **3** with a secondary amine in boiling ethanol afforded 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles[21] **4** in good yields (Scheme 1 and Table 1).

The structures of the 4-*sec*-amino-2-oxo-5,6-dihydrobenzo[*h*]chromene-3-carbonitriles **4**, have three electrophilic centers C-2, C-4, and C-10b in which the latter is highly electrophilic and prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the chromene ring. The nucleophile used in this reaction is the carbanion generated in situ from acetyltrimethylsilane by base. Thus a mixture of **4**, acetyltrimethylsilane **5** and powdered KOH in DMF was stirred for 2–2.5 h under nitrogen in the dark to avoid side reactions and decomposition. The progress of the reaction was monitored by TLC and on completion the mixture was poured onto crushed ice with vigorous stirring and then neutralized with 10% HCl. The precipitate obtained was filtered, washed with water several times and dried. The crude product was purified by column chromatography. This reaction was also carried out in aerobic and dark conditions but the yield of the final product decreased

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

4	N—	R	Yields (%)
a	Piperidin-1-yl	H	94
b	4-Methylpiperidin-1-yl	H	93
c	4-Benzylpiperidin-1-yl	H	86
d	4-Benzylpiperazin-1-yl	H	79
e	4-Morpholin-1-yl	H	89
f	Tetrahydroisoquinolin-2-yl	H	87
g	Piperidin-1-yl	OCH_3	81
h	4-Methylpiperidin-1-yl	OCH_3	77



6	N—	R	Yields (%)
a	Piperidin-1-yl	H	68
b	4-Methylpiperidin-1-yl	H	71
c	4-Benzylpiperidin-1-yl	H	66
d	4-Benzylpiperazin-1-yl	H	61
e	4-Morpholin-1-yl	H	56
f	Tetrahydroisoquinolin-2-yl	H	71
g	Piperidin-1-yl	OCH_3	61
h	4-Methylpiperidin-1-yl	OCH_3	72

Scheme 2. Mechanism involved in the synthesis of 9,10-dihydro-1-*sec*-aminophenanthrene-2-carbonitriles (**6**).

to half possibly due to decomposition of acetyltrimethylsilane in air. The product isolated was characterized as 9,10-dihydro-1-*sec*-aminophenanthrene-2-carbonitrile (**6**) and not the expected 9,10-dihydro-1-*sec*-amino-3-trimethylsilylphenanthrene-2-carbonitrile **7**, as shown in Scheme 2.

Since hydrolysis of acetyltrimethylsilane in the presence of aqueous base is well documented[22] at room temperature into silanol and acetaldehyde, the reactions were carried out in dry DMF under an inert atmosphere. The reaction is possibly initiated by attack of the carbanion of **5** generated in situ by base, at the highly electrophilic center at C-10b with Michael addition followed by intramolecular cyclization involving C-3 of the chromene ring and the carbonyl functionality of acetyltrimethylsilane to form an intermediate. The intermediate diene after elimination of carbon dioxide undergoes elimination of trimethylsilanol, to produce the phenanthrene derivatives.

In summary, the synthesis of phenanthrenes possessing electron-withdrawing and donating substituents is reported for the first time through base catalyzed ring transformation of suitably functionalized 2-oxo-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromenes with acetyltrimethylsilane under very mild reaction conditions.

The procedure opens a new avenue for the construction of phenanthrene derivatives in good yields. All the products were characterized[23] by spectroscopic techniques.

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23. *General procedure for the synthesis of 9,10-dihydro-1-sec-aminophenanthrene-2-carbonitriles* (**6**): A mixture of **4** (0.5 mmol), acetyltrimethylsilane **5** (0.6 mmol) and KOH (0.8 mmol) in dry DMF was stirred under a nitrogen atmosphere in the dark. The reaction was monitored by TLC. After completion of the reaction excess DMF was removed under reduced pressure. The reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% aqueous HCl. The precipitate obtained was filtered, washed with water, dried, and purified by neutral alumina column chromatography using 40% chloroform in hexane as eluent (**6a**). Viscous oil, yield: 68%; IR (KBr): 2208 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70–1.75 (m, 6H, CH_2), 2.78–2.83 (m, 2H, CH_2), 2.87–2.92 (m, 2H, CH_2), 3.22 (br s, 4H, CH_2), 7.25–7.37 (m, 3H, ArH), 7.47 (d, $J = 8.37$ Hz, 1H, ArH), 7.50 (d, $J = 8.37$ Hz, 1H, ArH), 7.67–7.70 (m, 1H, ArH); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 22.06, 22.89, 25.51, 27.25, 51.0, 105.29, 118.66, 123.39, 125.85, 126.66, 127.35, 131.37, 132.62, 136.58; MS (ESI) m/z 289 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{20}H_{20}N_2$ 288.16265 (M^+) found m/z 288.16244. Compound (**6d**): Viscous oil, yield: 61%; IR (KBr): 2211 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (m, 4H, CH_2), 2.78–2.83 (m, 2H, CH_2), 2.87–2.95 (m, 2H, CH_2), 3.32 (br s, 4H, CH_2), 3.61 (s, 2H, CH_2), 7.14–7.40 (m, 8H, ArH), 7.49 (d, $J = 8.16$ Hz, 1H, ArH), 7.53 (d, $J = 8.22$ Hz, 1H, ArH), 7.66–7.69 (m, 1H, ArH); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 22.41, 27.17, 49.54, 52.58, 61.88, 98.50, 119.16, 123.41, 125.90, 126.65, 127.45, 127.92, 131.36, 132.47, 134.40, 136.47; MS (ESI) m/z 380 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{26}H_{25}N_3$ 379.20485 (M^+) found m/z 379.20491.